The Proceedings of the
16th Annual Research Day
Department of Medicine

April 30 & May 1, 2018

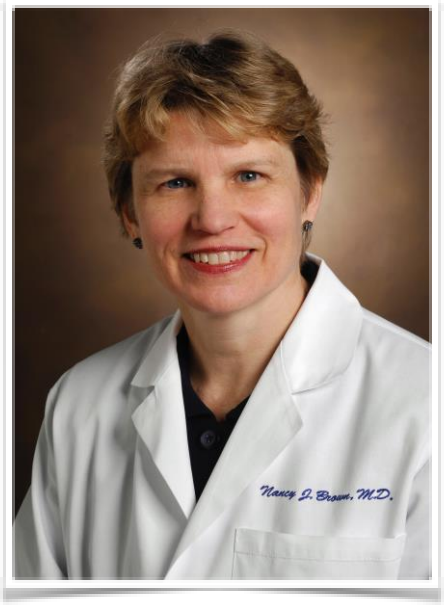
Table of Contents

Schedule of Events	Pages 3-5
Keynote Speaker: Nancy J. Brown MD	Pages 6
Oral Presenters: April 30, 2018	Pages 7-23
Oral Presenters: May 1, 2018	Pages 24-37
List of Judges	Pages 38-44
Poster Author Index: RESIDENTS – April 30, 2018	Pages 45-50
Poster Abstracts: RESIDENTS – April 30, 2018	Pages 51-103
Poster Author Index: SESSION A – May 1, 2018	Pages 104-112
Poster Abstracts: SESSION A – May 1, 2018	Pages 113-211
Poster Author Index: SESSION B – May 1, 2018	Pages 212-221
Poster Abstracts: SESSION B – May 1, 2018	Pages 222-329
Acknowledgments	Pages 330

APRIL 30, 2018 – CLINICAL RESEARCH: RESIDENTS UNIVERSITY CLUB – BALLROOM B	
5:00 pm	**Registration & Poster Viewing**
5:15 pm	**Welcome & Opening Remarks** **Mark Gladwin MD** Chair, Department of Medicine Director, Vascular Medicine Institute Professor of Medicine, Division of PACCM **Alison Morris MD, MS** Vice Chair, Clinical Research Professor of Medicine Director, University of Pittsburgh HIV Lung Research Center UPMC Chair, Translational Pulmonary and Critical Care Medicine
5:30-6:30 pm	**Oral Presenters**
6:30-7:30 pm	**Poster Viewing Session & Discussion**
7:30-8:00 pm	**Guest Speaker Presentation:** ***Do what I say, not what I did . . .*** **Dr. Nancy J. Brown** Hugh Jackson Morgan Professor of Medicine and Pharmacology Chair of the Department of Medicine Physician-in-Chief at Vanderbilt Hospital
8:00 pm	**Awards Presentation**

Schedule of Events

MAY 1, 2018 – RESEARCH DAY BIOMEDICAL SCIENCE TOWER SOUTH FOYER & S-100	
9:00 am	**Registration & Continental Breakfast Available**
9:30-11:30 am	**SESSION A:** **Poster Viewing & Judging**
11:30 am	**Lunch Available**
12:00-1:00 pm	**Keynote Presentation:** ***Cardiovascular effects of incretin-based anti-diabetic therapies*** **Dr. Nancy J. Brown** Hugh Jackson Morgan Professor of Medicine and Pharmacology Chair of the Department of Medicine Physician-in-Chief at Vanderbilt Hospital
1:15-3:15 pm	**SESSION B:** **Poster Viewing & Judging**
3:30-4:30 pm	**Oral Presentations**
4:30 pm	**Awards Presentation**



Keynote Speaker - Nancy J. Brown, M.D.

Nancy J. Brown, MD is Hugh Jackson Morgan Professor of Medicine and Pharmacology, Chair of the Department of Medicine, and Physician-in-Chief at Vanderbilt Hospital. A graduate of Yale College and Harvard Medical School, Dr. Brown leads a translational research program that focuses on pharmacological strategies to prevent diabetes and end-organ damage in hypertension. In 2000, Dr. Brown co-founded the Vanderbilt Master of Science in Clinical Investigation program to train investigators in patient-oriented research. From 2006-2010, she served as Associate Dean for Clinical and Translational Scientist Development, and established infrastructure to promote the development of physician-scientists. Dr. Brown is an active member of the American Heart Association Council for High Blood Pressure and the American Society of Hypertension. Dr. Brown served on the NIH National Advisory Research Resources Council from 2007-2011 and currently serves on the National Heart, Lung, and Blood Advisory Council. Her honors include the American Society of Hypertension Young Scholar Award, American Federation for Clinical Research Outstanding Investigator Award, the Grant Liddle Award, the E.K. Frey - E. Werle Foundation Promotion Prize, the AHA Harriet Dustan Award, and membership in the American Society for Clinical Investigation and in Association of American Physicians. Dr. Brown is a fellow of the American Association for the Advancement of Science, and member of the National Academy of Medicine.

Oral Presenter – April 30, 2018

Brian Ahn, MD

Resident, PGY-2 - Bench Research

Bio: Brian is a second-year internal medicine resident and plans to pursue a career as a clinician-scientist in Pulmonary and Critical Care Medicine. He is a California native and completed his undergraduate training in immunology at the University of California, Berkeley. Being drawn to both clinical and basic sciences, he spent his pre-doctoral years studying immune suppressive mechanisms in glioblastoma multiforme. He then went on to earn his MD at the University of Pittsburgh. Due to his interest in host-pathogen interactions in the critically ill, Brian began work with Dr. Janet Lee of Pulmonary and Critical Care Medicine and Dr. Yohei Doi of Infectious Diseases examining host innate immune response to multidrug-resistant extracellular Gram-negative nosocomial pathogens. In his free time, he enjoys rock climbing and hiking.

Presentation: ***Development of human serum resistance in carbapenemase-producing Klebsiella pneumoniae and persistent bacteremia***

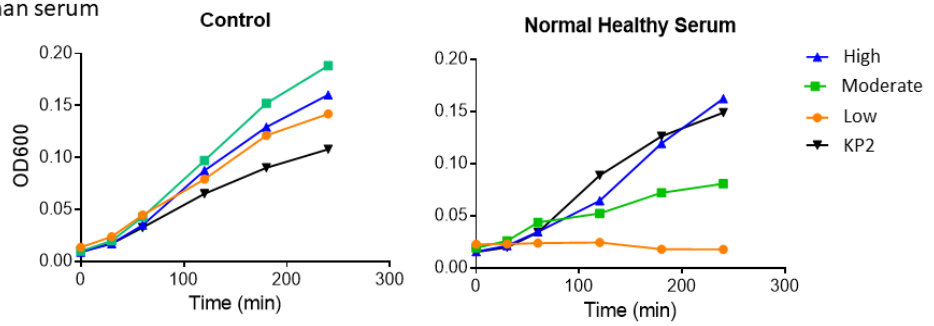
Summary: *Klebsiella pneumoniae* (KP) is a Gram-negative bacterial pathogen that is a major cause of nosocomial lung infections. Furthermore, *K. pneumoniae* strains expressing K1 or K2 capsular antigen can cause community-acquired invasive syndromes including necrotizing pneumonia, bacteremia, endophthalmitis, and hepatic abscesses. These strains have been shown to evade serum killing and phagocytosis, which are paramount to clearance of these pathogens by healthy host. Whereas, multidrug-resistant strains such as those producing *Klebsiella pneumoniae* carbapenemase (KPC) are associated with increased morbidity and mortality in the critically ill in hospital settings. KPC-producing *K. pneumoniae* (KPC-KP) of sequence type 258, the most prevalent strain in the US, have been previously reported to be highly susceptible to human serum killing and are virtually avirulent in mouse septicemia models. In contrast to the hypermucoviscous K1/K2 serotype KP strains evade serum and complement-mediated killing and are highly pathogenic in mouse models. More recently, there have been reports of development of hypervirulent KPC in hospital settings.

Objective: We hypothesize that some KPC-KP ST258 may demonstrate increased pathogenicity via serum resistance.

Methods: KPC-KP isolates from patients were acquired from three academic centers from Pittsburgh, PA; Miami, FL; and Madison, WI. KP strains were grown in tryptic soy broth at 37°C overnight to early logarithmic phase then incubated in the presence of 85% pooled human serum from healthy donors or polymyxin B with 5% TSB. The serum-resistant KP2 strain 43816 (K2 serotype, ATCC research strain) was used as a reference control. Growth was assessed by measurement of optical density at 600 nm (OD_{600}) at 0, 30, 60, 120, 180, and 240 minutes in various growth media: TSB broth alone and in addition to polymyxin B or normal healthy serum. Serum resistance was defined as the inability of human serum to inhibit KP growth *in vitro*, where the ratio of final to initial OD_{600} was utilized to characterize the degree of serum resistance: high (ratio ≥5), moderate (ratio ≥2 and <5), or low or no resistance (ratio <2) (Figure 1). *G. mellonella* waxworms, which possess humoral and cellular innate defenses but lack adaptive immunity, were infected with KPC-KP clinical isolates. 12 waxworms were randomly selected for each isolate. They were inoculated by injection with 10^6 CFU of each isolate. Waxworms were incubated at 37°C in atmospheric air and observed every 24h for 4 days.

Results: 76 clinical strains were isolated from various sites of infection including but not limited to blood, sputum, urine, and peritoneal fluid. There were no differences observed in KP growth between strains in TSB broth alone (Figure 1, Control panel). Of these isolates, 12 (15.8%) exhibited high resistance, 17 (22.4%) exhibited moderate resistance, and 47 (61.8%) demonstrated low or no serum resistance (Figure 1, Normal Healthy Serum panel). We identified 8 serial isolates obtained from one patient with persistent KPC-KP bacteremia during a three-month period exhibiting progressive serum resistance. Characteristics of location and date isolated are shown in Table 1. The patient had persistent bacteremia and the presumable source was peritoneal in origin as patient had a history of liver disease and peritoneal cultures growing one of the isolates (Table 2). Initial isolates were fully suppressed by human sera, but isolates collected later during the patient's hospitalization demonstrated moderate then high serum resistance (Figure 2). Interestingly, there was concordant development of polymyxin resistance with highly serum resistant isolates. *G. mellonella* waxworms infected with the 8 serial isolates showed similar progressive reductions in survival with development of increasing serum resistance and polymyxin resistance. Survival analysis of serial KPC-KP isolates composited into three groups based on serum sensitivity showed that isolates with high resistance had a statistically significant reduction in survival compared to moderate and low resistance isolates ($p < 0.0001$). No difference was observed between moderate and low resistance groups.(Figure 3).

Figure 1: Representative graph of variable growth of KPC-KP isolates in Control TSB broth and human serum



Degree of NHS resistance	High	Moderate	Low	Total
Number of isolates	12 (15.8%)	17 (22.4%)	47 (61.8%)	76

Figure 2: Growth of serial KPC-KP isolate from a single patient in Control TSB broth, polymyxin B and normal healthy serum

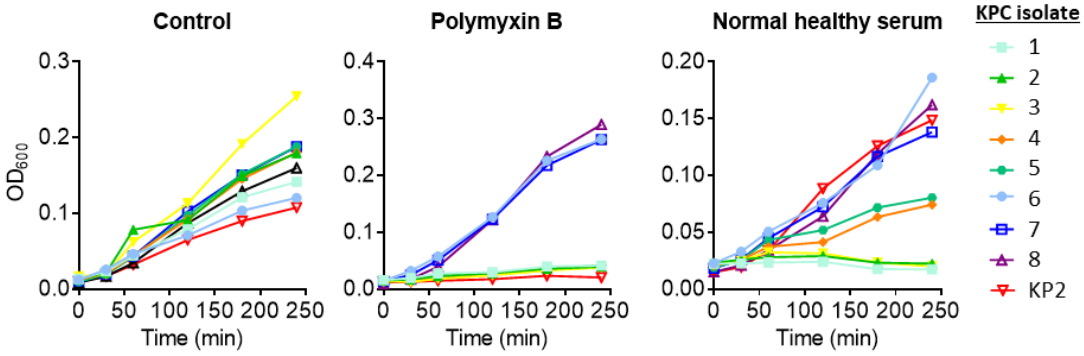


Figure 3: Waxworm survival by serial KPC-KP isolates and based on serum sensitivity

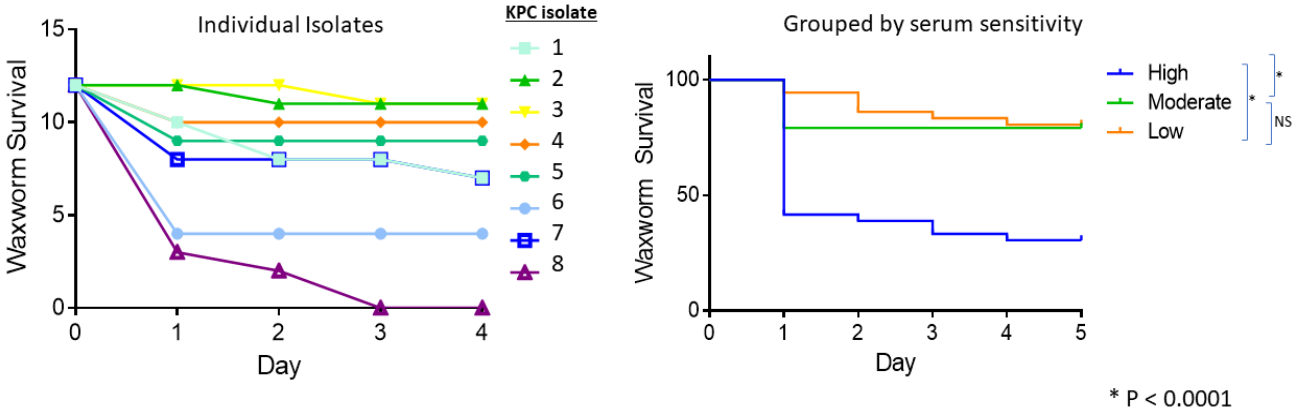


Table 1: Summary of serial KPC-KP clinical isolates

KPC Isolate	Date Isolated	Source	Serum Resistance	PolymyxinB MIC
1	3/19/2012	Blood	Low	0.25
2	3/24/2012	Blood	Low	0.25
3	3/25/2012	Blood	Low	0.25
4	3/27/2012	Blood	Moderate	0.25
5	3/29/2012	Hepatic fluid	Moderate	0.25
6	3/30/2012	Blood	High	128
7	4/23/2012	blood	High	>128
8	6/18/2012	blood	High	>128

Table 2: Patient characteristics for source of serial KPC isolates

Age	Site	Sex	Comorbidities	Type of Infection	Treatment
63	UPMC	Female	Liver Transplant	Blood stream, intrabdominal abscess	PolymyxinB, Doripenem, Ertapenem

Conclusion: While KPC-KP strains are generally thought to be relatively avirulent and susceptible to serum killing, analysis of clinical strains revealed ~38% of samples exhibiting serum resistance using normal human serum. Evaluation of serial clinical isolates from a single patient demonstrated progressive serum resistance, suggesting de novo development of resistance to complement-mediated killing, alterations in the outer cell wall membrane based upon polymyxin B resistance, and persistent bacteremia.

Oral Presenter – April 30, 2018

Brendan Filardo, MD

Resident, PGY-3 - Medical Education Research

Bio: Brendan Filardo is a third year categorical Internal Medicine resident. He will be starting as a hospitalist at Indian River Medical Center in Vero Beach, FL after he completes his residency training. He will miss Pittsburgh but is looking forward to starting a new chapter in his career. Brendan graduated with his MD from the University at Buffalo School of Medicine and Biomedical Sciences after obtaining a BS in Biochemistry from SUNY Geneseo. In his free time, he plays guitar and enjoys spending time with his fiancée, Leah, and their dog Odin. He keeps in regular contact with his college friends through online Xbox sessions.

Presentation: ***An electrifying effect: Targeted workflow rewiring improved rates of electronic prescribing at discharge***

Summary: Electronic prescribing (eRx) at discharge enhances safety and quality of care transitions by decreasing prescribing error and the need for pharmacist intervention. The Centers for Medicare and Medicaid Services incentivizes hospitals to generate eRx at discharge through the Electronic Health Records Incentive Program (EHRIP). Stage 3 goals of EHRIP include discharge eRx rates of greater than 25%. As of September 2017, our academic medical center had a year-to-date discharge eRx rate of 18.3%, which we identified as an opportunity for improvement.

Our meds-to-beds (MTB) program uses the hospital-based outpatient pharmacy (HBP) to deliver medications directly to the patient prior to discharge. Prior to our intervention MTB was a paper-based prescription process. As part of our goal of improving discharge eRx rates, we aimed to analyze and convert the MTB workflow to an eRx-based process.

Methods: The intervention took place over five house staff rotations, each 4-5 weeks in length. Eight general internal medicine house staff teams at UPMC MUH/PUH participated per rotation. Prior to our intervention, we performed a root cause analysis of barriers to using MTB and eRx by house staff. These were missing eRx profile accounts for a subset of intern prescribers and lack of knowledge about the eRx workflow. We worked with information services analysts to identify and correct prescriber profiles, pharmacy staff to accept inpatient eRx, and case management to transfer a patient demographics face sheet to the pharmacy. For the intervention we taught house staff the eRx for MTB workflow during the orientation sessions for each rotation.

Results: Post-intervention, the rotation average eRx sent to our HBP increased dramatically (237 vs 60, p=0.002). This coincided with an increase in average overall discharge eRx rate (48.4% vs 24.6%, p=0.005) (Table 1). Improvements were sustained over multiple post-intervention rotations except when the educational session was compromised due to holiday scheduling (Figure 1). Data analysis was limited by inability to directly measure eRx for MTB, instead using eRx sent to the HBP as a surrogate. When eRx to HBP was excluded from post-intervention data, an increase in average rotation discharge eRx rate was observed but was not statistically significant (36.0% vs 24.6%, p=0.067).

Table 1: Average eRx to HBP* and discharge eRx rates pre- and post-intervention

	Pre-Intervention	Post-Intervention	*P* Value⁺
All Prescriptions, n	4695	7314	—
Avg. Rotation eRx to HBP, n	60	237	0.002
Avg. Rotation Discharge eRx rate	24.6%	48.4%	0.005

*HBP = Hospital-based outpatient pharmacy; ⁺Unpaired (two sample) t-test

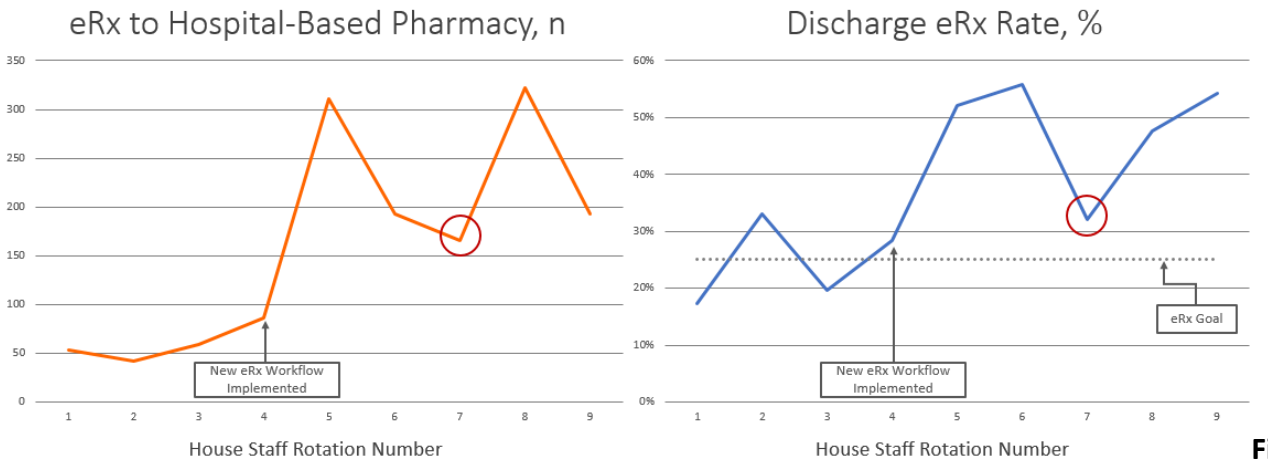


Figure 1. Post-intervention improvements were sustained over multiple rotations except when the educational component was compromised due to holiday scheduling (rotation number 7, red circle).

Conclusion: Using the hospital-based outpatient pharmacy for MTB eRx significantly improved discharge eRx rates. Addressing pre-intervention barriers to eRx may have improved discharge eRx rates in addition to the benefits of the MTB intervention alone. The novel MTB workflow was relatively straight forward to implement and demonstrates that simple, targeted QI interventions can yield significant results. Based on our results we plan to expand the initiative to other hospital units as well as other teaching hospitals within our health system.

References:

1. Donyai P, O'Grady K, Jacklin A, Barber N, Franklin B. The effects of electronic prescribing on the quality of prescribing. British Journal of Clinical Pharmacology. 2008;65(2):230-37.
2. Electronic Health Records (EHR) Incentive Programs - https://www.cms.gov/Regulations-andGuidance/Legislation/EHRIncentivePrograms/index.html?redirect=/EHRIncentivePrograms. Updated February 28, 2018. Accessed March 26, 2018.
3. Jochum J, Findley T, Powers K, Feterik K. Electronic-Prescribing at Discharge from Acute Hospitalization: System and Educational Interventions to Improve e-Rx Rates. Poster presented at: 2018 SGIM Annual Meeting; April 2018; Denver, CO.

Oral Presenter – April 30, 2018

Benjamin Smith, MD

Resident, PGY-2 - Clinical Research

Bio: Ben Smith is a second year categorical Internal Medicine resident at the University of Pittsburgh Medical Center. He hails from Charleston, WV and earned an M.D. from West Virginia University School of Medicine in 2016. Early in residency, he became interested in Cardiology as a future career, and has since been involved with research in the specialty. He has been fortunate to work with mentors including Dr. Sandeep Jain and Dr. Stephen Chan. Outside of the hospital, he is an avid reader, amateur writer, and feels most at home outdoors.

Presentation: ***Cryoballoon Ablation in Patients with Non-conventional Pulmonary Vein Anatomy***

Summary: Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, with a particularly high incidence in the aging population, affecting 5% of those seventy or older. In patients with a high burden of symptoms, a rhythm control strategy has been shown to significantly reduce symptoms and improve quality of life, and AF ablation has increasingly become a mainstay in the restoration of sinus rhythm in this population. AF ablation involves electrical isolation of the pulmonary vein as these are often the sites for triggering AF. Initially, the only available means to achieve this was via radiofrequency ablation in which resistive and conductive heating results in tissue necrosis, but more recently, cryoballoon ablation, which utilizes a balloon within the vein ostia that is then cooled to very low temperatures to form scar tissue, has emerged as a viable alternative. While cryoballon ablation has been shown to be generally non-inferior to radiofrequency ablation, most notably in the 2016 FIRE and ICE trial, how the efficacy of the procedure is impacted in specific patient subsets has yet to be fully investigated. One such situation is the presence of non-conventional pulmonary vein anatomy, where as opposed to the standard two right and two left pulmonary veins, there may instead be one large vein in place of two, or extra veins in addition to the usual four. Our study sought to better define the effect of various non-conventional pulmonary vein (PV) anatomies on procedural characteristics and efficacy outcomes of cryoballoon ablation for AF.

Methods: We used a single center comprehensive prospective registry of all procedures performed from May 2013 through December 2015 with the 2nd generation Cryoballoon catheter. All patients included underwent a pre-procedure cardiac CT. Non-conventional PV anatomy was defined as any deviation from 4 pulmonary veins and was based on radiologist review of CT images. Those patients with non-conventional PV anatomy were compared to those with conventional anatomy in terms of baseline covariates, procedural characteristics, and efficacy outcomes. Statistical analysis was performed using Microsoft Excel and Kaplan-Meier analyses were performed to compare recurrence rates using statistical software Prism 7.

Results: Of 355 total ablation procedures, 279 (78.6%) of patients were determined to have conventional PV anatomy while 76 (21.4%) had non-conventional anatomy. Presence of a left common PV was the most common non-conventional anatomical configuration with 51 instances (67.1%). Between the conventional and non-conventional groups, there was no significant difference among baseline covariates, including $CHA_2DS_2VASc_2$ conditions, CAD, renal function, or rates of persistent AF (Table 1). Total procedure time (121 vs. 135 min, $p<0.05$) and left atrial dwell times (89 vs. 98 min, p-value <0.05) were longer in the non-conventional group, but otherwise procedural characteristics did not differ significantly, including the rate of phrenic nerve injury. Pulmonary vein isolation (PVI) was achieved in all patients in both groups with low rates of need for radiofrequency ablation (Table 2). There was no significant difference in atrial arrhythmia recurrence at 6 months (21.9% vs. 22.7%, p=0.89) or at 1 year (31.7% vs. 34.7%, p=0.62). There was also no difference in overall recurrence rates when extended beyond one year (43.3% vs. 45.3%, p=0.76) (Figure 1).

Table 1. Baseline demographics

	Conventional	Non-conventional	p-value
Patients	279	77	NA
Age (median years)	61 ± 9.7	59 ± 9.3	0.32
Female	27%	33%	0.27
BMI	31.1±6.0	31.3±5.5	0.73
CHF	9%	17%	0.05
HTN	57%	59%	0.74
Age>75	4%	1%	0.23
DM2	14%	11%	0.47
CVA/TIA	8%	10%	0.59

Age 65-75	30%	32%	0.66
Vascular disease	14%	21%	0.15
CHADS2 score	1.16	1.11	0.71
CHADS2VASc score	1.67	1.89	0.23
Persistent AF	25%	21%	0.56
Valvular disease	6%	10%	0.27
CAD	17%	19%	0.77
Tobacco use	14%	20%	0.25
Creatinine	0.95±0.37	0.93±023	0.71

Note: BMI: body mass index; CHF: congestive heart failure; HTN: hypertension; DM2: type 2 diabetes mellitus; CVA/TIA: cerebral vascular accident/transient ischemic attack; CAD: coronary artery disease.

Table 2. Procedural characteristics

	Conventional	Non-conventional	p-value
Total procedure time (min)	122±42	135±49	0.03
LA dwell time (min)	90±27	98±38	0.03
Total fluoro time (min)	28±12	27±14	0.59
IV contrast (ml)	34±23	32±22	0.48
Long-term phrenic nerve injury	2.1%	1.0%	0.47
RFA use	1.0%	1.0%	0.79
Successful PVI	1.00	1.00	NA

Note: LA: left atrium; fluoro: fluoroscopy; RFA: radiofrequency ablation; PVI: pulmonary vein isolation

Table 3. Recurrence rates

	Conventional	Non-conventional	P-value
Recurrence	0.43	0.45	0.76
Recurrence at 6 months	0.22	0.23	0.89
Recurrence at 12 months	0.32	0.35	0.62

Limitations: All procedures were performed by a relatively small number of experienced operators, so generalizability of our findings may be limited. While this study focused on the pattern of pulmonary vein anatomy, we did not investigate the impact of vein size and shape, which has been reported as a complicating factor in other studies. Given the evolving use of a new technology over this time period, procedural techniques may have changed resulting in outcomes differences.

Conclusion: In patients with non-conventional PV anatomy who are candidates for AF ablation, Cryoballoon ablation is a reasonable approach with an increase in procedure time, but no difference in long term efficacy or rates of phrenic nerve injury.

References:

1. Andrade, J.G., et al., *Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies.* Heart Rhythm, 2011. **8**(9): p. 1444-51.

2. Packer, D.L., et al., *Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial.* J Am Coll Cardiol, 2013. **61**(16): p. 1713-23.

3. Sarabanda, A.V., et al., *Efficacy and safety of circumferential pulmonary vein isolation using a novel cryothermal balloon ablation system.* J Am Coll Cardiol, 2005. **46**(10): p. 1902-12.

4. Luik, A., et al., *Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study.* Circulation, 2015. **132**(14): p. 1311-9.

5. Cardoso, R., et al., *Cryoballoon versus Radiofrequency Catheter Ablation in Atrial Fibrillation: A Meta-Analysis.* J Cardiovasc Electrophysiol, 2016. **27**(10): p. 1151-1159.

6. Guhl, E.N., et al., *Incidence and Predictors of Complications During Cryoballoon Pulmonary Vein Isolation for Atrial Fibrillation.* J Am Heart Assoc, 2016. **5**(7).

7. Koektuerk, B., et al., *Cryoballoon Ablation for Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation: One-Year Outcome Using Second Generation Cryoballoon.* Circ Arrhythm Electrophysiol, 2015. **8**(5): p. 1073-9.

8. Neumann, T., et al., *Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study.* J Am Coll Cardiol, 2008. **52**(4): p. 273-8.

9. Defaye, P., et al., *Efficacy and safety of pulmonary veins isolation by cryoablation for the treatment of paroxysmal and persistent atrial fibrillation.* Europace, 2011. **13**(6): p. 789-95.

10. Jongbloed, M.R., et al., *Atrial fibrillation: multi-detector row CT of pulmonary vein anatomy prior to radiofrequency catheter ablation--initial experience.* Radiology, 2005. **234**(3): p. 702-9.

11. Ghaye, B., et al., *Percutaneous ablation for atrial fibrillation: the role of cross-sectional imaging.* Radiographics, 2003. **23 Spec No**: p. S19-33; discussion S48-50.

12. Ho, S.Y., J.A. Cabrera, and D. Sanchez-Quintana, *Left atrial anatomy revisited.* Circ Arrhythm Electrophysiol, 2012. **5**(1): p. 220-8.

13. Marom, E.M., et al., *Variations in pulmonary venous drainage to the left atrium: implications for radiofrequency ablation.* Radiology, 2004. **230**(3): p. 824-9.

14. Shan, F., et al., *[Variations of pulmonary venous drainage and venous ostium index detection in atrial fibrillation patients prior to radiofrequency catheter ablation by MDCT pulmonary venography].* Zhonghua Xin Xue Guan Bing Za Zhi, 2007. **35**(4): p. 329-32.

15. Kato, R., et al., *Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging.* Circulation, 2003. **107**(15): p. 2004-10.

16. Khoueiry, Z., et al., *Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy.* Europace, 2016. **18**(9): p. 1343-51.

17. Krum, D., et al., *Left Atrial Anatomy in Patients Undergoing Ablation for Atrial Fibrillation.* J Atr Fibrillation, 2013. **5**(6): p. 755.

18. Schmidt, M., et al., *Cryoballoon in AF ablation: impact of PV ovality on AF recurrence.* Int J Cardiol, 2013. **167**(1): p. 114-20.

19. Stroker, E., et al., *Second-generation cryoballoon ablation in the setting of left common pulmonary veins: Procedural findings and clinical outcome.* Heart Rhythm, 2017. **14**(9): p. 1311-1318.

20. Monteiro, M.M., et al., *Characterization of pulmonary vein morphology using multi-detector row CT study prior to radiofrequency ablation for atrial fibrillation.* Rev Port Cardiol, 2009. **28**(5): p. 545-59.

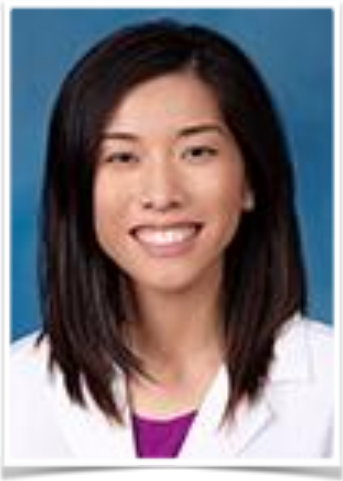
21. Canpolat, U., *What makes pulmonary vein anatomy important and preprocedural imaging useful during catheter ablation for atrial fibrillation?* Europace, 2017. **19**(10): p. 1754.

22. Kaseno, K., et al., *Prevalence and characterization of pulmonary vein variants in patients with atrial fibrillation determined using 3-dimensional computed tomography.* Am J Cardiol, 2008. **101**(11): p. 1638-42.

23. Sorgente, A., et al., *Pulmonary vein ostium shape and orientation as possible predictors of occlus on in patients with drug-refractory paroxysmal atrial fibrillation undergoing cryoballoon ablation.* Europace, 2011. **13**(2): p. 205-12.

24. Saitoh, Y., et al., *Persistence of Phrenic Nerve Palsy Following 28-mm Cryoballoon Ablation: A Four-Year Single Center Experience.* Pacing Clin Electrophysiol, 2015. **38**(7): p. 807-14.

25. Mugnai, G., et al., *Incidence and characteristics of complications in the setting of second-generation cryoballoon ablation: A large single-center study of 500 consecutive patients.* Heart Rhythm, 2015. **12**(7): p. 1476-82.



Oral Presenter – April 30, 2018

Sunny Tao, MD

Resident, PGY-2 - Health Science/Clinical Epidemiology Research

Bio: Sunny is a second year categorical Internal Medicine resident at the University of Pittsburgh Medical Center. Originally from Dayton, Ohio, Sunny completed her undergraduate training at Vanderbilt University. She earned her MD at the University of Pittsburgh School of Medicine before starting her residency in 2016. After residency, Sunny plans to pursue a career in Gastroenterology and Hepatology. Her research interests include liver transplant outcomes and sarcopenia and frailty in chronic liver disease. In her free time, she enjoys hiking with her dog, exploring the Pittsburgh restaurant scene, and experimenting with photography.

Presentation: ***"Is more transplant care better? Geographic proximity is associated with more post-liver transplant visits but has no effect on outcomes"***

Summary: Health care after liver transplantation (LT) is complex and resource intensive, involving collaboration between local and transplant center providers.[1,2] While geographic proximity to a transplant center improves the likelihood of cirrhotic patients receiving transplantation,[3,4] it is not known whether proximity might also influence late outcomes after transplantation. To date, there has not been a single-center evaluation of the impact of geographic distance on post-LT outcomes independent of inter-center care variation. As such, we conducted a retrospective cohort study of recipients of LT performed at the University of Pittsburgh Medical Center (UPMC) from 1980 through 2015 and compared recipient survival and late post-transplant outcomes stratified by distance of residence from UPMC.

Methods: We reviewed the electronic records of patients aged 18 years and older who received a first single-organ liver transplant at UPMC between January 1, 1980 and December 31, 2015. A total of 4,427 recipients had a zip code of residence recorded, comprising our study cohort. Patients were stratified into three groups by distance from their residence address to UPMC: ≤50, 51-150, and >150 miles. We compared post-LT survival among these three distance groups. For the 1,352 patients alive on January 1, 2017, we evaluated two laboratory indicators of post-LT health, liver biochemical testing and creatinine, and compared the percentages of recipients with normal liver biochemical testing and adequate renal function among the distance groups using chi-squared analysis. We defined normal liver biochemical testing as AST ≤55 IU/ml, ALT ≤55 IU/ml, alkaline phosphatase ≤115 IU/ml, total bilirubin ≤1.2 mg/dl,

albumin ≥3.3 g/dl, and INR ≤1.3. We defined adequate renal function as creatinine ≤1.5 mg/dl. If a patient had more than one set of laboratory values recorded in 2016, we used the most recent data.

Results: Our study cohort comprised of 4,427 LT recipients who had a zip code of residence recorded in our system. The geographic distribution of recipients' residence in relation to UPMC is shown in **Figure 1**. The median post-LT survival for the entire cohort was 10.6 years (**Table 1**). Survival was not significantly different among the three distance groups (P=0.36), as depicted by the Kaplan-Meier plot (**Figure 2**). By January 1, 2017, slightly fewer than one third of recipients were still alive. Most (93.9%) of these patients had a creatinine recorded in 2016, while 43.3% had complete liver biochemical testing recorded. For the 1,352 LT recipients alive in 2016, the mean number of UPMC visits in that year was 3.78, ranging from a mean of 6.1 in recipients living ≤50 miles away to a mean of 0.7 for those living >150 miles away (**Table 2**). The mean number of UPMC visits that were specifically transplant-related ranged from 1.07 to 0.30 for the closest and farthest distance groups, respectively (P=0.0001). Among the 586 LT recipients who had a full liver biochemical panel in 2016, 47.2% had normal results on their most recent testing (**Table 2**). Of the 1,270 recipients with creatinine measured in 2016, 69.6% had adequate renal function defined as creatinine ≤1.5 on their most recent measurement. Distance from the transplant center was not associated with these favorable outcomes (P=0.46 and 0.34 for liver and creatinine results, respectively).

Table 1: Post-Liver Transplant Survival of LT recipients By Proximity to UPMC

Distance from UPMC (miles)	LT recipients	Survival post- LT in Years*
≤50	1,640	10.3 (9.6, 11.1)
51-150	920	10.9 (9.9, 12.1)
>150	1,867	10.8 (10.3, 11.6)
Total	4,427	10.6 (10.3, 11.2)
P-value	---	0.36

*Median (95% confidence interval)

Table 2: Post-transplant survival, number of visits to UPMC, and health status by geographic proximity to UPMC

Distance from UPMC (miles)	Number of recipients alive in 2016	Number of UPMC visits in 2016*	Number of transplant-related visits in 2016*	% with normal liver testing **	% with Cr ≤1.5 mg/dl**
≤50	632	6.10 (6.64)	1.07 (2.61)	49.2%	68.4%
51-150	365	2.96 (4.12)	0.63 (1.65)	44.0%	68.6%
>150	355	0.67 (1.81)	0.30 (1.34)	45.5%	73.0%
Total	1,352	3.78 (5.58)	0.75 (2.11)	47.2%	69.6%
P-value	---	0.0001	0.0001	0.46	0.34

*Mean (± SD)
**Percentage of 586 LT recipients with liver biochemical panel data recorded in 2016
**Percentage of 1,270 LT recipients with creatinine recorded in 2016

Figure 1: Geographic distribution of University of Pittsburgh Medical Center liver transplant recipients, 1980 to 2015

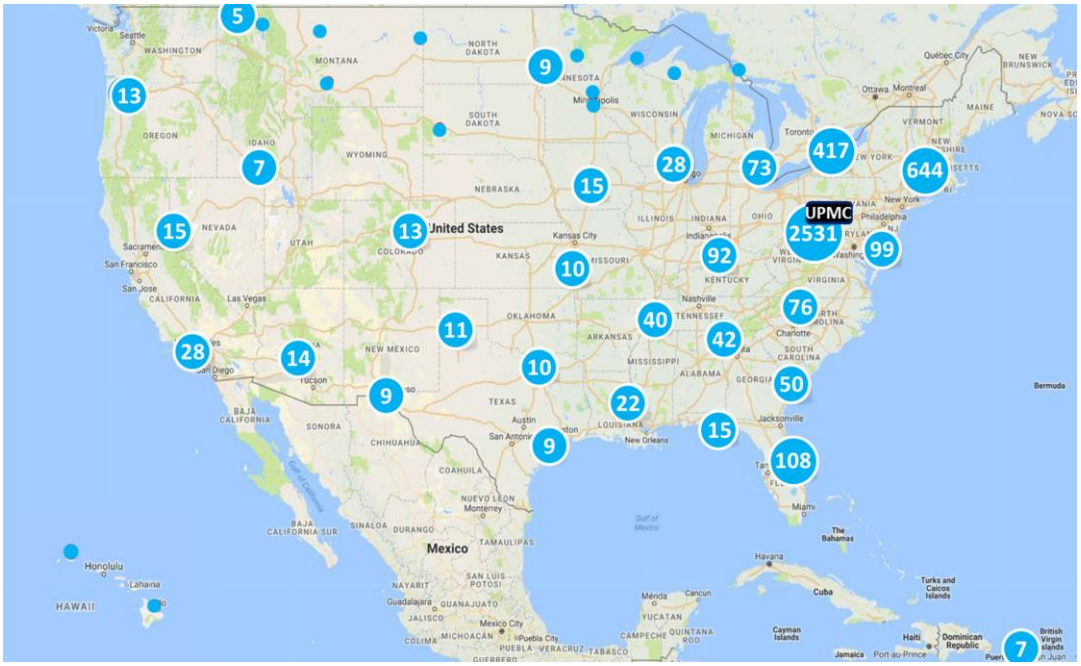
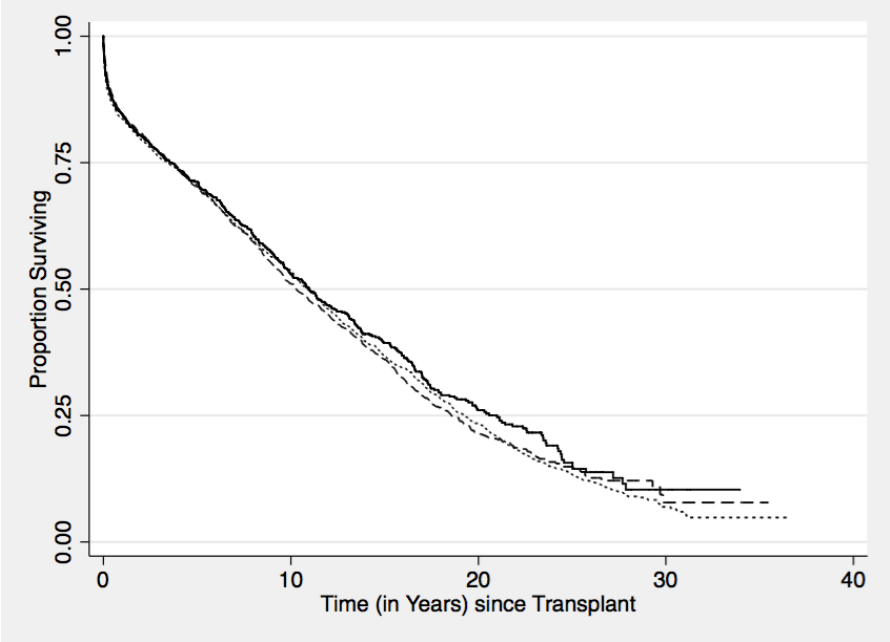


Figure 2: Post-LT survival based on distance of post-LT residence from UPMC



Kaplan-Meier curves showing survival of 4,427 liver transplant recipients based on the distance of their post-transplant residence from UPMC. The dashed line shows survival of 1,640 recipients living <50 miles, the solid line shows survival of 920 recipients living 51-150 miles, and the dotted line shows survival of 1,867 recipients living >150 miles from UPMC.

Conclusion: In a large, single-center population spanning the 35-year history of liver transplantation, we found, as expected, a significant association between frequency of post-LT visits and proximity of residence to UPMC. However, distance from the center did not significantly impact post-LT survival or health as indicated by two objective outcome measures: liver biochemical testing and renal function. We conclude that well-managed patients who live more remotely from their transplant center may expect outcomes equivalent to those of recipients living nearby.

References:

1. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19:3-26.
2. Cheung A, Levitsky J. Follow-up of the post-liver transplantation patient: A primer for the practicing gastroenterologist. Clin Liver Dis. 2017;21:793-813.
3. Goldberg DS, Newcomb C, Gilroy R, et al. Increased distance to a liver transplant center is associated with higher mortality for patients with chronic liver failure. Clin Gastroenterol Hepatol. 2017;15:958-960.
4. Goldberg DS, French B, Forde KA, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. JAMA. 2014;311:1234-1243.

Oral Presenter – May 1, 2018

Michael Genuardi, MD

Fellow - Clinical Research

Bio: Michael V. Genuardi, MD, is a third-year cardiology fellow at UPMC and a post-doctoral fellow at the Graduate School of Public Health. He completed his undergraduate degree at Boston University, medical degree at Tufts University School of Medicine, and internal medicine residency at Massachusetts General Hospital. He works with Drs. Sanjay Patel and Jared Magnani investigating sleep and cardiovascular outcomes, leveraging clinical data extracted from the UPMC electronic medical record. When not at work, he enjoys spending time with his wife and daughters and attempting to make sense of Pittsburgh streets through jogging.

Presentation: ***Short sleep time is associated with increased risk of incident atrial fibrillation***

Summary: Sleep apnea has long been associated with atrial fibrillation (AF), and may have a role in the causal pathway.[1,2] Recently, short sleep duration has emerged as a novel potential risk factor. Shortening of Stage 3 NREM sleep has been linked to prevalent AF,[3] and short self-reported sleep duration has been shown to be associated with risk of incident AF in an all-male cohort.[4] However, investigations of the association between objectively measured sleep duration and incident AF in a general population are lacking. We hypothesized that objectively measured short sleep duration is a risk factor for both prevalent and incident AF.

Methods: The electronic medical records of all patients age ≥ 18 years undergoing diagnostic full night in-lab polysomnography (PSG) at 6 sleep laboratories within the University of Pittsburgh Medical Center system between March 1999 and December 2015 were examined. Total sleep time (TST), cardiac rhythm during PSG, and apnea-hypopnea index (AHI), a measure of sleep apnea severity, were extracted from PSG reports. Cardiovascular comorbidities were identified using International Classification of Disease (ICD) codes. In a cross-sectional analysis, the association between TST and prevalent AF was examined, using multivariable logistic regression to adjust for age, sex, site, body mass index (BMI), hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, and AHI.

The association between TST and risk of incident AF was then examined prospectively. Patients with prevalent AF, identified by cardiac rhythm during PSG, prior electrocardiogram showing AF, or prior ICD code for AF, were excluded. Incident AF was identified using ICD codes and EKGs obtained during outpatient and inpatient visits. Cox proportional hazards modeling was used to estimate the impact of TST on AF risk adjusting for age, sex, site, BMI, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure and AHI.

Results: In total, 30,061 individuals were included for cross-sectional analysis (age 51.0 ± 14.5 years, 51.6% women). In patients who slept <3 hours, the odds ratio (OR) for AF was 2.10 [95% CI 1.21-3.94] compared to those who slept ≥6 hours after adjustment for demographics, comorbidities, and sleep apnea severity. In continuous analysis, each hour shorter sleep was associated with an OR of 1.17 [95% CI 1.08-1.27] for prevalent AF in adjusted analysis.

After excluding patients with prevalent AF, 27,519 patients were available for prospective follow-up. Over a median follow-up of 5.0 yrs [interquartile range, 2.5-8.1], 1,864 cases of incident AF were identified. Shorter TST on baseline PSG was associated with an increased risk of subsequent AF (Figure). Incidence rates were 6.2, 7.8, 12.2, 18.0, and 25.3 cases per 1,000 patient-years for those sleeping ≥6, 5-6, 4-5, 3-4, and <3 hours, respectively. After adjusting for age and sex, the hazard ratio (HR) for AF was 1.16 [95% CI 1.13-1.21] per 1-hour reduction in TST. After further adjustment for BMI, AHI, and comorbidities, the HR for AF was 1.11 [95% CI 1.07-1.15] per 1-hour reduction in TST. There was not significant interaction between AHI and TST on the risk of incident AF or the odds of prevalent AF.

Conclusion: Short sleep duration is an independent risk factor for both prevalent and incident AF in a clinical cohort. The effect does not appear to be modified by sleep apnea. Further research is needed to identify mechanisms by which curtailed sleep may predispose to development of AF and to determine whether interventions to extend sleep duration can lower AF risk.

Table: Odds of prevalent atrial fibrillation by total sleep time

	Model 1[a]		Model 2[b]	
Total sleep time	**OR [95% CI]**	**P-value**	**OR [95% CI]**	**P-value**
≥ 6 hrs	1.0	-	1.0	-
5-6 hrs	1.17 [0.68, 2.15]	0.59	1.24 [0.71, 2.32]	0.48
4-5 hrs	1.33 [0.79, 2.43]	0.31	1.27 [0.74, 2.37]	0.41
3-4 hrs	1.94 [1.13, 3.54]	**0.02**	1.75 [1.00, 3.27]	0.06
< 3 hrs	2.51 [1.47, 4.59]	**0.001**	2.10 [1.21, 3.94]	**0.01**

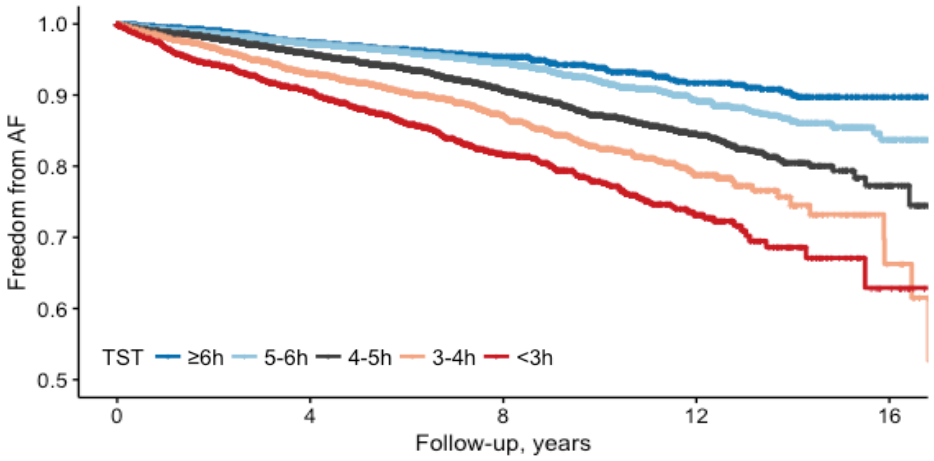
OR=odds ratio; CI=confidence interval

[a] Model 1: adjusted for age, age squared, sex, and site

[b] Model 2: adjusted for covariates included in model 1 plus BMI, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, and AHI

Bold p-value denotes significance at α=0.05

Figure: Atrial fibrillation free survival by total sleep time on PSG



Includes N=27,519 patients free of AF at baseline. Log rank test, P<0.001.

References :

1. Iwasaki YK, Kato T, Xiong F, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol*. 2014;64(19):2013-2023. doi:10.1016/j.jacc.2014.05.077.
2. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110(4):364-367. doi:10.1161/01.CIR.0000136587.68725.8E.
3. Kwon Y, Gharib S a, Biggs ML, et al. Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2015:873-879. doi:10.1136/thoraxjnl-2014-206655.
4. Khawaja O, Sarwar A, Albert CM, Gaziano JM, Djoussé L. Sleep duration and risk of atrial fibrillation (from the Physicians' Health Study). *Am J Cardiol*. 2013;111(4):547-551. doi:10.1016/j.amjcard.2012.10.038.

Oral Presenter – May 1, 2018

Jeongkyung Lee, PhD

Junior Faculty - Bench Research

Bio: Jeongkyung Lee is a junior faculty in the division of endocrinology and metabolism, department of medicine. She received her Ph.D. from University of Tokyo, Japan and had her post-doctoral training in Baylor college of Medicine, Houston, Texas before she moved to the University of Pittsburgh as a junior faculty. Her research has focused on developing targeted therapies that target beta cell mass and function in the pathogenesis of diabetes.

Presentation: ***Regulation of β-Cell Stress Response by the Molecular Clock***

Summary: Circadian disruption is strongly associated with diabetes. Endoplasmic reticulum (ER) stress plays a role in the pathogenesis of diabetes, by contributing to β-cell dysfunction. β-cells secrete insulin in response to meals, driven by circadian feeding activity (Fig. 1a). Hence, it is logical that the circadian clock should regulate ER processing capacity and Unfolded Protein Response (UPR) (Fig. 1b), so that β-cells synthesize and process insulin in the ER when demand is high. However, not much is known about this regulation.

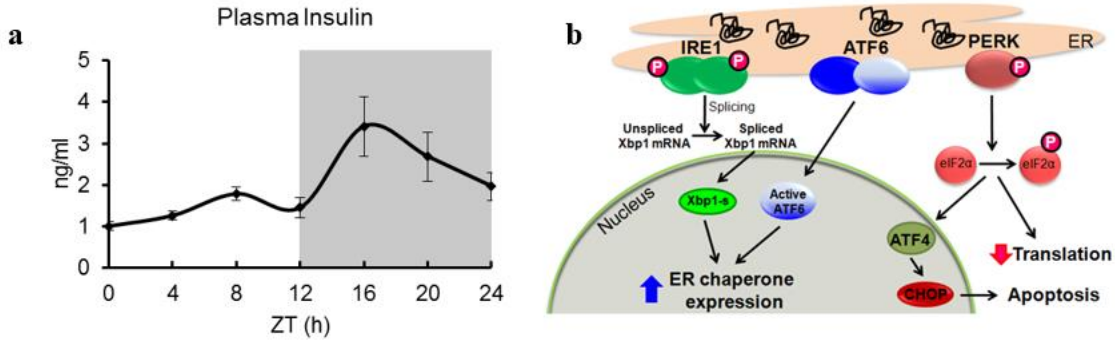


Figure 1. Insulin secretion (a) and UPR pathway to resolve ER stress (b)

Methods: To investigate this, we disrupted the circadian clock, environmentally and genetically, and assessed whole body glucose homeostasis and β-cell function in mice. Environmental clock disruption was achieved by a shift work simulation, in which the mice are exposed to normal 12hour light/dark cycles (Lights on 7AM-7PM) for 3 days, followed by an advancement of the light cycle for 4 days (Lights on 1AM-1PM) of the week (Fig. 2a). Genetic disruption of the

circadian clock was achieved by a stable knockdown of Bmal1, the non-redundant core clock gene, in insulinoma cell line for in vitro studies, and in vivo, by deleting Bmal1, specifically in β-cells (Fig. 2b). Students t-test or ANOVA was used to test statistical significance with $p<0.05$ considered significant.

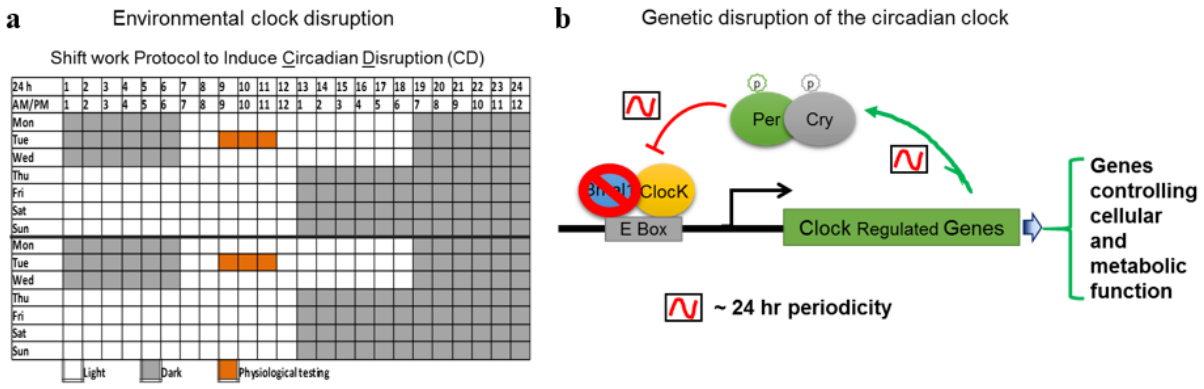


Figure 2. Environmental (a) and Genetic (b) disruption of the circadian clock

Results: Mice exposed to environmental circadian disruption display increase in fasting blood glucose with a decrease in plasma insulin (Fig. 3a), suggesting impairment of β-cell function. Isolated islets from these mice had an impairment of glucose stimulated insulin secretion. Assessment of ER stress markers in these islets revealed an upregulation of the pro-apoptotic gene CHOP, suggestive of irremediable ER (Fig. 3b). Bmal1 knockdown insulinoma cells led to a significant increase in expression of BiP, Xbp1-spliced and GADD34, critical effectors of UPR, at baseline, which increased further with exposure to chemical ER-stress inducers (Tunicamycin/Thapsigargin). Mice with a deletion of Bmal1 in β-cells (β-Bmal1$^{-/-}$) become diabetic due to β-cell failure. β-Bmal1$^{-/-}$ islets have increased expression of many UPR and ER stress related transcripts, including Xbp1-s, as compared to controls (Fig. 3c). β-cells from β-Bmal1$^{-/-}$ display significantly distended ER on EM (Fig. 3d), evidence that deletion of Bmal1 results in ER stress. Interestingly, deletion of Rev-erbα, a negative regulator of clock function and a Bmal1 target gene, leads to similar induction of unfolded protein response (UPR) in β-cells (Fig. 3e).

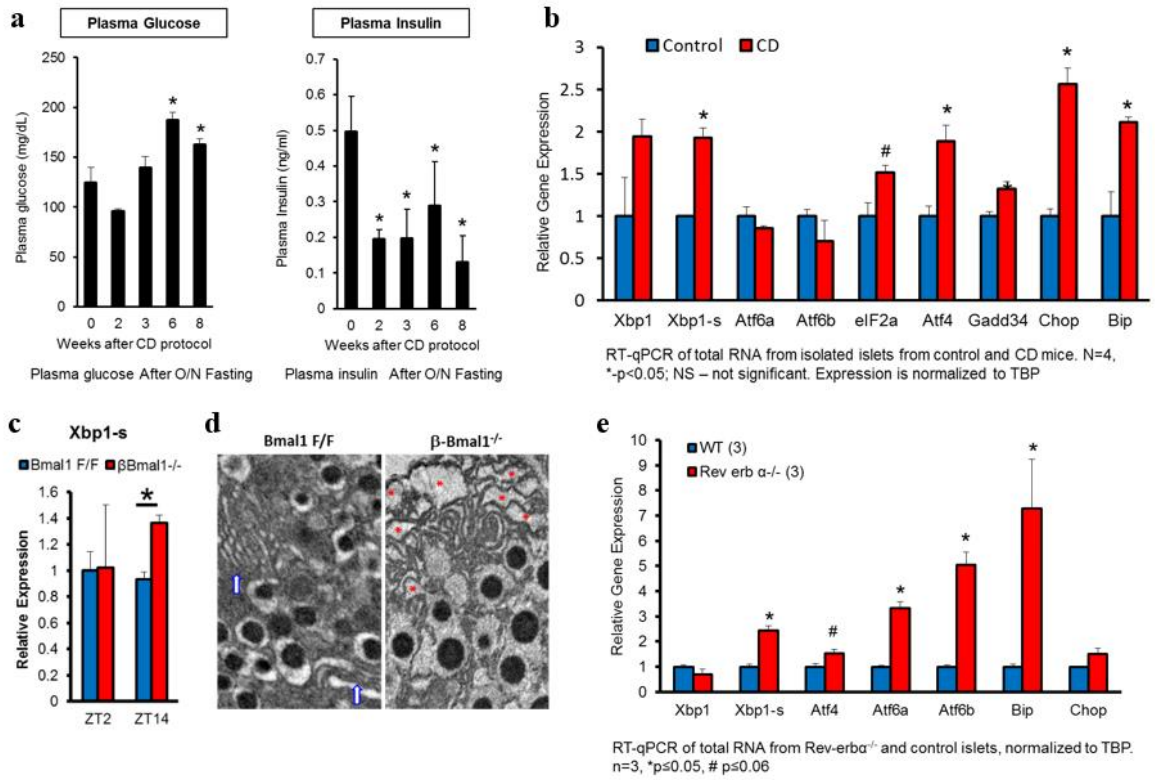


Figure 3. Circadian disruption and islet function

Conclusion: This data indicate that disruption of the β-cell clock leads to ER stress in β-cells. Thus, the cell-autonomous function of Bmal1 and the circadian clock is essential to maintain normal ER homeostasis and prevent ER stress.

References:

1. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS.Med. 2011 Dec;8(12):e1001141.

2. Kivimaki M, Batty GD, Hublin C. Shift work as a risk factor for future type 2 diabetes: evidence, mechanisms, implications, and future research directions. PLoS.Med. 2011 Dec;8(12):e1001138.

3. Scheuner D, Kaufman RJ. The unfolded protein response: a pathway that links insulin demand with beta-cell failure and diabetes. Endocr.Rev. 2008 May;29(3):317-33.

4. Eizirik DL, Cardozo AK, Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. Endocr.Rev. 2008 Feb;29(1):42-61.

5. Young MW, Kay SA. Time zones: a comparative genetics of circadian clocks. Nat.Rev.Genet. 2001 Sep;2(9):702-15.
6. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat.Rev.Genet. 2008 Oct;9(10):764-75.
7. Bunger MK, Wilsbacher LD, Moran SM, Clendenin C, Radcliffe LA, Hogenesch JB, Simon MC, Takahashi JS, Bradfield CA. Mop3 is an essential component of the master circadian pacemaker in mammals. Cell 2000 Dec 22;103(7):1009-17.
8. Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, Mangelsdorf DJ, Evans RM. Nuclear receptor expression links the circadian clock to metabolism. Cell 2006 Aug 25;126(4):801-10.

Oral Presenter – May 1, 2018

Mehret Birru Talabi, MD

Junior Faculty - Health Science/Clinical Epidemiology Research

Bio: Mehret Birru Talabi, M.D., Ph.D. is an Assistant Professor of Medicine in the Division of Rheumatology and Clinical Immunology. She is a graduate of Kenyon College, and earned her medical degree and Ph.D. in Epidemiology from the University of Pittsburgh. She was an Internal Medicine resident at UPMC, and participated in the Women's Health and Clinical Scientist Training Pathways. She completed Rheumatology fellowship with research support from a T32 award in Immunology and Immunopathology. She is currently a recipient of the Patient-Centered Outcomes Research K12. Her research focuses on improving reproductive health care among women with rheumatic diseases.

Presentation: ***Contraception Use Among Reproductive-Age Women with Rheumatic Diseases***

Summary: Contraception may help reproductive-age women with rheumatic diseases to avoid or plan pregnancies so that they may first achieve disease quiescence on safe medications. However, little is known about contraceptive usage among these women. This study examines the prevalence and predictors of prescription contraception among women receiving rheumatologic care from a large, multi-site health care system in Pittsburgh, Pennsylvania.

Methods: We examined administrative data for women aged 18-50 years with ≥ 1 of 18 rheumatic diagnoses based on ICD-9 codes, and ≥ 2 visits to a rheumatology outpatient clinic between years 2013 and 2014. Prescription contraceptive methods were identified and categorized by highest level of efficacy. Highly-effective contraceptive methods included female sterilization, intrauterine devices, and subdermal implants; records of these procedures were abstracted from years 2003-2014. Moderately-effective methods included pills, rings, patches, and injections. Patients' medications were categorized by FDA pregnancy risk classes (Class A/B/C medications: lower fetal risk, Class D/X medications: higher fetal risk). Logistic regression was used to evaluate associations of 1) any prescription contraception or 2) use of highest efficacy contraception, adjusting for frequency of visits to health care providers, medications by FDA pregnancy risk class, and demographic variables (age, race, marital status). Women with prior record of hysterectomies (n=97) were excluded from analyses.

Results: In our sample of 2455 women, most were married (52.6%) and White (81.8%), with mean age of 39.4 (S.D. 7.7). Women had a median of 3 rheumatology visits, but most had no documented visits with primary care providers (PCPs) (60.1%) or gynecologists (67.8%) over the 2-year study timeframe. Contraception was prescribed to 32.1% of women, and 7.9% used highly-effective methods. Class D or X medications were prescribed to 71.7% of women. Women who saw gynecologists (aOR 3.35, 95%CI: 2.77-4.05) and PCPs (aOR 1.43 95%CI: 1.18-1.73) were more likely to use prescription contraception than were women who did not see these providers in unadjusted and fully adjusted models. Among prescription contraception users (n=787), women who used potentially teratogenic medications were more likely to use highly effective as compared to less effective methods (aOR 2.26, 95%CI: 1.44-3.54). Women with at least one gynecology visit were also more likely to use highly effective contraceptive methods than women who did not see a gynecologist during the study timeframe (aOR 1.51, 95%CI: 1.07-2.14).

Fig 1. Patients' Prescription Contraception Use (n=787) by Key Independent Variables, %

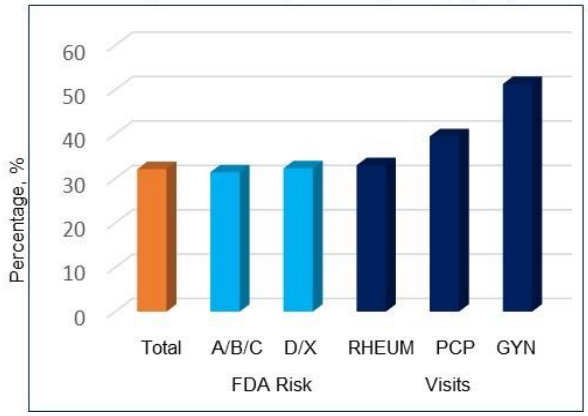


Table 1. Factors Associated with Prescription Contraception Use (n=787) vs None		
	aOR (95% CI)	*P* value
FDA Risk Category		
Class D/X	1.04 (0.84-1.29)	0.69
Visits		
Rheum > 2	1.22 (1.0-1.50)	0.06
PCP≥1	1.43 (1.18-1.73)	<0.0001
Gyn≥1	3.35 (2.77-4.05)	<0.0001

Table 2. Factors Associated with Highly Effective Prescription Contraception Use (n=194) vs None		
	aOR (95% CI)	*P* value
FDA Risk Category		
Class D/X	2.26 (1.44-3.54)	<0.0001
Visits		
Rheum > 2	0.80 (0.54-1.17)	0.25
PCP≥1	1.31 (0.92-1.86)	0.13
Gyn≥1	1.51 (1.07-2.14)	0.02

Conclusion: Overall prescription contraceptive use was low in this sample. Care from PCPs or gynecologists enhanced the overall prescription of contraception. Teratogenic medication use was also associated with use of highly-effective methods. One approach to improving contraception use among these women is to increase the involvement of PCPs and gynecologists in their reproductive health care.

Oral Presenter – May 1, 2018

Polakit Teekakirikul, MD

Fellow - Bench Research

Bio: Polakit Teekakirikul is a cardiology fellow at UPMC Heart and Vascular Institute. He obtained his medical degree from Chulalongkorn University in Thailand, and subsequently completed his internal medicine residency at Mount Auburn Hospital in Cambridge. He also trained at Brigham and Women's Hospital and Department of Genetics, Harvard Medical School in Boston for both cardiovascular genetics and clinical molecular genetics fellowship. His research has focused on studying the genetic basis of inherited cardiomyopathies and congenital heart diseases.

Presentation: ***Identification of a Novel TPM1 Mutation in Congenital Atrial Septal Defect with Autosomal Dominant Inheritance***

Summary: Atrial septal defect (ASD) accounts for 10-15% of all congenital heart defects (CHD). While a genetic contribution in ASD is well described, its underlying genetic architecture remains largely unknown. Here we investigated the genetic etiology of isolated ostium secundum ASD in a 5-generation non-consanguineous Caucasian pedigree. We hypothesized that rare variants might cause ASD in a multigenerational pedigree of dominantly inherited ASD.

Methods: A pedigree comprising 8 individuals with secundum ASD and 3 unaffected family members was genotyped using the Illumina Omni2.5 BeadChip SNP Array (Figure 1A). The genotype data generated comprising ~2.3 million SNP markers were analyzed using MERLIN and MCLINK for genome wide linkage analysis. Further analysis was conducted with whole exome sequencing analysis using Agilent SureSelect v5 Exome Capture and Illumina Hiseq sequencing with 150 nucleotide paired-end reads at 100X coverage. The functional mechanism of disease pathogenesis is investigated in vivo using *Xenopus* embryos and at the cellular level in vitro using cardiomyocytes obtained from patient-derived induced pluripotent stem cells (iPSC).

Results: Genome linkage analysis identified three chromosome intervals (8p11-q11, 15q22-26, 18q21) segregating with the ASD with a peak LOD score of 1.8. Three rare haplotypes were identified in these three chromosome intervals. The data obtained from whole exome sequencing was analyzed for rare variants with filtering using < 1% allele frequency in ExAC combined with functional prediction and conservation scoring using Genomic Evolutionary Rate Profiling (GERP) score of > 2. From this analysis, rare variants causing coding changes shared among the affected but not unaffected relatives were identified. Focusing this analysis on sequence variants found within the LOD score peaks identified a single novel rare heterozygous 3-base in-frame deletion causing loss of a highly conserved amino acid (p.K5del) in alpha-tropomyosin, *TPM1*, a gene known to encode an actin-binding protein. The *TPM1* variant showed complete segregation with ASD in the pedigree and was absent in >500 CHD cases and 66,000 subjects from the ExAC cohort. Functional assessment with MO knockdown of *tpm1* in *Xenopus laevis*, a model organism with distinct left and right atria and common ventricle, showed severe pericardial edema indicating heart failure. This was observed in 81% of the injected embryos (N=482), while only 6% of control embryos had pericardial edema (N=437; $p=3x10^{-114}$, Figure 1B, 1D). In addition, the heart rate was reduced in *tpm1* MO knockdown embryos (62 ± 9 beats/minute; N=4) as compared with uninjected control embryos (95 ± 6 beats/minute; N=4; p=0.0009, Figure 1C). Histological analysis of MO embryos (N=6) showed atria septation defect. Induced pluripotent stem cells (iPSC) was generated from the index patient, and analysis of the iPSC derived cardiomyocytes immunostaining using an antibody to Ki-67, a marker of proliferation cells, showed reduced proliferation.

Conclusion: We identified *TPM1* as a candidate gene for familial ASD and provide functional data showing an essential role for *tpm1* in atrial septation. The pathogenic mechanism is being further investigated using *Xenopus* embryos and patient-derived iPSC-cardiomyocytes. Preliminary evidence suggests involvement of a cell proliferation defect.

Figure 1A, 1B, 1C

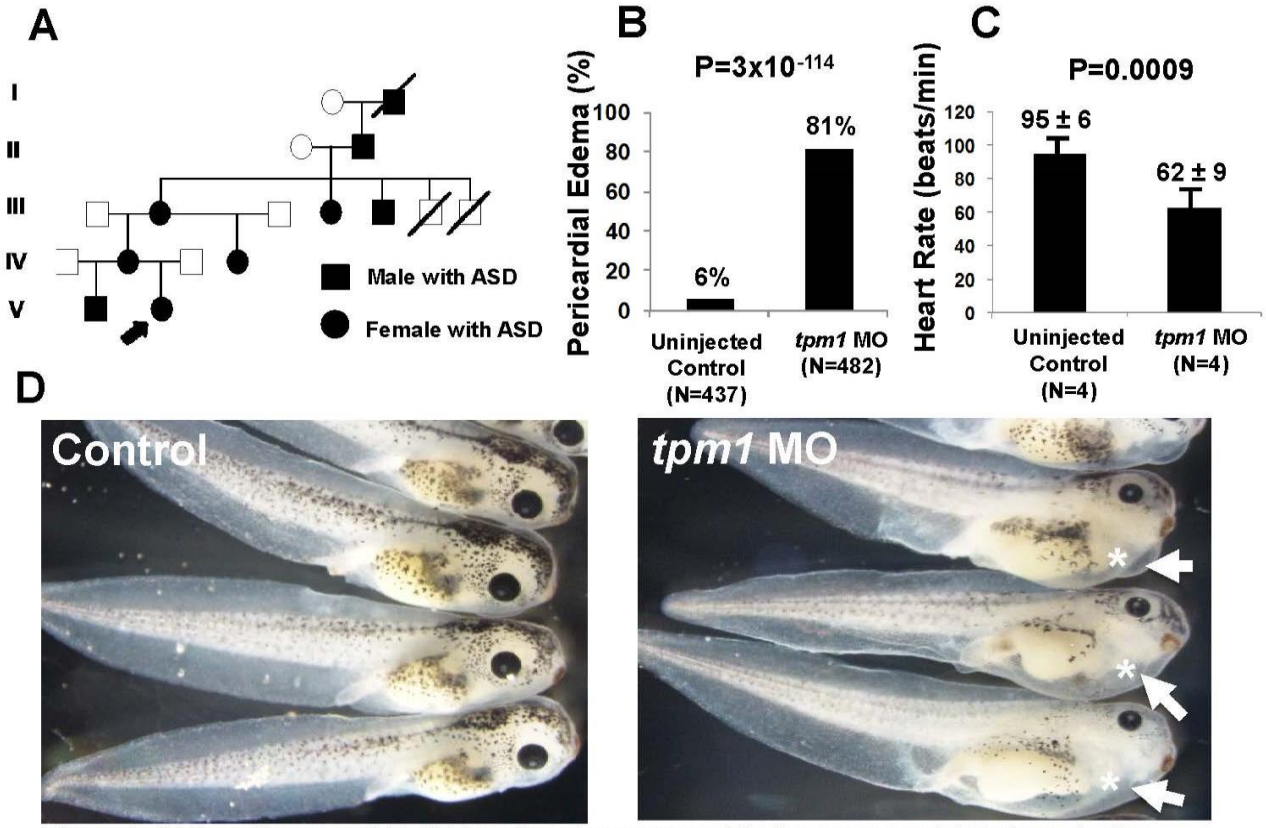


Figure 1: ASD pedigree and *TPM1* functional assessment in Xenopus model system. A. Five-generation ASD pedigree. B,C. *Tpm1* morpholino gene knockdown in Xenopus embryos caused pericardial edema and reduction in heart rate compared to uninjected control embryos. D. Significant pericardial edema (white arrows) were observed in *tpm1* MO knockdown embryos stage 40 (right panel, magnification 4X) compared with uninjected controls (left panel, magnification 4X); * asterisks indicate Xenopus hearts.

References:

1. Hoffman JI, Kaplan S. J Am Coll Cardiol. 2002 Jun 19;39(12):1890-900.
2. Khaitlina SY. Int Rev Cell Mol Biol. 2015;318:255-91.

Kaleab Abebe, PhD
Associate Professor of Medicine
Division of General Internal Medicine
Director, Center for Clinical Trials and
Data Coordination (CCDC)
Co-Director, Career Education and
Enhancement for Health Care Research
Diversity (CEED) Program

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

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

Jessica Bon Field, MD, MS
Assistant Professor of Medicine
Division of Pulmonary, Allergy and
Critical Care Medicine

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

Cary Boyd-Shiwarski, MD, PhD
Post-Doctoral Scholar, Department of Medicine
Division of Renal-Electrolyte

Tullia Bruno, PhD
Research Assistant Professor
Department of Immunology

Stephen Chan, MD, PhD, FAHA
Associate Professor of Medicine
Division of Cardiology
Director, Center for Pulmonary Vascular Biology and Medicine
Associate Program Director, Fellowship Research, Cardiology

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

Judges

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

Matthew Culyba, MD, PhD
Assistant Professor of Medicine
Division of Infectious Diseases

Esa Matius Davis, MD, MPH, FAAFP
Associate Professor of Medicine
Clinical and Translational Science
Director of UPMC Tobacco Treatment Service

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

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

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

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

Krystle Frahm, PhD
Research Instructor in Medicine
Department of Medicine
Division of Endocrinology and Metabolism

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

Walid Gellad, MD, MPH
Associate Professor of Medicine
Division of General Internal Medicine
Associate Professor of Health Policy and Management, School of Public Health
Co-Director, Center for Pharmaceutical Policy and Prescribing

Leslie Hausmann, PhD
Assistant Professor of Medicine
Division of General Internal Medicine
Core Faculty, Center for Health Equity
Research and Promotion (CHERP),
VA Pittsburgh Healthcare System

Charles Jonassaint, PhD
Assistant Professor of Medicine
Division of General Internal Medicine,
Social Work and Clinical & Translational Science

Michael Jurczak, PhD
Assistant Professor of Medicine
Division of Endocrinology and Metabolism

Dio Kavalieratos, PhD
Assistant Professor of Medicine
Division of General Internal Medicine
Director of Implementation Research,
UPMC Palliative & Supportive Institute
Associate Director of Palliative Care Research

Kang Kim, MD
Associate Professor of Medicine
Division of Cardiology
Associate Professor of Bioengineering

Georgios Kitsios, MD, PhD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine

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

Phillip Lamberty, MD
Assistant Professor of Medicine
Director, Medical Intensive Care Unit UPMC Presbyterian Hospital
Director, Pulmonary and Critical Care Ultrasonography, Medical Director, Select Specialty Hospital Pittsburgh

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

Judges

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

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

Yang Liu, PhD
Associate Professor of Bioengineering
Division of Gastroenterology, Hepatology and Nutrition
Director, Biomedical Optical Imaging Laboratory

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

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

Kathleen McTigue, MD, MPH, MS
Associate Professor of Medicine & Epidemiology
Director, Clinical Scientist Track, Internal Medicine Residency, Associate Director for Research
International Scholars Track, Internal Medicine Residency

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

Jessica Merlin, MD, PhD
Visiting Professor of Medicine
Division of General Internal Medicine, Division of Infectious Diseases

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

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

Judges

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

Suresh Mulukutla, MD
Associate Professor of Medicine
Division of Cardiology

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

Enrico Novelli, MD, MS
Associate Professor of Medicine
Division of Hematology/Oncology
Director, UPMC Adult Sickle Cell Disease Program,

Robert O'Doherty, PhD
Professor of Medicine, Division of Endocrinology & Metabolism,
Professor of Biochemistry & Molecular Genetics, Director, T32 Diabetes & Endocrinology Training Program, Co-Director, Center for Metabolic & Mitochondrial Medicine (C3M)

Thomas R. Radomski, MD MS
Assistant Professor of Medicine
Division of General Internal Medicine

Bruce Rollman, MD, MPH
Professor of Medicine, Psychiatry, Biomedical Informatics, and Clinical and Translational Science, UPMC Endowed Chair in General Internal Medicine, Director, Center for Behavioral Health & Smart Technology

David Rometo, MD
Clinical Assistant Professor of Medicine
Division of Endocrinology & Metabolism

Yael Schenker, MD, MAS
Associate Professor of Medicine
Director, Palliative Care Research

Roy Semaan, MD
Assistant Professor of Medicine
Director, Interventional Pulmonary Program at UPMC

Faraaz Ali Shah, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine

Judges

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

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

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

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

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

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

Holly Thomas, MD, MS
Assistant Professor of Medicine
Division of General Internal Medicine
Section of Women's Health

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

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

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

Judges

Ora A. Weisz, PhD
Professor of Medicine and of Cell Biology
Assistant Vice Chancellor for Faculty Excellence, Health Sciences,
Associate Dean for Faculty Development, Vice Chair for Faculty Development

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

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

Jing Zhao, MD, PhD
Associate Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine

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

RESIDENTS- APRIL 30, 2018

University Club

Ahn	Michelle	2-R	Over-the-Scope Clip for Closure of Fistulas and Perforations: Single Center Experience and Analysis of Chronicity as a Potential Predictive Parameter
Ahuja	Ashish	3-R	Ketamine as a novel abortive therapy for cyclic vomiting syndrome attacks
Belecanech	Ryan	4-R	Left Atrial Volume Index Fails to Predict Exercise-Induced Pulmonary Hypertension on Exercise Right Heart Catheterization
Berger	Kristin	5-R	Donor umbilical cord blood transplantation with and without total body irradiation: a single-center experience
Berhane	Hebist	6-R	Bacteremia after endoscopic procedures
Chablani	Sumedha	7-R	Small bowel cancer complicating inflammatory bowel disease: A tertiary referral center experience
Chandrasekaran	Neena	56-R	A Systemic Review of Sepsis AssociatedMacrophage Activation Syndrome (S-MAS)
Cheng	Andy	8-R	Developing a Chronic Kidney Disease Screening Algorithm for the Primary Care Setting
Chin	Katherine	51-R	Bridging the Divide: A Quality Improvement Project on Antipsychotics with Medical Housestaff on Transfer from the Medical ICU to Floors
Ertem	Furkan	9-R	Biomarkers associated with early anti-TNF prophylaxis treatment failure in postoperative Crohn's Disease
Ertem	Furkan	10-R	Biomarkers of Early Endoscopic Recurrence for Postoperative Crohn's patients
Ertem	Furkan	11-R	Does surgical anastomosis type impact rates of endoscopic recurrence in post-operative Crohn's Disease? An 8-year observational cohort study

Fleshner	Michelle	46-R	Incorporating Advance Care Planning into HIV Primary Care: A Quality Improvement Initiative
Gibbs	Kelly	12-R	Seven-Year Period Prevalence and Characteristics of Hypertension in a Large US Inflammatory Bowel Disease Cohort
Gougol	Amir	13-R	Organ failure without necrosis is uncommon in acute pancreatitis and has a better prognosis
Gougol	Amir	16-R	Utilization of tube feedings in acute pancreatitis patients at a large US referral center
Gougol	Amir	14-R	Regional variations of clinical characteristics in acute pancreatitis from a large, international, multi-center prospective study (apprentice study group).
Gougol	Amir	15-R	Timing and sequence of organ failure in a large prospective cohort of patients with acute pancreatitis
Hamilton	Phillip	47-R	Cigarette Smoking and its Impact on Biologic Effectiveness in Crohn's Disease: A Cross-Sectional Study
Han	Katrina	17-R	Accuracy of Electronic Health Record Family History in Predicting Genetic Susceptibility to Pancreatic Ductal Adenocarcinoma
Harter	Lauren	53-R	Changing resident prescribing practices for VTE prophylaxis using peer-to-peer education
Hashmi	Sulman	18-R	Benefits of use of Professional CGM in low socioeconomic population
Hussain	Aliza	19-R	Predictors Of Super-response To Cardiac Resynchronization Therapy In Left Bundle Branch Block Associated Idiopathic Nonischemic Cardiomyopathy
Jain	Seema	20-R	Patient perspectives on weight management in primary care
Kanakis	Allison	22-R	Bone Health Assessment in Patients with Chronic Pancreatitis

Kennedy	Amy	54-R	Impact of Attending a Mutual Support Group Meeting on Resident Trainee Attitudes toward Patients with Substance Use Disorder
Kennedy	Amy	55-R	Resident Trainee Reflections on Patients with Substance Use Disorder after Attending a Mutual Support Group Meeting
Klar	Natalie	23-R	Features Associated with Long-Term Survival in Metastatic Breast Cancer
Kotok	Daniel	24-R	The evolution of radiographic edema in ARDS and its association with clinical outcomes: a prospective cohort study in adult patients.
LaRosa	Anna	48-R	Income is associated with atrial fibrillation outcomes: a nationwide health claims analysis
Lehmann	H. Immo	25-R	Dofetilide in Patients with Atrial Fibrillation and Severe Left Ventricular Hypertrophy
Lipkin	Jacob	26-R	Predictive Value of Acute Pancreatitis Diagnosis Code in Diabetic Patients is Similar to Non-Diabetic Patients
Lipkin	Jacob	49-R	Using Classification and Regression Trees to Identify Sociodemographic Subgroups of Veterans at High Risk for Chronic High-Dose Opioid Prescribing
Marino	Christopher	50-R	Expanding access to colorectal cancer screening for uninsured patients in western Pennsylvania: A two-year collaborative free clinic and academic medical center model experience
McQuade	Casey	27-R	Pulmonary Hypertension is Associated with Increased Mortality and Readmission in Patients with Obstructive Sleep Apnea Admitted for Heart Failure Exacerbation
Mullally	Jimmy	28-R	Exploratory study evaluating the feasibility of patient reported outcomes assessment in metastatic prostate cancer undergoing newer hormonal therapies
Nieves	Ricardo	29-R	Effect of Syringe Type on Retained Radiotracer Fraction and Scan Time: A Quality Improvement Analysis

Pati	Prateeth	30-R	Perception of Isolation Patients and Health Care Workers on Contact Precautions for Multi Drug Resistant Organisms in Health Care Settings
Quinn	Catherine	59-R	Palbociclib plus Letrozole as first-line therapy in ER/PR-positive/HER2-negative metastatic breast cancer: How does UPMC match up to national data?
Rajaratnam	Arun	31-R	Retrospective Case Series of Thirty-Two Patients with Biopsy-Proven Chronic Eosinophilic Pneumonia
Rajaratnam	Arun	32-R	Right Ventricular Outflow Velocity Time Integral as a Non-Invasive assessment of Right Ventricular maladaptation related to HIV-related Pulmonary Arterial Hypertension
Rao	Anjali	33-R	Gender Differences in Myocardial Histology and Ventricular Remodeling in Recent Onset Cardiomyopathy
Saygin	Didem	57-R	Identification of differentially expressed genes in pulmonary endothelial and vascular smooth muscle cells of patients with idiopathic pulmonary arterial hypertension using single cell RNA sequencing
Sharma	Prerna	36-R	'pre-COPD'-A Clinical Entity
Sharma	Prerna	37-R	Epidemiology of Tuberculosis
Simonson	Michael	58-R	Pre-Existing Emphysema Affects Soluble Receptor for Advanced Glycation End-Product Levels in ARDS
Sistla	Divya	38-R	Autoimmune progesterone dermatitis- diagnostic and treatment challenges
Sistla	Divya	39-R	Endogenous Hyperinsulinemic Hypoglycemia: Diagnostic Challenges and Treatment Dilemma
Sistla	Divya	40-R	Successful treatment of bisphosphonate refractory hypercalcemia with denosumab in a patient who presented with possible immune mediated calcinosis cutis

Zou	Richard	43-R	Evaluating Disease Severity and Location of Death on Palliative Care Referral in Patients with Idiopathic Pulmonary Fibrosis
Zou	Richard	44-R	Markers of Diastolic Dysfunction Correlate with Filling Pressures on Right Heart Catheterization During Leg Raise in a Mixed Population
Zupa	Margaret	45-R	Durability of Glycemic Control in a Diabetes Education Insurer-based Intervention in Primary Care

2-R Poster: Over-the-Scope Clip for Closure of Fistulas and Perforations: Single Center Experience and Analysis of Chronicity as a Potential Predictive Parameter

Presenter: Michelle Ahn, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Kenneth Fasanella MD

Funding Source: N/A

Authors: Michelle Ahn MD, Shiv Desai MD, Jennifer Chennat MD, Asif Khalid MD, Kevin Mcgrath MD, Adam Slivka MD, Kenneth Fasanella MD

Introduction: The over-the-scope clip (OTSC) is a novel means of closure for fistulas and perforations in the gastrointestinal tract. Advantages over a standard clip include its larger diameter allowing larger amounts of tissue to be grasped for increased durability, and greater compressive force allowing full-thickness closure. There are, however, scant published data on clinical outcomes. This study evaluates the efficacy of these clips based on experience at our center. The primary aim was to evaluate institutional experience with the clips and determine factors associated with successful closure; here we hypothesized that the age of defect is significantly associated with closure success rate. The secondary aim was to review clip complications.

Methods: This is a retrospective review done at a single center. A search of the EMR database using specific diagnostic codes and keywords was performed to identify subjects >18 years of age who underwent OTSC placement 1/1/2012-10/4/2016. A chart review was then performed to examine the indications for the procedures and clinical characteristics; length of follow-up; and outcomes including immediate success, 30-day success, and need for additional intervention. A Fisher's exact test and time-to-event analysis compared 30-day success and time to surgical intervention, respectively, between acute (<4 weeks) or chronic fistulas and perforations.

Results: 37 subjects were recruited, of which 17 (46%) were male. Mean age was 55.6, and 15 (41%) had smoking history. 9 (24%) had acute fistulas or perforations. 35 (95%) had immediate procedural success. Mean duration of follow-up was 8 months. Among all subjects 34 had >1 month follow-up, and 16 (47%) had 30-day success. Those with acute defects had 86% (6/7) 30-day success vs. 37% (10/27) in patients with chronic defects (p=0.03). There was no significant difference in time-to-event analysis of subsequent surgery (p=0.22). Clinically significant bleeding occurred in 2 patients, one due to the wall anchor becoming lodged within the clip.

Conclusion: Here the OTSC had 95% immediate procedural success in closing fistulas or perforations, 5% risk of adverse complication of bleeding, and an overall 47% 30-day success rate in subjects who had >1 month follow-up. 30-day success was significantly higher in acute fistulas and perforations than chronic ones, indicating that chronicity may be a useful predictor of procedural failure. There was, however, no significant difference in a time-to-event analysis. This may be due to limitations such as small sample size, and this data would be useful in the design of larger prospective studies in the future

3-R Poster: Ketamine as a novel abortive therapy for cyclic vomiting syndrome attacks

Presenter: Ashish Ahuja, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: David Levinthal MD, PhD

Funding Source: N/A

Authors: Ashish Ahuja MD, David Levinthal MD, PhD

Introduction: Cyclic vomiting syndrome (CVS) is an idiopathic disorder characterized by recurrent bouts of nausea and vomiting, often with significant abdominal pain. Some CVS patients suffer from frequent and debilitating attacks that lead to numerous emergency department (ED) visits and hospitalizations. There is an unmet need to develop effective, non-opiate based therapies to abort CVS attacks in the ED. To address this issue, our center recently began to offer low-dose ketamine therapy to abort CVS attacks with some reported successes. However, the efficacy of ketamine in this setting has not been formally evaluated.

Methods: We performed a retrospective chart review of 20 adult CVS patients administered at least one dose of ketamine, among other medications, in a UPMC-affiliated ED with the therapeutic intent of aborting a CVS attack. We extracted data including demographic and clinical information, including total CVS-attack related ED visits and their associated outcome (either discharge to home or inpatient admission), and the dose and route of ketamine administration. Statistical comparisons used chi square tests, with significance taken as $p<0.05$.

Results: The cohort compromised 13 females and 7 males (mean age 36.6 yrs) with CVS; 30% were daily marijuana users, comorbidities included migraine (35%), anxiety, depression and/or bipolar disorder (75%), and 75% of the cohort typically received opiates to abort a CVS attack. The median observation period prior to first ketamine exposure was 6 years [range 0.4 – 11.3 years], during which time the cohort made 736 CVS-related ED visits associated with 312 admissions (baseline admission rate 42.4%). The index ketamine exposure in the ED (mean dose 24.4 mg, 95% IV route) successfully aborted a CVS attack in 11 of the 20 patients (admission rate 45%), but the response was strongly dose-dependent (<15 mg dose, 100% admission rate [n=4]; >15 mg dose, 31.2% admission rate [n=16]). Overall, the cohort totaled 108 ED ketamine exposures for CVS, associated with 40 hospital admissions (admission rate 37.0%; compared to baseline rate, $p=0.29$). However, among the 13 CVS patients who received ketamine on at least two occasions, 8 patients aborted their attack 50% or more of the time (admission rate 31.4%; compared to baseline rate, $p<0.05$), 1 had a partial response, and 4 had complete non-response.

Conclusion: We provide the first description of ketamine as an abortive therapy for adult CVS patients in the ED. Our findings imply that ketamine is at least as effective in aborting CVS attacks as currently used approaches, and a majority of patients achieve a 50% or greater response rate when administered ketamine during independent ED visits. Ketamine appears to be a viable, non-opiate abortive therapy for adult CVS patients in the ED setting.

4-R Poster: Left Atrial Volume Index Fails to Predict Exercise-Induced Pulmonary Hypertension on Exercise Right Heart Catheterization

Presenter: Ryan Belecanech, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: N/A

Funding Source: N/A

Authors: Ryan Belecanech MD, Richard Zou MD, Seyed Mehdi Nouraie PhD, Michael Risbano MD

Introduction: Exercise-induced pulmonary hypertension (EIPH), most often defined as peak exercise mean pulmonary artery pressure (MPAP) >25, has been postulated as a distinct phenotype of exercise intolerance. In previous invasive and noninvasive studies, left atrial dilatation, as defined by left atrial volume index (LAVI) on transthoracic echocardiography (TTE), has been shown to correlate with EIPH. Our group sought to determine whether elevated LAVI predicts pathologic rise in mPAP and pulmonary capillary wedge pressure (PCWP) in a population of patients referred for unexplained dyspnea undergoing exercise right heart catheterization (eRHC).

Methods: Within our database, 83 subjects underwent eRHC at the University of Pittsburgh Medical Center between March 2012 and May 2017. Subjects with abnormal pulmonary artery hemodynamics on resting right heart catheterization (i.e. mPAP >25mmHg or PCWP >15mmHg) or without TTE reporting LAVI within the 12 months prior to eRHC were excluded. 44 subjects were included in this analysis. We used LAVI >35ml/m2 to define left atrial dilatation.

Results: Of the 44 patients who qualified for inclusion, 7 patients had left atrial dilatation at baseline. Compared to the 37 patients without left atrial dilatation, there was no difference in the change in mPAP (p=0.9) or PCWP (p=0.6) during exercise.

Conclusion: Our study finds no correlation between LAVI and EIPH on eRHC as defined by the change in mPAP and PCWP during exercise. This finding is in contrast to previous studies. As none of our subjects with elevated LAVI had other markers of diastolic dysfunction on TTE, it possible that there was sufficient ventricular compensation during exercise as to prevent pathologic rise in PCWP and mPAP. In this growing registry, the small number of subjects available for analysis is an obvious limitation. Future studies are needed, as LAVI could be an important screening tool for EIPH in referred patients with unexplained dyspnea.

5-R Poster: Donor umbilical cord blood transplantation with and without total body irradiation: a single-center experience

Presenter: Kristin Berger, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Jeffrey Pu MD, PhD

Funding Source: N/A

Authors: Kristin Berger MD, Elizabeth Miller MD, PhD , Christopher Davis , Arthur Berg , Melanie Comito MD , Robert Greiner , W. Christopher Ehmann MD, David Claxton MD, Witold Rybka MD , Jeffrey PU MD, PhD

Introduction: Umbilical cord blood is rich in hematopoietic stem cells that can reconstitute the hematopoietic system in recipients under proper conditioning. Because of its loose HLA-matching requirement and rapid availability, umbilical cord blood transplant is emerging as an effective alternative therapy for hematopoietic stem cell transplants. However, the optimal conditioning regimen for umbilical cord blood transplant remains under debate. While most published umbilical cord blood transplant studies utilize total body irradiation as part of conditioning regimens, experience with conditioning regimens without total body irradiation is more limited.

Methods: This is a retrospective study that analyzes the outcomes of 47 patients with various diseases receiving umbilical cord blood transplants in the last 13 years. The lengths of follow up ranged from 0.9 to 12.8 years with a mean of 6.8 years. Thirty-seven patients did not use TBI as part of their conditioning regimens, whereas 10 patients did undergo total body irradiation. The outcomes and the post transplant complications are compared between patients who did and did not undergo TBI as part of their conditioning regimen.

Results: There were no statistically significant difference in overall survival, progression-free survival, and transplant-related mortality between the TBI cohort and the non-TBI cohort (p=0.70, 0.72, and 0.43, respectively) with 5-year OS rates of 50% and 44% (p=0.77) and 5-year TRM rates of 40% and 27% (p=0.46). The neutrophil engraftment rates (88.9% vs 97.2%, p=0.36), severe acute GVHD incidence rates (11.15% vs 22.9%, p=0.66), severe chronic GVHD incidence rates (33.3% vs 14.3%, p=0.33), transplant related systemic infection rates (60% vs 58.3%, p=1.0), and transplant caused growth impairment rates (14.3% vs 16.7%, p=1.0) also had no statistically significant differences between the TBI and non-TBI cohorts.

Conclusion: The transplant outcomes and post transplant complication occurrence were comparable between patients who did and did not undergo total body irradiation as part of conditioning regimens during umbilical cord blood transplant.

6-R Poster: Bacteremia after endoscopic procedures

Presenter: Hebist Berhane, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: N/A

Funding Source: N/A

Authors: Hebist Berhane MD, Noreen Chatta , Brendan Gill MD, E Magee , D Sandstrom , S DiNucci , Mohamed Yassin MD

Introduction: Endoscopic examination is an essential part of medical care for both diagnostic and therapeutic indications. Infections after endoscopic procedures are either endogenous (related to patients own flora) or exogenous (related to contaminated endoscopes). Multiple outbreaks were reported due to contaminated endoscopic procedures hence, the CDC recommends, but not mandates, decontamination measures and safety intervention to minimize this risk. The aim of the study is to estimate the risk of bacteremia (either endogenous or exogenous) within 30-day of endoscopic procedure and to improve endoscopic safety.

Methods: Sample of endoscopic procedures were reviewed 2016-2017. A report of endoscopic procedures was matched with infection control data of positive blood cultures. We reviewed all data and tabulated characteristics of patients who had positive blood cultures within 30 days of the procedure. The data was interpreted by Microbiology and Infection control to assess the possibility of exogenous infection. All possibly contaminated endoscopes were subjected to additional microbiologic cultures.

Results: A total of 1044 endoscopic procedures during the 1st quarter of 2017 (duodenoscopes, colonoscopies, gastroscopes) and a sample of randomly selected 199 bronchoscopic procedures from 2016 were reviewed. Bacteremia was noted in 19/ 1044 gastro-intestinal (GI) endoscopes (1.8%) and in 2.5% bronchoscopes. Candidemia were reported in 4/9 bronchoscopes and 3/19 GI endoscopes. No pattern emerged linking specific pathogen to a specific endoscope.

Conclusion: Safety of endoscopic procedures could be improved by retrospective analysis of positive patient cultures post procedure in addition to routine endoscopic cultures. The presence of candidemia after endoscopic procedures is an interesting finding that needs to be verified by a larger study sample.

7-R Poster: Small bowel cancer complicating inflammatory bowel disease: A tertiary referral center experience

Presenter: Sumedha Chablani, Resident General Internal Medicine

Research Interest: Clinical

Mentors: David Binion MD

Funding Source: Division of Gastroenterology

Authors: Sumedha Chablani MD, Carlita Shen MD, Claudia Ramos-Rivers MD, David Binion MD

Introduction: The incidence of small bowel cancer is rising in the U.S. While the association between inflammatory bowel disease (IBD) and colorectal cancer has been demonstrated, recent studies have suggested that IBD, specifically Crohn's disease (CD), may be associated with an increased risk of small bowel cancer. Data on the relationship between CD and small bowel cancer is limited.

Methods: We performed an 8-year longitudinal analysis (2009-2016) of demographic, clinical, laboratory, and treatment data from an IBD registry at the University of Pittsburgh Medical Center to investigate the period prevalence of small bowel cancer in this referral population. Patients were identified using computer searches of comprehensive pathology and treatment data, with manual confirmation.

Results: A total of 2,259 IBD patients were included (mean age 46, 52.5% women) of whom 848 had ulcerative colitis (UC) and 1,411 had CD. There were no cases of small bowel cancer in patients with UC. There were 8 cases (0.57%) of small bowel cancer in patients with CD. Five of these patients had adenocarcinoma, 2 patients had carcinoid tumors, and 1 patient had lymphoma. Of the 5 patients with small bowel adenocarcinoma, the mean age was 63.8, 3 (60%) were women, 3 (60%) had a history of smoking, and all were Caucasian. The average duration of CD to time of diagnosis of adenocarcinoma was 30 years. While 4 patients (80%) had exposure to immunosuppressive therapy, only 1 patient (20%) had exposure to anti-TNF biologic therapy. Two of the 5 patients (40%) with adenocarcinoma died from this complication during the observation period.

Conclusion: Small bowel adenocarcinoma is a rare, albeit significant, complication of CD. Development of adenocarcinoma may be associated with longstanding disease and low rates of anti-TNF biologic use. In CD patients with longstanding disease and limited therapy, clinical suspicion for this complication is warranted. Future studies are necessary to better define the incidence and clinical characteristics of small bowel cancer in this population.

8-R Poster: Developing a Chronic Kidney Disease Screening Algorithm for the Primary Care Setting

Presenter: Andy Cheng, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Manisha Jhamb MD
Amar Kohli MD
David Demoise MD

Funding Source: SHY Hospital Foundation, Competitive Research Fund

Authors: Andy Cheng MD, Manisha Jhamb MD, David Demoise MD, Amar Kohli MD

Introduction: CKD in the US not only has a significant prevalence, but also has an alarming projected incidence. Current guidelines for CKD screening are discordant, and few studies have been performed in evaluating various screening algorithms. This retrospective cohort study aims to propose a potential CKD screening algorithm for the primary care setting.

Methods: Adult patients aged 18-69 years seen for primary care visits at a tertiary hospital primary care clinic in Western PA were identified. Those with CKD, defined as two eGFR values of less than 60mL/min/1.73m2 per MDRD calculation spaced at least 90 days apart in the EHR, were eligible for study inclusion. Characteristics including age =55, African American race, and comorbid DM or HTN were abstracted from the EHR. Statistical analyses, including percentage of CKD patients identified and number of patients needed to screen, were then performed using a reverse screening cohort of 650 patients to assess four potential screening algorithms.

Results: Known comorbid DM or HTN (81.8%) outperformed age =55 (69.7%) or African American race (49.5%) in identifying the largest percentage of CKD patients. Inclusion of age =55 to known comorbid DM or HTN yielded a greater percentage of CKD patients compared to addition of African American race to known comorbid DM or HTN (Table 1). A comprehensive screening algorithm including all four aforementioned variables mildly increased percentage of CKD patients identified, but at the expense of a moderate increase in number of patients needed to screen (Table 1).

Conclusion: A screening algorithm consisting of age =55 or known comorbid DM or HTN appeared to optimize percentage of CKD patients identified with number of patients needed to screen. Given that the proposed screening algorithm was derived via a reverse screening approach originating from a patient population with 100% CKD prevalence, further study applying the algorithm to a blanket primary care population is necessary to fully assess the algorithm's efficacy.

9-R Poster: BIOMARKERS ASSOCIATED WITH EARLY ANTI-TNF PROPHYLAXIS TREATMENT FAILURE IN POSTOPERATIVE CROHN'S DISEASE

Presenter: Furkan Ertem, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: David Binion MD

Funding Source: N/A

Authors: Furkan Ertem MD, Claudia Ramos Rivers MD, Miguel Regueiro MD, Ioannis Koutroubakis MD, Andrew Watson MD, Marc Schwartz MD, Jana Hashash MD, Benjamin Click MD, Dmitriy Babichenko MD, Micheal Dunn MD, David Binion MD

Introduction: After small bowel resection and re-anastomosis for Crohn's disease (CD), endoscopic recurrence is high, reaching 60-80%. Various types of postoperative prophylactic medical treatments including anti-TNF agents to prevent recurrence of CD has been shown to be beneficial however, this is not universally effective and recurrence rates remains high. In this study we aim to describe characteristics of patients who receive anti-TNF medications as postoperative prophylaxis and identify factors associated with endoscopic recurrence despite anti-TNF treatment.

Methods: We conducted an observational study of consented CD patients followed prospectively in a natural history registry between 2009 and 2016, at a tertiary center. Patients with small bowel surgery, anti-TNF post-op treatment (infliximab, adalimumab) and a minimum of 2 years of follow-up formed the study population. Demographics, clinical characteristics, health care utilization and Rutgeert's scores recorded at the time of colonoscopy were analyzed. Anti-TNF prophylaxis failure was defined as a Rutgeert's score of i2, i3 or i4 within two years of surgery (early endoscopic recurrence).

Results: There were 162 CD surgery patients who received anti-TNF prophylaxis to prevent post-op recurrence, who formed the study group. Among them 80 (49%) had early endoscopic recurrence despite post-op anti-TNF treatment. Rates of combination immunomodulator (azathioprine, 6MP or methotrexate) and anti-TNF treatment were not different between early and late/no endoscopic recurrence groups (80% for early recurrence group; 62% for late/no recurrence group; p=NS). Early endoscopic recurrence despite anti-TNF and combination treatment was significantly associated with elevated CRP (P=0.001), ESR (P=0.001), and lower hemoglobin (P=0.01) and albumin levels (P=0.003). Over 8 years, patients with early endoscopic recurrence required more bowel surgeries (P<0.001) and had higher numbers of hospital admissions (P=0.02), ER visits (P=0.003), along with higher Harvey-Bradshaw Index disease activity scores (P=0.012). In addition, higher Rutgeert's scores were correlated with smoking at the time of surgery (P=0.01).

Conclusion: This 8-year observational cohort study suggests that almost half of the patients who receive post-op prophylaxis with anti-TNF inhibitors along with combination immunomodulator therapy progressed within 2 years of surgery with endoscopic recurrence. Anti-TNF failure was associated with abnormal inflammatory biomarkers (CRP, ESR ,hemoglobin and albumin). Postoperatively, the presence of abnormal biomarkers could suggest failed response to anti-TNF and a need to switch to an alternate mechanism of action therapy.

10-R Poster: Biomarkers of Early Endoscopic Recurrence for Postoperative Crohn's patients

Presenter: Furkan Ertem, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: David Binion MD

Funding Source: N/A

Authors: Furkan Ertem MD, Claudia Ramos Rivers , Miguel Regueiro MD, Benjamin Click MD, Ioannis Koutroubakis MD, Marc Schwartz MD, Andrew Watson MD, Jana Hashash MD, Micheal Dunn MD, Dmitriy Babichenko MD, David Binion MD

Introduction: The majority of Crohn's disease (CD) patients require small bowel surgery. Although surgically induced remission is rapid, it is not curative, as CD inflammation recurs at the anastomosis site at variable trajectories regarding timing and severity. Endoscopic CD recurrence defined by the Rutgeert's score within 2 years of surgery is considered the best objective assessment, identifying patients with rapid post-op recurrence and more severe disease, who may benefit from acceleration of therapy. At present it is unknown if routinely available blood tests may also function as non-invasive and less costly biomarkers identifying CD patients at risk of early endoscopic recurrence and more severe disease trajectories. We sought to characterize patterns of routine serum blood tests and their association with early endoscopic recurrence in CD patients defined by Rutgeert's score.

Methods: We conducted an observational study of consented CD patients followed prospectively in a natural history registry maintained at a referral center between 2009 and 2016. Patients with complete data and a minimum of 2 year post-operative follow-up were eligible for analysis. Early endoscopic recurrence (Rutgeert's score =2, less than 2 years postoperatively) were compared to late or no recurrence group (maximum Rutgeert's score i0 or i1 within 2 years of surgery).

Results: Out of 233 post-op CD patients, 52% (n=106) had early endoscopic recurrence, while 48% formed the late/no recurrence group. Mean follow up time for early and late/no endoscopic recurrence groups were 46.1 ± 23.7 and 46.9 ± 22.0 months respectively. Early endoscopic recurrence was associated with elevated CRP ($P<0.001$), ESR ($P<0.0001$), anemia ($P<0.001$), and lower albumin levels ($P<0.01$) within 2 years of surgery. Over 8 years, patients with early endoscopic recurrence required more surgeries ($P=0.004$) and had increased hospital admissions ($P=0.01$), ER visits ($P=0.01$), CT scan imaging charges per year ($P<0.01$) compared to patients with late/no recurrence. In the first two years following surgery, higher Rutgeert's scores were associated with active smoking at the time of surgery ($P<0.002$) and peripheral blood eosinophilia ($P=0.03$).

Conclusion: These data suggest that early aggressive endoscopic post-op CD recurrence is associated with routine biomarkers of inflammation, peripheral blood eosinophilia, and active smoking at the time of surgery. Individuals with early post-op endoscopic recurrence had higher health care utilization, hospital admissions, ER visits and abdominal imaging charges. These data suggest that routine blood tests and clinical data can also risk stratify post-operative CD patients, readily identifying individuals at risk of more severe post-operative disease trajectories.

11-R Poster: DOES SURGICAL ANASTAMOSIS TYPE IMPACT RATES OF ENDOSCOPIC RECURRENCE IN POST-OPERATIVE CROHN'S DISEASE? AN 8-YEAR OBSERVATIONAL COHORT STUDY

Presenter: Furkan Ertem, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: David Binion MD

Funding Source: N/A

Authors: Furkan Ertem MD, Claudia Ramos Rivers MD, Miguel Regueiro MD, Andrew Watson MD, Marc Schwartz MD, Ioannis Koutroubakis MD, Jana Hashash MD, Benjamin Click MD, Micheal Dunn MD, Dmitriy Babichenko MD, David Binion MD

Introduction: The majority of Crohn's disease (CD) patients with ileocecal and small bowel disease will develop strictures requiring resective surgery and anastomosis. Types of surgical reconstruction vary and can employ side-to-side anastomosis (STSA), which aligns longitudinal segments of bowel next to one another in an anti-peristaltic orientation and transects surgical muscle layers using a linear stapling device or an end-to-end anastomosis (ETEA), which reconstructs the bowel as an intact tube. Although numerous factors have been associated with CD recurrence after surgery, the long-term impact of anastomosis type on post-op recurrence has not been fully defined. We sought to compare long-term patterns of CD recurrence by anastomosis type.

Methods: We conducted an observational study of consented CD patients who underwent ileal resection and anastomosis and were followed post-operatively in a tertiary referral center between 2009-2016. Surgical anastomosis technique, post-operative medical therapy and endoscopic evaluation was at the discretion of the performing physicians. Demographics, clinical characteristics, health care utilization and disease activity of patients were by anastomosis technique. Multiple linear regression of endoscopic Rutgeert's score was performed. Patients with at least 2 years of follow-up data were included for analysis.

Results: A total of 237 CD patients underwent ileal resection and anastomosis and formed the study group (ETEA n=154; STSA n=83). STSA patients had an earlier age of diagnosis (21.8 ± 10.1 vs. 28.6 ± 14.3 yrs, P=0.0001), higher smoking rate at the time of surgery (34% vs. 18%, P=0.003) and longer follow up time (50.6 ± 24.6 vs. 44.5 ± 21.3 mo, P=0.01) compared to the ETEA group.There was no difference between groups regarding rates of post-op complications, inflammatory biomarkers (i.e. CRP, ESR) and hemoglobin levels over the follow up period. The STSA group had significantly lower mean levels of albumin (3.99 ± 0.44 vs. 4.11 ± 0.4, P=0.02) and 25-OH vitamin D (32.7 ± 12.6 vs. 36.4 ± 13.1, P=0.02) compared with the ETEA group. Despite significantly more patients receiving post-op medical prophylaxis (anti-TNF 77% vs. 63%, p=0.03), the STSA group had more aggressive endoscopic recurrence (mean Rutgeert's score 1.86 vs 1.37, P=0.01), clinical recurrence (mean Harvey-Bradshaw Index 5.8 vs. 4.5 P=0.02) and more healthcare utilization.On multiple linear regression controlling for diagnosis age, smoking status, and length of post-op follow up, STSA remained significantly associated with higher Rutgeert's scores (coefficient= -0.5, P=0.01) compared with ETEA patients.

Conclusion: This multiyear observational cohort study demonstrates that compared to side-to-side anastomosis, end-to-end technique is associated with less severe endoscopic and clinical CD recurrence and may be the superior anastomotic technique.

12-R Poster: Seven-Year Period Prevalence and Characteristics of Hypertension in a Large US Inflammatory Bowel Disease Cohort

Presenter: Kelly Gibbs, Resident
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: David Binion MD
Claudia Ramos Rivers MD

Funding Source: 5TL1TR000145-09, 5T32DK063922-12, W81XWH-11-2-013

Authors: Kelly Gibbs MD, Alyce Anderson PhD, Benjamin Click MD, Ioannis Koutroubakis PhD, Miguel Regueiro MD, Michael Dunn MD, Marc Schwartz MD, Jana Hashash MD, Dmitriy Babichenko MS, David Binion MD

Introduction: Inflammatory bowel disease (IBD; Crohn's disease, ulcerative colitis) is characterized by chronic inflammation that can alter microvascular physiology. Previous studies suggest that IBD patients experience increased rates of atherosclerosis and vascular disease likely related to systemic inflammation, similar to other chronic inflammatory diseases with increased risk for premature atherosclerosis, cardiovascular disease, and stroke. The role of hypertension (HTN) as a risk factor for vasculopathy, cardiovascular disease, and thromboembolic disease in IBD patients has not been defined. The aim of this study was to determine the prevalence and clinical characteristics of HTN and the frequency of adverse vascular outcomes in IBD patients followed in a US tertiary referral center.

Methods: Demographic, clinical, laboratory, and treatment data from a prospective, consented, longitudinal IBD registry between 2010-2016 were analyzed. HTN was defined using three-factor characterization including ICD-9 codes, Eighth Joint National Committee guideline blood pressure criteria, or an active prescription for antihypertensive medications. Outcomes were identified using ICD-9 codes. Composite vascular outcomes included acute myocardial infarction, heart failure, venous thromboembolism, peripheral vascular disease, aortic aneurysm or dissection, cerebrovascular occlusion, transient ischemic attack, and acute mesenteric ischemia.

Results: A total of 524 IBD patients (median age 42.2 y, 41.8% male) were included. HTN was observed in 302 patients. The 7-year period prevalence of HTN in IBD patients was 57.6%. HTN in IBD was associated with increased age ($P < 0.001$), male gender ($P < 0.005$), active and previous tobacco exposure ($P = 0.001$), higher BMI ($P < 0.001$), longer IBD disease duration ($P = 0.023$), steroid use ($P = 0.032$), diabetes mellitus ($P < 0.001$), dyslipidemia ($P < 0.001$), coronary artery disease ($P < 0.001$), chronic kidney disease ($P = 0.010$), and depression ($P < 0.001$). A higher rate of the composite outcome was observed in IBD patients with HTN than those without HTN ($P = 0.002$), but no difference was observed in the frequency of individual outcomes. IBD patients with HTN had higher emergency department visits ($P < 0.001$), hospitalizations ($P = 0.012$), and cumulative financial charges ($P < 0.001$) but lower quality of life scores ($P = 0.003$) compared to those without HTN.

Conclusion: HTN has a high period prevalence in IBD patients followed at a tertiary center. HTN in IBD is associated with adverse vascular outcomes, lower quality of life, higher healthcare utilization, and higher overall healthcare charges. HTN is a common and underappreciated comorbidity in IBD which is associated with a worse clinical course.

13-R Poster: ORGAN FAILURE WITHOUT NECROSIS IS UNCOMMON IN ACUTE PANCREATITIS AND HAS A BETTER PROGNOSIS

Presenter: Amir Gougol, Resident
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Georgios Papachristou MD

Funding Source: VA merit

Authors: Amir Gougol MD, Pedram Paragomi MD, Peter Lee MD, Xiaotian Gao MS, Adam Slivka MD, David Whitcomb MD, Dhiraj Yadav MD, Georgios Papachristou MD

Introduction: Organ failure (OF) and pancreatic necrosis (PNec) frequently occur together, and they are determinants of mortality in acute pancreatitis (AP). However, little is known about the prognostic significance of OF in the absence of PNec. Objective of this study was to characterize the clinical profile and prognosis of this subgroup.

Methods: AP Patients admitted to the University of Pittsburgh were prospectively enrolled (SAPS/PROOF study). Subjects with available contrast-enhanced CT (CECT) scan performed at least 48 hours after the pain onset were included in the analysis. Revised Atlanta classification definitions were utilized for OF and PNec. Charlson comorbidity index (CCI) was calculated for pre-existing comorbid conditions. Outcomes of interest included duration of OF, length of stay (LOS), multisystem organ failure (MOF), and death.

Results: In total 558 AP patients were prospectively recruited. One hundred and thirty AP patients developed OF (115 persistent, 15 transient); of which 82 underwent a CECT, thus were included in the final analysis. PNec occurred in 66 patients. Compared with patients with PNec (OFcN), subjects without necrosis (OFsN) had similar baseline characteristics except drinking history and Charlson Comorbidity Index score (Table). OFsN patients had a shorter LOS, less progression to persistent OF and multiple OF, and a lower mortality rate compared to patients with OFcN (Table).

Conclusion: Among AP patients with OF, only 20% did not develop concomitant necrosis. This subgroup had a significantly better prognosis than patients with both PNec and OF. Mechanistic studies are needed to explore treatment strategies.

14-R Poster: REGIONAL VARIATIONS OF CLINICAL CHARACTERISTICS IN ACUTE PANCREATITIS FROM A LARGE, INTERNATIONAL, MULTI-CENTER PROSPECTIVE STUDY (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, Bassem Matta MD, Pedram Paragomi MD, Peter Lee MD, Rakesh Kochar MD, Mahesh Goenka MD, Aiste Gulla MD, Jose A. Gonzalez-Gonzalez MD, Tyler Stevens MD, Haq Nawaz MD, Vikesh Singh MD, Miguel Ferreira MD, Carlos Ocampo MD, Sorin T. Barbu MD,

Introduction: Clinical characteristics of acute pancreatitis (AP) across different regions of the world have not been well elucidated. We aim to describe etiology, demographics, management, and outcomes of AP across different geographic areas using an international multi-center prospective cohort of AP.

Methods: Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE); is an international collaboration of different centers throughout the world. Data was collected prospectively using online standardized detailed questionnaires, and recorded via REDCap (Research Electronic Data Capture). Twenty one international centers: 5 from Europe, 3 from India, 5 from Latin America (LA), 8 from North America (NA) were included. Enrollment, and quality of data were monitored centrally at University of Pittsburgh.

Results: Patients enrolled between 7/2015 and 9/2017, yielding 1,612 total cases (Europe 409, India 365, LA 325, NA 512). Mean cohort age was 50, highest among Europeans at 59 years (Table 1). Males comprised 52.5%, while in India accounted for 74.8%. Obesity was more common in NA at 43.3% compared to an average of 28%. Biliary pancreatitis was the leading etiology across groups (45.3%), with a higher proportion in LA (78.1%). Alcoholic pancreatitis accounted for the majority of cases in India (44.4% vs. overall average of 20.9%). Narcotic use was most common in NA at 92.5% compared to 50.8% across all geographic areas. ERCP rates in biliary pancreatitis were highest in NA (60% vs. average 28.7%), and cholecystectomy during the same admission was more common in LA (58.2% vs. average 38.5%) (Table 2). Our cohort encompassed 65.1% mild, 22.1% moderate, and 12.1% severe cases of AP. Severe AP was most common in India 22.6% (vs. population mean 12.1%), where organ failure as well as pancreatic necrosis were mostly commonly present (28.8% and 34.4% respectively). Pancreatic debridement and/or drainage among subjects with pancreatic necrosis within 6 months of AP attack was more frequent in India (54.6% vs. 32.7% average). Shorter hospital stay was noted in NA; 7.2 days vs. overall mean of 11 days. Mortality among severe AP was highest in Europe at 47.9% in contrast to 23.5% cohort average.

Conclusion: Our results underscore important variations in demographics, etiology, management trends, and outcomes of AP across different parts of the globe. European population seems to be older with markedly higher mortality. Alcoholic pancreatitis is more predominant in India where drainage, surgical debridement are more common. Biliary pancreatitis accounts for the large majority of cases in LA. Obesity is more common in NA. Narcotic use appears to be quasi universal in NA, where mortality is the lowest. Additional investigational studies are needed for clarifying factors responsible for these differences.

15-R Poster: TIMING AND SEQUENCE OF ORGAN FAILURE IN A LARGE PROSPECTIVE COHORT OF PATIENTS WITH ACUTE PANCREATITIS

Presenter: Amir Gougol, Resident
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Georgios Papachristou MD

Funding Source: VA merit

Authors: Amir Gougol MD, Pedram Paragomi MD, Phil Greer MS, Adam Slivka MD, Xiaotian Gao MS, Vijay Singh MD, David Whitcomb MD, Dhiraj Yadav MD, Georgios Papachristou MD

Introduction: Organ failure (OF) is the main determinant of poor clinical outcomes in Acute Pancreatitis ¬(AP). Current literature on the dynamics of OF is limited. In this study, we aimed to characterize the timing and sequence of OF, the factors associated with OF onset, and their impact on AP-related mortality.

Methods: Clinical data were prospectively recorded in an ongoing observational study at the University of Pittsburgh (SAPS/PROOF). Pearson chi-square, and non-parametric tests were used to compare categorical and continuous variables, respectively.

Results: In total, 558 AP patients have been prospectively enrolled. Median age was 51, 50% were male, median BMI 28, and biliary was the etiology in 41%. Persistent OF (lasting > 48 hours) developed in 115 patients at a median of 48 hours [inter-quartile range (IQR), 24-96] after pain onset. The majority of patients (63%) developed OF within 72 hours of pain onset (early onset), 23% between the 3rd and 7th day (intermediate), and 14% after day 7 (late onset; table). The incidence of OF peaked between 24-48 hours and declined after 72 hours for all three systems (figure). Seventy one patients (62%) developed multisystem (>1 system involved) OF (MOF); the median interval between OF onset and development of MOF was 24 hours (IQR, 0-48). Among patients with MOF, renal was the first organ to fail in 61% at a median of 24 hours (IQR, 24-72), followed by respiratory in 36% at 48 hours (IQR, 24-96); cardiovascular system failed first in only 1 patient. Overall, 24 patients with OF (21%; all with MOF) succumbed to death at a median of 31 days (IQR, 8-56). Comparing the three groups based on OF onset (early, intermediate, and late onset), patients with early onset OF were more likely to have positive SIRS score on admission ($p=0.01$). Infection identified more commonly in patients with late onset OF ($p<0.01$). Mortality rate was increased in MOF patients with all three organs involved (23/24; $p<0.01$) and in those with late onset OF (47%, $p<0.01$). Mortality was not influenced by which organ failed first.

Conclusion: In a large prospective AP cohort, the median time of OF onset was 48 hours from pain onset with renal being the most common organ to fail first. The majority of OF (63%) started within 72 hours (early onset). Positive SIRS on admission was associated with higher risk of early onset OF. Late onset OF (after day 7) was associated with higher rates of infection. Mortality was more common in patients with all three organs involved and in those with late onset OF, but was not influenced by which organ failed first.

16-R Poster: UTILIZATION OF TUBE FEEDINGS IN ACUTE PANCREATITIS PATIENTS AT A LARGE US REFERRAL CENTER

Presenter: Amir Gougol, Resident
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Georgios Papachristou MD

Funding Source: VA merit

Authors: Amir Gougol MD, Jorge Machicado MD, Pedram Paragomi MD, Stephen O'Keefe MD, Adam Slivka MD, David Whitcomb MD, Dhiraj Yadav MD, Georgios Papachristou MD

Introduction: Clinical trials on timing of onset, delivery route, and type of formula of tube feedings (TF) in acute pancreatitis (AP) have not been sufficiently powered to change practice patterns. The only consensus in recent guidelines is that TF should be administered through either a NG or NJ route. Furthermore, TF duration, need for endoscopic tube replacements, and healthcare visits due to TF complications, have not been studied. Thus, we aimed to describe the use and resource utilization of TF in AP patients at a large US referral center.

Methods: Of 423 AP patients prospectively enrolled at the University of Pittsburgh Medical Center from 2004-2014, 139 (33%) received TF. Data on TF including timing of onset, delivery route, type of formula, duration, complications, and resource utilization due to complications (repeated endoscopies, ER visits, hospitalizations), was assessed in 100/139 (72%) patients with complete data available. Bivariate comparisons were performed using Chi-square for categorical data and Mann-Whitney U test for continuous data.

Results: Patients who received TF (n=139) were more likely to be male (62 vs. 44%), obese (53 vs. 40%), have alcohol etiology (19 vs. 9%), and moderately severe (34 vs. 19%) or severe AP (62 vs. 3%) than those who did not receive TF (n=284) (all $p<0.05$). Among 100 AP patients with complete TF data, TF were started at a median of 5 days (IQR, 3-8) from initial admission, because of moderately severe or severe AP in 98% of patients. The majority of patients had NJ feedings through either an endoscopically placed NGJ (51%) or NJ (44%) tube. Only 5% underwent bedside NG tube placement, but all transitioned to NJ feedings later. An oligomeric formula (92%) was preferred over other formulas. Feeding tube complications led to at least one endoscopic feeding tube replacement in 42% of patients, and to an unexpected healthcare visit in 29% of those discharged on TF (16/55 patients). The median time for endoscopic tube replacement was 25 days (IQR, 10-32). The median duration of TF was 39 days (IQR, 19-58). Duration was longer in those who underwent pancreatic intervention (62 days; IQR, 41-103) compared to those who did not (36 days; IQR, 18-55) ($p=0.01$).

Conclusion: Delayed nasojejunal TF (at day 5 of admission), with an oligomeric formula, and administered for 6 weeks, was the preferred nutrition strategy in AP patients in this large US prospective cohort. Almost half required at least one endoscopic tube replacement and almost a third had an unexpected healthcare visit due to a feeding tube complication. Further studies should define the optimal utilization of TF and ways to reduce TF-related complications.

17-R Poster: Accuracy of Electronic Health Record Family History in Predicting Genetic Susceptibility to Pancreatic Ductal Adenocarcinoma

Presenter: Katrina Han, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Randall Brand MD

Funding Source: N/A

Authors: Katrina Han MD, Beth Dudley MS, Eve Karloski MS, Virginia Speare PhD, Randall Brand MD

Introduction: Electronic health records (EHR) are widely utilized by healthcare providers (HCPs) and researchers and allow for rapid centralized access to patient information, but studies have demonstrated decreased accuracy in documentation of a patient's cancer family history (FH) by HCPs when compared to history obtained by trained genetic professionals. Accurate FH is imperative for genetic risk assessment in individuals with pancreatic adenocarcinoma (PC) since guidelines for genetic testing in individuals with PC primarily focus on cancer FH. We hypothesized that EHR-documented cancer FH would fail to identify individuals with PC that meet genetic testing criteria and limit identification of clinically actionable genetic variants.

Methods: We reviewed EHR of 186 consecutive, unselected patients with PC who participated in a study that included collection of 3-generation pedigrees by a genetic counselor and testing for 32 cancer susceptibility genes. Cancer FH was ascertained by reviewing the FH from HCP clinical notes prior to study enrollment. Data was also extracted from the FH tab in the EHR. The FH information from these sources and from the pedigree was used to determine if patients met criteria for genetic evaluation or testing using the National Comprehensive Cancer Network (NCCN) guidelines for BRCA1 and BRCA2 testing and Lynch syndrome evaluation and the American College of Gastroenterology (ACG) guidelines for familial PC.

Results: As shown in Table 1, a lower percentage of patients met criteria for genetic testing based on data obtained from the FH tab (16%) and clinical notes (24%) compared to the pedigree (41%); the differences were statistically significant ($p = <0.00001$ when comparing the FH tab to the pedigree and $p=0.0006$ when comparing clinical notes to the pedigree). Of the 22 patients who had a clinically actionable variant (pathogenic or likely pathogenic), a lower percentage of patients met criteria for genetic testing based on data obtained from the FH tab (36%) and clinical note (50%), compared to the pedigree (73%); the difference between the FH tab and the pedigree was significant ($p= 0.0154$).

Conclusion: Our findings suggest that providers should take caution when utilizing FH documented in the EHR to guide decisions about genetic testing. Our data demonstrate that using the EHR alone to determine genetic testing eligibility based on current guidelines results in failure to identify a genetic susceptibility in up to 64% of individuals with PC; whereas, 27% of clinically actionable variants would be missed when using the pedigree. Identifying genetic susceptibility in individuals with PC is important given potential implications for PC treatment and in directing testing for family members.

18-R Poster: Benefits of use of Professional CGM in low socioeconomic population

Presenter: Sulman Hashmi, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Sann Mon MD

Authors: Sulman Hashmi MD, Sann Mon MD

Funding Source: N/A

Introduction: Self-monitoring blood glucose (BG) using a glucometer is the standard of care for patients with diabetes. However, up to 67% of patients fail to routinely monitor BG, which is one of the major challenges to optimize glycemic management. With an emergence of technology, continuous glucose monitoring devices (CGM) are now used by many patients for guiding therapeutic changes. However, such technology is not always available in low socioeconomic areas.The objective of this study was to examine the ability of professional CGM for guiding therapeutic changes in a population with limited access to technology to improve glycemic control as measured by A1c, patient glucometer data, hypoglycemia events, and total daily insulin requirements before and after the testing period.

Methods: Professional CGM (Freestyle Libre Pro) was placed for 10-14 days in 19 patients age = 18 years (mean age 47.6 years +/-19.6 SD, 58.42% female) with T1DM or T2DM on insulin therapy. CGM data was downloaded after the testing period, glucose results were retrospectively reviewed with the patient, and insulin dose adjustments were made.

Results: 66 % of patients showed improvement in A1c with a median decrease of 0.8%. Mean A1c pre 9.2 and post 8.77 with the p value=0.13Fewer hypoglycemic episodes and higher total daily use of insulin are noted in the post-CGM period. 7 episodes of severe hypoglycemic before and none following CGM use. There was an increase in the mean dose of insulin from 51.79 units to 56.93 units , p=0.14 post CGM.Statistically significant decrease in episodes of hyperglycemia Post CGM (Pre 11.66 to Post 4.18 , p=0.03)

Conclusion: Professional CGM is useful for improving glycemic control in a low socioeconomic population with limited access to current technology. Despite a relatively small sample size, our study showed that there was an improvement in HbA1c and the decrease in the number of episodes of hyperglycemia and hypoglycemia after CGM placement.

19-R Poster: Predictors Of Super-response To Cardiac Resynchronization Therapy In Left Bundle Branch Block Associated Idiopathic Nonischemic Cardiomyopathy

Presenter: Aliza Hussain, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Norman C. Wang MD

Funding Source: N/A

Authors: Aliza Hussain MD, Michael S. Sharbaugh MPH, Evan C. Adelstein MD, Sandeep K. Jain MD, Samir Saba MD, Alaa A. Shalaby MD, Andrew H. Voigt MD, Andrew D. Althouse PhD, Norman C. Wang MD

Introduction: Cardiac resynchronization therapy (CRT) benefits many with heart failure (HF) and reduced left ventricular ejection fraction (LVEF). It has shown to improve both symptoms and survival in select individuals. Predictors of super-response to CRT in those with left bundle branch block (LBBB)-associated idiopathic nonischemic cardiomyopathy (NICM) are unknown.

Methods: A single-center retrospective study included CRT recipients with idiopathic NICM, LVEF =35%, and LBBB. Super-response was defined as improvement in LVEF to =50%. Logistic regression assessed associations between baseline characteristics and post-CRT LVEF =50% versus LVEF <50%. Variables associated with super-response at p<0.1 in univariable analyses were used in multivariable analyses.

Results: The study included 105 subjects with mean age 61 years, 46 (44%) male, mean initial LVEF 22.6% ± 6.6%, 85 (81%) New York Heart Association class III, and 103 (98%) CRT-defibrillators. CRT super-response was observed in 56 (54%) subjects. In univariable analyses, characteristic associated with poor odds of super-response were history of hypertension, higher baseline heart rate, and higher serum BUN. A modest association with diabetes was observed (odds ratio (OR), 0.42; 95% confidence interval (CI), 0.17-1.01; p=0.054). These associations were maintained in multivariable analysis: hypertension (OR, 0.40; 95% CI, 0.17-0.95; p=0.04), heart rate (OR per 10 bpm 0.69; 95% CI 0.48- 0.99; p=0.048), and serum BUN (OR, 0.94; 95% CI, 0.88-0.99; p=0.04). Super-responders also had lower risk for adverse cardiac events (heart failure hospitalizations, appropriate defibrillator therapies, and all-cause death) over a median follow-up time of 76 months, compared to non- super-responders (hazard ratio, 0.38; 95% CI, 0.17-0.88; p=0.02).

Conclusion: In LBBB-associated idiopathic NICM, CRT super-response was associated with absence of hypertension, lower baseline heart rate,and lower serum BUN. Super-responders had reduced risk of adverse cardiac events. Focusing on these factors may improve outcomes.

20-R Poster: Patient perspectives on weight management in primary care

Presenter: Seema Jain, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Kathleen McTigue MD

Funding Source: N/A

Authors: Seema Jain MD, Scott Rothenberger PhD, Wendy Bennett MD, Jeanne Clark MD, Molly Conroy MD, Sharon Herring MD, Jennifer Kraschnewski MD, Michelle Lent PhD, Nickie Cappella BS, Harold Lehmann MD, Kathleen McTigue MD

Introduction: Patients with obesity have previously reported not receiving weight loss counseling from their health care providers, despite convincing evidence of its utility. An updated examination of patient perspectives on weight management could inform efforts to improve the health care of patients with overweight and obesity. We surveyed primary care patients across five health care systems to determine: 1. What are patients' perceived weight status and weight-related goals? 2. To what extent are health care providers counseling patients on weight, diet, and physical activity?

Methods: Through the PaTH Clinical Data Research Network, online surveys were distributed to adult patients of primary care providers (PCPs) across five US health care systems. Demographics of survey participants were obtained from self-report. Survey questions addressed height, weight, perceived weight status, weight-related goals, and frequency of advice from health professionals regarding diet, physical activity, and weight management. Those who reported receiving advice on weight were also asked which health professionals provided this advice.

Results: Primary care patients surveyed (n = 1308) had a mean age of 56.6 years; 67.4% were female; 79.7% were white; average BMI was 30.2 kg/m2. Of patients classified as overweight (n=240) or obese (n=346), most (86.3% and 91.6%, respectively) described their weight as slightly or very overweight. While 76.3% of overweight patients and 88.1% of obese patients reported currently trying to lose weight, the remainder reported either trying to maintain weight or not doing anything about their weight. 55.6% of overweight patients and 26.5% of obese patients reported receiving no weight-related advice from a health professional in the past 12 months. Further, 51.7% of overweight patients and 36.9% of obese patients reported their providers have not helped them develop healthy diet and physical activity patterns in the past 12 months. When patients with overweight and obesity did receive advice on weight, 89.2% reported that it came from their PCP. The most common other health professionals to provide weight advice were nutritionists (15.4%), cardiologists (11.3%), orthopedic surgeons (9.7%), and mid-level providers (9.4%).

Conclusion: Over 85% of patients with overweight and obesity describe themselves as overweight and over 75% report trying to lose weight. However, a considerable percentage are still not receiving advice from providers about weight, diet or physical activity. Patients report that PCPs are the primary source of weight loss advice in the healthcare setting. Further study of interventions to improve weight-related counseling by PCPs is needed.

22-R Poster: Bone Health Assessment in Patients with Chronic Pancreatitis

Presenter: Allison Kanakis, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Dhiraj Yadav MD

Funding Source: N/A

Authors: Allison Kanakis MD, Kishore Vipperla MD, Georgios Papchristou MD, Randall Brand MD, Adam Slivka MD, David Whitcomb MD, Dhiraj Yadav MD

Introduction: Chronic pancreatitis (CP) patients are at high risk of major osteoporotic fractures (MOF). The primary aim of this study was to determine how often DEXA and other markers of bone health are performed in CP patients. The secondary aim was to determine if the use of the Fracture Risk Assessment (FRAX®) score helps to predict fracture risk in CP.

Methods: Medical records of CP patients age =40 years prospectively enrolled in The North American Pancreatitis Study 2 from UPMC from 2000-2014 were retrospectively reviewed to gather relevant data. FRAX® scores in study patients were compared to the general population in the 2017 National Health Statistics Report. Fracture prevalence in study patients was compared to two separate cohorts of non-CP patients.

Results: 239 patients (mean 56±11 years, median follow-up 4.9 years) were evaluated. About 54% were males, 84% were Caucasian, 54% had alcohol etiology of CP, 33% had endocrine insufficiency, 34% had exocrine insufficiency, and 9% had fragility fracture. DEXA was performed in only 21% of patients. DEXA was performed more often in females, non-alcohol etiology of pancreatitis, prior fragility fracture, longer duration of contact, and higher FRAX® risk of MOF. There was no difference in whether or not DEXA was performed with regards to patient age, ethnicity, BMI, or steroid use. Observed prevalence of osteoporotic fracture at last follow up was 8% in those age 45-65 years and 13% in those age = 65 years ($p < 0.01$ compared to healthy controls). However, FRAX® score was not significantly different compared to controls. The 10-year probability of MOF = 20% was 8.3% in CP patients compared to 5% in the US population, and the 10-year probability of hip fracture (HF) = 3% was 19% in CP patients compared to 18.3% in the US population ($p > 0.05$).

Conclusion: BMD testing in CP patients is suboptimal, and the FRAX® score does not adequately assess fracture risk in these patients. Assessment of bone health using DEXA should be incorporated into the routine clinical care of CP patients. More data is needed to evaluate the mechanisms that affect bone health in CP patients. Further studies should evaluate the barriers to screening and methods to improve screening in these patients at risk for osteoporotic fractures.

23-R Poster: Features Associated with Long-Term Survival in Metastatic Breast Cancer

Presenter: Natalie Klar, Resident **Research Interest:** Clinical General Internal Medicine

Mentors: Adam Brufsky MD, PhD **Funding Source:** University of Pittsburgh, Dept. Oncology

Authors: Natalie Klar MD, Margaret Rosenzweig PhD, Brenda Diergaarde PhD, Adam Brufsky MD, PhD

Introduction: 5-10% of women with metastatic breast cancer (MBC) survive =5 years. Predictors of long-term survival are not clearly elucidated. We used data from 122 long-term MBC survivors (=5-year survival from date of MBC dx) and 191 short-term MBC survivors (=2-year survival from date from MBC dx) to identify clinico-pathologic and socioeconomic features associated with MBC survival.

Methods: Women initially diagnosed with breast cancer (BC) in or after 1999, and diagnosed with MBC at Magee Women's Cancer Program of UPMC were included (N=313). Data abstracted from medical records included: stage at initial BC diagnosis, body mass index (BMI), Charlson Comorbidity Index (CCI), age, menopausal status, tumor receptor status at initial BC diagnosis, site of initial metastases, time between initial diagnosis and MBC, household income, race, employment status, and partner status. Differences between groups were assessed using t-tests and Chi-square or Fisher's exact tests. Odds ratios and 95% confidence intervals were calculated using multivariate logistic regression models.

Results: Long-term survivors were significantly ($P<0.05$) younger, and had more ER positive, PR positive, and Her2 positive disease, lower CCI, lower rates of visceral metastases, higher household income, and positive partner status than short-term survivors. Long-term term survivors were also significantly more often diagnosed with de novo MBC compared to short-term survivors; less often with early-stage BC. The association with long-term survival remained significant after adjustment for age, tumor receptor status, and CCI, 3.0 (1.6-5.4). Time interval between initial diagnosis and MBC, BMI, menopausal status, race, and employment status were not associated with survival.

Conclusion: Diagnosis of de novo MBC, ER- and/or Her2-positive primary tumor, higher household income, and having a partner are associated with long-term survival after diagnosis of MBC.

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: Edwin Ravano MD **Funding Source:** N/A

Authors: Daniel Kotok MD, John Evankovich MD, William Bain MD, Sarah F. Rapport MPH, Yingze Zhang PhD, Janet S. Lee MD, Alison Morris MD, Bryan J. McVerry MD, Georgios D. Kitsios MD

Introduction: Diagnosis of Acute Respiratory Distress Syndrome (ARDS) requires bilateral infiltrates on chest radiography, but beyond diagnostic purposes, radiographic abnormalities in ARDS are not used for risk stratification. The Radiographic Assessment of Lung Edema Score (RALE) score, a semi-quantitative method for assessing severity of pulmonary edema, has been correlated with hypoxemia and fluid management strategies in ARDS. We sought to demonstrate the longitudinal evolution of pulmonary edema using the RALE score in a cohort of patients with ARDS and examine for associations with host-response biomarkers, ARDS subphenotypes and clinical outcomes.

Methods: We included patients from the Pittsburgh Acute Lung Injury Registry study with ARDS (cases) or cardiogenic pulmonary edema (CHF-controls). The RALE score quantifies consolidation extent (0-4) and density (0-3) on four CXR quadrants. Quadrant score is obtained by multiplying consolidation extent and density and the total RALE score by summing individual quadrant scores. We recorded RALE scores on CXRs obtained on the day of intubation (day 0) and on days 3, 5, 7 and 10. Each CXR was reviewed by two reviewers. Inter-reviewer agreement was assessed using Pearson's correlation. We measured baseline validated plasma biomarkers of injury and inflammation (RAGE, IL-6, IL-8, TNFR1) with a Luminex template and recorded clinical data from the electronic medical record.

Results: 134 patients (111 ARDS and 23 CHF, mean age 53, 55% male) were included. A total of 504 CXR images were reviewed. Inter-reviewer agreement was good ($r=0.82$, $p=10\text{-}9$). Baseline RALE scores for ARDS patients (median 9.5, IQR [6-14]) were significantly higher compared to CHF patients (median 5, IQR [2.5-8], $p=0.0014$). There was progressive decline of RALE scores over time in both groups (repeated measures ANOVA with random subject intercept $p<0.0001$). By day 7 postintubation, RALE scores had declined to 8 (ARDS, 4-12) and 3 (CHF, 2-6). Higher RALE scores (above median of 8) correlated significantly with degree of hypoxemia ($p=0.002$). There were no significant associations between baseline RALE scores with biomarkers of host-injury and inflammation (RAGE, IL-6, IL-8, TNFR1) or clinical outcomes (30-day mortality, shock incidence).

Conclusion: Our findings indicate that RALE scores are associated with severity of hypoxemia at baseline and decline over time, suggesting resolving edema in patients with ARDS. The lack of associations of RALE scores with host biomarkers and clinical outcomes suggests that the substantial phenotypic heterogeneity in ARDS is not accounted for by the degree of radiographic edema.

25-R Poster: Dofetilide in Patients with Atrial Fibrillation and Severe Left Ventricular Hypertrophy

Presenter: H. Immo Lehmann, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Sandeep Jain MD

Funding Source: N/A

Authors: H. Immo Lehmann MD, Dinxin Quin MD, Madhurmeet Singh MD, Evan Adelstein MD, Samir Saba MD, Sandeep Jain MD

Introduction: Dofetilide is a class III anti-arrhythmic used for rhythm control in patients with atrial fibrillation (AF), but recommendations limit use to patients without severe left ventricular hypertrophy (LVH). This study sought to explore all-cause-mortality in patients with severe LVH and AF, treated with off-label use dofetilide.

Methods: In this observational study, a cohort of 739 consecutive patients with AF, treated with dofetilide from 2002-2017 at the University of Pittsburgh Medical Center was retrospectively analyzed. Patients with an intraventricular septum (IVS) thickness =15mm on transthoracic echocardiography were classified as severe LVH group. Patients with severe LVH were pair-matched in a 1:2 pattern according to sex and age for comparison to a group without severe LVH (IVS<15mm) and incidence of all-cause-mortality on dofetilide was compared.

Results: Forty patients with and 80 patients without severe LVH were included, 78% were male. Median age at start of dofetilide was 64.0 (range: 29.9-84.5) years. Mean LVEF was 46±8% in severe LVH vs. 43±13% in non-LVH patients (p=0.11), respectively. Median treatment time on dofetilide in patients with severe LVH was 3.6 (range: 0.6-13.1) vs. 3.2 (range: 0.1-11.76) years in patients without severe LVH (p=0.60). Kaplan-Meier survival analysis revealed no difference in all-cause mortality between the two groups at 5 years of follow-up while treated on dofetilide (n=0 in severe LVH on dofetilide vs. n=3 in patients without severe LVH on dofetilide; p=0.55).

Conclusion: Patients with severe LVH that were treated with dofetilide did not have higher mortality than patients without severe LVH in this AF cohort. These data suggest the safety of off-label use of dofetilide for the treatment of AF, even when severe LVH is present.

26-R Poster: Predictive Value of Acute Pancreatitis Diagnosis Code in Diabetic Patients is Similar to Non-Diabetic Patients

Presenter: Jacob Lipkin, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Dhiraj Yadav MD

Funding Source: N/A

Authors: Jacob Lipkin MD, Adam Slivka MD, Melissa Saul MS, Georgios Papachristou MD, Jennifer Chennat MD, David Whitcomb MD, Dhiraj Yadav MD

Introduction: Diabetes Mellitus (DM) has a bidirectional relationship with acute pancreatitis (AP). The role of prevalent DM on the severity of AP is less clear. Administrative datasets are useful in large cohorts to study outcomes and predictors of severity in AP. Since DM patients have frequent elevations in serum pancreatic enzymes, the utility of administrative data in diabetic patients to study AP related outcomes in diabetic patients is unclear.

Methods: We retrospectively reviewed data from all unique patients who received a primary inpatient discharge code of AP at our institution between June 2009 and August 2014. Demographics, etiology and clinical variables were obtained by manual chart review. Patients were stratified into diabetic and non-diabetic groups based on the presence of DM diagnosis in the electronic record or use of antihyperglycemic agents. A diagnosis of AP was established by the presence of at least 2 of 3 features (upper abdominal pain, =3-fold increase in serum pancreatic enzymes, and imaging findings).

Results: Of 579 patients who received a primary inpatient discharge diagnosis of AP during the study period, 161 (27.8%) were identified to have prevalent DM. Of 161 diabetic patients, 124 met the diagnostic criteria for AP (PPV=0.77, 95% CI 0.71-0.83), which was similar to the PPV for AP diagnosis in patients without DM (336/418, PPV=0.80, 95% CI 0.76-0.84; p = 0.47). AP patients with prevalent diabetes were similar to those without prevalent diabetes in age (56.0 vs. 53.1, p = 0.13), sex (%male 58.8% vs. 54.5%, p = 0.40), ethnicity (%white 62.9% vs. 69.0%, p = 0.21), current tobacco use (30.6% vs. 34.2%, p = 0.47), and presentation with a sentinel episode of AP (71.0% vs. 76.2%, p = 0.25). While gallstones were the most common cause of AP with and without prevalent DM (36.3% vs. 31.0%, p = 0.28), diabetic patients were significantly more likely to have hypertriglyceridemia as the etiology (12.9% vs. 2.1%, p < 0.001), while alcoholic pancreatitis was more common in the non-diabetics (26.2% vs. 12.1%, p = 0.001). These findings were similar when data was analyzed for patients who presented with a sentinel episode of AP.

Conclusion: About 1 in 5 patients are over-diagnosed with AP when using administrative data – this PPV is reasonable when evaluating large datasets. Administrative data can be used to study outcomes of AP in diabetic patients. The etiologic spectrum of AP in diabetic patients differs from non-diabetic patients.

49-R Poster: Using Classification and Regression Trees to Identify Sociodemographic Subgroups of Veterans at High Risk for Chronic High-Dose Opioid Prescribing

Presenter: Jacob Lipkin, Resident
Epidemiology
General Internal Medicine

Research Interest: Health Services/Clinical

Mentors: Leslie Hausmann PhD
Walid Gellad MD

Funding Source: N/A

Authors: Jacob Lipkin MD, Joshua Thorpe PhD, Walid Gellad MD, Joseph Hanlon PharmD, Xinhua Zhao PhD, Carolyn Thorpe PhD, Florentina Sileanu MS, John Cashy PhD, Jennifer Hale BA, Maria Mor PhD, Thomas Radomski PhD, Chester Good MD, Michael Fine MD, Leslie Hausmann PhD

Introduction: Prolonged prescribing of high-dose opioids is associated with overdose and death. Past studies aimed at identifying high-risk populations have focused on factors such as age, sex, race, and region and have understudied community-level variables or the ways in which these social determinants of health interact. We aimed to identify how individual and community-level sociodemographic characteristics intersect in influencing the risks of high-dose opioid prescribing.

Methods: We examined all Veterans dually enrolled in the Department of Veterans Affairs (VA) and Medicare Part D who received an opioid prescription from either system in 2012. We used VA, Medicare, and US census data to compute 15 sociodemographic indicators (8 interval; 7 categorical with 22 possible levels). Individual-level indicators included age, sex, race, Medicare enrollment due to disability, and low-income subsidy (LIS) eligibility. Community-level indicators included region, and neighborhood socioeconomic status, safety, racial/economic diversity, and internet connectivity. The primary outcome was prolonged prescription of high-dose opioids, defined as being prescribed >120 morphine milligram equivalents (MME) for >90 consecutive days. We used classification and regression tree (CART) analyses to identify the interacting associations between individual and community-level sociodemographic indicators and the rates of chronic high-dose opioid prescriptions.

Results: Of 525,714 Veterans, 17,271 (3.3%) were prescribed chronic high-dose opioids. CART analyses revealed wide variation in risk across 24 subgroups defined by age, disability, race/ethnicity, region, LIS, neighborhood wealth, and neighborhood safety. The frequency of high-dose opioid prescriptions was lowest (0.19%) among the 2109 (0.4%) Veterans who were >85 years old, not disabled, receiving LIS, and of Non-white race/ethnicity. High dose opioid prescribing was highest (12.4%) among 12,584 (2.4%) Veterans who were <65 years old, disabled, of White or non-Black/Hispanic race/ethnicity, and living in high income neighborhoods. Younger age, disability, and White race were consistent risk factors for high-dose prescriptions, while the role of LIS, region, and neighborhood wealth and safety varied across subgroups.

Conclusion: Using CART analyses, we identified 5 individual-level and 4 neighborhood-level sociodemographic indicators that classified patients into groups whose risk of chronic high dose opioid prescribing varied 65-fold (0.19 to 12.4%). This analytical approach, which can identify complex interactions between variables that are difficult to discover using regression-based methods, may help identify appropriate high-risk subgroups to target for opioid safety initiatives within a heterogeneous population of Veterans with relatively low-levels of baseline chronic high dose opioid use.

27-R Poster: Pulmonary Hypertension is Associated with Increased Mortality and Readmission in Patients with Obstructive Sleep Apnea Admitted for Heart Failure Exacerbation

Presenter: Casey McQuade, Resident Cardiology

Research Interest: Clinical

Mentors: Gavin Hickey MD

Funding Source: N/A

Authors: Casey McQuade MD, Andrew Althouse PhD, Jennifer Prince BS, Alex Sommerfeld MD, Charles Atwood MD, Suresh Mulukutla MD, Gavin Hickey MD

Introduction: Pulmonary hypertension (PH) is common among patients with heart failure (HF) and obstructive sleep apnea (OSA) but little data exists regarding how it influences readmission and mortality.

Methods: We retrospectively examined consecutive patients admitted to the hospital for ADHF between September 2014 and September 2015 and identified patients with OSA. For patients admitted multiple times, only the index admissions were included. The primary endpoints were readmission for heart failure and all-cause readmission. All-cause mortality was a secondary endpoint. The severity of PH was assessed using transthoracic echocardiography. Estimated pulmonary artery systolic pressures (PASP) were individually verified by a single reviewer. Right atrial pressures were estimated using American Society of Echocardiography guidelines on inferior vena cava diameter. Multivariable Cox proportional-hazards regression was used to assess the relationship between PASP and outcomes.

Results: Of 263 patients admitted for ADHF, 62 (24%) had OSA. Patients were 70±7 years old, predominantly white (77%) and male (100%). Thirty-eight (61%) of the OSA patients had PH classified as PASP>36 mmHg; 11 (18%) had severe PH as classified as PASP >60 mmHg. Of the 38 patients with OSA and PH, 17 (44%) had heart failure with preserved ejection fraction, and 21 (55%) had some degree of right ventricular dysfunction as noted on the echocardiogram report. ADHF+OSA patients with PH were more likely to be readmitted within 90 days than those without PH (55% vs 37%). Over a mean follow-up duration of 15 months, ADHF+OSA patients with PH also had significantly increased risk of mortality (HR=2.74, 95% CI 1.01-7.49, p=0.048).

Conclusion: Patients with HF and OSA have a high prevalence of PH and right ventricular dysfunction. The presence of PH as estimated by echocardiography is associated with readmission and mortality in these patients.

28-R Poster: EXPLORATORY STUDY EVALUATING THE FEASIBILITY OF PATIENT REPORTED OUTCOMES ASSESSMENT IN METASTATIC PROSTATE CANCER UNDERGOING NEWER HORMONAL THERAPIES

Presenter: Jimmy Mullally, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Rahul A. Parikh MD

Funding Source: Hillman Cancer

Authors: Jimmy Mullally MD, Christopher D'Avella MD, Rahul A. Parikh MD, Hong Wang PhD, Leonard J. Appleman MD, G van Londen MD

Introduction: Prostate cancer is one of the most frequently diagnosed cancers, accounting for approximately 10% of cancer deaths in men worldwide. In cases of metastatic castrate resistant prostate cancer (mCRPC), clinical trials have established survival benefit with use of abiraterone (ABI) with prednisone or enzalutamide (ENZ). Abiraterone is a CYP 17 inhibitor which blocks androgen synthesis; enzalutamide is an androgen receptor pathway inhibitor. Both agents have been widely utilized since FDA approval in 2011 and 2012 respectively; however, there is still minimal information regarding quality of life (QOL) and patient reported outcome comparisons between ABI and ENZ. Our study is a pilot project that evaluates feasibility of standardized questionnaires for patient reported outcomes assessment.

Methods: Twenty-two patients with mCRPC were initially enrolled in an open label, nonrandomized manner on UPCI 15-119 to receive oral ENZ (n=12) or ABI/prednisone (n=6) per oncologist's discretion. Subjects completed multiple QOL validated questionnaires, including EPIC-26, FACT-P, and FACT-COG, at baseline, 1,2,3,6,9 and 12 months or until progression/change of therapy. Surveys were individually scored and summarized by treatment group using mean, median, range, and standard deviations. We compared scored QOL parameters between the two treatment groups with two-sided, two-sample T test. Rate of change was also compared between the two groups using linear mixed models.

Results: Mean age for ENZ was 71 years and ABI was 66 years. Surveys discontinued prior to one year secondary to disease progression/change of therapy for ENZ was 58%, and ABI was 33%. By month three, 50% of surveys were returned for ENZ and 33% for ABI. Month to month comparisons of QOL parameters, including urinary irritation, incontinence, bowel, sexual, hormonal function, and overall well-being showed no significant differences between treatment groups; Linear mixed models also did not reveal significantly different rates of change. There was significance in Perceived Cognitive Impairment favoring ABI in month 3, however Perceived Cognitive Ability favored Enzalutamide in months 2 and 3. All other data points for cognition were non-significant.

Conclusion: Data from FACT-COG shows discordance in perceived Cognitive Impairment and Abilities between ENZ and ABI in months 2-3. Other QOL domains indicated no difference between the two groups. The study was limited by a significant portion of patients with disease progression/change of therapy. For those on therapy, there were high compliance rates completing surveys. Thus, using questionnaires in this exploratory study demonstrates a feasible way to assess patient outcomes and can be adapted to larger studies.

29-R Poster: Effect of Syringe Type on Retained Radiotracer Fraction and Scan Time: A Quality Improvement Analysis

Presenter: Ricardo Nieves, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Prem Soman MD, PhD

Funding Source: N/A

Authors: Ricardo Nieves MD, Christopher Pray MD, Andrew Althouse PhD, Prem Soman MD, PhD

Introduction: Previous studies have shown that a fraction of the radiotracer dose is retained in the syringe, with the magnitude depending on syringe design. Among syringe design considerations are the construction material, lubricant type and piston design. Tracer retention has a bigger impact on low dose imaging protocols, and thus is relevant in the current era of CZT crystal imaging. It is also likely to affect the low dose rest study more that the high-dose stress study. We tested three different syringes for retained radiotracer fraction and its impact on delivered dose and imaging time.

Methods: The syringes tested in this study included the Duo-Pro SS, Sol-M, and BD. Data were collected over six months with each syringe serving as the delivery system for two contiguous months. Perfusion imaging was performed on a CZT-crystal system using a single day rest/stress protocol with 5 mCi/15 mCi of Tc-99 sestamibi for patients in accordance with a weight base dosing scheme. Image acquisition was programmed to acquire 1.5M counts for rest and 2.5M counts for stress scans within the left ventricle. Thus, the dose delivered could hypothetically affect scan time. The measured/calculated variables included pre-injection radiotracer counts, post-injection radiotracer counts, fraction retained-- calculated as a ratio of pre and post radiotracer counts, and scan time required to collect the predefined number of counts. Data were reported as mean ± standard deviation or frequency where appropriate for the residual radiotracer counts and groups were compared using ANOVA testing.

Results: The greatest radiotracer retained fraction was found in the B-D syringe as compared to Sol-M and Duo-Pro SS for both rest and stress scans. Statistical significance noted in global comparison of the syringes. B-D syringe found to deliver least amount of intended radiotracer in rest scans for patient <199lbs (p-value: <.001). No statistically significant difference in the delivery of intended dose of radiotracer for remaining groups. Rest and stress scan times were not significantly affected by the syringe type that is used in the delivery of radiotracer, even when accounting for patient weight.

Conclusion: Significant differences were found in the retained radiotracer fraction and delivery efficiency among three commercially available syringes for Tc-99m myocardial perfusion imaging. This translated into a significant difference in the % of patients <199lbs who received the intended dose of radiotracer for rest scans only, but not reflected in clinical scan times for count-based solid-state imaging.

30-R Poster: Perception of Isolation Patients and Health Care Workers on Contact Precautions for Multi Drug Resistant Organisms in Health Care Settings

Presenter: Prateeth Pati, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Yassin Mohamed MD

Funding Source: N/A

Authors: Yassin Mohamed MD, Ruhee Jain MPH, Prateeth Pati MBBS, Heather Dixon MS, Ifeoma Okafor MPH, Jamila Ivy MPH, Martha Terry PhD

Introduction: Contact precautions (CP) against multi-drug resistant organisms (MDRO) are an essential aspect of infection control within a hospital setting. CP include personal protective equipment (PPE), such as gloves, masks, and gowns, and hand hygiene (HH). It is a common intervention to place CP patients in isolation to prevent exposure to MDRO. Despite its importance, the use of CP with isolation patients is thought to have a negative impact on patient care. CP can lead to psychological and physical problems for a patient. Health care workers (HCW) may spend less time with a patient in isolation due to the added time and effort needed to follow CP protocol. This study investigates the effects of CP and isolation on patient care satisfaction and HCW perception of CP protocol to delineate the true benefits of CP against MDRO.

Methods: The perceptions on care of isolation patients and HCWs were evaluated quantitatively using self-administered and anonymous surveys. 189 patient surveys and 259 HCW surveys were distributed and analyzed. Data was analyzed using Microsoft Excel.

Results: 76% of the 189 surveyed patients are aware of why they are in isolation, however only 59% of patients were told why they are in isolation by a HCW. Furthermore, 70% of patients would be comfortable with a change in hospital CP policy. 60% of the 259 surveyed HCW responded “yes” when asked if PPE delays their work. 56% of HCW feel that PPE affects the time or frequency that they interact with an isolation patient. Finally, 62% of HCW responded “no” when asked if they evaluate their patient in isolation for a shorter time or less frequently.

Conclusion: Patients’ overall perception of care while in isolation was not affected by CP. However, a large population of patients was not told why they were placed in isolation, which could lead to adverse outcomes in patient satisfaction of care. Furthermore, HCW felt that PPE does delay their work, which could prevent them from giving their full attention to a patient in need. CP protocol for isolation patients is an important intervention to prevent transmission of MDRO, however, it must be improved to improve patient and HCW perception of care.

31-R Poster: Retrospective Case Series of Thirty-Two Patients with Biopsy-Proven Chronic Eosinophilic Pneumonia

Presenter: Arun Rajaratnam, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Faraaz Shah MD

Funding Source: N/A

Authors: Arun Rajaratnam MD, John Tso MD, Faraaz Shah MD

Introduction: Chronic eosinophilic pneumonia (CEP) is a rare disorder with an incidence of less than 1 per 100 thousand that is characterized by pulmonary eosinophilia, migratory opacities on chest imaging, and responsiveness to corticosteroids. CEP is often diagnosed with clinical history and bronchoalveolar lavage or with lung biopsy, with the latter reserved typically for cases of diagnostic uncertainty. In this study, we present the first case series of patients specifically with biopsy-proven CEP.

Methods: Study design was approved by a local institutional review board. Initial screen consisted of natural language case search for "eosinophilic pneumonia" among lung biopsy diagnoses from 1998 to 2016 at a single tertiary-care center in Pittsburgh. Further review of pathology reports and electronic medical record identified cases of CEP after excluding alternate causes of eosinophilic and non-eosinophilic lung disease. Demographics, past medical history, medication use, laboratory and imaging results, and spirometry data prior to lung biopsy were collected for cases of CEP. Data are reported as median [interquartile range].

Results: Initial screen yielded 263 cases of eosinophilic pneumonia and subsequent review identified 32 patients with biopsy-proven CEP. Median age at time of biopsy was 53 years [43, 64]. Patients were primarily Caucasian (91%) with no significant gender predominance(53% female, 47% male). Thirty-eight percent reported ongoing tobacco use. In the week prior to biopsy, 41% received oral corticosteroids and 38% received antibiotics. Peripheral eosinophilia was mild at 3% total blood count [0.2, 8]. Patients had radiographic evidence of involvement of a median of 3 distinct lung lobes [2, 6] prior to biopsy. Interestingly, only 34% reported a pre-existing history of asthma with a low prevalence of obstruction on spirometry (median FEV1/FVC 73% [70, 77], although median FEF (25-75) was reduced at 60% [43, 75].

Conclusion: In our cohort of patients with biopsy-proven CEP, patients were older, reported a lower prevalence of asthma, and had milder obstructive disease than previously reported studies of CEP.

32-R Poster: Right Ventricular Outflow Velocity Time Integral as a Non-Invasive assessment of Right Ventricular maladaptation related to HIV-related Pulmonary Arterial Hypertension

Presenter: Arun Rajaratnam, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Marc Simon MD
Alison Morris MD, MS

Funding Source: NIH

Authors: Arun Rajaratnam MD, Christopher Link MD, Sofiya Rehman MD, Vikas Singh MD, Melissa Saul MS, Rebecca Vanderpool PhD, Mark Gladwin MD, Marc Simon MD, Alison Morris MD, MS

Introduction: Pulmonary Arterial Hypertension (PAH) occurs with increased prevalence in HIV affected individuals. Earlier detection of increased afterload by non-invasive means may improve screening and treatment of HIV-associated PAH. Right Ventricular Outflow Tract Velocity Time Integral (RVOT VTI) is readily available by Doppler echocardiography. Various aspects of the RVOT Doppler signal, such as acceleration time, and mid-systolic notching, have been related to PAH. As RVOT VTI evaluates flow into the pulmonary vasculature throughout the cardiac cycle, we hypothesized that it may be sensitive to early changes in disease.

Methods: Thirty-four patients with HIV who underwent screening 2D echocardiography followed by right heart catheterizations (RHC) were retrospectively studied. Patients were divided into PAH and No PAH based on mean pulmonary artery pressure (MPAP) > 25 mmHg and pulmonary artery wedge pressure (PCWP) < 15 mmHg as assessed by RHC. Echocardiographic data was reviewed by two independent physicians. RVOT VTI was measured by tracing the Doppler velocity signal averaged over a single beat.

Results: MPAP and pulmonary vascular resistance (PVR) was higher in PAH (37.47 ± 11.76 vs 17.94 ±3.61 mmHg ,p <0.01, 4.03 ± 2.56 vs 1.25 ±0.65 Woods units p <0.01, respectively). Right ventricular systolic function as measured by fractional area of change (FAC) was significantly lower (35.98±14.60% vs 46.81±10.51%, p 0.049) but TAPSE was not significantly different (1.96 ±0.68 vs 1.56 ±0.26 cm, p 0.280). RVOT VTI was significantly reduced in patients with PAH (0.15±0.05m vs 0.31±0.22m, P=0.03). There were no significant differences in cardiac output between the groups (5.85±1.65 vs 6.72±2.56 L/min, p 0.53) or mean pulmonary artery acceleration time (142.51 ±90.67 vs 142.5 ±62.22 ms, p 0.79).

Conclusion: In patients with HIV, RVOT VTI may be a sensitive non-invasive maker of afterload and may be an additional useful parameter when screening high-risk patients' for PAH.

33-R Poster: Gender Differences in Myocardial Histology and Ventricular Remodeling in Recent Onset Cardiomyopathy

Presenter: Anjali Rao, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Dennis McNamara MD

Funding Source: NHLBI contracts

Authors: Anjali Rao MD

Introduction: For subjects with recent onset non-ischemic cardiomyopathy (ROCM), the mechanism through which gender influences myocardial recovery remains unknown. We examined the interaction of gender, ventricular remodeling and myocardial histology for subjects in the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) multicenter investigations.

Methods: Endomyocardial biopsies were available on 104 subjects including 62 patients in the IMAC 1 and 42 subjects from IMAC2. All subjects had ROCM and were within six months of symptoms onset with an LVEF<0.40 at time of entry. Histopathology was noted based on clinical reports by the local pathologist, and the presence or absence of cellular inflammation, fibrosis, and myocyte hypertrophy noted. For assessment of left ventricular remodeling, left ventricular end diastolic diameter (LVEDD) was measured by transthoracic echo, and the histology of subjects with minimal remodeling (LVEDD<6.0cm) compared to those with moderate (6.1 to 7.0) or severe remodeling (>7.0 cm).

Results: For the overall cohort (62M/42F) the mean age was 42+13, duration of symptoms 2.0+1.6 months, LVEF 0.25+0.08, and there were no significant differences by gender. Women had a higher overall NYHA class (% I/II/ III/IV for W=5/38/36/21, M=14/47/26/13, p=0.04). Comparison of myocardial histology revealed significantly more evidence of fibrosis in men (M=66%/F=45%, p=0.03), with trends towards more hypertrophy (M=56%/F=40%, p=0.11) and less myocarditis (M=11%/F=24%, p=0.09). Fibrosis was more evident with greater remodeling (% fibrosis for mild/moderate/severe remodeling= 41/74/70, p=0.01) while myocarditis was more evident with less remodeling (% myocarditis mild/mod/ severe = 26/14/0, p=0.004). The mean LVEDD was significantly greater in men (6.8+1.1 vs 5.9+1.0 cm, p<0.001), as was the percentage of men with greater remodeling (%mild/mod/severe M=24/39/37, F=60/30/10, p<0.001). Women demonstrated a significantly higher LVEF at 6 months (M=0.37+0.15 vs F=0.44+0.1g. p=0.03)

Conclusion: In a cohort of 104 subjects from the IMAC investigation with endomyocardial biopsies, women had less fibrosis, less ventricular remodeling and more myocardial recovery. Gender differences in myocyte response to injury and left ventricular remodeling may result in better recovery in women with ROCM.

34-R Poster: A new tool to assess muscle strength in polymyositis and dermatomyositis: Hand-held dynamometry

Presenter: Didem Saygin, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Rohit Aggarwal MD

Funding Source: N/A

Authors: Didem Saygin MD, Chester V Oddis MD, Siamak Moghadam-Kia MD, Courtney Ward , Diane Koontz , Rohit Aggarwal MD

Introduction: Idiopathic inflammatory myopathies (IIM) is a group of systemic autoimmune diseases characterized by proximal muscle weakness. Muscle strength, a key outcome measures in IIM, is assessed by using manual muscle test (MMT) in clinical practice and trials. Several studies have shown that patient's weight and examiner's experience and strength may bias muscle strength with MMT. Therefore, more objective tools are required to quantify muscle strength to assess treatment responses in IIM. Hand-held dynamometry (HHD) is a quantitative, inexpensive, compact device with reported validity and reliability in several neuromuscular diseases. In this study, we aimed to assess reliability, validity and responsiveness of HHD in IIM in the hands of rheumatologists.

Methods: IIM patients were seen at baseline, 3 and 6 months. Each visit consisted of strength assessment using HHD (Micro FET2, Hoggan Health Industries, UT) as well as 6 core set measures (CSMs) and 3 functional tests [six-minute walk distance (6MWD), timed up-and-go (TUG) and sit-to-stand (STS) tests). These CSMs include MMT, creatine kinase (CK), patient and physician global disease activity, Extra-muscular disease activity and Health Assessment Questionnaire (HAQ). HHD was repeated three times for bilateral deltoid and iliopsoas muscles and both average and max values in Ib were recorded. Clinical response was assessed with total improvement score (TIS, 0-100 scale), ACR/EULAR myositis response criteria and physician-reported responses. Spearman correlation was used.

Results: Thirty IIM patients [12 polymyositis; 2 dermatomyositis; 16 anti-synthetase syndrome] were enrolled so far with mean age of 51.6 (±14.7), 60% female and 94% Caucasian. Mean strength (in Ibs) by HHD showed strong test-retest reliability (r: 0.96) and excellent internal consistency (Cronbach-a: 0.95). HHD correlated strongly with MMT (r:0.75, $p<0.0001$), physician muscle and global disease activity (r:-0.8 and -0.6, $p<0.001$), HAQ (r:-0.7, $p<0.0001$), STS (r:0.6, $p<0.0001$), TUG (r:-0.5, $p=0.002$) and 6MWD distance (r:0.6, $p=0.001$), and moderately with patient global (r:-0.4, $p=0.04$), but did not correlate with CK, cutaneous, pulmonary and extra-muscular disease activity as clinically expected. The relative percent change in HHD correlated with TIS (r:-0.6, $p=0.01$), demonstrating responsiveness. HHD improved significantly in physician-reported improvement groups. MMT and HHD showed similar correlations with the conventional outcome measures, however, effect size and standardized response mean of HHD was better than MMT (0.56 vs 0.20 vs; 0.33 vs 0.20).

Conclusion: To our knowledge, this is the first study assessing the use of HHD in IIM. HHD demonstrates strong test-retest reliability, construct validity and responsiveness in a large cohort of IIM patients.

36-R Poster: 'pre-COPD'-A Clinical Entity

Presenter: Prerna Sharma, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Noor Khan MD

Funding Source: N/A

Authors: Prerna Sharma MD

Introduction: Chronic Obstructive Pulmonary Disease is a chronic debilitating disease which affects more than 5% population in the United States of America. According to the current guidelines, diagnosis of COPD requires FEV1/FVC ratio of less than 0.70. Spirometry is the single established means of diagnosis of this morbid disease. However, there exists an unknown level of disparity between the number of patients labelled as COPD and those who, in actuality, have documented spirometry denoting obstructive disease with airflow limitation.

Methods: Retrospective chart review of medicine clinic patients with a diagnosis of COPD from Epic database from year 2013-2016 was performed. Obstructive defect was defined as FEV1/FVC ratio <0.701.

Results: Patients with a diagnosis of COPD were identified (n=208). Patients with less than three visits were excluded from the study (34). Data review of 174-patients revealed that 73 out of 174 (41.9%) had either normal PFTs (22) or no PFTs (51). Patients without documented obstructive defect were analysed further and it showed that most of these patients were getting treated (66/73, 90%). Eight patients were using short-acting bronchodilators (SABA) and 58-patients had a combination of SABA with either inhaled corticosteroid (ICS) or anti-cholinergic (AC). Eighty-four percent of patients who were being treated without having an obstructive defect were smokers (62/66). Out of those who were being treated, 29 patients (29/66, 43%) had CT-Chest with evidence of emphysema. This study revealed that 35% (62/174) patients were diagnosed with COPD on the basis of smoking history and symptoms rather than PFTs.

Conclusion: Our study demonstrates a growing trend of COPD diagnosis and treatment without PFT diagnosis. Patients without obstructive defect are sometimes labelled and treated as COPD as they have radiographic evidence of emphysema. Without PFTs, restrictive lung diseases could be underdiagnosed and this would hamper prognostication & treatment. There are smoking-associated restrictive diseases like desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis, that could potentially go undiagnosed if smokers are empirically treated. Moreover, FEV1 is used for staging of disease which not only guides treatment, but also is a major criteria for referral for lung transplantation in late-stage disease refractory to treatment. In conclusion, treating early respiratory symptoms temporarily with SABAs in smokers is acceptable, however appropriate diagnosis and staging with PFTs is imperative before escalating therapy. Recent studies show there might be a subset of patients with preserved pulmonary function who have symptoms of COPD. The scope for defining a potential 'pre-COPD' entity merits further research.

37-R Poster: Epidemiology of Tuberculosis

Presenter: Prerna Sharma, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Mohamed Yassin MD, PhD

Funding Source: N/A

Authors: Prerna Sharma MD, Brandon Smith MD, Kylee Dawson MD

Introduction: Center of Disease Control estimated the national incidence rate of tuberculosis in 2016 was 2.9 cases per 100,000 persons which represents a 3.6% decrease from 2015. Sixty-eight percent of reported TB cases in the United States were in non-US born persons; additional risk factors reported were diabetes, alcohol abuse, HIV, etc. We performed a retrospective observational study to identify risk factors of tuberculosis in our population.

Methods: This study was approved by the Quality Improvement Committee at University of Pittsburgh Medical Center. Retrospective chart review of patients diagnosed with tuberculosis from 2012-2016 was performed. Patients were further classified based on demographic variables and risk factors like high-risk travel, history of HIV or malignancy, immunocompromised status, etc.

Results: Chart review of 53-patients with tuberculosis revealed that the mean age of patients was 51, with 35-males and 18-females. There were 20 US-born (17-white and 3-black) and 33 foreign-born patients. Sixty-two percent of the patients were foreign-born. The average years since immigration was 8.5 years; India and Nepal were the most commonly identified countries followed by China, Indonesia, Mexico and Zambia. Most of the patients had pulmonary tuberculosis (69.8%) and lymph node was the second most common organ involved (9%). It is important to note that none of our patients had a history of incarceration or homelessness. Subset analysis of the 20 US-born patients were performed to identify risk factors in this population (table 3). Out of US-born patients, 17 (32.1%) were white and 3 (5.7%) were black. Further analysis of 20 US-born patients showed that 11-patients had underlying factors like high-risk travel, HIV, immunosuppressive medications, or chronic steroids. The rest of the patients (9 out of 20) did not have any documented risk factor.

Conclusion: This study signifies the importance of ascertaining demographic characteristics of tuberculosis patients in the local population. It is important to know the risk factors and population based prevalence to screen appropriately. Due to a low positive predictive value of tuberculosis screening in low-risk population2, identifying high-risk population for testing is key and the population characteristics can vary in different regions. Furthermore, it is crucial to recognize latent TB and treat it at an early stage to prevent reactivation disease. Screening in high-risk groups especially foreign-born individuals and household contacts is essential to treat LTBI in a timely manner.

38-R Poster: AUTOIMMUNE PROGESTERONE DERMATITITIS – DIAGNOSTIC AND TREATMENT CHALLENGES

Presenter: Divya Sistla, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Reena Karnik MD
Sann Mon MD

Funding Source: N/A

Authors: Divya Sistla MD, Preethi Polavarapu MD, Munira Abbasi MD

Introduction: Autoimmune progesterone dermatitis is a rare autoimmune hypersensitivity reaction- affecting women in their reproductive age due to fluctuation of endogenous progesterone during woman's menstrual cycle. The diagnosis and treatment of this condition can be challenging.

Methods: CASE REPORT A 35-year-old woman with primary hypothyroidism presented with cyclical, pruritic, generalized maculopapular rash noted to occur few days prior to the commencement of menstrual cycles. The initial symptoms started four years ago with progressively increasing frequency as well as generalized distribution of the rash. In last 4 years, she had these symptoms intermittently during her pregnancies as well. There was transient improvement with short course of steroids. Allergy testing eliminated possible food and drug allergies. Skin biopsy was consistent with folliculitis. Finally, Autoimmune progesterone dermatitis was diagnosed with skin prick Progesterone sensitivity test. Patient was treated with oral contraceptive pills to suppress ovulation along with prednisone taper therapy with significant improvement in her symptoms.

Results: - Autoimmune progesterone dermatitis was diagnosed with skin prick Progesterone sensitivity test. Patient was treated with oral contraceptive pills to suppress ovulation along with prednisone taper therapy with significant improvement in her symptoms.

Conclusion: Autoimmune progesterone dermatitis can present with a spectrum of clinical presentation depending on levels of progesterone. The pathophysiology is unclear at this point. Possible mechanisms are sensitization of immune cells by exogenous exposure of progesterone or by cross reactivity to other steroids. Presence of progesterone receptors on keratinocytes was observed in some studies. Main treatment is to suppress ovulation, thereby blocking the production of progesterone, with hormonal contraception. Conjugated estrogen, GnRH and desensitization with progesterone have been reportedly lead to complete remission. Salpingo-oophorectomy is a definitive treatment. We suggest considering autoimmune progesterone dermatitis as a differential diagnosis for women presenting with dermatological manifestations associated with menstruation or pregnancy.

REFERENCES. Nguyen, A. Razzaque AhmedAutoimmune progesterone dermatitis: update and insightsAutoimmun Rev, 15 (2016), pp. 191-197

39-R Poster: Endogenous Hyperinsulinemic Hypoglycemia: Diagnostic Challenges and Treatment Dilemma

Presenter: Divya Sistla, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Reena Karnik MD
Sann Mon MD

Funding Source: N/A

Authors: Divya Sistla MBBS, Jack El-Sawda MD, Preethi Polavarapu MD, Sann Mon MD, MPH, Ibrahim Ghobrial MD, FACP, MRCP

Introduction: Endogenous-hyperinsulinemic hypoglycemia, characterized by symptomatic hypoglycemia and inappropriate hyperinsulinemia is most commonly due to insulinoma. Nesidioblastosis and insulin autoimmunity are less frequently reported. We report the diagnostic and treatment challenges in a patient with endogenous hyperinsulinemic-hypoglycemia.

Methods: Case Report: A 50-year-old female with history of congenital hypogonadotropic-hypogonadism, growth hormone deficiency, and congenital gut malrotation was diagnosed with endogenous hyperinsulinemia following frequent hypoglycemic episodes and a positive 72-hour fasting test. Factitious hypoglycemia, insulin autoimmune syndrome, adrenal insufficiency and thyroid disorders were ruled out. Multiple MRI, pancreatic-protocol-CT, and endoscopic ultrasound studies failed to localize any lesions. There was a four-fold rise in the hepatic venous insulin concentration following selective intra-arterial calcium injection into the superior mesenteric artery. Due to congenital variant anatomy of pancreas, surgical treatment was not advised. Pharmacological therapy with somatostatin analog, diazoxide, and growth hormone were deferred due to her comorbidities. Severe hypoglycemic episodes were reduced with diet modification and steroids therapy. After 4 years she developed new onset hyperglycemia. Wide fluctuation in serum glucose concentrations (30 to 290 mg/dl) was observed during hospitalization at supervised unit without use of additional agents.|

Results: - Insulin resistance and hyperglycemia are rare in patients with Endogenous hyperinsulinemic hypoglycemia. This patient was managed by dietary interventions.

Conclusion: To the best of our knowledge, insulin resistance and significant hyperglycemia have not yet been reported in patients with proven endogenous hyperinsulinemic hypoglycemia. However, animal studies demonstrated that prolonged exposure to exogenous insulin leads to insulin resistance, whether such similar hypothesis can apply to our patient is yet to be studied. We also highlight the limitations and challenges of localization studies in patients with congenital pancreatic anatomical variants.

40-R Poster: Successful treatment of bisphosphonate refractory hypercalcemia with denosumab in a patient who presented with possible immune mediated calcinosis cutis

Presenter: Divya Sistla, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Reena Karnik MD
Sann Mon MD

Funding Source: N/A

Authors: Divya Sistla MD, Preethi Polavarapu MD, Munira Abbasi MD

Introduction: The efficacy and safety of Denosumab in non-malignancy related hypercalcemia is uncertain. We describe a rare case of hypercalcemia associated with calcinosis cutis who was successfully treated with Denosumab.

Methods: CLINICAL CASE A 67-Year-old male long-standing history of Multiple sclerosis on chronic steroids, Calcium and vitamin D supplements presented with lower extremity cellulitis involving inner thigh and buttock region with radiographic evidence of extensive calcification of bilateral buttock, left pelvis, perineum and thigh. Excision biopsy of the left groin mass showed dense superficialperivascular lymph histiocytic infiltrate with numerous eosinophils along with fibrous and fatty tissue calcification.Prior to admission, he had normal calcium level at baseline. On presentation, he had acute hypercalcemia with corrected Calcium of 12 mg/dl (8.5-10.1 mg/dl), ionized Calcium of 6.1 mg/dl (4.8-5.6 mg/dl). Further lab work revealed Non-PTH dependent hypercalcemia, with suppressed PTH, normal phosphate, 25 OH Vitamin D, 1,25 OH Vitamin D, PHTrP, SPEP and UPEP levels. No evidence of malignancy based on further imaging studies.He was treated for presumed immune mediated dystrophic calcinosis with minocycline. Due to persistent hypercalcemia despite adequate IV hydration and discontinuation of calcium supplements, he received IV bisphosphonates Zoledronic acid with transient improvement in Ca levels but readmitted with severe hypercalcemia a month later. He was then treated with IV Denusomab. This was followed by a steadier decline in both corrected and ionized Calcium levels with total corrected Calcium of 9.3 mg/dl and Ionized Calcium of 5.3 mg/dl. This remained within normal range even after one year of treatment.

Results: - Calcium levels remained within normal range even after one year of treatment in this patient.

Conclusion: Denosumab is a monoclonal antibody that specifically binds to human receptor activator of nuclear factor kappa-B ligand RANKL, blocks the binding of RANKL to RANK and thereby reduces the function of osteoclasts, which decreases bone resorption. It is approved for the treatment of osteoporosis, bone metastasis from solid tumor and Giant cell tumor of the bone and hypercalcemia of malignancy. We report a rare case of non-malignancy related hypercalcemia refractory to bisphosphonate therapy treated successfully with Denosumab therapy.

43-R Poster: Evaluating Disease Severity and Location of Death on Palliative Care Referral in Patients with Idiopathic Pulmonary Fibrosis

Presenter: Richard Zou, Resident
Other

Research Interest: Clinical

Mentors: Daniel Kass MD
Kathleen Lindell PhD

Funding Source: N/A

Authors: Richard Zou MD, Seyed Nouraie MD, Melissa Saul MS, Xiaoping Chen MS, Kevin Gibson MD, Daniel Kass MD, Kathleen Lindell PhD

Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease with an unpredictable course and a median survival of 3 to 4 years. This timeline challenges providers to approach diagnosis, oxygen therapy, rehabilitation, transplantation and end-of-life discussions in limited encounters. We previously reported that only 13.7% of IPF decedents at our specialty center received formal palliative care (PC) referral, the majority being within 30 days of death.1 There currently exists no widely accepted algorithm for determining when a patient should be referred. We hypothesize that IPF patients who receive PC have more severe baseline disease and lower rates of in-hospital death.

Methods: This is a follow-up to our previous study. Patient data were retrospectively extracted from the healthcare system repository of a single university for all IPF patients seen for the first time between January 2013 and December 2016 (n=180). Exclusion criteria included transplant recipients, underlying rheumatologic disease and unclear diagnoses.

Results: Thirty (39.0%) IPF decedents and 38 (21.1%) total IPF patients received PC referral. PC patients were older (73 years v. 70 years, p=0.004) and had more severe baseline disease, as measured by percent predicted forced vital capacity (54% v. 69%, p<0.001), percent predicted diffusing capacity of lungs for carbon monoxide (38% v. 50%, p=0.002) and Gender, Age and Physiology (GAP) Index (5 v. 4, p=0.013). PC patients trended toward higher oxygen requirement at initial visit (1.4L v. 0.9L), more outpatient visits (7.8 v. 6.5), shorter distance from our specialty center (23 miles v. 39 miles), less in-hospital deaths (50% v. 72%) and more in-home and hospice deaths (50% v. 25%).

Conclusion: Due to the unpredictable course of IPF, it is routine clinical practice to refer IPF patients who may be eligible for lung transplantation early in the treatment course. No such practice exists for PC referral. We found that IPF patients who were referred to PC were older and had more severe baseline disease. There was a trend toward more deaths at home and fewer deaths in the hospital. Borderline associations of distance and number of visits with the frequency of PC referral suggest that providers may feel more comfortable introducing PC and end-of-life discussions to patients who had more frequent follow-up. Further data are needed to develop guidelines for the timing of PC referral.

44-R Poster: Markers of Diastolic Dysfunction Correlate with Filling Pressures on Right Heart Catheterization During Leg Raise in a Mixed Population

Presenter: Richard Zou, Resident
Other

Research Interest: Clinical

Mentors: Michael Risbano MD

Funding Source: N/A

Authors: Richard Zou MD, Ryan Belecanech MD, Aman Gupta MD, Joao Cavalcante MD, Marc Simon MD, William Wallace BS, Seyed Nouraie MD, Stephen Chan MD, Michael Risbano MD

Introduction: Early stages of diastolic dysfunction often present with non-specific clinical features, including exertional dyspnea and decreased exercise tolerance. Doppler echocardiography is widely used in the initial assessment of cardiac etiologies, although right heart catheterization (RHC) may be necessary for evaluation of non-cardiac etiologies.Three markers of diastolic dysfunction on echocardiography are used in clinical practice: left atrial volume index (LAVI), mitral early diastolic/average early diastolic e' velocity ratio (E/e') and mitral early diastolic/atrial diastolic velocity ratio (E/A). There exist positive correlations between these markers and filling pressures during peak exercise on RHC in patients with diastolic dysfunction.Graded exertion and leg raise, which serves as a modified form of fluid challenge, are associated with higher filling pressures in healthy adults >50 years of age. Therefore, it is reasonable to assume that leg-raise may alter markers of diastolic dysfunction in this population. However, it is unclear if these markers can be used to predict hemodynamics from exercise RHC (exRHC). We hypothesize that LAVI, E/e' and E/A correlate with filling pressures from supine to legs-up on exRHC in patients >50 years of age.

Methods: Patient data were retrospectively extracted from our healthcare system repository between January 2012 and May 2017. We evaluated exRHC studies in patients referred for exertional dyspnea who had resting echocardiography within 6 months. This cohort included patients with normal (n=37) and elevated (n=11) resting hemodynamics. Normal resting hemodynamics were defined as mean pulmonary artery pressure (mPAP) <25mmHg and pulmonary capillary wedge pressure (PCWP) <15mmHg. Patients were stratified into age =50 and >50.

Results: The change from supine to legs-up in mPAP was greater in patients >50 years of age compared to those =50 (p=0.004) and the change in PCWP trended towards greater (p=0.09) for the same age group comparisons. In patients >50 years of age, supine to legs-up demonstrated positive correlations between mPAP and E/e' (p=0.005, r=0.57), PCWP and E/e' (p=0.03, r=0.46) and mPAP and E/A (p=0.049, r=0.41).

Conclusion: In our mixed referral population, patients >50 years of age exhibited elevated right- and left-sided filling pressures, as measured by mPAP and PCWP, with fluid augmentation from supine to legs-up. This correlated with elevated markers of diastolic dysfunction, as measured by E/e' and E/A. This directionality suggests that legs-up positioning on echocardiography may be useful in estimations of filling pressures on exRHC. Prospective studies with resting echocardiography immediately prior to exRHC are needed to further characterize this correlation.

45-R Poster: Durability of Glycemic Control in a Diabetes Education Insurer-based Intervention in Primary Care

Presenter: Margaret Zupa, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Linda Siminerio RN, PhD, CDE

Funding Source: N/A

Authors: Margaret Zupa MD, VIncent Arena PhD, Margaret Thearle RN, CDE, Patricia Johnson RN, CDE, Linda Siminierio RN, PhD, CDE

Introduction: Models that address the needs of patients with diabetes mellitus (DM) in primary care (PC) are needed, as health systems move to value-based care. To support DM patients at high risk, an insurer-based program that paired nurse practice care managers (PCM) with certified diabetes educators (CDE) was designed to improve outcomes for DM patients with complex needs. The objective of this study was to assess the durability of glycemic improvement after a diabetes self-management education and support (DSMES) intervention within a model that relies on a PCM to identify, refer and provide ongoing support to complex patients who received a CDE intervention in primary care clinic.

Methods: Two CDEs, serving rural and urban areas, were introduced as active team members into PC practices. CDEs provided DM training to PCMs, who then proactively identified and referred patients under clear criteria (DM-related ER visits or hospitalizations, HbA1c >9, reported barriers to care) for DSMES in collaboration with PC provider and PCM. Post-CDE intervention, the PCM was available for follow-up and ongoing support. HbA1c was monitored every 3 months after intervention and compared to baseline value to assess durability of improvement in glycemic control.

Results: Of 222 patients referred, 108 had 6 and 80 and 12-month follow-up data for analysis. Patients were 52% female; mean age 57 (SD 13.43). Mean HbA1c decreased from 9.6 to 8.4 over 6 months and 9.2 to 8.1 over 12 months ($p<0.001$). Improvement in glycemic control was maintained for at least 1 year after intervention. There was no significant change in BMI over this time.

Conclusion: A model where CDEs parter with PCMs, who identify, refer and provide ongoing support to patients post-CDE delivered DSMES, is an effective and feasible intervention to improve and sustain DM outcomes in PC. This collaborative approach expands opportunities to meet complex needs of DM patients and can contribute to the ability of practices and health plans to provide an effective intervention that produces sustainable improvements through ongoing patient support.

46-R Poster: Incorporating Advance Care Planning into HIV Primary Care: A Quality Improvement Initiative

Presenter: Michelle Fleshner, Resident
Epidemiology
General Internal Medicine

Research Interest: Health Services/Clinical

Mentors: Peter Veldkamp MD

Funding Source: N/A

Authors: Michelle Fleshner MD, Linda Despines , Julie Childers MD, Peter Veldkamp MD

Introduction: Little is known about the rates of advance care planning (ACP) among patients living with HIV, yet these patients have significant non-medical comorbidities and are likely to benefit from ACP. The objective of this program is to increase the proportion of patients seen at an HIV clinic with the following elements of ACP completed: advance care conversation held, surrogate decision maker identified, and follow-up plan for ACP established.

Methods: The intervention was performed in a university-based HIV primary care clinic in Pittsburgh. An exploratory meeting was conducted to identify barriers and engage interest. The intervention consisted of a brief training led by a palliative care physician who provided simple communication skills and instruction on documenting ACP to primary HIV physicians. A framework for documentation of ACP into a new "Advance Directive" tab in the local Electronic Medical Record (EMR) was provided. Emphasis was placed on documentation of surrogate decision maker, presence of an advance directive, and follow-up plan. Internal medicine residents and fellows who rotated through the clinic were similarly educated by a HIV primary care provider at the beginning of their rotation. Providers will be emailed monthly with their progress. Data were queried from the Advance Directive tab at baseline and monthly.

Results: EMR database was queried between 8/1/17 and 11/22/17 during which 1039 patients were seen. In the first month post-intervention, 345 patients were seen. Findings were significant for an increase in documented decision maker from 0.9 % pre-intervention to 23.5% post-intervention ($p<0.0001$). Documentation of the presence of an advance directive increased from 1.1% to 24.3% post-intervention ($p<0.0001$). Finally, the percentage of patients with an ACP follow-up plan increased from 0.8% pre-intervention to 18.8% post-intervention ($p<0.0001$). Further findings will be discussed as the project progresses.

Conclusion: By providing a brief training to primary HIV providers on discussing and documenting ACP with their patients, we have significantly increased the proportion of patients with a documented surrogate decision maker, advance directive conversation, and ACP follow-up plan. We suspect that as providers continue to familiarize themselves with this system these numbers will increase further. Crucial in this project is the involvement of trainees, both residents and fellows, who often have more time with patients per visit. The most prominent barrier to this project was documentation in the EMR, highlighting the need for a more efficient and user-friendly method of documenting and retrieving ACP in any EMR.

47-R Poster: Cigarette Smoking and its Impact on Biologic Effectiveness in Crohn's Disease: A Cross-Sectional Study

Presenter: Phillip Hamilton, Resident
Epidemiology
General Internal Medicine

Research Interest: Health Services/Clinical

Mentors: David Binion MD

Funding Source: N/A

Authors: Phillip Hamilton MD, Brittney Keller-Hamilton MPH, Claudia Ramos-Rivers MD, David Binion MD

Introduction: Cigarette smoking is an established, powerful environmental factor that worsens the disease trajectory for patients with Crohn's disease. However, few studies have examined the relationship between smoking and the effectiveness of biologic therapy for Crohn's disease management. This is potentially important for counseling patients and initiation of biologic therapy. The purpose of this study was to evaluate whether smoking status modified the effectiveness of biologic therapy for patients with Crohn's disease.

Methods: This cross-sectional study used an electronic health record (EHR) registry derived from 1851 patients with inflammatory bowel disease receiving care at UPMC. We evaluated the effects of 2016 smoking status (current, former, or never) and use of infliximab, certolizumab, or adalimumab (i.e., biologics) on two outcome variables assessed in 2016: number of hospital admissions (0, 1, or 2+) and number of emergency department (ED) visits (0, 1, or 2+) using multinomial logistic regression. Next, we added product interaction terms to determine whether smoking status modified the effect of biologics on hospital admissions or ED visits. Patients without complete data for smoking status, biologic use, hospital admissions, and ED visits were excluded from analyses, as were subjects who initiated use of biologics in 2016.

Results: There were 754 patients with complete data for this study. Current smokers represented 14.2% of patients (N=107), 224 were former smokers (29.7%), and 423 were never smokers (56.1%). One-third of patients (N=255) used biologics. Main effects models identified no significant effect of biologics on odds of hospitalization or ED visits. For hospital admissions, current smokers had higher odds of 1 vs. 0 admissions (odds ratio [OR] = 1.99; 95% confidence interval [CI]: 1.02, 3.90) and 2+ vs. 0 admissions (OR = 2.59; 95% CI: 1.34, 5.00) compared to never smokers. For ED visits, current smokers had higher odds of 2+ vs. 0 visits compared to never smokers (OR = 3.30; 95% CI: 1.87, 5.82). The interaction models identified no modification by smoking status on biologic effectiveness on these variables.

Conclusion: Our cross-sectional study of patients with Crohn's disease supports prior studies that found a relationship between cigarette smoking and increased hospitalization. We did not find a statistically significant effect of the efficacy of biologic therapy on these factors, nor did we find that smoking modified the efficacy of biologic therapy. Future research could focus on longitudinal data analysis, to provide more powerful analysis of the interaction between cigarette smoking and biologic efficacy.

48-R Poster: Income is associated with atrial fibrillation outcomes: a nationwide health claims analysis

Presenter: Anna LaRosa, Resident
Epidemiology
Cardiology

Research Interest: Health Services/Clinical

Mentors: Jared Magnani MD

Funding Source: N/A

Authors: Anna LaRosa MD, Jared Magnani MD, Alvaro Alonso MD, J'Neka Claxton MPH

Introduction: Atrial fibrillation (AF) is associated with social and medical morbidity. Social determinants of health – race, income, education, and neighborhood – increase adversity in cardiovascular and non-cardiovascular conditions, but investigation in AF remains limited. We examined the associations of income and outcomes specifically related to AF (heart failure, myocardial infarction, and stroke) in a nationwide health claims database. We hypothesized that lower income would be associated with increased risk of adverse outcomes.

Methods: We analyzed administrative claims for the period 2009-2015 from Optum Cliniformatics, an administrative database of privately insured and Medicare Advantage enrollees. We identified patients with AF as having 1 inpatient or 2 outpatient claims for AF. We collected age, sex, race and clinical covariates (hypertension, diabetes, prior coronary disease, prior heart failure, prior stroke, chronic obstructive pulmonary disease, and chronic kidney disease), and categorized annual income quintiles (<$40k; $40-59k; $60-74k; $75-99k; and =$100k). We examined incident event rates and determined risk of adverse outcomes in multivariable-adjusted Cox proportional hazards models using the highest income quintile as our referent.

Results: Our analytic dataset included 336,736 individuals (age 72.7±11.9, 44.5% women, race: 82.6% white, 8.4% black, 7.0% Hispanic, and 2.0% Asian) with AF. We identified demographic differences across income quintile: a greater proportion of individuals of black race or Hispanic ethnicity belonged to the lowest income quintile, as did those with lower education (< high school). In contrast a greater proportion of individuals with white race and higher education (=bachelor degree) were in the highest income quintile. Median follow up time was 1.46(IQR 0.58,2.95) years. The hazard ratio [HR] for heart failure was 1.41 (95% confidence interval [CI], 1.28, 1.55), when comparing the lowest to highest income quintile and adjusting for age, sex and race. This risk was attenuated to HR 1.17 (95% CI, 1.05, 1.30) in the comprehensive multivariable-adjusted model. The HR for myocardial infarctions was 1.35 (95% CI, 1.14, 1.60) when comparing the lowest to highest income quintile and adjusting for age, sex, and race. The association was attenuated (HR 1.18, 95% CI, 0.98, 1.41) in the fully adjusted multivariable model. We did not observe associations between income and stroke.

Conclusion: We identified strong associations between income and adverse outcomes in a large administrative claims database. Our results underscore the relevance and significant contributions of social determinants to adverse outcomes and AF.

50-R Poster: Expanding access to colorectal cancer screening for uninsured patients in western Pennsylvania: A two-year collaborative free clinic and academic medical center model experience

Presenter: Christopher Marino, Resident
Epidemiology
General Internal Medicine

Research Interest: Health Services/Clinical

Mentors: Maggie Benson MD, MS

Funding Source: N/A

Authors: Christopher Marino MD, John Hayes BS, Lauren Gochenaur BS, Linda Robertson RN, MSN, DrPH, Adam Slivka MD, PhD, Maggie Benson MD, MS

Introduction: Uninsured patients face myriad barriers to accessing colorectal cancer (CRC) screening and have been found to have decreased rates of CRC screening and more advanced disease at diagnosis. While the use of fecal immunohistochemical test (FIT) screening and patient navigation to increase access to CRC screening has been described in safety-net health systems, there remains limited data on the role of free clinics in CRC screening. The Birmingham Free Clinic (BFC) is a Pittsburgh-area free clinic that provides primary care services to approximately 1200 uninsured patients annually. The BFC CRC screening program began in 2015 as a collaborative effort between the BFC, UPMC Hillman Cancer Center and UPMC Digestive Disorders Center to provide FIT-based screening and colonoscopies to uninsured patients at no cost. Patients with positive FIT results are offered a colonoscopy with support of a community outreach nurse, and patients found to have disease requiring further treatment are provided health insurance navigation to obtain insurance coverage or emergency medical assistance.

Methods: As part of a quality improvement initiative to improve CRC screening completion rates, a retrospective medical record review was performed for all patients offered CRC screening at BFC from December 2015 to November 2017. Descriptive statistics were used to analyze demographic data, FIT results, endoscopic findings, and screening completion rates.

Results: A total of 122 patients (age 57.6 ± 6.8, 50% female) were offered FIT testing in the 24-month period. Fifty-two (43%) patients completed FIT testing and 12 (23%) of the FIT results were positive. All patients with positive FIT results were referred to colonoscopy. Seven of these patients received colonoscopy, four of which were significant for adenomatous polyps. Of the remaining five patients with positive FIT results, three are awaiting colonoscopy and two moved. Furthermore, three additional patients with high-risk clinical history received colonoscopies without prior FIT screening, including one with endometriosis of the colon requiring resection.

Conclusion: Limited access to CRC screening remains a significant barrier to care for uninsured patients. Our results indicate that this is a high-risk population with an elevated rate of positive FIT results and findings on colonoscopy requiring close follow up. A free clinic and academic medical center partnership model can be used in locations with limited safety-net care to expand CRC screening access to uninsured patients. While screening completion rates among BFC patients were suboptimal, we have begun a quality improvement project to enhance patient navigation services and improve completion rates.

51-R Poster: Bridging the Divide: A Quality Improvement Project on Antipsychotics with Medical Housestaff on Transfer from the Medical ICU to Floors

Presenter: Katherine Chin, Resident
General Internal Medicine

Research Interest: Medical Education

Mentors: Bryan McVerry MD

Funding Source: N/A

Authors: Katherine Chin MD, Mikhaila Rice , Pamela Smithburger PharmD, Bryan McVerry MD

Introduction: The transfer between the ICU and the medical floors is a time when the medical needs of the patient have deescalated. The use of antipsychotics started in the ICU is of particular interest due to the high frequency of use of these medications and evidence of short term and long term adverse effects. In the teaching hospital, discussion between providers for indications for initiation of medications is frequent, but current evidence suggests that discussion of deprescribing is less frequent.

Methods: We retrospectively identified patients in the UPMC Presbyterian medical ICU (MICU) who received antipsychotic medications via the local pharmacy database during two 3-month periods (May-Oct 2018). Patients were excluded if they had record of outpatient antipsychotic use or if they stayed in the MICU for <48 hr. During the second 3 month time period, we implemented a brief education program for each medical ICU housestaff team regarding practice recommendations for use of antipsychotics in the treatment of delirium with a reference tool for bedside use. We assessed frequency of appropriate use and clear documentation of indications for use on ICU to floor transfer via chart review of physician progress notes.

Results: Sixty-six (66) and 47 patients received antipsychotics for treatment of delirium in the pre- and post-intervention periods respectively. There was no significant difference in the proportion of patients (pre v. post intervention, respectively) who had active antipsychotic orders at transfer out of the MICU (39% v. 45%, p=0.8) or at hospital discharge (17% v. 13%, p=0.36). Transfer from the MICU without a documented indication for continued antipsychotic use was common in both groups (50% v. 24%, p=0.24). There was a trend toward more frequent documentation of indication for antipsychotic at MICU transfer post intervention that did not reach statistical significance (34% v. 20%, p=0.24). Mean cost of antipsychotic use in the MICU were similar pre ($213 v. $156, p=0.37) and post intervention ($144 v. $112, p=0.66).

Conclusion: Antipsychotics are commonly used in the ICU for delirium and continued on transfer to the floor without a clearly communicated indication or discussion about de-escalation of therapy. This common situation may be due to omissions in communication or due to lack of recognition of the current indications for antipsychotic usage, but may lead to inappropriate overuse of these medications. Further study of systems measures to guide provider practice in deprescribing these medications is warranted.

53-R Poster: Changing resident prescribing practices for VTE prophylaxis using peer-to-peer education

Presenter: Lauren Harter, Resident
General Internal Medicine

Research Interest: Medical Education

Mentors: Gregory Bump MD
Allison Dekosky MD

Funding Source: Division of GIM and GME at UPMC

Authors: Lauren Harter MD, Jennifer Rodriguez MD, Sinthana Umakanthan DO, Terence Harrington MS, Allison Dekosky MD, Gregory Bump MD

Introduction: Prior to initiation of this project, there were no established guidelines for VTE prophylaxis at UPMC Presbyterian/Montefiore for hospitalized medical patients. ACCP guidelines recommended unfractionated heparin (UFH), enoxaparin (LMWH) or fondaparinux; as such, prescribing practices between these (particularly UFH and LMWH) varied widely. A review of in-hospital VTE events revealed that second or third doses of UFH were refused by patients, missed while patients were off the floor, and required more nursing time. At this institution, UFH and LMWH were cost-neutral. Thus, LMWH is our preferred agent for VTE prophylaxis.

Methods: The intervention was conducted at a university hospital amongst housestaff general medicine teams. We first created a flowchart to help guide clinicians on VTE selection, which was placed in each housestaff team room. Additionally, a lecture focusing on this new recommendation was given to all housestaff, plus several mentions during morning report.We implemented a peer-to-peer education and feedback process on half of our medicine teams, with a non-randomized, convenience sample. The intervention teams were educated in-person at the beginning of each rotation regarding the new recommendations. They subsequently received in-person feedback, once to twice a month. Beginning August 2017 in a continuous process, biweekly data was collected regarding current VTE prescription on all patients admitted to the housestaff medicine teams. This data was analyzed by run charts and to ensure accuracy for indications and contraindications.

Results: Prior to study initiation, UFH was prescribed 55% of the time in patients for whom enoxaparin was preferred (LMWH 45%). With interim data for 1261 total patients (581 intervention, 680 control), we observed an improvement in LMWH prescription for those in whom it was appropriate (i.e. patients requiring pharmacologic prophylaxis and without kidney disease), from 68.6% to 92.7% (control group from 72.4% to 90.9% and intervention group from 63.6% to 94.7%) over the course of three months. We also found that overall appropriate VTE prophylaxis prescription (including UFH in kidney disease and SCDs when pharmacologic prophylaxis contraindicated) improved from 81.2% to 89.9% (intervention from 77.8% to 97.1%, control from 83.7% to 84.4%).

Conclusion: While this study is important due to its implications in providing better VTE prophylaxis, its true value lies in the demonstration of effective change in the practices of our housestaff. We effectively used peer-to-peer education and feedback, along with other educational tools, to implement a new guideline. We feel this is broadly applicable for other interventions aimed at changing housestaff practice.

54-R Poster: Impact of Attending a Mutual Support Group Meeting on Resident Trainee Attitudes toward Patients with Substance Use Disorder

Presenter: Amy Kennedy, Resident
General Internal Medicine

Research Interest: Medical Education

Mentors: Andrea Carter MD
Melissa McNeil MD

Funding Source: DGIM Development Award

Authors: Amy Kennedy MD, Andrea Carter MD, Melissa McNeil MD

Introduction: Alcohol and opioid substance use disorders (SUDs) are a significant cause of morbidity and mortality. 12 Step Mutual Support Groups (MSGs) such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) are mainstays of recovery, yet physicians receive little training in their use. To fill this need, we implemented and evaluated a curriculum to expose trainees in the University of Pittsburgh Internal Medicine Residency Program to MSGs. We hypothesized that resident trainees' attitudes toward patients with a history of SUD and toward MSGs would improve after observing and reflecting on patient experiences shared at MSG meetings.

Methods: Residents on an ambulatory rotation during Oct-Nov 2017attended a MSG meeting (AA or NA) and were asked to complete a written survey pre- and post- curriculum. The survey contained 7-point Likert scale questions from 1=strongly disagree (negative attitude) to 7=strongly agree (positive attitude) with 14 questions assessing attitudes toward patients with SUD and 4 questions assessing attitudes toward MSGs. Composite attitude scores for each resident were calculated using the mean Likert-scale responses. Residents' composite attitude scores and responses on each question were compared pre- vs. post-curriculum using paired Students t-tests with 2-sided p-value<0.05 considered statistically significant.

Results: Of 31 eligible residents, 22 (71%) completed the pre- and post- survey and were included in the analysis. Compared to pre-curriculum, residents post-curriculum had more positive attitudes toward patients with SUD (composite mean 4.9 vs 4.6, p=0.01) and toward MSGs (composite mean 5.4 vs 5.0, p=0.01). Specifically, compared to pre-curriculum, residents post-curriculum felt they knew enough about causes of SUDs to more appropriately counsel patients about SUDs (p<0.05). Post-curriculum residents were also more aware of the basic principles of MSGs and were more comfortable counseling patients on the utility of MSGs (p<0.05 for each).

Conclusion: Resident trainees had more positive attitudes toward patients with SUD after attending and reflecting on a MSG meeting. They also were more comfortable counseling patients on the utility of MSGs. Implementing a curriculum on MSGs gives trainees an experience to empathize with SUD patients and a chance to better educate themselves on MSGs.

55-R Poster: Resident Trainee Reflections on Patients with Substance Use Disorder after Attending a Mutual Support Group Meeting

Presenter: Amy Kennedy, Resident
General Internal Medicine

Research Interest: Medical Education

Mentors: Andrea Carter MD
Melissa McNeil MD

Funding Source: DGIM Development Award

Authors: Amy Kennedy MD, Andrea Carter MD, Melissa McNeil MD

Introduction: Alcohol and opioid substance use disorders (SUDs) are a significant cause of morbidity and mortality. Mutual Support Groups (MSGs) such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) are mainstays of recovery but physicians receive little formal training in their use. We developed a curriculum to expose internal medicine resident trainees to MSGs through a direct observational experience. The goal of our curriculum was to improve trainees' attitudes toward patients with SUDs after reflecting on shared patient experiences expressed at MSGs.

Methods: 31 internal medicine residents within the University of Pittsburgh Internal Medicine Residency Program who completed their ambulatory rotation during October–December 2017 participated in the curriculum. Prior to attending the MSG meeting, residents were given a brief introductory handout explaining the basic principles of MSGs. All residents attended an assigned open speaker-type MSG meeting (AA or NA) where a group member described their experiences with SUD and MSGs. After attending the meeting, residents wrote a one-half page reflection and attended a 1-hour group debrief session.

Results: In total, 27/31 (87%) of residents completed the written reflective piece and 28/31 (90%) attended the group debrief session. We have completed preliminary qualitative analysis to identify overall themes of the written pieces and audio-taped group sessions. Three major themes were identified: perspective taking, a sense of community, and religious overtones. Trainees appreciated hearing perspectives from patients in recovery--residents wrote it was helpful to "be able to truly relate to a patient's circumstances" and "challenge my long-held biases". Many residents noted the positive effects of community--one trainee wrote, "I was so impressed with the non-judgmental support, I hope to emulate that in my clinical practice". A reservation residents expressed was related to the religious themes. For example, one resident wrote that they were "uncomfortable with the religious overtone of the meeting".

Conclusion: The written and audio-recorded reflections demonstrated perspective taking by residents of their patients with SUD and more positive attitudes toward caring for these patients. Trainees expressed feeling more comfortable counseling patients on the utility of MSGs, but expressed concern about the typical religious overtones of MSGs, which may be a barrier to future referrals.

56-R Poster: A Systemic Review of Sepsis AssociatedMacrophage Activation Syndrome (S-MAS)

Presenter: Neena Chandrasekaran, Resident General Internal Medicine

Research Interest: Translational

Mentors: Hernando Gomez MD

Authors: Neena Chandrasekaran MD, Syed Mahmood MD, Holt Murray MD, Joseph Carcillo MD, John Kelllum MD, Hernando Gomez MD

Funding Source: N/A

Introduction: Sepsis Associated Macrophage Activation Syndrome (S-MAS)occurs in children,but little is known about S-MAS in adults. We conducted a systematic review to investigate rates, mortality, pattern of organ compromise and treatment strategies for adult S-MAS.

Methods: We reviewed EMBASE, Cochrane and MEDLINE 2001-2017, usingmedical subject heading terms and text words with Boolean logic. We included observational and interventional studies in adult (>18 y) patients with sepsis/infectionand MAS, or hemophagocytic lymphohystiocytosis (S-HLH). We excluded studies enrolling patients with rheumatological disorders, family history of HLH or malignancy.

Results: We found 3,692 articles and excluded 3,663 for duplications, not reporting outcomes, and including patients with rheumatologic conditions, malignancies or < 18 years. We selected 29 articles, including 1,272 patients- 10 case reports, 1 case series, 17 cohort studies, and 1 post-hoc analysis of a randomized trial (ph-RCT) on IL-1Rantagonist (IL-1Ra) for treatment of sepsis. Only the ph-RCT reported on the rate of S-MAS(6.1%). Mortality was reported in 12 studies, ranging from 50% in case reports to 60% in the ph-RCT. Six studies reported on organ dysfunction, most often citing hepatobiliary and renal compromise. All 29 studies reported treatment. Eight studies of S-MAS reported treatment with pulse methylprednisolone+etoposide, IL-1Ra, cyclosporine, intravenous immunoglobulin (IVIG) + fresh frozen plasma, IVIG + prednisolone. A case series described 3 patients treated with IL-1Ra and IVIG +/-steroids, with 50% survival. The ph-RCT reported mortality reduction from 60 to 29.7% with Anti-IL-1Ra. Nineteen studies on S-HLH reported as most common treatments steroids +/-etoposide, etoposide, cyclosporine, IVIG, plasmapheresis, stem cell transplant and Alemtuzumab.

Conclusion: There is very little evidence on the frequency, outcome, and potential therapeutic interventions in adult S-MAS. Although the incidence is low, mortality is very high. Treatment strategies varied, however, the best evidence suggested a promising therapeutic role for IL-1Ra.

57-R Poster: Identification of differentially expressed genes in pulmonary endothelial and vascular smooth muscle cells of patients with idiopathic pulmonary arterial hypertension using single cell RNA sequencing

Presenter: Didem Saygin, Resident
General Internal Medicine

Research Interest: Translational

Mentors: Robert Lafyatis MD

Funding Source: N/A

Authors: Didem Saygin MD, Tracy Tabib , Nina Morse , John Sembrat , Mauricio Rojas , Robert Lafyatis MD

Introduction: Idiopathic pulmonary arterial hypertension (IPAH) is a disease characterized by elevated pulmonary arterial pressure in the absence of underlying cardiopulmonary disease. Etiology of IPAH is currently unclear, however vascular endothelial (EC) and smooth muscle cells (VSMC) are thought to play key roles in pathogenesis. Despite aggressive treatment, mortality remains high, therefore new targeted treatments are needed. Single-cell RNA sequencing is a new technique that dissects gene expression profiles of individual cells, enabling identification of novel gene networks and offering a great potential for discovery of new therapeutics. In this study, we aimed to identify differentially expressed genes in pulmonary ECs and VSMCs of patients with IPAH by single-cell RNA sequencing.

Methods: We studied lung explants of one IPAH patient and two healthy individuals. Tissues were digested into single-cell suspensions, transcripts from each cell reverse transcribed and tagged using cell-associated barcode primers, cDNA libraries constructed and amplified from pooled cDNAs, and the resulting libraries sequenced. Sequences were mapped to a reference genome, deconvoluted to identify cell origins and a gene expression matrix profile generated.

Results: Seurat, an R package developed for single-cell analysis, was used to identify clusters using t-distributed stochastic neighbor embedding plot. Distinct EC and VSMC populations were identified on the basis of known gene markers for these cell types such as VWF and DES, respectively. Expression of genes was compared between IPAH and control ECs and VSMCs. EC marker genes such as ESM1, ENG and SELE as well as transcription factors that may mediate signals controlling these genes such as EGR1 and FosB were found to be expressed at higher levels in ECs of IPAH compared to ECs from healthy lungs. Of note, autotaxin was also found to be upregulated in IPAH, a gene which catalyzes production of lysophosphatidic acid, a phospholipid mitogen and activator of intracellular Rho kinase.In VSMCs from IPAH lung, several activator-protein-1-(AP1)-associated transcription factors, such as Jun, JunB and FosB, were expressed at higher levels than VSMCs of healthy lungs.

Conclusion: Using single-cell RNA sequencing, we were able to identify genes that are differentially upregulated in ECs and VSMCs in IPAH. These results suggest previously unknown roles for autotaxin in aberrant EC function and AP1 transcription factors in regulation of aberrant VSMC function in IPAH. Further analysis and samples will be needed to confirm and extend these findings. However, these preliminary results suggest new pathways altered in IPAH that might be targeted to treat this deadly disease.

58-R Poster: Pre-Existing Emphysema Affects Soluble Receptor for Advanced Glycation End-Product Levels in ARDS

Presenter: Michael Simonson, Resident
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: John Evankovich MD
Bryan McVerry MD

Funding Source: Individual NRSA (F32)

Authors: Michael Simonson MD, John Evankovich MD, Sarah Rapport BS, Kitsios Georgios MD, Bryan McVerry MD

Introduction: ARDS is characterized by destruction of alveolar epithelium and the Receptor for Advanced Glycation End-Products (RAGE) is highly enriched on the basal surface of alveolar type I cells. The cleaved isoform Soluble RAGE (sRAGE) increases in the plasma of ARDS patients relative to the severity and quantity of alveolar epithelial damage. Conversely, sRAGE levels in stable emphysema patients are inversely correlated with severity of disease, as there is a loss of alveolar epithelium in these patients. As such, a pre-existing deficiency of alveolar epithelium in emphysema patients may prevent robust sRAGE elevation in ARDS. We hypothesize that sRAGE levels would not be elevated in ARDS patients with pre-existing emphysema compared to mechanically-ventilated control patients without lung injury.

Methods: Patient data was obtained from the IRB-approved Acute Lung Injury Biospecimen Repository at University of Pittsburgh. sRAGE concentration was measured in plasma within 48 hours of presentation to the Medical ICU with a magnetic bead Luminex bioassay. Control patients were mechanically ventilated without pneumonia, acute lung injury, or congestive heart failure. No differentiation was made within the control group between patients with emphysema and those without. ARDS patients were mechanically-ventilated, had chest CT prior to or during admission to document emphysema, and met Berlin criteria for ARDS as determined by an expert physician panel. Data were analyzed using Mann-Whitney Rank U test.

Results: In control patients, sRAGE=2395.2 (range 1094-5110, n=11). Compared to controls, sRAGE levels were higher in ARDS patients without radiographic emphysema, sRAGE= 3715 (range 411-29067, n=28), P=0.03 by Mann-Whitney Rank U test. sRAGE was not statistically increased in ARDS patients with prior documented radiographic emphysema compared to controls, sRAGE = 2998.4 (range 381.55-6048.29, n=7), P=0.69 by Mann-Whitney Rank U test (Figure 1).

Conclusion: Pre-existing emphysema may be a confounding factor in sRAGE level interpretation in patients with ARDS, as there was no difference between control patients and ARDS patients with pre-existing emphysema. Pathophysiologically, this phenomenon may reflect a baseline reduction in the quantity of RAGE-expressing alveolar epithelial cells. The presence of emphysema might help explain the large variability in sRAGE measurement in large ARDS cohorts and should potentially be taken into consideration when examining ARDS phenotypes. The current data are drawn from a relatively small patient panel, and these findings justify further investigation in a larger cohort to fully examine differences in sRAGE levels in ARDS patients with pre-existing emphysema.

59-R Poster: Palbociclib plus Letrozole as first-line therapy in ER/PR-positive/HER2-negative metastatic breast cancer: How does UPMC match up to national data?

Presenter: Catherine Quinn, Resident
General Internal Medicine

Research Interest: Clinical

Mentors: Adam Brufsky MD

Funding Source: N/A

Authors: Catherine Quinn MD, Rachel Jankowitz MD; Margaret Rosenzweig NP PhD, Adam Brufsky MD

Introduction: The advent of cyclin-dependant kinase 4/6 inhibitors combined with endocrine therapies in the treatment of women with HR+/HER2- advanced breast cancer has changed the landscape in the arena of progression-free survival (PFS) for metastatic disease. The PALOMA study demonstrated a clear clinical benefit as well as a favorable safety profile for using palbociclib in the first-line in combination with an aromatase inhibitor for hormone-receptor positive metastatic disease. In the recent multi-center phase 3 analysis of PALOMA 2 for patients on palbociclib plus letrozole, a median PFS benefit of 27.6 months vs. placebo of 14.5 months was demonstrated after 37-month follow-up. In our study, we aim to confirm that the data reported in this large multi-center trial will remain similar when compared to a single-center population.

Methods: We are performing a cohort analysis of patients who have been on palbociclib plus letrozole at the University of Pittsburgh Medical Center with a primary goal of evaluating median PFS on this therapy compared to national data. Once all of our patients have progressed through palbociclib therapy, we intend to use a Kaplan-Meier Curve to analyze the data. A secondary goal is to analyze patients who progressed through 2nd line therapies to determine if PFS was preserved in the 2nd line. Another secondary goal is to measure if there is a correlation between responsiveness to adjuvant therapy and PFS on palbociclib plus letrozole.

Results: 58 patients were analyzed and 40 met our selection criteria. 9 patients have progressed through palbociclib and some through 2nd line therapies, with the remaining 31 currently being treated with palbociclib plus letrozole. All 40 patients were previously treated with adjuvant hormone suppression therapy prior to progression to metastatic disease. The median PFS for the 9 patients that progressed was 10 months.

Conclusion: We are continuing to analyze the data, which will allow us to more accurately measure our PFS on palbociclib plus letrozole compared with national controls when the data has matured. Additionally, we are currently following progression through 2nd line agents and expect PFS will be preserved given current trends. Finally, we hypothesize that the correlation coefficients will indicate that there is not a strong correlation between responsiveness to any of the adjuvant therapies and median PFS on palbociclib plus letrozole in metastatic disease. Were this to be the case, it will match national data, and indicates that all patients may benefit from palbociclib therapy regardless of response to adjuvant therapies.

SESSION A- MAY 1, 2018

Biomedical Science Tower - Foyer

Aggor	Felix	1-A	IL-22/IL-22RA1 signaling axis is protective during oropharyngeal candidiasis
Ahsan	Maaz	44-A	FINDING THE SWEET SPOT: THE ASSOCIATION BETWEEN ADDED DIETARY SUGARS AND INFLAMMATORY BOWEL DISEASE SEVERITY
Al-bataineh	Mohammad	83-A	Regulation of the Vacuolar H+ATPase (V-ATPase) by Mucin 1 in the Kidney
Allsup	Kelly	45-A	Impact of Nitrite Therapy on Change in Steady State Submaximal Exercise in Older Adults
Amatya	Nilesh	2-A	IL-17 integrates multiple self-Aeinforcing, feed-forward signaling cascades through an RNA binding protein Arid5a
Bachman	Timothy	46-A	Hemodynamic Changes during LVAD implantation may be associated with Subsequent Right Ventricular Failure: Opening the Black Box of the Operating Room
Badrane	Hassan	3-A	Regulation of phosphatidylinositol-(4,5)-bisphosphate, cell wall integrity and cytokinesis in Candida albicans.
Balchak	Deidra	4-A	Cleavage of ENaC alpha and gamma subunits evolved with the terrestrial migration
Bandi	Kiran	84-A	Differences in the Adenosine Signaling Pathway among HIV+ Individuals with COPD
Bansal	Amar	47-A	Decisional Satisfaction and Perceptions of Inpatient Dialysis Initiation
Blobner	Brandon	85-A	The burden of rare ENAC variants associated with increases or decreases in blood pressure
Britton	Noel	86-A	The Composition of the Lung Mycobiome in Adult Critically Ill Patients With or At Risk For The Acute Respiratory Distress Syndrome
Britton	Noel	87-A	Comparison of Fungal DNA Extraction Methodologies for Mycobiome Analysis

Cahill	Benjamin	49-A	Contact Frequency and Older Adult Participation in Cardiac Rehabilitation
Chandra	Divay	88-A	The SCF FBXO3 E3 Ligase regulates inflammation in atherosclerosis
Chang	Hannah	71-A	Quality of Care in Adult Primary Care Physicians is Not Associated with Physician Electronic Medical Record Efficiency.
Cheng	Shaoji	5-A	A Candida albicans damage resistance protein family regulates cell wall biosynthesis and pathogenesis
Choi	Jaeyeon	50-A	Combination treatment of VLA-4 targeted radionuclide therapy and Immunotherapy for treating metastatic melanoma
Cooper	Bryce	6-A	Influence of Early Enteral Dextrose on Large Intestine Microbiome Composition in a Septic Murine Klebsiella Pneumoniae Model
Culley	Miranda	7-A	Frataxin deficiency induces endothelial metabolic dysregulation to promote pulmonary hypertension
Eaton	Amity	8-A	Regulation of Bladder Umbrella Cell Paracellular Permeability by Stretch
Eleazu	Rachel	89-A	Nitrite Improves Skeletal Muscle Mitochondrial Coupling and Walking Efficiency in Older Adults
Eshbach	Megan	9-A	Hemoglobin Inhibits Uptake of Filtered Proteins by Proximal Tubule Cells: Implications for Sickle Cell Disease and Vitamin D Status
Evankovich	John	10-A	Toll-Like Receptor 8 (TLR8) Protein Degradation Limits Inflammatory Signaling
Ferguson	Annabel	90-A	A Type I IFN Response to Donor Genomic DNA and RNA As A Novel Immune Driver of Chronic Lung Allograft Dysfunction: A Prediction Based Upon A Cutting-Edge Upstream Regulator Discovery and In-Depth Transcriptome Analysis of The Airway Brush Sample

Feroze	Rafey	91-A	Mir-29b Mimic Delivery via Ultrasound Targeted Microbubble Destruction to Suppress Cardiac Fibrosis
Fuschiotti	Patrizia	92-A	14-3-3z sequesters cytosolic T-bet, up-Aegulating IL-13 in Tc2 and systemic sclerosis CD8+ T lymphocytes.
Goetz	Breanna	11-A	The E138A Mutation Amplifies Resistance to Dapivirine in Combination with NNRTI Mutations
Gupta	Aman	51-A	Electrical Failure of Non-Aecalled Defibrillator Leads
Gupta	Aman	52-A	Extent of Cardiac Damage in Aortic Stenosis Relates to TAVR Outcomes - ?A Validation of a New Staging System
Gupta	Aman	53-A	Lung Hyperinflation and Coronary Atherosclerosis in Smokers: the Pittsburgh COPD SCCOR and COPDGene Cohorts
Gurkar	Aditi	12-A	Endogenous DNA damage contributes to cardiac failure and dilated cardiomyopathy
Harvey	Lloyd	93-A	HIV-infected Macrophages Induce Endothelial Cell Dysfunction and Metabolic Reprogramming to Promote HIV-associated Pulmonary Arterial Hypertension
Holber	Julia	54-A	Is objectively assessed physical activity associated with cardiac ejection fraction, health-Aelated quality of life, and NYHA class among patients recently hospitalized with systolic heart failure?
Ikeda	Youko	13-A	Spinal cord injury induced neural degeneration in the mouse urinary bladder via pro-apoptotic p75NTR signalling
Istvanic	Filip	94-A	Sonoreperfusion of Microvascular Obstruction: a Step towards Clinical Translation
Judge	Colleen	72-A	The association between mental health disorders and unintended pregnancy among women Veterans in the ECUUN study
Kitsios	Georgios D.	95-A	Next-Generation Sequencing Of The Respiratory Microbiome As A Diagnostic Tool Of Severe Bacterial Pneumonia In Mechanically Ventilated Patients.

Kitsios	Georgios D.	96-A	Gut Microbiome Dysbiosis And Delirium In Mechanically Ventilated Adult Patients: A Prospective Cohort Study.
Koch	Carl	97-A	Oral Microbial Alterations in Tryptophan Metabolism and Nicotinamide Adenine Dinucleotide (NAD) Synthesis in Individuals with Pulmonary Arterial Hypertension.
Koldhekar	Amol	56-A	Associations of Grip Strength with Mood Symptoms and Health-Aelated Quality of Life Among Patients with Systolic Heart Failure
Kostra	James	57-A	Functional Capacity And Cardiac Self-efficacy Measures Are Associated With Health Literacy In Cardiac Rehabilitation
Kowalski	Aneta	14-A	Impact of CREBRF and its obesity risk variant on glucose homeostasis and insulin action in mice
Kullmann	Aura	15-A	Mind-body interactions: autonomic and mitochondrial dysregulation play key roles in Interstitial Cystitis/Bladder Pain Syndrome
Kullmann	Aura	16-A	Putative role of stress-induced abnormal neuronal calcium homeostasis in Interstitial Cystitis/Bladder Pain Syndrome
Lee	Jeongkyung	18-A	Tead1 reciprocally regulates adult ß-cell proliferation and function
Li	Gang	19-A	From GWAS to functional SNPs and to Mechanisms
Liang	Kelly	58-A	Are Traditional Biomarkers of Lupus Associated with Renal Pathology in Lupus Nephritis?
Liang	Kimberly	59-A	Relationship of Serum Inflammatory and Vascular Biomarkers with Subclinical Atherosclerosis and Cardiovascular Risk Factors in Rheumatoid Arthritis and Controls
Lindell	Kathleen	60-A	Feasibility and Acceptability of an Early Palliative Care Intervention in Patients with Idiopathic Pulmonary Fibrosis (IPF) and their Caregivers

Maximous	Stephanie	80-A	A Novel Program to Leverage Resources Of An Organ Procurement Organization for Teaching Medical Procedures
Mutchler	Stephanie	22-A	The epithelial sodium channel in the endothelium alters vascular reactivity with high salt diet
Nyunoya	Toru	99-A	TACC2 PROTEIN MEDIATES EPITHELIAL CELL SURVIVAL AND ALVEOLAR INTEGRITY AGAINST CIGARETTE SMOKE EXPOSURE
Olonisakin	Tolani	23-A	Aggravated erythrophagocytosis impairs IFN?-mediated Irg1 expression in response to Klebsiella pneumoniae.
Pace	Rachel	81-A	MICU Crisis, Communication, and Skills Workshop: development and evaluation of a mock code training program
Parekh	Natasha	73-A	Relationship Between Provider-Led Health Plans and Healthcare Quality, Utilization, and Patient Satisfaction
Qin	Shulin	61-A	Association between Systemic Inflammation and Lung Dysfunction in HIV-infected Individuals
Radomski	Thomas	74-A	Variation in Low-Value Health Service Use within the Department of Veterans Affairs
Rana	Sangeeta	62-A	MULTIDISCIPLINARY CARE OF A PATIENT WITH COWDEN SYNDROME AT A GERIATRIC CENTER.
Rangachar Srinivasa	Vatsala	75-A	Hospital-associated Clostridium difficile infection (CDI); how much we blame the current environment?
Ray	Evan	24-A	Response of BK-alpha intercalated cell knock out mice to a high K diet
Ray	Evan	25-A	Characterization of A Mouse ENaC Gamma Subunit Hypomorph in the Lungs and Beyond
Ren	Qidong	26-A	Exposure of proximal tubule cells to fluid shear stress alters transcription of metabolic pathway enzymes

Ries	John	63-A	Asthma Variables and Associations with HIV Status
Robbins-Welty	Gregg	64-A	Interventionist Training and Intervention Fidelity Monitoring and Maintenance for CONNECT, a Nurse-led Primary Palliative Care in Oncology Trial
Rondon-Berrios	Helbert	65-A	Urea in the Treatment of Hyponatremia: The First Reported US Inpatient Experience
Rooney	James	27-A	ASIC3 fine-tunes bladder sensory signaling
Schmitz	Emily	66-A	Multidrug-Aesistant organisms (MDRO) surveillance: how do we look at the picture, horizontally or vertically?
Schwenk	Amanda	67-A	Opioids, NSAIDs, and AKI: Unintended Consequences of the PA Prescription Drug Monitoring Program
Sembrat	John	100-A	Designing Perfusate for Prolonged Normothermic Ex Vivo Lung Perfusion to Investigate Diseased Lungs
Shah	Faraaz	101-A	Low-Level Enteral Dextrose Infusion Increases the Incretin Glucose-Dependent Insulinotropic Peptide and Maintains Euglycemia in a Murine Klebsiella Pneumoniae Model of Sepsis
Shelton	Celeste	28-A	Classification of Pancreatitis Subtypes Using Rna-Seq from Human Pancreatic Tissue
Shen	Ding	69-A	PSMA-targeted SPECT imaging for prostate cancer in mice model using 177Lu-labeled agent CTT1403
Sheth	Heena	76-A	Evaluating adequacy of VTE prophylaxis for overweight and obese patients
Sheth	Heena	77-A	Infection as Risk Factor for Venous Thromboembolism in Hospitalized Patients
Shi	Shujie	29-A	Regulation of the epithelial Na+ channel by paraoxonase-2
Shipman	Katherine	30-A	Mathematical model of megalin trafficking in differentiated proximal tubule cells

Squires	Kevin	31-A	CD101 Exhibits Low Minimum Inhibitory And Mutant Prevention Concentrations Against Candida glabrata Clinical Isolates
Squires	Kevin	32-A	C. albicans DDI1 is involved in DNA damage responses, morphogenesis and pathogenesis during hematogenously disseminated candidiasis and at different stages of intra-abdominal candidiasis.
Sun	Quanhong	33-A	TBK1 expression and activity inOCL lineage cells generates a pagetic-like bone disease in mice
Tan	Roderick	34-A	Nrf2 enhancement increases proteinuric renal injury in mice
Tilstra	Jeremy	35-A	T cell Exhaustion in Lupus Nephritis
Trevejo- Nunez	Giraldina	36-A	More than a decoy receptor? Interleukin 22 Binding Protein (IL-22BP) in bacterial pneumonia
Truschel	Steven	37-A	Age-Aelated Lysosome Dysfunction in Rat Urothelium
Vargas	Benni	38-A	Identification of small molecules that inhibit reactivation of latent HIV-1
Vodovotz	Lena	102-A	Association of Antiretroviral Therapy with Peripheral Inflammatory Mediators, Lung Function in HIV-infected Individuals
Vodovotz	Lena	103-A	Assessment of Th17 Pathway and Association with Lung Function in HIV-Infected Individuals Initiating Antiretroviral Therapy
Wang	Xueqi	39-A	Identification of multiple functional variants at the extracellular domain core of the epithelial Na+ channels
Wolfe	Rachel	40-A	Lack of CD73 in mVSMCs causes increased TGF-ß signaling and elastin expression under mechanical stretch
Wolgemuth	Tierney	78-A	Associations Between Pregnancy Intention, Attitudes, and Contraceptive Use Among Women Veterans in the ECUUN Study

Yang	Libing	104-A	Longitudinal Assessment of Plasma Biomarkers of Injury and Inflammation In Patients With the Acute Respiratory Distress Syndrome (ARDS): A Prospective Cohort Study In Adults.
Yochum	Zachary	41-A	TWIST1 is a key mediator of HGF-MET-driven resistance to targeted therapies in EGFR mutant and MET-driven lung cancer
Yu	Gary	42-A	Co-administration of Sodium Nitrite during Ultrasound Targeted Microbubble Cavitation Therapy Enhances Nitric Oxide Generation and Increases Microvascular Perfusion
Zabbarova	Irina	105-A	Amelioration of detrusor sphincter dyssynergia following spinal cord injury with LM11A31, a small molecule p75 neurotrophin receptor antagonist
Zhan	Wei	106-A	SELENIUM DEFICIENCY IS ASSOCIATED WITH EXOCRINE PANCREATIC INSUFFICIENCY IN PATIENTS WITH CHRONIC PANCREATITIS
Zhan	Wei	70-A	GERMLINE VARIANTS AND RISK FOR PANCREATIC CANCER: A SYSTEMATIC REVIEW AND EMERGING CONCEPTS.
Zhao	Jingsi	107-A	Computational Repurposing of Chemotherapies for Cardiomyopathies
Zhou	Chunsheng	43-A	Developing A New Tool to Understand the Role of IL-17F in Anti-Fungal Immunity
Zhu	Lei	79-A	The Influence of Racial and Social Economic Factors on the clinical course of men and women with Rheumatoid Arthritis

1-A Poster: IL-22/IL-22RA1 signaling axis is protective during oropharyngeal candidiasis

Presenter: Felix Aggor, Graduate Student
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Sarah Gaffen PhD
Robert Binder PhD
Daniel Kaplan MD, PhD

Funding Source: RO1

Authors: Felix Aggor MS, Natasha Whibley PhD, Heather Conti PhD, Giraldina Trevejo-Nunez MD, Bianca Coleman MS, Nathaniel Weathington MD, Jay Kolls MD, Sarah Gaffen PhD

Introduction: Oropharyngeal candidiasis (OPC) is an opportunistic fungal infection of the oral mucosa predominantly caused by the commensal fungus Candida. OPC commonly affects immunocompromised individuals particularly with T cell or STAT3 deficiencies. In humans and mice, IL-17 deficiency is associated with mucosal candidiasis. Additionally, the incidence of mucocutaneous candidiasis correlates with the elevation of IL-17A/F and also IL-22 autoantibodies in patients with certain thymomas and AIRE (Autoimmune regulatory gene) deficiency. However, the role of interleukin 22 (IL-22) and the IL-22-Aesponding cells remain largely unexplored in the context of OPC. IL-22 signals through a heterodimeric receptor complex consisting of IL-22RA1 and IL-10RB resulting in activation of STAT3 and MAPK pathways. While IL-10RB is ubiquitously expressed, IL-22RA1 is only present in non-hematopoietic cells. IL-22RA1 is known to maintain barrier integrity and promote mucosal immunity. We therefore hypothesized that the IL-22/IL-22RA1 signaling axis is critical for host defense during OPC.

Methods: To assess the induction of Il22 during primary and secondary OPC, gene expression analysis was performed by qRT-PCR. The localization of IL-22RA1 in murine tongue was identified by immunohistochemistry and global changes in transcriptome in response to OPC was assessed by RNASeq analysis.

Results: We found that Il22 is induced in murine tongue in response to primary and secondary C. albicans infection. Strikingly, the IL-22RA1 subunit is expressed only on the suprabasal epithelial cells in the dorsal base of murine tongue in a pattern that is very different from IL-17RA. We also found that both Il22-/- and IL22RA1-/- mice are susceptible to OPC similar to IL-17RA-/- mice. Surprisingly, conditional deletion of STAT3 within the suprabasal oral epithelial cells using a Keratin-13- driven CRE system did not enhance susceptibility to OPC. RNASeq analysis of C. albicans-infected murine tongue identified gene subsets that are uniquely targeted by IL-22 and IL-17RA as well as those that are dependent on both IL-22 and IL-17RA.

Conclusion: IL-22/IL-22RA1 signaling axis contributes in a non-Aedundant manner to protection during OPC. Although there are some common genes targeted by both IL-22 and IL-17RA, some are unique to IL-22 regulation. These IL-22 dependent genes will be further explored to assess their functional relevance and mechanism of action in the context of OPC.

2-A Poster: IL-17 integrates multiple self-Aeinforcing, feed-forward signaling cascades through an RNA binding protein Arid5a

Presenter: Nilesh Amatya, Graduate Student
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Sarah Gaffen PhD

Funding Source: R01-AI107825

Authors: Nilesh Amatya BS, J. Agustin Cruz PhD, Felix Aggor BS, Abhishek Garg PhD, Andrea Berman PhD, Ulus Atasoy PhD, Sarah Gaffen PhD

Introduction: Interleukin-17A (IL-17) is a proinflammatory cytokine essential for clearance of microbial pathogens, but conversely drives immunopathology in autoimmune settings. Although IL-17 is consistently found to be a modest activator of gene transcription in experimental settings, its biological impact in vivo is profound. In addition to de novo transcription, IL-17 also upregulates inflammatory gene expression by stabilizing their transcripts. mRNA stabilization is a central, but poorly understood facet of IL-17 signaling, which is often attributed to profound biological activity of IL-17. Here, we report an RNA binding protein Arid5a (AT-Aich interactive domain-containing protein 5A) as a novel mediator of IL-17-induced stabilization of inflammatory mRNAs.

Methods: To assess the role of Arid5a in IL-17 signaling, we performed gene knockdown using siRNA in the murine stromal cell line ST2. Following IL-17 treatment, expression of IL-17 target genes was analyzed using qRT-PCR, ELISA or Western Blot. mRNA half-life of IL-17 target genes was assessed after actinomycin D treatment. Arid5a-binding transcripts were identified via RNA immunoprecipitation and biotinylated-ANA pull-down assays. Co-immunoprecipitation assay was performed to study adaptor proteins that associate with Arid5a.

Results: IL-17 stimulation upregulated Arid5a expression, whereupon Arid5a was rapidly recruited to TRAF2. Arid5a stabilized multiple IL-17-induced cytokine mRNA transcripts, including Il6, Cxcl1 and Cxcl5, by binding to their 3' untranslated regions (UTR). In some cases, Arid5a counteracted mRNA degradation mediated by the endoribonuclease MCPIP1 (Regnase-1). Additionally, Arid5a enhanced IL-17-induced expression of the transcription factors - I Kappa B zeta (Nfkbiz) and C/EBPß (Cebpb), which could then transactivate IL-17-dependent promoters. Arid5a bound to Nfkbiz or Cebpb transcripts, but surprisingly did not detectably affect total Nfkbiz or Cebpb mRNA levels. Rather, Arid5a facilitated translation of - I Kappa B zeta and C/EBPß.

Conclusion: Thus, Arid5a orchestrates a feed-forward amplification loop within the IL-17 pathway. Our findings reveal a new function for Arid5a in controlling translation and demonstrate a role in controlling downstream IL-17 signaling.

3-A Poster: Regulation of phosphatidylinositol-(4,5)-bisphosphate, cell wall integrity and cytokinesis in Candida albicans.

Presenter: Hassan Badrane, Junior Faculty Infectious Diseases

Research Interest: Bench

Mentors: Neil Clancy MD

Funding Source: VA MERIT AWARD

Authors: Hassan Badrane PhD, Minh-Hong Nguyen MD, Cornelius J. Clancy MD

Introduction: We showed that C. albicans Irs4p and Inp51p interact to regulate levels and localization of phosphatidylinositol-(4,5)-bisphosphate (PI(4,5)P2) in the plasma membrane. The phenotypic signatures of irs4 or inp51 mutants are intracellular plasma membrane invaginations, which colocalize PI(4,5)P2, septins Sep7p and Cdc10p, and cell wall components like chitin and GPI-anchored protein Rbt5p. Among other activities in yeast, PI(4,5)P2 activates the cell wall integrity pathway and is linked to cytokinesis. C. albicans exposure to caspofungin results in rapid redistribution of PI(4,5)P2 and septins to aberrant plasma membrane foci. We studied PI(4,5)P2 and septin dynamics and protein kinase C (PKC)-Mkc1 cell wall integrity pathway activation following caspofungin exposure, and investigated PI(4,5)P2 association with cytokinesis.

Methods: PI(4,5)P2 and septins were visualized by live imaging of C. albicans coexpressing green fluorescent protein (CaGFP)-pleckstrin homology (CaPH) domain and red fluorescent protein (RFP)-Cdc10p, respectively. PI(4,5)P2 was also visualized in GFP-PH domain-expressing C. albicans mkc1 mutants. Mkc1p phosphorylation was measured as a marker of PKC-Mkc1 pathway activation. Fungicidal activity was assessed using 20-h time-kill assays.

Results: Caspofungin immediately induced PI(4,5)P2 and Cdc10p colocalization to aberrant foci, a process that was highly dynamic over 3 h. PI(4,5)P2 levels increased in a dose-Aesponse manner at caspofungin concentrations =4× MIC and progressively decreased at concentrations =8× MIC. Caspofungin exposure resulted in broad-based mother-daughter bud necks and arrested septum-like structures, in which PI(4,5)P2 and Cdc10 colocalized. PKC-Mkc1 pathway activation was maximal within 10 min, peaked in response to caspofungin at 4× MIC, and declined at higher concentrations. The caspofungin-induced PI(4,5)P2 redistribution remained apparent in mkc1 mutants. Caspofungin exerted dose-dependent killing and paradoxical effects at =4× and =8× MIC, respectively. Fluconazole, amphotericin B, calcofluor white, and H2O2 did not impact PI(4,5)P2 or Cdc10p distribution like caspofungin. We demonstrated a spatio-temporal association between the appearance of plasma membrane invaginations and cytokinesis. We are looking currently at colocalization of the PM invaginations with RFP-tagged Myo1p, a main component of the actomyosin contractile ring.

Conclusion: Caspofungin exerts rapid PI(4,5)P2-septin and PKC-Mkc1 responses that correlate with the extent of C. albicans killing. PI(4,5)P2-septin regulation is crucial in early caspofungin responses and PKC-Mkc1 activation. Live cell imaging of irs4 or inp51 mutant cells expressing Myo1p-AFP will further address associations between PI(4,5)P2 regulation, plasma membrane invaginations, and aberrant septation and cytokinesis.

4-A Poster: Cleavage of ENaC alpha and gamma subunits evolved with the terrestrial migration

Presenter: Deidra Balchak, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Ossama Kashlan PhD

Funding Source: N/A

Authors: Deidra Balchak BS, Clayton Gentilcore BS, Nathan Clark PhD, Ossama Kashlan PhD

Introduction: The epithelial Na+ channel (ENaC) is critical to extracellular fluid volume regulation through its activity in several epithelia, including the aldosterone-sensitive distal nephron and colon, and the airway and alveoli. Human ENaC subunits are subject to activating proteolysis. During processing in the trans-Golgi network, furin cleaves the subunit twice. This event liberates an imbedded 26-mer inhibitory tract, moderately activates the channel, and leaves 30 kDa and 65 kDa fragments as parts of the channel complex. Furin cleaves the subunit once. This event has no effect on channel activity, but leaves 18 kDa and 75 kDa fragments as parts of the channel complex. Once at the cell surface, one of a number of proteases may cleave the subunit in a region ~35-50 residues distal to the furin cleavage site. This second cleavage event of the subunit also releases an imbedded inhibitory tract, 43-Aesidues when prostasin is the second protease, and greatly activates the channel.

Methods: To examine the evolution of ENaC cleavage sites, we generated a phylogenetic tree of ENaC and ENaC-like subunits to identify key branch points in the evolution of ENaC subunits.

Results: The four ENaC subunits arose from three gene duplication events. First, a single gene diverged to an alpha/delta precursor and a beta/gamma precursor. Shortly after, the beta/gamma precursor diverged to beta and gamma subunits. These two events occurred in time for the emergence of jawless fishes, as lampreys have α , β , and γ subunits. Later, but prior to the terrestrial migration, α and δ diverged from the alpha/delta precursor; the lobe-finned coelacanth is the first known species to have all four subunits. Among the fishes, only the Australian lungfish γ subunit had two cleavage sites, and all tetrapod α and γ subunits had two apparent cleavage sites. We ran nested likelihood models in BayesTraits and found a significant relationship between terrestrial status and having two cleavage sites in the α and γ subunits. Both sites showed a statistically significant coevolutionary pattern with the terrestrial state: proximal site, $P = 0.00325$; distal site, $P = 0.0486$. This pattern contrasts with the C-terminal PY motif, which is important for aldosterone regulation through Sgk1/Nedd4-2, and was present in EnaC α, β, and γ subunits from all species, but not in the δ subunit of any species.

Conclusion: The vertebrate terrestrial migration is associated with many changes, including accessibility to dietary Na+, differences in osmotic stress, and the development of lungs. One or a combination of these factors may have provided the selection pressure to develop this form of channel regulation.

5-A Poster: A Candida albicans damage resistance protein family regulates cell wall biosynthesis and pathogenesis

Presenter: Shaoji Cheng, Junior Faculty Infectious Diseases

Research Interest: Bench

Mentors: N/A

Funding Source: NIH

Authors: Shaoji Cheng PhD, Kevin Michael Squires BSc, Neil Clancy MD, Minh-Hong Nguyen MD

Introduction: Damage resistance protein 1 (DAP1), a cytochrome b5-like heme-binding protein, is involved in ergosterol biosynthesis and virulence in pathogenic fungi. C. albicans DAP1 homologs are encoded by orf19.489, orf19.1034 and orf19.6867 (489, 1034 and 6867, respectively). Using RNASeq, we found that each gene was highly expressed in at 24-72 hrs during murine intra-abdominal candidiasis (IAC).

Methods: We created single (Δ489; Δ1034; Δ6867), double (Δ489+Δ1034) and triple (Δ489+Δ1034+Δ6867) null mutants in C. albicans SC5314

Results: 1034 or 6867 disruption increased 489 expression 1.8 and 3.6 fold in YPD at 30oC, respectively. Null mutants had no growth defects at 30oC in various liquid or solid media, or on hyphal-inducing media. At 37oC, 1034 single, double and triple mutants formed rough colonies on solid YPD and SD media. Δ489 displayed growth defects under iron-limited conditions and was more susceptible to fluconazole and itraconazole (triple~double~Δ489 > Δ1034~ Δ6867 ~ SC5314). Δ1034 and Δ489 mutants were more susceptible to SDS and caspofungin (triple ~ double~ Δ1034 > Δ489 > Δ6867 ~ SC5314). Δ1034 mutants were resistant to calcofluor white (CW) and Congo red (triple~double~ 1034 > Δ489 ~Δ6867 ~SC5314). Cell wall chitin content of triple, Δ1034, Δ489, Δ6867 mutants and SC5314 were 2.09 ± 0.09, 2.06± 0.48, 2.86± 0.53, 3.13± 0.24, 3.56± 0.79 ug/mg, respectively (p= 0.03, 0.048, 0.3, 0.44 vs SC5314, respectively). Δ1034 exhibited heightened resistance to chitin synthase inhibitor nikkomycin Z (triple~double~Δ1034 > Δ489 ~Δ6867~SC5314), but not to N-linked glycosylation inhibitor tunicamycin. Chitin synthase gene (CHS1, CHS2, CHS3, CHS4) expression was significantly diminished in Δ1034 (0.3-0.4 fold vs SC5314). 489 cording protein localized at both nuclei and cell wall. 1034 cording protein localized at nuclei exclusively. Transmission electron microscopy revealed that 1034 cell wall layers were intact, and cell wall thickness did not differ from SC5314. Median survival among mice with disseminated candidiasis due to triple mutant, Δ1034, Δ489, Δ6867 and SC5314 were 10, 8, 5, 4.5, 5 days, respectively. During IAC, mice infected with triple and Δ1034 had significantly lower abscess burdens at day 3 (log10 CFU/g: 2.6±2.9 and 3.5±2.7 vs. SC5314 5.9±0.4; p=0.08 and 0.03, respectively) and day 7 (0±0 and 0±0 vs. SC5314 3.4±1.7; p=0.005 and 0.005, respectively).

Conclusion: C.albicans DAP1 homologues have minimal functional redundance. 489 and 1034 is involved in ergosterol biosynthesis. 1034 is involved in chitin biosynthesis, and pathogenesis of DC and IAC. DAP1s are up-Aegulated during IAC which might activate essential pathogenicity. DAP1 may be target for antifungal therapeutics enhancing potency of current antifungals.

6-A Poster: Influence of Early Enteral Dextrose on Large Intestine Microbiome Composition in a Septic Murine Klebsiella Pneumoniae Model

Presenter: Bryce Cooper, Graduate Student
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Faraaz Shah MD
Bryan McVerry MD
Chris O'Donnell PhD

Funding Source: K23

Authors: Bryce Cooper BS, Faraaz A. Shah MD, Byron Chuan BS, Lanping Guo MD, Teresa Gallego-Martin PhD, Adam Fitch MS, Joseph Huwe BS, Georgios D. Kitsios MD, Barbara Methe PhD, Allison Morris MD, Christopher P. O'Donnell PhD, Bryan McVerry MD

Introduction: Sepsis, a syndrome characterized by an overwhelming inflammatory response to infection, is associated with disruptions in the gut microbiome induced both by pathologic processes and by sepsis-associated treatments, such as antibiotics. The purpose of this study is to test the effects of enteral dextrose infusions, previously shown in our lab to have beneficial effects on glucose metabolism in septic mice, on the composition of the gut microbiome in a bacteremic Klebsiella pneumoniae model.

Methods: 10 week old C57BL/6J male mice underwent femoral arterial catheterization in combination with either a femoral venous catheter for intravenous infusions or a gastric cannula for enteral infusions. Mice were inoculated with $2x10^4$ colony forming units of Klebsiella pneumoniae by oropharyngeal aspiration (serotype 2 ATCC 43816). Twenty-four hours after inoculation, mice were randomized to receive a continuous infusion of (1) enteral saline, (2) intravenous dextrose, or (3) enteral dextrose. Sixteen hours after the start of infusion, mice were sacrificed for terminal collection. Fecal contents were extracted using the Qiagen Powersoil kit following the manufacturer's instructions with slight modification. Barcoded amplicons of the 16S V4 region were made with PCR, purified, quantitated, and then combined in a sequencing pool. Paired-end sequencing was performed on the MiSeq with a V2 kit and 251x251 base read lengths.

Results: Mice exposed to Klebsiella pneumoniae receiving enteral saline in the absence of any dextrose developed hypoglycemia (median blood glucose 58 mg/dL [IQR 50, 72]) whereas mice receiving intravenous dextrose developed hyperglycemia (255 mg/dL [118, 367]); enteral dextrose infusion preserved euglycemia (124 mg/dL [101, 153], p=0.01) consistent with prior studies. Interestingly, enteral dextrose in septic mice shifted the microbiome towards Klebsiella pneumoniae dominance with greater than 50% abundance in the large intestine microbiome in 6 of 8 mice. None of the 8 mice receiveng enteral saline and only 1 of 6 mice receiving intravenous dextrose had similar Klebsiella pneumoniae dominance. No significant differences were noted between groups in bacterial cell counts, lung inflammation, or lung or intestine injury.

Conclusion: Enteral dextrose preserved euglycemia in a bacteremic Klebsiella pneumoniae model but was associated with a shift towards Klebsiella pneumoniae dominance in the large intestine. The potential clinical implications of such dominance in the gut microbiome remain unknown, but may suggest preferential growth of certain bacteria favored by specific enteral feed constituents in sepsis. Further studies will characterize the implications of the changes in the microbiome induced by enteral dextrose on incretin hormone release and host response.

7-A Poster: Frataxin deficiency induces endothelial metabolic dysregulation to promote pulmonary hypertension

Presenter: Miranda Culley, Medical Student Cardiology

Research Interest: Bench

Mentors: Stephen Chan MD

Funding Source: Individual NRSA (F32)

Authors: Miranda Culley BA, Jingsi Zhao MS, Ying Tang MS, Yi Yin Tai MS, Thomas Bertero PhD, Mingxia Gu PhD, Qiujun Yu PhD, Vinny Negi PhD, Catherine Corey MS, Sruti Shiva PhD, Stephen Chan MD

Introduction: Pulmonary hypertension (PH) is a progressive vascular disease that causes increased pulmonary arterial pressure, right heart failure, and death. We have previously shown iron-sulfur (Fe-S) cluster deficiency due to repression of iron sulfur cluster assembly protein 1 and 2 (ISCU1/2) promotes mitochondrial dysfunction and PH. Frataxin (FXN), a binding partner of ISCU1/2, is crucial to Fe-S cluster assembly. Genetic FXN deficiency causes Friedreich's ataxia, a disease of neurologic and cardiovascular dysfunction. The latter is often accompanied by PH, but the molecular etiology is unclear. Thus, there may be a direct role for FXN in PH. We hypothesized that FXN deficiency, due to genetic or acquired triggers, disrupts endothelial metabolic function to promote PH.

Methods: FXN expression was modulated in primary human pulmonary arterial endothelial cells (PAECs) by gene transfection and exposure to bromodomain inhibitor I-BET151, hypoxia, and IL-1. Simultaneously, analyses were performed in induced pluripotent stem cell-derived endothelial cells (iPSC-ECs) from patients with Friedreich's ataxia. Fe-S clusters were quantified by fluorescent sensor; glycolytic flux was measured by Seahorse assay. Phenotypic changes, such as apoptosis, migration, vasomotor gene expression, and angiogenesis, were measured. In vivo, cell-specific conditional FXN knockout mice and mice with FXN siRNA delivered to the vascular endothelium were studied.

Results: In PAECs, chronic hypoxia (0.48-fold change ± 0.05, P< 0.01) and IL-1 (0.47-fold change ± 0.01, P<0.05) down-Aegulated FXN expression. I-BET151 inhibition of bromodomain-containing protein 4 (BRD4) as well as siRNA knockdown of BRD4 restored FXN levels following hypoxia (1.91-fold change ± 0.04, P<0.01) while BRD2 inhibition by drug or siRNA restored FXN following IL-1 (1.99-fold change ± 0.10, P<0.01). FXN deficiency decreased Fe-S cluster assembly (0.57-fold change ± 0.05, P<0.01) and increased glycolytic flux (2-fold change ± 0.05, P<0.01) and ROS production (1.46 ± 0.14, P<0.05), leading to increased apoptosis, decreased migration, altered effectors of vasomotor tone, and decreased angiogenesis in vitro. Similar changes in vasomotor tone gene expression were also observed in iPSC-ECs from patients with Friedreich's ataxia. Both genetic (RVSP 32.43 ± 1.452 v. 28.74 ± 0.440, P<0.05) and pharmacologic (RVSP 34.31 mmHg ± 0.18 v. 29.77 ± 0.93, P<0.05) endothelial-specific FXN knockdown in chronically hypoxic mice promoted hemodynamic and histologic indices of PH in vivo.

Conclusion: FXN deficiency induced by hypoxia and IL-1 promotes endothelial-specific metabolic changes, leading to PH development in vivo. Our results may provide a target for diagnostic and therapeutic intervention for PH and may guide genetic identification of a novel cohort of patients at risk for PH.

8-A Poster: Regulation of Bladder Umbrella Cell Paracellular Permeability by Stretch

Presenter: Amity Eaton, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Gerard Apodaca PhD

Funding Source: N/A

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

Introduction: Tight junctions (TJs) encircle the apical borders of epithelial cells and must maintain their function in the face of mechanical forces such as air filling the lungs, blood pumping through the vasculature, or urine accumulating in the bladder. How this is accomplished is not well understood. Umbrella cells (UCs) form the outermost layer of the bladder epithelium. UCs impermeable TJs are a key component of the urothelial barrier to pathogens and toxic metabolites present in urine. TJ permeability depends on the expression of transmembrane claudin proteins, which can be cationic or anionic pore-formers, or can occlude the paracellular pathway. Claudin expression is dynamic, even at steady state; however, how bladder distention affects claudin trafficking is unknown. Despite the importance of the TJ in UC barrier function, and evidence that this barrier is disrupted in several bladder pathologies, we have limited information about the UC TJ barrier composition, or the structural and functional changes that allow it to accommodate cycles of filling and voiding.

Methods: Adenoviral transduction, Electrophysiology, Indirect immunofluorescence, Measurement of exo/endocytosis

Results: We observe that the apical TJ ring circumscribing each UC doubles in length when the bladder is filled. Surprisingly, this is accompanied by a significant increase in ionic permeability across the TJ. Both the length and permeability of the TJ recover to the relaxed state after voiding. Furthermore, we observe an increase in apical UC TJ expression of pore-forming claudins in full bladders, which could explain the observed increase in paracellular permeability.Our lab has shown that the apical membrane of UCs expands upon filling via Rab11-dependent exocytosis, and is internalized via endocytosis, upon voiding. We have, also, observed Rab13, which promotes assembly of functional TJs via exocytosis, localized near the TJ of UCs. Based on these observations it is plausible that during bladder filling a stretch-stimulated, Rab signaling cascade promotes TJ ring expansion and pore-forming claudin delivery via exocytosis, and upon voiding the TJ ring contracts and claudins are internalized via endocytosis. This is supported by our observations that inhibition of exocytosis prevents TJ ring expansion with bladder filling; conversely, inhibition of endocytosis prevents TJ contraction upon voiding. Additionally, transduction with DN-Aab11, DN-Aab13, or Rab13 shRNA prevents expansion of the TJ ring during bladder filling.

Conclusion: These data support my hypothesis that expansion and contraction of the UC TJ depends on Rab-dependent changes in membrane trafficking of claudins which then modulate TJ dynamics, and permeability during the bladder cycle.

9-A Poster: Hemoglobin Inhibits Uptake of Filtered Proteins by Proximal Tubule Cells: Implications for Sickle Cell Disease and Vitamin D Status

Presenter: Megan Eshbach, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Ora Weisz PhD

Funding Source: T32

Authors: Megan Eshbach BS, Amandeep Kaur MD, Youssef Rbaibi BS, Yash Agarwal current undergraduate, Qiangmin Zhang PhD, Dario Vitturi PhD, Thomas Nolin PharmD, PhD, Jesus Tejero PhD, Ora Weisz PhD

Introduction: Proximal tubule (PT) dysfunction, including tubular proteinuria, is a significant complication in sickle cell disease (SCD) that can eventually lead to chronic kidney disease. The PT is especially susceptible to cytotoxic damage, and tubular dysfunction in SCD is thought to result from prolonged exposure to hemoglobin (Hb) released from damaged red blood cells. Hb dimers are filtered by the glomerulus to enter the tubule lumen, and are internalized by PT cells upon binding to the multiligand receptors megalin and cubilin. These receptors bind to numerous proteins in the filtrate, including albumin and vitamin D binding protein, and are important for maintaining protein-free urine and vitamin D homeostasis. We hypothesized that toxicity from exposure to Hb could impair PT cell endocytic function, causing tubular proteinuria.

Methods: We used spectrofluorimetric and imaging approaches to quantify endocytic uptake of fluorescently labeled Hb, albumin, and vitamin D binding protein in a PT cell line. Heme oxygenase 1 (HO-1) expression was quantified by western blotting.

Results: We found that concentrations of Hb predicted to enter the tubule lumen during hemolytic crisis profoundly inhibit the uptake of other megalin/cubilin ligands (albumin and vitamin D binding protein) by PT cells. These effects were independent of heme reduction state, occurred in the absence of a cytotoxic response, and appear to be due to direct competition for megalin/cubilin binding. The Glu7Val mutant that causes SCD was equally effective at inhibiting albumin uptake compared with wild type Hb. Haptoglobin restored albumin uptake in the presence of Hb, suggesting that haptoglobin binding to the Hb aß dimer-dimer interface interferes with Hb binding to megalin/cubilin.

Conclusion: Our studies suggest that the primary cause of tubular proteinuria in SCD is impaired endocytosis of megalin/cubilin ligands due to competition from Hb in the filtrate, rather than toxicity. We established a robust, scalable assay that enables us to screen for selective inhibitors of Hb uptake that may have therapeutic implications in preserving PT function. Our data also suggest a potential explanation for the vitamin D deficiency commonly observed in sickle cell patients. Current studies are focused on characterizing the effects of Hb on vitamin D metabolism and signaling in PT cells.

10-A Poster: Toll-Like Receptor 8 (TLR8) Protein Degradation Limits Inflammatory Signaling

Presenter: John Evankovich, Junior Faculty **Research Interest:** Bench
Pulmonary, Allergy and Critical Care Medicine

Mentors: Rama Mallampalli MD
Bill Chen PhD

Funding Source: Individual NRSA (F32)

Authors: John Evankovich MD, Travis Lear BS, Bill Chen PhD, Rama Mallampalli MD

Introduction: Toll-Like Receptor 8 (TLR8) is a pattern recognition receptor that senses RNA in endosomes, initiating innate immune signaling through Nf-kB. In monocytes TLR8 is activated in response to bacterial RNA, which is present in bacterial infection, a well-established risk factor for ARDS. Thus, TLR8 signaling may be a previously unrecognized contributor to innate immune activation in severe infection and ARDS. Mechanisms regulating TLR8 protein abundance and activation are not completely understood. Protein degradation is a cellular mechanism controlling protein abundance, accomplished through ubiquitin transfer by E3-Ligase proteins. The E3-Ligase protein Triad3A targets similar TLRs for degradation in different cell types. We hypothesized that TLR8 protein degradation, coordinated by the E3-Ligase Triad3A, would reduce TLR8-dependent Nf-kB activation in the presence of activating signals.

Methods: THP-1 cells were treated with cycloheximide (CHX, 0ug/mL), MG-132 (40mMol), Leupeptin (40mMol), or their combination to determine TLR8 protein half-life. Experiments were repeated in the presence of a TLR8 agonist R848 (1 ug/mL). TLR8 ubiquitination was examined by agarose conjugated Tandem Ubiquitin Binding Entities (TUBEs) reagent (LifeSensors, Inc). TLR8 activation was examined by using HEK-Blue TLR8 cells (Invivogen). HEK-Blue TLR8 cells were transfected with an empty vector or a plasmid containing Triad3A and stimulated with the TLR8 agonist R848.

Results: TLR8 half-life was 60 minutes in THP-1 cells, but pretreatment with both the proteasomal inhibitor MG-132 and the lysosomal inhibitor Leupeptin stabilized TLR8 protein levels in CHX chase experiments. Ubiquitinated TLR8 was detected by TUBEs pull-down. Treatment with the TLR8 agonist R848 decreased TLR8 protein levels at 4 h, an effect that was similarly prevented with MG-132 or Leupeptin pre-treatment. In HEK-Blue TLR8 cells, TLR8 agonist R848 treatment increased TLR8-dependent NF-kB activation. This affect was exacerbated by MG-132 and Leupeptin pretreatment. Lastly, TLR8-dependent Nf-Kb activation was abrogated by Triad 3A over-expression.

Conclusion: TLR8 undergoes protein degradation and has a short half-life of 60 minutes. Subcellularly, both the proteasome and the lysosome may participate in TLR8 disposal. TLR8-dependent Nf-Kb signaling is enhanced by preventing TLR8 degradation, and the E3-Ligase Triad3A reduces TLR8-dependent Nf-Kb signaling. Thus, TLR8 degradation, coordinated by Triad3A, may be a mechanism to limit excessive inflammatory signaling response to activating signals. Future studies will examine if these mechanisms are operant in humans with severe infection and ARDS.

11-A Poster: The E138A Mutation Amplifies Resistance to Dapivirine in Combination with NNRTI Mutations

Presenter: Breanna Goetz, Junior Faculty Infectious Diseases

Research Interest: Bench

Mentors: Urvi Parikh PhD

Funding Source: USAID, NIH/NIAID

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

Introduction: The reverse transcriptase (RT) polymorphism E138A occurs naturally in 5% of treatment-naïve HIV-1-subtype C-infected individuals, but is also selected by the diarylpyrimidine (DAPY) class of NNRTIs causing 3-fold resistance to etravirine and rilpivirine. In ASPIRE, frequency of E138A was independent of study arm and conferred modest reductions in DPV susceptibility in some RT backgrounds but not others. We evaluated the genetic basis of reductions in DPV susceptibility by E138A alone and in combination with other NNRTI mutations among recombinant subtype C viruses with E138A derived from seroconverters in ASPIRE.

Methods: ASPIRE was a safety and effectiveness study of a DPV intravaginal ring for HIV-1 prevention conducted at 15 sites in South Africa, Zimbabwe, Malawi and Uganda. Three cases of infection in ASPIRE seroconverters with E138A-containing HIV-1 with and without other NNRTI mutations whose IC50 differed significantly from wild-type (WT) HIV-1 ($p<0.001$) underwent site directed mutagenesis on the plasma-derived recombinant virus to systematically revert each DRM to WT. DPV susceptibility of each plasma-derived mutant and in vitro reverted recombinant HIV-1 was determined in TZM-bl cells. Fold-change (FC) values were calculated comparing the IC50 of viruses containing DRMs to both a bulk-cloned WT control from the same arm and a single colony isolate with DRMs reverted to WT.

Results: In case 1 (placebo arm), HIV-1-E138A had 4-fold change in DPV susceptibility (FC) from HIV-1WT. In case 2 (DPV arm), bulk-cloned HIV-1-E138A/V108IV had 2-FC over WT. A single colony isolate containing only E138A/V108I had 3-FC over WT. This reduced susceptibility was due to E138A, which alone conferred 2-FC over WT, while IC50 of HIV-1-V108I was not different from WT. In case 3 (DPV arm), bulk-cloned HIV-1-E138A/V179IT had 6-FC over WT. The combination of V179I or V179T with E138A had a synergistic effect on resistance; HIV-1-E138A/V179I had 23-FC over WT and HIV-1-E138A/V179T had 13-FC over WT. HIV-1 with E138A, V179I or V179T alone conferred no or modest FC over WT (1 to 5-FC). Reversion of all known DRMs, including E138A, to WT codons resulted in full restoration of DPV susceptibility for all samples.

Conclusion: E138A conferred low level phenotypic DPV resistance in several ASPIRE trial seroconverters. In one seroconverter, E138A with V179I or V179T had a synergistic effect in elevating DPV resistance. This is a novel finding in the understanding of resistance profiles for DPV and highlights the need to continue resistance monitoring in seroconverters using investigational antiretroviral products for HIV prevention.

12-A Poster: Endogenous DNA damage contributes to cardiac failure and dilated cardiomyopathy

Presenter: Aditi Gurkar, Junior Faculty
Geriatric Medicine

Research Interest: Bench

Mentors: N/A

Funding Source: N/A

Authors: Aditi Gurkar PhD, Rebecca Vanderpool PhD, Sara McGowan BS, Mark Ross PhD, Charles McTiernan PhD, Claudette St. Croix PhD, Simon Watkins PhD, Smitha Pillai DVM, John Gorscan MD, Ana Mora MD, Laura Niedernhofer MD

Introduction: With aging, muscle degeneration is universal, affecting both motor and cardiac function. This drives two of the most common aging-Aelated diseases: cardiovascular and musculoskeletal disease. The etiology of age-Aelated decline in myocyte function is not well-defined. Bulky DNA lesions block transcription and thus can negatively impact virtually all other cellular processes. Therefore post-mitotic cells are anticipated to be particularly vulnerable to damage to the nuclear genomes. Genotoxic stress caused by radiation or cancer chemotherapeutic drugs promote degenerative cardiovascular disease. However, it is not known if spontaneous, endogenous DNA damage, which is known to accumulate with age, is sufficient to cause muscle damage.

Methods: We knocked-out ERCC1-XPF, a DNA repair endonuclease required for nucleotide excision repair of bulky lesions, in differentiated myocytes of mice to increase the burden of endogenous DNA damage and determined the impact on muscle function. Echocardiography studies were performed with images collected after the induction of anesthesia and when heart rates were steady as described previously. Left ventricular (LV) function was assessed from pressure and volume loops measured using an admittance pressure-volume catheter.

Results: Loss of DNA repair caused sudden death by 6 months due to myocardial disease. Although, hearts of 2-3 month old *Ckmm-Cre;Ercc*$^{-/fl}$ mice appeared similar to controls, by 4-6 months of age they were dramatically enlarged compared to littermate controls. Gross examination of the heart revealed ventricular wall thinning as well as markedly dilated ventricular lumen in older, but not younger, mutant animals. By 4-6 months of age, the ejection fraction and fractional shortening were significantly reduced in the *Ckmm-Cre;Ercc*$^{-/fl}$ mice compared to age-matched controls. Molecular markers of cardiac failure, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and cardiac troponin were significantly greater in mutant mice at 4-6 months of age. An increase in apoptosis was observed in heart sections from *Ckmm-Cre;Ercc*$^{-/fl}$ mice with age. Expression of Cat, Hmox1 and Nqo1 antioxidant genes were reduced significantly in mutant mice. Transgenic mice expressing mitochondrial-targeted catalase in *Ckmm-Cre;Ercc*$^{-/fl}$ reduced serum cardiac troponin I compared to *Ckmm-Cre;Ercc*$^{-/fl}$ littermate controls.

Conclusion: These data support a role for endogenous DNA damage in cardiomyocyte dysfunction and congestive heart failure and define a novel murine model of this age-Aelated degenerative disease for rapidly testing therapeutic interventions.

13-A Poster: Spinal cord injury induced neural degeneration in the mouse urinary bladder via pro-apoptotic p75NTR signalling

Presenter: Youko Ikeda, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: Anthony Kanai PhD

Funding Source: P01DK093424

Authors: Youko Ikeda PhD, Irina Zabbarova PhD, F. Aura Kullmann PhD, Samuel Getchell PhD, Lori Birder PhD, Pradeep Tyagi PhD, Evan Carder BSc, Peter Wipf PhD, Anthony Kanai PhD

Introduction: The role of neurotrophins in neurogenic bladder dysfunction has been extensively investigated, however, the role of its precursor, proneurotrophins, has received less attention. Proteolytically processed mature neurotrophins can bind to the p75 neurotrophin receptor (p75NTR)-TrkA/B complex to promote cell growth and differentiation. Interestingly, proneurotrophins can also bind to p75NTR-sortilin dimer to initiate apoptotic pathways. Therefore, proneurotrophins may elicit different effects to the mature proteins following nerve injury. Our aim was to determine the expression of the p75NTR in control and spinal cord transected (SCT) mice and evaluate changes in expression caused by treatment with the small molecule p75NTR modulator, LM11A-31.

Methods: Female C57Bl/6 mice were used for this study and spinal cord injury was induced by completely transecting between the T8-T9 vertebrae. Mice were sacrificed at seven days after surgery and bladders, dorsal root ganglia and spinal cords were isolated (N=3). LM11A-31 (100 mg/kg in water) was administered daily by gavage starting one day before surgery. Freshly isolated tissues from control and seven day post-SCT mice were embedded for cryo-sectioning. Tissues were examined for immunoreactivity to p75NTR, the sensory nerve marker calcitonin gene related peptide (CGRP), sympathetic nerve marker tyrosine hydroxylase (TH), and nuclei were stained with DAPI. Images from were obtained using an Olympus FV3000 confocal microscope system.

Results: Control mouse bladders demonstrated the expression of p75NTR on nerve-like structures throughout the bladder wall that co-localised with TH and CGRP. In bladders from SCT mice there was decreased TH-immunoreactivity and no apparent co-localisation with p75NTR. At this time-point, CGRP-immunoreactivity was increased specifically in the lamina propria which again did not co-localise with p75NTR. LM11A-31 treatment preserved localization with TH but not CGRP. In the L6-S1 spinal cord segment of control mice (where the majority bladder innervation arises) p75NTR was localized to the dorsal horn. Following, SCT there was alteration in the pattern of p75NTR expression, with higher levels near the central canal. Treatment with LM11A-31 further enhanced remodelling the p75NTR nerves throughout the dorsal horn.

Conclusion: These data demonstrate that p75NTR is robustly expressed on sensory and sympathetic nerves innervating the mouse urinary bladder and the dorsal horn of L6-S1 spinal cord. Following spinal cord injury, the surge of proneurotrophins likely activate neural degenerative processes. Treatment with the p75NTR modulator prevented peripheral degeneration and even enhanced neural sprouting in the spinal cord. Therefore, modulators of p75NTR may be a potential therapeutic for neural degenerative conditions.

14-A Poster: Title: Impact of CREBRF and its obesity risk variant on glucose homeostasis and insulin action in mice

Presenter: Aneta Kowalski, Medical Student
Endocrinology and Metabolism

Research Interest: Bench

Mentors: Erin Kershaw MD

Funding Source: UPSOM Physician Scientist Training Program

Authors: Aneta Kowalski BS, Michael Jurczak PhD, Erin Kershaw MD

Introduction: The prevalence of obesity and diabetes are escalating worldwide. Identifying genes/pathways that influence the pathogenesis of these disorders could improve prevention and treatment. Recently, a novel missense variant in CREB3 Regulatory Factor (CREBRFR457Q) was identified by GWAS in Samoans1. This variant increases the risk of obesity but paradoxically protects against diabetes in humans. Although virtually nothing is known about this gene, its Drosophila homolog mediates the transcriptional response to nutritional stress downstream of the cellular energy sensor TORC1. Furthermore, both flies and mice with global deletion of CREBRF have impaired glucose tolerance despite lower fat mass. These data support an important role for CREBRF in energy/metabolic homeostasis and suggest that the CREBRFR457Q variant may be gain-of-function with respects to energy/metabolic homeostasis. The goal of the current study was to determine the impact of CREBRF and its missense variant on glucose homeostasis and insulin sensitivity in vivo using animal models. We hypothesized that global deletion of CREBRF in mice would impair glucose homeostasis, in part, by impairing insulin action in insulin-sensitive target tissues (liver, muscle, adipose tissue).

Methods: We performed hyperinsulinemic euglycemic clamps, the "gold standard" technique for determining whole-body and tissue-specific insulin sensitivity, on 10-12 week-old, high fat diet-fed, Crebrf KO and control mice.

Results: CrebrfKO mice tended to have lower body weight ($p=0.09$) and lean mass ($p=0.07$) than control mice, but similar fasting plasma glucose and insulin. Whole-body glucose turnover, a reflection of hepatic glucose production (HGP), was lower in CrebrfKO mice at baseline ($p<0.05$) but not during the clamp. CrebrfKO mice required a 28.5% lower glucose infusion rate (GIR) to maintain euglycemia during the clamp, consistent with greater whole-body insulin resistance. This insulin resistance could be attributed, in part, to reduced peripheral insulin sensitivity, as evidenced by 22.6% lower total peripheral glucose uptake. Tissue-specific glucose uptake was lower in skeletal muscle ($p<0.01$) and inguinal white adipose tissue ($p<0.07$), but not in perigonadal adipose tissue or cardiac muscle, implicating the former tissues in the impaired insulin sensitivity of CrebrfKO mice.

Conclusion: These data indicate that CrebrfKO have impaired glucose homeostasis and greater peripheral insulin resistance that is primarily due to lower insulin-mediated glucose uptake in skeletal muscle and inguinal adipose tissue. Additional studies are required to evaluate the underlying mechanisms by which CREBRF influences insulin action in these tissues. Similar studies in CrebrfKI mice are ongoing. Together these studies are expected to provide insight into how CREBRF and its risk variant influence human disease.

15-A Poster: Mind-body interactions: autonomic and mitochondrial dysregulation play key roles in Interstitial Cystitis/Bladder Pain Syndrome

Presenter: Aura Kullmann, Junior Faculty Renal-Electrolyte

Research Interest: Bench

Mentors: N/A

Funding Source: AUA Urology Care Foundation

Authors: Aura Kullmann PhD, Bronagh McDonnell PhD, Amanda Wolf-Johnston BS, Andrew Lynn BS, Rebecca Bergman BS, Tony Kanai PhD, Sruti Shiva PhD, Lori Birder PhD

Introduction: Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a debilitating chronic condition characterized by persistent pain related to bladder filling, urinary frequency and nocturia. In humans and animals with IC/BPS, psychological stress exacerbates associated hyperalgesia and pain. There is exciting new evidence that mitochondrial dysfunction and oxidative stress are implicated in chronic pain as well as autonomic dysregulation. Our novel concept is that abnormal processing of chronic stress involving autonomic and mitochondrial dysregulation can negatively impact urothelial signaling, leading to altered sensations and pain in patients with PBS/IC. The aim of this study was to examine the influence of chronic stress and autonomic signalling on mitochondrial dysfunction in bladder urothelium.

Methods: Female Wistar Kyoto rats (3-4 months old) were exposed to chronic water avoidance stress (WAS; 1hour/day for 10days). To test the involvement of the sympathetic nervous system, some rats were treated with guanethidine which depletes catecholamines (50mg/kg, i.p.; every other day starting two days prior to WAS and throughout the WAS protocol) or the adrenergic receptor (a1/a2-AR) antagonist, phenoxybenzamine (2mg/kg i.p. every day starting on day 1of WAS and throughout the WAS protocol). Bladders were collected and utilized for urothelial cell cultures (UTC). UTC were loaded with various intracellular dyes to examine functional responses. These included: fura-2AM (to measure intracellular calcium concentration, [Ca2+]i), DHR123 (to measure reactive oxygen species-AOS) and TMRM (to measure mitochondria membrane potential, ?m).

Results: WAS UTC exhibit a more depolarized ?m compared to control UTC, a higher baseline [Ca2+]i and inability to buffer [Ca2+]i after a stimulus (i.e., mitochondria uncoupler FCCP 5-10μM). Both guanethidine and phenoxybenzamine treatment of WAS animals normalized these alterations, supporting sympathetic nervous system involvement. Basal ROS was similar between WAS and control UTC. In contrast, ROS generation in response to stressors (H2O2) was significantly higher in WAS UTC. ROS were also generated in both control and WAS UTC by stimulation of a-ARs with phenylephrine but not of ß-ARs with isoproterenol.

Conclusion: Taken together, these results suggest alterations in urothelial cell homeostasis related to compromised mitochondria function and involving the autonomic nervous system. Our findings in an animal model of chronic stress induced IC/BPS, support the view that impaired mitochondria function may play a role in impaired voiding and pain sensations in IC/BPS. Mitochondria targeted therapies may hold future promise to restore abnormal signalling in functional pain disorders such as IC/BPS and may contribute to improvement of symptoms in these patients.

16-A Poster: Putative role of stress-induced abnormal neuronal calcium homeostasis in Interstitial Cystitis/Bladder Pain Syndrome

Presenter: Aura Kullmann, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: N/A

Funding Source: Bider NIH grants

Authors: Aura Kullmann PhD, Bronagh McDonnell PhD, Andrew Lynn BS, Rebecca Bergman BS, Amanda Wolf-Johnston BS, Lori Birder PhD

Introduction: Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a debilitating chronic condition characterized by persistent pain related to bladder filling, urinary frequency and nocturia. Chronic stress exacerbates bladder hyperalgesia in patients and animal models. Recent studies have shown that mitochondrial dysfunction is implicated in chronic pain in disorders impacted by chronic stress. Bladder hyperalgesia is characterized by hyperexcitability of the primary sensory neurons. Calcium signaling in these neurons, which is critically regulated by mitochondria, is a key player influencing detection and processing of noxious signals. Thus, our aim was to assess whether chronic stress impacts calcium homeostasis and mitochondrial signaling in bladder primary sensory neurons.

Methods: Female Wistar Kyoto rats (3-4 months old) were exposed to chronic water avoidance stress (WAS; 1hour/day for 10days). On day 11 rats were placed in metabolism cages for 24 hours to assess bladder function, then sacrificed. Dissociated L6-S1 dorsal root ganglion (DRG) neurons from control and WAS rats were loaded with fura-2AM (to measure intracellular calcium concentration - [Ca2+]i) or tetramethylrhodamine, methyl ester (to measure mitochondria membrane potential, ?m). In some experiments DRG neurons innervating the bladder were identified by pre-labelling with FAST DiI injected into the bladder wall.

Results: WAS rats showed increased voiding frequency and decreased voided volume. WAS DRG cells exhibited higher baseline [Ca2+]i and a trend towards smaller changes in [Ca2+]i in response to the mitochondria protonophore FCCP. There were no significant differences in the ?m or FCCP-induced ?m depolarizations. There were a number of alterations in the [Ca2+]i changes in response to stimulation of nociceptive TRPV1 and TRPA1 channels.

Conclusion: These results suggest that WAS produced changes in bladder function that are consistent with those reported in IC/BPS patients. Changes induced in the primary afferent neurons (abnormal calcium homeostasis and buffering mechanisms) may result from alterations in the mitochondria and/or expression and function of ion channels involved in pain (TRPV1, TRPA1). These can alter the excitability of primary afferent neurons and contribute to urgency, frequency and pain.

18-A Poster: Tead1 reciprocally regulates adult ß-cell proliferation and function

Presenter: Jeongkyung Lee, Junior Faculty
Endocrinology and Metabolism

Research Interest: Bench

Mentors: Vijay Yechoor MD

Funding Source: VA

Authors: Jeongkyung Lee PhD, Ruya Liu MD PhD, Byung Kim BS, Yiqun Zhang PhD, Pradip K. Saha PhD, Omaima Sabek MD, Cristian Coarfa PhD, Chad J. Creighton PhD, Mark O. Huising PhD, Mousumi Moulic MD, Vijay K. Yechoor MD

Introduction: The transcriptional factor, Tead1, mediates the transcriptional output of the evolutionarily conserved organ size control mammalian Hippo pathway. Tead1 activates the transcription of downstream genes, including cyclins and cyclin-dependent kinases that lead to cell proliferation in other tissues, but its role in ß-cells is unknown. Tead1-null mice are embryonically lethal due to severe cardiac developmental disorders, limiting the study of Tead1 in ß-cells. To circumvent this, we deleted Tead1, only in ß-cells to test its function.

Methods: We generated ß-cell Tead1 knockout (ß-Tead1-/-) mice by crossing floxed Tead1 mice with Rip-Cre deletor mice. Whole body glucose homeostasis, ex vivo insulin secretion in isolated islets, western blotting, gene expression studies were carried out in these mice and compared to appropriate controls. Students t-test or ANOVA was used to test statistical significance with a $p<0.05$ considered to be significant.

Results: Deletion of Tead1 in ß-cells was confirmed in these ß-cell Tead1 KO (ß-Tead1-/-), by a significant decrease in transcript and protein from whole islet lysates and by immunostaining. The ß-Tead1-/- mice had normal body weight as compared to controls, but developed significantly higher fasting and fed glucose levels starting at 5 weeks of age and progressed to frank diabetes by 8 weeks, with fasting blood glucose >300 mg/dl, accompanied by hypoinsulinemia as compared to floxed control mice. 8 week old ß-Tead1-/- mice display severe glucose intolerance that was secondary to an abrogation of glucose stimulated insulin secretion, in vivo, during the glucose tolerance test along with a complete loss of first phase insulin secretion, as compared to controls. Deletion of Tead1 in ß-cells led to a significant decrease in pancreatic insulin content by ~50%. This is secondary to a decrease in the expression of many mature ß-cell genes including, Pdx1, Nkx6.1 and MafA, all of which we show to be direct transcriptional targets of Tead1. Tead1 also was bound to the proximal promoter at the Ink4a locus, on ChIP assay, to regulate p16/p19, critical cell cycle inhibitors, and this loss of activation in Tead1-deficient ß-cells led an enhanced entry into cell cycle.

Conclusion: Our results demonstrate Tead1 to be a transcriptional switch that is required for ß-cells to maintain mature function and remain in the quiescent state. Targeting this novel regulatory pathway may be required for ß-cell replacement therapy for diabetes to achieve ß-cell proliferation without a loss of mature function.

19-A Poster: From GWAS to functional SNPs and to Mechanisms

Presenter: Gang Li, Junior Faculty Cardiology

Research Interest: Bench

Mentors: N/A

Funding Source: RO1, R21

Authors: Gang Li PhD

Introduction: Genome wide association studies (GWAS) open a new era to study complex diseases. This is done by identifying numerous disease-associated genetic variants. Most of these variants are single nucleotide polymorphism (SNP) in the non-coding region of human genome. However, GWAS cannot distinguish the functional SNPs (fSNPs) from the many non-Aandomly associated SNPs that are in linkage disequilibrium (LD).

Methods: To identify the fSNPs and characterize the mechanisms underlying the contribution of the disease-associated, non-coding fSNPs, we developed fSNP-seq (fSNP-next generation sequencing) to experimentally identify fSNPs in an unbiased high throughput screen and FREP-MS (Flanking Restriction Enhanced DNA Pulldown-Mass Spectrometry) to identify regulatory proteins that control risk gene expression by binding specifically to the fSNPs with great efficiency.

Results: By using fSNP-seq and FREP-MS as a tandem, in a low throughput experimental trial, we identified 3 fSNPs together with 4 CD40 regulatory proteins functioning via the 3 fSNPs on a disease-associated CD40 locus. In a high throughput screening, we identified 148 potential fSNPs out of 608 juvenile idiopathic arthritis (JIA)-associated SNPs. We further proved 2 fSNPs on a JIA-associated STAT4 locus together with multiple STAT4 regulatory proteins.

Conclusion: We developed a potentially transformative approach to bridge the gap between GWAS and biological mechanisms underlying the contribution of disease-associated, non-coding fSNPs.

22-A Poster: The epithelial sodium channel in the endothelium alters vascular reactivity with high salt diet

Presenter: Stephanie Mutchler, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Thomas Kleyman MD

Funding Source: T32

Authors: Stephanie Mutchler BS, Mahpara Hasan , Thomas Kleyman MD

Introduction: The epithelial sodium channel (ENaC) is an important regulator of fluid clearance and sodium transport in epithelial tissues throughout the body, including the kidney and lung. More recently, it has been discovered that ENaC is present in both the endothelial and smooth muscle components of the vasculature, extending its role to include modulation of nitric oxide (NO) signaling and myogenic tone, respectively. While others have shown that endothelial ENaC (EnENaC) is involved in nitric oxide signaling and flow mediated vasodilation, it is not known what role this protein plays in advancement of cardiovascular disease due to stresses such as high salt diet (HSD). Here, we aim to test the role of this protein in vascular reactivity and remodeling with various lengths of HSD.

Methods: Mice were given an 8% NaCl diet for two/four/eight weeks. Arteries were dissected and mounted on a pressure myograph to test responsiveness to stimuli including phenylephrine, acetylcholine, and sodium nitroprusside (SNP) either with or without amiloride, an ENaC inhibitor, present in the lumen. An endothelial-specific ENaC KO mouse was generated utilizing the cre-lox system, which we are currently assessing vascular reactivity in.

Results: EnENaC inhibition did not significantly alter acetylcholine response in vessels taken from control animals. However, EnENaC inhibits acetylcholine-induced vasodilation at 8-weeks HSD as shown by amiloride's leftward shift of the dose response curve. This finding was hypothesized given previous work showing EnENaC inhibits NO signaling in cell culture. However, EnENaC at 4-weeks HSD appears to promote vasodilation as shown by the rightward shift of the curve with EnENaC inhibition. Furthermore, 4-week HSD vessels when treated with amiloride cannot sustain vasodilation, but instead have a transient dilatation before constricting again. All vessels treated with amiloride have a slightly leftward shifted response to SNP, and there is no significant difference in phenylephrine response.

Conclusion: Our surprising results suggest the role of EnENaC in the vasculature is more dynamic than previously thought. While EnENaC does seem to limit acetylcholine-mediated vasodilation (and potentially NO production) with long-term HSD administration, the protein may initially serve to help promote vasodilation. The SNP data suggests that under all circumstances ENaC inhibition in the smooth muscle may serve to increase sensitivity to NO, which suggests the differential response seen here is due to changes in the endothelium. Further experiments will examine the signaling mechanism through the use of various inhibitors. Additionally, an endothelial-specific KO mouse will be used to assess vascular phenotypes further.

23-A Poster: Aggravated erythrophagocytosis impairs IFN-γ -mediated Irg1 expression in response to Klebsiella pneumoniae.

Presenter: Tolani Olonisakin, Medical Student **Research Interest:** Bench
Pulmonary, Allergy and Critical Care Medicine

Mentors: Janet Lee MD

Funding Source: R01HL136143 (JSL), R01HL086884 (JSL),R21AI119042

Authors: Tolani Olonisakin BA, Zeyu Xiong MD, Janet Lee MD

Introduction: Aggravated erythrophagocytosis — as occurs with transfusion of aged, damaged red blood cells (RBC) — results in an acute increase in mammalian iron recycling and a concurrent rise in transferrin bound and non-transferrin bound iron that may serve as nutrition for opportunistic extracellular pathogens such as Klebsiella pneumoniae. While enhanced delivery of effete RBC to macrophages may increase pathogen virulence by boosting nutritional iron source to the pathogen, heightened erythrophagocytosis may weaken immunity through dysregulated iron metabolism in the host cell. We hypothesized that aggravated erythrophagocytosis overwhelms physiologic RBC disposal and suppresses the host innate immune response to bacterial infection.

Methods: 8 to12-week-old male and female C57BL/6J mice were inoculated intratracheally with K. pneumoniae strain (ATCC 43816) and were transfused an hour later with 200 µL of syngeneic leukoreduced fresh RBC (0-1 day old) or aged RBC (11 day old). This transfusate volume approximates one unit of packed RBC in humans. 24h later, livers were excised and gene expression was evaluated by PCR Array and qPCR. Protein expression in liver tissue was evaluated by ELISA and immunoblotting. The murine macrophage cell line RAW 264.7 was utilized in vitro to delineate cell signaling.

Results: As the liver is the primary organ that mediates damaged RBC removal, we evaluated innate immune transcriptional responses in livers of mice transfused with either fresh or aged RBCs 24h following acute intrapulmonary K. pneumoniae infection. We observed selective suppression of Ifng, gamma-inducible Cxcl10, and immunoresponsive gene 1 (Irg1) that encodes the mitochondrial citric acid cycle intermediate, cis-aconitate decarboxylase, in livers of aged RBC-transfused mice. Suppression of IFN-γ signaling pathway was validated by protein expression, as we observed attenuated IFN-γ, phosphorylated STAT-1, and IRF-1 protein expression in livers of aged RBC-transfused mice. We further demonstrated that IFN-γ augments intracellular killing of K. pneumoniae and that IFN-γ induces Irg1 expression in macrophages.

Conclusion: Using an established model of K. pneumoniae infection and comparative damaged RBC, we demonstrate that aggravated erythrophagocytosis suppresses IFN-γ and downstream Irg1 expression. Our findings invite the possibility that aged RBC-mediated suppression of Irg1, which is highly expressed in mammalian macrophages during bacterial infection and has been ascribed multiple roles in immunity, may be detrimental to the host during infection.

24-A Poster: Response of BK-alpha intercalated cell knock out mice to a high K diet

Presenter: Evan Ray, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: Thomas Kleyman MD
Rebecca Hughey PhD
Edwin Jackson PhD

Funding Source: K08

Authors: Rolando Carrisoza-Gaytan PhD, Allison Marciszyn PhD, P Wu , Leah Liu , Arohan Subramanya MD, Wenhui Wang MD, Daniel Flores PhD, Donald Kohan MD, Lisa Satlin MD, Thomas Kleyman MD

Introduction: Flow-induced K secretion (FIKS) in the cortical collecting duct (CCD) is mediated by apical Ca2+-/stretch-activated BK channels. These channels also contribute to the renal adaptation to dietary K intake. BK channels are expressed in both intercalated (ICs) and principal cells (PCs) in CCDs. It remains unclear whether IC or PC BK is more important for FIKS. We asked whether BK deletion in ICs altered FIKS.

Methods: We generated a mouse with targeted deletion of BKa, the pore forming subunit of the BK channel, in ICs (IC-BKa-KO) by crossing floxed BKa mice with B1 V-ATPase Cre mice, after confirming that the B1 Cre was expressed primarily in ICs in the kidney. As the targeted deletion in exon 7 of the BKa sequence was not expected to lead to a frame shift, immunodetectable BKa was identified in ICs of IC-BKa-KO CCDs using an antibody directed against the BKa C terminus. Animals were placed on a high K diet for 10 days to induce BK expression. Perforated whole cell recordings were performed to assess currents attributable to BK. Animals were given isotonic saline injection to stimulate renal tubular flow, and urinary Na and K excretion were measured over 6 hours. Plasma electrolytes were measured via iSTAT.

Results: Electrophysiology: in IC-BKa-KO mice, 4 ICs had no BK currents, and 3 ICs had low charybdotoxin-sensitive K currents (37, 65, 90 pA). Currents were readily detectable in 2 ICs in WT mice fed a control K diet (600-800 pA). Over 6 hours following saline injection, rates of urinary Na (39.1±11.1 vs. 36.0±15.2 μmol/hr) and K (165.5±50.1 vs. 171.9±76.0 μmol/hr) excretion were similar in IC-BKa-KO (n=10) and floxed (n=17) mice of both sexes. KO mice exhibited a higher blood [K] (5.5±0.8 vs. 5.0±0.7 mM; $p<0.05$) and BUN (25.3±5.7 vs. 20.6±5.1 mg/dL; $p<0.03$) vs. floxed controls although BW did not differ (21.0±2.7 vs. 22.6±3.4.gm, respectively). The difference in blood [K] between male IC-BKa-KO and floxed mice was highly significant (5.7±0.7 vs.5.0±0.7 mM; n=14 and 16, $p<0.02$). In the absence of volume expansion, rates of urinary Na (1.3±0.8 vs. 1.3±1.3 μmol/hr) and K (50.9±23.7 vs. 40.4±22.5 μmol/hr) excretion were similar in the two groups over a 6 hr period (n=9 and 15, respectively).

Conclusion: These results suggest that in the absence of IC BKa, mice have a limited capacity for adaptation to a HK diet, as evidenced by the higher blood [K], but still demonstrate FIKS.

25-A Poster: Characterization of A Mouse ENaC Gamma Subunit Hypomorph in the Lungs and Beyond

Presenter: Evan Ray, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: Thomas Kleyman MD
Rebecca Hughey PhD
Edwin Jackson PhD

Funding Source: K08

Authors: Evan Ray MD PhD, Aaliyah Winfrey BS, Allison Marciszyn PhD, Yanyan Qu PhD, Mei Hulver PhD, Irina Tourkova PhD, Lyubov Kublo MD, Stephanie Mutchler BS, Yaacov Barak PhD, Harry Blair MD, Janet Lee MD, Thomas Kleyman MD

Introduction: The epithelial sodium channel (ENaC) is expressed in numerous epithelia, including renal tubular and bronchial epithelium. a, ß, and γ subunits participate in channel formation. Experiments in exogenous expression systems suggest that the γ subunit may be the subject of extensive post-translational regulation, through mechanisms such as activation by proteolytic cleavage and cysteine palmitoylation. Studies of the function of this subunit have been impaired by perinatal mortality in knock-out mice. We generated a γ subunit hypomorph that dramatically reduces expression of the subunit without significantly reducing mouse viability. We tested the hypothesis that ENaC known to be expressed in airway epithelial cells of the lungs will enhance clearance of P. aeruginosa following acute-intrapulmonary infection.

Methods: Transgenic mouse generation: Transgenic mice were generated via classical homologous recombination and back-crossed in the 129sv background. Renal expression was examined via rtPCR and western blot. Plasma creatinine was measured at the University of Texas P30 O'Brien Kidney Center. Aldosterone levels were measured via ELISA. Plasma electrolytes were measured via iSTAT. Clearance of P. aeruginosa from the lower respiratory tract was examined following intratracheal inoculation of 10^6 CFU. Twenty hours after inoculation, mice were euthanized and the left lung was harvested for CFU determination.

Results: Quantitative PCR and Western blot confirm under-expression of the ENaC γ subunit in kidney relative to controls. Consistent with this observation, plasma aldosterone was noted to be elevated. Plasma K was not significantly elevated. Preliminary results suggest reduced lung bacterial burden of P. aeruginosa in the lungs of mice under-expressing the EnaC γ subunit.

Conclusion: These results are consistent with the participation of γ subunit in influencing pulmonary mucociliary clearance. Further studies will address whether this clearance is specific to P. aeruginonsa and whether mutations that alter post-translational regulation of the γ subunit also alter mucociliary clearance. Continued experiments will examine the physiologic role of ENaC's ? subunit in tissues outside the kidney and lung.

26-A Poster: Exposure of proximal tubule cells to fluid shear stress alters transcription of metabolic pathway enzymes

Presenter: Qidong Ren, Medical Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Ora Weisz PhD

Funding Source: Tsinghua MD Scholars Program
NIH R01 DK101484

Authors: Qidong Ren Medical Student, Megan Eshbach BS, Natalie Rittenhouse BS, Kimberly Long PhD, Youssef Rbaibi BS, Joseph Locker MD, Amanda Poholek PhD, Lia Edmunds PhD, Michael Jurczak PhD, Ora Weisz PhD

Introduction: Cells lining the proximal tubule (PT) of the kidney are specialized for efficient recovery of ions, glucose, and proteins from the glomerular filtrate. Despite their high glucose levels, PT cells in vivo utilize gluconeogenic rather than glycolytic pathways to maintain the robust metabolic activity needed to carry out their functions. In contrast, the reliance of PT cell cultures on glycolytic metabolism has been a significant limitation in studying the regulation of PT function in vitro.

Methods: We performed RNA Seq on OK cells maintained under static conditions or exposed to FSS for up to 96 h. Principal component analysis confirmed significant time- and FSS-dependent changes in gene expression.

Results: We discovered recently that opossum kidney (OK) cells cultured under continuous fluid shear stress (FSS) develop morphological and functional characteristics that more closely resemble PT cells in vivo compared with cells cultured under static conditions. Consistent with enzyme activity profiles described in the PT, we observed an increase in transcripts encoding enzymes in the gluconeogenic pathway in OK cells cultured under FSS, and a concomitant reduction of transcripts encoding glycolytic enzymes.

Conclusion: Current studies are underway to extend and validate our observations using complementary approaches. Our data provide further support that OK cell culture under FSS provides an improved model of the PT.

27-A Poster: ASIC3 fine-tunes bladder sensory signaling

Presenter: James Rooney, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Marcelo Carattino PhD

Funding Source: NIH

Authors: James Rooney BS, Nicolas Montalbetti PhD, Allison Marciszyn BS, Marcelo Carattino PhD

Introduction: Acid-sensing ion channels (ASICs) are trimeric proton-activated cation selective neuronal channels that are believed to play important roles in mechanosensation and nociception.

Methods: Here we investigated the role of ASIC3, a subunit primarily expressed in sensory neurons, in bladder sensory signaling and function.

Results: We found that extracellular acidification evokes a transient increase in current, consistent with the kinetics of activation and desensitization of ASICs, in ~ 25% of the bladder sensory neurons harvested from both wild type (WT) and ASIC3 knockout (KO) mice. The absence of ASIC3 increased the magnitude of the peak evoked by extracellular acidification and reduced the rate of decay of the ASIC-like currents. These findings suggest that ASICs are assembled as heteromers and that the absence of ASIC3 alters the composition of these of channels in bladder sensory neurons. Consistent with the notion that ASIC3 serves as a proton sensor, 59% of the bladder sensory neurons harvested from WT, but none from ASIC3 KO mice, fired action potentials in response to extracellular acidification.

Conclusion: Our findings indicate that ASIC3 is part of a proton receptor expressed in a set of bladder sensory neurons where it plays an important role tuning bladder afferent signaling.

28-A Poster: Classification of Pancreatitis Subtypes Using Rna-Seq from Human Pancreatic Tissue

Presenter: Celeste Shelton, Graduate Student
Gastroenterology, Hepatology and Nutrition

Research Interest: Bench

Mentors: David Whitcomb MD PhD

Funding Source: T32

Authors: Celeste Shelton MS, David Whitcomb MD PhD

Introduction: Pancreatitis is a complex acute and chronic inflammatory disorder in which different genetic and environmental factors produce a similar clinical phenotype and for which no effective preventive or therapeutic agents exist. The etiology of inflammation, how it becomes continuous and irreversible, and why there is variability in pain and loss of function remains obscure, in part because human tissue has been largely unavailable for study. For some patients, the pain, disability and potential outcomes are so severe, progressive, or unpredictable that they opt for total pancreatectomy with islet autotransplantation (TPIAT). Leftover tissue from TPIAT is collected at the optimal time to evaluate the underlying pathogenesis – after a pathogenic, progressive natural history is predicted, but before the insulin-producing islets are lost. This tissue represents a rich resource to study biological drivers of chronic pancreatitis (CP) progression in humans.

Methods: Two separate studies were used to evaluate underlying gene expression. First, RNA was extracted from 18 pancreata (6 control, 3 CP, 6 pancreatic adenocarcinoma, 3 neuroendocrine tumors) and used for mRNA-Sequencing to demonstrate feasibility. Second, RNA was extracted from TPIAT RNA later samples (1 PRSS1 CP; 2 idiopathic CP; 1 alcoholic recurrent acute pancreatitis (RAP)) and histologically normal tissue from pancreatic cancer. RNA integrity was consistent among samples, and total RNA-sequencing was used for optimal coverage.

Results: On principal component analysis (PCA), clear separation was seen between normal tissue, pancreatic cancer, neuroendocrine tumors and CP. Further analysis of phase 2 data demonstrated clear separation between TPIAT tissue by stage and etiology. Tissue expression profiles provided functional insights into disease mechanisms and drivers of CP progression. Pathway-dependent differences in gene expression enabled subclassification of pancreatitis tissue by stage and underlying molecular pathogenesis, such as activation of the humoral immune response.

Conclusion: We demonstrate that RNA-Seq can be used to effectively classify human pancreatic tissue by diagnosis (normal, cancer, CP, neuroendocrine tumor). Clustering of pancreatitis subtypes (e.g. RAP, CP) from TPIAT tissue provides a framework to predict disease stage and etiology, as well as possible therapeutic targets from underlying expression pathways. Differences in expression profiles reveal divergent disease mechanisms and provide functional clues into etiopathogenesis.

29-A Poster: Regulation of the epithelial Na+ channel by paraoxonase-2

Presenter: Shujie Shi, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: Thomas Kleyman MD

Funding Source: K01

Authors: Shujie Shi PhD, Teresa Buck PhD, Carol Kinlough BS, Allison Marciszyn PhD, Jeffrey Brodsky PhD, Rebecca Hughey PhD, Thomas Kleyman MD

Introduction: Epithelial sodium channel (ENaC) mediates the rate-limiting step of Na+ uptake across the apical membrane of specific epithelia. Functional ENaC complexes in the kidney consist of three homologous subunits, namely a, ß, and γ. ENaC-dependent Na+ absorption in the kidney has important roles in regulating extracellular fluid volume, blood pressure and extracellular [K+]. And thus, ENaC expression is tightly regulated by both intracellular and exogenous factors. Several molecular chaperones have been implicated in key steps during ENaC biogenesis. Paraoxonase-2 (PON-2) is a membrane-bound protein that shares structural features with MEC-6, an ER-Aesident chaperone in worm's touch receptor neurons. MEC-6 is required for the proper folding, assembly and surface expression of the C. elegans MEC-4/MEC-10 channel, members of the ENaC/degenerin family. However, it remains unknown whether PON-2 also function as a chaperone and whether PON-2 regulate ENaC functional expression.

Methods: The role of PON-2 in regulating ENaC expression was examined in both Xenopus oocytes and FRT cells. The effect of PON-2 on ENaC activity was assessed by measuring whole cell Na+ currents in oocytes expressing WT or mutant ENaC in the presence or absence of PON-2. We performed biochemical and electrophysiological assays in FRT cells to address whether ENaC surface expression and channel activity are altered in polarized epithelial cells under conditions in which PON-2 is either over-expressed or silenced.

Results: When expressed in Xenopus oocytes, PON-2 inhibits ENaC activity, at least in part, by reducing the number of functional channels at cell surface. The enzymatic activity of PON-2 is dispensable for its inhibitory effect on ENaC activity. PON-2 is expressed in the principal cells of the distal nephron, where ENaC resides, and forms a complex with ENaC subunits when expressed in HEK293 cells. In addition, PON-2 also reduces whole cell expression of ENaC (both the full length and the cleaved forms), or subunit in FRT cells, likely by facilitating protein degradation.

Conclusion: Taken together, our results suggest that PON-2, like MEC-6 functions as a chaperone to regulate ion channel expression. Regulation of ENaC by PON-2 may represent a key regulatory mechanism in ENaC biogenesis.

30-A Poster: Mathematical model of megalin trafficking in differentiated proximal tubule cells

Presenter: Katherine Shipman, Graduate Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Ora Weisz PhD

Funding Source: GSR

Authors: Katherine Shipman BS, Kimberly Long PhD, Youssef Rbaibi BS, Catherine Baty DVM, PhD, Ora Weisz PhD

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 the endocytosis in the proximal tubule is dysfunctional, tubular proteinuria results. Tubular proteinuria is often an early sign of kidney damage and is observed in many clinical settings, including genetic disorders, diabetes, sickle cell disease, and after renal transplantation.

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. Using biochemical techniques in conjunction with this system, we have estimated endocytic and recycling rates and the half-life of surface megalin. These data were used to construct a model of megalin trafficking.

Results: We present an ordinary differential equation (ODE) model of megalin trafficking describing surface and internalized pools of megalin with estimated kinetic parameters. The model is capable of achieving a steady-state with a much larger pool of internalized megalin compared to surface within a range of realistic parameters; this is consistent with observations made by our biochemical assays and by indirect immunofluorescence of endogenous megalin.

Conclusion: Future work includes estimated surface delivery kinetics and defining the structure and markers of the apical endocytic pathway in OK cells and mouse kidney sections using quantitative imaging. With these data, our model can be expanded and used to predict changes in megalin trafficking in disease states and in response to changes in filtration rates and hormones.

31-A Poster: CD101 Exhibits Low Minimum Inhibitory And Mutant Prevention Concentrations Against Candida glabrata Clinical Isolates

Presenter: Kevin Squires, Graduate Student
Infectious Diseases

Research Interest: Bench

Mentors: Cornelius Clancy MD
Minh-Hong Nguyen MD

Funding Source: Cidara

Authors: Kevin Squires BS, Cornelius Clancy MD, Yanan Zhao PhD, David Perlin PhD, Minh-Hong Nguyen MD

Introduction: Candida species are leading causes of invasive fungal infections and mycosis-associated mortality in the US. Resistance to echinocandins, the agents of choice against most types of invasive candidiasis (IC), occurs when FKS genes encoding ß-1,3-D-glucan synthase, the echinocandin target enzyme, are mutated. CD101 is a novel echinocandin with a notably long serum half-life. We measured minimum inhibitory concentrations (MICs) of CD101 and existing echinocandins against Candida glabrata clinical isolates, and compared mutant prevention concentrations (MPCs) of CD101 and micafungin.

Methods: MICs against 40 C. glabrata clinical isolates, harboring wild-type (28/40) and mutant FKS (12/40) genes, were measured by CLSI reference broth microdilution. MPCs were determined by inoculating isolates (1x107 CFU) in RPMI 1640 medium for 24 hours in the presence of 0 – 128 ug/mL of CD101 or micafungin in serial increments, plating on SD, and counting colonies after 1-2 days at 37º C. MPC was defined as the drug concentration at which reduction in colony number to the limit of detection was observed. C. krusei ATCC 6258 and C. parapsilosis ATCC 22019 were included as quality controls.

Results: Fks mutations included D632Y, D632H, F659L, F659S, F659del, S663F, and S663P. CD101 MICs against C. glabrata isolates harboring wild-type and mutant FKS ranged from =0.015 to 0.06 and =0.015 to 2 ug/mL, respectively. Micafungin, caspofungin and anidulafungin MICs against isolates with wild-type FKS ranged from 0.03 to 0.06, 0.03 to 0.5, and =0.015 to 0.06 ug/mL, respectively. Corresponding MICs against isolates with mutant FKS were 0.25 to 4, 0.12 to >8, and 0.12 to 2 ug/mL. CD101 and micafungin MPCs against echinocandin susceptible C. glabrata ranged from 4 to 16 and >128 ug/mL, respectively. Preliminary MALDI-mass spectrometry imaging experiments in a mouse model of intra-abdominal candidiasis demonstrated that CD101 attains better penetration for prolonged durations within abscesses, compared to micafungin.

Conclusion: CD101 is a promising agent for the treatment of Candida infections, which demonstrates low MICs against echinocandin-susceptible and –resistant C. glabrata and MPCs lower than those of micafungin. The data suggest that CD101 may be able to suppress emergence of resistance and FKS mutations. The unique pharmacokinetics of CD101 at tissue sites of infection, including robust and sustained penetration into abscesses, also suggests an important role in suppressing resistance, and may support extended dosing intervals in patients.

32-A Poster: C. albicans DDI1 is involved in DNA damage responses, morphogenesis and pathogenesis during hematogenously disseminated candidiasis and at different stages of intra-abdominal candidiasis.

Presenter: Kevin Squires, Graduate Student
Infectious Diseases

Research Interest: Bench

Mentors: N/A

Funding Source: NIH

Authors: Kevin Michael Squires BS, Shaoji Cheng PhD, Neil Clancy MD, Minh-Hong Nguyen MD

Introduction: We used RNA-Seq to identify temporal-spatial C.albicans gene expression during intra-abdominal candidiasis (IAC) in humans and a mouse model. Genes involved in responses to DNA damage were enriched among the most highly-expressed genes. CaDDI1 (orf19.7258), an orthologue of S. cerevisiae DDI1, was one of the most strongly expressed genes during IAC. ScDDI1 and CaDDI1 share 29.5% identity and 43.8% similarity at the protein level. ScDDI1 plays a role in suppression of protein secretion, protein targeting to the proteasome, and control of cell cycle. Ddi1 orthologs in C. elegans and Leishmania major are aspartyl proteinases involved in the proteasome. Recent reports indicated that CaDDI1 is a potential metacaspase substrate.

Methods: Using the SAT-flipper method, the entire DDI1 coding region was deleted. To generate the revertant stain, one copy of DDI1 was reinserted to null mutant at the native locus. To track subcellular localization, single copy DDI1 was fused to GFP at the N-terminus (under control of the DDI1 promotor, was reinserted at the native locus. The role of DDI11 in virulence was assessed in mouse models of hematogenously disseminated candidiasis (DC) and IAC.

Results: DDI1*knockout* displayed no defect in growth at 30oC in various liquid (YPD, YPGlycerol) or solid media (YPD containing 0.01% MMS, 1mM H2O2, 1M NaCl, 20 ug/ml CW, 250 ug/ml congo red, or 0.02% SDS). DDI1*knockout* were more susceptible to ultraviolet stress (survival: 13.8±2.6% vs. 29.7±15.3%; p=0.04), but not to DNA damage reagent methyl methanesulfonate or hydroxyurea. DDI1*knockout* were more susceptible to proteinsome inhibitor bortezomil. DDI1*knockout* formed fewer hyphae in liquid and on solid hyphal-inducing media (M199, Spider YPD+FBS). The null mutant was hypo-adherent to fresh human buccal epithelial cells (14.7±4.7% vs. 63.5±13.4%; p=0.0001). DDI1*knockout* was more susceptible than SC5314 to heat shock at 45oC. GFP tagging shown CaDdi1 is expressed in both nuclei and cytoplasm. Unlike in S. cerevisiae, CaDDI1*knockout* did not display increased protein secretion. Mortality was attenuated significantly in mice with DC due to DDI1*knockout*; death was not noted until day 6, compared to day 2 for mice infected with SC5314. In the IAC model, there were significantly lower Candida burdens in mice infected with DDI1*knockout* in peritoneal fluid (24 hour log10CFU/g: 4.03±0.6 vs 4.64±0.54; p=0.04) and abscesses (day 3 log10CFU/g: 6.5±0.6 vs 7.1±0.6; p=0.01; day 7: 3.9±0.6 vs 4.8±0.7; p= 0.009).

Conclusion: CaDDI1 plays roles in DNA damage responses, yeast-to-hyphal morphogenesis and pathogenesis of both DC and IAC. Contributions of pathogenesis are evident in both early (peritonitis) and late (abscess) stages of IAC. We are currently testing the function/mechanism of action of CaDDI1.

33-A Poster: TBK1 expression and activity inOCL lineage cells generates a pagetic-like bone disease in mice

Presenter: Quanhong Sun, Junior Faculty Hematology/Oncology

Research Interest: Bench

Mentors: Deborah Galson PhD

Funding Source: RO1

Authors: Quanhong Sun PhD, Peng Zhang PhD, Juraj Adamik PhD, Mark Subler PhD, Noriyoshi Kurihara PhD, Laetitia Michou PhD, Jacques Brown PhD, David Roodman PhD, Philip Auron PhD, David Dempster PhD, Jolene Windle PhD, Kostas Verdelis PhD, Hua Zhou PhD, Deborah Galson PhD

Introduction: Paget's disease of bone (PDB) is a very common late-onset metabolic bone disease affecting 1 million Americans. Measles virus nucleocapsid protein (MVNP) expression in osteoclast (OCL) precursors contributes to the development of abnormally active OCL in Paget's disease in concert with aberrant excess woven bone formation. In addition, MVNP expression targeted to OCL in transgenic mice induces pagetic-like lesions in vivo and OCL with a pagetic phenotype in vitro. We reported that MVNP activation of TBK1, an IKK family member, plays a critical role in mediating the effects of MVNP on OCL differentiation. Further, MVNP expression up-Aegulated TBK1 protein in BMM Importantly, over-expression of TBK1 in BMM by lentiviral transduction generated pagetic-like OCL. Therefore, to assess if over-expression of TBK1 was sufficient to phenocopy the effects of MVNP in mice, we generated a new mouse model with TBK1 targeted to the OCL lineage (TG-TBK1).

Methods: Primary bone marrow monocytes from WT and three TG-TBK1 founder lines (F1, F3, F4) were assessed for osteoclastogenesis in vitro. Bones of WT and TG-TBK1 founder line F4 (TG-TBK1-F4) mice were analyzed at 4, 10, and 16 months using both histology and microCT.

Results: Analysis of all three founder lines compared to WT mice revealed that TG-TBK1 BMM form increased OCL numbers with increased nuclei/OCL that were capable of resorbing bone at significantly higher rates (resorbing a greater pit area/OCL) and produced more IL-6 mRNA. Thus, indicating that the BMM isolated from TG-TBK1 mice generated pagetic OCL in vitro. The TG-TBK1-F4 bones had both increased OCL surface, and increased MS/BS, MAR and BFR when compared to WT at both 10 and 16 month. These led to a decrease in the trabecular number along with increased trabecular width at 10 month in TG-TBK1 vs WT. These data indicate that increased expression and activity of TBK1 in OCL-lineage cells is sufficient to generate both increased OCL formation and increased bone formation characteristic of PDB. No lesions were found in the 4-month TgTBK1-F4 or WT mice. Histologic analyses confirmed 2 pagetic bone lesions in 10-month TgTBK1-F4 mice (n=17), but none were found in 10-month WT mice (n=16). Histology analysis confirmed 3 pagetic lesions in 16-month TgTBK1-F4 mice (n=17) and in 2 pagetic lesions in 16-month WT mice (n=14).

Conclusion: Together these data indicate that increased TBK1 expression and activity in OCL lineage cells generates a pagetic-like bone disease in mice, with both increased osteoclast activity and increased bone formation.

34-A Poster: Nrf2 enhancement increases proteinuric renal injury in mice

Presenter: Roderick Tan, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: N/A

Funding Source: AHA, UPP, CMRF, NIHT32

Authors: Brittney Rush BSc, Corry Bondi PhD, Kacie Barry , Sean Stocker PhD, Soma Jobbagy BS, Dionysios Chartoumpekis PhD, Roderick Tan PhD

Introduction: Chronic kidney disease (CKD) is the permanent loss of kidney function that can eventually lead to end stage renal disease. The excretion of abnormally large amounts of albumin and other plasma proteins into the urine (proteinuria) generally portends a worse renal and cardiovascular prognosis. Proteinuria is most commonly caused by diabetes and can be both a marker of, and possibly contribute to, severe kidney damage and progressive renal failure. Nrf2 (nuclear factor erythroid 2 like 2) is a transcription factor that increases cellular protective mechanisms including antioxidants and detoxifying genes. Keap1 (kelch-like ECH-associated protein 1) binds and inhibits Nrf2 under normal conditions and prevents its activity. However, under conditions of oxidative stress or xenobiotic exposure, Keap1 releases Nrf2 which then translocates to the nucleus for transcription of target genes. While this is theoretically protective against disease, some preclinical and clinical data suggest that Nrf2 can paradoxically aggravate proteinuric disease. We therefore hypothesize that Nrf2 accelerates progression of proteinuric CKD.

Methods: Keap1 hypomorphic mice with genetic enhancement of Nrf2 expression, and wild type C57BL/6 mice were subjected to a variety of proteinuric injuries including angiotensin II, adriamyacin, and bovine serum albumin overload. Urinary albumin excretion was measured with ELISA and glomerular damage was quantified using transmission electron microscopy (TEM) and confocal immunofluorescence (IF) for Nephrin and WT-1. In order to rule out changes in blood pressure and glomerular filtration rate (GFR) as a cause for the proteinuric differences, both groups were assessed using radiotelemetry measurements and FITC-Sinistrin excretion, respectively.

Results: Keap1 hypomorphs had significantly increased proteinuria in all three disease models. Podocyte effacement increased and Nephrin/WT-1 expression decreased significantly in the glomeruli of the Keap1 mice, suggesting increased glomerular damage in the hypomorphs. There were minor nonsignificant diurnal changes in blood pressure and no differences in GFR. The changes in proteinuria and glomerular damage were out of proportion to any blood pressure difference, suggesting that blood pressure alone could not be the only cause of the increased proteinuria.

Conclusion: Our data suggests that a genetic model of Nrf2 upregulation significantly promotes proteinuric kidney disease and is detrimental to glomerular health. Future studies will determine the mechanism of these effects.

35-A Poster: T cell Exhaustion in Lupus Nephritis

Presenter: Jeremy Tilstra, Junior Faculty
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: N/A

Funding Source: N/A

Authors: Jeremy Tilstra MD, Lyndsay Avery BS, Shuchi Smita PhD, Rachael Gordon PhD, Lawrence Kane PhD, Maria Chikina PhD, Greg Delgoffe PhD, Mark Shlomchik MD

Introduction: Kidney disease is a hallmark of systemic lupus erythematosus (SLE), affecting 50-60% of patients within 10 years of diagnosis. Current treatments have suboptimal response rates and considerable side effect profiles. Prior studies have focused on peripheral immune cells, but few have evaluated immune cells after invasion into the target organ. Little is known about how T cells act when they enter the target organ in the setting of autoimmunity. It has been hypothesized that these are activated cells, which contribute to tissue damage and end-organ damage seen in autoimmunity. However, this hypothesis has not been formally tested.

Methods: T cells were isolated from lupus prone mice, and kidney infiltrating T cells (KITs) were compared to T cells isolated from matched spleens and non-lupus control spleens. T cells were evaluated for (1)|Functional capacity via cytokine production and proliferation, (2)|Metabolic activity via glucose utilization, mitochondrial number and mitochondrial activity, (3)|Cell surface markers for inhibitory receptors(4)|Transcriptional profile via RNAseq analysis

Results: KITs from lupus prone mice were not activated effector cells as hypothesized by experts in the field of autoimmunity. Rather these infiltrating T cells were remarkable similar to exhausted T cells described in the setting of chronic viral infection and tumor infiltration. Not only did KITs have cell surface markers of exhaustion including PD-1, Lag3, Tim-3 and 2B4, but they were functionally inert with reduced cytokine production and lacked a proliferative capacity. Further, KITs exhibited a suppressed metabolic profile with limited glucose uptake and suppressed mitochondrial function. KITs also had a transcriptional profile that correlated with exhaustion profiles observed in both tumor infiltrating T cells and those observed in chronic infection. Moreover, we show that PD-L1, an important mediator of T cell exhaustion phenotype, is overexpressed in the kidneys of lupus prone mice with nephritis compared to pre-nephritic mice.

Conclusion: Herein, we describe a novel role for T cell exhaustion in the setting of autoimmunity. Our data reveals that the tissue parenchyma has the capability to suppress T cell responses and limit damage to self. These findings open novel avenues for the treatment of autoimmunity based on selectively exploiting the exhausted phenotype of tissue-infiltrating T cells. Additionally, the findings herein may be informative beyond the field of autoimmunity, specifically in organ transplantation and cancer therapy.

36-A Poster: More than a decoy receptor? Interleukin 22 Binding Protein (IL-22BP) in bacterial pneumonia

Presenter: Giraldina Trevejo- Nunez, Junior Faculty Infectious Diseases

Research Interest: Bench

Mentors: Sarah Gaffen PhD
Jay Kolls MD
Anurhada Ray PhD

Funding Source: K01

Authors: Giraldina Trevejo-Nunez MD, Waleed Elsegeiny PhD, Zoe Kaplan , Patricia Castillo , Kong Chen PhD, Jay Kolls MD

Introduction: IL-22 is secreted by lymphoid cells such as Th17 cells and ILC3s. The IL-22 receptor is composed of IL-22Ra1 and IL-10R beta. In the lung, the IL-22R localizes in the upper airway epithelial cells. We reported that IL-22 contains pneumococcal lung infection due to hepatic activation of C3 and improved cellular phagocytosis. IL-22 also binds to a natural antagonist, known as IL-22BP or IL-22Ra2. In vitro, IL-22BP binds to IL-22 with high affinity, competing with IL-22R and neutralizing IL-22 activity. Studies have shown that IL-22BP controls tumor development in the colon, regulates inflammation in autoimmune encephalitis and promotes bacterial uptake in Peyer's patches. However, it is unclear whether these multifaceted effects associated with IL-22BP are due solely to IL-22 binding and neutralization, given discrepant phenotypes in IL-22-/- versus IL-22BP-/- mice. Furthermore, surprisingly little is known about IL-22BP in the lung.

Methods: We interrogated the role of IL-22BP in a mouse model of bacterial pneumonia. Mice were infected with Streptococcus pneumoniae at 10^6 cfu/mouse by oropharyngeal aspiration for 48 hours. We assessed lung bacterial burden, IL-22BP expression by flow cytometry sorting of cell lung populations as well as chemokine expression and cellular recruitment in broncheolaveolar fluid . Furthermore, lung tissue was analyzed for gene expression by qPCR as well as by RNA seq.

Results: In naïve lungs, we saw that IL-22BP is mostly expressed in alveolar and airway epithelial cells. IL-22BP-/- mice were less susceptible than controls to Streptococcus pneumoniae infection. This resistance was not due to differences in cellular recruitment, neutrophil phagocytosis or chemokine expression. RNA-Seq analyses of total lung tissue that compared infected IL-22BP-/- cohorts versus wild type revealed differential expression of several genes in the oxidative phosphorylation pathway. Thus, we hypothesize that IL-22BP may regulates mitochondria metabolism during pneumonia.

Conclusion: IL-22BP is expressed in alveolar and upper airway epithelial cells.IL-22BP may have a role in regulating oxidative phosphorylation to the advantage of the host.We propose to investigate which cellular component in the lung is inducing the changes in the mitochondrial genes, as well as assess glycolysis and oxidative phosphorylation status upon infection. These data were strikingly different from prior findings made in IL-22-/-mice, leading us to speculate that IL-22BP may have functions beyond the IL-22 system.

37-A Poster: Age-Aelated Lysosome Dysfunction in Rat Urothelium

Presenter: Steven Truschel, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: N/A

Funding Source: N/A

Authors: Steven Truschel PhD, Dennis Clayton , Jonathan Beckel PhD, Jonathan Yabes PhD, Yi Yao PhD, Amanda Wolf-Johnston MS, Lori Birder PhD, Gerard Apodaca PhD

Introduction: Lysosomal dysfunction and/or impairment of autophagy-lysosomal pathways is associated with a number of age-Aelated pathologies that affect all organ systems. While much research has focused on neurodegenerative diseases and aging-induced changes in neurons, much less is known about the impact that aging has on bladder function and the urothelium, which lines the inner surface of the lower urinary tract.

Methods: Use transmission electron microscopy to examine morphological changes in the urothelium from young rats (~3 months), adult rats (~12 months), and aged rats (~26 months old). Use stereology to measure any age-Aelated changes in the volumes of organelles of the lysosomal pathway. Compare enzymatic activity of lysosomal hydrolases to look for age-induced defects in function. Determine organelle pH in young and aged animals to identify possible mechanisms of impaired degradation

Results: Our results demonstrated a progressive age-induced accumulation of aberrantly large endolysosomes (= 7µm in diameter) that contained undigested content, likely indicating impaired degradation. Aged endolysosomes occupied approximately 300% more volume than their younger counterparts while no age-Aelated change was observed in multivesicular bodies and lysosomes, which fuse to form endolysosomes. Thus, aging may selectively impair endolysosomal function.• Consistent with decreased degradation, we observed that cathepsin B activity was significantly decreased in aged versus young urothelial cell lysates as well as in live cells. The endolysosomal pH of aged urothelium was higher than that of young adult (pH 6.0 vs pH 4.6) indicating a possible mechanism of impaired degradation.

Conclusion: Our results indicate that there is a progressive decline in urothelial lysosome function during aging. The decline may result from at least two mechanisms including impaired enzymatic activity and decreased acidification of endolysosomes. How urothelial lysosomal dysfunction contributes to impaired urinary bladder function in the elderly is discussed.

38-A Poster: Identification of small molecules that inhibit reactivation of latent HIV-1

Presenter: Benni Vargas, Graduate Student
Infectious Diseases

Research Interest: Bench

Mentors: Nicolas Sluis-Cremer PhD

Funding Source: T32

Authors: Benni Vargas BS, Nicholas Giacobbi MS, Phil Han MS, Phalguni Gupta PhD, Nicolas Sluis-Cremer PhD

Introduction: A major barrier to curing HIV-1 infection is the persistence of a quiescent but replication-competent latent viral reservoir in resting CD4+ T cells. Theoretically, if one could manipulate the epigenetic state of the HIV-1 provirus, or interfere with the epigenetic control mechanisms involved in viral transcriptional activation, one could silence the latent proviruses for an extended time-period, or possibly for a lifetime, thus enabling a functional cure. In this regard, the primary goal of this study was to identify small molecules that can effectively block the reactivation of latent HIV-1, independent of the stimulus used to reverse latency.

Methods: We screened a unique collection of 418 kinase inhibitors (Selleckchem) that target a wide range of cellular signaling pathways using the 24ST1NLESG cell line of HIV-1 latency. The screen was carried out with the kinase inhibitors alone (2μM), or in combination with 3 latency reversing agents (LRAs): 1μM prostratin, 10nM panobinostat or 1μM JQ-1. Follow-up studies included screening the kinase library for cellular toxicity and detailed dose-Aesponse analyses.

Results: We identified 21 kinase inhibitors, mostly targeted toward PKC, MEK or ERK, that blocked the activity of prostratin only. Twenty-three kinase inhibitors, targeting mTOR, PI3K or GSK-3, were identified that inhibited panobinostat activity only. We identified 4 inhibitors which blocked the activity of JQ-1 only. We found an additional 30 compounds that inhibited the activity of all 3 LRAs. Of these, Danusertib, an Aurora kinase inhibitor; and PF-3758309, a PAK4 inhibitor, were found to be the most potent. The concentration of Danusertib required to inhibit 50% (i.e., IC50) of HIV-1 latency reversal in the 24ST1NLESG cell line by prostratin, panobinostat, JQ-1 and TNF-a was determined to be 40±16, 110±43, 147±21 and 192±23 nM, respectively. The concentration of Danusertib that resulted in 50% cytotoxicity (i.e., CC50) was 29.7±3.4μM (therapeutic index > 150). The IC50 values determined for PF-3758309 for inhibition of prostratin, panobinostat, JQ-1 and TNF-a activity were 0.07±0.04, 0.4±0.03, 1.2±0.3 and 0.8±0.09 nM, respectively. The CC50 for PF-3758309 was 4.3±1.2 μM (therapeutic index > 3,300). Ongoing studies are evaluating the activity of the inhibitors in cells from HIV-infected individuals.

Conclusion: We have identified 2 kinase inhibitors, Danusertib and PF-3758309, which potently block the reactivation of latent HIV-1, independent of the stimulus used to reverse latency.

39-A Poster: Identification of multiple functional variants at the extracellular domain core of the epithelial Na+ channels

Presenter: Xueqi Wang, Medical Student
Renal-Electrolyte

Research Interest: Bench

Mentors: Thomas Kleyman MD
Shaohu Sheng MD

Funding Source: P30 DK079307

Authors: Xueqi Wang Xiangya Scholar, Jingxin Chen MD, Thomas Kleyman MD, Shaohu Sheng MD

Introduction: Epithelial Na+ channel (ENaC)-mediated Na+ transport is essential in the regulation of extracellular fluid volume and blood pressure. Human ENaC mutations cause hypertensive or hypotensive disorders and selected ENaC variants have been associated with high blood pressure or salt-sensitivity. However, the functional consequences of the clear majority of human ENaC variants remain unknown. In this study, we investigated functional roles of several non-synonymous ENaC variants located at a beta strand within a core beta-ball structure of the extracellular domain.

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

Results: In the structure of the ENaC-homologous acid sensing ion channel 1, five short beta strands form a beta-ball domain at the core of the extracellular domain. We first examined three variants located at the beta 7 strand. R350W and G355R mutants showed 2.6 and 1.8-fold greater amiloride-sensitive currents than WT channels ($p < 0.001$, n=58-89), respectively. V351A had a reduced current (48% of WT channels, $p < 0.001$, n=58-59). None of the mutations significantly alter channel surface density ($p > 0.05$, n=15-38). Both R350W and G355R reduced Na+ self-inhibition response, correlating to an increased open probability. In addition, R350L and R350Q also increased channel activity ($p < 0.05$, n=29-38) and reduced Na+ self-inhibition. However, R350G did not significantly alter channel currents ($p > 0.05$, n=28-30).

Conclusion: R350W, R350L, R350Q and G355R are gain-of-function ENaC variants and V351A is a loss-of function variant. The gain-of-function variants increase ENaC activity by relieving Na+ self-inhibition. The beta 7 strand where the variants reside may have an important role in ENaC gating regulation.

40-A Poster: Lack of CD73 in mVSMCs causes increased TGF-ß signaling and elastin expression under mechanical stretch

Presenter: Rachel Wolfe, Medical Student
VMI

Research Interest: Bench

Mentors: Cynthia St Hilaire PhD

Funding Source: PSTP summer stipend, and NHLBI HL117917

Authors: Rachel Wolfe Medical Student, Pouya Joolharzadeh Medical Student, Evelyn Garchar MS, Marie Billaud PhD, Cynthia St Hilaire PhD

Introduction: The genetic disease Arterial Calcification due to Deficiency of CD73 (ACDC) is characterized by inactivating mutations in the gene encoding the enzyme CD73, which converts extracellular AMP to adenosine. Patients with this disorder have excessively calcified and tortuous arteries in their lower extremities and suffer from intense cramping due to lack of blood flow. The tortuous vessels in ACDC patients are phenotypically like aneurysms. Two genetic diseases that lead to a high prevalence of aneurysms are Marfan syndrome and Loeys-Deitz syndrome and both these syndromes exhibit high levels TGF-ß signaling, indicating a connection between extracellular matrix destabilization and increased TGF-ß signaling. We hypothesize that CD73 and downstream adenosine signaling protect VSMCs under mechanical stress, and that lack of CD73 activity leads to upregulation of TGF-ß signaling and extracellular matrix remodeling.

Methods: Wildtype (WT) and CD73 knockout (CD73) murine vascular smooth muscle were used for in vitro studies to quantify changes in expression and protein levels of genes that comprise and regulate extracellular matrix homeostasis. The FlexCell 3000 system was used to induce 1 Hz 10% mechanical stretch over 48 hrs.

Results: Gene expression analysis showed TGF-ß3 levels were increased at baseline and under stretched conditions in CD73 mVSMCs compared to WT. Immunoblotting for mediators of the TGF-signaling pathway showed a 3-fold increase in p-SMAD3 levels and a 0.3-fold increase p-SMAD2 signaling in CD73 mVSMCs compared to WT mVSMCs under stretch. MMP2 gene expression was similarly increased, indicating that CD73 VSMCs exhibit enhanced TGF-ß signaling. Elastin gene expression and protein levels were also increased after 48hr of stretched, and a long-term treatment of 5ng/mL TGF-ß for 7 days produced elastin visualized by immunocytochemistry.

Conclusion: Our results show that CD73-deficient VMSCs exposed to mechanical stress exhibit enhanced TGF-ß production and signaling, resulting in increased production of the TGF-ß targets MMP2 and elastin. This increase in elastin protein is similar to ACDC vessel pathology, where there is duplication of the elastic lamina. Our data suggest a potential link between tortuosity in ACDC vessels and increased TGF-ß signaling.

41-A Poster: TWIST1 is a key mediator of HGF-MET-driven resistance to targeted therapies in EGFR mutant and MET-driven lung cancer

Presenter: Zachary Yochum, Graduate Student Hematology/Oncology

Research Interest: Bench

Mentors: Timothy Burns MD, PhD

Funding Source: Individual NRSA (F32)

Authors: Zachary Yochum BS, Suman Chatterjee PhD, Eric Huang DVM, Deena Maurer BS, Myriam Attar PhD, Sanja Dacic MD, PhD, Laura Stabile PhD, Timothy Burns MD, PhD

Introduction: The c-Met (MET) receptor and its ligand, hepatocyte growth factor (HGF), have been shown to mediate epithelial-mesenchymal transition (EMT), proliferation, invasion, motility, and angiogenesis. The HGF/MET pathway is frequently altered in non-small cell lung cancer (NSCLC) and has emerged as a targetable oncogenic driver, as patients with MET-amplification and/or mutations have demonstrated marked responses to the MET tyrosine kinase inhibitor (TKI), crizotinib. However, long-term efficacy of MET TKIs is limited as acquired resistance is inevitable. HGF overexpression has been identified as a mechanism of resistance to both MET and EGFR TKIs in MET-altered and EGFR-mutant NSCLC. Furthermore, MET-amplification has been implicated in EGFR TKI resistance. However, the mechanism(s) by which the HGF-MET pathway causes resistance are poorly understood. Here, we investigated the requirement of the EMT-transcription factor, TWIST1 in HGF-mediated resistance to MET and EGFR TKIs and the role of TWIST1 in de-novo and acquired resistance to MET and EGFR TKIs.

Methods: We utilized MET and EGFR-driven NSCLC cell lines and a novel transgenic mouse model of Hgf-driven, Twist1 overexpressing lung cancer to evaluate TWIST1 as a driver of EGFR and MET TKI resistance.

Results: We found that HGF treatment induced EMT in NSCLC cell lines and increased TWIST1 protein expression through a post-translational mechanism. We demonstrated that targeting TWIST1 pharmacologically with the TWIST1 inhibitor, harmine, overcame HGF-mediated resistance to both MET and EGFR TKIs in MET and EGFR-driven NSCLC. This suggests that TWIST1 is required for HGF-mediated resistance to targeted therapies. We also found that TWIST1 overexpression was sufficient to cause resistance to MET and EGFR TKIs. In MET-driven and EGFR-mutant cell lines that express TWIST1 and are resistant to TKIs, we demonstrated that harmine treatment re-sensitized resistant cells to MET and EGFR TKIs respectively. To investigate the role of TWIST1 overexpression in Hgf-driven lung cancer, we utilized a CCSP-Hgf (CH) mouse model that constitutively overexpresses Hgf in the lung and develops crizotinib sensitive tumors following treatment with the tobacco carcinogen, nicotine-derived nitrosamine ketone (NNK). We demonstrated that the Twist1 overexpressing CTH (CCSP-AtTA/Twist1-tetO-luc/CCSP-Hgf) mice developed significantly larger tumors following NNK treatment as compared to CH and CCSP-AtTA/Twist1-tetO-luc (CT) mice.

Conclusion: We established that HGF-Aegulated TWIST1 expression and that TWIST1 expression is required for resistance to MET and EGFR TKIs in the presence and absence of HGF. These studies suggest that targeting TWIST1 may be an effective therapeutic strategy to overcome HGF-MET-driven resistance in EGFR-mutant NSCLC and MET TKI resistance in MET-driven NSCLC.

42-A Poster: Co-administration of Sodium Nitrite during Ultrasound Targeted Microbubble Cavitation Therapy Enhances Nitric Oxide Generation and Increases Microvascular Perfusion

Presenter: Gary Yu, Graduate Student
VMI

Research Interest: Bench

Mentors: John Pacella MD

Funding Source: T32

Authors: Gary Yu BS, Filip Istvanic BS, Xucai Chen PhD, Sruti Shiva PhD, Mark Gladwin MD, Adam Straub PhD, John Pacella MD

Introduction: Percutaneous coronary intervention (PCI) is the mainstay therapy for recanalization of infarct-Aelated coronary arteries and restoring myocardial perfusion. Despite successful PCI, many patients suffer from failure of microvascular perfusion known as microvascular obstruction (MVO), which results from microvascular spasm, ischemia-Aeperfusion injury, and thrombotic occlusion. We have demonstrated reperfusion efficacy of ultrasound-targeted microbubble cavitation (UTMC) therapy in MVO, resulting in both mechanical dissolution of obstructing thrombi and upregulation of nitric oxide (NO). Previous literature shows that nitrite has significant cardioprotective effects in settings of ischemia-Aeperfusion and MVO, while enhancing vascular bioavailability of NO. Accordingly, we sought to determine whether co-administration of nitrite could enhance reperfusion efficacy of UTMC therapy.

Methods: Long pulse ultrasound was applied to a rat hindlimb for 2 minutes during intra-femoral infusion of lipid microbubbles. Sodium nitrite (4 mg/kg) was administered via a pre-treatment bolus (plasma concentration 100 uM). After UTMC therapy, burst-Aeperfusion contrast ultrasound imaging was performed with imaging microbubbles over 30 minutes. Ultrasound image intensities were measured in the treatment region to obtain microvascular blood flow. An NO catheter probe was placed in the gastrocnemius muscle of the treated hindlimb to measure real-time NO concentration. Repeated measures two-way ANOVA was used to assess differences between groups, with Tukey's HSD for post-hoc analysis.

Results: There was over a 5-fold decrease in NO concentration over 30 min for UTMC-only ($n = 4$) and nitrite-only ($n = 5$) versus UTMC+nitrite ($n = 5$), which revealed sustained NO concentration over time ($p < 0.0001$ between groups). Post-hoc analysis showed significance for UTMC + nitrite from 8 min onward post-treatment ($p < 0.05$). UTMC+nitrite had higher blood flow than UTMC-only at all time points, with mean differences of 1.93, 0.99, 1.46, and 1.38 dB/s at 3, 6, 10, and 30 min respectively ($p < 0.05$ except for 6 min). At 3 min, UTMC-only showed a 1.19 dB/s drop in blood flow from baseline ($p < 0.05$), indicating a transient microvascular vasospasm (reported in previous ultrasound literature) not present in UTMC+nitrite.

Conclusion: These results show that co-administration of sodium nitrite during UTMC therapy enhances NO concentration and increases microvascular perfusion compared to UTMC or nitrite alone, suggesting a synergistic interaction between UTMC and nitrite. In addition, the absence of transient microvascular spasm in UTMC+nitrite suggests nitrite improvement of UTMC therapeutic efficacy. Further studies to assess the efficacy of nitrite in our model of MVO are ongoing.

43-A Poster: Developing A New Tool to Understand the Role of IL-17F in Anti-Fungal Immunity

Presenter: Chunsheng Zhou, Graduate Student **Research Interest:** Bench Rheumatology and Clinical Immunology

Mentors: Sarah Gaffen PhD

Funding Source: NIH (DE022550, DE023815, and AI107825)

Authors: Chunsheng Zhou BS, Leticia Monin PhD, Erin Childs MSc, Rachael Gordon PhD, Mark Shlomchik PhD, Sebastien Gingras PhD, Sarah Gaffen PhD

Introduction: The IL-17 family of cytokines promote inflammation in autoimmunity and antifungal host defense. The best characterized are IL-17A and IL-17F, which form homodimers and heterodimers. In 2011, a heritable chronic mucocutaneous candidiasis disease (CMCD) was reported in an Argentinian family, a fungal infection caused by the commensal fungus Candida albicans. By exome sequencing, a dominant negative point mutation in IL-17F was determined to cause CMCD. Specifically, a serine residue at position 65 of the mature IL-17F protein was replaced by a leucine residue (S65L). The residue is situated in the cavity that IL-17F uses to bind to its receptor and decreases its binding affinity of IL-17F. However, this mutation has no effect on IL-17F dimerization with either IL-17F or IL-17A. Consistently, it led to impaired signaling (cytokine and chemokine release from fibroblasts) after stimulation with the mutant IL-17F homodimer (IL-17FS65L/IL-17F) or heterodimer (IL-17A/IL-17FS65L) in vitro. This CMCD case provides compelling evidence that IL-17F is essential in the anti-C. albicans immune response in humans. However, the in vivo function of IL-17F against C. albicans infection has been challenging to define. Specifically, IL17F-/- mice treated with IL-17A/IL17AF neutralizing antibodies are more susceptible to C. albicans infection then wildtype mice treated with the same antibodies. However, mice given IL-17F neutralizing antibodies and IL-17F-/- mice are resistant to C. albicans challenge, similar to WT mice. Furthermore, no neutralizing antibody has been developed to specifically target the IL-17A/F heterodimer, and it is impossible to make an IL17A/F knockout without interfering with the normal expression of IL-17A and IL-17F homodimers. Therefore, the S65L mutation could be an ideal tool to determine the role of IL-17F in vivo because it appears to block the function of IL-17F and IL-17A/F without affecting IL-17A.

Methods: The IL-17F S65L mutation was induced by CRISPR/Cas9. The mutation was screened by Restriction enzyme digestion and confirmed by DNA sequencing.

Results: 5 founder mice with the IL-17-S65L mutation were created by CRISPR/CAS9. No off-target mutations were detected in all of the five founder mice.

Conclusion: We successfully created the S65L point mutation in a mouse model by CRISPR/CAS9. This mouse model will help us to get a better understanding of the biological function of IL-17F.

44-A Poster: FINDING THE SWEET SPOT: THE ASSOCIATION BETWEEN ADDED DIETARY SUGARS AND INFLAMMATORY BOWEL DISEASE SEVERITY

Presenter: Maaz Ahsan, Medical Student **Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

Mentors: David Binion MD

Funding Source: 5TL1TR000145-09, 5T32DK063922-12, W81XWH-11-2-0133

Authors: Maaz Ahsan BS, Alyce Anderson BS, Dmitriy Babichenko , Claudia Ramos Rivers MD, Stephen O'Keefe MD, Miguel Regueiro MD, Marc Schwartz MD, Jana Hashash MD, Benjamin Click MD, Ioannis Koutroubakis MD, Michael Dunn MD, David Binion MD

Introduction: Prior epidemiologic studies associated increased sugar consumption with Crohn's disease (CD), and animal models of inflammatory bowel disease (IBD) have implicated negative effects of sugars on microbiome composition and worsening of gut inflammation, but little is presently known regarding the impact of sugar consumption on disease severity in IBD. We hypothesized that IBD patients with diets high in added sugars would experience more severe disease.

Methods: Prospective diet data was collected using the 2005 National Health Interview Survey (NHIS) Diet and Nutrition Questionnaire which contains specific questions regarding sugar intake from consented IBD patients followed in a tertiary referral center over a two-year period. Based on the calculated consumption of added sugars, patients were classified into 5 categories in relation to the population average consumption of sugar as determined from the National Health and Nutrition Examination Survey from the CDC (>50% below average, 10%-50% below average of mean, ±10% of average,10%-50% above average, and >50% above average). For statistical analysis, low sugar consumption group (Categories 1 and 2) were compared with the high sugar consumption group (Categories 4 and 5). Disease severity was approximated based on the use of IBD medications (5-ASA, antibiotics, systemic steroids, immunomodulators, and biologics) clinical activity indices [Harvey-Bradshaw index (HBI) for CD patients, and ulcerative colitis activity index (UCAI) for UC], healthcare utilization (number of clinic visits, phone calls to clinic, and ER visits) quality of life measurement (short inflammatory bowel disease questionnaire, SIBDQ), and two biomarkers of inflammation (ESR and CRP).

Results: Among 859 patients (69.2% CD, 41.7% male) 12.5% were in category 1, 41.5% in category 2, 20.8% in category 3, 12.3% in category 4 and 13% in category 5. The low sugar group (37.7% male, 66.3% CD) had a lower occurrence of abnormal CRP when compared to the high sugar group (60.6% male, 73.5% CD) (p=0.042). The high sugar group utilized more immunomodulators than the low sugar group (p=0.005). For patients with CD, disease activity scores were significantly lower for the low sugar group when compared to the high sugar group (p=0.002). Lastly, quality of life scores were significantly better for the low compared to the high sugar group (p=0.01).

Conclusion: IBD patients with increased sugar consumption have increased biomarkers of inflammation, disease activity, healthcare utilization and use of immunomodulators and worse quality of life, compared with patients who consumed less sugar. These multiyear data suggest that excess sugar consumption is associated with worse clinical status in patients with IBD. The underlying mechanism has yet to be determined.

45-A Poster: Impact of Nitrite Therapy on Change in Steady State Submaximal Exercise in Older Adults

Presenter: Kelly Allsup, Graduate Student Geriatric Medicine

Research Interest: Clinical

Mentors: Daniel Forman MD

Funding Source: University of Pittsburgh Mitochondria, Aging and Metabolism

Authors: Kelly Allsup BS, Rachel Eleazu BS, Nancy Glynn PhD, Jessica Shultz MSc, James Kostra MSc, Ross Arena PhD, Daniel Forman MD

Introduction: The population of older adults is growing, with increasing prevalence of detrimental geriatric risks, particularly sedentariness and downstream risks of cardiovascular disease, disability, and frailty. Nitrate therapy may enable physiological efficiency such that oxygen demands for submaximal workloads are reduced, and daily activity more easily tolerated. We explored the impact of chronic oral nitrite therapy in a cohort of older healthy adults. Nitrites (40 mg) were administered as capsules 3 times daily over one month. Changes in oxygen uptake (VO2) during steady state walking in association with rate of perceived exertion (RPE [10-20 scale]) were analyzed.

Methods: 9 adults (5 male, 4 female) aged =70 (mean 77.7±6.3 years, range 70-88) were studied. Functional capacity was assessed at baseline and 4 weeks based on steady state VO2 and RPE during a 5 minute treadmill walk (1.5 mph).

Results: Steady state VO2 decreased significantly in the older adults using nitrite therapy (13.29±4.14 vs. 11.27±2.75 change of 2.02±2.75, p=0.029). RPE also trended downward (7.66±1.32 vs 7±1.8 change 1±0, p=0.23).

Conclusion: This promising pilot work in older adults showed that chronic nitrite was well-tolerated and was associated with increased walking efficiency. Further study is needed to better understand the impact on physical activity and health in this large and growing patient demographic.

46-A Poster: Hemodynamic Changes during LVAD implantation may be associated with Subsequent Right Ventricular Failure: Opening the Black Box of the Operating Room

Presenter: Timothy Bachman, Graduate Student VMI

Research Interest: Clinical

Mentors: Marc Simon MD

Funding Source: N/A

Authors: Timothy Bachman MS, Ling Tian MD, Mehdi Nouraie PhD, Courtney Vu , Yousif Shwetar , Lauren Williams , Christopher Link MD, Michael Boisen MD, Luigi Lagazzi MD, Christopher Sciortino MD, Robert Kormos MD, Marc Simon MD

Introduction: Approximately 20% of LVAD recipients experience acute RV Failure (RVF) post-implant. Studies have investigated hemodynamic parameters at the pre- and post-operative phase of LVAD therapy; none have looked at hemodynamics during implant. In this pilot study, we collected hemodynamic data during various stages of implantation to determine if changes in values can determine outcomes.

Methods: Pulmonary arterial (PA) waveform printouts or screenshots, acquired via Swann-Ganz catheter, were obtained at 5 stages of LVAD implantation: T(-2) Pre-operative with conscious patient in catheterization lab 9 ± 11 days pre-op, T(-1) Perioperative with patient under anesthesia pre-sternotomy, T(0) Chest open with LVAD on, T(1) Chest closure with LVAD on, and T(2) In the ICU 4-24 hrs post- chest closure (Figure). Custom MATLAB scripts re-digitized the captures and generated an average representative waveform at each stage. PA pulsatility index (PAPI) and CVP/PA DBP were also calculated. Rate of hemodynamic change from LVAD on to post-op in ICU (T(-1) to T(2)) was calculated with mixed effect models. Association between RVF and baseline values as well as change was calculated using Odds ratio.

Results: Data were obtained for 32 patients. Five patients experienced RVF defined as >14 days post-operative inotropic support (21 male, median age (IRQ) 55 (41-66) vs 4 male, age 59 (53-65) for no RVF and RVF, respectively). As previously reported, baseline RAP and RAP/PCWP were associated with RVF. No changes reached statistical significance; however, smaller decreases in PA DBP, mPAP, and CVP from T(-1) to T(2) showed trend of association with RVF (Odds ratios 1.34 ($p = 0.12$), 1.43 ($p = 0.13$), and 1.22 ($p = 0.17$), respectively.

Conclusion: Preliminary data indicate that there may be important hemodynamic changes during implantation which may be associated with a patient's odds of subsequent RVF. A larger sample size is required to confirm these findings.

47-A Poster: Decisional Satisfaction and Perceptions of Inpatient Dialysis Initiation

Presenter: Amar Bansal, Junior Faculty
Renal-Electrolyte

Research Interest: Clinical

Mentors: David Casarett MD
Nina O'Connor MD

Funding Source: N/A

Authors: Amar Bansal MD, Nina O'Connor MD, David Casarett MD

Introduction: Dialysis is often initiated in a hospital setting where acute kidney injury and critical illness drive clinical decision making. Little is known about how patients or their surrogate decision-makers feel about the process of dialysis initiation.

Methods: All patients or surrogate decision-makers who consented to initiating dialysis at a large academic medical center during a five-week period were prospectively approached for enrollment. Patients who had previously been on dialysis were not eligible. The decision attitude scale (DAS) was used to measure post-decisional satisfaction. Semi-structured interviews to qualitatively assess participants' feelings about the process were also conducted. In order to minimize recall and outcome bias, study participants were approached within 72 hours of dialysis initiation.

Results: A total of 31 patients were eligible, of which 21 enrolled. The mean baseline creatinine prior to dialysis was 2.3 mg/dL. Out of the 21 patients, 14(67%) were started on a continuous dialysis modality, 13(62%) had a surrogate provide consent for dialysis, and 8(38%) died in the hospital or were discharged on hospice. The mean DAS score for all patients was 4.1 (3.8 – 4.3, 95% CI) with a maximum score of 5 implying the highest post-decision satisfaction. Zero subjects responded "agree" or "strongly agree" on a five-item Likert scale when asked if consent for dialysis was a waste of time, but 9(43%) responded "agree" or "strongly agree" when asked if consent for dialysis was mainly to protect the hospital.

Conclusion: Despite having almost 40% inpatient mortality, dialysis initiation at a large academic medical center is characterized by high post-decisional satisfaction and a prevalent perception that consent for dialysis was intended to "protect the hospital." A majority of patients were not able to participate in the decision to initiate dialysis and consent was provided by a surrogate decision-maker. Further efforts to clarify ways to improve communication related to dialysis initiation are needed.

49-A Poster: Contact Frequency and Older Adult Participation in Cardiac Rehabilitation

Presenter: Benjamin Cahill, Medical Student
Geriatric Medicine

Research Interest: Clinical

Mentors: Daniel Forman MD

Funding Source: T32

Authors: Benjamin Cahill , Kelly Allsup , Andrew Althouse PhD, Daniel Forman MD

Introduction: Background: While site-based cardiac rehabilitation (CR) provides unambiguous benefits to older adults (OA) with cardiovascular disease (CVD), few eligible candidates participate. New CR models are being developed in efforts to make CR more accessible and practical for an OA population. However, many of the new CR models entail less direct clinician contact frequency (CF). Efficacy of lower CF models of CR remains particularly uncertain for OA CVD patients. The objective of this study is to compare outcomes among OA who completed CR at different CF. We hypothesized that a higher CF CR would correspond to greater improvement in outcomes.

Methods: Methods: Retrospective analysis of outcomes of patients aged =60 years who participated in on-site CR. Patient cohorts were delineated by frequency of on-site training sessions during the 12 weeks following initial evaluation. High CF was defined as >18 sessions and low CF was defined as 9-18 sessions. Outcomes included physical function, measured as gait speed, and self-confidence, measured as a cardiac self-efficacy (CSE) score.

Results: Results: 64 patients were studied who met the requirements for the high CF cohort (median age 67.0, range 60.0-86.0) or low CF cohort (median age 69.0, range 60.0-92.0) and completed a final evaluation. The cohorts were primarily male, as only two females met the inclusion criteria. The table shows differences between the high and low CF cohorts in gait speed and CSE. Gait speed improved significantly only in the high CF cohort, but the difference between groups post-CR was not significant. Both cohorts demonstrated marked improvements in CSE scores, with no significant difference between groups.

Conclusion: Conclusions: Among a predominantly male population, only two females met the criteria for age =60, high and low CF cohorts both benefitted from CR with indices suggesting improvements in physical function and self-confidence. These data bolster rationale for CR models with lower CF for OA with CVD. Nonetheless, more study is needed for older women and men CVD patients to evaluate each new model of CR.

50-A Poster: Combination treatment of VLA-4 targeted radionuclide therapy and Immunotherapy for treating metastatic melanoma

Presenter: Jaeyeon Choi, Graduate Student
VMI

Research Interest: Clinical

Mentors: Carolyn Anderson PhD

Funding Source: N/A

Authors: Jaeyeon Choi PhD candidate

Introduction: The overall goal of the research is to enhance the therapeutic efficacy of 177Lu-LLP2A with immunecheckpoint inhibitors (anti-PD-L1, anti-PD-1 and anti-CTLA- 4) in the treatment of metastatic melanoma. Thepeptidomimetic LLP2A (RT) is bound with high affinity and specificity to activated VLA-4. It has been demonstrated asan excellent diagnostic and therapeutic agent for in mouse models of B-cell lymphoma, and melanoma tumors. Theimmune-checkpoint inhibitors (IT) has been known as the most well-established method for metastatic melanoma so far.Nivolumab (anti-PD- 1), ipilimumab (anti-CTLA4) and BMS936559 (anti-PD- L1) are approved by FDA for treatingmetastatic melanoma. We performed combination treatment with RT and IT in B16F10 subcutaneous tumor-bearing miceand plot Kaplan-Meier curves in different treatment groups.

Methods: 1 x 10 6 B16F10 tumor cells were implanted subcutaneously on the right flank of B16F10 tumor-bearing C57BL/6 mice. At day 8, the tumor-bearing mice were randomly separated into eight groups (n=4 female mice, n=4 male mice, total n=8 per group). 177 Lu-LLP2A was intravenously injected intravenously on day 8 (single dose), and antibodies were continuously administered on days 9, 12 and 15 given Intraperitoneal injection post-tumor implant. Tumor growth was monitored by caliper measurements.

Results: 177Lu-LLP2A alone (n=11), anti-PD-L1+anti-CTLA-4 antibodies (n=8), or 177 Lu-LLP2A + anti-PD- L1+anti-CTLA-4 antibodies (dual immunotherapy) (n=8) showed statistically significant survival benefit than non-treated mice(n=12) (p-value;0.0001). The mean survival time post-tumor implant of 177 Lu-LLP2A, dual immunotherapy and 177Lu-LLP2A + dual immunotherapy is 17, 16,5 and 19 days, respectively. The combination of 177Lu-LLP2A + dual immunotherapy also showed statistically significant survival benefit compared to either single treatment alone (p-value;0.0003).

Conclusion: The combination of 177 Lu-LLP2A and dual immunotherapy has the significant therapeutic efficacy to VLA-4expression in B16F10 tumors in C57BL/6 mice compared to either 177 Lu-LLP2A treatment or immunotherapy.

51-A Poster: Electrical Failure of Non-Aecalled Defibrillator Leads

Presenter: Aman Gupta, Junior Faculty
General Internal Medicine

Research Interest: Clinical

Mentors: Samir Saba MD

Funding Source: N/A

Authors: Aman Gupta MD, Furqan Khattak MD, Krishna Alluri MD, Nassir Shariff MD, Samir Saba MD

Introduction: Implantable cardioverter defibrillator (ICD) leads have been referred to as the 'weakest link' in defibrillator systems due to FDA recalls and advisories involving popular lead models from major manufacturers. The rate of electrical failure of ICD leads not implicated in a recall is however not well determined.

Methods: Medical records of patients implanted with ICDs at the hospitals of the University of Pittsburgh Medical Center between 2002 and 2014 were analyzed. Leads were classified as having electrically failed if they had to be removed and replaced for reasons other than infection or heart transplantation. Patients were followed to the endpoint of death or electrical lead failure.

Results: 2,410 consecutive ICD recipients (age 66±13 years, women 22%, single/dual/CRT-ICD 20%/44%/36%, Single-coil 9%) were included and followed for 3.9±3.3 years. During follow-up, 813 patients (33%) died, 61 (2.5%) had ICD lead electrical failure, 89 (4%) had ICD system explantation for infection (n=44) or heart transplantation (n=45), and 1,474 (60.5%) patients were alive with functional leads at the time of last follow-up. Univariate predictors of electrical lead failure included better patient functional status (p=0.049), a wider QRS complex (p=0.011), and a higher number of implanted leads (p=0.032). In a logistic multivariate model, the only predictors of electrical failure were higher number of implanted leads (HR 1.78 per incremental lead, 95% CI 1.09 - 2.91, p=0.021) and a better functional status (HR 0.52 per 1 class increase, 95% CI 0.35 - 0.77, p=0.001).

Conclusion: Only 2.5% of ICD recipients with non-Aecalled leads experience electrical failure of their ICD lead (0.6% per year). Higher number of implanted leads and better patient functional status are associated with higher rates of ICD lead failure.

52-A Poster: Extent of Cardiac Damage in Aortic Stenosis Relates to TAVR Outcomes - ?A Validation of a New Staging System

Presenter: Aman Gupta, Junior Faculty
General Internal Medicine

Research Interest: Clinical

Mentors: Joao Cavalcante MD

Funding Source: N/A

Authors: Aman Gupta MD, Islam Abdelkarim MD, Michael Sharbaugh MPH, Andrew Althouse PhD, Miho Fukui MD, Hesham Elzomor MD, Dustin Kliner MD, Joon Lee MD, John Schindler MD, Thomas Gleason MD, Joao Cavalcante MD

Introduction: A new staging system encompassing the extent of cardiac damage has been recently proposed for patients with aortic stenosis undergoing surgical or transcatheter aortic valve replacement (TAVR). We sought to validate this staging system using our large, single-center cohort of patients who have undergone TAVR.

Methods: Staging classification were chosen based on their broad acceptance and validation as markers of abnormal cardiac function. The classification algorithm used was similar to recently published by Genereux et al. The criteria used was defined as: stage 1 (LV damage - increased LV mass index, E/e' > 14, LVEF = 50%); stage 2 (LA/mitral damage - LA volume index > 34 ml/m2, moderate-severe mitral regurgitation, atrial fibrillation, AFib); stage 3 (PA/tricuspid damage - PA systolic pressure = 60 mmHg, moderate-severe TR); stage 4 (RV damage - moderate-severe RV dysfunction). Kaplan-Meier analysis was performed to test the association of AS staging system and all-cause mortality.

Results: A total of 480 patients with severe AS who underwent TAVR had complete data for analysis. The prevalence of stage 1, 2, 3 and 4 was 13%, 62%, 21% and 4%, respectively. Higher STS-PROM and Afib burden increased at each stage, whereas stroke volume index and tricuspid annular plane systolic excursion, a measurement of RV function, progressively decreased at each stage. There was a graded relationship of AS staging system vs. all-cause mortality (HR=x.x, 95% CI, p=0.016)

Conclusion: The newly proposed staging classification demonstrates a strong relationship between the baseline extent of cardiac damage and 2-year survival after TAVR. Extent of cardiac damage can be easily computed in patients undergoing TAVR evaluation. Better understanding might improve risk-stratification and assessment of prognosis in TAVR patients.

53-A Poster: Lung Hyperinflation and Coronary Atherosclerosis in Smokers: the Pittsburgh COPD SCCOR and COPDGene Cohorts

Presenter: Aman Gupta, Junior Faculty
General Internal Medicine

Research Interest: Clinical

Mentors: Frank Sciurba MD

Funding Source: K23

Authors: Aman Gupta MD, Divay Chandra MD, Gregrory Kinney PhD, Carl Fuhrman MD, Joseph Leader PhD, Jessica Bon MD, Yingze Zhang PhD, Graham Barr MD, George Washko MD, Matthew Budoff MD, John Hokanson PhD, Frank Sciurba MD

Introduction: Although reduced forced expiratory volume in one second (FEV1) is a potent independent predictor of coronary vascular events and mortality, causal mechanisms remain elusive. A reduced FEV1 usually coexists with varied pulmonary phenotypes in smokers including airway remodeling, emphysema, and lung hyperinflation. Among these, lung hyperinflation is associated with endothelial dysfunction, systemic inflammation, and increased left ventricular mass. We hypothesized that lung hyperinflation was responsible for the association between FEV1 and coronary artery disease.

Methods: We examined the association between lung hyperinflation and coronary artery calcium among 481 participants in the Pittsburgh SCCOR cohort, and 2580 participants in the COPDGene multicenter cohort

Results: Reduced FEV1 was independently associated with greater coronary artery calcium; however, this association was explained by lung hyperinflation in both cohorts. Lung hyperinflation was the only pulmonary phenotype associated with coronary calcium in the Pittsburgh cohort (OR=2.5 per 0.2 increase in residual volume/total lung capacity, 95%CI 1.4-4.6, p=0.002) and the COPDGene cohort (OR=1.3 per 0.2 increase in functional residual volume/total lung volume, 95%CI 1.1-1.5, p=0.003) in adjusted models. Also, hyperinflation was independently associated with all-cause mortality in the Pittsburgh cohort (HR=2.8 per 0.2 increase in RV/TLC, 95% CI 1.3-5.9, p=0.006) and the higher coronary calcium scores in patients with greater hyperinflation explained this association.

Conclusion: Our findings provide the first evidence that lung hyperinflation may be contributing to the disproportionate occurrence and mortality from coronary atherosclerosis in smokers.

54-A Poster: Is objectively assessed physical activity associated with cardiac ejection fraction, health-Aelated quality of life, and NYHA class among patients recently hospitalized with systolic heart failure?

Presenter: Julia Holber, Graduate Student
General Internal Medicine

Research Interest: Clinical

Mentors: Bruce Rollman MD

Funding Source: R01

Authors: Julia Holber BA, Kaleab Abebe PhD, Amy Anderson MS, LPC, John Jakicic PhD, Bea Herbeck Belnap PhD, Bruce Rollman MD

Introduction: Studies involving patients with stable heart disease typically show that increased self-Aeported physical activity is associated with better health-Aelated quality of life (HRQoL). We examined the relationship between objectively assessed physical activity as measured by armband accelerometers and HRQoL among recently hospitalized patients with systolic heart failure (HF) who consented to enroll in an NIH-funded trial presently examining the impact of treating depression.

Methods: From 3/14 to 10/17, we screened patients with systolic HF (ejection fraction (EF) =45%) and NYHA class II-IV symptoms for depression using the Patient Health Questionnaire (PHQ-2) at 8 Pittsburgh-area hospitals. Two weeks after discharge, we telephoned consented patients to confirm protocol-eligibility and administer the: PHQ-9 to measure depression symptoms; Kansas City Cardiomyopathy Questionnaire (KCCQ-12) for disease-specific HRQoL; and the Short Form Health Survey (SF-12 Physical Composite Score (PCS)) for generic HRQoL. Afterwards, we mailed a Bodymedia™ Sensewear armband to patients and instructed them to wear the device for 7 days before returning it. We classified the armband data as usable if the patient wore the device for at least 10 hours daily on 4 separate days. We calculated univariate Pearson correlation coefficients between objective daily step counts and EF and HRQoL, and standardized beta coefficients using multivariable regressions with square root transformed step counts adjusted for age, gender, and NYHA classification.

Results: Of the 757 enrolled HF patients (83% depressed), 261 (34%; 84% depressed) provided usable armband data (mean age: 64 years (SD: 13), 56% male, 73% Caucasian, NYHA: 38% class II, 52% class III, mean score (SD) KCCQ-12: 46.6 (23.8) and SF-12 PCS 30.9 (10.5)). Most enrolled HF patients were inactive (median daily step count: 1,351 (Q1=539, Q3=2,796)). Although their median daily step counts did not correlate with EF (R=-0.05, P=0.44), it did vary by NYHA classification (class II: 1,969, class III: 1,110, and class IV: 850 steps a day (P=0.002)), and were positively correlated with both disease-specific and generic HRQoL (KCCQ-12 (Beta=0.31, P<0.001) and SF-12 PCS (Beta=0.30, both P<0.001).

Conclusion: Clinicians should be aware that patients with systolic HF are often physically inactive following hospital discharge, and objective physical activity is associated with NYHA class and HRQoL, but not EF. Upon opening our study blind, we plan to examine the impact of physical activity on recovery from HF, depression, and other outcomes of interest to clinicians and policy makers.

56-A Poster: Associations of Grip Strength with Mood Symptoms and Health-Aelated Quality of Life Among Patients with Systolic Heart Failure

Presenter: Amol Koldhekar, Medical Student
General Internal Medicine

Research Interest: Clinical

Mentors: Bruce Rollman MD
Bea Belnap PhD

Funding Source: NIH

Authors: Amol Koldhekar BS, Elsa Strotmeyer PhD, Kaleab Abebe PhD, Amy Anderson MSc, Bea Herbeck Belnap PhD, Bruce Rollman MD

Introduction: Poor handgrip strength is an indicator of sarcopenia which has been associated with functional impairment and disability in older adults with heart failure (HF). We examined if grip strength is associated with depression and health-Aelated quality of life (HRQoL) among patients with systolic HF enrolled in an NIH-funded trial presently examining the impact of treating depression.

Methods: From March 2014 to October 2017, we screened patients with systolic HF (cardiac ejection fraction (EF) <45%) and NYHA class II-IV symptoms for depression using the Patient Health Questionnaire (PHQ-2) at 8 Pittsburgh-area hospitals. We used digital JAMAR dynamometers to measure grip strength in both hands using the highest averaged value of two attempts in our analyses. Two weeks after discharge, we telephoned consented patients to confirm protocol-eligibility and administered our baseline assessment battery. It included the PHQ-9 to assess mood symptoms; and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and Short Form Health Survey (SF-12 Physical Component Score (PCS)) to determine disease-specific and generic HRQoL, respectively. We categorized PHQ-2 screen-positive patients who scored >= 10 on the PHQ-9 as "depressed," and PHQ-2 screen-negative patients who scored < 5 on the PHQ-9 as "non-depressed." Afterwards, we grouped patients by gender into quartiles of grip strength and used Fisher's Exact or Kruskall-Wallis tests for significance testing.

Results: Of the 757 enrolled HF patients, 524 (69%) had usable grip strength data (mean age: 64 years (SD: 13), 56% male, 73% Caucasian, 82% depressed, NYHA: 38% class II, 52% class III, mean score (SD) KCCQ-12: 46.6 (23.8), SF-12 PCS 30.9 (10.5)). Within both gender groupings, older age was associated with lower grip strength (both $P < 0.01$), however, grip strength quartile was not associated with mood or disease-specific or generic-HRQOL.

Conclusion: Inpatient grip strength was associated with age but not mood or HRQoL assessed shortly following hospitalization with systolic HF. Upon opening our Trial's study blind in 2018, we plan to examine the longitudinal impact of baseline grip strength on hospital readmission, mortality, and other outcomes of interest to clinicians and policy makers.

57-A Poster: Functional Capacity And Cardiac Self-efficacy Measures Are Associated With Health Literacy In Cardiac Rehabilitation

Presenter: James Kostra, Graduate Student Geriatric Medicine

Research Interest: Clinical

Mentors: N/A

Funding Source: Office of Rural Health

Authors: Kelly Allsup BS, Amanda Delligatti BS, Andre Althouse PhD, Daniel Forman MD

Introduction: Health literacy (HL) defines the degree to which individuals can obtain, process, and understand basic health information and services needed to make proper health decisions. Low HL (LHL) is associated with reduced adherence to exercise, medications, healthy nutrition, and low utilization of preventive health services. Cardiac Rehabilitation (CR) is a secondary prevention program that improves functional capacity and risk factor profile, leading to improved health status. The purpose of the present study is to assess the how the effectiveness of CR, as measured by functional capacity and cardiac self-efficacy (CSE), may differ between patients with LHL and high HL (HHL) who attend CR.

Methods: In a quality improvement project, we evaluated the impact of LHL versus HHL on change in functional capacity and CSE measures. HL of patients enrolling in CR was evaluated by the REALM-SF. HL was divided into two groups: LHL was less than 9th grade reading level and HHL was greater than 9th grade reading level. We assessed changes in functional capacity by six-minute walk distance (6MWD) in relation to scores from the 13 question CSE scale that measures controlling and maintaining cardiac symptoms.

Results: 134 patients that completed CR were assessed: 42 LHL and 92 HHL. LHL patients had lower baseline 6MWD and CSE scores compared to HHL patients. There were clinically significant gains in 6MWD (>30 m) and statistically significant improvements for CSE in both groups. Additionally, LHL and HHL patients both had significant correlations between 6MWD and CSE.

Conclusion: This work indicates a positive correlation between improvements in functional capacity and CSE over the course of CR for both LHL and HHL groups, highlighting the utility of CR in overcoming some of the risks of diminished functional capacity and CSE associated with LHL. The study also reflects the importance of HL as a criterion of risk and associated management modification.

58-A Poster: Are Traditional Biomarkers of Lupus Associated with Renal Pathology in Lupus Nephritis?

Presenter: Kelly Liang, Junior Faculty
Renal-Electrolyte

Research Interest: Clinical

Mentors: N/A

Funding Source: K23

Authors: Kelly Liang MD, Kimberly Liang MD, Tina Tomko , Sheldon Bastacky MD

Introduction: Traditional biomarkers for systemic lupus erythematosus (SLE) and lupus nephritis (LN) include serum creatinine (Cr), complement (C3/C4), double-strand DNA antibody (dsDNA), erythrocyte sedimentation rate (ESR), C-Aeactive protein (CRP), urine red blood cells (uRBC), and urine protein/Cr ratio (uPCR). However, these biomarkers are limited in their specificity for active LN and are inconsistent predictors of renal pathology. Whether these biomarkers of SLE are associated with LN class has important implications in therapeutic decision-making.

Methods: Using the University of Pittsburgh Health Sciences Tissue Bank (HSTB) and Renal Pathology Department stored biopsy specimens, we identified 35 cases of LN diagnosed on renal biopsy from 2010-2016. Using the electronic database, we obtained the LN classes as well as traditional biomarkers checked within a few days to a month of the biopsy date for each sample. Descriptive analyses were used to summarize the relationship between the biomarkers and LN.

Results: Of the 35 LN samples, 1 had class I, 3 had class II, 10 had class III, 15 had class IV, and 14 had class V (5 with isolated class V) LN. Excluding those with missing data, 14/30 (47%) had Cr >1.3 mg/dL. There were 22/30 (73%) with low C3 or C4 (17 [57%] with low C3, 18 [60%] with low C4). dsDNA was positive in 21/27 (78%). Of the 6 samples negative for dsDNA, four had class IV, one had class II, and one had class V LN. ESR was elevated in 18/27 (67%), whereas CRP was elevated in only 8/24 (33%). Hematuria was variably reported, but only 10/29 (34%) had >5 RBC on urinalysis. Proteinuria (uPCR >0.2) was present in 21/24 (87.5%) and nephrotic proteinuria (uPCR >3.5) was present in 7/24 (29%). Of the 14 LN class V cases, nephrotic proteinuria was present in 4/12 (33%).

Conclusion: Traditional laboratory and urine biomarkers of SLE and LN are imperfect predictors of LN class on renal biopsy. Renal dysfunction (Cr >1.3 mg/dL) was seen in only 47%. Low C3/C4 and positive dsDNA Ab were seen in over 70%, but there were 6 cases in which LN occurred in the absence of dsDNA Ab positivity. ESR was a better biomarker of LN than CRP. uRBC was a poor biomarker of LN. Although variable proteinuria was present in 87.5%, uPCR was unable to differentiate between the LN classes. The lack of consistent association between traditional biomarkers of SLE and renal pathology suggests that more specific LN biomarkers are urgently needed.

59-A Poster: Relationship of Serum Inflammatory and Vascular Biomarkers with Subclinical Atherosclerosis and Cardiovascular Risk Factors in Rheumatoid Arthritis and Controls

Presenter: Kimberly Liang, Junior Faculty
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Larry Moreland MD
Douglas Landsittel PhD

Funding Source: K23

Authors: Kimberly Liang MD, Yaming Li MD, Douglas Landsittel PhD, Suresh Mulukutla MD, Steven Reis MD, Marc Levesque MD, Donald Jones MS, Rachel Gartland MD, Ali Shoushtari MD, Flordeliza Villanueva MD, Larry Moreland MD

Introduction: Rheumatoid arthritis (RA) is independently associated with cardiovascular disease (CVD). Mechanisms of atherosclerosis include (1) Endothelial dysfunction/activation mediated by intercellular adhesion molecules (e.g., ICAM-1, VCAM-1, E-selectin) and oxidative stress (e.g., through MPO activity); (2) Inflammation mediated by cytokines (e.g., IL-6); (3) Plaque stability mediated by CD40-CD40L interactions; and (4) Proteolysis/Plaque rupture mediated by proteolytic enzymes (e.g. MMP-9). Inflammatory and immune biomarkers important in RA pathogenesis include erythrocyte sedimentation rate (ESR), C-Aeactive protein (hsCRP), and IL-17. This study evaluates whether serum biomarkers are associated with disease status, subclinical carotid atherosclerosis, and CVD risk factors.

Methods: Carotid ultrasounds measured intima-media thickness (as maximum cIMT) and plaque presence, and serum biomarkers (ICAM-1, VCAM-1, E-selectin, MPO, IL-6, CD40L, MMP-9, ESR, CRP, IL-17) were measured on 87 RA cases and 101 controls. Differences between cases and controls were tested using the Wilcoxon rank-sum test (for continuous data) or chi-square test. Relationships between biomarkers and number of CVD risk factors with cIMT were assessed with correlations.

Results: Demographics were similar between RA and controls except for age (mean 59.6+/-12.0 in RA vs. 54.0+/-14.7 years in controls; p=0.005), as were CVD risk factors except for hypertension (46.4% in RA vs. 23.3% in controls). Number of risk factors was higher in RA (40.2% with 3 or more versus 22.8% with 3 or more in controls) (p=0.007). cIMT was higher in RA (0.86+/-0.20 versus 0.79+/-0.17; p=0.02). MPO was lower in RA (422.8+/-516.4 versus 610.4+/-449.4) (p=0.009), and ESR was higher in RA (21.2+/-16.1 versus 16.6+/-12.6) (p=0.04). Plaque presence was found in 48.3% of cases vs. 35.0% of controls (p=0.07). None of the other serum biomarkers were significantly different between groups. E-selectin (r=0.29, p=0.004) and ICAM-1 (r=0.19, p=0.05) were associated with cIMT in controls, whereas only VCAM-1 (r=0.27, p=0.01) was associated with cIMT in RA. Number of risk factors were significantly correlated with cIMT in controls (p=0.0001) but not RA (p=0.38). In controls, number of risk factors correlated only with E-selectin (p=0.004); in RA, number of risk factors correlated with MPO (p=0.03), hsCRP (p=0.0002), and ESR (p=0.02).

Conclusion: This study confirms previous observations that cIMT is higher in RA. The differences found in markers of endothelial dysfunction and correlation of number of risk factors with cIMT may suggest possible common pathways of atherosclerotic progression, but also potential differential effects of CVD risk factors on cIMT and biomarker elevations. Results may inform future studies to develop CVD risk stratification algorithms.

60-A Poster: Feasibility and Acceptability of an Early Palliative Care Intervention in Patients with Idiopathic Pulmonary Fibrosis (IPF) and their Caregivers

Presenter: Kathleen Lindell, Junior Faculty
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Clinical

Mentors: Margaret Rosenzweig PhD
Kevin Gibson MD

Funding Source: K23

Authors: Kathleen Lindell PhD, Medhi Nouraie MD, Melinda Klesen BS, Sara Klein MS, Kevin Gibson MD, Daniel Kass MD, Margaret Rosenzweig PhD

Introduction: IPF is a progressive life-limiting lung disease affecting approximately 128,000 newly diagnosed individuals in the US annually. Median survival from diagnosis is 3.8 years; many of these patients succumb to a rapid death within 6 months. As the disease progresses, IPF patients and their caregivers experience stress, symptom burden, poor quality of life (QOL), and inadequate preparedness for advance care planning (ACP). We are conducting a randomized trial to test the hypothesis that early palliative care could improve stress, symptom burden, quality of life, and ACP in IPF patients and their caregivers. We were unsure of the feasibility or recruitment and acceptability of the intervention within this population. In this abstract we describe early results of trial recruitment.

Methods: In this trial, termed SUPPORT, patients with IPF and their caregivers are randomized to SUPPORT intervention or usual care. The intervention includes information about the disease, self-management strategies, and introduction to ACP in a format with enhanced content available across multiple domains (face-to-face, printed material, website) delivered by an interventionist. The usual care group receives routine printed patient education. Patient and family caregiver dyads (target 80 dyads) are recruited after confirmation of the diagnosis (typically =1 month after referral to a comprehensive IPF center) at the patient's next scheduled clinic visit. The SUPPORT intervention is delivered by the study interventionist and involves 3 research visits aligned with the patient's clinic visits over a 6-8 month period. Outcomes measured will be: stress, symptom burden, quality of life, preparedness, and completion of ACP.

Results: Eighty-nine subjects were screened from March to October 2017. Among the eligible dyads, 26 (47%) were consented. Main reasons for refusal to participate were: "not interested in participating in research" or "wanting to delay to next visit". Of note, three of the caregivers appeared interested to participate when the patient declined. Of the 26 participants, mean (SD) age was 71 (6.0), FVC% 67% (15.5) and 5 (19%) were females. Six (23%) were withdrawn from study after first visit, including 3 who died in 60-154 days after recruitment, one who underwent transplant, and two who withdrew their consent.

Conclusion: There is a willingness to participate in a palliative care intervention among patients and caregivers with IPF. The high rate of withdrawal is to be expected in this severely ill IPF population. This feasibility and acceptability information will inform future studies.

61-A Poster: Association between Systemic Inflammation and Lung Dysfunction in HIV-infected Individuals

Presenter: Shulin Qin, Junior Faculty **Research Interest:** Clinical
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 compare levels of peripheral circulating inflammatory mediators and determine associations between these inflammatory mediators and phenotypes of pulmonary dysfunction in HIV-infected and uninfected individuals.

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-Aeport. Percent predicted post-bronchodilator (BD) forced expiratory volume in 1 second (FEV1), post-BD forced vital capacity (FVC), and single breath diffusing capacity for carbon monoxide (DLCO) adjusted for hemoglobin and carboxyhemoglobin were measured in accordance with ATS/ERS recommendations. Plasma levels of 17 inflammatory cytokines and chemokines 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-γ, CCL2 and CCL4 were measured by Luminex (Bio-Aad Laboratories Hercules, CA, USA). Levels of these inflammatory cytokines and chemokines were compared between HIV-infected and uninfected individuals using sign rank test, and they also were compared to FEV1% predicted (airway obstruction phenotype) and DLco% predicted (diffusion impairment phenotype) using Pearson correlations.

Results: Five hundred and seven participants were included in this study and 360 (71%) were HIV-infected. Average age was 51 years. 333 (93%) HIV-infected individuals received current antiretroviral therapy (ART). Compared to HIV-uninfected individuals, the levels of all inflammatory cytokines and chemokines except IL-10 and CCL4 were significantly higher in HIV-infected individuals. Correlation analyses showed that levels of multiple different inflammatory cytokines (Th1, Th2 and Th17) and chemokines were inversely correlated with FEV1% predicted, and only Th1 and Th2 cytokines levels were negatively associated with DLco% predicted in HIV-infected individuals. In contrast, levels of Th1, Th2 and Th17 inflammatory cytokines and chemokines were inversely correlated with DLco% predicted, but not with FEV1% predicted in HIV-uninfected individuals.

Conclusion: We found that levels of peripheral circulating inflammatory cytokines and chemokines were higher in HIV-infected individuals. Certain patterns of cytokines were associated with different aspects of lung function. In HIV-infected individuals, Th1, Th2, Th17 cytokines and chemokines were related to airway obstruction, and Th1, Th2 cytokines were related to impairment of diffusing capacity for carbon monoxide, suggesting COPD phenotypes may be associated with different inflammatory pathways and systemic inflammation may play an important role in lung dysfunction in HIV-infected individuals.

62-A Poster: MULTIDISCIPLINARY CARE OF A PATIENT WITH COWDEN SYNDROME AT A GERIATRIC CENTER.

Presenter: Sangeeta Rana, Junior Faculty Geriatric Medicine

Research Interest: Clinical

Mentors: N/A

Funding Source: N/A

Authors: Sangeeta Rana MD

Introduction: Cowden syndrome is caused by a genetic mutation that manifests as recurrent benign or malignant tumors over the life time of patients. We present the diagnostic and therapeutic challenges of managing Cowden Syndrome in a geriatric patient and the role of a geriatric center in coordination of care.

Methods: Chart Review

Results: Patient is a 71-year-old retired nun with history of multiple skin cysts, moles, neurofibromas,hemangiomas and warts from childhood to adulthood. Three decades ago, she underwent right subtotal thyroidectomy for nodular goiter with benign pathology and later had left thyroid lobectomy. At the age of 31 years she underwent surgery for uterine cancer. She developed a cerebellar mass at age 62 years which was initially followed conservatively. A couple of years later the brain lesion grew, prompting retro mastoid craniotomy in 2010. Pathology showed ganglioglioma of the cerebellum. With her history of multiple malignancies, she was suspected to have Cowden Syndrome. Genetic testing revealed PTEN mutation confirming the diagnosis. At age 66 years she was referred to our geriatric center for further management. Over the next five years shecontinued to have a turbulent course with development of invasive ductal carcinoma of right breast, numerous colonicpolyps (benign), granulosa cell tumor of the tongue, etc. She has required intense medical surveillance by amultidisciplinary medical team of GI, Endocrinology, Gynecology, Neurosurgery, Neurology, Dermatology, Urology, ENT specialties coordinated by the Geriatrician. Additionally, patient has had age related functional decline and has developed Parkinson's disease, anxiety and depression, constipation, osteoporosis, urinary incontinence, etc. To help her meet these challenges, she moved from independent living into personal care and was recommended to discontinue driving with which she complied. Despite her tumultuous course she has remained resolute and actively participated in treatment decisions.

Conclusion: Cowden syndrome is a rare genetic disorder that predisposes patients to a variety of benign andmalignant tumors. In elderly patients with this syndrome, optimal long term care and surveillance are best provided ina geriatric center in coordination with other medical disciplines

63-A Poster: Asthma Variables and Associations with HIV Status

Presenter: John Ries, Graduate Student **Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

Mentors: Alison Morris MD **Funding Source:** R01, K24, KHL, R56

Authors: John Ries BS, Megan Fitzpatrick MD, Alison Morris MD, Matt Gingo MD

Introduction: Prior research suggests a link between HIV and asthma. HIV-specific risk factors, including lipodystrophy, systemic inflammation, and oxidative stress, may play a role in asthma development. This study compared spirometry markers of asthma between HIV-infected and HIV-uninfected individuals and assessed potential links between phenotypic and systemic indicators of asthma and HIV infection.

Methods: Participants with HIV infection were recruited from the Pittsburgh AIDS Clinic for Treatment, and HIV-uninfected individuals were matched based on age, race, gender, body mass index (BMI), and smoking. Participants completed a questionnaire, fractional exhaled nitric oxide (FeNO) measurement and pulmonary function testing. Methacholine challenge was performed unless contraindicated. Blood samples and optional fat pat biopsy were obtained. Enzyme-linked immunosorbent assay was performed to quantify plasma adiponectin, leptin, and oxidized low density lipoprotein. Immunoglobulin E (IgE) levels were measured in the clinical laboratory. Real-time polymerase chain reaction was used for gene expression of PPAR , adiponectin, leptin, and IL-6 in peripheral-blood mononucleocytes (PBMC) and adipose. Biomarker data were log transformed to approximate normality. Bivariate regression analyses were performed comparing HIV status and data collected.

Results: 176 participants were enrolled. 105 HIV-infected individuals (67.5% male) had mean age of 49 and BMI of 28.5 kg/m2, and a median pack-years smoked of 15.9. 71 HIV-uninfected individuals (60.6% male) had mean age of 50, BMI of 28.7 kg/m2, and median pack-years smoked of 13.1. There were no differences in spirometry between HIV-infected and uninfected participants except in pre-bronchodilator FEV1/FVC (0.79 vs 0.74, p=0.03). Asthma-specific variables (bronchodilator response, methacholine challenge positivity, or combined phenotype 'airway hyperresponsiveness') were similar between groups. Plasma markers were similar between HIV-infected versus uninfected participants. PBMC Leptin and adipose IL-6 gene expression were significantly higher in HIV-uninfected participants (26.2 vs 24.7, p=0.01; 35.3 vs 34.0, p=0.002), otherwise levels were similar. IgE and PBMC leptin were higher in those with methacholine responsiveness (5.32 vs 3.85, p=0.003; 3.32 vs 3.22, p = 0.01), but relationships did not differ by HIV status. Similarly, higher adipose leptin was associated with bronchodilator responsiveness (3.23 vs 3.20, p=0.03).

Conclusion: Comparison of phenotypic indicators of asthma between HIV-infected and uninfected persons did not reach significance in this sample, but differences in gene expression of inflammatory markers leptin and IL-6 were found. IgE and leptin levels were associated with markers of asthma.

64-A Poster: Interventionist Training and Intervention Fidelity Monitoring and Maintenance for CONNECT, a Nurse-led Primary Palliative Care in Oncology Trial

Presenter: Gregg Robbins-Welty, Medical Student
Geriatric Medicine

Research Interest: Clinical

Mentors: Yael Schenker MD

Funding Source: T32

Authors: Gregg Robbins-Welty , Yael Schenker MD, Chandler Mitchell , Nicole Pope , Robert Arnold MD, SeoYoung Park PhD, Doug White MD, Kenneth Smith MD, Charles Reynolds MD, Margaret Rosenzweig PhD, Marie Bakitas PhD

Introduction: Intervention fidelity is a critical component of behavioral research that has received inadequate attention in palliative care studies. With increasing focus on the need for palliative care models that can be widely disseminated and delivered by non-specialists, rigorous yet pragmatic strategies for training interventionists and maintaining intervention fidelity are needed. Objectives: (1) Describe components of a plan for interventionist training and monitoring and maintaining intervention fidelity as part of a primary palliative care trial (CONNECT) and (2) present data about perceived training effectiveness and delivery of key intervention content.

Methods: Methods: Post-training evaluations, visit checklists, and visit audio-Aecordings.

Results: Results: Data were collected from June, 2016 through April, 2017. We include procedures for (1) identification, training and certification of oncology nurses as CONNECT interventionists; (2) monitoring intervention delivery; and (3) maintaining intervention quality. All nurses (N=14) felt prepared to deliver key competencies after a 3-day in-person training. As assessed via visit checklists, interventionists delivered an average of 95% (SD 13%) of key content for first intervention visits and 86% (SD 14%) for subsequent visits. As assessed via audio-Aecordings, interventionists delivered an average of 85% (SD 8%) of key content for initial visits and 85% (SD 12%) for subsequent visits.

Conclusion: Conclusion: We present a 3-part strategy for training interventionists and monitoring and maintaining intervention delivery in a primary palliative care trial. Training was effective in having nurses feel prepared to deliver primary palliative care skills. As assessed via nursing checklists and visit audio-Aecordings, intervention fidelity was high.

65-A Poster: Urea in the Treatment of Hyponatremia: The First Reported US Inpatient Experience

Presenter: Helbert Rondon-Berrios, Junior Faculty

Research Interest: Clinical Renal-Electrolyte

Mentors: N/A

Funding Source: N/A

Authors: Helbert Rondon-Berrios MD, Srijan Tandukar MD, Maria Mor PhD, Steven Weisbord MD

Introduction: Hyponatremia is associated with increased morbidity, mortality, and health resource utilization. Most therapies for hyponatremia have not been systematically studied, while vasopressin antagonists have safety risks and cost limitations. Small European studies suggest urea is safe and effective. With the recent availability of an American formulation of urea, we assess its effectiveness, safety, and tolerability for the treatment of inpatient hyponatremia.

Methods: We identified all patients hospitalized between July 2016 and August 2017 diagnosed with hyponatremia who received urea (cases). We also identified hyponatremic patients admitted the year prior when urea was unavailable and were treated with other therapies (controls). Controls were matched on key demographic and clinical characteristics to cases who received urea as the sole therapy: urea-only cases. We used paired and unpaired Student's t-test to compare plasma sodium concentration (PNa) at different points during hospitalization within urea-only cases, and PNa and length of hospital stay between urea-only cases and controls, respectively. We recorded all patient-Aeported adverse events associated with urea.

Results: Fifty-eight patients, of whom 47 (81%) had SIADH, received urea (15-60 g/day) for a mean duration of 5.4 ± 3.7 days. Urea therapy was associated with a PNa increase from 123.7 ± 4.4 mEq/L to 130.3 ± 4.6 mEq/L ($P<0.0001$) in all cases. Among urea-only cases, PNa increased from 124.3 ± 3.3 mEq/L to 131.8 ± 4.6 mEq/L($P=0.0001$) with a mean PNa increase in first 24h of 2.4 ± 2.4 mEq/L. PNa overcorrection was not seen. Urea-only cases had a larger increase in PNa both in the first 24h and at the end of therapy compared to controls but these were not statistically significant. There was also a trend towards shorter length of stay in urea-only cases compared to controls. No adverse events were reported. One patient stopped urea due to poor palatability.

Conclusion: Urea is well tolerated and effective for the treatment of inpatient hyponatremia. Randomized trials comparing the effect of urea to other therapies on patient-centered clinical and economical outcomes are needed.

66-A Poster: Multidrug-Aesistant organisms (MDRO) surveillance: how do we look at the picture, horizontally or vertically?

Presenter: Emily Schmitz, Graduate Student Infectious Diseases

Research Interest: Clinical

Mentors: Mohamed Yassin MD, PhD

Funding Source: The Beckwith Institute

Authors: Emily Schmitz BS, Mohamed Yassin MD, PhD, Emily Magee MPH, Yohei Doi MD, PhD

Introduction: Multidrug-resistant organisms (MDRO) pose a significant risk to patient safety and require continued careful surveillance. As all infection prevention efforts, surveillance should be inexpensive, easy to apply and sensitive. Clinical patient characteristics are a major component of the risk of spread of MDRO within the health care environment. Retrospective review of these criteria was performed over the last two years with excellent correlation.

Methods: The aim of the study is to prospectively examine if clinical patient criteria (horizontal surveillance) predict colonization with MDRO better than current surveillance (vertical or organism-based). We also wanted to examine the burden of MDRO in patients with longer length of stay (LOS). The current standard surveillance at our facility is screening every ICU admission for MRSA and MDR Acinetobacter using nasal swab and axillary sponge. The five clinical criteria are: admission from an outside facility, readmission within 90 days, presence of chronic wound, tracheostomy or indwelling catheters. MDRO includes *Methicillin-resistant Staph aureus (MRSA), Vancomycin resistant Enterococci (VRE), Carbapenem resistant enterobactericiae (CRE) and extended spectrum Beta lactamase producing organisms (ESBL).* We developed an automated daily report that alerted the infection control department of new admissions with at least 2 of these five criteria to the intensive care unit (ICU). Nurses collected rectal swabs and groin samples using a pre-moistened sponge. Both specimens were tested for MRSA, ESBL, CRE and VRE. We are collecting samples from newly admitted patients to the ICU fulfilling the two criteria, patients who stayed in ICU for 7 days and control sample of patients admitted to ICU not fulfilling these clinical criteria.

Results: Samples were collected at a single medical center starting Oct. 1st, 2017 and is ongoing. From Oct 1st, 2017 through Nov. 30th, 2017 there were total of 155 patients and we collected 74 patients who met our clinical criteria. Additional 26 patients who met our 7-day length of stay criteria were also screened. There were 52% men, with an average age of 60.1 years. The mean severity index was 38.8. There was evidence of MDRO (CRE, ESBL, VRE & MRSA) in 30% of patients with at least 2 clinical criteria, 27% in 7-day LOS patients and 5% in current surveillance.

Discussion: Clinical-based horizontal surveillance is a more effective way of identifying MDRO colonization and infection. This data is compared to our historical cohort. The next step is to perform cost-effectiveness analysis and include a larger data sample to verify initial data results.

67-A Poster: Opioids, NSAIDs, and AKI: Unintended Consequences of the PA Prescription Drug Monitoring Program

Presenter: Amanda Schwenk, Graduate Student

Research Interest: Clinical Renal-Electrolyte

Mentors: Evan Ray MD, PhD

Funding Source: K08

Authors: Amanda Schwenk BS, Andrew Bilderback MS, Dilhari DeAlmeida PhD, John Kellum Jr MD, Evan Ray MD, PhD

Introduction: In response to the opioid epidemic, all 50 states now have a Prescription Drug Monitoring Program (PDMP) to track prescribing of controlled substances. Voluntary access to the Pennsylvania PDMP became available August 25, 2016, with mandatory participation beginning January 1, 2017. Initiation of PDMPs has been associated with reduced opioid prescribing, but there is little data to address how these programs impact non-opioid analgesia use, such as NSAIDs, and whether they are associated with increased NSAID-associated adverse effects, like acute kidney injury (AKI) or gastrointestinal bleeding. We asked whether there has been an increase in the prescribing of NSAIDs and the occurrence of NSAID-Aelated adverse effects at UPMC hospitals in association with initiation of the Pennsylvania PDMP.

Methods: In-patient data from January 1, 2016 to December 31, 2017 at 16 UPMC hospitals were analyzed. Exclusion criteria included patients with ICD-10 codes indicating end-stage renal disease and those experiencing AKI due to clearly non-medical causes, such as obstruction or trauma.Outcomes included the percent of admissions in which patients received opioids or NSAIDs, the average number of days patients received these agents, the percent of admissions with AKI and the percent of admissions with GI bleeding. AKI was determined by the presence of both an EHR-based indicator and an ICD-10 code consistent with AKI. Outcomes prior to the PA PDMP were compared to those after voluntary and mandatory use. Statistical analysis: Interrupted time-series analyses were used to examine slopes of outcomes before and after the voluntary and mandatory implementations of the PA PDMP, as well as assessing outcome frequency changes immediately after implementation. A two-tailed p-value of less than .05 was used to determine significance.

Results: There was an increase of 1.4% in the receipt of NSAIDs after the PDMP became available on a voluntary basis ($p < .001$). After mandatory implementation of the PDMP, there was a marginally significant 0.7% increase in AKI incidence ($p = .06$) and 1.7% decrease in the receipt of opioids after mandatory implementation ($p = .05$).

Conclusion: At UPMC facilities, the Pennsylvania PDMP has been associated with only a marginal decrease in opioid use, whereas a significant increase in the prescribing of NSAIDs was observed. A marginally significant increase in AKI was also observed, though no increase in GI bleeding was seen. On-going analysis will examine whether certain subgroups are at greater risk for AKI and/or more likely to benefit from opioid reduction. These findings will help evaluate whether the PDMP can be improved by personalization tied to individual risk-benefit analysis.

69-A Poster: PSMA-targeted SPECT imaging for prostate cancer in mice model using 177Lu-labeled agent CTT1403

Presenter: Ding Shen, Medical Student Hematology/Oncology

Research Interest: Clinical

Mentors: Carolyn Anderson PhD

Funding Source: N/A

Authors: Xiaoxi Ling PhD, Cindy J. Choy PhD, Joseph D. Latoche PhD, Ding Shen BS, Jonathan J. Geruntho PhD, Yijen Wu PhD, Nathan Salamacha PhD, Beatrice Langton-Webster PhD, Carolyn J. Anderson PhD, Clifford E. Berkman PhD

Introduction: Prostate-specific membrane antigen (PSMA) is a promising biomarker for prostate cancer related research and treatment. PSMA is known for its overexpression in most prostate cancer cells, yet low expression in the rest of human body. Moreover, the expression level of PSMA is proportional to the extent of disease and metastatic stages. While many small-molecule PSMA targeting molecules have been developed with strong PSMA binding properties, their common structures are highly hydrophilic. Therapeutic agents based on these PSMA targeting molecules often suffer from rapid renal clearance leading to limited target uptake. One solution to enhance pharmacokinetics is to modify the agent with albumin binding moiety, which slows down blood clearance, and can enhance tumor uptake. We used this strategy to develop CTT1403, a 177Lu-labeled PSMA targeted radionuclide therapy (TRT) agent, which showed excellent efficacy in a human xenograft mouse model. Here, we explored the possibility of using CTT1403 as an imaging agent with single-photon emission computed tomography (SPECT) using the same mouse model.

Methods: Male NCr nude mice were implanted with PC3-PIP (PSMA+) human tumor cells and tumors were allowed to grow to 100-300 mm3. CTT1403 was administrated in therapeutic doses (29 MBq or 0.75 mCi) in 8 mice via tail vein injection. All mice were imaged at 4 h, 24 h, 48 h, 72 h and 148 h post injection using SIEMENS Inveon scanner. SPECT/CT images were analyzed using IRW software. Regions of interest were selected and analyzed. The results were compared with biodistribution data from a previous study. CTT1751 (29 MBq or 0.75 mCi), a 177Lu-labeled albumin binding agent without the PSMA binding moiety, was injected into two mice for SPECT/CT imaging as a negative control.

Results: Mice injected with CTT1403 had SPECT signal in the tumor and kidneys, which was retained up to 7 days post injection. At early time points, there was activity in the bladder and heart. Tumor uptake gradually increased over the imaging time frame, peaking at 24-48 h post injection. The change of tumor to background (blood, muscle, kidneys) ratios were similar to results obtained from previous biodistribution study. In contrast, SPECT signals were not found in tumors in mice that received CTT1751.

Conclusion: CTT1403 successfully imaged PSMA expression in mice bearing PSMA+ tumors. Based on the SPECT imaging results, the uptake and clearance of CTT1403 uptake in the PC3-PIP tumor over one week is similar to our previous biodistribution study. These results suggest that CTT1403 therapy can be followed by SPECT imaging post-treatment.

70-A Poster: GERMLINE VARIANTS AND RISK FOR PANCREATIC CANCER: A SYSTEMATIC REVIEW AND EMERGING CONCEPTS.

Presenter: Wei Zhan, Medical Student
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: David Whitcomb MD

Funding Source: R01

Authors: Wei Zhan Medical Student, Celeste Shelton MS, Phil Greer MS, Randall Brand MD, David Whitcomb MD

Introduction: Genetic analyses from association studies and candidate gene testing have revealed multiple germline variants that may contribute to different steps in pancreatic oncogenic process. The aim of this study was to identify and evaluate pancreatic cancer-associated germline variants across different studies.

Methods: We systematically reviewed literatures to identify germline pancreatic cancer risk variants. Variants were scored across multiple criteria and binned by evidence for pathogenicity. The genes and variants were further annotated with published functional studies and associated biological systems/pathways.

Results: Twenty-two previously identified pancreatic cancer risk genes and 337 germline variants were identified from 97 informative studies that met our inclusion criteria. Fifteen genes contained 66 variants predicted to be pathogenic, with 20 variants in 7 genes (ATM, BRCA1, BRCA2, CDKN2A, CHEK2, PALB2, SPINK1) being classified as highly pathogenic. Pancreatic cancer risk genes were organized into key biological mechanisms that promote various stages of pancreatic oncogenesis.

Conclusion: Multiple well-defined pathogenic genetic variants are identified in pancreatic cancer patients for 4 steps proposed in an oncogenic model. Combining continuously updated variant information within the framework of an oncogenic progression model may be useful for interpreting early biomarkers and directing pathway-specific treatment for pancreatic cancer in the future.

71-A Poster: Quality of Care in Adult Primary Care Physicians is Not Associated with Physician Electronic Medical Record Efficiency.

Presenter: Hannah Chang, Medical Student
General Internal Medicine

Research Interest: Health Services/Clinical Epidemiology

Mentors: Janel Hanmer MD, PhD
Jonathan Arnold MD, MSE

Funding Source: N/A

Authors: Hannah Chang MS, MBA, Jonathan Arnold MD, MSE, Janel Hanmer MD, PhD

Introduction: Electronic medical records (EMRs), such as Epic, have been widely deployed in the United States. When surveyed, physicians have reported reduced efficiency as a significant concern with EMR deployments. The provider efficiency profile (PEP) is a tool developed by Epic Systems to measure provider efficiency in the use of the Epic EMR. Quality metrics (QMs) are used to measure how effectively physicians are applying generally accepted standards of care to their patient populations. We hypothesize that increased efficiency in EMR use as measured by PEP will be associated with higher QM scores in primary care physicians (PCPs) when adjusting for weighted relative value units (wRVUs).

Methods: We conducted an analysis of the association between overall QM scores for management of coronary artery disease (CAD), diabetes mellitus (DM) and health maintenance/screening (HM) with PEP score, and wRVUs for primary care physicians at a large health system in Western Pennsylvania. We included all providers with at least 6 days of EMR usage from the PEP reporting periods and quality metrics data from at least 50 patients for each of the three domains during 2016. We performed separate analysis using for each QM. The PEP score for EMR efficiency is reported on a 0-10 scale and was averaged between two time points 1 month apart. We included wRVUs for the 2016 calendar year. We used multivariable linear regression to evaluate the association between QMs and PEP score, adjusted for wRVUs.

Results: The study population includes 222 adult primary care providers (internal medicine and family medicine specialties). After adjustment for wRVUs, PEP scores were a significant positive predictor of HM QM ($p=0.014$) and DM QM ($p=0.003$), but not CAD QM ($p=0.08$). Despite statistical significance, very little variance in the QMs was explained by efficiency scores; adjusted R-square was 0.02 for the HM QM and was 0.03 for the DM QM.

Conclusion: In this dataset of 222 adult primary care providers, EMR efficiency is not associated with quality metrics; the quality of care that a physician provides is independent from the physician's EMR efficiency.

72-A Poster: The association between mental health disorders and unintended pregnancy among women Veterans in the ECUUN study

Presenter: Colleen Judge, Graduate Student
General Internal Medicine

Research Interest: Health Services/Clinical Epidemiology

Mentors: Sonya Borrero MD

Funding Source: TL1TR001858 (PI: Wishwa Kapoor)

Authors: Colleen Judge BS, Lisa Callegari MD, Xinhua Zhao PhD, Maria Mor PhD, Sonya Borrero MD

Introduction: Women Veterans have high rates of mental health disorders which, along with medical comorbidities and other psychosocial factors, may render this population particularly vulnerable to the negative outcomes associated with unintended pregnancy. However, little is known about the relationship between mental illness and unintended pregnancy among women Veterans.

Methods: This is a secondary analysis of data from the Examining Contraceptive Use and Unmet Need among women Veterans (ECCUN) study. ECUUN includes a nationally representative, cross-sectional survey of women Veterans ages 18-45 who used the Veterans Affairs (VA) Healthcare System for primary care. Predictors were any and number of self-Aeported mental health disorders (depression, anxiety, post-traumatic stress disorder, bipolar disorder or schizophrenia); outcomes were any and number of unintended pregnancies. Multivariable logistic and ordinal logistic regression were used to assess relationships between mental illness and unintended pregnancy while adjusting for age, race/ethnicity, marital status, education, religion, income, parity, additional (non-VA) insurance, deployment history, history of military sexual trauma, and census region. The proportional odds assumption was assessed by Brant test and satisfied for all ordinal models.

Results: Among 2297 women Veterans in our study population, 1580 (68.8%) reported a history of at least one mental health disorder, with 20.1%, 21.6%, and 27.0% reporting one, two, or three or more conditions, respectively. Any history of unintended pregnancy was reported by 1315 women (57.3%), among whom 49.4% reported one, 27.3% reported two, and 23.4% reported three or more unintended pregnancies. Women with any mental health disorder were more likely to report any unintended pregnancy compared to women with no mental illness (60.3% vs. 50.5%, adjusted OR:1.49; 95% CI:1.18, 1.87). Among women with at least one unintended pregnancy, women with any mental health disorder were more likely than women with no mental illness to have experienced greater numbers of unintended pregnancies (2 or =3 versus 1, and =3 versus 1 or 2; adjusted ordinal OR:1.40; 95% CI:1.09, 1.80). Greater numbers of mental health disorders were associated with greater numbers of unintended pregnancies (adjusted ordinal OR for 3 or more vs. 1 mental health disorder: 1.48, 95% CI:1.08, 2.02).

Conclusion: Women Veterans with mental health disorders are more likely to have experienced any and greater numbers of unintended pregnancies than are Veterans without mental health disorders. Further work is needed to explore mechanisms of unintended pregnancy among women Veterans with mental illness.

73-A Poster: Relationship Between Provider-Led Health Plans and Healthcare Quality, Utilization, and Patient Satisfaction

Presenter: Natasha Parekh, Junior Faculty
General Internal Medicine

Research Interest: Health Services/Clinical Epidemiology

Mentors: William Shrank MD

Funding Source: N/A

Authors: Natasha Parekh MD, Inmaculada Hernandez PhD, Thomas Radomski MD, William Shrank MD

Introduction: As healthcare providers accept increasing financial risk in alternative payment models, more provider organizations are expected to operate their own health insurance plans, known as provider-led health plans (PLHPs). Our knowledge of the impact of PLHPs on outcomes remains limited and inconsistent. Furthermore, it remains unknown how PLHP characteristics including size, nonprofit status, and geographic distribution may affect outcomes. The objectives of this study were to 1) determine the association between receipt of care within PLHPs and healthcare quality, utilization, and patient satisfaction; and 2) determine whether the association between receipt of care within PLHPs and outcomes differed by plan size, nonprofit status, and region.

Methods: We performed an observational study of 2016 Medicare Advantage plans. We included three quality outcomes (Medicare Advantage star ratings, Healthcare Effectiveness Data and Information Set (HEDIS®) effectiveness of care aggregate score, and HEDIS® access of care aggregate score), four utilization outcomes (HEDIS® average procedure rates, discharge rates, inpatient days, and readmission probability), and one patient satisfaction outcome (National Committee for Quality Assurance (NCQA) Consumer Satisfaction rating). We performed regression to compare the eight selected outcomes between PLHPs and non-PLHPs, controlling for key covariates including region, profit status, patient-Aelated demographics such as race, income, comorbidities, urban residence, and education, and provider-Aelated demographics such as hospital bed and physician distribution. We conducted subgroup analyses to evaluate how the association between PLHP contracts and outcomes differed by PLHP characteristics including plan size, profit status, and region.

Results: Our sample included 64 contracts offered by 31 PLHPs representing 3,197,284 enrollees, and 311 contracts offered by 55 non-PLHPs representing 13,881,210 enrollees. Compared with non-PLHPs, PLHPs were associated with higher star ratings (beta=0.43, CI 0.17-0.70), effectiveness of care scores (beta=2.98, 95% CI 1.14-4.82), and patient satisfaction (beta=0.46, CI 0.18-0.75), and lower procedure rates (beta=-0.67, CI -1.05-(-0.29)). There were no significant differences in access, discharges, inpatient days, and readmission probability. These relationships were maintained after excluding Kaiser. We further found that PLHP effects vary by plan size, nonprofit status, and region, with larger and nonprofit PLHPs performing better than their smaller and for-profit counterparts, respectively.

Conclusion: The receipt of care within a PLHP was associated with improved quality, effectiveness, and patient satisfaction, and lower procedure rates. As providers bear increasing financial risk under alternative payment models, there is momentum to integrate healthcare provision and payment through PLHPs. Our results demonstrate the potential of such organizations to deliver high-quality care.

74-A Poster: Variation in Low-Value Health Service Use within the Department of Veterans Affairs

Presenter: Thomas Radomski, Junior Faculty

General Internal Medicine

Research Interest: Health Services/Clinical Epidemiology

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

Funding Source: KL2

Authors: Thomas Radomski MD, MS, Yan Huang MS, Florentina Sileanu MS, Seo Young Park PhD, Joshua Thorpe PhD, MPH, Carolyn Thorpe PhD, MPH, Michael Fine MD, MSc, Walid Gellad MD, MPH

Introduction: Although the use of low-value health services (i.e., a test or procedure whose costs or harms exceed its benefits) is a major driver of wasteful healthcare spending among Medicare beneficiaries, less is known about the use of such services within the Department of Veterans Affairs (VA). We sought to assess the overall prevalence of and variation in the use of 2 specific low-value health services across VA Medical Centers (VAMC), and determine if there was an association between VAMC-level low-value health service use and geographic location.

Methods: We compiled a 20% random sample of all Veterans continuously enrolled in VA in FY2015. We adapted a Medicare claims-based metric to identify Veterans who underwent the following low-value health services commonly performed in Medicare beneficiaries: 1) Prostate Specific Antigen (PSA) testing in Veterans =75 years without a history of prostate cancer, and 2) low back imaging (LBI) for non-specific low back pain, done within 6 weeks of the first back pain diagnosis, and without a co-occurring diagnosis to warrant imaging, such as paralysis. We determined the overall percentage of eligible Veterans who underwent PSA testing and LBI and the range of use for both low-value health services across 127 VAMCs. We used logistic regression to determine the association between geographic location and PSA testing or LBI, controlling for sociodemographics and facility-level factors (i.e., academic affiliation, VAMC size, and VAMC complexity score).

Results: We identified 1,022,987 Veterans who received care in 127 VAMCs; 214,480 were aged =75 years and eligible to undergo PSA testing; and 343,024 had a back pain diagnosis and were eligible to undergo LBI. Overall, 51,388 (24.0%) Veterans underwent PSA testing and 19,736 (5.7%) underwent LBI. At the VAMC level, a median of 29.8% (range 8.8%-81.5%) of Veterans underwent PSA testing and 6.6% (range 2.6%-15.3%) underwent LBI. In comparison to Veterans who received care in the Northeast, Veterans who received care in the South (OR for PSA 2.13, CI 2.05-2.20; OR for LBI 1.30, CI 1.23-1.37), Midwest (OR for PSA 1.65, CI 1.59-1.70; OR for LBI 1.10, 95% CI 1.04-1.16), or West (OR for PSA 1.59, CI 1.53-1.65; OR for LBI 1.20, CI 1.14-1.27) were significantly more likely to undergo PSA testing or LBI.

Conclusion: In a national sample of Veterans enrolled in VA, we identified substantial overall use, 6 to 8-fold variation in LBI and PSA testing across VAMCs, and significant variation in the use of these low-value tests across geographic regions.

75-A Poster: Hospital-associated Clostridium difficile infection (CDI); how much we blame the current environment?

Presenter: Vatsala Rangachar Srinivasa, Graduate Student
Other
Research Interest: Health Services/Clinical Epidemiology
Mentors: Mohamed Yassin MD
Funding Source: N/A

Authors: Vatsala Rangachar Srinivasa MPH, Rahman Hariri PhD, Marian Pokrywka MS, Emily Magee MPH, Mohamed Yassin MD

Introduction: Clostridium difficile infection is a common hospital-associated infection with attributable cost of $3-15 K per episode. Hospital associated (HA) CDI are two thirds of CDI with increased mortality rate to 30K/ year nationwide. Sub-optimal environmental disinfection was highly suspected to be a major cause of CDI spread within healthcare systems. The aim of this study is to investigate the role of the environment in spread of CDI within hospital environment.

Methods: This study was conducted at a 495-bed academic University-affiliated single center. The first step was to identify all patients who had CD testing within our hospital between Jan 1st, 2016 until June 15th, 2017. All CDI were traced regardless if they were community (CA) or HA. Bed tracing was performed for these patients using Infection Control electronic medical records (EMR; Theradoc). The bed tracing was performed for the same admission and any subsequent admission within the study period. The 2nd step was to perform environmental cultures for these areas to uncover in lapses in environmental cleaning.

Results: An average of 1200 tests of CD are conducted annually in our institution (compared to 15K for the whole medical system). The rate of positive tests was overall 6-9% of unique patient testing. We reviewed the bed-tracing of 211 patients with positive CDI (115 HA and 96 CA) within the study period. CDI patients had mean age of 63 years old with a mean Chalreson Comorbidity index of 4, mean length of stay (LOS) 18 days and 15% had readmission within 30 days. Bed-tracing showed specific medical and intensive care unit rooms with highest CD patient-days. Environmental cultures using selective CD medium failed to show evidence.

Conclusion: There is no clear evidence of environmental spread of CDI within hospital environment that we could detect. It is possible that the manual disinfection and the additional Ultraviolet use were very effective. It is also possible that our culture method is not sensitive despite previous published data. It is also possible that the bulk of these hospital-associated CDI are endogenous and manifested as patients are ill for related or unrelated condition.

76-A Poster: Evaluating adequacy of VTE prophylaxis for overweight and obese patients

Presenter: Heena Sheth, Junior Faculty
Other

Research Interest: Health Services/Clinical Epidemiology

Mentors: Franziska Jovin MD
Ann Perrin MD
Roy Smith MD

Funding Source: N/A

Authors: Heena Sheth MD, Ann Perrin MD, Victoria Snyder CRNP, Allison Dekosky MD, Roy Smith MD, Franziska Jovin MD

Introduction: UPMC PUH VTE events in 2016 showed 70% of the cases occurring in patients with BMI>=25. American College of Chest Physicians, ACCP recommend weight based dosing for VTE prophylaxis in obese patients (grade 2C) (3,4) as the standard dosing regimen may not be adequate for these patients. The anti Xa range of 0.2 - 0.44 is considered effective prophylaxis. Currently at UPMC obese patients do not receive weight based dosing or anti Xa monitoring to ensure adequate prophylaxis.

Methods: From June 2017 - January 2018 all patients with BMI>=25 admitted to Ortho-medical-trauma service at Presbyterian hospital who were prescribed enoxaparin for prophylaxis were monitored for steady state Anti Xa trough levels. Designated study team member reviewed anti Xa monitoring on daily basis for all patients. Descriptive analysis of demographics, BMI, enoxaparin dose, adverse events (VTE and bleeding), adequacy of standard dosing regimens (Anti Xa levels) are presented.

Results: 267 patients on OMT service with BMI 25 or greater were prescribed enoxaparin prophylaxis and had Anti Xa trough levels. 150 (56%) female patients, age 17 to 89 years (median 55 years), median BMI 31.2. 238 patients received 30 mg and 29 patients 40 mg or higher enoxaparin BID doses. 49 patients had BMI >=40.Only 18 (7%) patients had trough levels in prophylactic range. Even at 40 mg BID doses 2/29 (7%) patients had prophylactic range antiXa. Only 1 of 49 (0.02%) patients with BMI >=40 had prophylactic range trough.In univariate logistic regression the trough antiXa levels were more likely to be prophylactic with increasing age (OR 1.07, p=0.004) and male gender (OR 4.2, P=0.03) while less likely to achieve prophylactic range with increasing BMI (OR 1.1, P=0.04) and higher creatinine clearance (OR 1.02, P=0.005).There were 6 VTE events (6/267, 2.2%); 3 (3/49, 6%) in patients with BMI>=40 which was significantly higher (p=0.04) than 3 VTEs (3/218, 1.4%) in 25 to 39 BMI group. Five were PE and 1 DVT. None of these patients had anti Xa levels in prophylactic range and all were on enoxaparin 30 mg BID dose. There was one minor bleeding event.

Conclusion: 93% of study patients failed to achieve adequate prophylaxis at prescribed enoxaparin doses. The overweight and obese patients should be considered for weight based enoxaparin dosing. Influence of age, gender, BMI and creatinine clearance on achieving adequate prophylaxis warrants further evaluation. VTE incidence was significantly higher in obese patients with BMI>40.

77-A Poster: Infection as Risk Factor for Venous Thromboembolism in Hospitalized Patients

Presenter: Heena Sheth, Junior Faculty
Other

Research Interest: Health Services/Clinical Epidemiology

Mentors: Franziska Jovin MD

Funding Source: N/A

Authors: Heena Sheth MD, Ann Perrin MD, Amy Lukanski DNP, RN, CPN, Roy Smith MD, Franziska Jovin MD

Introduction: Infection is not recognized as a significant risk factor for venous thromboembolism although it is included in commonly used VTE risk assessment tools. A recent outpatient study demonstrated two fold increase in VTE risk due to viral or bacterial infection in the past 30 days compared to matched controls. We evaluated all 2017 venous thromboembolism events to identify association to infection with an aim to develop education and awareness for this important risk factor.

Methods: All VTE events in 2017 in medical surgical units at Presbyterian Shadyside hospital were identified for hospital quality metrics. These patients were further evaluated for demographics, VTE risk scores at admission, prior or active infection at the time of VTE event. Descriptive analysis is presented.

Results: There were 52 patients with VTEs that occurred during the hospitalization. 25 (48%) were medical service and 27 (53%) surgical/trauma patients. 29 (56%) females, average age 57 years (range 26 to 89 years), VTE locations: 23 (44%) DVTs: 2 upper extremity, 19 lower extremity, 2 intraabdominal veins, 29 (56%) pulmonary embolisms. Three pulmonary embolism patients were diagnosed with DVTs in extremities as well. 25 patients (48%) had active or prior infection in the past 7 days before diagnosis of VTE. 12/25 (48%) patients were low or moderate risk for VTE as per PADUA for medical patients and CAPRINI scoring system for surgical patients. 12/25 (48%) patients had BMI>30.

Conclusion: A high percentage of patients who developed VTE had infection prior to developing VTE. Failure to identify them by PADUA and CAPRINI scores warrant evaluation of infection as risk factor in larger samples. Obesity and immobility are important risk factors for VTE in hospitalized patients, which require a matched controlled study to demonstrate increased risk of VTE with infection.

78-A Poster: Associations Between Pregnancy Intention, Attitudes, and Contraceptive Use Among Women Veterans in the ECUUN Study

Presenter: Tierney Wolgemuth, Medical Student
General Internal Medicine

Research Interest: Health Services/Clinical Epidemiology

Mentors: Sonya Borrero MD

Funding Source: VA Merit Award IIR 12-124

Authors: Tierney Wolgemuth BS, Colleen Judge BS, Sonya Borrero MD, Lisa Callegari MD, Maria Mor PhD, Xinhua Zhao PhD

Introduction: Despite access to the full range of contraceptive methods through the Veterans Affairs (VA) healthcare system, women Veterans experience high rates of unintended pregnancy comparable to the general U.S. population. Little is known about the interaction between pregnancy intention and attitudes, and their impact on contraceptive use in this population.

Methods: Cross-sectional data from a national sample of 858 women VA users aged 18-44 at risk for unintended pregnancy were used to examine relationships among pregnancy intention (in next year, in >1 year, never, not sure), attitude towards a hypothetical pregnancy (worst thing, neutral, best thing), and contraceptive use. Bivariate and multivariate analyses assessed associations between intention and attitude, both separately and jointly, with contraceptive use. Multinomial regression assessed the relationship of variables with contraceptive method effectiveness.

Results: Bivariate analysis demonstrated that pregnancy intention and attitude were associated with each other, but not perfectly aligned. In logistic regression models that included both variables, intention of "never" versus "in next year" (adjusted odds ratio, 2.78) and attitude of "worst thing" versus "best thing" (2.86) were each positively associated with use of any contraception. Among women using contraception, intention of "never" and attitude of "worst thing" were also positively associated with use of highly effective versus least effective methods (3.17 and 2.09, respectively).

Conclusion: These findings build on prior research indicating that intention alone does not fully explain contraceptive behaviors, and suggests that attitudes towards pregnancy have an important role in shaping contraceptive use independent of pregnancy intentions. These findings indicate that traditional contraceptive counseling, which relies predominantly on assessing pregnancy intention, may not appropriately elicit the full range of women's attitudes towards pregnancy, and may limit a provider's ability to best guide patients in contraceptive decision-making.

79-A Poster: The Influence of Racial and Social Economic Factors on the clinical course of men and women with Rheumatoid Arthritis

Presenter: Lei Zhu, Graduate Student
Rheumatology and Clinical Immunology

Research Interest: Health Services/Clinical Epidemiology

Mentors: Larry Moreland PhD

Funding Source: N/A

Authors: Lei Zhu MS, Evelyn Talbott PhD, Larry Moreland PhD

Introduction: There is growing evidence that racial and SES disparities affect both the risk and clinical course of individuals with RA, a debilitating illness affect up to 1% of all adults. The National Health and Nutrition Examination Survey-III and other investigations in the US and Europe reported associations between lower education level and increased risk of RA. The results indicate that many social and health disparities influence both the risk as well as the clinical course of the disease. We have a unique opportunity using our Pittsburgh RA cohort to study this further. Our objectives are to utilize this valuable cohort to: 1) evaluate whether there are differences in RA disease activity at baseline for different SEF groups, including different race group (white vs. black), education (=college vs. high school education), and income (high vs. low income); and 2) assess whether there are differences in RA disease activity over 5-year for different SEF groups.

Methods: Data was drawn from the University of Pittsburgh RA Comparative Effectiveness Research observational registry (2010-2015) on visits where patients had rheumatoid factor (RF) data available, which allows us to evaluate associations for overall RA and the 2 subgroups of RA: RF+ and RF-. Th potential confounding variables for assessing SEF and RA risk association, including demographic data, disease duration and morbidity are included for model building. The study outcome is Disease Activity Score-28 joint (DAS28), which were collected at baseline and time of patients' each appointment.

Results: To evaluate the impact of SEF on RA, we analyzed the RA registry data including approximately 1100 RA patients seen by rheumatologists from University of Pittsburgh Medical Center in 2010-2015. We will test the differences by SEF groups (race, education, and income) on RA using DAS28 mean scores at baseline. Unadjusted and adjusted multivariable model will be created for assessing association between DAS28 and SEF. Longitudinal multilevel models will be used to evaluate repeated measurements of DAS28 at baseline and the corresponding improvements and their association with different SEF. Interaction term of SEF by time will be tested to determine if the SEF variances explain differences in DAS28 over 5-year.

Conclusion: We hypothesize that the lower SEF (only for race, black; and low education) is associated with higher DAS28 at baseline, but not with the DAS28 longitudinal changes. These findings will provide us guidance for future model building regarding whether to include SEF as confounders, in cross-sectional and longitudinal analyses.

80-A Poster: A Novel Program to Leverage Resources Of An Organ Procurement Organization for Teaching Medical Procedures

Presenter: Stephanie Maximous, Junior Faculty **Research Interest:** Medical Education Pulmonary, Allergy and Critical Care Medicine

Mentors: Phillip Lamberty MD

Funding Source: Division Educational Budget

Authors: Phillip Lamberty MD, Stephanie Maximous MD, Roy Semaan MD, Jared Chiarchiaro MD

Introduction: Cadaver based procedural training remains arguably the highest fidelity simulation. Costs can be prohibitive. Our facility charges $7000 for 2 fixed cadavers. In concert with our local organ procurement organization (OPO), we approached donor families for permission to teach procedures. We have had two sessions for pulmonary fellows. Sessions consisted of 4 hours of training on 2 recently deceased donors at our OPO facility.

Methods: The training program was first approved by an oversight committee. A consent form was created to obtain permission for teaching specific procedures on tissue donors. Next of kin were approached by representatives from the Center for Organ Recovery and Education (CORE, Pittsburgh, PA) for permission. These patients were suitable for tissue donation but not organ harvesting. CORE provided an operating room used for harvesting organs as well as an ultrasound machine, bronchoscope, and video laryngoscope. Two tissue donors were used for each session, and two CORE organ technicians were available to facilitate each session. A fee of $500 to cover costs for technicians and supplies was charged by the OPO. The procedure session was the final activity of a 4-day fellowship orientation. Sessions were facilitated by 4 instructors and involved 8 trainees revolving around 2 cadavers. Trainees were taught and performed several procedures including: intubation, chest tube insertion, thoracentesis, pleural pig tail insertion, and interosseous catheter insertion. Trainees had completed tutorials on high-fidelity simulators prior to the OPO session. Instructors were PCCM faculty, who supervised tasks until the trainees demonstrated subjective competence. Trainees were encouraged to continue repeating all of the procedures until our session ended. A questionnaire was distributed later to gauge the effectiveness and elicit feedback on the program.

Results: All eligible fellows (14) completed the questionnaire from sessions offered in July 2016 and July 2017. Fellows mostly agreed that their learning experience was effective, added to the previous simulation sessions, and positively impacted their ability to perform the procedure on patients (strongly agree = 5, strongly disagree 1). Scores for intubation, chest tube insertion, and bronchoscopy were higher than for thoracentesis and pleural pigtail insertion. The cost savings were $6500 per session.

Conclusion: We developed a procedure training curriculum that was perceived by learners to be effective and impactful and generated significant cost savings. This curriculum may serve as a model for other programs seeking to develop cadaver-based training.

81-A Poster: MICU Crisis, Communication, and Skills Workshop: development and evaluation of a mock code training program

Presenter: Rachel Pace, Medical Student **Research Interest:** Medical Education
Pulmonary, Allergy and Critical Care Medicine

Mentors: Jared Chiarchiaro MD
Stephanie Maximous MD

Funding Source: N/A

Authors: Rachel Pace BS, Steven Fox MD, Ian Barbash MD, Phillip Lamberty MD, Jared Chiarchiaro MD, Stephanie Maximous MD

Introduction: Management of cardiopulmonary arrests requires a high level of physician skill; however, their infrequent nature makes it hard to obtain the necessary exposure to develop that skill. Prior studies suggest that residents feel underprepared to manage cardiopulmonary arrests. Few mock code training programs have been reported in the literature for the adult population. We developed an adult mock code training curriculum and are reporting on its development, feasibility, and acceptability for housestaff in the medical intensive care unit (MICU).

Methods: The mock code curriculum (MICU crisis, communication, and skills workshop) consists of online training materials for independent review and a 90-minute integrated didactic and simulation session. Trainees participate in a single mock code then rotate through four didactic modules: bag-mask ventilation, effective chest compressions, identification and treatment of shockable rhythms, and effective communication techniques. Finally, trainees participate in three additional mock code scenarios designed to synthesize the information from the didactics. We created a brief survey based on curriculum learning objectives and previously reported pediatric mock code programs. Our survey assesses residents' perceived confidence level in their ability to manage a cardiopulmonary arrest, as well as their confidence in skills taught during the didactic session. Confidence was measured on a 5 point Likert scale. Trainees completed the survey prior to and again immediately following the training session.

Results: To date, 21 residents have participated in and evaluated the MICU crisis, communication, and skills workshop over 4 months. Survey completion rate is 100%. For all skills assessed, there was an increase in resident confidence between baseline and immediately after the session. The mean overall confidence in managing a cardiopulmonary arrest increased from 1.91 to 3.19. Mean confidence using an oral airway increased from 2.68 to 4.14. Mean confidence using a bag-valve mask increased from 3.10 to 3.81. Mean confidence performing effective chest compressions increased from 3.50 to 4.10. Mean confidence identifying shockable rhythms increased from 2.95 to 3.48. Mean confidence using the defibrillator increased from 2.59 to 3.81. Mean confidence using effective communication techniques increased from 2.91 to 4.10.

Conclusion: Preliminary results suggest that the MICU crisis, communication, and skills workshop is feasible and acceptable to housestaff. Residents' confidence increased overall and in all key skill domains required to run a cardiopulmonary arrest. Future work includes analyzing objective data on CPR effectiveness, bag-valve-mask ventilation effectiveness, and time to defibrillation as well as collecting six month follow up data.

83-A Poster: Regulation of the Vacuolar H+-ATPase (V-ATPase) by Mucin 1 in the Kidney

Presenter: Mohammad Al-bataineh, Junior Faculty

Research Interest: Translational Renal-Electrolyte

Mentors: Thomas Kleyman MD
Rebecca Hughey PhD

Funding Source: K01 DK109038, P30-DK-079307

Authors: Mohammad Al-bataineh PhD, Evan Ray MD, Kendrah Kidd , Anthony Bleyer MD, Surui Hou , Jonathan Yabes PhD, Carol Kinlough BSc, Rebecca Hughey PhD, Thomas Kleyman MD

Introduction: The V-ATPase is a protein complex that mediates transport of H+ across membranes. The V-ATPase is present at the apical membrane of proton secreting cells, such as kidney type A intercalated cells (ICs). Defects in the V-ATPase may cause renal tubular acidosis. Mucin 1, (human MUC1, mouse Muc1), is expressed in many segments of the kidney tubule, but its expression is especially prominent in ICs. A frame-shift mutation in MUC1 causes MUC1 Kidney Disease (MKD). It was recently reported that the TRPV5 calcium channel is stabilized on the cell surface by galectin-dependent cross-linking to mucin 1, providing a novel mechanism for regulation of ion channels and normal electrolyte balance. As MUC1 and the V-ATPase are highly expressed in the same cells, we tested the hypothesis that MUC1 influences V-ATPase expression and function, and asked whether mice and humans with genetic MUC1 deficiency exhibit enhanced sensitivity to metabolic acidosis.

Methods: Animal studies: Muc1 KO and control mice were given 0.28 M NH4Cl with 2.5% sucrose or 2.5% sucrose in drinking water for 7 days. Plasma electrolytes, urine pH and NH4+ were measured. Kidneys were processed for immunoblot and microscopy experiments. Human studies: We compared plasma tCO2 from 47 patients (286 measurements) with MKD to 49 control subjects (719 measurements) with uromodulin kidney disease (UKD). Both mutations result in progressive chronic kidney disease in adults, associated with progressive metabolic acidosis. Linear mixed effects model was used to determine the association between eGFR and tCO2 while accounting for within-subject correlation. Differences in tCO2 slopes between the two mutation groups were assessed via an interaction term.

Results: Confocal immunofluorescence microscopy 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 while V-ATPase remained cytosolic in Muc1 KO mice. The a4-subunit of V-ATPase also co-immunoprecipitated with Muc1 in extracts of mouse kidney and isolated ICs. In response to acid-loading, Muc1 KO mice exhibited impaired urinary acidification and greater metabolic acidosis. Preliminary results from MKD patients demonstrate that tCO2 declines with a steeper slope in MKD patients as compared to UKD patients.

Conclusion: These results suggest that MUC1 interacts directly with the V-ATPase in kidney, influences cell surface localization in ICs, and is necessary for a normal renal response to a metabolic acid load in mice and humans.

84-A Poster: Differences in the Adenosine Signaling Pathway among HIV+ Individuals with COPD

Presenter: Kiran Bandi, Medical Student Infectious Diseases

Research Interest: Translational

Mentors: Bernard Macatangay MD

Funding Source: U01 funding

Authors: Kiran Bandi BA, Seyed Nouraie MD, PHD, Edwin Jackson PhD, Peter Nam BS, Delbert Gillespie BS, Cynthia Klamar-Blain MS, Cathy Kessinger RN, Sharon Riddler MD, Alison Morris MD, MS, Bernard Macatangay MD

Introduction: Aberrant purinergic signaling is believed to play a role in COPD pathogenesis. CD39 has ATPase activity and is hypothesized to be protective in cigarette smoke-induced lung damage. CD73 is the rate-limiting enzyme that breaks down AMP to adenosine (ADO), which in turn has anti-inflammatory effects. CD26 binds ADO deaminase which metabolizes ADO and can influence extracellular ADO levels.

Methods: Using flow cytometry, we evaluated differences in the expression of CD39, CD73, and CD26 on peripheral CD4+/CD8+ T cells among ART-treated HIV(+) and HIV(-) individuals with and without COPD [HIV(+)COPD(+) n=16; HIV(+)COPD(-) n=14; HIV(-)COPD(+) n=11; HIV(-COPD(-) n=12], and determined whether expression is associated with plasma levels of inosine (surrogate for ADO; INO) obtained by mass spectrometry and with pulmonary function testing (PFT; forced expiratory volume, FEV1; forced vital capacity; diffusing capacity).

Results: With CD39 expression, HIV(-)COPD(+) had a trend for increased %CD4+CD39+ T cells compared to HIV(-)COPD(-) [12.7% vs 8.7, p=0.07; Kruskal-Wallis with Dunn's post-test]. However, HIV(+)COPD(+) did not have higher %CD4+CD39+ T cells compared to HIV(+)COPD(-). There were no associations between CD39 expression and PFTs. With CD73 expression, HIV(+) participants with or without COPD, had lower %CD4+CD73+ [p values=0.004-0.006] and %CD8+CD73+ [p values=0.001-0.015] compared to all HIV(-) participants. In all participants with COPD, %CD8+CD73+ T cells significantly correlated with FEV1 (Spearman r=0.45, p=0.01). This correlation was not observed among all COPD(-) participants. Expression of CD39 or CD73 did not correlate with plasma INO levels. With CD26 expression, HIV(+)COPD(+) had lower %CD4+CD26+ than HIV(+)COPD(-) [p=0.035], HIV(-)COPD(+) [p=0.0005], and HIV(-)COPD(-) [p=0.02]. Similarly, %CD8+CD73+ was lower in the HIV(+)COPD(+) group compared to the HIV(-) groups, but similar to the HIV(+)COPD(-) group. In all participants, %CD4+CD26+ T cells modestly correlated with INO levels (r=0.25, p=0.09); among all COPD(+) participants, INO levels in turn, modestly correlated with FEV1 (r=0.35, p=0.06).

Conclusion: Compared to HIV(-)COPD(+) individuals, HIV(+)COPD(+) individuals do not have increased CD39 expression relative to HIV(+)COPD(-) individuals and have lower frequencies of CD4+ and CD8+ T cells expressing CD73 or CD26. Given these differences, COPD therapeutic strategies targeting the ADO signaling pathway may result in different outcomes for the HIV(+) population.

85-A Poster: The burden of rare ENAC variants associated with increases or decreases in blood pressure

Presenter: Brandon Blobner, Graduate Student Renal-Electrolyte

Research Interest: Translational

Mentors: Thomas Kleyman MD

Funding Source: R01

Authors: Brandon Blobner BS, Xueqi Wang Xiangya scholar, Jingxin Chen MD, Shaohu Sheng MD, Thomas Kleyman MD

Introduction: Proper maintenance of extracellular fluid volume and extracellular [Na+] is critical for controlling blood pressure. The kidney has a major role in regulating extracellular [Na+] and extracellular fluid volume through the reabsorption and excretion of Na+ and water. The epithelial Na+ channel (ENaC) is part of the mechanism for fine-tuning Na+ reabsorption in the distal nephron. Gain-of-function or loss-of-function ENaC mutations have profound effects on renal Na+ reabsorption and blood pressure. While several ENaC single nucleotide variants (SNVs) with large effect sizes on blood pressure have been identified, the impact of rare ENaC SNVs on blood pressure has not be assessed.

Methods: With the recent availability of a large genomic sequencing consortium, Trans-Omics for Precision Medicine (TOPMed), we are able to explore the functional effects of human ENaC variants, many of which are rare (MAF < 0.01), sequenced from 62,784 individuals.

Results: By prioritizing ENaC SNVs based on proximity to key functional domains, conservation across species and among ENaC subunits, and online resources for predicting SNV deleteriousness, we have identified a subset of 33 ENaC SNVs that affect ENaC protein expression or function.

Conclusion: Using burden tests and sequence kernel association tests (SKAT), as well as single variant analyses, we have analyzed the burden of rare ENaC variants associated with blood pressure phenotypes from a subset of studies in TOPMed.

86-A Poster: The Composition of the Lung Mycobiome in Adult Critically Ill Patients With or At Risk For The Acute Respiratory Distress Syndrome

Presenter: Noel Britton, Graduate Student
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD, MS
Maria Mori Brooks PhD
Barbara Methe PhD

Funding Source: K24 HL123342

Authors: Noel Britton MPH, Georgios Kitsios MD, PhD, Adam Fitch MS, Sarah Rapport MPH, Kelvin Li PhD, Joseph Huwe BS, Katherine Fair MDc, Barbara Methe PhD, Bryan McVerry MD, Alison Morris MD, MS

Introduction: Microbiome research has primarily focused on the bacteriome although there is increasing awareness of the importance of the mycobiome. Microbiome perturbations (dysbiosis) have been observed to occur rapidly in patients with critical illness and the Acute Respiratory Distress Syndrome (ARDS). In the setting of heavy antibiotic treatment potentially altering the bacterial community in the lung, the lung mycobiome may play an important role in the progression of ARDS. However, the lung mycobiome in ARDS remains unexplored and understanding of the potential impact of mycobiome dysbiosis on ARDS progression and outcomes remains limited. Our objective is to describe the composition of the lung mycobiome in patients with ARDS versus critically-ill controls and examine for discriminating features of the mycobiome in association with clinical outcomes.

Methods: We prospectively recruited mechanically ventilated patients within the Pittsburgh Acute Lung Injury Registry and Biospecimen Repository. Patients were classified into ARDS according to the Berlin Criteria, patients at-Aisk for ARDS (i.e. patients with risk factors for ARDS who did not meet radiographic or hypoxemia criteria) and patients not-at-Aisk for ARDS (i.e. without risk factors and intubated for airway protection). We collected endotracheal aspirates at enrollment. Fungal rRNA gene sequencing (internal transcribed spacer (ITS) region 1 to 2) was performed on clinical samples and reagent controls. Taxonomic analyses were performed using Dada2 and Phyloseq.

Results: 92 patients (30 with ARDS, 42 controls at-Aisk and 20 controls not at-Aisk for ARDS; mean age 54.9 years; 58% males) were included. 47 (51%) patients had a positive blood or sputum culture. Beta diversity analyses showed significant differences between groups (permutational analysis of variance, p=0.001). At the species level, taxonomic differences were observed between patients with ARDS and at-Aisk and not at-Aisk controls with ARDS patients having a more diverse taxonomic composition than at-Aisk and not at-Aisk controls.

Conclusion: Next-generation sequencing analysis identifies taxonomic differences in the mycobiome of patients with ARDS compared to both at-Aisk and not at-Aisk controls. Further study including functional network interactions between bacterial and fungal communities as well as correlation with clinical outcomes are needed to determine the role of mycobiome in ARDS.

87-A Poster: Comparison of Fungal DNA Extraction Methodologies for Mycobiome Analysis

Presenter: Noel Britton, Graduate Student
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD, MS
Maria Mori Brooks PhD
Barbara Methe PhD

Funding Source: K24 HL123342

Authors: Noel Britton MPH, Adam Fitch MS, Barbara Methe PhD, Alison Morris MD, MS

Introduction: Microbiome research has primarily focused on the bacteriome although there is increasing awareness of the importance of the mycobiome. Through interaction with the bacteriome and virome, the lung mycobiome may be a factor in host immune response and inflammation and may lead to a decline in lung function and respiratory disease progression. Extraction of DNA from the lung mycobiome presents a challenge due to the lack of relative abundance compared to the bacteriome as well as the low biomass of bronchial alveolar lavage (BAL) and tracheal aspirate specimens. Research shows that extraction methods account for significant variability in the microbial species identified by sequence analysis. However, there is not consensus on effective extraction methods for mycobiome analysis. We aim identify a DNA extraction protocol that will allow for the most accurate survey of the mycobiome.

Methods: Three commercially available DNA extraction kits (PowerSoil DNA Isolation (Qiagen), MasterPure Yeast Purification (Epicentre), the AllPrep Fungal DNA/RNA/Protein (Qiagen)) were used to extract DNA from pure culture of Saccharomyces cerevisiae (ATCC 9763) and Candida albicans (ATCC 18804). PowerSoil DNA and AllPrep Fungal extractions were performed using test human stool samples. DNA was quantified using fluorometry. Amplification was performed using polymerase chain reaction (PCR) with primers targeting the internal transcribed region (ITS). Genomic DNA and amplicons were examined using gel electrophoresis.

Results: Concentrations of DNA quantified from pure culture extractions were significantly different between the 3 kits on both pure culture samples (S. cerevisiae p=0.0089, C. albicans p=0.0006). The PowerSoil DNA provided higher concentrations of DNA than MasterPure Yeast on both pure culture samples (S. cerevisiae, p=0.00286, C. albicans p=0.0020) and higher concentrations of S. cerevisiae than AllPrep Fungal (p=0.0413). PowerSoil DNA extractions from test stool samples had a higher concentration of DNA than AllPrep Fungal extractions (p=0.03211). On gel electrophoresis, amplified DNA extracted with MasterPure Yeast was not identified.

Conclusion: Effective DNA extraction from fungi is essential to accurate characterization of the mycobiome. Our data suggest that a kit that includes both temperature mediated and mechanical lysis steps, such as PowerSoil DNA, may provide higher concentrations of DNA, allowing for a more precise survey of the mycobiome. Application of these techniques to the lung mycobiome will facilitate more accurate studies of fungal communities in the respiratory tract.

88-A Poster: The SCF FBXO3 E3 Ligase regulates inflammation in atherosclerosis

Presenter: Divay Chandra, Junior Faculty
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Rama Mallampalli MD
Frank Sciurba MD

Funding Source: K23

Authors: Divay Chandra MD, James Londino PhD, Shaun Alexander BS, Joseph Bednash MD, Yingze Zhang PhD, Robert Friedlander MD, Grant Daskivich MS, Diane Carlisle PhD, Toru Nyunoya MD, Frank Sciurba MD, Bill Chen PhD, Rama Mallampalli MD

Introduction: Inflammation is critical in the pathobiology of atherosclerosis. An essential player in the inflammatory process in atherosclerosis are macrophages that scavenge oxidatively modified low-density lipoproteins (OxLDL) deposited in the subendothelial space of systemic arteries and secrete a myriad of pro-inflammatory mediators. Here, we report that a subunit of the Skp-Cullin-F-box ubiquitin E3 ligase apparatus, termed FBXO3, modulates the inflammatory response in atherosclerosis.

Methods: Human data:1. SCCOR cohort: The cohort included 40-79 year-old participants with minimum ten pack-years of current or prior smoking. Carotid sonography was performed to identify the number of plaque in the carotid arteries and the thickness of the carotid intima-media per standardized guidelines. 2. FBXO3 genotyping: An analysis of human SNP database revealed a naturally occurring nonsynonymous C/T polymorphism (rs1402954) in FBXO3 (V221I) in individuals of European descent with an allele frequency of 6.2%. Genomic DNA was extracted from PBMCs of individuals in the SCCOR cohort followed by genotyping using a specific primer and probe set. 3. Carotid plaque tissues: Carotid plaque was surgically removed for clinical indications in asymptomatic and symptomatic individuals (not part of the SCCOR cohort). Clinical information was extracted from the medical record by a physician blinded to experimental findings. In vitro data:Cell culture data were based on THP-1 cells that were matured into a macrophage phenotype by incubation with 30 nM PMA for 48-72 hours. FBXO3 gene silencing was performed in these cells using small interfering RNAs (siRNA). Highly oxidized low-density lipoprotein was obtained from Kalen Biomedical (Germantown, MD). The oxidized LDL was certified LPS free (<0.5 EU per mg of protein) and LDL free (>97% by gel electrophoresis) by the vendor prior to shipment. Immunoblotting, ELISA, RT-PCR, flow cytometry, and immunofluorescence was performed using standard methodology.

Results: Individuals with a hypofunctioning genetic variant of FBXO3 develop less atherosclerosis. Carotid plaques from individuals with more atherosclerosis express higher levels of FBXO3 protein. Further, depleting FBXO3 or inhibiting it with a small molecule antagonist abolished the inflammatory response to OxLDL by macrophages without altering OxLDL uptake.

Conclusion: FBXO3 potentiates vascular inflammation and atherosclerosis that can be mitigated by a small molecule inhibitor.

89-A Poster: Nitrite Improves Skeletal Muscle Mitochondrial Coupling and Walking Efficiency in Older Adults

Presenter: Rachel Eleazu, Student
Geriatric Medicine

Research Interest: Translational

Mentors: Daniel Forman MD

Funding Source: N/A

Authors: Rachel Eleazu BS, Kelly Allsup BS, Giovanna Distefano PhD, Subashan Perer PhD, Daniel Forman MD

Introduction: Older adults commonly experience fatigue and decreased capacity to tolerate activity workloads. While therapeutic options are few, age-Aelated changes in skeletal muscle mitochondrial bioenergetics likely contribute to these susceptibilities, and may offer therapeutic targets. Chronic nitrite therapy can alter bioenergetics; reducing electron transport chain, and may increase mitochondrial efficiency in skeletal muscle. To determine whether these benefits extend to older adults, we studied the association between mitochondrial efficiency and oxygen uptake (VO2) at a steady-state submaximal walking workload following nitrite therapy.

Methods: Mitochondrial bioenergetics and VO2 consumption assessed pre vs. post oral nitrite therapy (40 mg nitrite capsules tid for 4 weeks) in 7 healthy older adults (mean age 78.1 years; 4M, 3F). VO2 was assessed during treadmill walking at a steady-state of 1.5 mph Mitochondrial respiration (Oroboros) was assessed in skeletal muscle biopsies from the non-dominant vastus lateralis. Leak/OXPHOS (L/P) coupling control ratios were determined as an estimation of mitochondrial coupling efficiency.

Results: L/P showed a significant decreased from pre to post (p value 0.034). VO2 showed a clinically significant change (2.8±2.48) and is trending toward statistically significant decrease from pre- to post-nitrite therapy(p value 0.073. |

Conclusion: Decreased L/P signifies increased mitochondrial coupling efficiency, consistent with reported effect of nitrite benefit. In addition, the decrease in VO2 during steady state suggests a clinically significant increase in exercise efficacy to perform the same level of work. More study is needed to further establish the efficacy of nitrite to improve mitochondrial function and physical function in older adults.

90-A Poster: A Type I IFN Response to Donor Genomic DNA and RNA As A Novel Immune Driver of Chronic Lung Allograft Dysfunction: A Prediction Based Upon A Cutting-Edge Upstream Regulator Discovery and In-Depth Transcriptome Analysis of The Airway Brush Sample

Presenter: Annabel Ferguson, Graduate Student **Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Kong Chen PhD
John McDyer MD

Funding Source: Mentors' R01

Authors: Annabel Ferguson MS, Aki Hoji PhD, Carlo Iasells PharmD, Joseph Pillewski MD, Mathew Morrel MD, Kong Chen PhD, John McDyer MD

Introduction: Chronic lung allograft dysfunction (CLAD) is the major cause that limits long-term survival of lung transplant recipients (LTRs). To gain new insights into the pathogenesis of CLAD at molecular and cellular level, we embarked on a RNA-seq study of the airway brush sample from 13 CLAD and 11 healthy (non-CLAD) LTRs and aimed to discover the novel immune driver of CLAD. We found that the Interferon a (IFNa) upstream regulator network was significantly activated in CLAD samples. Moreover, our further analysis implicated donor genomic DNA and RNA as a potent immunogen. Overall, these results suggest that donor derived genomic DNA induce the robust host type I IFN production and drives downstream inflammatory and Th1 responses akin to CLAD. While the role of IFNa in antiviral and bacterial responses is well defined, its role in CLAD has not been elucidated. Our study is the first of its kind to implicate the host type 1 IFN response to donor derived nucleic acids as a driver of CLAD.

Methods: Total RNA from was extracted from distal bronchial brush samples from 13 CLAD and 11control LTR patients and sequenced using an Illumina instrument to obtain bulk RNA-seq data which were subsequently analyzed by CLC Genomics Workbench (Qiagen) for differential gene expression (DGE) profiling. DGE profiles were further analyzed by Ingenuity Pathway Analysis (IPA) (Qiagen) to generate IPA upstream regulator network.

Results: CLC genomic Workbench found 153 differentially expressed genes (FDR adjusted $p<0.05$), and IPA identified potential activated upstream regulators (fold changes >1.14) with a rank based on the z-score (range, 9.980 - 2.00 for activated regulators) IFNa (activation z-score=6.12; $p<1.14E-16$) and related IFNa-A2 (activation z-score=2.82, $p<2.27E-11$) regulator networks are in the top 10 activated signal regulators, despite the fact that a majority of the top 10 regulator networks involve in inflammation and Th1 Immune response, among the most notable, IFN-γ (activation z-score=9.98, $p<2.23E-41$) . TLR7 (activation z-score=4.19 and $p<1.27E-04$), TLR9 (activation z-score=4.12 and $p<2.06E-06$) and PolyIC:LC (activation z-score=7.492, $p<1.60E-41$) upstream regulators, all of which feed into the type I IFN pathways are also significantly unregulated in CLAD samples.

Conclusion: While findings are preliminary, our DGE analysis and IPA analysis strongly suggest that the type I IFN pathway is significantly activated in CLAD.

91-A Poster: Mir-29b Mimic Delivery via Ultrasound Targeted Microbubble Destruction to Suppress Cardiac Fibrosis

Presenter: Rafey Feroze, Medical Student
Cardiology

Research Interest: Translational

Mentors: Flordeliza Villanueva MD

Funding Source: R01

Authors: Rafey Feroze BS, Jonathan Kopechek PhD, Linda Lavery , Jissy Cyriac MSc, Jianhui Zhu MD, Xucai Chen PhD, Flordeliza Villanueva MD

Introduction: Cardiac fibrosis contributes to adverse ventricular remodeling in ischemic or hypertensive heart disease and confers increased heart failure risk. Loss of MiR-29b is associated with cardiac fibrosis; overexpression blunts fibrosis and improves cardiac function. These data suggest MiR-29b delivery may mitigate fibrosis, but a targeted delivery strategy is needed. We previously showed that nucleic-acid loaded microbubbles (MB) facilitate therapeutic nucleic acid delivery when exposed to ultrasound (US). We therefore tested the hypothesis that MBs loaded with MiR-29b mimic + US targeted microbubble destruction (UTMD) inhibit cardiac fibrosis in-vitro and in-vivo.

Methods: MiR-29b mimic or negative control (NC) miRNA was loaded on lipid MBs. Cultured neonatal cardiac fibroblasts received 10 sec US in the presence of miRNA-loaded MBs. Cells were harvested 24 hrs later to assess downstream fibrotic mediators by RT-PCR. A mouse model of Angiotensin II infusion was used to induce hypertension and cardiac fibrosis. Mice received miRNA-loaded MBs and UTMD (n= 8-9) at days 0, 3, and 7. Serial echo was performed to assess cardiac function. Cardiac tissue was harvested at day 10.

Results: UTMD with MiR-29b mimic loaded MBs caused a 543% ± 50.7% increase in miR-29b ($p < 0.01$) and knockdown in downstream targets including collagen 1A1 (25.5% ± 6.2%, $p<0.01$), collagen 1A2 (52.9% ± 8.4%, $p<0.01$), collagen III (31.25% ± 5.2%, $p<0.01$), and fibrillin (42.8% ± 10.4%, $p<0.05$) vs. negative control in cultured cardiac fibroblasts (N=4/group). Similar results were observed during in-vivo studies (N=8-9/group) with significant knockdown in fibrillin (36.7% ± 8.4%, $p<0.05$) and trends of decreased expression in collagen IA1, 1A2, and III. Western blot analysis showed a significant decrease in a-SMA expression with MiR-29b treatment in vivo ($p < 0.05$). Preservation of cardiac ejection fraction ($p<0.01$) and fractional shortening ($p<0.01$) was observed with in-vivo treatment of MiR-29b vs. negative control following the induction of heart failure with Angiotensin II.

Conclusion: UTMD-mediated delivery of a MiR-29b mimic blunts expression of fibrosis markers in vitro (fibroblasts) and in vivo (cardiac tissue), and is associated with improved cardiac function in a pilot study of hypertension-induced murine cardiac fibrosis. To our knowledge, this is the first study using UTMD-delivery of a miRNA mimic for mitigating cardiac fibrosis.

92-A Poster: 14-3-3z sequesters cytosolic T-bet, up-Aegulating IL-13 in Tc2 and systemic sclerosis CD8+ T lymphocytes.

Presenter: Patrizia Fuschiotti, Junior Faculty
Rheumatology and Clinical Immunology

Research Interest: Translational

Mentors: Patrizia Fuschiotti PhD

Funding Source: R03 AR065755-02

Authors: Sandra Cascio PhD, Thomas Medsger MD, William Hawse PhD, Simon Watkins MD, Christine Milcarek PhD, Larry Moreland MD, Robert Lafyatis MD, Patrizia Fuschiotti PhD

Introduction: Interleukin (IL)-13-producing CD8+ T cells have been implicated in the pathogenesis of type-2 driven inflammatory human conditions. We have shown that CD8+IL-13+ cells play a critical role in cutaneous fibrosis, the most characteristic feature of systemic sclerosis (SSc). However, the molecular mechanisms underlying IL-13 and other type-2 cytokine production by CD8+ T cells remain unclear. Here we report on the molecular mechanism underlying GATA-3 up-Aegulation by SSc CD8+ T cells, focusing on T-bet modulation of GATA-3 activity, which we showed to underlie IL-13 over-production in SSc CD8+IL-13+ cells.

Methods: Biochemical and biophysical methods were employed to determine expression and association of T-bet, GATA-3 and regulatory factors in CD8+ T cells isolated from the blood and lesional skin of SSc patients with severe skin thickening. ChIP analysis determined GATA-3 binding to the IL-13 promoter. ImageStream analysis and confocal microscopy visualized the subcellular localization of T-bet and GATA-3. Transcript levels were decreased by small interfering RNAs.

Results: The interaction of T-bet with the adaptor protein 14-3-3z in the cytosol of SSc CD8+ T cells reduces T-bet translocation into the nucleus and its ability to associate with GATA-3, allowing more GATA-3 to bind to the IL-13 promoter and inducing IL-13 up-Aegulation. Strikingly, we show that this mechanism is also found during type-2 polarization of healthy donor CD8+ T cells (Tc2).

Conclusion: We identified a novel molecular mechanism underlying type-2 cytokine production by CD8+ T cells revealing a more complete picture of the complex pathway leading to SSc disease pathogenesis.

93-A Poster: HIV-infected Macrophages Induce Endothelial Cell Dysfunction and Metabolic Reprogramming to Promote HIV-associated Pulmonary Arterial Hypertension

Presenter: Lloyd Harvey, Medical Student
Cardiology

Research Interest: Translational

Mentors: Stephen Chan MD, PhD

Funding Source: R01 HL138437

Authors: Lloyd Harvey BS, Yi Yin Tai MS, Ying Tang MS, Moses Bility PhD, Zandrea Ambrose PhD, Stephen Chan MD,PhD

Introduction: Pulmonary arterial hypertension (PAH) is an enigmatic vascular disease characterized by complex pulmonary vascular remodeling, an increase in pulmonary vascular resistance, subsequent right ventricular hypertrophy, and right heart failure. There is an increased predisposition to PAH in HIV-infected populations, and as a historically neglected vascular disease, the pathogenesis of HIV-induced PAH (HIV-PAH) remains largely unknown. Recently, our laboratory has demonstrated that extracellular matrix stiffening induces the mechanosensitive transcriptional co-activators YAP and TAZ, resulting in the upregulation of the microRNA (miR) cluster miR-130/301 and glutaminase (GLS1) in human pulmonary arterial endothelial cells (HPAECs). The implications of this discovery are two-fold: (1) increased miR-130/301 further promotes matrix remodeling, (2) while upregulated GLS1 increases glutaminolysis—an anaplerotic reaction that sustains energetic demands in proliferating, neoplastic-like HPAECs. In addition, our laboratory has demonstrated that miR-21 is upregulated in the plasma of HIV-PAH patients, and that miR-21 is linked to the miR-130/301 cluster to exert broad influence over PAH. Taken together, we hypothesize that HIV-infected macrophages actively secrete miR-21 to promote vessel stiffening, glutaminolysis, and the pathogenesis of HIV-PAH.

Methods: Peripheral blood mononuclear cells are isolated from human blood by pull-down of CD14+ monocytes. CD14+ monocytes are then stimulated with granulocyte-macrophage colony stimulating factor (50 ng/mL) for five to seven days to produce monocyte-derived macrophages (MDMs). MDMs are infected with the HIV-1BaL strain for two days using a multiplicity of infection of one or left uninfected. MDMs are subsequently co-cultured with HPAECs for two days before experiment termination.

Results: Our data are consistent with a previously defined model of the YAP/TAZ-miR-130/301-GLS1 axis as a novel paradigm in PAH. Using a co-culture system, miR-21 expression is upregulated in HPAECs, MDMs, and the conditioned media in which the cells were raise—suggestive of possible cell-to-cell transmission. Additionally, inducers of vessel stiffening and glutaminolysis—YAP/TAZ and the miR-130/301 cluster—are increased in HPAECs. Downstream targets of YAP/TAZ and the miR-130/301 cluster are also upregulated, such as the collagen isoform 3 and its cross-linking enzyme lysyl oxidase and the anaplerotic enzymes GLS1 and pyruvate carboxylase.

Conclusion: Taken together, the upregulation of the matrix remodeling components and anaplerotic enzymes implies that HIV infection may be acting through our previously established YAP/TAZ-miR-130/301-GLS1 axis in the development of PAH, and that upregulation of this axis may be under regulatory control of miR-21. The implications of our data suggest that GLS1 may have a critical role in HIV-PAH pathogenesis, and that the GLS1 inhibitor CB-839 may be rapidly repurposed for this devastating vascular disorder.

94-A Poster: Sonoreperfusion of Microvascular Obstruction: a Step towards Clinical Translation

Presenter: Filip Istvanic, Medical Student Cardiology

Research Interest: Translational

Mentors: John Pacella MD

Funding Source: HHMI Medical Research Fellows Program

Authors: Filip Istvanic BS, Francois Yu PhD, Xucai Chen PhD, John Pacella MD

Introduction: Microembolization during percutaneous coronary intervention for acute myocardial infarction causes microvascular obstruction (MVO). We have 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. For clinical translation of this technique, we compared the reperfusion efficacy of an experimental long-pulse US scanner to that of a clinical short-pulse US scanner in a rat hindlimb model of MVO. We hypothesized that the experimental long-pulse US delivery system would relieve MVO to a greater extent than would the clinical short-pulse US delivery system.

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 two 10-minute sessions using either a long pulse (1600 cycles, 1.6 MHz, 1.1 MPa, 0.33 Hz framerate) or a "short" pulse (5 cycles repeated 7 times, 1.3 MHz, 1.3 MPa, 0.33 Hz framerate). Control rats were injected with microthrombi but did not receive US therapy. Contrast enhanced US perfusion imaging (Sequoia, CPS, 7 MHz) of the microvasculature was conducted at (1) baseline (BL), (2) post-MVO, (3) post-treatment 1, and (4) post-treatment 2 (Tx2). Microvascular blood volumes (MBV) were calculated from videointensity-time data measured in hindlimb muscle regions of interest. Data are expressed as mean ± SD.

Results: MBV were similar at baseline and markedly reduced after MVO for all groups. In the long-pulse group (n=4), MBV increased to 91% of BL after Tx2 (15.7 ± 1.9 dB, n.s vs BL, adj p value <0.0001 vs MVO, adj p value <0.0001 vs Short-pulse Tx2, adj p value <0.0001 vs No Treatment Tx2). In the short-pulse group (n=4), MBV remained reduced at 22% of BL after Tx2 (4.0 ± 5.0 dB, n.s. vs MVO). In the "No Treatment" group (n=4), MBV remained reduced at 7.2% of BL after Tx2 (0.98 ± 1.0 dB, n.s. vs MVO).

Conclusion: These data demonstrate the superior reperfusion efficacy of a long pulse (1600 cycles) vs. short pulse (5 cycles repeated 7 times) US delivery system. This in vivo observation aligns with our previous in vitro findings, showing that longer pulse length is associated with greater reperfusion efficacy. Results obtained from this study should inform clinical translation and optimization of sonoreperfusion of MVO.

95-A Poster: Next-Generation Sequencing Of The Respiratory Microbiome As A Diagnostic Tool Of Severe Bacterial Pneumonia In Mechanically Ventilated Patients.

Presenter: Georgios D. Kitsios, Junior Faculty
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD
Bryan McVerry MD

Funding Source: K23

Authors: Georgios Kitsios MD, Adam Fitch MSc, Dimitris Manatakis PhD, Sarah Rapport MPH, Kelvin Li MS, Shulin Qin MD, Joseph Huwe BSc, Panayiotis Benos PhD, Barbara Methe PhD, Alison Morris MD, Bryan McVerry MD

Introduction: Current diagnosis of severe bacterial pneumonia relies on identification of causative pathogens by microbiologic cultures, which require extended incubation periods and have limited sensitivity. Next-generation sequencing of microbial DNA directly from patient samples may improve diagnostic accuracy and lead to timely, tailored antibiotic prescriptions. Our objective was to examine whether bacterial 16S rRNA sequencing would improve respiratory pathogen detection in mechanically-ventilated patients and correlate with host-Aesponses.

Methods: We prospectively recruited mechanically ventilated patients with acute respiratory failure within 72hrs from intubation. We collected mouth swabs (oral) and tracheal aspirates (lung) for bacterial DNA extraction and 16S rRNA gene sequencing (V4 region), and plasma samples for measurement of lung epithelial injury (RAGE) and host-inflammation (IL-6, TNFR1, procalcitonin) biomarkers. We performed analyses with QIIME, R, custom pipelines, and machine learning algorithms.

Results: 56 patients (25 with clinical diagnosis of pneumonia and 31 without; mean age 56 years; 61% males) were included. Twelve patients had positive respiratory specimen cultures with common pathogens (e.g. Staphylococcus aureus, Klebsiella pneumoniae). Lung microbial communities from patients with clinical pneumonia had significant differences in bacterial composition ($p=0.03$ for Bray-Curtis dissimilarity) and contained fewer bacterial taxa ($p=0.02$ for Shannon index) compared to samples without clinical pneumonia; these differences were even more pronounced between respiratory culture-positive and negative samples ($p=0.003$ and $p=0.02$, respectively). Culture-positive communities were dominated (>50% relative abundance) by taxa concordant to the cultivated patients in 9/12 cases (75%). Twenty percent of culture-negative sample communities were dominated by pathogenic taxa and the remaining had high abundance of oral taxa (e.g. Prevotella, Veillonella). Pathogen dominance in the lungs was strongly associated with culture positivity (odds-Aatio 20.2, $p<10-5$), an association also confirmed by machine-learning algorithms with mixed graphical models for causal analysis. Furthermore, pathogen dominance correlated with markers of host-injury (RAGE: $p=0.02$) and inflammation (IL-6: $p=0.007$; TNFR1: $p=0.03$) regardless of culture results. Oral community composition closely reflected the patterns observed in the lung communities.

Conclusion: 16S rRNA gene sequencing correctly identifies culprit pathogenic organisms in culture-confirmed cases, points towards missed pathogens by cultures in 20% of culture-negative samples and highlights abundance of (probably innocuous) oral bacteria in the remaining cases. Correlations of pathogenic taxa abundance with host-Aesponse biomarkers further support the plausible pathogenic role of these bacteria and the validity of next-generation sequencing as a pneumonia diagnostic tool. Clinical translation will require validation with point-of-care whole-genome sequencing approaches to guide real-time antibiotic management decisions.

96-A Poster: Gut Microbiome Dysbiosis And Delirium In Mechanically Ventilated Adult Patients: A Prospective Cohort Study.

Presenter: Georgios D. Kitsios, Junior Faculty, Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD, Bryan McVerry MD

Funding Source: K23

Authors: Georgios D. Kitsios MD, Katherine Fair BS, Maylene Xie MD, Faraaz Shah MD, Adam Fitch MS, Sarah Rapport MPH, Joseph Huwe BS, Sheila Alexander PhD, Alison Morris MD, Timothy Girard MD, Bryan McVerry MD

Introduction: Delirium is a common complication in critically ill patients associated with worse short- and long-term clinical and neurocognitive outcomes. Although accumulating evidence supports effects of gut microbiota metabolites on brain function (gut-brain axis), it has not been explored whether gut dysbiosis is associated with delirium during critical illness. Our objective was to test the hypothesis that gut microbiome profiles are associated with delirium in mechanically ventilated ICU patients.

Methods: We prospectively recruited consecutive ICU patients with acute respiratory failure and serially collected (every 72hr up to 7 days) rectal swabs or stool samples for bacterial DNA extraction and 16S rRNA gene sequencing (V4 region). Clinical ICU nurses assessed patients for delirium every 12 hours using the Intensive Care Delirium Screening Checklist (ICDSC). We analyzed delirium duration as the proportion of days over ICU stay (up to 7 days) that each patient was positive for delirium (i.e. ICDSC =4), and further considered two phenotypically discordant groups of high (>75%) vs. low delirium duration (<25%). We performed ecological analyses and regression models (linear and logistic) with the MicrobiomeAnalyst and R.

Results: Of 68 patients enrolled (mean age 56 years, 57% males), 52 (76%) scored positive for delirium at some point, and the median days with delirium was 2 (IQR:3). The median Sedation-Agitation Scale (SAS) was 3.6 (IQR:1.2). Delirium duration did not differ by hypoxemia, SOFA scores, glycemic control or calorie intake, but was strongly associated with the lung injury prediction score (LIPS, p=0.004). Gut microbiome profiles had overall low mean alpha diversity (Shannon=2.9 (SD:1.0)) indicative of intestinal dysbiosis. Profiles from rectal swabs and stool samples were significantly different at enrollment, but these communities became more similar after 48hr. No overall differences in community bacterial composition or diversity were observed with overall delirium duration or between patients with high vs. low delirium duration. Patients with higher delirium durations demonstrated a trend for higher Firmicutes abundance (p=0.07, mainly comprising Enterococcus and Staphylococcus taxa) and lower Proteobacteria abundance (p=0.08). We did not find any significant association between early nutritional support (within 48hrs) with gut microbiome profiles and delirium duration.

Conclusion: Gut microbial community profiles did not discriminate groups of patients with different delirium durations. Given the biological plausibility of the gut-brain axis in acute neurocognitive dysfunction, further study with deeper sequencing and functional assessment of the intestinal microbiome in larger patient cohorts is needed.

97-A Poster: Oral Microbial Alterations in Tryptophan Metabolism and Nicotinamide Adenine Dinucleotide (NAD) Synthesis in Individuals with Pulmonary Arterial Hypertension.

Presenter: Carl Koch, Junior Faculty Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD

Funding Source: N/A

Authors: Carl Koch MD, Adam Fitch BS, Marc Simon MD, Barbara Methe PhD, Kelvin Li MS, Sofiya Rehman MD, Mark Gladwin MD, Alison Morris MD

Introduction: Pulmonary arterial hypertension (PAH) has been associated with plasma and pulmonary alterations in numerous bioactive metabolites of the essential amino acid tryptophan and nicotinamide adenine dinucleotide (NAD) synthesis. Increased production of kynurenine, increased transport of serotonin via mutations in the serotonin transporter (SERT), and reduced antioxidant activity due to impaired NAD salvage have all been associated with PAH. As systemic metabolic profiles in vascular injury and disease are increasingly linked to changes in the composition and function of the oral and gut microbiome, we hypothesized that enteric metabolite profiles would reflect known plasma and pulmonary profiles associated with PAH and that associated differences in the microbiome would indicate a microbial influence on the development of PAH.

Methods: Subjects undergoing right heart catheterization (RHC) were classified either as PAH (mean pulmonary artery pressure [mPAP]>=25mmHg and pulmonary capillary wedge pressure<=15mmHg) or controls (mPAP<25mmHg). Controls were age, sex, and BMI-matched to those with PAH. Quantitative global biochemical profiles of OW samples were performed via Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (Metabolon Inc.). Bacterial community composition and predicted functional gene content were determined via 16S ribosomal RNA sequencing. Changes in metabolite profiles between individuals with PAH and controls were correlated with microbiota and predicted content of associated functional genes.

Results: Individuals with (n=27) and without (n=37) PAH were evaluated for 664 compounds in OW. 16S sequencing was performed in a subpopulation of n=14 and n=10, respectively. Tryptophan levels did not differ in PAH (p=0.5), but kynurenine and its metabolic product kynurenate were elevated 1.61-fold (p=0.03) and 1.57-fold (p=0.096) in PAH compared to controls (Figure 1). 16S-based gene content prediction revealed the absence of indoleamine 2,3-dioxygenase (which produces kynurenine via activation by inflammatory cytokines) in oral bacteria and a non-significant, 3.26-fold increase in tryptophan 2,3-dioxygenase (which catalyzes kynurenine production) in PAH (p=0.4). Reduced nicotinate mononucleotide (0.48-fold, p=0.096) and nicotinamide mononucleotide (NMN, 0.54-fold, p=0.03) reflected overall decreased NAD biosynthesis (0.51-fold, p=0.08) via impaired de novo and salvage pathways, respectively, despite a 110-fold increase in bacterial NMN metabolism by nicotinamide-nucleotide adenylyltransferase (p=0.003).

Conclusion: Overall, we found an increase in tryptophan metabolism to kynurenine and a reduction in NAD synthesis in the OW of individuals with PAH. The predicted function of the oral microbiota did not clearly explain these associations. However, identification of elevated kynurenine and decreased NAD synthesis in the oral cavity offer the potential for development of non-invasive biomarkers of PAH and novel targeted therapies.

99-A Poster: TACC2 PROTEIN MEDIATES EPITHELIAL CELL SURVIVAL AND ALVEOLAR INTEGRITY AGAINST CIGARETTE SMOKE EXPOSURE

Presenter: Toru Nyunoya, Junior Faculty **Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: N/A

Funding Source: VA merit review grant

Authors: Xiuying Li PhD, Aki Hoji PhD, Divay Chandra MD, Alyssa Gregory PhD, Chunbin Zou PhD, Rama Mallampalli MD, Toru Nyunoya MD

Introduction: Accumulating evidence suggest a causative role for DNA damage and alveolar cell apoptosis in chronic obstructive pulmonary disease (COPD) pathogenesis. However, the molecular basis for cigarette smoke (CS)-induced DNA damage and apoptosis remains to be elucidated. Our recent integrative analysis identified transforming acidic coiled-coil-containing protein 2 (Tacc2) as a COPD candidate gene.

Methods: We evaluated TACC2 gene and protein expression in the lung of smokers without or with COPD. Next, we determined if the genetic deletion of Tacc2 augments CS-induced DNA damage and emphysematous changes in vivo. We then determined the molecular mechanisms of CS-induced TACC2 protein depletion.

Results: We found that smokers with COPD exhibit a marked decrease in lung TACC2 protein levels as compared with smokers without COPD. CS triggered emphysematous changes accompanied by DNA damage in TACC2-/- compared to TACC2+/+ mice. In human bronchial epithelial cells, CS increased binding of TACC2 to the acetyltransferase, KAT2B, thereby increasing TACC2 acetylation. This modification triggered TACC2 degradation via the ubiquitin-proteasome system mediated by the ubiquitin (Ub) E3 ligase subunit, F box L7 (Fbxl7).

Conclusion: Our results suggest that TACC2 is destabilized in epithelia by CS-induced KAT2B-mediated acetylation that recruits Fbxl7 contributing to DNA damage, cytotoxicity, and emphysema.

100-A Poster: Designing Perfusate for Prolonged Normothermic Ex Vivo Lung Perfusion to Investigate Diseased Lungs

Presenter: John Sembrat, Graduate Student **Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Mauricio Rojas MD **Funding Source:** NIH

Authors: John Sembrat MS, Kentaro Noda PhD, Mauricio Rojas MD, Jonathan D'Cunha MD

Introduction: Clinically, ex vivo lung perfusion (EVLP) has provided the ability to evaluate the quality of marginal donor lungs prior to transplantation. In the lab, EVLP has the potential to serve as a unique pre-clinical platform of experimental treatment strategies using lungs declined for transplant or lungs from patients with end-stage lung diseases such as pulmonary hypertension and idiopathic pulmonary fibrosis. These studies often require prolonged and optimal perfusion settings including perfusate, temperature and time. In this study, we aimed to identify the essential components of perfusate that would allow for prolonged EVLP.

Methods: Using Krebs buffer as a base extracellular perfusate, we supplemented in various concentrations of albumin, dextran 40, and calcium, and measured viscosity. To enrich buffer capacity for a wide range of temperature, Good's buffer was included. Using rat heart-lung blocks following 1-hour cold preservation, we tested each perfusate in an acellular normothermic EVLP setting with a primary endpoint of 4 hours. To confirm the results seen in rats, human EVLP was then performed using the optimal perfusate from the rat studies and data were compared to Steen solution.

Results: Viscosity of the solution was dependent on the balance of albumin /dextran 40 and influenced PVR in the lungs during rat EVLP. In addition, prolonged EVLP was not able to be performed successfully >2 hours without an optimal dose of calcium in rat EVLP, even with optimal amount of colloid osmotic pressure. Perfusion pH was better maintained with the tested perfusate when compared with Steen solution. Lung function and physiological parameters were maintained on human EVLP when compared to STEEN Solution.

Conclusion: The successful chemistry of a perfusate for pro-longed EVLP depends on numerous factors: 1) strong buffering capacity with wide range temperature, 2) calcium content, 3) osmotic pressure in extracellular type solution may be essential to perform prolonged EVLP. The solution designed and tested here closely mimics STEEN Solution and allows for prolonged EVLP and could be a basal solution for the investigation regarding pulmonary disease physiology, preclinical pharmacology/pharmacokinetics test, regenerative medicine, and transplantation. In addition, vascular integrity is better maintained with the addition of calcium in the perfusate and limits the amount of interstitial edema seen in other setting of EVLP.

101-A Poster: Low-Level Enteral Dextrose Infusion Increases the Incretin Glucose-Dependent Insulinotropic Peptide and Maintains Euglycemia in a Murine Klebsiella Pneumoniae Model of Sepsis

Presenter: Faraaz Shah, Junior Faculty
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Christopher O'Donnell MD
Bryan McVerry MD

Funding Source: K23

Authors: Faraaz Shah MD, Byron Chuan BS, Lanping Guo MD, Bryce Cooper BS, Michael Landau MD, Georgios Kitsios MD, Keven Robinson MD, Janet Lee MD, Burton Wice MD, Christopher O'Donnell MD, Bryan McVerry MD

Introduction: Prior work in our lab has demonstrated that early low-level dextrose infusions, varying by route of delivery, influence glucose metabolism in a sterile murine lipopolysaccharide (LPS) model—intravenous (IV) dextrose worsens glucose disposal whereas enteral dextrose preserves glucose homeostasis through increases in intestine-derived incretin hormones. We now test the therapeutic effects of early enteral dextrose infusions on glucose metabolism in a bacteremic Klebsiella pneumoniae mouse model.

Methods: 10 week old C57BL/6J male mice underwent femoral arterial catheterization in combination with either a femoral venous catheter for IV infusions or a gastric cannula for enteral infusions. All mice (n=27) were inoculated with oropharyngeal Klebsiella pneumoniae (serotype 2 ATCC 43816) at 2 x 10^4 colony forming units (CFUs) in 100 µL of phosphate-buffered saline. Twenty-four hours after inoculation, mice were randomized to receive a continuous infusion of (1) enteral saline, (2) enteral dextrose, or (3) intravenous dextrose at a rate of 100 µL per hour. Forty hours after inoculation, mice were sacrificed for determination of circulating glucose, insulin, and incretin hormone levels and for organ collection. Results are reported as median [interquartile range]. Differences between groups were determined by one-way ANOVA or non-parametric test as appropriate.

Results: Mice exposed to Klebsiella pneumoniae receiving enteral saline infusion in the absence of any dextrose were hypoglycemic at 40 hours (58 mg/dL [50, 72]) with low plasma insulin levels (0.3 ng/mL [0.3, 0.5]) and low levels of the incretin glucose-dependent insulinotropic peptide (GIP, 104 pg/mL [67, 132]). By comparison, enteral dextrose treatment in mice exposed to Klebsiella pneumoniae restored euglycemia (124 mg/dL [101, 153], p=0.01), increased circulating insulin (1.3 ng/mL [0.6, 2.8], p=0.02), and increased GIP (394 pg/mL [333, 636], p<0.01). Importantly, enteral dextrose did not significantly worsen lung injury, bronchoalveolar lavage cell counts or protein levels, or bacterial counts in the lung or the spleen. In contrast, intravenous dextrose, which did not increase GIP levels (84 pg/mL [58, 113]), was associated with an increase in insulin (6.4 ng/mL [1.3, 8.3], p<0.01) that was ineffective in controlling hyperglycemia (255 mg/dL [118, 367], p<0.01).

Conclusion: Enteral, but not intravenous, dextrose preserved euglycemia in a bacteremic Klebsiella pneumoniae model associated with increases in the incretin hormone GIP without adversely affecting lung injury or bacterial dissemination. Targeting the incretin hormone pathway with enteral nutrients may provide a means of maintaining glycemic control while providing caloric support in critically-ill septic patients.

102-A Poster: Association of Antiretroviral Therapy with Peripheral Inflammatory Mediators, Lung Function in HIV-infected Individuals

Presenter: Lena Vodovotz, Graduate Student **Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Alison Morris MD **Funding Source:** R01, K24, UL1

Authors: Lena Vodovotz , Seyed Mehdi Nouraie PhD, Meghan Fitzpatrick MD, Laurence Huang MD, Marlena Hartman-Filson BA, Maggie McGing , Mathew Sommers , Cathy Kessinger , Alison Morris MD, Shulin Qin PhD

Introduction: Recent research suggests antiretroviral therapy (ART) initiation leads to decreased levels of proinflammatory mediators. The effect of ART on pulmonary function in HIV has been debated. Studies have shown that ART initiation has no major effect on rate of lung function decline one year post-initiation in cohorts with high initial CD4+ cell counts. Others find an association between airway obstruction and ART. Few studies have examined peripheral inflammatory mediator levels and lung function 6 months post-ART initiation. This study aimed to determine the impact of ART initiation on peripheral inflammatory mediators and lung function in HIV-infected individuals with a range of CD4+ cell counts and if lung function changes post-ART initiation are linked to a distinct peripheral inflammatory mediator phenotype.

Methods: Study participants were HIV-infected men and women starting ART at Zuckerberg San Francisco General Hospital. Demographic and clinical data were collected via chart abstraction or participant self-Aeport. All participants performed pulmonary function tests (PFTs) according to American Thoracic Society guidelines. Plasma levels of 17 inflammatory cytokines and chemokines (IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1ß, TNF-a) were measured by Luminex™ (Bio-Aad Laboratories Hercules, CA, USA). Cytokine/chemokine levels, CD4+ T cell counts, plasma HIV viral load, and PFTs were measured at baseline and 6 months post-ART initiation. Signed rank tests were used to determine significance ($P < 0.05$).

Results: Fifteen HIV-infected individuals (12 men) were included. Median age was 35 years (range 24-49), median CD4+ cell count was 523 cells/ul (range 37-1296), and median plasma HIV viral load was 4587 copies/mL (range 27-623935). CD4+ cell count did not change significantly between baseline and the 6-month visit, while plasma HIV viral load decreased significantly ($P < 0.001$). Twelve of 17 inflammatory mediators (IL-2, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12 (p70), IL-17A, GM-CSF, MCP-1, MIP-1ß, TNF-a) in plasma decreased significantly 6 months post-ART initiation. PFTs FEV1%, FVC%, FEV1/FVC and DLco did not change significantly with ART.

Conclusion: In a small group of ART initiators, plasma HIV viral load and levels of multiple peripheral inflammatory mediators decreased significantly after ART initiation, despite stable CD4+ cell counts, but pulmonary function did not change significantly at 6 months. These results indicate that ART could reduce systemic inflammation by inhibiting HIV and slowing lung function decline. A more extensive cohort study and extended pulmonary function testing will be needed to elucidate relationships between ART initiation, inflammation, and pulmonary function.

103-A Poster: Assessment of Th17 Pathway and Association with Lung Function in HIV-Infected Individuals Initiating Antiretroviral Therapy

Presenter: Lena Vodovotz, Graduate Student Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD

Funding Source: R01, K24, UL1

Authors: Lena Vodovotz , Seyed Mehdi Nouraie PhD, Meghan Fitzpatrick MD, Laurence Huang MD, Marlena Hartman-Filson BA, Maggie McGing , Mathew Sommers , Cathy Kessinger , Alison Morris MD, Shulin Qin PhD

Introduction: Chronic obstructive pulmonary disease is common in HIV-infected individuals, but its mechanisms are not well-understood. No studies have examined the impact of the Th17 inflammatory pathway on lung function in HIV+ individuals and changes following antiretroviral therapy (ART). We investigated if ART initiation is linked to changes in levels of Th17-Aelated inflammatory biomarkers and if these changes related to pulmonary function.

Methods: We enrolled HIV-infected men and women starting ART at Zuckerberg San Francisco General Hospital. Pulmonary function tests (PFTs) were conducted according to American Thoracic Society guidelines. 17 plasma inflammatory cytokines and chemokines (IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, G-CSF, GM-CSF, IFN-?, MCP-1, MIP-1ß, TNF-a) were measured using Luminex™ (Bio-Aad Laboratories Hercules, CA, USA). Cytokine/chemokine levels, PFTs, plasma HIV viral load, and CD4+ T cell counts were measured at baseline and 6 months post-ART initiation. Associations between cytokine/chemokine levels and PFTs were analyzed using linear regression and Spearman correlation ($P < 0.05$).

Results: Fifteen HIV+ individuals (12 men) were included. Median age was 35 years (range 24-49) with a median CD4+ cell count of 523 cells/ul (range 37-1296) and median plasma HIV viral load of 4587 copies/mL (range 27-623935). Compared to baseline, plasma HIV viral load, IL-17, IL-10 and GM-CSF levels decreased significantly 6 months post-ART initiation. IL-17 and GM-CSF levels were significantly associated (a hallmark of pathogenic Th17 cells) at baseline (rho = 0.764, P = 0.00057), but not 6 months post-initiation (rho = 0.347, P = 0.188). Similarly, IL-17 and IL-10 levels were significantly associated (a hallmark of non-pathogenic Th17 cells) at baseline (rho = 0.828, P = 7E-05), but not 6 months post-initiation (rho = 0.072, P = 0.792). IL-17 and DLco % predicted had a significant inverse association 6 months post-initiation (rho = -0.566, P = 0.028), and an inverse association trend at baseline (rho = -0.413, P = 0.182).

Conclusion: We saw a significant decrease in correlations between IL-17/GM-CSF and IL-17/IL-10 post-ART initiation and a significant inverse relationship between IL-17 and DLco only post-ART initiation. The significant decrease in these three cytokines and both correlations suggests a broad downregulation of Th17 cells. This, combined with the finding that levels of circulating IL-17 are inversely associated with poor DLco suggests ART may exert long-term benefit by driving T cell differentiation away from the pro-inflammatory Th17 pathway. Further research will be necessary to determine the relationship between Th17-associated biomarkers, pulmonary function, and ART initiation.

104-A Poster: Longitudinal Assessment of Plasma Biomarkers of Injury and Inflammation In Patients With the Acute Respiratory Distress Syndrome (ARDS): A Prospective Cohort Study In Adults.

Presenter: Libing Yang, Medical Student
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Georgios Kitsios MD
Alison Morris MD

Funding Source: K23

Authors: Libing Yang MDc, Georgios Kitsios MD, Sarah Rapport BS, Nouraie Mehdi MD, Yingze Zhang PhD, John Evankovich MD, William Bain MD, Janet Lee MD, Rebecca DeSensi MS, Beibei Chen PhD, Prabir Ray PhD, Rama Mallampalli MD, Alison Morris MD, Bryan McVerry MD

Introduction: Despite major advancements in the understanding of ARDS pathophysiology, the substantial clinical heterogeneity of the syndrome has impaired the ability to develop targeted efficacious therapies. Our objective was to characterize the longitudinal evolution of validated plasma biomarkers of host injury and inflammation in subjects with ARDS to identify subphenotypes associated with clinical outcomes.
Methods: We enrolled mechanically-ventilated patients diagnosed with ARDS per the Berlin criteria. We collected plasma samples at four time-points in the course of acute respiratory failure: Early (Day 1 upon enrollment), Middle (Days 3-5), Late (Days 7-10), and Very Late (>11 Days). We measured nine validated plasma biomarkers indicative of epithelial injury (Receptor for Advanced Glycation Endproducts – [RAGE]), endothelial injury (Angiopoetin-2), innate host response (interleukin-6 [IL-6], interleukin-8 [IL-8], soluble tumor necrosis factor receptor-1 [sTNFR1], interleukin-10 [IL-10], suppression of tumorigenicity-2 [sST2], pentraxin-3) and bacterial infection (procalcitonin). We assessed the longitudinal evolution of biomarkers with repeated measures ANOVA models with random intercepts for each subject.
Results: 115 ARDS subjects (mean age 53 years, 53% male) were included. Moderate-severe ARDS (PaO2/FiO2 ratio <200) was diagnosed in 80% of subjects and 30-day mortality rate was 30%. There was a significant decline over time in plasma levels of RAGE, IL-6, Angiopoetin-2, sST2, Pentraxin-3, and procalcitonin (repeated measures ANOVA p-values <0.0001). On the contrary, we noted a significant increase in the levels of sTNFR1 (p=0.006). Despite the overall trends, biomarker values for several individual patients followed divergent trajectories. We performed subgroup analyses by stratifying patients with available data at the Late time-point (Days 7-10) into those with a declining (n=37) versus increasing trend (n=14) of procalcitonin levels, to distinguish groups of resolving versus unresolving/superimposed bacterial infection, respectively. In the subgroup of patients with declining procalcitonin, there was a consistent significant decline in plasma levels of RAGE, Angiopoetin-2, sST2, IL-6 and Pentraxin-3 (p <0.0001), whereas in the subgroup of increasing procalcitonin levels, levels of these biomarkers of injury and inflammation remained unchanged from baseline while sTNFR1 levels increased (p<0.0001).
Conclusion: Our analyses overall patterns of resolving injury and inflammation within the first two weeks from ARDS onset. However, a distinct subgroup of patients with rising procalcitonin levels suggestive of superimposed bacterial infection showed persistently elevated levels of inflammatory markers and increasing sTNFR1 levels. This potentially highlights the presence of an identifiable subgroup with unresolving injury and inflammation in ARDS that may benefit from targeted interventions.

105-A Poster: Amelioration of detrusor sphincter dyssynergia following spinal cord injury with LM11A31, a small molecule p75 neurotrophin receptor antagonist

Presenter: Irina Zabbarova, Junior Faculty **Research Interest:** Translational Renal-Electrolyte

Mentors: N/A

Funding Source: NIH P01 DK093424, NIH R01 DK071085

Authors: Irina Zabbarova PhD, Youko Ikeda PhD, F. Aura Kullmann PhD, Lori Birder PhD, Evan Carder MS, Peter Wipf PhD, Anthony Kanai PhD

Introduction: One of the most debilitating consequences of spinal cord injury (SCI) is the inability to empty the bladder due to loss of coordination with the external urethral sphincter (EUS), detrusor sphincter dyssynergia (DSD), for which there is no effective treatment. This can lead to complications including vesicoureteral reflux and renal failure. p75 is a neurotrophin receptor binding uncleaved pro-neurotrophins, rapidly produced in the bladder and spinal cord following SCI. Activation of p75 receptors leads to neuronal and urothelial apoptosis that contribute to DSD. Accordingly, our aims were to assess the benefits of a small molecule p75 modulator, LM11A-31, in ameliorating DSD.

Methods: Female 4-6 weeks old C57Bl/6 mice were gavaged with 100 mg/kg LM11A-31 in 100 µl of water one day prior to SCI (complete T8-T9 transection) and daily thereafter. Following surgery, mice were treated with an analgesic and prophylactic antibiotic and their bladders manually expressed twice daily. Ten to fourteen days post surgery, animals were decerebrated for cystometry (CMG) and EUS electromyography (EMG) and their bladders isolated for histology (H&E). All experiments were carried out on n = 4 mice.

Results: Two weeks following SCI, bladder weights were dramatically increased (78 ± 5 mg versus 24 ± 2 mg) containing up to 500 µl of urine (versus 90 ± 9 µl in controls). Treatment with LM11A-31 decreased bladder sizes (to 41 ± 6 mg, $p < 0.05$) and urine volumes (to less than 100 µl) suggesting improved voiding function. Control mouse CMG and EUS-EMG recordings demonstrate guarding reflex preventing leaking as bladder pressure approaches voiding threshold. This is followed by bursting with decreased tonic activity during which the voiding occurs and bladder pressure returns to baseline. Two weeks post SCI, there is increased EUS tonic activity as the bladder contracts resulting in non-voiding contractions (detrusor overactivity, DO) and eventually overflow incontinence. LM11A-31 treatment prevented the development of DSD (revealed by quiescent intervals of EUS activity during bladder contraction) and DO permitting voiding. Bladders from untreated SCI mice exhibited urothelial hyperplasia and detrusor hypertrophy – a consequence of DSD and bladder overdistention. In animals treated with LM11A-31, the urothelial layer was preserved and the detrusor muscle not hypertrophied, similar to control.

Conclusion: Inhibition of p75 and pro-neurotrophins interactions is remarkably effective in maintaining the structural integrity of the bladder wall and preventing DSD permitting voiding. The mechanisms may include apoptosis inhibition of both neurons in spinal cord (preventing neuronal degeneration centrally) and urothelium in the bladder (reducing inflammation peripherally).

106-A Poster: SELENIUM DEFICIENCY IS ASSOCIATED WITH EXOCRINE PANCREATIC INSUFFICIENCY IN PATIENTS WITH CHRONIC PANCREATITIS

Presenter: Wei Zhan, Medical Student
Gastroenterology, Hepatology and Nutrition

Research Interest: Translational

Mentors: David Whitcomb MD

Funding Source: N/A

Authors: Wei Zhan Medical Student, Annette Wilson PhD, Celeste Shelton MS, Julia Greer MD, Phil Greer MS, Dhiraj Yadav MD, David Whitcomb MD

Introduction: Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress. Features of progression to end-stage CP, such as exocrine pancreatic insufficiency (EPI), are highly variable and may be modified by the response to oxidative stress. The pancreas expresses multiple antioxidant enzymes that utilize selenium at the catalytic site. Selenium deficiency in animals results in reduced expression of selenium-containing enzymes and significant pancreatic damage and/or dysfunction. Our aim is to determine if low selenium levels in patients with CP correlates with EPI.

Methods: We utilized clinical data and biological samples from North American Pancreatitis Study II (NAPS2). Serum samples were available on 278 CP cases and 263 controls. Serum trypsinogen levels were measured in a commercial laboratory by radioimmunoassay as a marker of pancreatic mass. Levels < 10 ng/ml were used to classify CP patients with EPI. Serum selenium concentrations were determined using inductively coupled plasma mass spectrometry. C-Aeactive protein (CRP) was measured by the Luminex platform, and vitamin levels were measured by high-performance liquid chromatography. Groups were compared using the Kruskal–Wallis test.

Results: Serum selenium levels were significantly lower in CP patients than in controls (127.49 ± 32.52 µg/L vs. 148.31 ± 27.15 µg/L, $p<0.001$). Subset analysis of CP patients indicated that CP patients had serum trypsinogen <10 ng/ml (2 SD below the mean of control) as a marker of EPI. CP patients with serum trypsinogen <10 ng/ml had significantly lower selenium levels than other CP patients (121.85 ± 32.25 µg/L vs. 129.90 ± 32.42 µg/L, $p=0.014$). CRP levels were measured to determine the effects of active inflammation on selenium levels. High CRP (>0.7mg/dl) levels correlated with low serum selenium level in CP patients (119.05 ± 33.4 µg/L vs. 131.28 ± 31.48 µg/L, $p=0.004$) but not controls ($p>.05$) suggesting that low selenium was associated with inflammation in CP, and that high CRP did not affect selenium uptake. There was a weak positive correlation between selenium and vitamins A and E in CP patients and controls not taking vitamin supplements. Multivitamin supplements did not significantly increase serum selenium levels ($p>.05$).

Conclusion: Low serum selenium levels are associated with higher CRP levels and EPI in chronic pancreatitis patients. Multivitamin supplementation did not appear to correct apparent selenium deficiency. The cause-effect relationship between low selenium levels and EPI in chronic pancreatitis requires further investigation.

107-A Poster: Computational Repurposing of Chemotherapies for Cardiomyopathies

Presenter: Jingsi Zhao, Medical Student
VMI

Research Interest: Translational

Mentors: Stephen Chan MD

Funding Source: PTP

Authors: Jingsi Zhao MS, Neil Kelly MD, Ning Feng MD, Manling Zhang MD, Bethann Weber BS, Ying Tang MS, Seungchan Kim PhD, Bernhard Kuhn MD, Lei Yang PhD, Yadong Wang PhD, Guy Salama PhD, Imad Al Ghouleh PhD, Stephen Chan MD

Introduction: There is increasing appreciation that numerous chemotherapies can modulate cardiac function, either impairing or improving intrinsic cardiomyocyte function and consequent dilated cardiomyopathy and congestive heart failure. There is global interest in the advancing field of cardio-oncology to predict effects of chemotherapies on heart function - either for repurposing in treatment of cardiovascular disease or for defining hidden cardiotoxicities. With advances in 'big data' approaches in biomedical research, there is an opportunity to leverage large scale - omics data in computational 'network pharmacology' approaches to predict unanticipated drug activity on cardiomyocytes.

Methods: In silico - We have combined high density RNA sequencing data with prior knowledge of gene regulatory networks in dilated cardiomyopathy (DCM) and novel computational algorithm, EDDY, to define gene dependency network re-wiring in response to specific chemotherapies (EDDY-CTRP-DCM).In vitro - We applied the chemotherapies of interest on 3 different cell lines including H9C2 rat myoblast cell line, primary rat neonatal cardiomyocytes, and human inducible pluripotent stem cell (iPSC)-derived cardiomyocytes, with stimuli of hypertrophy by phenylephrine, followed by assessment of gene expression and cardiomyocyte phenotypes.

Results: A 'hot-spot' gene cluster (Cluster 9) was identified by computational analysis, upon which converged multiple chemotherapies without known cardiac activity. Of these drugs, we focused on a FDA-approved histone methyltransferase inhibitor MI-2 and its more stable analog MI-503. MI-503 reversed hypertrophy induced by phenylephrine on human iPSC-derived cardiomyocytes, indicated by decrease of mRNA expression level of ANP and BNP. Both MI-2 and MI-503 down-Aegulated the expression level of Cluster 9 gene, ANKRD1 (Cardiac ankyrin repeat protein, CARP), where up-Aegulation can drive DCM. Apoptotic signaling in H9C2 cells was attenuated by both MI-2 and MI-503.

Conclusion: Guided by novel computational analysis and biological experimental data, we have found that MI-2/MI-503 can epigenetically control cardiomyocyte apoptosis and hypertrophy and can reverse pathogenic Cluster 9 gene changes seen with hypertrophic triggers. In vivo studies of DCM in mice are planned to identify the role of MI-503 in controlling cardiac hypertrophy and thus facilitate rapid drug repurposing for treatment of human heart failure in the near future.

SESSION B- MAY 1, 2018

Biomedical Science Tower - Foyer

Abdalla	Hossam	33-B	Association of sleep apnea severity with mortality in CKD and ESRD patients
Adamik	Juraj	1-B	Novel Cytoplasmic Roles of EZH2 Methyltransferase During RANKL Signaling, Cytoskeletal Organization and Resorption of Osteoclasts
Alfishawy	Mostafa	34-B	Retrospective Observational Study of Patients with Native Septic Arthritis and the Effect of Microbiological Screening at UPMC Presbyterian & Montefiore Hospitals
Ali	Hira	94-B	Wnt Pathway Inhibitor DKK1: A Potential Novel Biomarker for Ectopic Skeletal Muscle Adiposity
Allenbaugh	Jill	81-B	Effects of a Flipped Classroom Cardiology Curriculum on Internal Medicine Residents' Knowledge and Preparedness
Alvarez	Diana	96-B	Adult Stem Cells in combination with respiratory assistance devices protects cardiac mitochondrial function in a LPS-induced ARDS large animal model
Arnold	Jonathan	75-B	Measuring the efficiency of electronic health record usage: Epic's provider efficiency profile demonstrates high test-retest reliability for adult primary care providers
Bain	William	97-B	Reduced Alternative Complement Activity is Associated with Impaired Serum Control of Carbapenemase-producing Klebsiella pneumoniae in a Cohort of Critically Ill Patients
Barakat	Amr	37-B	A Risk Model to Identify Stable Patients with High Risk Coronary Artery Disease Anatomy
Barakat	Amr	36-B	Same Day Discharge After Inpatient Percutaneous Coronary Intervention: A Report from the Nationwide Readmission Database
Bednash	Joseph S	98-B	Further development of a small molecule inhibitor of the deubiquitinase STAMBP
Bondi	Corry	2-B	NRF2 and HIF1a signaling pathways are interrelated in human kidney proximal tubule epithelial cells
Bonifacino	Eliana	82-B	An Innovative Skill-based Clinical Reasoning Curriculum for Clerkship-level Medical Students

Boyd-Shiwarski	Cary	3-B	KS-WNK1 Expands the Dynamic Range of NCC Regulation by Dietary Potassium
Brunner	Emily	38-B	Stepping It Up: The Use of Physical Activity Monitors as an Outcome Measure in Juvenile Myositis
Camiolo	Matthew	4-B	Understanding Heterogeneity in Severe Asthmatics Using High Dimensional Analysis of Cellular Phenotypes
Carter	Andrea	83-B	Educating Faculty and Resident Physicians on Safe Opioid Prescribing for Chronic Pain: Impact of a Brief Curriculum on Knowledge, Confidence, and Attitudes
Chang	Woody	76-B	Analysis of clinical video telehealth consults as a method for optimizing medications of Veterans Affairs dementia patients
Chintamaneni	Preethi	39-B	LOW VISCERAL ADIPOSE TISSUE MASS IS ASSOCIATED WITH DECREASED TRANSPLANT-FREE SURVIVAL IN END-STAGE LIVER DISEASE.
Christensen	April	84-B	Piloting a Curriculum on Writing Simulated Patient Cases in a Teaching Communication Course
Christopher	Adam	40-B	Cardiac MRI native T1 time and extracellular volume fraction, but not myocardial strain, associate with pediatric heart transplant acute rejection.
Click	Benjamin	41-B	The Impact of an Inflammatory Bowel Disease Specialty Medical Home on Healthcare Utilization, Disease Activity, Mental Health, and Quality of Life
Click	Benjamin	42-B	The Impact of Serum Cortisol on Quality of Life and Dysautonomia in Inflammatory Bowel Disease
Cruz	Tamara	5-B	Altered phenotype of human Lung Mesenchymal Stem Cells in patients with COPD and IPF
Dalghi	Marianela	6-B	Role of Piezo channels in urothelial cell mechanotransduction

D'Auria	Stephen	7-B	Development of a Unique Tissue Plasminogen Activator (tPA) loaded Microbubble for the Treatment of Coronary Microvascular Obstruction
Detoya	Karla	77-B	Impact of Electronic Consultation Compared To Face-to-Face Encounters on Glycemic Control among Veterans with Type 2 Diabetes
Detoya	Karla	43-B	OPTIFAST® Medical Weight Loss Program – Outcomes in the Endocrinology Clinics at University of Pittsburgh Medical Center (UPMC)
Dunlap	Daniel	99-B	Use of magnetic activated cell sorting to identify immunoglobulin-bound bacteria in bronchoalveolar lavage fluid in individuals with HIV and COPD
Eden	Elizabeth	85-B	The Safe Discharge Curriculum: How We Standardized Trainees' Approach to Discharge to Target Hospital Readmissions
Edmunds	Lia	8-B	PARKIN E3 ligase and PINK1 kinase activity are reduced by acetylated ubiquitin.
Elzomor	Hesham	44-B	Suitability of Transcatheter Mitral Valve Replacement in Patients with Significant Mitral Regurgitation After Transcatheter Aortic Valve Replacement
Fisher	Molly	86-B	Health Policy Curricular Objectives for Residents in Internal Medicine
Florentin	Jonathan	9-B	Inflammatory macrophage expansion in pulmonary hypertension depends upon mobilization of blood-borne monocytes
Garcia	Christine	78-B	Standardization of Inpatient CPR Status Discussions and Documentation within the Division of Hematology-Oncology at UPMC Shadyside
Gauthier	Marc	100-B	CXCL9/10 Elevation in Severe Asthma is Refractory to Corticosteroid Therapy.

Gunturi	Nivedita	47-B	Patient-centered Goals of Care: Using the Chronic Care Management (CCM) code for cooperative goal setting in the multimorbid elderly
He	Mingyu	101-B	Ultrasound mediated antitumor efficacy of liposomal doxorubicin conjugated to polymer microbubbles with reduced cardiotoxicity in a mouse model of soft tissue sarcoma
Helfield	Brandon	10-B	Endothelial Cell Repair Biophysics during Ultrasound and Microbubble Sonoporation
Heller	Lucas	48-B	Glycemic Management as the Primary Determinant of One-Year Mortality after CABG
Herath	Kanchana	49-B	Osteoporosis and fracture risk in males with Rheumatoid Arthritis
Husain	Sara	50-B	Peritoneal Dialysis: In-hospital complications
Hwang	Jennifer	88-B	NURSING FACILITY TRAINING ENHANCES GERIATRIC MEDICAL KNOWLEDGE IN GRADUATE MEDICAL EDUCATION
Hwang	Jennifer	87-B	RESIDENT PHYSICIANS' PERCEPTIONS OF INTERDISCIPLINARY TEAM ROLES IN THE NURSING FACILITY
Iovleva	Alina	11-B	Reduced Ertapenem Susceptibility Due to OXA-2 Production in Klebsiella pneumoniae ST258
Irizarry	Taya	51-B	DEVELOPMENT AND PRELIMINARY FEASIBILITY OF AN AUTOMATED HYPERTENSION SELF-MANAGEMENT SYSTEM
Jawale	Chetan	13-B	Defect in neutrophil function accounts for impaired anti-fungal immunity in kidney dysfunction
Jawale	Chetan	12-B	IL-17 Receptor Signaling in Tubular Epithelial Cells is Essential for the Activation of Kallikrein-kinin System and Renal Defense against Disseminated Candidiasis
Johnston	Elyse	52-B	RISK OF UNRECOGNIZED FACIAL SPLASH DURING ENDOSCOPY

Karajgikar	Neha	53-B	Risk Factors for Hospital Readmission Following implementation of a Diabetic Ketoacidosis (DKA) Power Plan
Kocoloski	Amanda	54-B	Functional Measures and Patient Home Self-Assessments in the Idiopathic Inflammatory Myopathies
Kota	Karthik	55-B	Effect of Urinalysis with Reflex Testing on Urine Culture Testing and Treatment
Kudryashova	Tatiana V	102-B	Cross-talk between TGFß, Hippo and Akt Signaling Pathways in Pulmonary Vascular Smooth Muscle Cells in Pulmonary Arterial Hypertension
Lee	Jae	56-B	Best Practice Alerts Improve Rates of Appropriate Implantable Cardioverter-Defibrillator Therapy and Reduce All-Cause Mortality
Lennox	Alison	14-B	ATP12A PROMOTES MUCUS DYSFUNCTION IN T2 INFLAMMATION
Levine	Andrea	104-B	Acute Hemodynamic Effects of Oral Nitrite in PH-HFpEF
Levine	Andrea	103-B	Identification of Novel SIRT3 Activators as Therapeutic Prospects for PH-HFpEF
Li	Lian	16-B	Molecular regulation of the stability of SIGIRR in ubiquitin-proteasome system
Li	Lian	15-B	Trim21 inhibits human lung microvascular endothelial cell inflammatory responses through attenuation of NF-kB pathway and intercellular adhesion molecules expression
Li	Xiaoyun	17-B	Tyrosine phosphorylation of TOLLIP on C2 domain is important for TGF-beta pathway inhibition through modulation of Smad7 expression
Ling	Xiaoxi	105-B	Preclinical radiation dose optimization, dosimetry and maximum tolerated dose studies of Lu-177-labeled CTT1403, a phosphoramidate-based PSMA inhibitor for targeted radionuclide therapy of prostate cancer.

Majumder	Saikat	18-B	IL-17 drives the bio-energetic activity of lymph node fibroblastic reticular cells to promote expansion during Th17 cell activation
Masri	Ahmad	57-B	Non-invasive Diagnosis of ATTR Cardiac Amyloidosis: Insights from a Prospective Multimodality Registry
Masri	Ahmad	58-B	Sex Differences and Outcomes of Heart Failure Admissions Stratified by Left Ventricle Ejection Fraction
Massa	Ryan	59-B	Relationship between pre-treatment organ-specific tumor burden and response to immunotherapy in advanced melanoma
Mburu	Maureen	106-B	Age related cardiomyopathy in a transgenic knock-in mouse model of sickle cell disease
McCormick	Kevin	19-B	A comparative assessment of ultrasensitive HIV drug resistance NGS testing with and without unique molecular identifiers
McDonnell	Broangh	20-B	Stress-induced adrenergic dysregulation alters neural-glial distribution and phenotype
Mehta	Kathan	79-B	Overall survival based on oncologist density in the United States, do we need to redefine underserved areas for oncologic care?
Nikiforova	Tanya	90-B	Impact of a required, longitudinal scholarly project in medical school: a content analysis of medical students' reflections
Nikiforova	Tanya	89-B	We're Better Together: A Curriculum for Enhancing Interprofessional Care in Resident Clinic
Niznik	Joshua	80-B	Validating the MDS Mortality Risk Indes in Older Adult Veterans Using MDS Version 3.0
Nolley	Eric	60-B	Palliative Care Utilization by Lung Transplant Recipients in the Last Year of Life at the University of Pittsburgh

Nyiranshuti	Lea	108-B	PET imaging of upregulated VLA-4 in vaso-occlusive crisis using 64Cu-CB-TE1A1P-PEG4-LLP2A in a mouse model of sickle cell disease
O'Brien	Michael Emmet	61-B	Chest CT Pectoralis Muscle Size Validated with Dual Energy X-Ray Absorptiometry Measurements of Body Composition Is Associated with Lung Function in COPD
O'Brien	Michael Emmet	21-B	The E3 Ligase Subunit FBXL2 Is Required for Skeletal Myogenesis And Regulated by Inflammatory Stress That Indicates A Potential Role in Muscle Dysfunction in COPD
O'Connor	Anna	62-B	Relapse of Rheumatoid Arthritis Activity following Sustained Remission: a study of US Veterans
Pandey	Apurva	63-B	Analysis of Patients Mislabeled with Heparin Induced Thrombocytopenia
Phulpoto	Rameez	64-B	Rates of Inappropriate Antibiotic Prescribing are High within a Veterans Affair Hospital
Proksell	Siobhan	91-B	RANDOMIZED ADAPTIVE TRIAL OF DIGITAL BEHAVIORAL PROGRAM FOR ANXIETY AND DEPRESSION IN IBD PATIENT CENTERED MEDICAL HOME
Pulgarin	Andres	109-B	Role of LINE-1 Retroelement in Atherosclerosis Disease
Puli	Amoghavarsha	65-B	Acceptance of Erectile Dysfunction Treatment by Patients on Hemodialysis and Their Renal Providers
Raphael	Itay	22-B	STAT3 dependent mechanisms of regulation of effector Th17 cells
Revu	Shankar	23-B	IL-23 and IL-1ß drive human Th17 cell differentiation and metabolic reprogramming in absence of CD28 costimulation
Rhinehart	Zachary	66-B	Sex-differences in outcomes associated with atrial fibrillation: an analysis of the UPMC electronic health record, 2006-2017

Riva	Patricia	110-B	Identification of Novel Regulators of Right Ventricle Hypertrophic Remodeling with Implications for Pulmonary Hypertension
Rossiter	Brianna	92-B	The Bedside Swap: Perspective-Taking in a Narrative Writing Curriculum as a novel means to Strengthen the Trainee-Patient Relationship in the Ambulatory Setting
Samanta	Palash	24-B	Transcriptional Profiling During Intra-abdominal Candidiasis Reveals Site-specific Host-pathogen Interactions
Smith	Alyxzandria	111-B	Lymphocyte heterogeneity in cutaneous T cell lymphoma (CTCL) skin tumors.
Sun	Wei	112-B	RNA-Sequencing of Inducible Pluripotent Stem Cell Derived Endothelial Cells Carrying BMPR2 Mutations Identifies SCUBE1 as a Putative Pathogenic Effector in Pulmonary Arterial Hypertension
Swami	Janya	68-B	Hospital Readmission and Comprehension of Diabetes Education at Discharge
Tandukar	Srijan	69-B	Does kidney transplantation affect sleep and fatigue in patients with kidney disease?
Tasan	Laura	70-B	Analyze Myositis with Ultrasound and Exercise (AMUSE) Kids- Analysis of Baseline Data
Tehranian	Shahrzad	71-B	Is routine colonoscopy following acute diverticulitis necessary?
Thomas	Roby	72-B	Utilization of cell-free circulating tumor DNA for management of breast cancer: practices in academic and community oncology
Topoll	Alicia	73-B	Spousal support does not affect outcomes in patients with continuous flow left ventricular assist device
Tu	Lan	26-B	Unfolded protein response and mitochondria crosstalk drives PINK1 downregulation and mitochondrial dysfunction in endothelial cells

Vanderberg	Rachel	93-B	Exam Room Presentations in Resident Continuity Clinic
Vasamsetti	Sathish	27-B	Effect of Myocardial Infarction on Insulin Resistance: Role of Macrophage Subsets
Verma	Akash	28-B	The Fungal Toxin Candidalysin is a Feed-Forward Amplifier of Innate IL-17-Dependent Responses to Candida albicans
Wang	Xue-Ping	29-B	Epithelial sodium channel regulation by bile acids
Wilson	Annette	30-B	Biotransformation of bile acids by the gut microbiota contributes to the high risk of colorectal cancer in Alaska Native people
Winters	Spencer	113-B	Idiopathic Pulmonary Fibrosis after Lung Transplantation: Shortened Telomere Length, the DNA Damage Response, and Immune Senescence
Yu	Justin	74-B	System-Level Factors Associated with Utilization of Outpatient Specialty Palliative Care in Patients with Advanced Solid Tumor Cancer
Yu	Qiujun	114-B	A HIF-2a-long noncoding RNA Epigenetic Axis Modulates Histone Methylation and Mitochondrial Metabolism in Hypoxia: Implications for the Pathogenesis of Pulmonary Hypertension
Zhang	Manling	32-B	CamKII exacerbates heart failure progression through activation of class I HDAC signaling

1-B Poster: Novel Cytoplasmic Roles of EZH2 Methyltransferase During RANKL Signaling, Cytoskeletal Organization and Resorption of Osteoclasts

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

Mentors: Deborah L. Galson PhD **Funding Source:** N/A

Authors: Juraj Adamik PhD, Peng Zhang PhD, Quanhong Sun PhD, Jolene J. Windle PhD, Philip E. Auron PhD, Deborah L. Galson PhD

Introduction: EZH2, the methyltransferase subunit of Polycomb Repressive Complex 2, methylates histones on lysine residues, which induces gene repression. Using EZH2 knockdown and the small molecule inhibitor GSK126, we showed that EZH2 plays a critical epigenetic role during the first 24 hours of RANKL activation in osteoclast precursors (OCLp). Here we reveal that EZH2 changes its cellular partitioning and plays distinct roles during OCL differentiation.

Methods: We employed immunofluorescent confocal microscopy, Western blotting, co-immunoprecipitations, qPCR, osteoclast TRAP staining and resorption assays together with combinations of inhibitor treatments.

Results: Immunofluorescence microscopy revealed that EZH2 in OCLp is primarily associated with large punctate cytoplasmic structures. Consistent with cytoplasmic localization, EZH2 methyltransferase activity is required during early RANKL signaling for phosphorylation of cytoplasmic Akt (pSer473 and pThr 308), resulting in downstream activation of both cytoplasmic and nuclear mTOR complexes that are required for induction of OCL differentiation. Inhibition of pmTOR-pS6RP signaling by GSK126 altered the ratio of C/EBPß-LAP and LIP alternative translation isoforms, reducing the inhibitory LIP that is necessary for transcriptional repression of OCL negative regulatory factor MafB. RANKL treatment induced most of EZH2 to translocate to the nucleus. Surprisingly, this was blocked by GSK126. Inhibition of EZH2 during the initial phase of RANKL activation of OCLp prevented OCL fusion and formation, but not TRAP expression, and the cells exhibited impaired shape and actin morphology. While EZH2 in multinucleated OCL on glass was primarily cytoplasmic, EZH2 in OCL differentiated on bone was distributed between nuclei and the cytoplasm. We noted that EZH2 remained nuclear in mononuclear OCL in the same cultures. Mature OCL on bone treated with GSK126 (day 6-8) exhibited condensed cytoskeletal architecture with impaired sealing zone formation, impaired migration and reduced resorptive activity. Cytoplasmic EZH2 has been reported to methylate LIM domain kinase 1 (LIMK1) and inactivate its Ser/Thr kinase in megakaryocyte precursors, which results in increased remodeling of the actin cytoskeleton. As LIMK1 was reported to regulate OCL shape, future studies will examine EZH2 regulation of this protein's function in osteoclasts.

Conclusion: Here we present new evidence that EZH2 plays multiple novel non-histone roles during OCL differentiation by regulating early phases of p-Akt mediated-RANKL signaling and also cytoskeletal dynamics during OCL fusion and resorption.

2-B Poster: NRF2 and HIF1a signaling pathways are interrelated in human kidney proximal tubule epithelial cells

Presenter: Corry Bondi, Post-Doctoral Fellow Renal-Electrolyte

Research Interest: Bench

Mentors: Roderick Tan MD

Funding Source: AHA, UPP, CMRF, NIH-T32

Authors: Corry Bondi PhD, Brittney Rush BSc, Roderick Tan MD

Introduction: Acute kidney injury (AKI), or the sudden loss of kidney function, is a significant clinical problem affecting up to 1 in 5 hospitalized patients. Although AKI can be reversible to some extent, episodes of AKI are associated with an increased risk of developing permanent kidney damage or renal failure. AKI is most commonly caused by kidney ischemia and proximal tubular epithelia are particularly vulnerable to this injury. However, the intracellular signaling pathways leading to cellular injury and dysfunction have not been fully elucidated. HIF1a (Hypoxia-inducible factor-1 alpha) is a transcription factor with increased activity during AKI. NRF2 (Nuclear factor erythroid 2-related factor 2) is a transcription factor activated by the oxidative or electrophilic stress characteristic of AKI. Both pathways are cytoprotective. We have previously shown that recovery after a mild AKI injury in mice is associated with increased renal NRF2 activity. Meanwhile, severe AKI is associated with a paradoxical suppression of NRF2 activity and a lack of renal recovery. This loss of NRF2 signaling may be maladaptive in kidney repair. Because the effect was dependent on severity of hypoxic injury, we hypothesized that NRF2 and HIF1a signaling are interrelated in tubular epithelia.

Methods: To test this, we exposed human proximal tubule epithelial cells (HK-2cells) to a hypoxia mimic, cobalt chloride (CoCl2), to activate HIF1a in either nutrient (DMEM/F12+FBS) or nutrient deficient (HBSS) media. We used these conditions to simulate mild and severe cellular stress, respectively. Immunoblot and qPCR analyses were used to assess NRF2 and HIF1a nuclear translocation and target gene expression, respectively.

Results: We demonstrate that CoCl2 has disparate effects on NRF2 and HIF1a localization and activity when HK-2 cells are cultured under different conditions. CoCl2 induced nuclear localization of HIF1a in both conditions but induced nuclear localization of NRF2 in nutrient media only. Moreover, while HBSS alone induced NRF2 nuclear localization, the addition of CoCl2 inhibited this. Consistent with this, CoCl2-exposed cells increased expression of the NRF2 target gene, hNQO1, in nutrient media but not in HBSS.

Conclusion: Our data demonstrate differential regulation of NRF2 by a HIF1a activator based on whether there is co-exposure to nutrient or nutrient deficient media. This suggests that the stringency of culture conditions plays a major role in the interaction between the NRF2 and HIF1a pathways. It may also explain the paradoxical responses of NRF2 under severe AKI. The exact mechanisms of this phenomenon require further study and may provide molecular targets for AKI treatment.

3-B Poster: KS-WNK1 Expands the Dynamic Range of NCC Regulation by Dietary Potassium

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

Research Interest: Bench

Mentors: Arohan Subramanya MD

Funding Source: T32

Authors: Cary Boyd-Shiwarski MD/PhD, Lubika Nkashama BS, Kelly Connolly BS, Chou-Long Huang MD/PhD, Arohan Subramanya MD

Introduction: Dietary [K+] deficiency activates the Na-Cl cotransporter (NCC) of the renal distal convoluted tubule (DCT) through phosphorylation. NCC phosphorylation is regulated by the serine-threonine kinases WNK1 and WNK4 and the downstream kinase SPAK. During dietary [K+] loading and restriction, the WNK-SPAK pathway condenses into large membraneless cytosolic signaling puncta, termed "WNK bodies". These foci only appear during dietary [K+] imbalance and require KS-WNK1, a truncated WNK1 isoform that is highly expressed in the DCT. The role of KS-WNK1 and WNK bodies in NCC regulation during physiological shifts in [K+] remains unclear: early studies reported that KS-WNK1 inhibits NCC activity, while more recent data suggest that it can activate NCC. Our hypothesis unifies these conflicting reports, and proposes that KS-WNK1 can act as both an activator and/or inhibitor of NCC depending on plasma [K+] levels.

Methods: To analyze the role of KS-WNK1 in NCC regulation in vivo, we assessed NCC phosphoactivation (pNCC) at T53, T58, and S71 by immunoblot and IF microscopy in WT and KS-WNK1 KO mice across a wide range of plasma [K+]. WT and KS-WNK1 KO mice were treated with low [K+] (LK), control, or high [K+] (HK) diets for 10d. We also treated a group of HK animals with amiloride (2mg/kg/d x 7d) to induce frank hyperkalemia. This allowed us to study the effects of KS-WNK1 on pNCC over a range of plasma [K+] from 2 to 9 mmol/L.

Results: Our results confirm that in WT mice, there is an inverse relationship between plasma [K+] and pNCC, such that WT mice on [K+] deficient diets have the highest level of pNCC and form large (1-2 μm) subnuclear WNK bodies. Moreover, WT mice on high [K+] diets have the lowest level of pNCC and form small (0.5 μm) subapical WNK bodies. Interestingly, in KS-WNK1 KO mice the WNK bodies are absent, and the linear inverse relationship between plasma [K+] and pNCC is attenuated. This indicates a stimulatory role for KS-WNK1 on NCC activation during hypokalemia, and an inhibitory role during hyperkalemia.

Conclusion: KS-WNK1 amplifies NCC phosphorylation during hypokalemia and attenuates NCC during hyperkalemia, suggesting that KS-WNK1 augments the responsiveness of the WNK-SPAK pathway to a given change in extracellular [K+], converting small changes in plasma [K+] to large effects on NCC phosphorylation. These observations, which are likely WNK body dependent, provide insight into the role of KS-WNK1 in the [K+] stress response and potentially resolve conflicting data regarding the role of KS-WNK1 in NCC regulation.

4-B Poster: Understanding Heterogeneity in Severe Asthmatics Using High Dimensional Analysis of Cellular Phenotypes

Presenter: Matthew Camiolo, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Sally Wenzel MD
Anuradha Ray PhD

Funding Source: T32

Authors: Matthew Camiolo MD, Xiaoying Zhou PhD, Timothy Oriss PhD, 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 disease that is refractory to treatment and accounts for nearly half the health care expenditure on asthma in the United States. Recent efforts focused on understanding severe asthma pathophysiology suggest ontological heterogeneity. Most molecular phenotyping studies to date have relied on transcriptional profiling. The emergence of time of flight mass cytometry (CyTOF) offers an opportunity to characterize the inflammatory milieu present in bronchoalveolar lavage (BAL) cells at the protein level in unprecedented detail.
Methods: Healthy controls (HC) as well 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 directed against a panel of intracellular and extracellular proteins. Acquisition was performed on the Helios CyTOF instrument. Intact singlets were gated using Flowjo and clustering analysis performed using Phenograph. Metadata was used to inform principal component analysis (PCA). K-means clustering was then based off high dimension cell count.
Results: Study of 23 samples from 3 HC, 10 MMA and 10 SA patients revealed 27 clusters based on staining of 33 surface markers. Patient level analysis using PCA revealed 3 subsets of asthmatics. While the majority of MMA cases were similar in cell composition to HCs, PCA revealed multiple divergent subgroups within the known umbrella of clinically severe disease. These subgroups of 4 and 6 patients were significantly enriched for severe asthmatics and illustrated possible heterogeneity in cytokine signaling. They could be broadly defined as T-cell rich and T-cell poor and showed wide disparity in staining for IFN-γ, IL17 and type 2 cytokines. Divergence in clinical parameters such as lung function and T2 biomarkers were also evident. Machine learning classification of BAL samples proved superior to clinical disease severity assessment in predicting covariance of cell count and cytokine intensity. Correlation analysis between cell clusters and cytokine intensity across all patients supported the relationships illustrated group analysis.
Conclusion: Using machine learning algorithms to evaluate high-dimensional data generated from CyTOF analysis of lavage samples, we have identified and characterized subgroups within clinically severe asthma. Understanding the differences between these patients in a more granular way may help guide decisions regarding precision medicine. Ongoing studies are focused on integration of clinical characteristics of the severe asthmatics with their BAL cell immune profile.

5-B Poster: Altered phenotype of human Lung Mesenchymal Stem Cells in patients with COPD and IPF

Presenter: Tamara Cruz, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Mauricio Rojas MD

Funding Source: NIH

Authors: Tamara Cruz PhD, Alejandra Lopez-Giraldo MD, Guillaume Noel PhD, Sandra Casas PhD, Jacobo Sellares MD, Yating Peng MD, John Sembrat PhD, Nayra Cardenes PhD, Diana Alvarez MD, Mauricio Rojas MD, Alvar Agusti MD, Rosa Faner PhD

Introduction: Mesenchymal stem cells (MSC) have been described in many organs including the lung, but remains unclear their role in chronic diseases as COPD and IPF. Keeping with this, our objectives are isolate, characterize and compare LMSC in healthy subjects and patients with COPD and IPF.

Methods: We used fresh lung tissue from individuals undergoing lung resection surgery (mostly because of lung cancer or from transplants) to isolate LMSC. LMSC were isolated and expanded form fresh lung tissue using a new sphere based culture technique. Obtained LMSC were characterized using flow cytometry, , microarrays and confocal microscopy. Their functionality was assessed both with in vitro assays and LPS and bleomycine mice models.

Results: In all the studied groups we identified a group of cells, which mesenchymal characteristic as compared with BM-MSC (flow cytometry markers, mesenchymal transcription factors and differentiation capacity) that localized in the lung alveoli. In vitro, we observed that LMSC from current smokers with COPD had an impaired capacity to immunomodulate the proliferation of the CD8+γ T lymphocytes.

Conclusion: We have identified a population of LMSC in lungs not only from healthy subjects, also in COPD and IPF patients. These cells present functional abnormalities in disease subjects.

6-B Poster: Role of Piezo channels in urothelial cell mechanotransduction

Presenter: Marianela Dalghi, Post-Doctoral Fellow **Research Interest:** Bench Renal-Electrolyte

Mentors: Gerard Apodaca PhD

Funding Source: Urology Care Foundation Research Scholar Award

Authors: Marianela Dalghi PhD, Dennis Clayton , Wily Ruiz , Gerard Apodaca PhD

Introduction: During the micturition cycle, the ability to sense and transduce the degree of tension in the wall of the bladder allows the bladder to accommodate to changing urine volumes and to transmit the filling state to the CNS. The urothelium, and in particular the umbrella cells (UC), is proposed to play an important role in mechanotransduction: upon bladder filling, UC sense membrane stretch and transduce it into a number of cellular responses, including exocytosis of subapical discoidal/fusiform vesicles and release of neurotransmitters. The mechanosensor present in the UC that directly responds to membrane stretch is unknown. Piezo channels are a newly discovered family of mechanosensitive channels associated with the physiological responses to pressure, shear stress and tension. In this study, we sought to determine the involvement of Piezo channels in UC mechanosensation.

Methods: Piezos expression in the rat bladder was assessed by RT-PCR and immunofluerescence. Exocytosis was determined by measuring the release of hGH from umbrella cells of rat bladders transduced with adenoviruses encoding for hGH1-V5. Bladder activity was measured by cystometry during slow, continuous bladder filling on anaesthetised rats.

Results: We found that rat UC express both Piezo1 and Piezo2 channels which exhibit different subcellular localizations: Piezo1 is expressed at the apical region and at tight junction sites, whereas Piezo2 is found in the cytosol. Silencing Piezo1 expression by in-situ transduction of rat bladders with adenoviruses encoding Piezo1-shRNA showed a significant decrease in apical exocytosis (61 ± 9 %) compared to control upon ex vivo bladder filling. We also assessed the impact of knocking-down Piezo1 in bladder function by monitoring continuously the intravesical pressure on anesthetized rats previously transduced with either scrambled- or Piezo1-shRNA. We observed that loss of Piezo1 leads to a lower voiding frequency and also affects bladder compliance (defined as $\Delta V/\Delta P$ during filling).

Conclusion: All together, these results show the involvement of Piezo1 in sensing mechanical stretch required for normal bladder function.

7-B Poster: Development of a Unique Tissue Plasminogen Activator (tPA) loaded Microbubble for the Treatment of Coronary Microvascular Obstruction

Presenter: Stephen D'Auria, Fellow Cardiology

Research Interest: Bench

Mentors: John Pacella MD
Xucai Chen PhD

Funding Source: HVI Fellows Grant

Authors: Stephen D'Auria MD, Francois Yu PhD, Xucai Chen PhD, John Pacella MD

Introduction: Microvascular obstruction (MVO) occurs frequently during successful PCI for acute myocardial infarction, despite achieving epicardial coronary artery patency. MVO results from distal embolization of microthrombi and coronary plaque components and is associated with worse outcomes, and does not currently have an established, effective therapeutic strategy. Our previous work has demonstrated the potential of using ultrasound to insonify microbubbles (MBs) in order to relieve MVO, termed sonoreperfusion (SRP). In this study, we sought to develop a unique tPA loaded MB. Our ultimate goal is to determine whether targeted delivery of tPA during SRP would enhance the reperfusion efficacy while avoiding the potential bleeding complications associated with systemic administration of tPA.

Methods: tPA (1 mg/mL) was first modified via a maleimide linkage using BMCC-biotin, leading to a biotinylated protein. The biotinylated tPA (0.87 mg/mL) was then mixed with streptavidin labeled lipid shelled MB (1×109 MB/mL) in volumetric ratios of 1:1, 3:1, and 6:1. The linkage of the tPA to the MB was achieve through biotin-streptavidin bridging. The enzymatic activity of the tPA in these tPA loaded MBs were then tested against whole porcine blood thrombus in vitro and also with a commercially available tPA chromogenic activity kit. The loading capability of tPA onto the MBs was determined by BCA protein assay.

Results: tPA loaded MB showed successful lysis of whole porcine blood clot in vitro, as evidenced by decreased thrombus weight. Subsequent quantitative analysis of tPA activity showed that there was no significant difference in the activity of stock tPA when compared to the BMCC labeled tPA (42.0 IU vs 44.7 IU, p=0. 17), MB loaded with tPA at volumetric ratios of 3:1 (43.5 IU, p=0.38) and 6:1 (39.3 IU, p=0.15). MB loaded with tPA at a ratio of 1:1 showed decreased activity compared to stock tPA (42.0 IU compared to 8.6 IU, p=0.38). There was no significant difference in the activity between the 3:1 and 6:1 groups. The loading capability of tPA on the 3:1 tPA loaded MB was 6.2×10-7 µg per MB, corresponding to a loading efficiency of 10.4% of the stock tPA added to the MB.

Conclusion: We successfully loaded tPA onto the surface of a lipid encapsulated MB. The tPA retained its enzymatic activity throughout this process. The loading capacity was 6.2×10-7 µg per MB, suggesting we have achieved sufficient tPA to warrant further in vitro and in vivo evaluation.

8-B Poster: PARKIN E3 ligase and PINK1 kinase activity are reduced by acetylated ubiquitin.

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

Research Interest: Bench

Mentors: Michael Jurczak PhD

Funding Source: T32

Authors: Lia R. Edmunds PhD, Brydie R. Huckestein BS, Michael J. Jurczak PhD

Introduction: PARKIN, a ubiquitin E3 ligase, plays a critical role in a mitochondrial quality control process called mitophagy. During mitophagy, damaged mitochondria are selectively degraded following ubiquitination of outer mitochondrial membrane (OMM) proteins by PARKIN. Recruitment of PARKIN to the OMM and subsequent activation are promoted by PINK1-mediated ubiquitin and PARKIN phosphorylation. PARKIN then catalyzes formation of poly-UBIQUITIN(UB) chains on OMM proteins that consist primarily of lysine(K) 6,11,48&63 linkage types, which in turn recruit autophagy receptor proteins. Interestingly, mitophagy is reduced in liver of obese mice, despite mitochondrial dysfunction. Pan-protein lysine acetylation is increased in obese mouse liver, suggesting that ubiquitin lysine acetylation may be increased as well. We therefore hypothesized that UB acetylation increases during HFD feeding and would inhibit PARKIN-mediated mitophagy signaling.

Methods: Liver mitochondrial levels of PARKIN, PINK1, acetyl and total UB, as well as alternative mediators of mitophagy signaling, were compared in lean and obese mice. PARKIN E3 ligase and PINK1 kinase assays were performed using recombinant active PINK1(1µg) or kinase-dead PINK1(D358A, 1µg), PARKIN(2µg), E1(120nM) and E2(1µM) enzymes and either wild-type (WT) or K6,K11,K48&K63 acetylated UB (AC-UB). Kinase activity was assessed with either active or D358A PINK1 and 20µM WT-UB or AC-UB for 15-60 minutes. E3 ligase activity was determined after incubation with either active or D358A PINK1 to activate PARKIN, followed by incubation with E1, UBE2L3, and varying amounts of WT- and AC-UB totaling 50µM.

Results: Liver mitochondrial PINK1, PARKIN, and UB protein levels were ~50% reduced in obese compared with lean mice ($p<0.05$). In contrast, there were no differences in BNIP3 levels and NIX was undetectable. Acetylation of UB at K27, K29 and K48 was significantly increased in liver mitochondrial fractions from obese mice ($p<0.01$). PARKIN E3 ligase activity was 20-fold less in the presence of AC-UB compared with WT-UB. Increasing the amount of AC-UB relative to WT-UB similarly reduced PARKIN E3 ligase activity and the inhibitory effect of AC-UB exceeded its molar abundance. Finally, PINK1 kinase activity was reduced in by AC-UB compared with WT-UB at each time point tested (8-13-fold, $p<0.01$).

Conclusion: Our data demonstrate that HFD feeding reduced liver mitochondrial PINK1 and PARKIN localization, which was associated with increased acetylation of mitochondrial UB. Also, AC-UB inhibited PARKIN E3 ligase and PINK1 kinase activities in vitro. These observations suggest that increased hepatic AC-UB in the context of obesity may contribute to reduced mitochondrial quality control by mitophagy, and may contribute to mitochondrial dysfunction in liver that occurs during obesity.

9-B Poster: Inflammatory macrophage expansion in pulmonary hypertension depends upon mobilization of blood-borne monocytes

Presenter: Jonathan Florentin, Post-Doctoral Fellow
VMI

Research Interest: Bench

Mentors: Partha Dutta PhD
Stephen Chan MD, PhD, FAHA

Funding Source: R01

Authors: Jonathan Florentin PhD, Emilie Coppin PhD, Sathish Vasamsetti PhD, Jingsi Zhao MSc, Yi-Yin Tai MSc, Ying Tang MSc, Yingze Zhang PhD, Annie Watson MPH, John Sembrat MD, Mauricio Rojas PhD, Sara O' Vargas PhD, Stephen Chan MD, Partha Dutta PhD

Introduction: Pulmonary inflammation, characterized by the presence of perivascular macrophages, has been proposed as a key pathogenic driver of pulmonary hypertension (PH), a vascular disease with increasing global significance. However, the mechanisms of expansion of lung macrophages and the role of blood-borne monocytes in PH are poorly understood.

Methods: Using multicolor flow cytometric analysis of blood in mouse and rat models of PH and patients with PH, an increase in blood monocytes was observed. In correlation, lung tissue displayed increased chemokine transcript expression, including those responsible for monocyte recruitment such as Ccl2 and Cx3cl1, accompanied by an expansion of interstitial lung macrophages.

Results: These data indicate that blood monocytes are recruited to lung perivascular spaces and differentiate into inflammatory macrophages. Correspondingly, parabiosis between congenically different hypoxic mice demonstrated that most interstitial macrophages originated from blood monocytes. To define the actions of these cells in PH in vivo, we reduced blood monocyte numbers via genetic deficiency of cx3cr1 or ccr2 in chronically hypoxic male mice and by pharmacologic inhibition of Cx3cl1 in monocrotaline-exposed rats. Both models exhibited decreased inflammatory blood monocytes as well as interstitial macrophages, leading to a substantial decrease of arteriolar remodeling but with a less robust hemodynamic effect.

Conclusion: This study defines a direct mechanism by which interstitial macrophages expand in PH. It also demonstrates a pathway for pulmonary vascular remodeling in PH that depends upon interstitial macrophage-dependent inflammation yet at least is partially dissociated from hemodynamic consequences, thus offering guidance on future anti-inflammatory therapeutic strategies in this disease.

10-B Poster: Endothelial Cell Repair Biophysics during Ultrasound and Microbubble Sonoporation

Presenter: Brandon Helfield, Post-Doctoral Fellow Cardiology

Research Interest: Bench

Mentors: Liza Villanueva MD

Funding Source: American Heart Association Postdoctoral Fellowship

Authors: Brandon Helfield PhD, Xucai Chen PhD, Simon Watkins PhD, Flordeliza Villanueva MD

Introduction: Ultrasound (US)-stimulated microbubbles (MBs) are emerging as non-viral gene delivery vehicles for the treatment of cardiovascular disease. The MB-cell interactions that facilitate nucleic acid delivery across cell membranes and into cells outside the vasculature, and hence strategies to optimize this platform, remain poorly understood. The objective of this work is to gain mechanistic insight into the biophysical context of reversible sonoporation.

Methods: Live-cell 3D confocal microscopy was employed to image cultured human umbilical vein endothelial cells (HUVECs) during real-time sonoporation with lipid MBs exposed to a single US pulse (1 MHz, 8 μs; 0.1-0.9 MPa, n=54). Cell membrane impermeant propidium iodide (PI) was diluted into the media as a marker for model drug entry (sonoporation). We investigate the dynamics of plasma membrane perforation and consolidate the findings with theoretical biophysical modeling. We then probe cytoskeletal re-organization during sonoporation using LifeAct. Finally, to assess remote biochemical signaling, a subset of experiments examines Ca2+ signaling, with and without the inhibition of gap junctions.

Results: We show for the first time that sonoporation generates transendothelial perforations (TEPs) that confer intracellular permeability only during their opening phase, a process consistent with biophysical modeling. TEP opening (and thus membrane permeability) is an order of magnitude faster than its resealing phase ($p<0.001$), suggesting a distinct biophysical origin between enhanced cellular versus vascular permeability. The extent of actin breaching at the TEP site increases with TEP area and PI uptake ($p<0.001$). The resealing phase is led by actin recruitment along the TEP rim, and upon resealing results in a membrane protrusion, suggesting exocytosis as a sonoporation healing mechanism. Sonoporation initiates Ca2+ signaling to neighboring cells through gap junctions ($p<0.001$).

Conclusion: While the opening of TEPs is largely passive, actin recruitment plays a significant role in their resealing and occurs over much longer timescales (1 min versus 10-20 min). Further, we have shown that gap junctions play a crucial role in biochemical signaling induced by sonoporation. This work contributes towards understanding the biophysical context of reversible sonoporation, necessary for its translation to the clinic.

11-B Poster: Reduced Ertapenem Susceptibility Due to OXA-2 Production in Klebsiella pneumoniae ST258

Presenter: Alina Iovleva, Fellow Infectious Diseases

Research Interest: Bench

Mentors: Yohei Doi MD, PhD

Funding Source: N/A

Authors: Alina Iovleva MD, Roberta Mettus BSc, Christi McElheny MSc, Anthony W Pasculle PhD, Yohei Doi MD, PhD

Introduction: OXA-2 is a class D beta-lactamase which is primarily found in E. coli (Ec) and P. aeruginosa and confers resistance to penicillins as well as narrow-spectrum cephalosporins. However, recent reports suggest that OXA-2 also possesses carbapenem-hydrolyzing activity. We report a case of K. pneumoniae that confers reduced susceptibility to ceftazidime and ertapenem due to production of OXA-2.

Methods: K. pneumoniae (Kp) strain YDC787 was identified from the BAL culture of an inpatient in December 2016. The strain was initially reported as intermediate to ertapenem. MICs and carbapenemase production were confirmed by E-test and modified Hodge test (MHT), respectively. PCR for KPC was positive, however strain's sensitivity profile was not consistent with KPC production. Western blot did not detect presence of KPC. Ec TOP10 was transformed with purified plasmids followed by selection with ampicillin (TOP10 [pYDC787]), and the carbapenem resistance determinant was cloned into vector pBCSK using partial Sau3AI digestion (TOP10 [pOXA-2]).

Results: Kp YDC787, Ec TOP10 (pYDC787), and Ec TOP10 (pOXA-2) all showed reduced susceptibility to ertapenem and ceftazidime, but not meropenem, imipenem or cefepime. All isolates were positive for carbapenemase production by MHT. Sanger sequencing of pOXA-2 revealed 2,910-bp partial class 1 integron containing aacA4-blaOXA-2-qacE1-sul1. The presence of blaOXA-2 was confirmed by PCR in Kp YDC787 and Ec TOP10 (pYDC787).

Conclusion: These findings confirm that OXA-2 functions as carbapenemase and cephalosporinase, significantly reducing susceptibility to ertapenem and ceftazidime, but not to meropenem, imipenem, or cefepime.

12-B Poster: IL-17 Receptor Signaling in Tubular Epithelial Cells is Essential for the Activation of Kallikrein-kinin System and Renal Defense against Disseminated Candidiasis

Presenter: Chetan Jawale, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Partha Biswas PhD

Funding Source: NIH DK104680

Authors: Chetan Jawale PhD, Kritika Ramani PhD, Aakash Verma PhD, Bianca Coleman BS, Jay Kolls PhD, Partha Biswas PhD

Introduction: Kidney failure is a frequent outcome in patients with disseminated Candida albicans fungal infections. IL-17 receptor (IL-17R) signaling is well known to be essential for renal protection against disseminated candidiasis, but the identity and function of IL-17-responsive cell(s) in mediating renal defense remains an active area of debate. Since renal tubular epithelial cells (RTEC) are highly responsive to IL-17 in vitro, we hypothesized that RTEC might be the dominant target of IL-17 activity in the infected kidney.

Methods: We made bone chimera mice to define the role of IL-17R signaling in hematopoietic vs non-hematopoietic cells in renal antifungal immunity. We also generated mice with a conditional deletion of Il17ra in RTEC (RTECIl17ra-/-).Control and RTECIl17ra-/- mice were evaluated for susceptibility against disseminated candidiasis following systemic infection with C. albicans.

Results: Using bone marrow chimeras, we found that IL-17R signaling is required only in non-hematopoietic cells for immunity to systemic C. albicans infection. In line with this data, Il17ra?RTEC mice showed enhanced kidney damage and early mortality following systemic fungal infection, very similar to Il17ra-/- animals. Increased susceptibility to candidiasis in RTECIl17ra-/-?mice was associated with diminished activation of the renal protective Kallikrein-kinin system (KKS) in these mice, resulting in reduced apoptosis of kidney-resident cells during hyphal invasion. Moreover, protection was restored by treatment with bradykinin, the major end-product of KKS activation, which was mediated dominantly via bradykinin receptor b1.

Conclusion: These data for the first time show that IL-17R signaling in RTEC is necessary and likely sufficient for IL-17-mediated renal defense against fatal systemic C. albicans infection. Our results may pave the path for designing better targeted therapeutic approaches to counter this fatal nosocomial infection, with ramifications for other extracellular pathogens.

13-B Poster: Defect in neutrophil function accounts for impaired anti-fungal immunity in kidney dysfunction

Presenter: Chetan Jawale, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Partha Biswas PhD

Funding Source: NIH R01

Authors: Chetan Jawale PhD, Kritika Ramani PhD, Bianca Coleman MS, Partha Biswas PhD

Introduction: Chronic kidney disease is increasingly recognized as a major public health problem, and has a prevalence of 10% in the general population. Accumulation of uremic toxins results in systemic immunosuppression. Sepsis due to microbial infections accounts for 20% of deaths in patients with kidney diseases. Increased susceptibility of uremic patients to invasive fungal infections may attribute to impairment of innate immune defense. However, the molecular mechanisms of impaired anti-fungal immunity in kidney dysfunction are poorly understood.

Methods: In this study, we have used the mouse model of aristolochic acid nephropathy to investigate the effect of uremia on antifungal immunity.Mice were injected intraperitoneally (ip) with 10 mg/kg body weight aristolochic acid I (AAI). At day 4 post AAI injection, mice were intravenously infected with Candida albicans. For invitro experiments, mouse neutrophils were treated with serum isolated from control or uremic mice.

Results: A single IP injection of aristolochic acid I resulted in severe tubulointerstitial injuries accompanied by increased level blood urea nitrogen. Uremic mice showed increased Candida albicans burden in the internal organs following systemic infection. Increased fungal load was not attributed to defect in migration of neutrophils in the infected organs. Uremic condition impaired the ROS production and fungicidal activity of neutrophils. Interestingly, incubation of neutrophils with uremic serum led to impairment of their energy metabolism, indicated by reduced ATP content and lactate production. Neutrophils incubated with uremic serum showed reduced Glut1 protein expression and impaired glucose uptake capacity. Surprisingly, uremic serum inhibited PI3K/AKT pathway leading to aberrant activation of GSK3ß in neutrophils. Furthermore, inhibition of GSK3ß restored the glucose uptake in neutrophils incubated with uremic serum.

Conclusion: These results indicate that uremia suppresses the anti-fungal activity of neutrophils by inhibiting their immunometabolism.

14-B Poster: ATP12A PROMOTES MUCUS DYSFUNCTION IN T2 INFLAMMATION

Presenter: Alison Lennox, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Mike Myerburg MD

Funding Source: T32

Authors: Alison Lennox MD, Stefanie Coburn BS, John Leech BS, Elisa Heidrich MSc, Thomas Kleyman MD, Sally Wenzel MD, Joseph Pilewski MD, Timothy Corcoran PhD, Mike Myerburg MD

Introduction: Mucociliary clearance (MCC) is impaired when the airway surface liquid (ASL) is poorly hydrated. In Cystic Fibrosis (CF), these changes negatively impact host defense leading to a chronic cycle of inflammation, infection, and obstruction. Mucus dysfunction is also observed in airway diseases with high levels of Type 2 (T2) inflammation, such as asthma and APBA, however the pathophysiology of these changes is poorly understood.

Methods: Primary human bronchial epithelial (HBE) cells were cultured on an air liquid interface. After differentiation, interleukin 13 (IL-13) was added to the basolateral media (10 ng/mL) for 3-5 days prior to evaluation. The ASL volume, height, viscosity, and pH were measured using previously published methods. ATP12A, an apical H/K-ATPase previously shown to acidify the ASL, was knocked down with shRNA delivered by lentivirus.

Results: Exposure to IL-13 led to a profound decrease in ASL volume and dramatically reduced in the rate of mucociliary transport. In contrast to CF, the changes in ASL volume were not attributable to electrogenic ion transport given that IL-13 reduced ENaC activity and increased CFTR and TMEM activity. Interestingly, IL-13 did not alter the ASL height (as measured with confocal microscopy), however dramatic increases were noted in the viscosity of the ASL (as measured by fluorescence recovery after photobleaching, FRAP). The effect of IL-13 on ASL viscosity was additive to the increases in ASL viscosity already observed in CF HBE. IL-13 treatment did not alter the baseline ASL pH in bicarbonate/CO2 containing conditions, however, the rate of ASL acidification was increased by IL-13 in the absence of bicarbonate. IL-13 exposure increased ATP12A expression more than 3 fold. ATP12A knockdown and inhibition prevented the IL-13 mediated increases in ASL viscosity. ATP12A knockdown also reduced the proton secretion rate proportional to the level of residual protein expression, but did not alter the baseline ASL pH.

Conclusion: We have shown that Th2 inflammation promotes ASL dysfunction and impairs MCC in primary HBE cells. While the IL-13 driven mucus dysfunction requires ATP12A expression, these effects do not appear to be due to a change in the ASL pH. Although further studies are needed to delineate how ATP12A contributes to mucus dysfunction, we propose that ATP12A blockade may be beneficial in individuals with T2 inflammatory airway diseases.

15-B Poster: Trim21 inhibits human lung microvascular endothelial cell inflammatory responses through attenuation of NF-kB pathway and intercellular adhesion molecules expression

Presenter: Lian Li, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Jing Zhao MD

Authors: Lian Li PhD, Paine Fleisher BS, Jianxin Wei MD, Ban Wang MD, Mary Kaltreider BS, Shuang Li MD, Prithu Sundd PhD, Jing Zhao MD

Funding Source: R01GM115389

Introduction: Vascular endothelium lines the entire circulation system and maintains vessel integrity. Endothelial cell (EC) inflammation is an important pathogenic feature of many inflammatory diseases such as acute lung injury and sepsis. Increase in EC inflammation results in neutrophil infiltration from the blood to the site of inflammation, further promoting EC permeability. Ubiquitin E3 ligase Trim21 has been known to be implicated in human disorders; however, the role of Trim21 in EC inflammation has not been reported. Here, we show that Trim21 exhibits an anti-inflammatory property in lung microvascular cells.

Methods: Human lung microvascular cells (HLMVECs) were treated with IL-1ß, TNFa, or lipopolysaccharide (LPS) for 2-9 h, and then Trim21 levels were determined by Western blotting. Further, HLMVECs were transfected with plasmids coding V5 tagged-Trim21, and then cells were treated with LPS for 6 h.

Results: We found that Trim21 levels were reduced in response to these inflammatory stimuli. LPS treatment significantly increased expression of intercellular adhesion molecule-1 (ICAM1) and vascular adhesion molecule-1 (VCAM1), while the effects were attenuated in Trim21-V5-overexpressing cells. NF-κB pathway plays a critical role in ICAM1 and VCAM1 expression. We found that LPS-induced phosphorylation of I-κB was diminished by overexpression of Trim21-V5.

Conclusion: Our findings discover an anti-inflammatory role of Trim21 in lung endothelial cells. This study suggests that reduction of Trim21 may contribute to vascular inflammation. Future study will focus on the molecular regulation of NF-κB by Trim21 and role of Trim21 in neutrophil adhesion to lung microvascular cells.

16-B Poster: Molecular regulation of the stability of SIGIRR in ubiquitin-proteasome system

Presenter: Lian Li, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Yutong Zhao MD

Funding Source: NIH R01 HL131665

Authors: Lian Li PhD, Jianxin Wei MD, Shuang Li MD, Jing Zhao MD, Yutong Zhao MD

Introduction: SIGIRR is a critical receptor for anti-inflammatory cytokine IL-37. It mediates inflammation and immune responses through negatively regulation of ILR and TLR signaling. However, the molecular regulation of SIGIRR stability remains unclear.

Methods: Here we found that the degradation of SIGIRR induced by IL-37 was prevented with a proteasome inhibitor MG-132 in a time dependent manner. The degradation of SIGIRR was enhanced by overexpression of ubiquitin. SIGIRR was ubiquitinated in K48-linked chains and the 163 site of SIGIRR was critical for its stability. Furtherly lung injury mouse models were induced by intra trachea injection LPS for 24h or P. aeruginosa (strain PA103) for 4h. We demonstrate that the expression of SIGIRR was decreased in LPS or PA103 induced mouse lung tissues than that in PBS group. MAPK signaling is an important inflammation pathway. Here we show that overexpression SIGIRR in RAW cells attenuated LPS-induced phosphorylation of JNK and ERK in a time dependent.

Results: Here we found that the degradation of SIGIRR induced by IL-37 was prevented with a proteasome inhibitor MG-132 in a time dependent manner. The degradation of SIGIRR was enhanced by overexpression of ubiquitin. SIGIRR was ubiquitinated in K48-linked chains and the 163 site of SIGIRR was critical for its stability. Furtherly lung injury mouse models were induced by intra trachea injection LPS for 24h or P. aeruginosa (strain PA103) for 4h. We demonstrate that the expression of SIGIRR was decreased in LPS or PA103 induced mouse lung tissues than that in PBS group. MAPK signaling is an important inflammation pathway. Here we show that overexpression SIGIRR in RAW cells attenuated LPS-induced phosphorylation of JNK and ERK in a time dependent.

Conclusion: Our data suggest that SIGIRR degradation is mediated by the ubiquitin-proteasome system and is critical for pulmonary inflammation. In the future, detection the ubiquitin E3 ligases regulating SIGIRR stability might serve as a unique strategy for treatment of pulmonary inflammation.

17-B Poster: Tyrosine phosphorylation of TOLLIP on C2 domain is important for TGF-beta pathway inhibition through modulation of Smad7 expression

Presenter: xiaoyun Li, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Yingze Zhang PhD

Funding Source: N/A

Authors: Xiayun Li MD, Harinath Bahudhanapati PhD, Shibing Yu MD, Jing Zhao MD, Daniel Kass MD, Yingze Zhang PhD

Introduction: Toll interacting protein, also known as TOLLIP, is an inhibitory adaptor protein in TGF-beta pathway. Genetic variations of the TOLLIP gene are associated with the development and disease progression of idiopathic pulmonary fibrosis (IPF). Repetitive injury of the alveolar epithelium and aberrant wound healing are considered triggering events of IPF. TGF-beta1 plays a pivotal role in this abnormal re-epithelialization process by targeting many cellular processes such as epithelial proliferation and migration. TOLLIP is known to be a tyrosine kinase substrate during cancer development. Tyrosine phosphorylation of TOLLIP in IPF is unknown. We hypothesized that tyrosine phosphorylation of TOLLIP protein is important for its inhibitory role on TGF-beta/Smad3 pathway by regulating inhibitory Smad7.

Methods: Wild type and Y83A mutation of TOLLIP were cloned into pcDNA3.1/V5-His-TOPO vector. TOLLIP WT and Y83A mutant were transiently transfected in A549 cells along with a TGF-beta luciferase reporter. Cells were lysed for protein analysis and luciferase assays. Scratch assays were used to evaluate the effects of WT and Y83A TOLLIP on cell migration in A549 cells. The expression of Smad7 was detected by western blot.

Results: We have found the tyrosine residue at position 83 in the C2 domain of TOLLIP protein is phosphorylated. TOLLIP overexpression with Y83A mutation in A549 cells led to decreased protein levels of Smad7. Additionally, overexpression of the TOLLIP Y83A mutant partially abolished the inhibitory effects of TOLLIP on a TGF-beta luciferase reporter. Furthermore, cell migration of the A549 cells in a wound healing scratch assay model was impaired when TOLLIP Y83A mutant was overexpressed.

Conclusion: Tyrosine phosphorylation of amino acid 83 in the C2 domain of TOLLIP is important for its inhibitory role of TGF-beta pathway by modulating Smad7 expression levels in lung epithelial cells. Our study suggests that TOLLIP may have a critical role in modulating TGF-beta signaling in the respiratory epithelium in IPF.

18-B Poster: IL-17 drives the bio-energetic activity of lymph node fibroblastic reticular cells to promote expansion during Th17 cell activation

Presenter: Saikat Majumder, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Mandy McGeachy PhD

Funding Source: N/A

Authors: Saikat Majumder PhD, Nilesh Amatya MS, Shankar Revu PhD, Chetan Jawale PhD, Natalie Rittenhouse MS, Ashley Menk MS, Itay Raphael PhD, Amrita Bhattacharjee PhD, Timothy Hand PhD, Partha Biswas PhD, Greg Delgoffe PhD, Amanda Pohelek PhD, Sarah Gaffen PhD

Introduction: Fibroblastic reticular cells (FRC) form the stromal support network of T cell zones, playing important roles in lymph node (LN) homeostasis as well as induction of adaptive immunity. The inflammation that accompanies T cell priming causes rapid LN hypercellularity. This increased organ size is initially accommodated by relaxation of the FRC network following interactions with activated dendritic cells. FRC then proliferate to provide continuing support to the enlarged inflamed LN, but the signals driving this process remain to be elucidated.

Methods: Mouse inguinal lymph nodes were isolated from WT-EAE, IL17RA-/- EAE, IL-17A-/- EAE and IL23R-/- -EAE mice and the numbers of CD45-gp38+CD31- FRCs were quantified by flow-cytometry and immunofluorescence. Moreover, RNA-sequencing analyses were performed in WT and IL17RA-/- FRC.

Results: Herein, we demonstrate that before leaving the LN in which they are activated, Th17 cells profoundly impact the stromal support network of the T cell zone through IL-17-mediated activation of FRC. We analyzed LN from IL-17-/- and IL17RA-/- mice immunized for EAE, and observed a defect in FRCs network in the absence of IL-17 signaling. Along with this, fibronectin expression, majorly produced by FRC, increased in dLNs during the progression of EAE with similar kinetics but delayed peak compared to IL-17. We demonstrate a critical requirement for IL-17 in successful expansion of LN FRC during Th17 responses. In absence of IL-17R signaling, FRC undergo cell cycle arrest and ultimately apoptosis, along with signs of nutrient stress including AMPK activation. Rather than directly promoting proliferation, IL-17 drove mitochondrial activity and increased glucose uptake by activated FRC. Enhanced glucose uptake in response to IL-17 was mediated through induction of transcriptional coactivator IB, which in turn regulated glut1 and Cpt1a.

Conclusion: Taken together, our data suggests that during priming of the immune response, and before migrating to their peripheral target tissue, Th17 cells modulate the local LN environment in which they are activated through production of IL-17 to promote FRCs expansion and induction of ECM, and uncover a previously unexplored role of IL-17 in boosting bio-energetic fitness of a stromal cell population. This could have long-term consequences in the host upon future infectious challenge, as well as influencing chronicity of Th17-mediated autoimmune disease.

19-B Poster: A comparative assessment of ultrasensitive HIV drug resistance NGS testing with and without unique molecular identifiers

Presenter: Kevin McCormick, Post-Doctoral Fellow
Infectious Diseases

Research Interest: Bench

Mentors: Urvi Parikh PhD
John Mellors MD

Funding Source: USAID

Authors: Kevin McCormick PhD, Kerri Penrose MS, Rahil Sethi MS, Jacob Waldman MS, Uma Chandran PhD, John Mellors MD, Urvi Parikh PhD

Introduction: Unique molecular identifiers (UMIs) are used in next-generation sequencing (NGS) HIV drug resistance genotyping to reduce sequence artifacts from polymerase fidelity error, PCR bias and PCR recombination from premature terminated products priming subsequent rounds of synthesis (Boltz et al., 2016; Keys et al., 2015). However, the UMI-based NGS library preparation and pipeline processing is complex and inefficient which limits its use for HIVDR surveillance in low-middle income countries using dried blood spots. Considering that more affordable approaches could be employed to overcome PCR artifacts, an assessment of the sensitivity of HIVDR NGS without UMIs is urgently needed to implement NGS for HIVDR surveillance.

Methods: Using a previously characterized wild-type: drug-resistant HIV mixture panel, we investigated the following three major NGS library preparation steps that are most likely to have significant impact on the sensitivity of NGS for detecting low frequency drug resistance mutations: (1) inefficient cDNA synthesis with primers that contain long UMI overhangs, (2) skewed allelic amplification from PCR bias and (3) recombination from PCR adapter addition without UMIs. The reverse transcription efficiency (cDNA yield) was assessed by reverse transcribing HIV RNA with a concentration gradient of cDNA primers and by quantifying total cDNA copies (qPCR). HIV mixture panel cDNA templates were divided into multiple PCR reactions to reduce the potential effects of skewed allelic amplification. Finally, we compared possible sequencing artifacts of the two methods for incorporating MiSeq adapters onto the HIV amplicon libraries -- linker-ligation and 2-round PCR addition.

Results: At the highest concentrations of RT primer, the cDNA efficiency was equivalent irrespective of primer-binding site polymorphisms or long UMI overhangs. We did not observe any evidence of skewed allelic amplification, and UMIs were not needed to detect mutants present at 0.5% frequency, whether or not samples were partitioned into multiple PCR reactions. We detected inter-template recombinants when MiSeq adapters were added onto libraries by PCR amplification, rather than by linker-ligation; however, this recombination did not affect the detection of low frequency drug-resistance mutations.

Conclusion: We successfully detected HIV drug resistance mutations present at 0.5% of the initial population of 50,000 starting virions in both the UMI- and non UMI-based NGS assays. The use of a non-UMI-based NGS assay may be a viable approach to overcome the greater complexity of library preparation and bioinformatics analysis required for UMI-based assays. Further studies are needed to define the accuracy of mutation detection across a range of plasma HIV RNA and HIV subtypes.

20-B Poster: Stress-induced adrenergic dysregulation alters neural-glial distribution and phenotype

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

Mentors: N/A **Funding Source:** AUA Urology Care Foundation Research Scholar Award

Authors: Bronagh McDonnell PhD, Aura Kullmann PhD, Amanda Wolf-Johnston PhD

Introduction: There is evidence (in patients and preclinical models) that stress can enhance painful sensations in patients with functional pain syndromes such as interstitial cystitis/bladder pain syndrome (IC/BPS). Though the underlying mechanisms have yet to be fully explored, findings reveal increased autonomic (sympathetic) dysregulation as well as a role for central augmentation. In this regard, activation of spinal cord (SC) glial cells can increase excitability of neurons leading to the initiation and maintenance of bladder hyperalgesia and impaired bladder storage function (urgency, frequency). Our goal was to examine whether chronic stress (using the water avoidance stress or WAS model) can alter neural-glial distribution and chemistry, which may play a role in micturition and pain behavior.

Methods: Adult female Wistar-Kyoto rats were exposed to WAS by placement on a pedestal in a water-filled container (1hr/day x10 consecutive days) versus handled controls. Previous published findings have revealed WAS rats exhibit long-lasting urinary frequency and hyperalgesia. SC (L6) were harvested from anesthetized animals, and either cryosectioned (for immunocytochemistry) or homogenized (for RT-PCR). The following were investigated: calcitonin gene- related peptide (CGRP; sensory fibers), microglia (IBA-1), Toll-like receptor (TLR-4), purinergic receptor subtypes (P2X4, P2X7). Separate groups of both WAS and control animals were treated 2 days prior then every other day with the adrenergic antagonist phenoxybenzamine (PB; 2 mg/kg i.p.) or saline, respectively.

Results: WAS increased neural CGRP (40%) and IBA-1 (2 fold) expression in the L6 SC dorsal horn and central canal (regions receiving input from nociceptive fibers). We find PB reduced CGRP expression (92% decrease) as well as IBA-1 in WAS SC. Further, both TLR-4 as well as P2X4 and P2X7 purinergic receptor are increased (50%) in WAS, suggesting microglia activation with chronic stress.

Conclusion: Taken together, our findings suggest increased communication between the sympathetic nervous system and bladder sensory neurons that may play an important role in chronic pain conditions. This includes abnormal neural sprouting and altered morphology and chemistry of SC glial cells, which are likely to play an important role in modifying neural activity resulting in changes in bladder function and sensory mechanisms.

21-B Poster: The E3 Ligase Subunit FBXL2 Is Required for Skeletal Myogenesis And Regulated by Inflammatory Stress That Indicates A Potential Role in Muscle Dysfunction in COPD

Presenter: Michael Emmet O'Brien, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Bench

Mentors: Jessca Bon MD
Rama Mallampalli MD

Funding Source: Supported by a Merit Review Award from the US Department

Authors: Michael Emmet O'Brien MD, James Londino PhD, Nathaniel Weathington MD, Bill Chen PhD, Jessica Bon MD, Rama Mallampalli MD

Introduction: Skeletal muscle atrophy is an important clinical finding in chronic obstructive pulmonary disease (COPD). Therapeutic interventions that compliment pulmonary rehabilitation are needed to increase muscle mass and improve exercise capacity for affected individuals. Activation and proliferation of skeletal muscle myoblasts is required during regenerative myogenesis. We have previously demonstrated that the E3 ligase subunit FBXL2 targets TNF receptor associated factor 6 (TRAF6), an important regulator of myoblast proliferation and differentiation, for ubiquitin proteasomal degradation. TRAF6 is a signal transducer of the nuclear factor kappa B (NF??B) pathway that is activated by steroid treatment, oxidative stress, and by a number of pro-inflammatory cytokines, including TNFa, which are common factors implicated in the development of peripheral muscle dysfunction in COPD. The molecular pathways involving FBXL2 signaling in skeletal muscle are unknown. The hypothesis of this study is that FBXL2 partakes in the regulation of skeletal myogenesis and is affected by inflammatory stress.

Methods: C2C12 myoblasts were allowed to differentiate into myotubes by transition to low serum media under control conditions or with TNFa for five days. Cells were lysed at time points 0 to 120 hours. Protein levels were normalized using the Lowry protocol and resolved on SDS PAGE gels for immunoblotting. The mRNA levels were determined in cell lysates following RNA isolation, cDNA synthesis, and quantification using qRT-PCR using the relevant primer sequences for the genes of interest. For siRNA knockdown, control or FBXL2 siRNA was transfected overnight, grown to confluence and differentiated for 48 hours for protein analysis or 120 hours for cell morphology evaluation. C2C12 myotube morphology was determined by immunofluorescence. Images were obtained at room temperature by confocal microscopy. Image levels were equally adjusted and analyzed using Fiji software.

Results: Protein and mRNA levels of FBXL2 are markedly upregulated during myoblast differentiation into myotubes. In the presence of TNFa, FBXL2 was decreased and there was associated impaired myotube formation. Knockdown of FBXL2 triggered reduced protein abundance of myogenic regulatory factors, decreased myosin, and increased TRAF6 with augmented downstream NFkB signaling. Visualization of myotube morphology following FBXL knockdown revealed an increase in total cell nuclei indicative of increased myoblast proliferation and markedly reduced myotube differentiation.

Conclusion: FBXL2 expression appears to be required during skeletal myogenesis. FBXL2 is rapidly upregulated during myogenic differentiation and decreased under conditions of inflammatory stress. Maintenance of FBXL2 production may have important implications for muscle regeneration in chronic inflammatory disorders such as COPD.

22-B Poster: STAT3 dependent mechanisms of regulation of effector Th17 cells

Presenter: Itay Raphael, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Mandy McGeachy PhD

Funding Source: T32

Authors: Itay Raphael PhD, Mandy McGeachy PhD

Introduction: Th17 cells are key drivers of many autoimmune inflammatory conditions as well as defense against fungal pathogens. Early differentiation and expansion of Th17 cells relies on STAT3-dependent signals of IL-6 and IL-21. Later IL-23-mediated signals are critical for gain of effector Th17 inflammatory functions, and these are presumed to be delivered through STAT3. Thus, drugs that target STAT3 signaling are a major research focus to alleviate disease. However, complete STAT3 deletion in T cells has not allowed distinction between early and late STAT3 requirements in Th17 cells and therefore STAT3 functions during the late effector phase remain elusive.

Methods: Here, we developed a model to study the effect of STAT3 deficiency specifically in effector Th17 cells, termed Th17ΔSTAT3. Importantly, Th17ΔSTAT3 cells are expressing a YFP reporter thus allowing us to specifically track their development and function in vivo. Using experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis in which disease development is dependent IL-23 and Th17 cells, we studied the effects of STAT3 depletion in late-effector Th17 cells. We employed several tools to study the molecular mechanisms regulated by STAT3 in Th17 cells, including transcriptome analysis and flow cytometry.

Results: Our data show that Th17ΔSTAT3 mice are resistant to development of EAE, revealing the importance of STAT3 signaling to Th17 cell pathogenicity in EAE. We found that the frequencies of Th17 cells are significantly reduced in Th17ΔSTAT3 mice, however the gene expression levels of cytokines and the ability of these cells to produce cytokines upon PMA/Ionomycin stimulation was not impaired. Strikingly however, Th17ΔSTAT3 cells have reduced IL-17 and GM-CSF expression, but not IFN-γ upon antigen-restimulation. Furthermore, we found that IL-23 signals via STAT3 to enhance IL-17 expression in effector cells. Bioinformatics analysis of the transcriptome of effector Th17 cells isolated from lymph nodes showed that STAT3 promotes cell cycle progression by regulating key cell cycle genes which are critical for G1 to S phase and G2 to M phase transition. These corresponded to a decreased Th17ΔSTAT3 cells in S phase and accumulation in G2 and M phase.

Conclusion: In Th17 cells, STAT3 regulates gene expression of cell cycle mediators but not cytokines or lineage specific genes. Thus, STAT3 is critical for Th17 cell cycle progression and potentially maintains specific cytokine expression via post-transcriptional mechanisms. These data reveal hitherto unknown mechanisms for STAT3 in regulating effector Th17 cells, which have major implications for use of STAT3-targeted therapies in autoimmune and inflammatory diseases.

23-B Poster: IL-23 and IL-1ß drive human Th17 cell differentiation and metabolic reprogramming in absence of CD28 costimulation

Presenter: Shankar Revu, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Mandy McGeachy PhD

Funding Source: RRF

Authors: Shankar Revu PhD, Jing Wu MD, Matthew Henkel MS, Natalie Rittenhouse BS, Ashley Menk BS, Greg Delgoffe PhD, Amanda Poholek PhD, Mandy McGeachy PhD

Introduction: Th17 cells are important for protection from extracellular bacterial and fungal pathogens as well as homeostasis of commensal microbes. However, Th17 cells are best known for driving autoimmune diseases, and anti-IL-17 is now approved for therapy of psoriasis and ankylosing spondylitis. Generation of in vitro Th17 cells requires multiple inducing cytokines, and has been notoriously difficult for human naïve T cells. CD28 is a critical co-stimulatory molecule for T cell activation and is routinely stimulated with CD3 in human T cell activation cultures.

Methods: Human CD4 naive T cells were cultured on plate bound anti-CD3 with IL-23 + IL-1ß and or TGFß to induce Th17 cells, in the presence or absence of anti-CD28. Cells were cultured for 5 or 7 days and analyzed by flow cytometry, qRT-PCR and RNAseq.

Results: CD28 costimulation suppressed differentiation of Th17 cells in a dose-dependent manner. Activation of T cells with anti-CD3 alone resulted in few proliferating CD45RO+ cells, which was partially compensated by Th17-inducing cytokines. Th17 cells generated without CD28 were not anergic, expressed previously described markers of long-lived Th17 cells including Tcf7 and Lef1, and maintained IL-17 production following rest and restimulation. Activation of naïve T cells in the presence or absence of CD28 and Th17-inducing cytokines resulted in distinct metabolic profiles and effector markers, and both of these cell types were pro-inflammatory but through different mechanisms. Mechanistically, partial but not complete blockade of Akt reversed the CD28-mediated suppression of Th17 differentiation, indicating Akt as a negative regulator of Th17 development.

Conclusion: Strong costimulatory signals through CD28-Akt inhibit development of Th17 cells. Despite lack of 'signal 2', Th17 cells generated in the absence of CD28 are not anergic, and exhibit a unique transcriptional profile suggesting that Th17-inducing cytokines compensate for activating effects of CD28. Together, these data provide new insight into mechanisms that regulate generation of human Th17 cells, and have implications for approaches to target Th17 in autoimmune disease.

24-B Poster: Transcriptional Profiling During Intra-abdominal Candidiasis Reveals Site-specific Host-pathogen Interactions

Presenter: Palash Samanta, Fellow
Infectious Diseases

Research Interest: Bench

Mentors: Hong Nguyen MD
Cornelius Clancy MD

Funding Source: N/A

Authors: Palash Samanta MD, Cornelius Clancy MD, Shaoji Cheng PhD, William Nierman PhD, Hong Nguyen MD

Introduction: Intra-abdominal Candidiasis (IAC) is a common form of invasive candidiasis, and encompasses two entities: peritonitis (P) and localized abscesses (A). To better understand the differences between host-pathogen interactions in these entities, we performed gene expression profiling during 3 phases of IAC: early P (within 30 min of infection), late P (24 h) and A (48 h)

Methods: Mice were infected by intra-peritoneal inoculation of C. albicans (CA) SC5314 + sterile stool. RNA was extracted with RiboPure Yeast kit and bead beater, and RNA-Seq performed using Illumina Miseq. Ribosomal genes were filtered. Gene expression was reported as RPKM. Differentially expressed genes were defined as =2-fold difference with FDR=0.01.

Results: CA and mouse total reads were =7 and =22 million, respectively. The 50 CA genes most highly expressed during early P were associated with response to the environment (pH and oxidative stress) and adhesion/hyphal growth to initiate invasive infection (ALS 3, HWP1, ECM331, SAP6). The corresponding 50 CA late P genes were associated with response to neutrophils (PMNs)/macrophages and nutrient acquisition (glyoxylate cycle, fatty acid b-oxidation, transporters and iron homeostasis). Responses within A included DNA damage and copper/iron metabolism, reflecting CA stress response and nutrient/metal limitation. The top 50 core gene responses for all 3 stages were associated with adhesion genes, stress response and glucose transport. Among the most up-regulated genes in late P and A compared with early P genes were those promoting antifungal drug resistance (CDR family, MDR1 and FLU1 and ERG family), although SC5314 is azole-susceptible and mice were not exposed to antifungals. The core murine responses for all 3 phases were PMN chemotaxis, PMN and myeloid differentiation, regulation of phagocytosis and inflammation, innate immune activation, and stress response. During late P, upregulated murine genes were associated with B and T cell proliferation and lymphoid organ development. In A, upregulated genes were associated with IFN-γ, TNF-a, cytokine response, H2O2 response and regulation of wound healing and platelet aggregation

Conclusion: Our IAC model enables genome-wide transcriptional analysis of CA and the host. Gene expression by CA and murine host changes with time and infectious niches. Upregulation of CA drug-resistance genes in late P and A suggests that in vivo stresses during IAC may attenuate azole responses, even in the absence of phenotypic resistance in vitro.

26-B Poster: Unfolded protein response and mitochondria crosstalk drives PINK1 downregulation and mitochondrial dysfunction in endothelial cells

Presenter: Lan Tu, Post-Doctoral Fellow
VMI

Research Interest: Bench

Mentors: Ana Mora MD

Funding Source: HL131789 and Vascular Medicine Institute

Authors: Lan Tu PhD, Marta Bueno PhD, Lauren Voltz BS, Ana Mora MD

Introduction: Mitochondrial dysfunction has been demonstrated as a key contributor to the development of pulmonary arterial hypertension (PAH). The crosstalk between mitochondria and endoplasmic reticulum (ER) is recognized, including the unfolded protein response (UPR) triggering changes in mitochondrial function. PINK1, one of the key regulators of mitochondrial homeostasis is transcriptionally repressed by activation of the UPR. Therefore, we examined how PINK1 deficiency and ER stress affects mitochondrial function in human pulmonary artery endothelial cells (PAECs) and smooth muscle cells (PASMCs).

Methods: PINK1 expression level was analyzed in isolated PAECs and PASMCs from PAH patients and healthy donors. PINK1 was then knocked down by siRNA in human primary PAECs and PASMCs cell lines. Mitochondrial respiration was compared between PINK1 deficient cells and control cells using the Seahorse extracellular flux analyzer. Cells were also treated with Tunicamycin to induce ER stress. Mitochondrial mass, membrane potential (MMP) and superoxide were measured by Mitotracker Deep red, Tetramethylrhodamine methyl ester (TMRM) and Mitosox respectively to compare the changes among different groups.

Results: ATF3, an ER stress-induced transcriptional repressor of PINK1, was highly upregulated and PINK1 expression was significantly reduced in PAECs but not in PASMCs of PAH patients compared to the control donors. In primary PAECs cell line, loss of PINK1 caused a significant decrease in mitochondrial maximal respiration and spare respiratory capacity, an increase in mitochondrial mass, and a decrease in MMP by 50%. In PASMCs, PINK1 deficiency did not affect mitochondrial respiration, but also caused an increase in mitochondrial mass and a decrease in MMP albeit to a smaller extent compared to the changes in PAECs. Gene expression analysis showed that similar to PAECs from PAH patients, Tunicamycin-treated PAECs upregulated ATF3 and severely downregulated PINK1 while no changes were observed in PASMCs. Tunicamycin-treated PAECs also showed a significant increase in mitochondrial mass and a reduction in MMP, similar to PINK1-deficient PAECs.

Conclusion: Unlike PASMCs, PAECs downregulated PINK1 in response to ER stress. Loss of PINK1 caused more severe mitochondrial dysfunctions in PAECs than in PASMCs, making PAECs more fragile and susceptible to further injuries. Hence, PINK1 deficiency in PAECs might increase the susceptibility to PAH.

27-B Poster: Effect of Myocardial Infarction on Insulin Resistance: Role of Macrophage Subsets

Presenter: Sathish Vasamsetti, Post-Doctoral Fellow VMI

Research Interest: Bench

Mentors: Partha Dutta PhD

Funding Source: NHLBI (4R00HL121076-03), VMI seed grant

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

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

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

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

Conclusion: Here we show that MI induced myelopoiesis promotes infiltration and accumulation of inflammatory CX3CR1+CCR2+ macrophages in VAT. Concomitantly, the loss of tissue resident anti-inflammatory CX3CR1-CCR2- VAT macrophages due to loss of M-CSF causes IR.

28-B Poster: The Fungal Toxin Candidalysin is a Feed-Forward Amplifier of Innate IL-17-Dependent Responses to Candida albicans

Presenter: Akash Verma, Post-Doctoral Fellow
Rheumatology and Clinical Immunology

Research Interest: Bench

Mentors: Sarah Gaffen PhD

Funding Source: NIH R01

Authors: Akash Verma PhD, Sarah Gaffen PhD

Introduction: Candida albicans is a dimorphic commensal fungus that causes severe oral infections in immunodeficient patients.Invasion of C. albicans hyphae into oral epithelium is an essential virulence trait. Interleukin-17 (IL-17) signaling is required for both innate and adaptive immunity to C. albicans.

Methods: Flow cytometry was used to assess immune cell populations in the tongue. Nur77-eGFP mice were used as a genetic tool to study TCR activity in tongue-resident T cells. Expression of genes induced during oral infection was quantified using RT-PCR.

Results: During the innate response, IL-17 is produced by gamma-delta T cells and a poorly understood population of innate-acting CD4+ alpha-beta T cell receptor (TCRab)+ cells, but only the TCRab+ cells expand during acute infection. Confirming the innate nature of these cells, the TCR was not detectably activated during the primary response, as evidenced by Nur77-eGFP mice that report antigen-specific signaling through the TCR. Rather, the expansion of innate TCRab+ cells was driven by both intrinsic and extrinsic IL-1R signaling. Unexpectedly, there was no requirement for CCR6/CCL20-dependent recruitment or prototypical fungal pattern recognition receptors. However, C. albicans mutants that cannot switch from yeast to hyphae showed impaired TCRab+ cell proliferation and Il17a expression. This prompted us to assess the role of candidalysin, a hyphal-associated peptide that damages oral epithelial cells and triggers production of inflammatory cytokines including IL-1. Candidalysin-deficient strains failed to up-regulate Il17a or drive the proliferation of innate TCRab+ cells. Moreover, candidalysin signaled synergistically with IL-17, which further augmented the expression of IL-1a/b and other cytokines.

Conclusion: IL-17 and C. albicans, via secreted candidalysin, amplify inflammation in a self-reinforcing feed-forward loop. These findings challenge the paradigm that hyphal formation per se is required for the oral innate response and demonstrate that establishment of IL-1– and IL-17–dependent innate immunity is induced by tissue-damaging hyphae.

29-B Poster: Epithelial sodium channel regulation by bile acids

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

Mentors: Ossama Kashlan PhD

Funding Source: R01 DK098204-02

Authors: Xue-Ping Wang PhD, Evan Ray MD, Ossama Kashlan PhD

Introduction: Bile acids are synthesized in the liver and secreted into the duodenum to emulsify dietary fat. The majority of bile acids are reabsorbed in the intestine and return to the liver via the enterohepatic circulation. Liver disease can lead to cholestasis, which blocks bile flow and results in dramatically elevated circulating bile acids and bilirubin. These patients often experience elevated total body Na+ with edema, and are treated with aldosterone antagonists. We hypothesized that elevated concentrations of bile components activate the epithelial Na+ channel (ENaC), a major aldosterone target, and increase Na+ retention in these patients. ENaC is found at the apical surface of Na+-transporting principal cells in the distal nephron of the kidney, and plays a critical role in maintaining Na+ homeostasis and blood pressure. ENaC is assembled from three homologous subunits (a, ß and γ) and its activity is regulated by intracellular and extracellular factors. It has been reported that bile acids modulate the function of both human and rat ENaC.

Methods: We measured whole-cell amiloride-sensitive currents before and after bile acids or conjugated bilirubin (c-bilirubin) perfusion in Xenopus oocytes expressing wild type mouse ENaCs and silent channels, which lack the furin cleavage sites in the a and γ subunits.

Results: We tested the ability of bile acids (deoxycholic acid (DCA), cholic acid (CA), tauro-cholic acid (t-CA), chenodeoxycholic acid (CDCA), hyodeoxycholic acid (HDCA), tauro-hyodeoxycholic acid (t-HDCA)) and conjugated bilirubin (c-bilirubin) to modulate mouse ENaC. Our data show that different bile acids have distinct effects on ENaC currents. DCA, CA, t-CA, and CDCA and c-bilirubin stimulated ENaC currents to various degrees with DCA having the strongest effect, whereas HDCA and t-HDCA slightly suppressed ENaC activity. These results indicated that the varying effects of bile acids most likely correlated with the position of the hydroxyl groups in the steroid skeleton rather than the solubility of bile acids. In addition, all the bile acids we tested and c-bilirubin dramatically enhanced the activity of uncleaved channels, which have low activity. We also found that DCA cannot activate highly-active, fully-cleaved channels after trypsin treatment, suggesting DCA affects ENaC by regulating its open probability.

Conclusion: Bile acids and c-bilirubin are amphipathic compounds. We propose that bile acids or c-bilirubin regulate ENaC activity by modulating channel's association with cell membrane, resulting in conformation changes in the channel's pore.

30-B Poster: Biotransformation of bile acids by the gut microbiota contributes to the high risk of colorectal cancer in Alaska Native people

Presenter: Annette Wilson, Post-Doctoral Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Bench

Mentors: Stephen O'Keefe MBBS, MD, MSc, MRCS, FRCP

Funding Source: N/A

Authors: Annette Wilson PhD, Soren Ocvirk PhD, James DeLany PhD, Kathryn Koller , Christie Flanagan , Flora Sapp , Gretchen Day BSc, Peter Holck , Barbara Methe PhD, Alison Morris MD, Jia Li PhD, James Kinross MD, Jeremy Nicholson MD, Timothy Thomas MD, Stephen O'Keefe MBBS, MD, MSc, MRCS, FRCP

Introduction: Alaska Native (AN) people have the highest recorded incidence for colorectal cancer (CRC) (~100:100,000). In contrast, rural African (RA) people were shown to have the lowest risk for CRC (<5:100,000). Sporadic CRC is predominantly driven by environmental factors, particularly diet. A high consumption of fat is suggested to promote CRC risk by stimulating hepatic synthesis of bile acids (BA) and their delivery to the colon, where they undergo conversion by the microbiota to secondary BA that show tumorigenic activity, especially deoxycholic acid (DCA). Since the traditional diet of AN people is rich in fat, we investigated how high-fat consumption shapes the BA pool and metabolic functions of the gut microbiota, which may collectively promote CRC risk in AN people, and compared it to RA people who have a low-fat diet.

Methods: We collected fecal samples from 32 AN and 21 RA healthy 40-65 year old volunteers. The fecal BA pool was analyzed using LC-MS and abundance of 7a-dehydroxylating bacteria in fecal microbiota was assessed by qPCR. 16S rRNA sequencing was performed to analyze the fecal microbiome.

Results: Fecal levels of all major (un-)conjugated primary and secondary BA were significantly increased in AN in comparison to RA participants. AN participants exhibited a more than two-fold increase of tumor-promoting DCA in feces compared to RA (26.73 vs. 11.00 µmol/g feces; $p<0.01$). This was associated with significantly increased abundance of 7a-dehydroxylating bacteria in AN fecal samples (61 gene copies per 20ng DNA vs. below detection limit; $p<0.001$). The gut microbiota of AN participants showed an overall reduced diversity, but was enriched for the genus Blautia, which includes species closely linked to 7a-dehydroxylating bacteria detected in humans. Consistently, genera that cover species expressing bile salt hydrolases, involved in deconjugation of BA, were more abundant in AN fecal samples. In contrast, Prevotella and Ruminococcus were the dominant genera present in RA fecal microbiota.

Conclusion: A high-fat diet promotes changes in the BA pool, which are mediated by the gut microbiota and impact on their metabolic capacities for BA biotransformation. These interactions between diet, BA and the microbiota create a colonic environment with tumor-promoting activity, which may contribute to the high rate of CRC in AN people.

32-B Poster: CamKII exacerbates heart failure progression through activation of class I HDAC signaling

Presenter: Manling Zhang, Fellow
Cardiology

Research Interest: Bench

Mentors: Ning Feng MD
Iain Scott PhD

Funding Source: K08

Authors: Manling Zhang MD, Elizabeth Luczak PhD, Jonathan Granger BS, Mark Anderson MD, Ning Feng MD

Introduction: Persistent cardiac Ca2+/calmodulin dependent Kinase II (CaMKII) activation plays an essential role in heart failure development. The molecular mechanisms of CaMKII activation induced heart failure progression are still poorly understood. It is pivotal to understand the mechanisms and develop new mechanisms based therapeutic strategies. Histone deacetylases (HDACs) are critical for transcriptional genes reprogramming leading to adverse ventricular remodeling. Class I HDACs including HDAC 1, HDAC2 and HDAC3 promote pathological cardiac hypertrophy whereas class IIa HDACs suppress cardiac hypertrophy. It is known that CaMKII deactivates class IIa HDACs to promote cardiac hypertrophy, however, it is unknown whether CaMKII also regulates class I HDACs in heart failure development.

Methods: Combined with results session.

Results: In vitro assay shows CaMKII directly phosphorylates recombinant HDAC1 protein and increases its deacetylase activity by three-fold. HDAC1 activity is also increased in cardiac specific CaMKII transgenic mice (CaMKII-TG). Mass spec study reveals serine 395 of HDAC1 is the CaMKII phosphorylation site. Beyond direct phosphorylation, CaMKII also increases HDAC1 expression. In cultured rat neonatal cardiac myocytes (RNCM), overexpression of CaMKII markedly increases HDAC1 expression, and this CaMKII induced HDAC1 upregulation is mediated through JNK pathway as JNK inhibitor blunts this upregulation. HDAC1 expression is also significantly increased in CaMKII-TG mice. Consistently, the expression of HDAC1 is increased in failing hearts induced by myocardial infarction, and this upregulation is attenuated in cardiac specific CaMKII inhibitory peptide transgenic mice. Importantly, HDAC1 specific inhibitor prevents CaMKII overexpression induced NRVM hypertrophy, and administration of HDAC1 inhibitor in CaMKII-TG mice significantly slow down cardiac function deterioration. In addition, CaMKII does not only regulates HDAC1, but also HDAC2 and HDAC3. CaMKII also directly increases HDAC2 and HDAC3 deacetylase activity and their expression.

Conclusion: CaMKII activates class I HDACs in heart failure by increasing their activity and expression, and this CaMKII/class I HDACs axis is one of the key mechanisms of CaMKII induced heart failure progression. Our findings suggest class I HDAC inhibitors, which are already in clinical use for cancer therapy, could be a promising novel therapeutic avenue for heart failure treatment.

33-B Poster: Association of sleep apnea severity with mortality in CKD and ESRD patients

Presenter: Hossam Abdalla, Fellow
Renal-Electrolyte

Research Interest: Clinical

Mentors: Manisha Jhamb MD

Funding Source: N/A

Authors: Hossam Abdalla MD, Manisha Jhamb MD

Introduction: Association of severity of sleep apnea with mortality has been well studied in the general population but there is limited evidence on this in the chronic and end stage kidney disease patients. Our study investigates the association of sleep apnea severity with mortality in advanced chronic and end stage kidney disease patients.

Methods: 180 patients (87 CKD stage 4-5, 93 ESRD) underwent 1 night at-home polysomnography. Sleep apnea severity was assessed using apnea hypopnea index. Information on patients' demographics, comorbidities and laboratory values was obtained from patient interviews and chart review. Morality data until Dec 31, 2016 was obtained from National Death Index. Transplant status was determined through chart review. Chi-square and ANOVA were used to test between group differences and Cox proportional hazard model was employed to test association with mortality.

Results: Among 180 patients (mean age 53.9 years, 62.8%% males, 65.6% white, 38.8% diabetics, 51.1% of the patients had ESRD and 48.9% had CKD), 71% of the patients had sleep apnea (AHI =5) and 23% of the patients had severe sleep apnea (AHI>30). Over a mean follow up period of 9.37 years, there were a total of 31 deaths and 60 Kidney transplants. In both unadjusted and adjusted analyses (adjusted for age, sex, race, diabetes, kidney transplant status and CKD vs ESRD), there was no association between sleep apnea severity and all cause mortality.

Conclusion: Our study shows that sleep apnea severity is not associated with increased mortality in advanced chronic and end stage kidney disease patients.

34-B Poster: Retrospective Observational Study of Patients with Native Septic Arthritis and the Effect of Microbiological Screening at UPMC Presbyterian & Montefiore Hospitals

Presenter: Mostafa Alfishawy, Fellow
Infectious Diseases

Research Interest: Clinical

Mentors: Neel Shah MD
Mohamed Yassin MD

Funding Source: N/A

Authors: Mostafa Alfishawy MD, Neel Shah MD, Mohamed Yassin MD, Kenneth Urish MD, Karin Byers MD

Introduction: Septic arthritis is a medical emergency, and delayed management can result in significant rates of morbidity and even mortality. Appropriate antibiotic therapy depends on identifying the causative pathogens involved. However, empiric antibiotic therapy is often initiated based on generalized epidemiological data, rather than data associated specifically with joint cultures. Of note, no recent epidemiological study describing the characteristics of offending pathogens involving joints has been systematically performed.

Methods: Our goal in this study was to assess the most commonly isolated pathogens involving all native septic arthritis patients in order to determine the rate and prevalence of various pathogens associated with septic arthritis, as well as determine which patient populations were at higher risk of these pathogens. It is hoped that this data could in turn help with preadmission screening and help guide more specific empiric treatment for both immunocompetent as well as immunocompromised hosts who present with septic arthritis.

Results: All patients with either positive synovial fluid cultures or had the diagnosis of septic arthritis between January 2012 to December 2016 at UPMC Presbyterian & Montefiore Hospitals were retrospectively evaluated. The patients' clinical and epidemiological characteristics, the microorganisms that caused the infection and the patients' treatment and evolution as well as prehospital screening cultures were analyzed.

Conclusion: More than half of the patients had concomitant positive blood cultures with almost half of those with infective endocarditis. Staphylococcus aureus remains the most common pathogen for native septic arthritis. Mortality remains around 12 %. No significant correlation was found between MRSA screening and isolated Staphylococcus aureus strain. Providers should not base their therapeutic regimen based on MRSA screen.

36-B Poster: Same Day Discharge After Inpatient Percutaneous Coronary Intervention: A Report from the Nationwide Readmission Database

Presenter: Amr Barakat, Fellow Cardiology

Research Interest: Clinical

Mentors: Samir Saba MD

Funding Source: N/A

Authors: Amr Barakat MD, Ahmed Mahmoud MD, Raed Al Adham MD, Garret Brown MD, Michael Genuardi MD, Ahmad Masri MD

Introduction: Safety of same day discharge (SDD) following inpatient percutaneous coronary intervention (PCI) is unknown, thus it is poorly adopted. We sought to determine the prevalence, 30-day outcomes and cost of SDD vs. next day discharge (NDD) following inpatient PCI.

Methods: All PCI records were analyzed using the 2014 Nationwide Readmission Database. SDD was defined as having same day of procedure and discharge and NDD as difference of 1 day. Patients with STEMI and cardiogenic shock were excluded. The primary outcome was all-cause 30-day readmission. Secondary outcomes were 30-day readmission with acute myocardial infarction (AMI), stroke, MACE (major acute cardiovascular events), acute kidney injury (AKI), bleeding, and death. A multivariable hierarchical Cox proportional hazard model and 1:2 propensity score matching were adopted.

Results: We included 137,329 patients. SDD prevalence was 3.1%. The incidence of all-cause 30-day readmission was not statistically different in both groups (7.9% in SDD vs 8.9% in NDD; p=0.17). Results were similar in multivariate model (HR adjusted 0.96, 95% CI 0.83-1.12, P=0.63) and propensity score matching (HR 0.93, 95% CI 0.76-1.14, P=0.50). The incidence of AMI, stroke, MACE, AKI, bleeding and death during readmission were statistically not different in SDD vs NDD (all p>0.05). SDD was associated with lower median cost at the index admission (cost saving of 714$, p<0.01).

Conclusion: SDD utilization after inpatient PCI remains low, is associated with similar rates of 30-day all-cause readmission, and with a lower index hospitalization cost. These results could guide implementing SDD protocol following inpatient PCI in a similar patient population.

37-B Poster: A Risk Model to Identify Stable Patients with High Risk Coronary Artery Disease Anatomy

Presenter: Amr Barakat, Fellow Cardiology

Research Interest: Clinical

Mentors: Samir Saba MD

Funding Source: N/A

Authors: Amr Barakat MD, Bhuvnesh Aggarwal MD, Lei Kou MA, Ram Amuthan MD, Benico Barzilai MD, Wael Jaber MD, Stephen Ellis MD, Michael Rothberg MD

Introduction: In stable coronary artery disease (CAD) patients, revascularization reduces the risk of death, stroke or myocardial infarction only for left main (LM), 3-vessel (3V) CAD and selected patients with proximal left anterior descending artery (pLAD) disease. The accuracy of stress test variables alone in predicting the extent of CAD remains poor. We developed a risk prediction model based on patients' clinical characteristics and stress test variables to identify those with LM/3V CAD, who are likely to benefit from subsequent coronary angiography.

Methods: Our dataset included information on all patients who underwent non-invasive exercise stress testing followed by coronary angiography at Cleveland Clinic between 2005 and 2014. Using LM/3V/pLAD disease as our outcome, clinical and stress test predictors were related to the outcome in a multivariable logistic regression model with an entry p-value of 0.05. The model selection was then conducted to achieve the highest C-index. The predictive performance of the final model was evaluated with the receiver operating characteristics (ROC) curve. Bootstrap validation was performed with a bootstrap size of 1000 to compute the optimism-corrected C-statistic.

Results: Of 4,354 patients in the dataset, 345 (8%) had LM/3V/pLAD disease on coronary angiography. In the final multivariable model, 5 clinical variables (age, sex, hypercholesterolemia, diabetes and typical angina) and 3 stress test variables (total exercise time, chronotropic response index [CRI] and Duke Treadmill score [DTS]) were associated with the outcome. The strongest predictors of LM/3V CAD were DTS <-10 (OR 4.9), diabetes (OR 1.66) and age (OR 1.44, per 10-year increase), while the most protective variables were female sex (OR 0.14) and CRI =0.8 (OR 0.55). The model had a corrected C-statistic of 0.81; 56% of the patients had a predicted risk of LM/3V/pLAD disease of <5%.

Conclusion: In stable patients, a multivariable model based on clinical characteristics and exercise stress test variables was able to identify those at low risk of LM/3V/pLAD CAD, who could be treated medically without undergoing catheterization. After further validation, use of a similar model could help reduce coronary angiography in stable patients with low risk coronary anatomy.

38-B Poster: Stepping It Up: The Use of Physical Activity Monitors as an Outcome Measure in Juvenile Myositis

Presenter: Emily Brunner, Fellow
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Rohit Aggarwal MD
Chester Oddis MD
Kathryn Torok MD

Funding Source: CureJM

Authors: Emily Brunner DO, Laura Tasan MD, Kathryn Torok MD, Kimberly Francis MS, Emily Mirizio BS, Kaila Schollaert-Fitch MA, Chester Oddis MD, Rohit Aggarwal MD

Introduction: Juvenile myositis (JM) is a rare autoimmune disease featuring muscle weakness and impaired physical function. Robust, objective and continuous functional assessments should supplement currently validated core set measures (CSM) as established by Pediatric Rheumatology International Trials Organization (PRINTO) and International Myositis Assessment and Clinical Studies Group (IMACS). Use of physical activity monitors (PAM), which effectively quantify movement, may enhance assessment of physical function and complement current CSM. We examined the use of a commercially available PAM device, Fitbit® One, as an outcome measures in JM patients.

Methods: JM patients age 5-17 years were enrolled from rheumatology clinics. The following evaluations were performed at baseline, 1, 3 and 6 months: a) PRINTO and IMACS CSM including Manual Muscle Testing (MMT) and Childhood Myositis Assessment Scale (CMAS), b) Patient-Reported Outcome (PRO) Measurement Information System Mobility Short Form (PROMIS-SF) and Childhood Health Assessment Questionnaire (CHAQ), and c) office functional tests: Sit-to-Stand (STS), Timed Up and Go (TUG) and Six Minute Walk Distance (6MWD). Fitbit® One was worn for 7 consecutive days monthly for 6 months and average daily step counts (ADSC) were assessed. Spearman's correlation coefficient was used to associate Fitbit® ADSC with IMACS and PRINTO CSM, PROs and functional tests. The ability of Fitbit® ADSC to differentiate between the active vs. stable JM patients was assessed.

Results: As data collection is ongoing, the following results represents baseline cross-sectional analysis. Of the target 25 JM patients, 17 were enrolled, including 5 active and 12 stable, 76% female, 94% White with mean (SD) age of 11.5 years (3.4). The median values of Fitbit® ADSC differentiated between active vs. stable patients [4197.5 (IQR 3415.5–5744) vs. 7135 (IQR 5460-8863)]. Most other CSM and physical functional tests were different between active vs. stable patients at baseline. P values were not calculated due to small sample size. Spearman's correlation analyses demonstrated a moderate to strong correlation between Fitbit® ADSC and MMT (Rho: 0.76, p=0.002), patient/parent global (Rho: -0.49, p=0.07), PROMIS-SF (Rho: 0.49, p=0.08) and CHAQ (Rho: 0.68, p=0.007), but not with CMAS, MD Global, and functional tests including STS, TUG and 6MWD.

Conclusion: Fitbit® ADSC had moderate to strong correlation with key JM CSM except CMAS, supporting further study of the Fitbit® ADSC as an outcome measures in JM. Continued analysis of longitudinal data will help to determine the utility of a commercially available PAM as an outcome measure in JM.

39-B Poster: LOW VISCERAL ADIPOSE TISSUE MASS IS ASSOCIATED WITH DECREASED TRANSPLANT-FREE SURVIVAL IN END-STAGE LIVER DISEASE.

Presenter: Preethi Chintamaneni, Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Vikrant Rachakonda MD

Funding Source: N/A

Authors: Preethi Chintamaneni MD, Vikrant Rachakonda MD, Amir Borhani MD, Amit Tevar MD, Christopher Buros MD

Introduction: While previous studies have suggested that sarcopenia predicts mortality in end-stage liver disease (ESLD), the impact of adipose tissue remains poorly understood. Abdominal CT scans obtained for routine evaluation of cirrhotic patients are increasingly utilized for body composition assessment. Our aim was to determine the effect of visceral adipose mass on 1-year transplant-free survival in ESLD.

Methods: We obtained clinical and demographic data from cirrhotic patients at time of initial listing for liver transplant between August 2010 and July 2016. Inclusion criteria included availability of abdominal CT scans within 3 months of listing. Exclusion criteria included patients listed for multiple organ transplantation, acute liver failure, and noncirrhotic liver disease. Patients with hepatocellular carcinoma or prior solid organ transplants as well as recipients of living donor liver transplants were excluded. From CT images at the L3 paraspinal level, visceral fat (VFI) and skeletal muscle indices (SMI) were obtained from respective cross-sectional areas normalized to height (cm2/m2). SMI and VAFI were then stratified by gender-specific median cutoffs. Kaplan-Meier analysis and Cox proportional hazards models were used to determine the effect of body composition on 1-year transplant-free survival. P <0.05 was considered statistically significant.

Results: 126 out of 334 potential subjects met study inclusion criteria. Median age was 56 years (IQR 49-61 years), and 39.7% were women. Within one year of listing, 35.7% of listed candidates were alive, 30.2% were transplanted, and 34.1% were removed from listing or deceased. Waitlist candidates alive at 1 year had lower MELD-Sodium [18 (IQR 16-21) vs. 27 (IQR 22-34), p<0.0001] and higher hemoglobin [11.9 (IQR 10.6-13.0) g/dl vs. 9.9 (8.9-11.6) g/dl, p=0.0002]; there were no differences in baseline albumin, WBC or platelets. In men, median SMI was 47.6 cm2/m2 (IQR 40.8 – 50.9) cm2/m2, and median VFI was 27.2 cm2/m2 (IQR 15.5-51.3 cm2/m2). In women, median SMI was 36.9 cm2/m2 (IQR 32.3-42.6) cm2/m2), and VFI was 27.8 cm2/m2 (IQR 16.5-39.4 cm2/m2). In univariate analysis, only low VFI, hemoglobin, and MELD-Sodium exhibited significant hazards ratios for reduced transplant-free survival. In multivariate models adjust for age and low SMI, only low VFI [HR 1.93 (95% CI 1.23-3.02), p=0.004] and MELD-Sodium [HR 1.19 (95% CI 1.14-1.23), p<0.001] were associated with reduced transplant-free survival at 1 year.

Conclusion: Reduced visceral adipose tissue mass, but not skeletal muscle mass, is associated with decreased 1-year transplant-free survival in cirrhotic waitlisted patients. These findings suggest a role for adipose tissue depletion as a driver of malnutrition and mortality in cirrhotic transplant candidates.

40-B Poster: Cardiac MRI native T1 time and extracellular volume fraction, but not myocardial strain, associate with pediatric heart transplant acute rejection.

Presenter: Adam Christopher, Fellow Cardiology

Research Interest: Clinical

Mentors: Timothy Wong MD

Funding Source: N/A

Authors: Adam Christopher MD, Mark Kennedy , Susan Miller MD, Erik Schelbert MD, Peter Kellman PhD, Brian Feingold MD, Timothy Wong MD

Introduction: Noninvasive characterization of transplant graft status is of interest to risk-stratify patients for endomyocardial biopsy (EMB). In healthy pediatric heart transplant (PHT) recipients without acute rejection (AR), cardiac MRI (CMR) extracellular volume fraction (ECV) represents diffuse myocardial fibrosis. In the setting of AR, native T1 and ECV also rise due to myocardial edema. Myocardial strain may identify AR as well. We sought to compare the association of native T1, ECV, and myocardial strain (longitudinal and circumferential) in PHT recipients undergoing EMB and research CMR with the hypothesis of higher T1 times, higher ECV, and abnormal strain in acute rejection.

Methods: After informed consent, PHT recipients = 13 years of age and = 9 months post-transplant underwent CMR with gadolinium contrast on a 1.5T CMR (Siemens) within 24 hours prior to EMB. In addition to routine CMR of the left ventricle, T1 mapping and hematocrit were used to obtain native T1 time and ECV. Circle42 (Circle CV Imaging, Canada) derived strain from standard SSFP cine imaging. T-test and ANOVA compared groups.

Results: PHT recipients (n=29, mean age 18.4 ± 5.3 years) were compared to 12 healthy young adult controls. Among PHT recipients, 9 (31%) had EMB rejection grades 1R-2R (old grades 1A-3A), none with heart failure symptoms or hemodynamic compromise. There was no difference in LVEF or mass between recipients and controls. However, mean native T1 times and ECV were higher among PHT recipients with versus without AR (1054.9 ms and 28.2% vs. 1013.5 ms and 23.8%, respectively; $p < 0.002$). Neither strain measure differed by AR status. Application of a native T1 time of 1025ms and ECV 26% provides 100% sensitivity and 90.9% specificity for AR which when applied to our cohort would spare 20 patients from EMB with only 3 false positives.

Conclusion: Elevated native T1 time and ECV in PHT recipients are associated with grade 1R-2R AR by EMB, whereas myocardial strain did not discriminate. These data suggest combined T1 and ECV values identified by CMR prior to invasive EMB can predict likelihood of AR. ECV-guided decision-making in PHT rejection surveillance may be feasible should larger studies confirm these findings.

41-B Poster: The Impact of an Inflammatory Bowel Disease Specialty Medical Home on Healthcare Utilization, Disease Activity, Mental Health, and Quality of Life

Presenter: Benjamin Click, Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Miguel Regueiro MD
Eva Szigethy MD

Funding Source: T32

Authors: Benjamin Click MD, Alyce Anderson PhD, William Shrank MD, Jane Kogan PhD, Sandra McAnallen , Eva Szigethy MD, Miguel Regueiro MD

Introduction: Specialty medical homes (SMH) are a new model of healthcare delivery utilizing multidisciplinary team care, with a specialist managing a chronic disease patient population. As part of a large integrated payer-provider network, we formed an inflammatory bowel diseases (IBD) SMH and investigated the impact of the IBD SMH on healthcare utilization, disease activity, and quality of life (QoL). We also aimed to identify factors associated with continued healthcare utilization during IBD SMH treatment.

Methods: Launched in July 2015, patients enrolled in the IBD SMH with at least one year of follow-up were evaluated for changes in rates of emergency department (ED) visits and hospitalizations in the year prior to and following SMH enrollment. All episodes of inpatient hospitalization and emergency department visits including external health system utilization were obtained from the electronic medical record. Secondary measures evaluated for change from enrollment included IBD activity assessments, mental health metrics, and QoL. We performed multivariate logistic regression to determine baseline factors associated with unplanned care in year 1 of IBD SMH.

Results: There were 322 patients enrolled who met inclusion criteria (58% female, mean age 34.6 years, 62% Crohn's disease, and 32% prior IBD surgery). Compared to the year before enrollment, there was a 47.3% ($p<0.0001$) reduction in emergency department visits and 35.9% ($p=0.008$) in hospitalizations. There were significant improvements in disease activity scores (median Harvey Bradshaw Index 4 to 3.5, $p=0.002$; median Ulcerative Colitis Activity Index 4 to 3, $p=0.0003$), depression metrics (median Patient Health Questionnaire-9 6 to 5, $p<0.0001$), and QoL (median short inflammatory bowel disease questionnaire 50 to 51.8, $p<0.0001$). The most extreme quartiles demonstrated the most improvement. On multivariable regression, corticosteroids (odds ratio [OR] 2.72; 95% confidence interval [CI]1.32-5.66; $p=0.007$), opioids (OR 3.20; 95% CI 1.32-7.78; $p=0.01$), and low QoL (OR 4.44; 95% CI 1.08-18.25; $p=0.04$) at enrollment were significant predictors of persistent healthcare utilization.

Conclusion: Implementation of an IBD SMH resulted in significant reduction in one year unplanned care and improvement in disease activity, mental health metrics, and QoL. Patients with ongoing corticosteroid requirement, opiate pain management, and low QoL at enrollment are at increased risk of unplanned healthcare utilization in the first year. Further evaluation of the long-term, financial impact will help determine the full utility of this alternative healthcare model.

42-B Poster: The Impact of Serum Cortisol on Quality of Life and Dysautonomia in Inflammatory Bowel Disease

Presenter: Benjamin Click, Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: David Binion MD

Funding Source: T32

Authors: Benjamin Click MD, Claudia Ramos Rivers MD, David Binion MD

Introduction: While commonly discussed clinically, few studies have examined characteristics of serum cortisol and adrenal function in inflammatory bowel disease (IBD). We aimed to describe the patterns in serum cortisol levels, prevalence of adrenal insufficiency, and clinical outcomes in a large IBD population.

Methods: We performed a retrospective analysis of a consented, prospective, natural history IBD registry at a tertiary hospital that employs routine systematic testing for serum cortisol as standard outpatient clinical care. Patients with at least one low (< 2 ug/dl per lab reference) were categorized as low cortisol. Further evaluation, characterization, and treatment of cortisol levels was clinically driven. We compared demographics, disease characteristics, disease activity metrics, healthcare utilization, surgery, and quality of life (QoL) by cortisol status. Multiple linear regression of QoL scores and cortisol status was performed to control for confounding. Quality of life was assessed by Short Inflammatory Bowel Disease Questionnaire and dysautonomia was defined by a COMPASS-31 score >32.

Results: A total of 1743 patients (65% Crohn's disease, mean age 45.9 yrs, 52.7% female) amassed 6933 cortisol levels between 2009-2016, of which 385 (5.5%) were below normal in 240 (13.8%) individuals. A quarter (25.4%) of low cortisol patients had deficient cortisol levels in more than one year (range 1-5 yrs). The annual incidence of low cortisol levels ranged 5.4-8.0%. Only 19 patients (1.1% total, 7.9% low cortisol) had confirmed adrenal insufficiency, the majority (68%) of which was chronic (>6 mo). The most common cause was exogenous corticosteroid use (n=17, 88%). Low cortisol levels were significantly associated with active disease, steroid requirement, and worse quality of life during the study period (Table 1). However, on multivariable regression modeling controlling for disease activity, IBD medications including steroids, narcotic use, hospitalization, and surgery, low cortisol levels remained significantly associated with low quality of life (coefficient -4.35, $p<0.0001$; Table 2). Each year with low cortisol conferred a 2.4-point reduction in SIBDQ ($p<0.0001$). Furthermore, patients with low serum cortisol had significantly higher rates of dysautonomia in Crohn's (33.7% vs. 17.4%, $p=0.001$; Table 1).

Conclusion: Despite the majority of IBD patients being exposed to steroids, chronic adrenal insufficiency remains relatively infrequent. Low serum cortisol is associated with active disease and steroid requirement, but remains independently associated with worse quality of life. Dysfunctional autonomic nervous system may contribute to the suppressed adrenocortical axis in these patients. Further research into the implications of low cortisol in IBD are needed.

43-B Poster: OPTIFAST® Medical Weight Loss Program – Outcomes in the Endocrinology Clinics at University of Pittsburgh Medical Center (UPMC)

Presenter: Karla Detoya, Fellow
Endocrinology and Metabolism

Research Interest: Clinical

Mentors: David Rometo MD

Authors: Karla Detoya MD, David Rometo MD

Funding Source: N/A

Introduction: The OPTIFAST® program uses full meal replacement from nutritionally balanced, low calorie products by Nestle Corporation. At UPMC, the medically supervised program using OPTIFAST® focuses on an initial very low calorie diet (VLCD, ~800 kcal/day), nutrition counseling, emphasizing lifestyle and behavior modification, and transition to a maintenance low glycemic load whole food diet to maximize and sustain glycemic benefits of the weight loss. There are no published data on the efficacy of this specific program.

Methods: We evaluated the impact of our program on weight reduction in a 3-year (2014-2016) period at UPMC Endocrinology clinics, and secondary parameters defining cardiovascular risk factors (HBA1C, lipid panel and systolic blood pressure (SBP) measurements). Patients were divided into Completer (C) and Non-Completer (NC) cohorts, based on level of participation. The C-group completed the program from active weight loss phase (VLCD meal replacements x12 weeks) to transition phase (shift to self-prepared regular food) and to maintenance phase; the NC group did not complete these phases. For the C-group, HBA1C for diabetic patients, lipid profile values and SBP for all patients were compared at baseline and at >5 months. Analysis included difference between no. of insulin and non-insulin diabetic agents and no. of lipid-lowering and BP drugs at baseline and >5 months.

Results: A total of 100 patients (mean age=50.48, 70% female) had mean baseline and end weights of 260.8 and 225.8 lbs respectively, with significant 13.77% weight loss ($p=0.0002$). 44% completed the program; 56% did not. The C-group had 17.86% weight loss ($p<0.0001$). For the NC-group, weight difference from baseline was not significant.For the C-group, there was decrease in baseline HBA1C among diabetics from 8.133% to 6.1722% at >5 months ($p=0.0002$). The difference in mean baseline and >5 months SBP of 133.6 mmHg and SBP of 126.5 mmHg was significant ($p=0.0325$). There was a decrease from mean baseline to end values of total cholesterol, LDL and triglycerides, and an increase from baseline to end HDL, but these results were not significant.

Conclusion: The medically supervised VLCD program at UPMC Endocrinology clinics promotes significant weight loss, and results are greatest with patients who complete the program. For completers, there is significant glycemic (among diabetics) and SBP improvement (for all) over >5 months, but more patient data is needed to adjust for effect of DM and BP medications. There was no significant difference in lipid profiles over >5 months.

44-B Poster: Suitability of Transcatheter Mitral Valve Replacement in Patients with Significant Mitral Regurgitation After Transcatheter Aortic Valve Replacement

Presenter: Hesham Elzomor, Post-Doctoral Fellow Cardiology

Research Interest: Clinical

Mentors: João L. Cavalcante MD

Funding Source: N/A

Authors: Hesham Elzomor MD, Miho Fukui MD, Islam Abdelkarim MD, Michael Sharbaugh MPH, Andrew Althouse PhD, Dustin Kliner MD, Joon S. Lee MD, John T. Schindler MD, Thomas G. Gleason MD, João L Cavalcante MD

Introduction: Transcatheter aortic valve replacement (TAVR) has become the alternative to surgical aortic valve replacement (SAVR) in moderate to high risk patients with severe aortic stenosis (AS). Concomitant moderate to severe mitral regurgitation (MR) is a commonly seen in patients undergoing TAVR, an importantly shown to increase early and late mortality after TAVR. Cardiac computed tomography angiography (CCTA) allows for comprehensive imaging of mitral annulus and valve complex as well as suitability for Transcatheter Mitral Valve Replacement (TMVR). We sought to evaluate whether the suitability of TMVR in patients with persistent MR 1-month after TAVR.

Methods: Consecutive patients underwent TAVR at University of Pittsburgh Medical Center between July 2011 and January 2017 were included, comprehensive transthoracic echocardiography (TTE) studies pre TAVR and after one month were retrospectively evaluated at our core lab using quantitative assessment of MR severity (Mitral Valve Effective Regurgitant Orifice Area, PISA and Regurgitant Volume) in addition to other consequences of MR (Left atrium volume, Pulmonary artery pressure (PAP), pulmonary venous flow (PVF) pattern) to calculate the Mitral Regurgitation Index (MR Index). Available pre-TAVR CCTA images were analyzed for suitability of TMVR while accounting for annular diameter, distribution of mitral annular calcification and neo-left ventricular outflow tract area.

Results: Among 728 patients undergoing TAVR, 95 patients had moderate to severe MR (13 %) at the time of TAVR. Mean age 83±7 years, STS-PROM 6.6%, LVEF 59 ± 10%, aortic valve area 0.66 ± 0.15 cm2, mean aortic valve gradient 50±14 mmHg. Twenty-five TAVR patients with severe MR at baseline had adequate CCTA for TMVR analysis. At 1-month, 6/25 (24%) patients had severe MR, 16 moderate MR and 2 mild MR. Suitability of TMVR was present in 5/6 patients with severe MR, with mean neoLVOT area of 4.74 ± 1.92 cm2 (TMVR is feasible if neoLVOT area = 2cm2). None of the patients had prohibitive mitral annular calcification. One patient had emergent valve-in-valve TAVR due to device migration into the LVOT, making TMVR not possible.

Conclusion: Moderate to severe mitral regurgitation is frequent in patients with severe aortic stenosis undergoing TAVR. Approximately one quarter of those patients will have persistent significant MR after TAVR. In this limited case series, CCTA demonstrated TMVR suitability in 83% of patients suffering from significant MR after TAVR. Multi-modality cardiac imaging is key in severe concomitant valve disease as to guide patient selection, shared decision making and potential therapeutic approaches for double valve intervention strategies.

45-B Poster: Impact of Denovo Pulmonary Hypertension on TAVR Outcomes

Presenter: Miho Fukui, Post-Doctoral Fellow Cardiology

Research Interest: Clinical

Mentors: João Cavalcante MD

Funding Source: N/A

Authors: Miho Fukui MD, Hesham Elzomor MD, Islam Abdelkarim MD, Michael Sharbaugh , Andrew Althouse , Dustin Kliner MD, Joon Lee MD, John Schindler MD, Thomas Gleason MD, João Cavalcante MD

Introduction: Baseline pulmonary hypertension (PH) is prognostically important in patients undergoing transcatheter aortic valve replacement (TAVR). Persistency of PH post-TAVR also affects mortality in an adverse way. However, little is available on the evolution of pulmonary hypertension after TAVR. We sought to determine the hypothesis that PH can develop in the post-TAVR setting (Denovo PH) and its presence is associated with worse mortality despite TAVR.

Methods: We evaluated consecutive patients with severe aortic stenosis (AS) who received TAVR from 07/2011 through 01/2016 and had comprehensive transthoracic echocardiogram (TTE) and right heart catheterization (RHC) at baseline. We excluded patients with PH before TAVR defined by gold-standard RHC as mean pulmonary artery pressure (mPAP) = 25mmHg. Denovo PH was defined as baseline mPAP < 25mmHg and at 1-month follow-up TTE estimated pulmonary artery systolic pressure (PASP) = 45mmHg. PASP was calculated using the maximal tricuspid regurgitant jet velocity obtained from continuous wave Doppler and integrated into the modified Bernoulli equation plus the estimated right atrial pressure (from the inferior vena cava size and variability with respiration). All individual echocardiographic images, Doppler and RHC data were reviewed independently and blinded to the clinical information and outcomes. Cox regression and Kaplan-Meier analyses were performed to test the association of denovo PH with all-cause mortality.

Results: Out of the 505 patients who received TAVR, 430 (85%) had complete RHC and TTE available for analysis. A total of 125 patients did not have baseline PH (mPAP < 25mmHg) by RHC prior to TAVR and included in the final analysis (Mean age 85 years, STS-PROM 6.6%, LVEF 59 ± 10%, aortic valve area 0.66 ± 0.15 cm2, mean aortic valve gradient 50±14 mmHg). Denovo PH was found in 22 (18%) patients at 1-month post-TAVR. Denovo PH patients had more concomitant valvular disease, greater LV hypertrophy, higher PASP and larger LA volume index. No significant differences between two groups regarding procedural characteristics were noted. When compared to patients without PH, denovo PH was associated with worse survival, which remained unchanged after adjustment for comprehensive STS-PROM (HR=2.92, 95% CI 1.16-7.36, p=0.02).

Conclusion: The incidence of denovo PH post-TAVR is not uncommon (18%) and associated with higher mortality post-TAVR. Denovo PH is associated with greater LV hypertrophy, larger left atrium volume (both implying worse diastolic function) and more significant concomitant valvular disease. Future studies are needed to test treatment strategies, beyond TAVR, that could improve their outcomes.

47-B Poster: Patient-centered Goals of Care: Using the Chronic Care Management (CCM) code for cooperative goal setting in the multimorbid elderly

Presenter: Nivedita Gunturi, Fellow
Geriatric Medicine

Research Interest: Clinical

Mentors: Amelia Gennari MD

Funding Source: N/A

Authors: Nivedita Gunturi MD, Amelia Gennari MD, Kieran Bartels

Introduction: Patient-centered care is an integral element that contributes to quality healthcare delivery by aligning clinical outcomes with individual values and preferences, encouraging clinical care providers to consider patients' needs as articulated by patients themselves. Often, due to barriers such as limited time, lack of clinician training, and predetermined assumptions, shared decision-making and goal setting does not take place. It is particularly important in older adults, particularly those with multiple comorbidities, for the clinician and patient to cooperatively determine goals together. In recognition of the importance of care management and coordination in patients with multiple chronic conditions, Medicare approved payment for non face-to-face care management for selected patients with multi-morbidity, including a requirement to elicit goals and create a care plan.

Methods: Eligible patients were recruited in 2 outpatient geriatric clinics. Consent forms were reviewed with patient by one of 13 providers, and if signed, patient was added to CCM list. Goals of care and care plans were established and documented by an interdisciplinary team into electronic medical record using standard template, usually during an annual well visit. These were followed over time via telephone encounter. Non-face-to-face management time was recorded in flowsheets, reviewed monthly and billed by CRNP (>20 minutes required). Data was obtained by manual chart audit and electronic report.

Results: 70 eligible patients were enrolled, all of whom had goals established at initial visit. 89% of patients had goal follow up at least once per quarter. Patient goals fell into six categories: diet/weight (30%), function (26%), medical (19%), lifestyle (11%), medication (9%), and mood (5%). Disciplines involved were medicine, nursing, nurse practitioner, pharmacy and social work. Reasons for leaving the program included death (29%), transfer to hospice (14%), moving away (14%), and insurance causes (14%). An average of 7 minutes per patient per month was recorded on outreach encounters (range 5 to 60).

Conclusion: Having a structured format for cooperative goal setting and followup in the multimorbid elderly was helpful in ensuring that patient goals were established, monitored and documented consistently by a team of providers. A large proportion of patients met goal follow up criteria. Initial evaluation of the program suggests that cooperative goal setting and follow up is feasible with existing office staff and resources.

48-B Poster: Glycemic Management as the Primary Determinant of One-Year Mortality after CABG

Presenter: Lucas Heller, Fellow
Endocrinology and Metabolism

Research Interest: Clinical

Mentors: Harsha Rao MD

Funding Source: VAPHS

Authors: Lucas Heller MD, Margaret Zupa MD, Peter Perreiah MSc, Harsha Rao MD

Introduction: Factors linked to survival after coronary artery bypass graft (CABG) include glycemic management, with avoidance of hypoglycemia, and use of arterial grafts. It is not known, however, if there is an interaction between these factors, namely whether arterial grafts might be more resilient in the face of hypoglycemia than venous grafts.

Methods: In a cohort of 1323 patients who underwent CABG with intensive insulin therapy (IIT) in the ICU, we identified graft sources, glucometrics in the ICU, diabetes (DM) status and one-year mortality. Glucometrics included mean BG in ICU, and hypoglycemia excursions (incidence, severity [nadir <40, 40-69mg/dl], repetitive frequency [number of excursions/patient]). Chi-squared Automatic Interaction Detection (CHAID) analysis was used to detect the impact of different factors, individually and in combination.

Results: One year mortality was highest in those with BG<40mg/dl in the ICU (12/26, 46%) vs those without (67/1283, 5%, p<0.001). No other factor was significant in those with BG<40mg/dl. Of those without BG<40mg/dl, repetitive (>2) excursions of BG <70 had the highest mortality (17/96, 17%, p<0.001), vs those with one (13/190, 7%) or no excursions (37/997, 4%). Graft source played no role in one year mortality, except for the left internal thoracic artery which was protective only in patients with no hypoglycemia. Hyperglycemia contributed to mortality in patients who had a single hypoglycemic excursion <70 (Mean BG>152 4/17, 24% vs =152 9/173, 5%, p=0.039). Preexisting DM was highly protective in patients with repetitive hypoglycemia (DM 2/43, 5% vs 15/53 28%, p=0.003).

Conclusion: Hypoglycemia in the ICU has a durable impact on one-year mortality post-CABG, superseding graft source, which is only significant without hypoglycemia. Severe hypoglycemia poses the greatest risk, but even mild repetitive BG<70 is a threat to one-year survival. Hypoglycemia erases the survival benefit from arterial grafts, suggesting that it may be equally damaging, regardless of graft source, and far more durable than hitherto envisioned.

49-B Poster: Osteoporosis and fracture risk in males with Rheumatoid Arthritis

Presenter: Kanchana Herath, Fellow
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Larry Moreland MD
Lei Zhu MS
Melissa Saul MS

Funding Source: N/A

Authors: Kanchana Herath MD, Lei Zhu MS, Melissa Saul MS, Larry Moreland MD

Introduction: Osteoporosis is an asymptomatic disease complicated by fractures and is associated with an increased morbidity and mortality. Rheumatoid arthritis (RA) has been found to be a secondary cause for osteoporosis and it occurs more frequently in the RA population compared to healthy population. There is a generalized consensus concerning osteoporosis screening in women however no such consensus exists for men due to insufficient available data. Current recommendations are to screen using dual-energy x-ray absorptiometry (DEXA) scans in men >70 years and those ages 50-69 with increased risk for osteoporosis. However, with limited data available on appropriate screening guidelines, many are not being screened. The objectives of this study are to determine if there is an increased risk of fragility fractures in male patients with RA between the ages of 50-69 and if DEXA screening should be recommended for those under the age of 70.

Methods: This is a cohort study examining osteoporosis risk in male patients with RA. We retrieved outpatient clinic notes, DEXA scans, laboratory results for rheumatoid factor (RF) and anti-cycle citrullinated peptide (CCP), along with hospital medical record discharge abstracts for all patients who were males ages 50-69 with a RA diagnosis defined in an outpatient setting with an ICD 9/10 code, and currently or previously on treatment with disease-modifying antirheumatic drug (DMARD) or biologic seen at a UPMC outpatient clinic between the years of 2010-2017. Exclusion criteria included prior history of chronic obstructive pulmonary disease, transplant, hypogonadism, inflammatory bowel disease, and current treatment of anticonvulsants or chemotherapy. Our outcomes included DEXA scan results and incidence of fractures. RF and CCP status were also evaluated in these patients.

Results: There were 1972 patients identified that matched our inclusion criteria. Our preliminary results demonstrated 100 patients with DEXA scans completed within our institution. 5 of those patients had osteoporosis and 29 had osteopenia in their spine. 61 had a normal spine finding. Total hip was also evaluated with 4 having osteoporosis and 41 having osteopenia. 54 were normal.

Conclusion: A history of RA is a risk factor for osteoporosis however no screening guidelines exist for men. Our preliminary data show that in men less than 70 years of age there is evidence of osteopenia and osteoporosis. We plan to continue reviewing DEXA scans and to also evaluate the frequency of fractures in these patients to help determine the need for improved screening using DEXA scans.

50-B Poster: Peritoneal Dialysis ; in-hospital complications

Presenter: Sara Husain, Fellow
Renal-Electrolyte

Research Interest: Clinical

Mentors: Heena Sheth MD, MPH
Filitsa Bender MD, FACP

Funding Source: N/A

Authors: Sara Husain MBBS, Heena Sheth MD, MPH

Introduction: Although the number of End Stage Renal Disease (ESRD) incident cases plateaued in 2010, prevalent cases continue to rise annually by about 21,000 cases per year. According to the United States Renal Data System, there was an increase of 18,617 in prevalent cases from 2016 to 2017. As physicians are taking care of an increasing ESRD population there has been a continuing concern for using advances in care and providing quality care to further decrease morbidity and mortality in this vulnerable population . ESRD and dialysis patients are at increased risk of adverse events in any medical setting due to complex management requiring specific dosing adjustments, careful assessment of risk benefit which may differ for this population, comorbidities and other socio-economic issues. Hospitalized dialysis patients may be at higher risk of health care associated errors and adverse events due to differing level of knowledge, experience and awareness in physicians who are not specialized in caring for this patient population.

Methods: We are planning to conduct a descriptive study evaluating patients from the Peritoneal Dialysis Registry. We shall be reviewing charts of hospitalized PD patients at UPMC Presbyterian hospital from 2000 to 2017 who are participating in IRB approved registry project. In an attempt to examine quality of care; we will focus on dialysis related management (access, electrolytes and volume control, infections), hospital acquired infections, medication errors and adverse events related to anticoagulation, opioid, glycemic control and antibiotics. We will match our database to UPMC NHSN database and risk master to identify reported events for study patients a. We will compare quality indicators (infections and ADEs) and dialysis outcomes (access issues and infections, peritonitis, transfer to HD, mortality) between the hospitalized and non-hospitalized PD patients during the study period.

Results: In progress.

Conclusion: In progress.

51-B Poster: DEVELOPMENT AND PRELIMINARY FEASIBILITY OF AN AUTOMATED HYPERTENSION SELF-MANAGEMENT SYSTEM

Presenter: Taya Irizarry, Post-Doctoral Fellow Cardiology

Research Interest: Clinical

Mentors: Matthew Muldoon MD

Funding Source: Internal funding

Authors: Taya Irizarry PhD, Matthew Allen BS, Julian Einhorn BS, Brian Suffoletto MD, Lora E. Burke PhD, Thomas Kamarck PhD, Bruce Rollman MD, Matthew Muldoon MD

Introduction: Control of blood pressure (BP) is often poor and represents a challenge for patients with hypertension and their providers. Optimal hypertension self-management requires adequate health literacy and may be supported by ongoing feedback. The MyBP program provides access to online educational videos and text-based prompts to report BP readings four times weekly, plus instant recurring feedback of the rolling BP average with an additional bi-weekly summary report. The aim of this study was to assess the short-term feasibility of MyBP and examine changes in perceptions and behaviors regarding self-management among adult patients with hypertension.

Methods: Recruitment cites included: a specialty service (SS) referral hypertension center (n=11), a primary care (PC) clinic (n=10) and an urban emergency department (ED) (n=22). Primary inclusion criteria included community-dwelling adults with a prior diagnosis of hypertension and, for PC and ED patients, a current BP >140/90 mm Hg. After viewing the online videos, patients used the program for six weeks. Semi-structured exit-interviews assessed patients' perceptions of the program, shifts in the importance of measuring and understanding blood pressure, and changes in beliefs regarding health behaviors.

Results: The 43 participants (age 34-70, 58% female, 61% black) had an average baseline BP of 157/94 mm Hg. Patients submitted a BP reading in response to 76% of reminder messages. Three participants completed only 4 of the 6 week monitoring period. In the exit interview, 80% and 73% of patients reported that the program increased importance of, and their confidence in, BP self-monitoring, respectively. About 50% of participants reported an increase in importance and confidence regarding healthy diet habits and stress reduction, as well as changes in both behaviors as a result of the program. One in 3 reported such changes in exercise. Across all these outcomes, PC and ED patients reported change more frequently than did SS patients. Among PC and ED patients, 30% reported improved medication adherence. Finally, 73% of all participants reported an increase in their confidence in controlling their BP, and 88% indicated willingness to use the program long-term.

Conclusion: The MyBP program has favorable feasibility, utilization, and short-term effects on patient's perceptions and health behaviors.

52-B Poster: RISK OF UNRECOGNIZED FACIAL SPLASH DURING ENDOSCOPY

Presenter: Elyse Johnston, Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Asif Khalid MD

Funding Source: N/A

Authors: Elyse Johnston MD, Nadia Habib-Bein MD, Jeffrey Dueker MD, Barbara Quiroz RN, Enrico Corsaro RN, Megan Ambrogio RN, Michael Kingsley MD, Georgios Papachristou MD/PhD, Christianna Kreiss MD, Asif Khalid MD

Introduction: Non-universal use of facial protection during endoscopy may place endoscopists at risk of exposure to blood and body fluids; however, the frequency of exposure is unknown. We investigated the incidence of unrecognized facial splash to the endoscopist during endoscopy.

Methods: Prospective study of 4 gastroenterologists using a face shield during an AM (0730-1200hrs) endoscopy session at VAPHS over 6 months. Face shields were sampled with a sterile swab in a standardized fashion prior to first case (Pre-face) and at end of last case (Post-face). The endoscopist kept the face shield on and not permitted to touch it for the session, unless a splash was detected. Control 1 included pre- and post-swabs for face shields placed on the endoscopy unit wall, at face level, 6ft away from patient (Pre-/Post-Environment Control;EC). Control 2 included a swab after deliberate contamination of face shields with a scope immediately after colonoscopy (Positive Control;PC). The swabs were cultured for 48 hours in a CLIA certified microbiology lab and growth reported as no growth or by number of colony-forming units (CFU). The different groups were compared for +CFU utilizing Chi-square tests. Additionally, a survey of GI faculty and fellows working at 3 academic facilities regarding practice patterns and attitudes towards facial protection during endoscopy was performed.

Results: The survey found that 68% of gastroenterology attendings and fellows have experienced at least one facial splash during endoscopy and 33% use some type of facial protection. The 4 gastroenterologists performed 1100 procedures (~5 procedures/AM session). Of 239 sessions, 12 were excluded (4 recognized splashes, 8 due to touching/inadvertently taking off face shield). There was a low +CFU rate in the Pre-face and Pre-EC groups (4.85% & 3.42%, p=NS), which was significantly lower than the Post-face (45.4%, $p<0.001$) and Post-EC groups (23.1%, $p<0.001$). The +CFU rate in the Post-face was higher than the Post-EC group (45.4% vs. 23.1%, $p<0.001$). Using a cut-off of >30 CFU (>CFU than any Pre group and median CFU for the PC group) as an indicator of definite splash to face, the occurrence was 0.5%.

Conclusion: This study shows for the first time a direct correlation of incidence of exposure (as detected by positive cultures) during endoscopy with decreasing distance to the endoscope (endoscopy suite wall vs. endoscopist's face vs. endoscope). The risk of facial exposure/splash is at least 0.5% per procedure performed. While the clinical significance of this exposure is unknown, we recommend use of universal facial protection.

53-B Poster: Risk Factors for Hospital Readmission Following implementation of a Diabetic Ketoacidosis (DKA) Power Plan

Presenter: Neha Karajgikar, Fellow
Endocrinology and Metabolism

Research Interest: Clinical

Mentors: Mary Korytkowski MD

Funding Source: N/A

Authors: Neha Karajgikar MD, Amy Donihi PharmD, Rose Salata MD, Ronald Codario MD, Runa Acharya MD, Pooja Manroa MD, Mary Korytkowski MD

Introduction: Patients admitted to the hospital with DKA are at high-risk for readmission. We have previously demonstrated that implementation of a DKA PowerPlan (PP) that guides IV insulin dosing following acute management and transition to SC insulin reduces the frequency of recurrent DKA and rebound hyperglycemia during the index hospitalization. The purpose of this study was to determine whether the DKA PP reduces all cause and diabetes-related (recurrent DKA, hyperglycemia, hypoglycemia) hospital readmissions at 30 days and 1 year following an index hospitalization, as well to examine the contribution of high risk co-morbidities (psychiatric illness and/or history of alcohol/polysubstance abuse) associated with readmission risk in this group of patients.

Methods: Retrospective chart review was performed for patients admitted with primary diagnosis of DKA prior to (pre-PP, n=60) and following DKA PP implementation (Post-PP, n=60). The groups were similar in age (Pre- vs Post-PP: 38 ± 13.5 vs. 40 ± 16.6), BMI (26 ± 6.7 vs. 27 ± 7 kg/m2), gender (%Male: 38% vs. 48%), HbA1c (11.7 ± 2.4 vs. 11.3 ± 2.9%), admission BG (560 vs. 615 mg/dl) and anion gap (AG) (27.6 vs. 27.4), but differed in the prevalence of comorbidities which were higher in the pre-PP group (58 vs. 40%, p = 0.045).

Results: All cause readmissions were similar at 30 days (Pre vs. Post-PP: 1.4 ± 0.8 vs. 1.2 ± 0.4) but were lower at 1 yr in the post-PP group (5.2 ± 4.7 vs. 3.5 ± 2.7, p = 0.07). Patients with co-morbidities in the post-PP group had lower all-cause (p = 0.023) but not diabetes related readmissions at 1yr, compared to patients with co-morbidities in the pre-PP group.

Conclusion: In summary, these findings suggest that a DKA PP may be associated with a reduction in all cause hospital readmission in high risk patients with underlying psychiatric or substance abuse disorders. These results emphasize the need to identify and address patient specific factors that contribute to readmission in this high risk group.

54-B Poster: Functional Measures and Patient Home Self-Assessments in the Idiopathic Inflammatory Myopathies

Presenter: Amanda Kocoloski, Fellow
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Rohit Aggarwal MD
Chester Oddis MD

Funding Source: N/A

Authors: Amanda Kocoloski DO, Rohit Aggarwal MD, Chester Oddis MD

Introduction: Myositis leads to significant muscle weakness and loss of physical function. Our aims were to a) test validity and reliability of functional measures (sit to stand [STS], timed up and go [TUG], and 6-minute walk distance [6MWD]) in myositis patients against established myositis core set measures (CSM), and b) evaluate the same measures self-performed by patients at home.

Methods: Currently, there are 6 validated and accepted myositis CSMs for assessing disease activity including manual muscle testing (MMT) and physician global disease activity. Consenting myositis patients seen in the University of Pittsburgh Myositis Center were assessed for 6 established CSMs and 3 functional tests (STS, TUG, and 6MWD) at baseline, 3 and 6 months. STS is the number of times a patient can stand from a seated position and sit back down in 30 seconds. TUG is the time needed to stand, walk 3 meters, return, and sit down. Subjects then conducted these functional tests at home within 1 week of their clinic evaluation. To assess the validity of the functional measures, we correlated them with the CSMs. We examined the reliability/responsiveness of the measures. Mixed linear modeling and Pearson correlation were used to assess longitudinal and crossectional associations, respectively. Home self-assessed measures were compared with clinic assessments.

Results: 31 patients [58% females, 90% Caucasians, mean (SD) age 48 (+/-16)] were included in this analysis. At baseline STS showed moderate to strong correlations with patient global, MMT, physician global, and muscle enzymes. Baseline TUG showed strong to moderate correlation with physician global and MMT. The 6MWD showed moderate to strong correlation with MMT, physician global, HAQ and patient global. Longitudinally, all 3 functional measures were significantly associated with the physician global, MMT and HAQ (all $p < 0.01$). Test-retest reliability of STS and TUG was excellent within a single clinic or home assessment as well as when assessed over 3-6 months in clinically stable patients (STS $r = 0.88$, TUG $r = 0.92$, and 6MWD $r = 0.90$; $p < 0.01$). All functional measures showed improvement in patients with clinical improvement and worsening with clinical worsening, demonstrating responsiveness to change. At home, patient assessment of performance on all 3 functional measures showed excellent correlation with in-clinic assessments.

Conclusion: Preliminary data suggests STS, TUG and 6MWD showed associations with key CSMs, and demonstrated reliability and responsiveness in myositis. These tests were valid when self performed by patient at home.

55-B Poster: Effect of Urinalysis with Reflex Testing on Urine Culture Testing and Treatment

Presenter: Karthik Kota, Fellow
Geriatric Medicine

Research Interest: Clinical

Mentors: John Naumovski MD

Authors: Karthik Kota MD, Jennifer Hwang DO, Debbie McDonald RN, John Naumovski MD

Funding Source: N/A

Introduction: Though it is a well-known fact that older patients—particularly women, and particularly in nursing homes—can have bacterial colonization of their uroepithelial tract, an oft-used reflex when a patient has any change in condition—fever, mental status change, and even urinary symptoms—is to get a urinalysis and culture. Both are often ordered simultaneously in order to practice conservatively, but this can lead to issues if a culture comes back with ambiguous results (under 100,000 colony forming units, or a non-standard organism). Here, we look at the change in number of cultures obtained and percentage of positive results against number of urinalyses ordered in one nursing home after switching to a standardized order of urinalysis with reflex in August 2017

Methods: CM is a 159-bed skilled nursing facility divided approximately equally between short-stay (IE – rehabilitation) and long-term beds, with a locked dementia unit comprising one of its four main wings. Data on urinalyses and culture results—as well as treatment data—are collected by the nurse educator for infectious disease review. Data from the 3 months before the switch in urine protocol was compared to the three months after

Results: There were 15 urinalyses and eight positive urine cultures in May, 13 urinalyses and 10 positive cultures in June, and 12 urinalyses and 8 positive cultures in July, all before the order switch. Afterwards, there were 12 urinalyses and 9 cultures in August (8 positive), 5 urinalyses and 2 cultures in September (both positive), and 9 urinalyses with 8 cultures in October (7 positive). A similar rate of positive cultures is found before and after the order switch (65% vs 65%), with much fewer urine cultures than previous

Conclusion: The order switch going from urinalysis with culture to urinalysis with reflex to culture did not have a significant change in the percentage of positive cultures found, but was found to involve much fewer urine cultures ordered. Using a simple change in how the default urine lab tests were ordered led to a 30% decrease in number of urine cultures ordered relative to number of urinalyses obtained. Systems changes such as this are vital to ensuring low costs in long-term care facilities, even as the demand for quality care remains robust. Implementing such a solution will help to bend the cost curve as the United States ages and more seniors require long-term care

56-B Poster: Best Practice Alerts Improve Rates of Appropriate Implantable Cardioverter-Defibrillator Therapy and Reduce All-Cause Mortality

Presenter: Jae Lee, Fellow Cardiology

Research Interest: Clinical

Mentors: Samir Saba MD

Funding Source: Study was funded by Boston Scientific

Authors: Jae Lee MD, Libby Szeto BS, Deepak Pasupula MD, Aliza Hussain MD, Anam Waheed MD, Shubash Adhikari MD, Floyd Thoma BS, Michael Sharbaugh MPH, Andrew Althouse PhD, Samir Saba MD

Introduction: Sudden cardiac death (SCD) is the number one killer of adults in industrialized countries. Primary prevention trials of SCD have shown that implantable cardioverter-defibrillators (ICD) reduce total mortality in patients with an ejection fraction (EF) = 35%. Still, many eligible patients do not receive an ICD.Our objective was o assess whether best practice alerts (BPA) given to health care providers through the electronic medical record will improve rates of referral for ICD implantation and impact patient outcomes.

Methods: Between 2013-2015, providers were randomized to receive a BPA versus not receive a BPA. A BPA was triggered by an EF = 35%, prompting the provider to consider referring the patient for ICD implantation. Patients with prior ICD were excluded from the analysis. We followed patients for outcomes of EP referral, ICD implantation, or death through August 2016. Outcomes were analyzed using Kaplan-Meier curves and Cox proportional-hazards models.

Results: The current analysis includes 1834 patients (n=943 whose provider received BPA versus n=891 with no BPA). Patients were balanced on baseline characteristics and comorbidities. Over a median follow-up of 24 months, 612 patients were referred to EP, 505 received an ICD, and 410 died. Patients with a provider who received a BPA were more likely to be referred to EP (HR=1.16; 95% CI 0.99-1.36), receive an ICD, (HR 1.21; 95% CI 1.01-1.45) and less likely to die (HR 0.77; 95% CI 0.63-0.94).

Conclusion: Patients seen by providers who received a BPA were more likely to be referred to EP, receive an ICD, and less likely to die. These data support the routine use of BPAs to improve the management and outcomes of patients with ICD indications.

57-B Poster: Non-invasive Diagnosis of ATTR Cardiac Amyloidosis: Insights from a Prospective Multimodality Registry

Presenter: Ahmad Masri, Fellow Cardiology

Research Interest: Clinical

Mentors: Prem Soman MD, PhD, FRCP, FACC

Funding Source: T32

Authors: Ahmad Masri MD, Ricardo Nieves MD, Islam Abdelkarim MD, Michael Sharbaugh MD, Andrew Althouse MD, William Follansbee MD, Joao Cavalcante MD, Wong Timothy MD, Erik Schelbert MD, Alison Sehgal MD, Prem Soman MD, PhD, FRCP, FACC

Introduction: Technetium-99m pyrophosphate (Tc-99m PYP) scintigraphy has unmasked a significant population prevalence of CA, and resulted in increased referrals for testing. To inform optimal resource utilization, we used a prospective registry to determine the relative diagnostic value of clinical characteristics and imaging tests for cardiac amyloidosis (CA), using Tc-99m PYP as the reference standard.

Methods: A prospective observational study of 103 patients with suspected CA referred for multimodality imaging at a tertiary center between 06/2015 and 01/2017. A positive Tc-99m PYP scan was defined by cardiac uptake of PYP equal to or greater than ribs on visual assessment. Serum studies were routinely used in patients referred for PYP scanning to exclude or further evaluate for amyloid light-chain cardiac amyloidosis (AL-CA). Clinical, electrocardiographic (ECG), echo, global longitudinal strain (GLS), and gadolinium enhanced-cardiac magnetic resonance (CMR) patterns were compared

Results: Of the 103 patients referred for Tc-99m PYP scintigraphy, 34% had a positive study. Patients with a +ve Tc-99m PYP were older (80 vs. 73 years, 0.01), more often male (80% vs. 60%, p=0.049), more likely to have low voltage on ECG (20% vs. 4%, p=0.028), and a higher prevalence of = grade II diastolic dysfunction (49% vs. 29%, p<0.01). In 70 patients who had GLS analysis, relative apical sparing pattern had 63% sensitivity and 87% specificity for CA. In 37 patients, CMR had 100% sensitivity and 79% specificity for CA.

Conclusion: Clinical, ECG and echo features do not discriminate between patients with and without ATTR-CA with adequate specificity for clinical diagnosis. GLS and CMR improve diagnostic accuracy, but GLS has a lower sensitivity, and CMR has a lower specificity compared to Tc-PYP as the diagnostic standard. The findings of this pilot study may be used as the basis for future studies to refine algorithms for the cost-effective diagnosis of CA.

58-B Poster: Sex Differences and Outcomes of Heart Failure Admissions Stratified by Left Ventricle Ejection Fraction

Presenter: Ahmad Masri, Fellow Cardiology

Research Interest: Clinical

Mentors: Suresh Mulukutla MD

Funding Source: T32

Authors: Ahmad Masri MD, Andrew Althouse MD, Gavin Hickey MD, Jeffrey McKibben MD, Ravi Ramani MD, Michael Mathier MD, Joon Lee MD, Oscar Marroquin MD, Suresh Mulukutla MD

Introduction: In 2016, the European Society of Cardiology (ESC) HF guidelines adopted three types of HF: HF with preserved ejection fraction of = 50% (HFpEF), HF with mid-range EF between 40-49% (HFmrEF), and HF with reduced EF < 40% (HFrEF). We analyzed the gender-specific readmission and mortality across these HF groups.

Methods: From 2008 through 2015, our multi-site health system saw 14,737 unique HF patients (49% males) totaling 69,353 hospital admissions with an assessment of LVEF during the encounter. Patients were divided into three groups: HFpEF (36,131 admissions), HFmrEF (8,575 admissions), and HFrEF (24,617 admissions). Gender-specific outcomes of HF readmission and all-cause mortality were compared within each group. Hazard ratios (HR) were computed using the Andersen-Gill method in the Cox proportional-hazards model and adjusted for baseline characteristics.

Results: Of the 14,747 unique patients, 7,442 were HFpEF (37% males), 1,802 were HFmrEF (51% males), and 2,004 were HFrEF (64% males). Over 12 months, HF readmission rates for male vs female patients were 52% vs 55% in HFpEF (adjusted HR 0.91 (0.85, 0.97), p=0.003), 54% vs 60% in HFmrEF (adjusted HR 0.84 (0.75, 0.94), p=0.003), and 58% vs 59% in HFrEF (adjusted HR 0.96 (0.89, 1.04), p=0.299). All-cause mortality for male vs female within each group was not statistically different.

Conclusion: Females accounted for a higher proportion of HFpEF patients than HFmEF or HFrEF patients. Within each EF strata, female patients had higher rates of HF readmission in HFpEF and HFmrEF groups, but not the HFrEF group. Despite higher readmission rates, there were no differences in all-cause mortality. Further studies are needed to investigate the underlying factors affecting this heterogeneous outcome.

59-B Poster: Relationship between pre-treatment organ-specific tumor burden and response to immunotherapy in advanced melanoma

Presenter: Ryan Massa, Fellow Hematology/Oncology

Research Interest: Clinical

Mentors: John Kirkwood MD
Diwakar Davar MD

Funding Source: N/A

Authors: Ryan Massa MD, Mark Sparrow MD, Yan Lin PhD, Huang Lin BS, Amy Rose BS, David Mauro MD, PhD, Art Krieg MD, John Kirkwood MD, Yana Najjar MD, Diwakar Davar MD

Introduction: Prior reports have described an association with hepatic metastases and total tumor burden with reduced response rates to anti-PD1 treatment in subjects with advanced melanoma (MEL). We explored baseline organ-specific tumor burden as assessed by volumetric analysis to compare fractional burden of disease to response rates in patients treated on a phase IB/II study of PD-1 inhibitor pembrolizumab and intratumorally injected toll-like receptor 9 (TLR9) agonist, CMP-001.

Methods: Responders and non-responders were identified among patients with advanced MEL treated on a phase IB/II clinical trial of pembrolizumab/CMP-001 combination. Responders (n=8) and non-responders (n=10) were identified at first computed tomography (CT) imaging assessment 12 weeks after treatment initiation. All responders (stable disease, partial response, or complete response) had response lasting a minimum of 36 weeks. Volumetric assessment of baseline screening CT imaging was performed to assess total tumor burden prior to initiation of treatment. Tumor burden was delineated by site of disease (liver, non-liver visceral, lung, lymph node and subcutaneous). Fractional tumor burden was calculated by dividing site-specific tumor burden by total tumor burden.

Results: 18 subjects were included in the analysis. High fraction of visceral tumor burden was associated with lack of response to treatment (p=0.0016) and shorter progression-free survival (PFS, p=0.001). High fraction of lymph node tumor burden was associated with response to treatment (p=0.079) and longer PFS (p=0.029).

Conclusion: In subjects treated with pembrolizumab/CMP-001, high fraction of visceral tumor burden is associated with lack of response to treatment and shorter PFS. Conversely, high fraction of lymph node tumor burden is a favorable feature and is associated with response to treatment and longer PFS. Results suggest that organ-specific tumor burden is a prognostic marker in subjects with advanced melanoma treated with immunotherapy.

60-B Poster: Palliative Care Utilization by Lung Transplant Recipients in the Last Year of Life at the University of Pittsburgh

Presenter: Eric Nolley, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Clinical

Mentors: Yael Schenker, MD, MAS
Matt Morrell MD

Funding Source: T32

Authors: Eric Nolley MD, Seyed Mehdi Nouraie MD, PhD, Yael Schenker MD, MAS, Matt Morrell MD

Introduction: Lung transplant recipients may benefit from specialty palliative care (SPC), but utilization is poorly characterized. We examined SPC encounters by transplant recipients in the last year of life at the University of Pittsburgh. SPC services during the study period included inpatient consults and an outpatient clinic for non-malignant organ failure. We hypothesized that SPC encounters primarily occurred in the last months of life in the inpatient setting.

Methods: Retrospective cohort study of decedents who underwent lung transplantation at the University of Pittsburgh Medical Center from 1/1/2010 to 12/31/2015. Patients that underwent a second transplant in the study period were censored on date of re-transplant. Patients with unknown cause of death were excluded. Follow up was through 8/2017. Patient demographics at time of transplant, receipt of SPC pre-transplant, cause of death, post-transplant survival, and timing and location of palliative care encounters were abstracted from the electronic health record. Parametric and nonparametric statistics were used to compare characteristics of patients who did and did not receive SPC. Multivariate logistic regression was conducted using backwards elimination after identifying potential predictors by univariate analysis.

Results: Of 597 lung transplants, there were 246 decedents. 14 were excluded because of unknown cause of death. The remaining 232 patients had a mean age at death of 64.4 years (IQR 13.2). 41% received SPC in the last year of life. Decedents that received SPC had greater median survival than decedents that did not (1.8 vs 1.4 years, $p<0.001$). Otherwise there were no differences between patients that did and did not receive SPC. By multivariate logistic regression, longer survival (OR 1.4, 95% CI 1.160, 1.824) and younger age at death (OR 0.97, 95% CI 0.960, 0.998) were predictors of receiving SPC. Of 1098 encounters, only 12 occurred in the outpatient setting. 37% of inpatient encounters occurred in the ICU. Median time for all encounters to death was 71 days (IQR 148) and 11.5 days (IQR 69) from the last encounter preceding death.

Conclusion: A minority of lung transplant decedents received SPC in the last year of life and the majority encounters occurred in the last 3 months of life. 1% of SPC encounters occurred in the outpatient setting which suggests that outpatient SPC may be underutilized. Longer post-transplant survival may increase the likelihood of receiving SPC. Further studies are needed to understand reasons for SPC consultation, SPC services received, and transplant recipients palliative care needs.

61-B Poster: Chest CT Pectoralis Muscle Size Validated with Dual Energy X-Ray Absorptiometry Measurements of Body Composition Is Associated with Lung Function in COPD

Presenter: Michael Emmet O'Brien, Fellow **Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

Mentors: Rama Mallampalli MD
Jessica Bon MD

Funding Source: Funded by: P50 HL084948, P50 CA90440, 1R01HL128289

Authors: Michael Emmet O'Brien MD, Nathan Hyre , Joseph Leader , Divay Chandra MD, Frank Sciurba MD, Jessica Bon MD

Introduction: Loss of skeletal muscle mass is an important clinical finding in chronic obstructive pulmonary disease (COPD) that is characterized by altered muscle structure, sarcopenia, and impaired exercise capacity. Pectoralis muscle cross sectional area (CSA), a surrogate for skeletal muscle mass, has been previously shown to predict COPD-related morbidity, and can be conveniently quantified on chest CT images. We investigated the cross sectional and longitudinal relationships between pectoralis muscle CSA and measurements of body composition, including body mass index (BMI), fat-free mass index (FFMI) and appendicular skeletal muscle index (ASMI), and their interaction with clinical COPD phenotypes in a prospective cohort study of current and former smokers.

Methods: Data from the University of Pittsburgh SCCOR participants with baseline and 6-year chest CT scans, lung function measurements and dual energy x-ray absorptiometry (DXA) scans were analyzed (n=259). Pectoralis muscle CSA was manually segmented and measured using a single CT image at the level of the aortic arch. Body composition was determined using DXA and indicators of lean body mass, FFMI and ASMI, were calculated. The relationship between baseline and 6-year change in pectoralis CSA and DXA-derived FFMI and ASMI was determined by Pearson correlation. Linear regression analysis was performed with adjustment for co-variates including age, gender, and pack year smoking history. The presence of COPD was defined by using the GOLD spirometric criteria (FEV1/FVC <0.7).

Results: Baseline pectoralis muscle CSA was more strongly associated with FFMI ($r=0.75$, $p<0.0001$) and ASMI ($r=0.76$, $p<0.0001$) than BMI ($r=0.35$, $p<0.0001$). A significant correlation was also observed between longitudinal change in pectoralis muscle CSA and FFMI ($r=0.45$, $p<0.0001$), ASMI ($r=0.45$, $p<0.0001$) and BMI ($r=0.34$, $p<0.0001$). Gender stratified analysis showed that measurements of body composition were lower in subjects with COPD (n= 119) compared to control participants (n=140). Following adjustment for co-variates, a significant association was observed between FEV1 percent predicted and pectoralis CSA ($p=0.002$), FFMI ($p=0.01$), and ASMI ($p=0.02$), but not BMI ($p=0.49$) in subjects with COPD.

Conclusion: The findings of this study reveal that pectoralis muscle CSA is significantly correlated with the gold standard measurements of body composition and changes proportionally with these indices over time. In subjects with COPD, reduced pectoralis muscle mass is associated with lower FEV1 by univariate and multivariate analysis. This study supports the validity of utilizing pectoralis muscle CSA for the evaluation of skeletal muscle mass in individuals with COPD.

62-B Poster: Relapse of Rheumatoid Arthritis Activity following Sustained Remission: a study of US Veterans

Presenter: Anna O'Connor, Fellow
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: John Steuart Richards MD

Funding Source: N/A

Authors: Anna O'Connor MD, Joshua Baker MD, Bryant England MD, Brian Sauer PhD, Grant Cannon MD, John Steuart Richards MD

Introduction: Remission is the primary therapeutic goal in rheumatoid arthritis (RA) treatment, but it is unclear whether continuation of therapy is necessary in all patients in remission. Potential side effects and high costs of therapy make such considerations important. Our primary aims are to characterize RA patients who relapse after sustained remission or low disease activity (LDA) and evaluate for relapse predictors. We present our secondary aims here - to characterize and compare US veteran RA patients in either sustained versus non-sustained remission or LDA.

Methods: Data from the Veterans Affairs RA (VARA) registry was used. The VARA registry is a longitudinal multicenter cohort of US veterans who fulfill the 1987 American College of Rheumatology (ACR) criteria for the classification of RA. The database includes patient demographics and longitudinal markers of RA disease activity. The VA Informative and Computing Infrastructure (VINCI) provided detailed prescription data for RA medications. Patients were included if enrolled for = 1 year and in remission/ LDA state defined by DAS28 score (DAS28 = 2.6 defining remission and = 3.2 for LDA state). Sustained remission/LDA status was defined as maintenance of remission and/or LDA for at least six consecutive months measured at a minimum of 2 time points. Patients taking oral prednisone were excluded. Descriptive statistics were performed to compare characteristics of patients with sustained remission or LDA versus non-sustained remission or LDA patients.

Results: Of 2722 VARA patients, 332 (12.1%) met sustained and 289 (12.7%) met non-sustained remission/LDA. Of those in sustained remission/LDA, average age was 69.4 years (SD 11.2), 87.2% were male, 81.3% Caucasian, 49.5% were current smokers, 97% RF positive, 69.5% ACPA positive, 31.8% had rheumatoid nodules, and 54.4% had radiographic changes. Methotrexate was prescribed in 51.6% and anti-TNF agents in 30.0%. More patients with non-sustained remission had CCP positivity, nodules, and radiographic changes (80.3%, 42.9%, and 66.4%). At enrollment, baseline ESR, CRP, swollen joint count (SJC) and tender joint count (TJC) were lower in patients with sustained disease control (mean ESR 22.3 vs. 11.2; CRP 1.3 vs 0.7; SJC 4.5 vs. 0.62; TJC 5.8 vs. 0.6).

Conclusion: Our results characterize RA patients who achieved sustained versus non-sustained remission/LDA. Those in sustained remission/LDA had lower ACPA positivity, less nodules and radiographic changes. There was a trend towards more active disease at time of enrollment in those who did not reach sustained disease remission/LDA.

63-B Poster: Analysis of Patients Mislabeled with Heparin Induced Thrombocytopenia

Presenter: Apurva Pandey, Fellow Hematology/Oncology

Research Interest: Clinical

Mentors: Roy Smith MD

Funding Source: N/A

Authors: Christine Garcia MD, Roy Smith MD, Robert Szulawski MD, Catherine Quinn MD, Rhea Shrivastava

Introduction: Heparin-induced thrombocytopenia (HIT) is a rare diagnosis, although commonly tested. We hypothesize that the 4T score, a diagnostic tool to diagnose HIT, is underutilized by clinicians. We present preliminary data of our quality improvement study. Our aim was to analyze patients previously labeled with heparin allergy and analyze the 4T's scores, optical density values (OD), and serotonin release assay (SRA) results.

Methods: We conducted a retrospective study of patient at two tertiary care hospitals who were evaluated for HIT from October 2015- present. We were notified by pharmacy when a HIT panel was sent and alternative anticoagulation was started. Patients with unknown heparin administration from outside institutions were excluded from the study. We calculated the 4T's score and further categorized low (0-3), intermediate score (4-5), and high (6-8) score. We considered the patients to have "true HIT" if they had 4T's score > 5 or optical density values >0.4 and positive SRA.

Results: We analyzed 50 patients who were evaluated for HIT and placed on alternative anticoagulation. We observed that 64% (32/50) of the patients were listed as having heparin allergy secondary to HIT, while 36% (18/50) were not listed to have HIT as allergy on electronic health record. 19 of the 50 (38%) had scored had low 4T's score, of that two tested for HIT with a score of 0 (4%, n=50), 22 (44%) had intermediate, and 9 (18%) had high. When we utilized the 4T's score as pre-test clinical score, 0/13 patients with low score (6 not tested for SRA) and 0 /18 with intermediate score (4 were not tested) had positive SRA. 4 of the 9 (67%) high score were positive (3 were not tested). When we evaluated SRA results for patients with OD value >0.4, we observed 3 with OD value >2 and 1 with OD value of 0.798 had positive SRA. Interestingly, 1 with OD value of 2.136 had negative SRA. 8 patients with OD values > 1 had negative SRA.

Conclusion: Preliminary results show that patients are frequently tested for HIT, misdiagnosed with HIT, and mislabeled with HIT in electronic health record. When 4T's is used as clinical score, patients with low probability should not be further tested for HIT. Based on our preliminary data, none of the patients with low and intermediate score had true HIT when SRA was tested. We aim to decrease hospital cost by not only implementing a 4T score to be recorded in the EMR to prevent unnecessary HIT panel tests, but also reduce cost spent on costly alternative anticoagulation.

64-B Poster: Rates of Inappropriate Antibiotic Prescribing are High within a Veterans Affair Hospital

Presenter: Rameez Phulpoto, Fellow Infectious Diseases

Research Interest: Clinical

Mentors: Brooke Decker MD

Funding Source: N/A

Authors: Rameez Phulpoto MD, Nathan Shively MD, Deanna Buehrle PharmD, Cornelius Clancy MD, Brooke Decker MD

Introduction: Antibiotic overuse is a major healthcare problem. Antimicrobial stewardship is a national priority. The use of antibiotics in the Emergency Room setting at the Veterans Affairs Pittsburgh Healthcare System (VAPHS) was reviewed as part of a quality improvement initiative.

Methods: Emergency Room antibiotic prescriptions by Emergency Room (ER) providers within the VAPHS from June 2016 – July 2017 were catalogued. A random sample of prescriptions was compared to consensus guidelines for appropriateness of indication, antibiotic type and duration. Rates of antibiotic prescribing were identified as number of antibiotic prescriptions per 1000 patient encounters (antibiotic index).

Results: A total of 2997 antibiotic prescriptions were written by 30 ER providers caring for 21,372 patients (range of patient encounters per provider 29-1652) during the study period, for an overall antibiotic index of 140. Antibiotics most often prescribed were amoxicillin-clavulanate (19%), azithromycin (19%), trimethoprim-sulfamethoxazole (12%), cephalexin (10%), doxycycline (9%), ciprofloxacin (7%), and amoxicillin (6%). A total of 303 prescriptions were reviewed. The most common indications for reviewed prescriptions were urinary tract infection (18%), bronchitis (16%), cellulitis (16%), and COPD exacerbation (13%). Antibiotics were not indicated in 56.1% of prescriptions. Among indicated prescriptions, the prescribed antibiotic was a guideline-discordant agent in 27.8% of reviewed cases, and guideline-concordant agents were given for a guideline-discordant duration in 35.4% of reviewed cases. Opportunity for improvement was identified in 79.5% of reviewed antibiotic prescriptions.

Conclusion: Significant antibiotic overuse was seen. There is an opportunity for antimicrobial stewardship intervention in the emergency room to improve concordance with guidelines for common prescribing indications.

65-B Poster: Acceptance of Erectile Dysfunction Treatment by Patients on Hemodialysis and Their Renal Providers

Presenter: Amoghavarsha Puli, Fellow Renal-Electrolyte

Research Interest: Clinical

Mentors: Steven Weisbord MD

Funding Source: N/A

Authors: Amoghavarsha Puli MD, Hossam Abdalla MD, Steven Weisbord MD, Maria Mor PhD

Introduction: Erectile Dysfunction (ED) is highly prevalent in men receiving chronic hemodialysis (HD). Past studies demonstrate that treatment of ED with phosphodiesterase-5 inhibitors is safe and effective in this population. However, it is unknown whether these medications and other therapies are routinely used. We sought to investigate the acceptance of treatment for ED among men on chronic HD and their renal providers.

Methods: As part of a clinical trial of symptom management in patients on chronic hemodialysis, we assessed erectile dysfunction monthly using the Sexual Health Inventory of Men (SHIM) tool. For men with erectile dysfunction (SHIM score < 22), trained research nurses provided treatment recommendations and if patients and providers accepted them, helped facilitate their implementation . We assessed patients' acceptance of recommendations, reasons for refusal, and providers implementation of therapy. All data was analyzed at the level of monthly assessments.

Results: Of the 101 patients followed for up to 12 months, 46 of 47 (98%) men met criteria for erectile dysfunction. These 46 patients reported ED on 426 monthly assessments. In 49 of the 426 (11.5%) assessments, patients accepted the recommendation for treatment. On 59 assessments (14%) patients were already on treatment or had received a prescription. On 11 monthly assessments (2.5%) patients reported having financial obstacles precluding treatment. On 260 (61%) monthly assessments, patients refused the treatment recommendations. The primary reason patients refused the recommendations was no desire to discuss treatment options (53%) and not interested in being sexually active or not having a partner (38%). In 14 of the 27 assessments (51%) where patients accepted the recommendation, renal providers were unwilling to provide treatment.

Conclusion: Despite the high prevalence of ED in the hemodialysis population, a large majority of patients are not interested in pursuing treatment. For patients interested in treatment, renal providers are commonly unwilling to modify or initiate therapy. Future efforts should focus on identifying patients interested in treatment and improving the provision of therapy for these individuals.

66-B Poster: Sex-differences in outcomes associated with atrial fibrillation: an analysis of the UPMC electronic health record, 2006-2017

Presenter: Zachary Rhinehart, Fellow Cardiology

Research Interest: Clinical

Mentors: Jared Magnani MD

Funding Source: N/A

Authors: Zachary Rhinehart MD, Melissa Saul MS, Jared Magnani MD

Introduction: Atrial Fibrillation (AF) is the most common cardiac rhythm disorder. Clinical trials and registries have demonstrated that women with AF have increased risks of stroke and adverse clinical outcomes compared to men. Sex-based differences merit examination in large, regional health data because of the potential clinical implications. We used UPMC electronic health record (EHR) data to investigate sex differences in outcomes. We hypothesized that we would identify sex-specific differences in stroke and heart failure in our real-world clinical setting.

Methods: We queried the UPMC EHR from 2006-2017 to identify cases of AF employing validated ECG and ICD algorithms. We selected individuals living in Allegheny County to reduce misclassification and regional differences arising from differential EHR inclusion. We incorporated inpatient and outpatient ICD codes to define relevant clinical covariates and dates of incident ischemic stroke and heart failure. After confirming proportional hazards, we examined stroke risk in Cox proportional hazards models adjusted for CHA2DS2-VASc risk factors.

Results: We identified 275,998 unique patients with a diagnosis of AF. Of these 81,429 had a home address within Allegheny County and comprised the final cohort. The median follow-up time was 6.8 years (range 0 to 11.9 years). Women had a higher risk of stroke (Hazard Ratio (HR) =1.55, 95% Confidence Interval (CI) 1.44-1.66, P<0.0001) and heart failure (HR=1.21, 95% CI 1.16-1.27, P<0.0001). In multivariable-adjusted models, female sex (HR= 1.36, 95% CI 1.27-1.46, P<0.0001), age 75 or greater (HR= 1.43; 95% CI 1.3-1.59, P<0.0001), heart failure (HR=1.56, 95%CI 1.43-1.71, P<0.0001), hypertension (HR=3.92, 95% CI 3.27-4.70, P<0.0001), prior stroke or transient ischemic attack (HR=11.16, 95% CI 10.40-11.98, P<0.0001), peripheral vascular disease (HR=1.14, 95% CI 1.04-1.24, P=0.003), and diabetes (HR=1.11, 95% CI 1.03-1.19, P=0.005) were associated with increased risk of stroke, while age 65-75 was not (HR=1.07, 95% CI0.95-1.21, P=0.26).

Conclusion: Consistent with existing data, we observed that female sex is associated with increased risks of stroke and heart failure in patients with AF. This preliminary analysis using data from the UPMC EHR opens up multiple opportunities to enhance our understanding of sex differences among patients with AF. Ongoing work will incorporate risk stratification using additional clinical factors, medication prescriptions, laboratory data, and cardiac imaging. Our study has direct clinical implications for improving patient care at UPMC by identifying increased risks in women with AF.

68-B Poster: Hospital Readmission and Comprehension of Diabetes Education at Discharge

Presenter: Janya Swami, Fellow
Endocrinology and Metabolism

Research Interest: Clinical

Mentors: Mary Korytkowski MD

Funding Source: N/A

Authors: Janya Swami MD, Mary Korytkowski MD, Linda Siminerio PhD, Amy Donihi PharmD, Esra Karslioglu-French MD, Kristin Delisi CRNP, Deborah Hlasnik CRNP, Neeti Patel MD

Introduction: Diabetes (DM) is a major contributor to the frequency of hospital readmissions. DERRI (Diabetes Early Readmission Risk Indicator) is a previously validated predictor for 30-day readmissions in patients with DM that excludes DM-related factors as potential contributors to this risk including glycemic control (HbA1c) and variability (GV), differences between pre-admission and discharge DM therapy, and documentation of and patient comprehension of discharge instructions provided for home DM self-management.

Methods: Non-critically ill hospitalized patients with an underlying diagnosis of DM were recruited for consent to obtain demographic and glycemic variables, DERRI scores, 30-day readmission data and to assess understanding of instructions provided for home self-management using a Patient Comprehension (PC) Questionnaire administered by phone within 48 hours of discharge.

Results: To date, 74 subjects with DM (type 1 n = 9, type 2 n= 46, pancreatogenous n = 5) provided written consent (mean age 56.4 ± 12.4 years, BMI 31.2 ± 9.1 kg/m2, 55% men, 65% Caucasian, 70% unemployed, HbA1c 8.7± 2.07 %, duration of DM 19.7 ± 11.8 years, mean blood glucose (BG) 48 hours prior to discharge 211 ± 46.7 mg/dL). GV measured as SD of BG measures obtained 48 hours prior to discharge was 66.1 ± 37 mg/dL and as BG range was 192.6 ± 83.6 mg/dL. Discharge instructions were documented in the electronic medical record (EMR) for 93% of subjects. 31 subjects completed the PC questionnaire with a mean score of 79 ± 15.5%. Despite EMR documentation that instructions were provided in 29 of these subjects, 10 (32%) indicated that discharge instructions were not provided for home DM self-management. Of these 10, 4 were readmitted at 30 days.PC scores were numerically lower in the ten subjects who reported that they had not received discharge instructions for home self-management (69% vs 79%). Changes to pre-admission DM regimens were not associated with readmission. Of the 59 subjects who were at least one-month post-discharge, 22 (37.3%) had =1 readmission. Those who were readmitted had significantly higher DERRI scores compared to those not readmitted (26.1% vs 19.2%, p=0.006).

Conclusion: In summary, despite the small number of subjects recruited to date in this ongoing study, these results demonstrate that an underlying diagnosis of DM is associated with high risk for hospital readmission at 30 days and DERRI scores may be valuable predictors of early readmission risk.

69-B Poster: Does kidney transplantation affect sleep and fatigue in patients with kidney disease?

Presenter: Srijan Tandukar, Fellow
Renal-Electrolyte

Research Interest: Clinical

Mentors: Manisha Jhamb MD
Sundaram Hariharan MD
Mark Unruh MD

Funding Source: N/A

Authors: Srijan Tandukar MD, Surui Hou , Jonathan Yabes PhD, Mary Fletcher BS, Sundaram Hariharan MD, Mark Unruh MD, Manisha Jhamb MD

Introduction: Given the limited evidence on the effect of kidney transplantation (KTx) on sleep and fatigue, we examined changes in subjective and objective sleep apnea, sleep quality and fatigue after kidney transplant in patients with chronic-/end stage- kidney disease (CKD/ESKD).

Methods: This is a prospective cohort study of adult patients with advanced CKD (eGFR<30 mL/min/1.73 m2) or ESKD. Changes in subjective and objective sleep apnea, sleep quality and fatigue were evaluated and analyzed using paired t-test. Patients were divided into 2 groups - KTx and no-KTx. Objective sleep was assessed by one night in-home polysomnography (PSG). Subjective sleep was assessed using Pittsburgh Sleep Quality Index and Epworth Sleepiness Score; fatigue was assessed using Functional Assessment of Chronic Illness Therapy-Fatigue.

Results: Among 77 patients (mean age 51 years, BMI 29 kg/m2, 66% males, 23% ESKD), 44 received KTx. The mean duration between the 2 PSGs was 16.5 months; 2nd PSG was done after an average of 6.7 months post KTx. There were no significant differences among the KTx and no-KTx groups in the key socio-demographic variables, lab values and co-morbidities except that the KTx group had fewer diabetics (23% vs 63%; p=0.001) and had lower eGFR (14 vs 20 ml/min; p=0.002) as compared to the no-KTx group. There were no differences in sleep apnea severity in either the KTx [apnea hypopnea index (AHI) 16 vs 16; p=0.95] or no-KTx group (AHI 21 vs 22; p=0.76). In both groups, there was a significant improvement in Stage I non-rapid eye movement (NREM) sleep (as % of total sleep time, mean difference 3.9%; p<0.001) in KTx group and (4.3%; p=0.03) in the no-KTx group. There were no differences in any other objective (total sleep time, sleep latency, nocturnal hypoxemia and REM sleep) or subjective measures of sleep and fatigue in either group.

Conclusion: Kidney transplant improves NREM sleep but does not affect severity of sleep apnea, or subjective and objective measures of sleep quality and fatigue.

70-B Poster: Analyze Myositis with Ultrasound and Exercise (AMUSE) Kids- Analysis of Baseline Data

Presenter: Laura Tasan, Fellow
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Kathryn Torok MD
Rohit Aggarwal MD

Funding Source: CureJM Grant

Authors: Laura Tasan MD, Emily Brunner MD, Rohit Aggarwal MD, Chester Oddis MD, Emily Mirizio BS, Kaila Schollaert-Fitch MA, Judy Squires MD, Amisha Shah MD, Kathryn Torok MD

Introduction: There is an unmet need for more objective disease outcome measures for patients with Juvenile Myositis (JM). The aim of this pilot study is to test the reliability, validity and responsiveness of advanced ultrasound (US) modalities as dynamic imaging outcome measures in JM patients compared to Pediatric Rheumatology International Trials Organization (PRINTO) and International Myositis Assessment and Clinical Studies Group (IMACS) validated Core Set Measures (CSMs).

Methods: This prospective observational cohort study includes JM subjects recruited from rheumatology clinic for the collection of clinical, functional and US data at baseline, 3 and 6 months follow up. Clinical and functional variables include: demographics, clinical characteristics, PRINTO/IMACS defined CSMs, Sit To Stand (STS), Time Up and Go (TUG), and 6 Minute Walk Distance (6MWD). US modalities to evaluate muscle consistency and perfusion include: Gray Scale with Echogenicity (EI) and Muscle thickness (MT), Power Doppler (PD), 2D Shear wave© Elastography (SWE) and Contrast Enhanced US with Lumason© (CEUS) performed on unilateral proximal (vastus lateralis) and distal muscle (medial gastrocnemius) groups. At each study visit, US is performed before and after all functional measures and exercise to stress the muscles of interest. Spearman's correlation was utilized to evaluate the relationship of US measures with CSMs and functional tests.

Results: We have enrolled 9 JM patients currently out of our goal of 20 JM patients and 10 healthy controls. Patients enrolled in this pilot study are 89% Non-Hispanic females with a mean age of 11.5 and a mean disease duration of 36 months. Several US measures had moderate to strong correlations with JM CSMs (Manual Muscle Testing (MMT8), Myositis Disease Activity Score, Childhood Myositis Assessment Scale), including Echogenicity, Power Doppler, CEUS blood flow measurements (Time to Peak (Tp) and Peak Intensity (Ip)) and CEUS blood volume measurement (Area under the Curve (AUC)), both pre- and post-exercise, with most associations being stronger post-exercise (rs >0.35). Importantly, the US parameters EI, PD, CEUS, correlate moderately to strongly with MMT8, the pre-defined primary outcome measure for this study.

Conclusion: Preliminary results demonstrate that US measures of Echogenicity, Power Doppler and CEUS (both blood flow and blood volume) correlate moderately to strongly with myositis tools for quantifying physical function at baseline, supporting their potential to serve as disease outcome measures in JM studies thus reducing the need for invasive testing. Further longitudinal analysis is underway to examine which modality is more sensitive and specific to changes over time.

71-B Poster: Is routine colonoscopy following acute diverticulitis necessary?

Presenter: Shahrzad Tehranian, Post-Doctoral Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical

Mentors: Robert Schoen MD, MPH

Funding Source: N/A

Authors: Shahrzad Tehranian MD, Matthew Klinge MD, Melissa Saul MS, Michele Morris BA, Brenda Diergaarde PhD, Robert Schoen MD, MPH

Introduction: Practice guidelines recommend patients undergo colonoscopy following an episode of diverticulitis to exclude other pathology. Previous studies suggest that patients with complicated diverticulitis (abscess, perforation, mass, fistula, or obstruction) are at higher risk for neoplasia, but the vast majority of patients have uncomplicated diverticulitis. Whether colonoscopy is needed, especially in subjects who had testing prior to diagnosis, is unknown. Here, we examine colonoscopy findings including incidence of advanced adenoma (AA) and cancer (CA) in patients diagnosed with diverticulitis to determine if they differ from the established norms of screening colonoscopy.

Methods: We reviewed computed tomography (CT) scans performed from 1/2008-5/2013 at UPMC Presbyterian-Shadyside hospitals with mention of diverticulitis to identify a cohort with confirmed acute diverticulitis. In that cohort, we reviewed surgical pathology and colonoscopy/pathology reports and compared results to historical data from a meta-analysis of 68,324 patients undergoing screening colonoscopy (Niv et al, Dig Dis Sci 2008;53:3049) and to results from screening colonoscopy in the UPMC health system (UPMCHS) from 2013-15.

Results: A total of 5167 abdominal/pelvic CT scan reports were reviewed. This identified 978 patients with confirmed acute diverticulitis (24% complicated). After diagnosis, 179 underwent surgery, of whom 10 (5.6%) had CA and 2 (1.1%) had (AA). One hundred and forty-three underwent colonoscopy within 2 years of date of diagnosis of diverticulitis; 4 (2.8%) of these subjects had CA, 13 (9.1%) had AA. Compared to the historical meta-analysis (CA/AA: 0.8%/5%), our subjects had higher rates of CA/AA ($P<0.05$); compared to the UPMCHS 2013-15 cohort (0.3%/7.7%), their rate of CA was significantly higher ($P<0.05$) but the AA rate was similar ($P=0.53$). The rate of neoplasia (CA/AA) in complicated diverticulitis was 16.7% (5/30) and 10.6% (12/113) in uncomplicated diverticulitis ($P=0.35$). Excluding patients from our cohort who had a colonoscopy prior to date of diagnosis of diverticulitis did not change the results.

Conclusion: The incidence of CA/AA on colonoscopy within 2 years of diverticulitis was significantly higher compared to historical data. Cancer incidence was also higher compared to recent screening cohorts, but AA incidence was similar. Neoplasia rates were similar in complicated and uncomplicated diverticulitis. Our data suggest that colonoscopy is indicated and necessary after the diagnosis of diverticulitis.

72-B Poster: Utilization of cell-free circulating tumor DNA for management of breast cancer: practices in academic and community oncology

Presenter: Roby Thomas, Fellow
Hematology/Oncology

Research Interest: Clinical

Mentors: Adam Brufsky MD, PhD
Adrian Lee PhD
Steffi Oesterreich PhD

Funding Source: N/A

Authors: Roby Thomas MD, Natalie Klar MD, Lesli Kiedrowski , Rebecca Nagy , Adrian Lee PhD, Adam Brufsky MD, PhD

Introduction: Next-generation sequencing (NGS) of cell-free DNA (cfDNA) is increasingly being utilized to assess somatic genomic alterations in patients with breast cancer. We investigated the clinical use of such testing in breast cancer care in a major healthcare system with both academic and community-based practices. We also explored the observed genomic landscape in the analyzed patient cohort and whether treatment plans were modified based on the results.

Methods: A retrospective review of cfDNA NGS results (Guardant360) ordered at the University of Pittsburgh Medical Center for patients with breast cancer from 7/2015-3/2017 was performed. Test ordering patterns, the landscape of genomic alterations identified, and clinical use of select results were assessed.

Results: During this period 95 samples were submitted, 73 (77%) ordered by academic center providers and 22 (25%) from community providers. Alterations were detected in 88 samples (93%) with a median of 3 alterations per test. Five patients had serial samples ordered assessing dynamic cfDNA across clinical treatment and progressions, leaving 84 unique patients in the dataset. The average patient age was 57, and 95% of patients were female. Patients were most often observed to have alterations in TP53 (51%), PIK3CA (44%), and ESR1 (26%). Additional clinical data were collected for 48 patients with mutations or amplifications in PIK3CA, ESR1, and/or ERBB2 (HER2) to assess for clinical use of genomic information. Results were used to change clinical care in 13 (27%) of these cases. Community providers were more likely to use genomic results to guide clinical management in these cases (9/16, 56%) than academic providers (4/32, 12.5%), p=0.001. Of this patient subset, those with tests ordered by an academic provider had more lines of prior therapy at the time of testing vs. those in the community (average 5.9 vs 3.4 respectively, p=0.019).

Conclusion: CfDNA NGS analysis for somatic genomic alterations in breast cancer is being ordered clinically by both academic and community practices within this healthcare system. Results for a subset of clinically annotated patients were acted on more frequently by community-based ordering providers, which may be related to patients tested at academic sites having had more lines of prior treatment.

73-B Poster: Spousal support does not affect outcomes in patients with continuous flow left ventricular assist device

Presenter: Alicia Topoll, Fellow Cardiology

Research Interest: Clinical

Mentors: Gavin Hickey MD

Funding Source: N/A

Authors: Alicia Topoll MD, Andrew Althouse PhD, Kathy Lockard MBA, RN, CCTC, Elizabeth Dunn BSN, RN, CCTC, Nicole Kunz BSN, RN, CCTC, Mary Amanda Dew PhD, Arman Kilic MD, Chris Sciortino MD, Robert Kormos MD, Gavin Hickey MD

Introduction: Social support is a key component of evaluating patients prior to left ventricular assist device (LVAD) implantation. Prior studies have shown that caregiver support affects outcomes in transplant recipients. We investigated the relationship between primary caregiver, social support and clinical outcomes after LVAD implantation.

Methods: We performed a retrospective single-center study of all patients who received continuous flow LVAD from 2006-2017. Patients were evaluated based upon primary caregiver and quality of social support (assessed as Excellent, Good, Fair, or Poor by a single VAD coordinator). We analyzed the relationship between primary caregiver, quality of social support and clinical outcomes including survival and adverse events related to LVAD.

Results: A total of 255 patients (mean age 56.3 ± 12.8; 83% male; 81% white) received continuous-flow LVAD between 2006 and 2017. Social support was characterized as excellent (9.8%), good (81.6%), fair (4.7%), or poor (3.9%). Patients for whom the spouse was part of the care team had higher probability of Excellent or Good social support (12.7% Excellent + 84.7% Good) than patients for whom the spouse was not part of the care team (5.1% Excellent + 76.1% Good). Patients were followed for a mean of 483 days with device in place; during the study period 17 (6.7%) had device explanted, 88 (34.5%) received a transplant, 79 (31.0%) died, and 71 (27.8%) were alive with device in place as of last known follow-up. Survival and freedom from major adverse events were no different between LVAD patients with spouse as the primary caregiver when compared to no-spouse (see Figure). Similarly, there was no difference in outcomes based upon quality of social support.

Conclusion: Although involvement of the spouse was related to better social support, outcomes were no different between LVAD patients with or without spouse as primary caregiver. Larger and more diverse studies are needed to determine the importance of social support in evaluating potential LVAD patients pre-implantation.

74-B Poster: System-Level Factors Associated with Utilization of Outpatient Specialty Palliative Care in Patients with Advanced Solid Tumor Cancer

Presenter: Justin Yu, Fellow
General Internal Medicine

Research Interest: Clinical

Mentors: Yael Schenker MD
Kristin Ray MD

Funding Source: N/A

Authors: Justin Yu MD, Kristin Ray MD, Seo Young Park MD, Amanda Barry MPH, Cardinale Smith MD, Peter Ellis MD, Yael Schenker MD

Introduction: Utilization of outpatient specialty palliative care (OSPC) improves outcomes for patients with advanced cancer. Despite broad endorsement from national oncologic societies, use of OSPC remains suboptimal. The external, system-level barriers to OSPC utilization in this population have not been fully explored. This study aimed to 1) identify the rate of OSPC use among patients with advanced solid tumors, treated within the UPMC Hillman Cancer Center network where well-established, oncology-specific OSPC clinics exist, and 2) examine associations between oncology clinic co-location and geographic access (travel time) with OSPC utilization.

Methods: We performed a retrospective cohort analysis of adult patients with advanced solid tumors receiving oncologic treatment between January 1 and December 31, 2016 within the UPMC Hillman Cancer Center network (UPMC-HCCN). Patients were identified from records of VIA Pathways, a clinical decision-support tool used in over 94% of medical oncology visits occurring in the UPMC-HCCN. Patient characteristics and OSPC utilization was determined from the electronic health record and billing records of UPMC's outpatient oncology-specific palliative care clinics. Adjusted, multivariable logistic regression models evaluated associations between oncologist-OSPC co-location and geographic access with OSPC use, while controlling for patient-level characteristics.

Results: Of 9,485 patients with advanced solid tumors, 478 (5.0%) received OSPC services in 2016. After controlling for patient age, sex, marital status, cancer type, insurance status, treatment intent, and oncologist "surprise question," patients whose oncologist's practice was co-located with an OSPC clinic were more likely to utilize OSPC (odds ratio [OR], 19.2; 95% confidence interval [CI], 14.1-26.2). Compared to patients who lived >90 minutes from an OSPC clinic, patients with travel times of <30 minutes (OR, 3.2; CI, 2.2-4.6) and 31-60 minutes (OR, 2.4; CI, 1.6-3.6) were more likely to use OSPC.

Conclusion: Even at a comprehensive cancer center network with well-established, outpatient palliative care services, most patients with advanced solid tumor cancer do not utilize OSPC. Among this patient population, co-location of oncology and OSPC clinics and improved geographic access (shorter travel time) were associated with greater likelihood of using OSPC. Further work is needed to adapt health care delivery systems to overcome these external, system-level barriers to improve access to and utilization of outpatient palliative care for all patients with advanced cancer.

75-B Poster: Measuring the efficiency of electronic health record usage: Epic's provider efficiency profile demonstrates high test-retest reliability for adult primary care providers

Presenter: Jonathan Arnold, Fellow
Services/Clinical Epidemiology
General Internal Medicine

Research Interest: Health

Mentors: Janel Hanmer MD, PhD

Funding Source: T32

Authors: Jonathan Arnold MD, MSE, Hannah Chang MS, MBA, Janel Hanmer MD, PhD

Introduction: Electronic health records (EHRs) have been widely deployed in the United States, however concernsremain over perceptions of increased workload and decreased productivity following EHR adoption. Epic Systems developed the provider efficiency profile (PEP) report to measure the efficiency of EHR users, intending it to identify low-efficiency providers for targeted interventions. To date there are no published studies evaluating PEP's performance as a measurement tool. In this study we evaluate the test-retest reliability of PEP in a real-world clinical setting.

Methods: We ran PEP reports 3 times from August 2015 to July 2016 for non-trainee adult primary care providers (PCPs) at a large regional health system. Reports were run at months 0, 9 and 11. Each report used three weeks of EHR data. There were no system-wide attempts to improve EHR efficiency during this time. While the PEP algorithm is proprietary, it is known to measure a provider's scheduled workload and time spent in various EHR tasks. PEP scores are reported from 0 (low efficiency) to 10 (high efficiency). We calculated the individual intraclass correlation coefficients for absolute agreement (AA-ICC) of all three time points and separately for months 9 and 11 using twoway mixed effect models. Providers were included in the analysis if they had at least six days of EHR usage for all report periods.

Results: There were 457 PCPs included in the analysis. The mean PEP scores were 4.8 (sd 1.8), 4.8 (sd 1.9) and 4.8 (sd 1.9) for the 3 PEP reports. The AA-ICC was 0.75 [95% CI 0.71-0.78] when including all 3 reports spanning 11 months and 0.86 [95% CI 0.83-0.88] for the latter two reports spanning 2 months.

Conclusion: The PEP demonstrated high test-retest reliability in this sample of over 450 PCPs. The AA-ICC was higher for test-retest over 2 months compared to 11 months as would be expected. While the PEP has face validity, further work is needed to assess the validity of the PEP as a true measure of EHR efficiency. Assuming the PEP is a valid measure, our results support its use to measure changes in EHR efficiency over time and across interventions.

76-B Poster: Analysis of clinical video telehealth consults as a method for optimizing medications of Veterans Affairs dementia patients

Presenter: Woody Chang, Fellow
Services/Clinical Epidemiology
Geriatric Medicine

Research Interest: Health

Mentors: Michelle Rossi MD, MPH
Karen Scandrett MD, MPH

Funding Source: N/A

Authors: Woody Chang MD, Marcia Homer RN-BC, Michelle Rossi MD, MPH

Introduction: Community Based Outpatient Clinics (CBOCs) are centers that allow primary care to be delivered to veterans that are a long distance from a main Veterans Affairs (VA) campus. However, these CBOCs often do not have physicians who are trained in geriatric principles. A clinical video telehealth (CVT) dementia service based in the Pittsburgh VA offers geriatric expertise to optimize dementia patients' medications and can help deprescribe potentially inappropriate medications (PIMs).

Methods: We analyzed CVT patient data for a 12 month period from January 1, 2016 to December 31, 2016. We compared each kind of medication adjustment (additions, discontinuations, and dosage modifications per encounter) of all medications as well as the discontinuation of PIMs, as defined in the 2015 Beers Criteria as medications that should be avoided in most older adults, between those seen in the initial CVT consults and those seen in the follow up visits. T-tests were used to compare the two kinds of CVT sessions.

Results: We analyzed 199 separate encounters in the 12 month period, with 130 initial CVT consults and 69 follow-up visits. We found that the initial CVT consults, compared to follow up visits, had a greater number of added medications per encounter (0.731 vs. 0.434, p=0.0092), total overall medications changes per encounter (1.769 vs 1.130, p=0.0078), and discontinuation of 2015 Beers Criteria PIMs that should be avoided in most older adults per encounter (0.208 vs 0.072, p=0.0255). However, the differences were not significant when comparing all medication discontinuations per encounter (0.684 vs. 0.406, p=0.070) and dosage modifications (0.354 vs. 0.290, p=0.465).

Conclusion: The greater number of additions, total medication changes, and PIMs discontinued between initial CVT consults compared to follow up visits show that initial CVT consults can have a strong effect on modifying dementia patients' regimens. In addition, the lower number of these changes in the follow up visits show that our patients' medications tend to stay optimized between visits. The CVT dementia service represents an intriguing way to provide assistance to CBOC VA physicians that may not be comfortable taking care of dementia patients.

77-B Poster: Impact of Electronic Consultation Compared To Face-to-Face Encounters on Glycemic Control among Veterans with Type 2 Diabetes

Presenter: Karla Detoya, Fellow
Services/Clinical Epidemiology
Endocrinology and Metabolism

Research Interest: Health

Mentors: Archana Bandi MD

Funding Source: N/A

Authors: Karla Detoya MD, Neha Karajgikar MD, Archana Bandi MD, Janice Beattie RN,BSN,CDE, Stacey Lutz-McCain DNP, FNP-BC,CDE, Monique Kelly PhD

Introduction: Electronic consultation (EC) is a form of telemedicine that enhances access to specialty care. Neither long-term glycemic control by EC nor comparison to traditional face-to-face encounters (F2F) has been previously reported. We compared the effect of EC to F2F care on glycemic control, systolic blood pressure (SBP), and lipid profiles over 12 months.

Methods: Demographics, rurality, dates of request and completion, % HBA1c at consult and post-consult (3 to 6 months and 12 months), SBP, and lipid profile at date of consult and 12 months post-consult were collected from 442 EC and 407 F2F Veterans with type 2 diabetes (T2DM) referred to the VA Pittsburgh Healthcare System from remote VA facilities in 2010 to 2015. Based on level of engagement, EC cohort was subdivided into 3 groups: Full engagement (FE, n=253), Partial engagement (PE, n=109) and one time recommendation (OTR, n=80). Continuous measures were presented as mean ± standard deviation (SD) and compared across groups using Wilcoxon rank-sum tests. Categorical measures were compared between groups using chi-square tests.

Results: EC Veterans were younger (64.2±8.5 years), and predominantly male (98.4%), and rural (15.8%) than F2F Veterans (68.1±8.7 years, $p<0.0001$; 95.3% male, $p=0.01$; 3.7% rural, $p<0.0001$). Mean difference was 27 days between consult request and completion dates, comparing EC (10±10 days) to F2F care groups (37±33; $p<0.0001$). With equivalent baseline HBA1c for both cohorts (10%±1.6), there was glycemic improvement from baseline HBA1C to 3 to 6 months (EC: 8.98%±1.54, F2F: 8.75%±1.77) and again to 12 months (EC: 8.80%±1.61, F2F: 8.57%±1.72). The difference between the two cohorts for decline in HBA1C values between baseline and 3-6 months, and between baseline and 12 months were statistically significant (p:0.03 and 0.002, respectively). Within the EC cohort, decline from baseline HBA1C to 3-6 months was 9.8% to 8.7% (SD±1.4) in FE group, 10.3% to 9.29% (SD±1.66) in PE group, and 9.9% to 9.2%(SD±1.71) in OTR group, and was significant ($p=0.002$). The decline from baseline HBA1C to 12 months was 9.8% to 8.6 % (SD±1.4) in FE group, 10.3% to 9.03% (SD±1.8) in PE group, and 9.9% to 8.97 %(SD±1.69) in OTR group, and was significant ($p=0.014$). There was no significant difference in SBP and lipid profile values between the cohorts over 12 months.

Conclusion: EC provides expedient care and is comparable to F2F encounters for sustained glycemic improvement in Veterans with T2DM. There were no group differences for SBP control and lipid profiles over 12 months post-consult.

78-B Poster: Standardization of Inpatient CPR Status Discussions and Documentation within the Division of Hematology-Oncology at UPMC Shadyside

Presenter: Christine Garcia, Fellow
Services/Clinical Epidemiology
Hematology/Oncology

Research Interest: Health

Mentors: Edward Chu MD
Stanley Marks MD
Joshua Levenson MD

Funding Source: N/A

Authors: Christine Garcia MD, Mamta Bhatnagar MD, Rachel Rodenbach MD, Edward Chu MD, Stanley Marks MD, Abigail Graham-Pardus PA-C, Jamie Kriner PA-C, Melissa Winfield PA-C, Christopher Minnier PA-C, Janet Leahy NP, Emily Baird RN, Joshua Levenson MD

Introduction: Medical professionals are trained to provide life-sustaining and cardiac resuscitation measures for admitted hospital patients. However, not all patients desire such aggressive measures. Lack of discussion and/or documentation about resuscitation preferences has led to care incongruous with patient's wishes as previously documented or reported to providers or family members. In December 2016, 49% of adult patients admitted to the inpatient oncology service at UPMC Shadyside had a code status discussion documented prior to discharge. The aim of this project is to improve the quality and rates of CPR status conversations.

Methods: A workgroup was formed in January 2017 among key stakeholders representing oncology physicians and fellows, palliative care faculty, oncology nursing, advance practice providers (APPs), and internal medicine house staff. A quality improvement (QI) proposal was developed and approved by the UPMC Quality Improvement Committee in February 2017. All oncology faculty, fellows, house staff, and APPs were reminded weekly to complete CPR status conversations and documentation. APPs were formally trained by palliative care specialists to discuss and document code status with all admitted patients. Hospital leadership received a monthly update of CPR status documentation rates, and a formal CPR status assessment best practice guidelines document was developed by the workgroup, endorsed by oncology leadership and shared among oncology providers.

Results: Since project implementation in January 2017, CPR status assessment rates have improved from 49% to >80% sustained over the past year. There were >1400 more CPR status discussions documented in 2017 than in 2016. No patients received resuscitation against documented wishes, and no patients had resuscitation withheld against documented wishes on the inpatient hematology-oncology service at UPMC Shadyside.

Conclusion: Standardization of CPR status assessment with formal training of clinicians and APPs resulted in a significant increase in the number of CPR status assessments on the inpatient setting. In the next Plan-Do-Study-Act cycle, we will be reviewing the data on patients who did not have their code status assessed, to address missed opportunities to improve our rates. We plan to expand the project to involve hospitalists and nocturnists.

79-B Poster: Overall survival based on oncologist density in the United States, do we need to redefine underserved areas for oncologic care?

Presenter: Kathan Mehta, Fellow
Services/Clinical Epidemiology
Hematology/Oncology

Research Interest: Health

Mentors: N/A

Funding Source: N/A

Authors: Sudeep Maheshappa MD, Smit Patel MD, Tapan Mehta MD, Smith Giri MD, Leonard Appleman MD, Vida Passero MD, Rahul Parikh MD

Introduction: American society of clinical oncology has predicted shortage of 2,550 to 4,080 oncologists by 2020, disproportionately higher in underserved areas. The Conrad-30 program was established for international medical graduates, trained on J1 visas, to work in medically underserved areas (MUAs) and health professional shortage areas (HPSAs) to correct this disparity. Thirty spots per year are available for each state and primary care providers (PCPs) are given priority. The designation of an area as MUA or HPSA is based on shortage of PCPs but not specialists.

Methods: We evaluated the impact of oncologist density (OD) defined as number of oncologists per 100,000 (100K) population on overall survival and concordance with MUA or HPSA designation of areas by quartiles of OD. We studied the distribution of oncologists on visa in areas by quartiles of OD by merging SEER data with AMA physician's master file using Federal Information Processing Standards (FIPS) code of the area.

Results: We identified 68,791 adult patients with newly diagnosed hematologic malignancies or metastatic solid cancers (excluding CNS cancers and patients with CNS metastases) in 612 FIPS code areas captured by SEER in 2011. After controlling for confounders, compared to patients in areas with lowest quartile of OD (<2.9 oncologists per 100K population), patients in areas with 2nd, 3rd and 4th quartile (2.9-6.5, 6.5-8.4, >8.4 oncologists per 100K population respectively) of OD had better overall survival (HR 0.96, 95%CI 0.94-0.98, p=0.001; HR 0.93, 95%CI 0.91-0.96, p<0.001; HR 0.9, 95%CI 0.88-0.92, p<0.001 respectively). There was no difference in proportion of MUA or HPSA designated areas among the four quartiles (79.6%, 71.9%, 64.5%, and 76.5% from 1st to 4th quartile, p=0.1). There was no difference in proportion of oncologists working on visa among the 4 quartiles (7.2%, 4.9%, 6.4%, and 6.4% from 1st to 4th quartile, p=0.5).

Conclusion: Patients in areas with higher OD have better overall survival. MUA or HPSA designation is not concordant with OD in different FIPS code areas. Current provisions of the Conrad-30 program is not promoting placement of oncologists on visa in areas with low OD. The Conrad-30 program needs to be amended to create designated spots for specialists like oncologists in each state proportionate to the relevant underserved population.

80-B Poster: Validating the MDS Mortality Risk Indes in Older Adult Veterans Using MDS Version 3.0

Presenter: Joshua Niznik, Post-Doctoral Fellow
Services/Clinical Epidemiology
Geriatric Medicine

Research Interest: Health

Mentors: Carolyn Thorpe PhD
Joshua Niznik PharmD
Joseph Hanlon PharmD, MS

Funding Source: T32 and VA

Authors: Joshua Niznik PharmD, Song Zhang PhD, Maria Mor PhD, Xinhua Zhao PhD, Mary Ersek PhD, Sherrie Aspinall PharmD, Joshua Thorpe PhD, Walid Gellad PhD, Joseph Hanlon PharmD, MS, Loren Schleiden MPH, Sydney Springer PharmD, Carolyn Thorpe PhD

Introduction: Identifying limited life-expectancy is important in care planning for nursing home (NH)residents. The MDS Mortality Risk Index (MMRI-R) is a validated scale using a weighted set of 12 items from theMinimum Data Set (MDS) v2.0 to predict 6-month mortality in NH residents. The transition to MDS v3.0 involved minor changes to wording and responses for some MMRI-R items, but potentially substantive changes in items for poor appetite and recent cognitive status change. These changes raise questions about translatability of the MMRI-R to MDS v3.0. The MMRI-R has also not been validated in a Veteran population. The objective of this analysis was to validate the MMRI-R adapted to MDS v3.0 items in a sample of older Veterans.

Methods: Data sources included the VA Residential History File (RHF) linked to MDS records for all Veterans aged =65 admitted to VA NHs between 07/01/12-09/30/15. We linked MDS admission assessments to the VA Vital Status File to identify deaths within 6 months of admission. To calculate MMRI-R scores, we used the 10 MDS v3.0 items that were similar to v2.0, and two items that most closely approximated the poor appetite and cognitive status items. We weighted each item using the original MMRI-R weights. Logistic regression was used to calculate the RoC curve and c-statistic for 6-month mortality, with MMRI-R score as the predictor. As a sensitivity analysis, we randomly partitioned the cohort into 50% training and validation samples to determine whether applying weights generated by our sample changed prediction.

Results: The sample consisted of 63,024 Veteran NH admissions. The majority were male (97.7%) and white (79.3%) with a 32.9% 6-month mortality rate. Applying the original MMRI-R weights, the c-statistic was 0.81, indicating good prediction. Among 15,897 individuals with a score >40, 69.1% died within 6 months. When applying new weights generated by our cohort, the c-statistic was 0.82.

Conclusion: The MMRI-R can be successfully adapted to MDS v3.0 by substituting similar assessment items and has comparable accuracy in predicting 6-month mortality. In addition, the MMRI-R is valid for predicting 6-month mortality in Veteran NH residents, a population distinct from other NH populations.

81-B Poster: Effects of a Flipped Classroom Cardiology Curriculum on Internal Medicine Residents' Knowledge and Preparedness

Presenter: Jill Allenbaugh, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Carla Spagnoletti MD, MS
Kathryn Berlacher MD, MS

Funding Source: DGIM grant

Authors: Jill Allenbaugh MD, Carla Spagnoletti MD, MS, Kathyrn Berlacher MD, MS

Introduction: Needs and Objectives: The flipped classroom model was developed to reinvigorate modern education. With a basis in adult learning theory, the model utilizes "at home" time for learners to study concepts, and "in class" time for application. While there are studies showing improved knowledge and preparedness in undergraduate medical education, there is a paucity of data on the use of a flipped classroom in resident education. At UPMC, most internal medicine residents rotate on an inpatient cardiology service yearly; yet there is no curriculum to provide a standardized experience. Rotation evaluations reflected the desire for increased teaching and a faculty needs assessment demonstrated gaps in resident knowledge and preparedness. We hypothesized that our cardiology education could be enhanced through a flipped-classroom model. We developed a curriculum that pairs Medical Knowledge Self-Assessment Program (MKSAP®) content with group case discussions with a goal to improve resident knowledge and preparedness in cardiology.

Methods: Participants included 98 residents who rotated on an inpatient cardiology service over 8 months. Pseudorandomization was used to divide residents into a control group (N=51) and an intervention group (N=47) based on the month of their rotation. In control months, faculty and fellows taught as they normally would. During intervention months, residents were emailed weekly MKSAP® readings and a clinical case to review on their own. A facilitator guide supported the supervising attendings and fellows who led weekly didactic sessions with case review.

Results: A total of 74 residents completed pre/post matched surveys (response rate 75%, 37 per arm). Knowledge score (20 MKSAP® questions) did not improve significantly in either arm (control 58% pre vs. 59% post and intervention 56% pre vs 58% post; p-value 0.616) nor did preparedness (control 3.13 pre vs. 3.62 post and intervention 3.29 pre vs. 3.84 post; p=0.544 on a 5-pt Likert Scale). The number of reported teaching sessions/week did not differ (2.3 control vs 2.5 intervention, p=0.347). Most residents (92%) and faculty (81%) agreed the curriculum should continue, but reported barriers include time constraints, low faculty buy-in, and lack of resident preparedness for the sessions.

Conclusion: This flipped-classroom cardiology curriculum did not affect knowledge, preparedness, or number of teaching sessions when compared to "usual" teaching. However, half of the intervention group did not complete the "at home" MKSAP® portion, raising questions about learner engagement and feasibility. Because most recommended continuing the curriculum, future iterations will focus on buy-in from both faculty and residents.

82-B Poster: An Innovative Skill-based Clinical Reasoning Curriculum for Clerkship-level Medical Students

Presenter: Eliana Bonifacino, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Deborah DiNardo MD

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

Authors: Eliana Bonifacino MD, William Follansbee MD, Amy Farkas MD, Melissa McNeil MD, Deborah DiNardo MD

Introduction: A 2015 IOM report highlighted the urgent need for better training in medical decision-making. Within undergraduate medical education (UME), a recent national survey suggested that up to 57% of medical schools lack formal education dedicated to clinical reasoning. We sought to determine if formalized instruction in clinical reasoning through use of an innovative multi-modal curriculum is an effective means of improving clinical reasoning skills in third year medical students.

Methods: We conducted a pseudorandomized and controlled experiment to evaluate the impact of this curriculum on clinical reasoning knowledge and skills in third year medical students at a single allopathic U.S. medical school in 2017. Students in the intervention group completed interactive online modules focused on clinical reasoning concepts and participated in a skills-based workshop. Students in the control group participated in standard educational experiences. We assessed the impact of the curriculum on clinical reasoning knowledge, skills, and attitudes according to the following metrics: 1. Performance on a 20-item quiz about clinical reasoning concepts at the conclusion of the 4-week intervention period; 2. Clinical reasoning skills through blinded scoring of weekly student hospital admission notes using a validated clinical reasoning assessment tool; 3. Clinical performance as indicated by clinical rotation evaluations; and 4. Attitudes regarding clinical reasoning education.

Results: 67 students participated in the study, from whom we received a total of 256 hospital admission notes. Students in the intervention group demonstrated superior performance on the 20-item clinical reasoning quiz (67% correct vs. 54%, $p<0.05$). Admission notes from the intervention group received significantly higher average ratings for data synthesis (2.3 vs. 2.0 on a 3-point scale, $p<0.05$) and for diagnostic reasoning (2.2 vs. 1.9, $p<0.05$), while average scores for data gathering, reporting, and decision-making did not differ. Clinical evaluations by attending physicians did not differ between the two groups. Students in the intervention group reported more frequent use of clinical reasoning terminology and more explicit discussion of clinical reasoning by their attending physicians.

Conclusion: Exposure to our innovative multi-modal curriculum was associated with improved knowledge regarding clinical reasoning concepts and superior written demonstration of clinical reasoning skills in 3rd year medical students. Thus, interactive online modules paired with opportunity for skills practice is an effective and efficient means of delivering clinical reasoning education within UME. Our student survey responses suggest that participation in such experiences may prime students to identify demonstration of clinical reasoning by clinical role models, thus providing a scaffolding for development of medical decision-making skills in the clinical setting.

83-B Poster: Educating Faculty and Resident Physicians on Safe Opioid Prescribing for Chronic Pain: Impact of a Brief Curriculum on Knowledge, Confidence, and Attitudes

Presenter: Andrea Carter, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Melissa McNeil MD

Funding Source: DGIM Fellow Development Award

Authors: Andrea Carter MD, Carla Spagnoletti MD, Scott Rothenberger PhD, Melissa McNeil MD

Introduction: Physician education on safe opioid prescribing is widely recommended but the optimal strategy remains unclear. We implemented and evaluated a brief curriculum on safe prescribing of opioids for chronic pain for internal medicine residents and Division of General Internal Medicine faculty with the goal of increasing knowledge, confidence, and attitudes on safe opioid prescribing.

Methods: All residents and faculty who precept resident clinic were invited to participate in a curriculum consisting of a free online module on the 2016 Center for Disease Control and Prevention opioid prescribing guidelines followed by attending a 1-hour case-based lecture. Potential participants were asked to complete an online survey pre- and 3 months post-curriculum to evaluate knowledge, confidence, and attitudes on safe opioid prescribing. Survey questions were developed in conjunction with local content experts. Knowledge was assessed with 10 multiple choice questions, and confidence and attitudes were each assessed with 5-point Likert scale questions (from 1=low confidence/negative attitude to 5=high confidence/positive attitude). Demographics for participants (those who completed the module and/or attended the lecture) and nonparticipants were compared using Wilcoxon rank-sum tests. The percent correct on the knowledge questions and the mean composite confidence and attitude scores were compared pre- and 3 months post-curriculum for participants and non-participants using paired t-tests with 2-sided p-value<0.05 indicating significance.

Results: Overall, 32 of 40 invited faculty (80%) and 35 of 106 invited residents (33%) completed both the pre- and post-surveys and were included in the analysis. Of the survey respondents, 28 (88%) faculty and 28 (80%) residents participated in the curriculum. There were no differences between participants and nonparticipants in clinic site, years in practice, or estimated number of patients seen on chronic opioid therapy (p>0.3 for all). Compared to pre-curriculum, faculty participants had increases in knowledge at 3 months (mean number correct 8.7 vs 8.1, p=0.02), but both resident participants and all nonparticipants had no change in knowledge. All curriculum participants had increases in confidence (faculty: 4.1 vs 3.7, p<0.01; residents: 3.7 vs 3.2, p<0.01) and attitude (faculty: 2.9 vs 2.6, p<0.01; residents: 2.5 vs 2.2, p<0.01) at 3 months. Nonparticipants did not have changes in confidence or attitude.

Conclusion: Implementation of a curriculum on safe opioid prescribing created increases in knowledge, confidence, and attitudes for faculty participants and increases confidence and attitudes for resident participants which were sustained over 3 months with no changes among nonparticipants. This brief curriculum based on available online resources can be implemented widely and with little cost or time and can impact knowledge, confidence, and attitudes.

84-B Poster: Piloting a Curriculum on Writing Simulated Patient Cases in a Teaching Communication Course

Presenter: April Christensen, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Rene Claxton MD

Funding Source: DGIM Grant

Authors: April Christensen MD, Rene Claxton MD

Introduction: Patient communication is a crucial skill that impacts how patients cope with illness. The most effective form of communication training is facilitated practice with simulated patients (SPs), trained actors who portray patients based on written cases. Despite the importance of this education, little guidance exists on how to write effective SP cases and early educators struggle in this area. Poorly-written cases can negatively impact learner education and potentially patient outcomes.

Methods: To address these concerns, we developed a standardized case-writing curriculum in coordination with local and national communication educators. The curriculum included a guided case-development manual and an in-class case-writing session.We piloted the curriculum in the Institute for Clinical Research Education (ICRE) Teaching Communication Skills course. This course trains fellows and faculty how to teach communication skills in small groups and clinical settings. In the three years prior to the pilot, students received traditional in-class instruction and then wrote cases in groups.For the pilot, we instructed students to independently review the case-development manual. At the next session, we answered questions and then divided students into four groups to write cases. We administered two surveys, one after students reviewed the manual and one after the in-class exercise.We compared cases written during the in-class exercise to cases written with the previous curriculum. The primary outcome was the number of 24 prespecified criteria students' SP cases fulfilled. A secondary outcome was the perceived ease of portrayal on a 5-point Likert scale as evaluated by an experienced SP. Other secondary outcomes included student-reported confidence in writing cases and satisfaction with the curriculum.

Results: All 17 students in the Teaching Communication Skills class participated in the curriculum. Four SP cases were written with the new curriculum, and eight SP cases were available from previous years.SP cases written with the new curriculum scored 1.75 points higher on a 5-point Likert scale for ease of portrayal (4.5 vs. 2.75, $p<0.05$). Students' confidence in their ability to write SP cases as rated on a 5-point Likert scale significantly increased from 1.9 to 4.0 following the intervention. Students ranked the case-development manual highly on clarity (4.6/5) and effectiveness (4.5/5). Data analysis on the primary outcome is ongoing.

Conclusion: A new case-development manual combined with an in-class writing session significantly improved the quality of new cases compared to traditional, in-class instruction. Furthermore, students reported significantly increased confidence in writing cases along with high satisfaction. Final data analysis of the primary outcome will be available within two weeks.

85-B Poster: The Safe Discharge Curriculum: How We Standardized Trainees' Approach to Discharge to Target Hospital Readmissions

Presenter: Elizabeth Eden, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Anna Donovan MD
Carla Spagnoletti MD, MS

Funding Source: Shadyside Hospital Competitive Research Fund

Authors: Elizabeth Eden MD, Allison DeKosky MD, Scott Rothenberger PhD, Anna Donovan MD

Introduction: Hospital discharge is a challenging time for residents, requiring completion of many tasks to ensure safe transitions for patients. Readmission rates are used as a hospital quality metric, with about a quarter attributed to preventable causes. We aimed to reduce hospital readmissions on general medicine house staff teams with a curriculum standardizing the approach to discharge.
Methods: Internal medicine residents on ward teams at two academic hospitals from July to October 2017 participated in the curriculum. It was piloted with residents nearing the end of the previous academic year from March to June 2017. The intervention had three components: didactic, daily bedside "rounds rundown" highlighting discharge details, and Safe Discharge Checklist for review prior to discharges. Bedside rounds were observed twice monthly to assess implementation of the intervention. Participants were surveyed at the end of each rotation to assess confidence, attitudes, and reported frequency of skills surrounding discharge planning. The primary outcome was 30-day hospital readmission rate during the intervention compared to a historical control from July-October 2016. Secondary outcomes included 7-day hospital readmissions, Emergency Department (ED) return rates at 7 and 30 days, and resident reported confidence and behaviors. Intern pre-surveys from the pilot were also compared to post-surveys from the intervention phase.
Results: One-hundred and two residents participated, with 60 completing post-intervention surveys. Hospital readmission and ED return rates at 7 and 30 days were similar between the two groups. Observers documented 72% compliance with initiating the bedside rounds rundown. Participants indicated confidence in discharging patients and endorsed having a standard approach to discharge planning after the intervention. Compared to pilot group interns, new interns reported similar confidence with discharge planning and having a standard discharge routine. Intervention group interns endorsed completing 5 of 7 tasks of discharge planning more frequently than pilot interns, such as reviewing the medication reconciliation with their resident (4.3 vs 3.3 on a 1-5 Likert-type scale where 1=never and 5= always, $p<0.001$) and encouraging patients to schedule outpatient follow-ups (3.7 vs 4.3, $p=0.003$).
Conclusion: Our safe discharge curriculum was feasible and well-received. While it did not reduce the rate of hospital readmissions or returns, this finding likely reflects the multifactorial nature of hospital readmissions, which are not all targeted by an intervention focused on physician discharge planning. Interns exposed to the curriculum had a higher reported frequency of completing key discharge tasks and improved confidence surrounding discharge, when compared to end of the year interns from the pilot. These improvements suggest that the curriculum led to accelerated learning and skill with discharge practices.

86-B Poster: Health Policy Curricular Objectives for Residents in Internal Medicine

Presenter: Molly Fisher, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Melissa McNeil MD, MPH
Amy Farkas MD
Peggy Hasley MD, MHSc

Funding Source: DGIM Grant

Authors: Molly Fisher MD, Amy Farkas MD, Preston Reynolds MD, PhD, Peggy Hasley MD, MHSc, Melissa McNeil MD, MPH

Introduction: National health policy is rapidly evolving and these changes impact both patients and physicians. Multiple health care organizations recommend the promotion of physicians' understanding of health policy and the literature has demonstrated increased interest among trainees. What topics should constitute the core curriculum for health policy education remains uncertain. The objective of this project was to develop a prioritized list of topics that should be taught to all categorical internal medicine residents.

Methods: We conducted a Delphi survey of health policy experts asking them to rank order a list of health policy topics for consideration in a curriculum. Participants were physicians who were identified as having expertise in health policy. The participants were asked to rank each of the 69 health policy topics, using a 1-5 Likert scale, based on how important they thought each topic was for every internal medicine resident to learn. Those who completed the first round were invited to participate in the second round. For the second round, we included the same topics with their medians from the first round. Each expert was asked again to rank each topic. At the end of the second round, new medians were calculated.

Results: Twenty-four experts were contacted, and 16 completed the first round of ranking. Of the 16 who completed the first round of ranking, 13 completed the second round for a response rate of 81%. At the end of the second round, 19 topics were ranked as essential (median=5), 33 were very important (median=4) and 17 were moderately important (median=3). The essential topics primarily included Medicare, Medicaid, private insurance, the cost of healthcare, and social determinants of health.

Conclusion: This data demonstrates that all of the 69 topics were considered to be at least moderately important with a substantial number being ranked as very important and essential. There was consensus that the essential topics in a health policy curriculum include health insurance and the cost of healthcare. This prioritized list of topics should be helpful to educators when deciding how to focus a health policy curriculum when there is limited curricular time available.

87-B Poster: RESIDENT PHYSICIANS' PERCEPTIONS OF INTERDISCIPLINARY TEAM ROLES IN THE NURSING FACILITY

Presenter: Jennifer Hwang, Fellow
Geriatric Medicine

Research Interest: Medical Education

Mentors: N/A

Funding Source: N/A

Authors: NULL

Introduction: ACGME requirements for family medicine (FM) resident training include long-term care (LTC) education over a 24-month period. Many medical student and residents have little to no exposure with LTC patient care. Misconceptions and stigmas regarding LTC facilities with little understanding of the unique patient care concept in these diverse settings are prevalent. LTC facilities provide care through an interdisciplinary team (IDT) base approach that includes physician/providers, physical therapy and occupational therapy (PT/OT), audiology and speech language therapy, social work (SW) team, and nursing staff. Understanding and interacting with each team is essential to perfecting the interdisciplinary approach that maximizes a patient's overall care. In this project, we followed FM residents over the course of three years and assessed basic perceptions regarding the contributory roles of IDT members. We aimed to assess if experiencing a LTC setting affected understanding of IDT roles.

Methods: Identified FM residents working in one continuity post-acute (PAC)/LTC facility during 2014-2017. Physicians-in-training completed surveys at the beginning and end of nursing home training fulfilling 2 years of long-term care training. By drawing a pie circle totaling 100%, each resident physician rated the contributing value percentage out of 100% for PT/OT, SW, medical provider and nursing team.

Results: Prior to joining the IDT team, majority (64%) of FM residents viewed the physician as the most important role and nursing staff and SW team as the least valued role. After 2 years of continuity training, only 18% of learners viewed the medical provider as the most important team member. Post survey results demonstrate that learners viewed each IDT member equally (25%) across the four main team members. All FM residents scored the medical provider contributing value lower in the post survey

Conclusion: Prior to LTC facility exposure, most medical residents identified the physician as most valuable within the IDT model. However, after 2 years of continuous LTC facility training, most medical residents' views of the IDT shifted towards an equal role. This small pilot study demonstrated that continuous exposure to a LTC facility helps FM residents to understand each member's role. Currently, we are looking to survey more resident physicians at different LTC facilities. In the future, the goal is to survey and obtain internal medicine residents perceptions on the IDT model and assess correlations to amount of training in LTC setting. Ultimately, the goal is to incorporate more IDT experiences and therefore, enhance geriatric education in resident physicians.

88-B Poster: NURSING FACILITY TRAINING ENHANCES GERIATRIC MEDICAL KNOWLEDGE IN GRADUATE MEDICAL EDUCATION

Presenter: Jennifer Hwang, Fellow
Geriatric Medicine

Research Interest: Medical Education

Mentors: N/A

Funding Source: N/A

Authors: Jennifer Hwang DO

Introduction: As the geriatric population grows, the demand for physicians qualified in nursing home training rapidly increases. Medical residents have little to no exposure with continuous skilled nursing facility (SNF) or long-term patient care (LTC). However, medical residents play pivotal roles in transition of care to and from SNF and LTC transfers. Accreditation Council for Graduate Medical Education (ACGME) requirements for family medicine resident training includes long-term care education over a 24-month period. In this project, we followed family medicine residents over the course of two years and assessed basic geriatric knowledge through a geriatrics knowledge test consisting of board-style geriatric questions and surveys. We hypothesize that incorporation of nursing facility training increases resident- physician knowledge of geriatric medicine and therefore, LTC training is a crucial part of graduate medical education (GME).

Methods: Family medicine residents of the same residency program working in one continuity long-term care facility during the July 2014 to July 2017 were identified. Physicians-in-training were given surveys and randomized board-style geriatric questions at the beginning and end of nursing home training with a total of 2 years of long-term care training. The knowledge test included a mixture of geriatric and nursing home pertinent multiple-choice questions (MCQ) and true or false assessment (TFA). The survey results were collected and analyzed. Administered knowledge-based questions assessed for geriatric syndromes, pharmacology, end-of life, and interdisciplinary team understanding.

Results: All resident physicians demonstrated improved scores in multiple choice questions and true-false assessments. The baseline knowledge score average was 52% and increased to 81% after completion of LTC training.

Conclusion: After 2 years of continuous nursing facility training, all medical residents scored better on geriatric knowledge assessment. The improved scores suggest better understanding and knowledge of geriatric medicine when learners are actively training in a post-acute and long-term setting.

89-B Poster: We're Better Together: A Curriculum for Enhancing Interprofessional Care in Resident Clinic

Presenter: Tanya Nikiforova, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Peggy Hasley MD
Carla Spagnoletti MD, MS

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

Authors: Tanya Nikiforova MD, Carla Spagnoletti MD, MS, Scott Rothenberger PhD, Peggy Hasley MD

Introduction: An interprofessional, team-based approach is essential for optimal patient care, yet residents receive little formal training on collaboration with interprofessional teams in the outpatient setting. We developed a structured curriculum promoting collaboration between residents and the interprofessional team in their continuity clinic. Aims include to increase residents' knowledge of team members' roles and responsibilities, attitudes towards team-based care, and patient referrals to team members.

Methods: The curriculum was implemented for 71 internal medicine (IM) residents with continuity clinic at UPMC Montefiore. Residents participated in five 45-minute small group sessions, each dedicated to an interprofessional team member's discipline: pharmacy, psychology, social work, care management, and diabetic/nurse education. The session material, co-written by team members and investigators, was presented in the form of interactive, case-based discussions. IM residents with clinic at UPMC Shadyside did not participate in the curriculum and served as controls; at baseline, the interprofessional team is better integrated in resident clinic at this site. A survey assessing knowledge and attitudes related to team-based care was administered to control and intervention residents before and after curriculum implementation. A chart audit objectively assessing impact of the curriculum on referrals placed to team members is underway.

Results: Of residents surveyed, 89% completed the pre-test and 76% completed the post-test. Following curriculum implementation, awareness of resources provided by team members, appropriate situations to consult team members, and methods for consulting team members improved among intervention residents (mean score 3.4 pre vs 3.9 post on Likert-type scale from 1-5, $p<0.001$). On the pre-test, control residents were more knowledgeable regarding use of the team (4.0 control vs 3.4 intervention, $p<0.001$), but after the curriculum, there was no difference between the groups (4.0 control vs 3.9 intervention, $p=0.3$). Intervention residents' knowledge of team members' names improved after curriculum implementation (32% correct pre vs 47% correct post, $p=0.009$). Attitudes towards team-based care did not change after curriculum implementation, but were high at baseline (mean score 3.6 pre vs 3.7 post on Likert-type scale from 1-5, $p=0.11$).

Conclusion: Our curriculum improved residents' knowledge regarding working with the interprofessional team, and we are assessing its impact on referral patterns. The collaborative approach to this curriculum enhanced buy-in from all parties. Dedicating a full session to each team member allowed for an in-depth look at the scope of services provided. Our curriculum can effectively introduce residents to the interprofessional team in a clinical practice and could be adapted to other resident clinics.

90-B Poster: Impact of a required, longitudinal scholarly project in medical school: a content analysis of medical students' reflections

Presenter: Tanya Nikiforova, Fellow
Education
General Internal Medicine

Research Interest: Medical

Mentors: Judy Chang MD, MPH

Funding Source: N/A

Authors: Tanya Nikiforova MD, Andrea Carter MD, Judy Chang MD, MPH

Introduction: Scholarly projects are a diverse set of programs that provide medical students with research experience during medical school. These programs offer students many potential advantages, including mentorship, career guidance, opportunities to produce scholarly work, and acquisition of knowledge and skills. At the University of Pittsburgh School of Medicine (UPSOM), medical students are required to participate in a longitudinal Scholarly Research Project (SRP) throughout all four years of medical school. The outcomes of the SRP have not been evaluated, and we aimed to better understand the impact of participation in this program on medical students.

Methods: UPSOM students submit a written reflection on their experience with the SRP at the end of medical school training. We performed qualitative content analysis of 120 reflections submitted between 2012 and 2017; twenty reflections were randomly selected from each year. Reflections were coded by 2 investigators using an inductive approach and reviewed for overarching themes.

Results: Four themes were identified: 1) After completion of the SRP, medical students were able to identify the various steps of the research process, from generating a research question to preparing findings for dissemination. Many students reported experience with all aspects of this process. 2) Through the SRP, students had opportunity to assume responsibility and leadership over a project from start to finish and found this to be a meaningful facet of their experience. 3) Students developed appreciation for the difficulty of the research process through the challenges they encountered and overcame during their project. 4) Students described specific skills learned that will be useful regardless of career choice, including critical appraisal of scientific literature, teamwork, and research skills they can use in future scholarly endeavors.

Conclusion: Through participation in a required scholarly project at the UPSOM, medical students learned and engaged in all steps of scientific inquiry. The longitudinal nature of the SRP allowed students to gain skills in leadership and professionalism as they assumed responsibility over a project throughout their medical school training. Medical students reported developing critical thinking skills that are essential for physicians regardless of career path. Given the positive impacts of the SRP, other programs may consider implementing required and/or longitudinal research experiences for medical students.

91-B Poster: RANDOMIZED ADAPTIVE TRIAL OF DIGITAL BEHAVIORAL PROGRAM FOR ANXIETY AND DEPRESSION IN IBD PATIENT CENTERED MEDICAL HOME

Presenter: Siobhan Proksell, Fellow **Research Interest:** Medical Education Gastroenterology, Hepatology and Nutrition

Mentors: Eva Szigethy MD, PhD **Funding Source:** UPMC Enterprises

Authors: Siobhan Proksell MD, Benjamin Click MD, Eva Szigethy MD, Megan Oser PhD, Meredith Wallace PhD, Emily Weaver LCSW, Alyssa Culp CRNP, Jane Kogan PhD, Miguel Regueiro MD

Introduction: Anxiety and depression are common and treatable disorders in patients with IBD, yet many gastrointestinal (GI) clinical settings lack the resources for integrated behavioral care. Given the robust effectiveness of cognitive behavioral therapy (CBT) to treat behavioral disorders and the paucity or mixed findings of CBT in IBD, a digital CBT program embedded into a stepped integrated model of care is evaluated within an IBD subspecialty medical home (SMH).

Methods: A sequential multiple assignment randomized trial (SMART) design was used to evaluate the efficacy of integrating digital behavioral screening and digital cognitive behavioral program in improving anxiety, depression, IBD activity, and care efficiency in an IBD SMH. The IBD SMH is an integrated medical-behavioral team-based care model. Adults with IBD who screened positive for clinically significant anxiety (GAD-7) were randomized to either digital CBT (active) or symptom monitoring (control) for 3 months. Patients were re-evaluated at 3 months and those with inadequate behavioral improvement were re-randomized to the digital CBT program or face-to-face (FtF) CBT with a social worker (control); or re-randomized to use the digital CBT program plus FtF CBT with the social worker or FtF CBT with the social worker alone (active) and reassessed at 6 months. Digital CBT is a self-guided program with guidance from coaches via text. Primary outcomes were improvements in anxiety, depression and quality of life (SIBDQ). Standard linear mixed models were used for main effects for the initial wave.

Results: 69 patients were randomized (n=34 active and 35 control group); mean age 34; 65% F, and 64% with CD. No significant difference in baseline characteristics. There was a significantly greater reduction in anxiety in the active group over 3 months (delta 5.8; CI (3.9, 7.6); p<.001; n=24) than in the control group (delta 2.5; CI (0.5, 4.6); p=.02; n=24) and greater reduction of depression (delta 2.6; CI (.6, 4.6); p=.01 in active group vs. delta 0.4; CI (-2.2, 3.1); NS in control group. In the active group, 96% of patients engaged with the digital CBT app with 69% practicing at least 3 distinct techniques (mean 6 sessions and 9 techniques completed). Over this period, the control group received 3x as many sessions with the social worker than the active group (1.3 vs 0.4).

Conclusion: The ability to show how behavioral health technology can improve patient clinical outcomes and team efficiency within a stepped care model provides a powerful solution for patients to access feasible effective behavioral care in GI medical settings.

92-B Poster: The Bedside Swap: Perspective-Taking in a Narrative Writing Curriculum as a novel means to Strengthen the Trainee-Patient Relationship in the Ambulatory Setting

Presenter: Brianna Rossiter, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Melissa McNeil MD
Gaetan Sgro MD

Funding Source: N/A

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 medicine.. Interactions with so-called "challenging" patients in the ambulatory setting are often cited as drivers of burnout. 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. This approach can help trainees "see" the world through their "difficult patients'" eyes. We describe an ongoing curriculum assessing internal medicine residents' response to the implementation of a perspective-taking exercise.

Methods: This curriculum is currently taking place within the PGY3 Ambulatory rotation of the UPMC Internal Medicine Residency, which all PGY3 residents complete as part of their training. Residents are required to participate in our curriculum but can opt-out of our research evaluation. Our curriculum includes: 1) a brief introductory session on perspective-taking, 2) a self-directed perspective-taking exercise in which all residents are asked to respond to a prompt about a "challenging" patient in their ambulatory clinic, and 3) a de-briefing session in which PT pieces are shared in a facilitator-guided, group reflection.

Results: Our evaluation includes both quantitative and qualitative components. Participants complete a validated, empathy measure, the Jefferson Empathy Scale, both before and after completion of the PT exercise. A follow-up focus group will be conducted 2-5 months following the intervention (June 2018) to elicit residents' perceptions of the curriculum. We hypothesize that compared to baseline, participants who complete the PT curriculum will demonstrate increased empathy and a greater appreciation for the individual, patient factors that influence interactions with the healthcare system. While evaluation will be ongoing, preliminary data including an initial, descriptive assessment of the PT exercises. Excerpts from PT exercises include such insightful thoughts as, "It's hard enough living by myself in a house with no hot water and no income to clean myself without having to worry about getting to see the doctor".

Conclusion: Altruism and empathy may by supplanted by cynicism and detachment after residents are subjected to the rigors of training. Existing literature suggests that increased empathy correlates with high patient satisfaction and improved patient care. Therefore, residencies need to develop novel approaches to preserve and enhance empathy.

93-B Poster: Exam Room Presentations in Resident Continuity Clinic

Presenter: Rachel Vanderberg, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Melissa McNeil MD
Carla Spagnoletti MD, MS

Funding Source: University of Pittsburgh Division of General Inter

Authors: Rachel Vanderberg MD, Tanya Nikiforova MD, Megan Hamm PhD, Carla Spagnoletti MD, MS, Melissa McNeil MD

Introduction: Current literature suggests exam room presentations (ERPs) in resident continuity clinic (RCC) have several benefits. ERPs facilitate direct observation, improve patient satisfaction, and provide an opportunity to return to the bedside. However, the majority of case presentations take place in the conference room. We aimed to explore the feasibility of ERPs as a precepting model in RCC.

Methods: Participants included University of Pittsburgh General Internal Medicine faculty (n=16) and residents (n=20) across all three RCC sites who participated in a one month pilot of ERPs. We defined an ERP as the case presentation and discussion taking place in the exam room with the attending and patient present. We conducted a descriptive qualitative study using semi-structured one-on-one phone interviews with faculty and four focus groups with residents (average 5/group). Transcripts were analyzed using the constant comparative method.

Results: Advantages and disadvantages of ERPs fell into two domains: medical education and patient care. Within medical education, two themes emerged: 1) ERPs create unique learning opportunities regarding role modeling, physical exam, and communication while limiting learning opportunities about guidelines, research, and clinical decision making; and 2) direct observation during ERPs provides meaningful formative feedback; however, constructive feedback may negatively impact the resident-patient relationship. Within patient care, four themes emerged: 1) verification of the resident's history and exam improved quality care, but trouble reviewing objective data in the electronic medical record (EMR) hindered quality care, 2) ERPs enhanced patient centeredness, but too much patient participation led to unfocused encounters, 3) some patients enjoyed seeing the medical decision making process, while for others clinical discussions were confusing, and 4) ERPs sometimes provided an opportunity to highlight the resident's skill, while at other times detracted from resident's role as the primary provider. Other barriers included: 1) ERPs are time consuming, 2) the design of exam rooms make ERPs awkward, and 3) difficulty reviewing the EMR in real-time.

Conclusion: ERPs can have substantial educational and patient care benefit, but use in appropriate situations is key. Patients with abnormal exam findings or counseling visits were identified as ideal for ERPs, while sensitive issues or clinical uncertainty were best discussed in the conference room. Strategies to preserve the resident's role as the primary provider included having the resident sit closest to the patient, tolerating stylistic differences in management, and providing tactful correction.

94-B Poster: Wnt Pathway Inhibitor DKK1: A Potential Novel Biomarker for Ectopic Skeletal Muscle Adiposity

Presenter: Hira Ali, Post-Doctoral Fellow
Endocrinology and Metabolism

Research Interest: Translational

Mentors: Iva Miljkovic MD
Erin Kershaw MD
Joseph Zmuda MD

Funding Source: T32

Authors: Hira Ali MD, Joseph Zmuda MD, Ryan Cvejkus MSc, Erin Kershaw MD, Alison Kuipers PhD, Clareann Bunker PhD, Iva Miljkovic MD

Introduction: Emerging evidence indicates that ectopic skeletal muscle adiposity (i.e. myosteatosis) is greater in African than in European ancestry individuals, and may be a novel risk factor contributing to increased diabetes risk. However, the biological mechanisms underlying myosteatosis are largely unknown. In vitro studies suggest that a Wnt pathway inhibitor, Dickkopf related protein 1 (DKK1), could be a novel biomarker with a role in adiposity regulation.

Methods: We measured fasting serum DKK1 in a pilot study of 159 elderly Afro-Caribbean men (mean age 63.4yrs, mean BMI 27.8 kg/m2), a random subset of a population-based study comprising ~3000 African Ancestry men with fasting morning blood collections for biomarker analyses. DKK1 was measured in duplicate in previously unthawed serum with ELISA.Also assessed were anthropometrics, DXA measured adiposity, and lower leg CT measured myosteatosis (intermuscular adiposity (mm2)) and skeletal muscle density (which reflects the intra-muscular fat content ((mg/cm3) such that greater intra-muscular adiposity reflects lower muscle density).

Results: In Spearman correlation analysis DKK1 was positively associated with BMI (R=0.19, p=0.01), waist circumference (R=0.15, p=0.05), DXA total body fat (R=0.22, p=0.004), and DXA trunk fat (R=0.19, p=0.01), independent of age. In addition, DKK1 was associated positively with intermuscular fat (R=0.19, p=0.01), and inversely with muscle density (R=-0.29, p=<0.001), independent of age and BMI. No significant association was found between DKK1 and fasting serum glucose and insulin levels, and HOMA-IR.

Conclusion: Our findings suggest for the first time that higher serum levels of DKK1 may be associated with greater overall adiposity, and ectopic skeletal muscle adiposity. Further studies are needed to unravel the potential role of DKK1 in the regulation of body fat among African ancestry and other population groups with a high risk of developing obesity and related metabolic disorders

96-B Poster: Adult Stem Cells in combination with respiratory assistance devices protects cardiac mitochondrial function in a LPS-induced ARDS large animal model

Presenter: Diana Alvarez, Post-Doctoral Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Mauricio Rojas MD

Funding Source: Department pf Defense

Authors: Diana Alvarez MD, Nayra Cárdenes PhD, Ergin Kocyildirim MD, Andrea Elliott MD, Thomas Drabek MD, John Sembrat MS, Brian Kimball BS, Paola Aranda MD, Jacobo Sellarés MD, Luigi Lagazzi MD, Anthony Ting PhD, Mauricio Rojas MD

Introduction: Acute Respiratory Distress Syndrome (ARDS) is an inflammatory process often caused by sepsis and associated with high mortality. Refractory hypoxia from ARDS is treated with veno-venous extra corporeal membranous oxygenation (ECMO) which increases inflammatory markers. Stem cells modulate the immune system and thereby influence inflammation. Infusion of mesenchymal stem cells (MSCs) improves oxygenation and promotes recovery of pulmonary tissue in ARDS, but their effect on cardiac tissue is unknown. Another emerging therapy for ARDS is Hemolung, a low flow, single cannulation, CO2 removal system. Mitochondria is a key player in the maintenance of cellular function, but little is known about the effect of ARDS and respiratory assistance devices on this organelles.

Methods: 5 groups were included as follow: E. coli endotoxin, lipopolysaccharide (LPS) treated with mechanical ventilation alone; LPS and ECMO; LPS and Hemolung; LPS, ECMO and MSCs; LPS, Hemolung and MSCs. Sheep were kept under anesthesia and mechanical ventilation, and LPS was administered. 1 hr after LPS infusion, the animals were started on therapy according to their assigned group. Vital signs, hemodynamic measures, and blood samples were collected at 1 hr intervals. Hemodynamic measures and bronchoscopy were completed at baseline, 1 hr after LPS and at 6 hrs/completion. Tissue samples were harvested from lung and cardiac tissue for evaluation of mitochondrial function, using Clark electrode and protein analysis.

Results: ARDS-related changes were found after LPS injection. Upon instillation of MSC, we observed recovery of hypoxemia and improvement in hemodynamic function. Respiratory assistance devices were not helpful on recovering of lung function, but showed to help cardiac function and protect mitochondria. Changes in mitochondrial complexes expression were found in between groups.

Conclusion: Our results suggest that mitochondrial coupling is preserved in Cardiac Tissue with the use of Hemolung and ECMO as compared to LPS treated with mechanical ventilation alone. In Lung tissue, no differences were found in the groups.

97-B Poster: Reduced Alternative Complement Activity is Associated with Impaired Serum Control of Carbapenemase-producing Klebsiella pneumoniae in a Cohort of Critically Ill Patients

Presenter: William Bain, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Janet Lee MD

Funding Source: T32

Authors: William Bain MD, Tolani Olonisakin BS, Huihua Li MD, Zeyu Xiong MD, Seyed Mehdi Nouraie MD/PhD, Georgios Kitsios MD, Alison Morris MD, Yingze Zhang PhD, Bryan McVerry MD, Yohei Doi MD, Janet Lee MD

Introduction: Mortality in patients with ARDS remains high, in part due to infectious complications such as nosocomial pneumonia. Klebsiella pneumoniae Carbapenamase (KPC)-producing K. pneumoniae (KPC-Kp) strains can cause nosocomial pneumonia and are increasingly recognized as a public health threat due to their antibiotic resistance profile. In contrast to K1/K2 serotypes known to evade complement-mediated killing, prior reports have shown KPC-Kp of sequence type 258 to be highly susceptible to killing by serum from healthy donors. We hypothesized that reduced complement activity in critically ill patients may impair serum control of KPC-Kp growth.

Methods: Prospectively-collected serum samples from 213 consecutive patients enrolled in an Acute Lung Injury Registry (ALIR) were tested for classical (CH50) and alternative (AH50) complement pathway activity. Serum samples were incubated with antibody-fixed sheep erythrocytes (CH50) in the presence of Ca2+/Mg2+ or rabbit erythrocytes (AH50) in the presence of MgEGTA. Optical density (OD) of the supernatant from lysed erythrocytes was measured to calculate complement activity. Serum from ALIR patients and pooled healthy controls were also incubated with KPC5, a KPC-Kp ST258 isolate resistant to all antibiotics tested including colistin, to assess serum control of bacterial growth independent of patient antibiotic usage. KPC5 growth was determined by OD (600nm) at baseline and every 60 minutes for four hours. A multi-level mixed-effects linear regression model was used to assess the association between complement activity and KPC5 growth.

Results: The majority of enrolled patients (median age 57.1 years, 43% female) were either diagnosed with ARDS (n=77, 36%) or were at risk for ARDS with an identifiable risk factor (n=88, 41%). Sepsis was confirmed or probable in 68.5% of patients (n=146). Median time to sample collection was 48 hours following ICU admission. We identified a strong correlation (Spearman r=0.72, p <0.0001) between AH50 and CH50 values. Reduced AH50 activity was significantly associated with increased in vitro KPC5 growth in the two lowest AH50 quartiles compared to the highest AH50 quartile (p<0.001). There was no difference in control of KPC5 growth between CH50 quartiles.

Conclusion: Serum from a subset of critically ill patients fail to control relatively avirulent KPC-Kp growth in vitro, and impaired serum control of this pathogen is associated with reduced alternative but not classical complement activity. These findings suggest the possibility that a portion of critically ill patients exhibit functional defects in humoral immunity that may predispose them to certain opportunistic Gram-negative infections.

98-B Poster: Further development of a small molecule inhibitor of the deubiquitinase STAMBP

Presenter: Joseph S Bednash, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Rama Mallampalli MD

Funding Source: T32

Authors: Joseph S Bednash MD, Nathaniel Weathington MD PhD, Bill B Chen PhD, Rama K Mallampalli MD

Introduction: Innate immune signaling by the inflammasome contributes to the pathogenesis of the acute respiratory distress syndrome (ARDS). Inflammasomes are multi-protein complexes that critically regulate the early immune response by facilitating the maturation and release of the potent pro-inflammatory cytokines IL-1 and IL-18. Increased circulating IL-1 and IL-18 are associated with increased mortality in ARDS. Pharmacologic targeting of the deubiquitinase (DUB) STAMBP reduces inflammation in pre-clinical models by reducing inflammasome activity and secretion of IL-1 .Targeting of the ubiquitin-proteasome system in cancer has led to the development of multiple small molecule proteasome inhibitors. To date, there exist no FDA-approved DUB inhibitors for any indication. Development of a small molecule inhibitor of STAMBP deubiquitinase activity provided proof of concept for targeting DUBs as anti-inflammatory targets. Further optimization of a lead compound targeting STAMBP is necessary prior to use in animal and human models.

Methods: Cell culture and treatment, ELISA, Western blotting, co-immunoprecipitation, qPCR, in silico modeling and drug design, and in vitro DUB and caspase activity assays.

Results: In a fluorescence-based DUB enzyme assay, our lead compound STAMBP antagonist decreased the initial velocity of STAMBP DUB activity as well as the maximum velocity of this enzymatic reaction. We then tested nine additional compounds with a similar backbone structure to the lead compound with substituted functional groups on the periphery of the lead compound molecular structure. Results of these studies were used to further modify the lead compound, which will subsequently be used for additional testing in our enzymatic assay.

Conclusion: Our small molecule inhibitor establishes STAMBP as a potential therapeutic target to reduce the effects of injurious inflammasome-driven pro-inflammatory stress. Prior development of a lead compound targeting STAMBP provided proof of concept, but further development is necessary prior to further testing in pre-clinical models. Using a fluorescence-based enzymatic assay, we identified functional group modifications that decrease the mean inhibitory concentration of this compound in cell-based systems. Further efforts in DUB inhibitor optimization may lead to use in clinical studies and eventual development of a novel class of anti-inflammatory agents for clinical use.

99-B Poster: Use of magnetic activated cell sorting to identify immunoglobulin-bound bacteria in bronchoalveolar lavage fluid in individuals with HIV and COPD

Presenter: Daniel Dunlap, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Alison Morris MD
Bryan McVerry MD

Funding Source: National Institutes of Health: RO1HL138630

Authors: Daniel Dunlap MD, Lauren Mullinax MD, Adam Fitch MS, Kelvin Li MS, John Ries BS, Laurence Huang MD, Barbare Methe PhD, Timothy Hand PhD, Alison Morris MD

Introduction: Greater than 70% of HIV+ outpatients manifest at least one lung function abnormality, with many developing COPD. However, the mechanisms are poorly understood. Alterations in the lung microbiome that occur in HIV may increase risk of COPD, but there are limited taxonomic differences in lung bacterial communities between HIV+ and HIV- individuals detected by 16S rRNA gene sequencing. Although bacterial communities may be similar, there may be differences in bacterial recognition by the host that contribute to lung dysfunction in HIV. Using magnetic activated cell sorting (MACS), immunoglobulin-bound bacteria can be sorted from bronchoalveolar lavage (BAL) fluid and analyzed using flow cytometry and 16S rRNA gene sequencing to elucidate the amount and type of Ig-bound bacteria in the lungs.

Methods: BAL fluid was obtained from individuals with and without HIV and with varying degrees of lung dysfunction. Fluid was stained with SYTO BC and IgG, IgA, or IgM PE, centrifuged, and supernatant removed. The pellet was suspended with buffer mixed with anti-PE micro beads, creating a magnetic label on Ig-bound bacteria. The fluid was then run through MACS columns composed of ferromagnetic spheres, embedded in a super magnet (MACS sorter). Unbound bacteria freely flowed through the column while immunoglobulin-bound material, including bacteria, were held in suspension within the column until being manually expelled and collected in separate tubes. The immunoglobulin-bound and unbound material was then analyzed using flow cytometry.

Results: Four individuals (2 HIV+, 2 HIV-) were included in preliminary results. Half of the individuals were male with an average age of approximately 50 years. Both HIV+ individuals were taking antiretroviral therapy. HIV+ individuals tended to have a greater number of IgG-bound bacteria detected in BAL. The greatest number of IgG-bound bacteria were recovered from the individual with both COPD and HIV. 16S rRNA sequencing demonstrated distinct bacterial communities between IgG-bound and IgG-unbound samples.

Conclusion: We used magnetic activated cell sorting to identify immunoglobulin-bound bacteria in BAL samples. This technique enables determination of which bacteria are recognized by the host and provoke an adaptive immune response. Future 16S rRNA gene sequencing of Ig-bound and unbound bacteria promises to elucidate functional differences between microbial communities, allowing us to better define the impact of the lung microbiome in HIV and COPD.

100-B Poster: CXCL9/10 Elevation in Severe Asthma is Refractory to Corticosteroid Therapy.

Presenter: Marc Gauthier, Post-Doctoral Fellow **Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Anuradha Ray PhD
Sally Wenzel MD

Funding Source: Individual NRSA (F32)

Authors: Marc Gauthier MD, Merritt Fajt MD, Anuradha Ray PhD, Sally Wenzel MD

Introduction: Patients with severe asthma account for 5-10% of all asthma patients, and are by definition poorly responsive to corticosteroids. The inflammatory picture is heterogeneous, and a better understanding of underlying molecular phenotypes will allow development and targeting of novel therapies. We recently identified a group of patients in the Severe Asthma Research Program (SARP) 1-2 study with high bronchoalveolar lavage cell CXCL10 levels in association with the Type-1 cytokine IFN-γ. Patients with these characteristics were more likely to be taking oral corticosteroids, consistent with more severe disease. SARP3 is the longitudinal follow up of SARP1-2, which includes an evaluation of patients before and 3 weeks after triamcinolone 40 mg IM. We hypothesized that a subgroup of severe asthma patients would be identified in sputum samples with elevated CXLC10 mRNA which was poorly suppressed by triamcinolone.

Methods: Severe (SA), Mild-moderate asthma (MMA) patients and healthy controls (HC) from the University of Pittsburgh SARP site were extensively characterized at baseline, including lung function, allergy testing, questionnaires, FeNO and sputum induction. Asthmatics all received 40mg triamcinolone IM and 3 weeks later induced sputum was again collected, along with pulmonary function testing, FeNO and clinical symptom questionnaires. Sputum RNA was isolated and CXCL9, CXCL10, GAPDH and GUSB assessed. Levels were compared across groups using ANOVA and Spearman's non-parametric correlation and Wilcoxon matched pairs testing was used to assess changes in paired samples.

Results: 33 patients (HC=7, MMA=7, SA=19) were included in the initial analysis. 13 of 19 SA patients had high levels (3SD above the HC mean) of CXCL9 and CXCL10, which were highly correlated $r=0.896$, $p<0.001$). CXCL10 high SA patients had higher eosinophil counts in sputum and blood than CXCL10 low, as well trends towards higher ACQ7 scores and greater oral corticosteroid (CS) utilization. 18 patients were examined pre and 3 weeks post triamcinolone. CXCL9 and CXCL10 levels were minimally affected in both the CXCL10 high group and in all asthmatic patients.

Conclusion: We have confirmed a CXCL10 high phenotype in association with severe asthma, using induced sputum. Levels of both CXCL9 and CXCL10 were refractory to corticosteroid therapy, suggesting this chemokine is poorly responsive to CS therapy. As CXCL10 recruits IFN-γ producing Th1 cells which promote further CXCL10 expression, this may lead to a steroid-refractory feed forward loop enhancing Type-1 inflammation.

101-B Poster: Ultrasound mediated antitumor efficacy of liposomal doxorubicin conjugated to polymer microbubbles with reduced cardiotoxicity in a mouse model of soft tissue sarcoma

Presenter: Mingyu He, Post-Doctoral Fellow
VMI

Research Interest: Translational

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. Anti-tumor efficacy, similarly dependent on Dox dose, is compromised when dosage must be decreased due to cardiotoxicity. An alternative preparation, pegylated liposomal Dox (Doxil®), putatively reduces cardiotoxicity. However, in clinical studies, Doxil® did not improve the maximal tolerated dose compared to free Dox, and prolonged circulation of encapsulated Dox caused a new dose-limiting toxicity, palmar plantar erythrodysesthesia (PPR). Thus, an optimal delivery platform for Dox remains elusive. Microbubbles (MBs) are intravenously injectable gas-filled microspheres that are clinically used as ultrasound (US) contrast agents. MBs can also be used as drug or gene carriers that undergo disease site-specific US-triggered unloading of cargo via navigation of the US beam. Accordingly, we hypothesized that MBs carrying liposomal Dox + tumor-targeted US will inhibit tumor growth in a murine sarcoma model while avoiding cardiotoxicity.

Methods: Liposomal Dox-loaded polymer MBs (Dox lipopolyplexes [DoxLPX]) were developed (~6×10-7 μg/MB). US was delivered (1 MHz, 5-cycle duration at 1,000 kPa followed by 495-cycle duration at 170 kPa, repeated every 2.5 sec) for 15 min during i.v. infusion of DoxLPX. Controls received an equivalent dose (5 mg/kg equiv. Dox per treatment) of free i.v. Dox, i.v. liposomal Dox, or i.v. saline, and treated with the same US regime. Treatments were given every 3-4 days (total 4 treatments). Tumor volume and cardiac function were serially monitored with high resolution ultrasound imaging. Histologic myocardial fibrosis in DoxLPX+US- treated animals was compared with that from controls.

Results: At one week after the last treatment, tumor volume (normalized to day 0) in mice treated with DoxLPX+US (n=3) was significantly lower than that in mice treated with liposomal Dox+US (32% lower, n=3) or free Dox+US (36% lower, n=2). Echocardiographic left ventricular (LV) ejection fraction, fractional shortening, LV mass and global radial strain were stable in mice getting DoxLPX+US, liposomal Dox+US and saline+US, whereas free Dox+US treated mice showed a relative decrease in these echo indices of systolic function and increase in LV mass. DoxLPX+US treated mice also showed less myocardial collagen deposition compared with free Dox or liposomal Dox treated mice.

Conclusion: DoxLPX + US targeted to the tumor site inhibits sarcoma growth while reducing Dox-induced cardiotoxicity, suggesting a new effective delivery platform for this important chemotherapeutic drug.

102-B Poster: Cross-talk between TGFß, Hippo and Akt Signaling Pathways in Pulmonary Vascular Smooth Muscle Cells in Pulmonary Arterial Hypertension

Presenter: Tatiana V Kudryashova, Post-Doctoral Fellow Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Elena A Goncharova PhD

Funding Source: NIH/NHLBI

Authors: Tatiana V Kudryashova PhD, Dmitry Goncharov MS, Andressa Pena BS, Arnab Ray , Analise Rode , Anastasia Eichler , Elena A Goncharova PhD

Introduction: Increased proliferation and survival of pulmonary arterial vascular smooth muscle cells (PAVSMC) are key pathological features of pulmonary arterial hypertension (PAH). Transforming growth factor beta (TGFß)-Smad and Hippo-Yap/Taz axis are deregulated in PAH and control proliferation/apoptosis imbalance. Relationship between TGFß and HIPPO pathways in regulating PAH PAVSMC is not known.

Methods: Quantitative enzyme-linked immunosorbent assay, immunocytochemical and immunoblot analyses, cell count assays, cell transfection, TUNEL-based apoptosis analysis.

Results: We found that PAVSMC from patients with idiopathic PAH secrete significantly higher amounts of TGFß1 compared to non-diseased controls (1287.5 pg/ml for PAH group vs. 147.7 pg/ml for control group; $p<0.05$ by Mann-Whitney U). Surprisingly, increased TGFß1 secretion in PAH PAVSMC was associated with reduced nuclear localization of Smad2 (shown by decreased nuclear/cytoplasmic ratio) and increased Smad2 phosphorylation in linker region at Thr220 and at Ser245/250/255, which is known to prevent Smad2 translocation to nucleus. That was accompanied by increased phosphorylation rates of pro-proliferative/pro-survival protein kinase Akt, non-canonical downstream effector of TGFß, and increased levels of major reciprocal effectors of Hippo, transcriptional co-activators Yap/Taz. ShRNA Yap and Akt inhibitor VIII selectively suppressed phosphorylation of Smad2 at Ser245/250/255 and at Thr220, respectively. Inhibition of either Akt or Yap significantly reduced proliferation and induced apoptosis in human PAH PAVSMC.

Conclusion: Our data demonstrate that Smad2 is down-regulated in human PAH PAVSMC compared to control cells, which is associated with activation of pro-proliferative/pro-survival Akt and Yap/Taz. Together with our findings on increased unstimulated TGFß1 secretion by PAH PAVSMC, this data suggest autocrine mechanism of TGFß1-dependent pathological switch from canonical Smads to pro-proliferative Akt. We also report that Akt and Yap cross-talk at Smad2, promoting it's phosphorylation and cytoplasmic translocation. Further studies are needed to determine potential role of cytoplasmic Smad2 in PAH pathogenesis.

103-B Poster: Identification of Novel SIRT3 Activators as Therapeutic Prospects for PH-HFpEF

Presenter: Andrea Levine, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Mark Gladwin MD

Funding Source: T32

Authors: Andrea Levine MD, Travis Lear BS, Bill Chen PhD, Yen-Chun Lai PhD, Elena Goncharova PhD, Mark Gladwin MD

Introduction: SIRT3 is a protein deacetylase which regulates mitochondrial metabolism and bioenergetics. In humans, a single nucleotide polymorphism which encodes for catalytic domain of SIRT3 is linked to the metabolic syndrome. SIRT3 deficiency has been identified in animal models of pulmonary hypertension and the metabolic syndrome. Our laboratory has demonstrated that rats with the metabolic syndrome and accompanying pulmonary hypertension associated with heart failure with preserved ejection fraction (PH-HFpEF) have SIRT3 deficiency exclusively in the skeletal muscle. Nitrite and metformin clinically improve PH-HFpEF in animals in a skeletal muscle SIRT3 dependent manner. This suggests a casual role of skeletal muscle SIRT3 activation in the management of metabolic syndrome-associated PH-HFpEF and offers a potential therapeutic target for PH-HFpEF, which currently lacks any pharmacologic therapies. In this study, we attempt to identify more potent SIRT3 activators using high throughput screening (HTS) as potential novel therapies for PH-HFpEF

Methods: 1100 FDA-approved drugs were screened for SIRT3 activity via high throughput screen. Each drug was incubated (at final concentration 10uM) with human recombinant SIRT3, NAD+, and substrate which comprises the protein sequence Gln-Pro-Lys-Lys(e-acetyl)-AMC. The assay was carried out at 37 degrees for 45 minutes. Developer cleaves the substrate and results in sample fluorescence. Compounds identified in this cell free system were then assayed in vitro using C2C12 murine skeletal muscle cells. Western blots and cell morphology analysis were done to assess SIRT3 activation and downstream effects.

Results: Five novel SIRT3 activators were identified by HTS: Dolutegravir, Chlortetracycline, Prazosin, Terazosin, and Alfusozin. Preliminary Western blot analysis confirms that a subset of the compounds identified by HTS activate skeletal muscle SIRT3 and the downstream target AMPK in vitro in C2C12 skeletal muscle cells. Furthermore, we trialed and validated previously reported SIRT3 activators in our skeletal muscle cell culture system.

Conclusion: We identified five potential SIRT3 activators by HTS with a small library of FDA-approved drugs. Our data suggests that Dolutegravir, Chlortetracycline, Prazosin, Terazosin, and Alfusozin function as skeletal muscle SIRT3 activators, which may offer a new avenue for treating PH-HFpEF. We plan to replicate the SIRT3 enzyme assay and in vitro experiments at physiological doses. Efficacious drugs will be trialed in primary human skeletal muscle cell culture and our ZSF1 sugen-hypoxia rat model of PH-HFpEF with metabolic syndrome. This study indicates that repurposing of several FDA approved, well tolerated drugs may confer a previously unrecognized benefit to cardiovascular health and offer novel therapeutic agents to PH-HFpEF.

104-B Poster: Acute Hemodynamic Effects of Oral Nitrite in PH-HFpEF

Presenter: Andrea Levine, Fellow
Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: Mark Gladwin MD

Funding Source: tPPG 2P01HL103455

Authors: Andrea Levine MD, Nicole Helbling RN, BSN, MS, Nydia Chien MSN, RN, Tim Bachman MS, Bruce Freeman PhD, Alison Morris MD, Marc Simon MD, Mark Gladwin MD

Introduction: Pulmonary hypertension (PH) occurs in 35-83% of patients with heart failure with preserved ejection fraction (HFpEF). PH is associated with worse outcomes in patients with HFpEF. The mortality rate of PH-HFpEF is 19.3% at one year and 43.5% at five years and there remain no effective therapeutic options for these patients. Oral nitrite has demonstrated promise in pre-clinical models of PH-HFpEF. Recently, a phase 2 clinical trial demonstrated that a single dose of inhaled nitrite significantly lowered pulmonary, right atrial, and pulmonary artery wedge pressures and substantially increased pulmonary artery compliance in patients with PH-HFpEF. We are currently evaluating the efficacy of chronic oral nitrite as a novel therapeutic agent in PH-HFpEF patients. We now report, for the first time, our initial findings of the acute hemodynamic effects of a single dose of oral nitrite.

Methods: This is part of an ongoing blinded 10-week cross-over treatment trial of oral nitrite in PH-HFpEF (NCT03015402). Patients were defined as having PH-HFpEF based on an ejection fraction > 40% and right heart catheterization (RHC) with a mPAP= 25 mmHg, PAWP =15 mmHg and TPG = 12 mmHg. Patients without RHC within 12 months underwent a screening RHC and if enrollment criteria were met, were given a single open label dose of 40 mg of sodium nitrite. Cardiopulmonary hemodynamics were obtained by RHC and were recorded at baseline and 30-minutes after single dose of 40mg oral nitrite. We are actively enrolling patients with the intent to provide open label oral sodium nitrite to ten patients.

Results: Five patients have currently been enrolled in the cross-over trial, of which two have required a screening RHC and have been given open label oral nitrite during the RHC. Oral nitrite administration was well tolerated in both patients without any reported adverse events. Both patients demonstrated a reduction in systolic blood pressure (-11 mmHg, -28 mmHg), right atrial (-1 mmHg, -4 mmHg), right ventricular systolic (-2 mmHg, -3mmHg), mean pulmonary artery (-3 mmHg, -10 mmHg), and pulmonary artery wedge pressures (-4 mmHg, -7 mmHg). There were slight reductions in cardiac output, cardiac index and a trivial increase in pulmonary vascular resistance. Pulmonary artery compliance increased 27% in one patient but was unchanged in the second patient.

Conclusion: Administration of oral nitrite acutely results in an improvement of right ventricular and left ventricular filling pressures without any significant reduction in cardiac output, cardiac index, or mean arterial pressure. Oral nitrite may be a novel therapeutic agent for patients with PH-HFpEF.

105-B Poster: Preclinical radiation dose optimization, dosimetry and maximum tolerated dose studies of Lu-177-labeled CTT1403, a phosphoramidate-based PSMA inhibitor for targeted radionuclide therapy of prostate cancer.

Presenter: Xiaoxi Ling, Post-Doctoral Fellow Hematology/Oncology

Research Interest: Translational

Mentors: Carolyn Anderson PhD

Funding Source: National Institutes of Health (HHSN261201500074C)

Authors: Xiaoxi Ling PhD, Joseph Latoche BS, Cindy Choy PhD, Jonathan Geruntho PhD, Charles Laymon PhD, Brenda Kurland PhD, Beatrice Langton-Webster PhD, Clifford Berkman PhD, Carolyn Anderson PhD

Introduction: Prostate-specific membrane antigen (PSMA) has proven to be an exceptional biomarker for prostate cancer as it is expressed on nearly all prostate cancers, and increased expression correlates with progression to metastatic disease and castration resistance. The performance of PSMA-targeted imaging and therapeutic agents is often limited by unfavorable rapid renal clearance. Previously, we developed a new PSMA targeted radiotherapeutic agent, CTT1403, which contained an albumin binding motif that extends blood circulation time with an irreversible PSMA inhibitor. Building upon the superior therapeutic efficacy of CTT1403 in a PSMA+ PC3-PIP human xenograft model, we performed translational studies on CTT1403 in rodent models, including dose optimization, dosimetry, and maximum tolerated dose (MTD).

Methods: For the dose optimization study, tumor-bearing mice received 1 to 3 reduced doses of CTT1403 or put into an untreated control group, and tumor growth was monitored for up to 120 days. In the dosimetry study, rats were euthanized at various time points up to 5 weeks post administration of CTT1403 for biodistribution. Their organs as well as excretion were collected and counted in a gamma counter for dosimetry analysis using OLINDA/EXM to estimate the equivalent human doses. In MTD study, rats were given increasing CTT1403 doses based on weight and closely monitored for up to 7 weeks. Blood samples were collected weekly for complete blood count (CBC) and liver and kidney enzyme analysis.

Results: In the dose optimization study, therapeutic responses were observed in mice receiving CTT1403 treatment compared to controls. Half of the mice receiving 2 or 3 doses of CTT1403 survived longer than the duration of the study. Dosimstry data demonstrate the kidney to be the dose limiting organ, with an effective dose of 5.18 mSv/MBq, which corresponds to a limit of 3.5 GBq in humans. In the MTD study, mice receiving a dose equivalent to 10.5 GBq in humans did not have dose-limiting toxicity, which is more than twice what was dose limiting from the dosimetry study.

Conclusion: Multiple lower doses of CTT1403 were found to be effective in the PSMA+ PC3-PIP human xenograft model, extending the potential administration options for CTT1403. Kidney was found to be the dose limiting organ, with an administration limit of 3.5 GBq in humans; this is one-third of the estimated MTD (10.5 Gbq). Overall, the preclinical efficacy and toxicity of CTT1403 suggests this agent will be safe and efficacious in humans.

106-B Poster: Age related cardiomyopathy in a transgenic knock-in mouse model of sickle cell disease

Presenter: Maureen Mburu, Post-Doctoral Fellow Cardiology

Research Interest: Translational

Mentors: Flordeliza S. Villanueva MD
Solomon Ofori-Acquah PhD

Funding Source: T32

Authors: Maureen W. Mburu MD, Rafey Feroze BS, Daniel Whitehurst BS, Samit Ghosh PhD, Xucai Chen PhD

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 indicate mice with homozygous SCD (SS) recapitulate the age-related clinical deterioration seen in humans. This is evidenced by the sudden decline in survival of SS mice during the transition from adolescence to adulthood; we have previously determined that the severity of intravascular hemolysis increases during this transition period. Hitherto, the cardiac phenotype of this murine model of SCD, which appears the most versatile, has not been defined.

Methods: In this study, we imaged the hearts of one, three, six and ten-month-old Townes SS mice and littermates with the normal adult human hemoglobin A (AA mice) using high resolution ultrasound (Vevo 2100, VisualSonics). Standard indices of LV systolic function, size, and mass, were derived from measurements made on short axis B-mode images of the heart.

Results: Major differences in the cardiac phenotype in SS compared to AA littermates were observed at six and ten months. At ten months, the SS mice had larger hearts (5.6 ? 0.2 mg/g, n=8, $p<0.0001$) compared to AA littermates (7.8 ? 0.3 mg/g, n=14). The LV internal dimensions in both systole and diastole were larger in the SS mice, accompanied by higher LV Mass Index (5.2 ? 0.5, n=9 versus 3.9 ? 0.2, n= 13, $p=0.03$) indicating LV hypertrophy in the SS mice. Systolic volume ($p<0.0001$) and diastolic volume ($p=0.0002$) were also higher in the SS mice compared to AA littermates, with a trend towards an increase in stroke index ($p=0.06$) as well as cardiac index (0.06). LV systolic dysfunction was evidenced by a decline in both ejection fraction ($p=0.0006$) and fractional shortening ($p=0.001$). The LV mass, LVID, cardiac volumes and LV systolic dysfunction significantly increased with age in the SS but not in the AA mice. SS mice were also anemic with significantly higher markers of intravascular hemolysis.

Conclusion: Our study shows progression of LV systolic dysfunction, LV enlargement and dilation in the Townes SS mice. Future studies are aimed at delineating the specific molecules and cognate pathways downstream of intravascular hemolysis that promote cardiomyopathy in SCD.

107-B Poster: Multiple genetic risk haplotypes in the autophagy gene [ATG] complex are associated with human chronic pancreatitis.

Presenter: Tanvi Nagpal, Fellow
Gastroenterology, Hepatology and Nutrition

Research Interest: Translational

Mentors: David Whitcomb MD

Funding Source: NIH DK061451

Authors: Tanvi Nagpal MS, Phil Greer MS, Guy Groblewski PhD, David Whitcomb MD

Introduction: Chronic pancreatitis (CP) is a syndrome of multiple etiologies causing ongoing stress, injury, inflammation and recurrent acute pancreatitis (RAP). Recent studies implicated the unfolded protein response (UPR) as a driver of acinar cell stress in some cases of CP. The acinar cell responds to misfolded proteins that are retained in the endoplasmic reticulum by forming autophagosomes that are trafficked to lysosomes for degradation and recycling components (i.e. autophagy). Autophagosomes are formed by recruitment of ATG16L1, ATG12 and ATG5 that form a complex which causes lipidation of LC3 to LC3-II encoded by MAP1LC3A/B/C (mammalian homologues of ATG8). Disruption of this process in experimental pancreas models cause cell stress and/or CP. Different genetic variants in regulatory elements of ATG genes increase risk or protect humans from inflammatory bowel disease (IBD).

Methods: North American Pancreatitis Study II (NAPS2) samples with SNP genotyping array data were analyzed for association between RAP/CP and controls at the ATG16L1, ATG12, ATG5 and MAP1LC3A/B/C loci using PLINK.

Results: We identified multiple haplotypes that were associated with protection or risk for RAP/CP. One rare missense variant from MAP1LC3B (Met60Val) was identified in a patient with RAP (P= 0.0009432). 4 intronic variants from 2 haplotype blocks in ATG16L1 had $P < 0.05$ and OR ~ 0.85 for association analysis of All Pancreatitis v/s Controls indicating its protective effect on Pancreatitis in general. 3 ATG5 variants in the same haplotype block had $P < 0.05$ and OR ~ 1.35 for RAP v/s Controls association analysis. Finally, an ATG12 variant had $P = 0.00309$ and OR = 2.59 for CP v/s Controls association analysis. These results indicate that ATG5 and ATG12 increase risk of RAP and CP respectively.

Conclusion: Using a candidate gene approach we demonstrated that several gene regulatory haplotypes are associated with protection from, or risk of CP, as previously demonstrated in IBD. The "protective" ATG16L1 haplotype variants are in linkage with the protective IBD variants that affect enhancer histone marks and may affect gene expression. Loss of function or expression is predicted to increase the risk of CP by impeding autophagosome formation, resulting in sustained UPR and stress signaling.

108-B Poster: PET imaging of upregulated VLA-4 in vaso-occlusive crisis using 64Cu-CB-TE1A1P-PEG4-LLP2A in a mouse model of sickle cell disease

Presenter: Lea Nyiranshuti, Post-Doctoral Fellow **Research Interest:** Translational Cardiology

Mentors: Carolyn J. Anderson PhD

Funding Source: P3HVB and P30CA047904

Authors: Lea Nyiranshuti PhD, Joseph D. Latoche BS, Lynda Little-Ihrig BS, Kathryn E. Day BS, Enrico M. Novelli MD, Carolyn J. Anderson PhD

Introduction: The painful blockade of small vessels is a hallmark of vaso-occlusive crisis (VOC) in sickle cell disease (SCD). VOC is a direct consequence of the adhesion of sickle erythrocytes (SSRBCs) to the endothelium and is characterized by a proinflammatory state. To date, there are no imaging modalities for VOC, so the patient's report of pain is often the only indication of VOC. Objective evidence of VOC may improve care by validating the patient's report and provide quantitative biomarkers of vaso-occlusion for clinical research outcomes. Very late antigen-4 (VLA-4 or integrin a4ß1) mediates the adhesion of SSRBCs to endothelium, and is therefore a potential biomarker for imaging VOC. The ultimate goal of this project is to validate whether the 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 (M21 Townes, n=5), and non-sickling control (M22 Townes, n=5) mice 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 (SUVs) of liver, lung and femur were measured using VivoQuant software (InviCRO; Boston, MA). After obtaining 24 h post-LPS images, mice were sacrificed, and organs (liver, lung and femur) were harvested for histology studies.

Results: The sickle (M21) mice showed significant uptake of 64Cu-LLP2A post-LPS challenge in the femur, a common area of pain related to vaso-occlusion in humans, with an SUVmean of 0.33±0.02 at 24 h p.i. compared with baseline (0.16±0.04). The SUVmean of the control mice did not show any significant change at 24 h p.i. Further data analysis and histology studies are underway.

Conclusion: Increased 64Cu-LLP2A uptake post LPS challenge in sickle (M21) mice, but not in control mice, suggests possible localization of the tracer in areas of vaso-occlusion. These results suggest a potential application of 64Cu-LLP2A in imaging vaso-occlusive events.

109-B Poster: Role of LINE-1 Retroelement in Atherosclerosis Disease

Presenter: ANDRES PULGARIN, Post-Doctoral Fellow Cardiology

Research Interest: Translational

Mentors: Dennis Bruemmer PhD
Cynthia St. Hilaire PhD

Funding Source: NIH/NHCBI

Authors: J. Andres Pulgarin PhD, Eric Hyzny , Genevieve Doyon , Cynthia St. Hilaire PhD, Dennis Bruemmer PhD

Introduction: Long interspersed element-1 (L1) retrotransposons constitute an abundant class of transposable elements that comprise approximately 17% of the human genome. L1-retrostransposed elements have the ability to move within the genome and are therefore considered mutagenic. New L1 insertions can profoundly alter gene function and have been implicated in a variety of diseases. In humans, the leading causes of death are atherosclerotic cardiovascular disease and cancer. While a causal relationship between L1 retrotransposition and cancer has been proposed, its function in atherosclerosis remains unknown.

Methods: We first analyzed L1 mRNA expression by RT-PCR in postmortem coronary artery specimens from healthy control subjects and patients with atherosclerosis. Immunohistochemistry and Western Blotting was next performed for ORF1p, an L1 encoded polypeptide required for active retrotransposition. L1 expression was analyzed for correlation with age and disease state. In vitro, the expression and regulation of L1 was analyzed in human aortic endothelial cells (HAEC) stimulated with various proatherogenic stimuli.

Results: In human coronary specimens, L1 mRNA expression was increased in samples from patients with atherosclerotic disease. There was a positive correlation between L1 expression and the extent of atherosclerosis assessed by histology. In addition, L1 transcript levels were positively correlated with age in patient samples and increased in vitro by genetic depletion of telomerase expression. ORF1p expression was further identified in endothelial cells of atherosclerotic plaques indicative of increased L1 activity. Finally, L1 expression was regulated in HAEC and induced by pro-inflammatory stimuli, including TNFa, IL-6, oxidized LDL.

Conclusion: In conclusion, our results identify L1 expression in atherosclerosis. L1 transcript levels increase with age of patient, correlate with the extent of the disease, and are regulated by pro-inflammatory stimuli causally involved in atherosclerosis development. These data may point to a previously unrecognized mechanism of atherosclerosis formation.

110-B Poster: Identification of Novel Regulators of Right Ventricle Hypertrophic Remodeling with Implications for Pulmonary Hypertension

Presenter: Patricia Riva, Post-Doctoral Fellow Cardiology

Research Interest: Translational

Mentors: Imad Al Ghouleh PhD

Funding Source: N/A

Authors: Patricia Riva PhD, Alexander Hoyt , Stephanie Mutchler , Mohammad Alhamaydeh MD, Jian Hu , Jeffrey Baust , Imad Al Ghouleh PhD

Introduction: The molecular mechanisms underlying right ventricle (RV) hypertrophic remodeling (both adaptive and maladaptive) in response to sustained pressure overload, such as that experienced during pulmonary hypertension (PH), are still poorly understood. Our previous work demonstrating a role for the cytosolic Nox organizer protein p47phox in pressure overload-induced RV hypertrophy and our recent publication on a direct interaction between p47phox and the ERM-binding cytoskeletal protein Nherf1 lead us to hypothesize that Nherf1 is a regulator of RV cardiomyocyte hypertrophic responses.

Methods: Cardiomyocyte-derived H9C2 cells and RV rat neonatal cardiomyocytes isolated from 1-day-old pup hearts (RV-RNCM) were subjected to neurohormonal hypertrophic stimulation using angiotensin II (AngII, 1 & 10 mM). RV pressure overload was induced in mice by pulmonary artery banding (PAB; 3wk). AngII treatment resulted in H9C2 and RV-RNCM hypertrophy and induced Nherf1 protein expression.

Results: The AngII-induced hypertrophy was attenuated by Nherf1 gene knockdown using siRNA. Moreover, Co-IP studies revealed an Nherf1-p47phox association in H9C2 cells that is enhanced by pro-hypertrophic AngII-treatment. Sequential loss of function strategies educated by novel in silico gene network analyses of PH gene intersected with cardiomyopathy gene networks, combined with a careful consideration of our previous findings and the literature, identified potential involvement of Hippo pathway transcriptional co-activators Yap/Taz, the water channel aquaporin1 (Aqp1) and apoptosis signal-regulating kinase 1 (Ask1) in this pathway. In vitro, co-IP studies revealed a Nherf1-Yap association and interruption of Ask1 or Aqp1 reduced AngII-induced cardiomyocyte cellular hypertrophy. In vivo, PAB induced an increase in Nherf1 expression and association with p47phox.

Conclusion: The present study supports a new role for Nherf1 in mediating pro-hypertrophic cellular responses in cardiomyocytes and implicates a network of molecular targets previously not connected to either the RV or Nherf1. These data identify potential therapeutic targets for RV dysfunction in PH and shed light on novel molecular mechanisms previously untested in the pressure overloaded right heart.

111-B Poster: Lymphocyte heterogeneity in cutaneous T cell lymphoma (CTCL) skin tumors.

Presenter: Alyxzandria Smith, Lab Technician III
Rheumatology and Clinical Immunology

Research Interest: Translational

Mentors: Patrizia Fuschiotti PhD

Funding Source: R21CA209107-01

Authors: Alyxzandria Smith BSc, Tracy Tabib BSc, Claire-Audrey Bayan MD, Larisa Geskin MD, Robert Lafyatis MD, Patrizia Fuschiotti PhD

Introduction: Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of T lymphocyte malignancies that primarily affect skin. Mycosis fungoides (MF) is the most common form of CTCL and typically runs an indolent course. However, in a significant number of patients the disease may progress and tumor cells spread to other sites of the body leading to a fatal outcome. Diagnosis of MF, especially in the early stages, is difficult to establish due to the absence of specific markers for malignant lymphocytes. Limited treatment options are available for patients with advanced-stage MF, a reflection of the poor understanding of disease pathogenesis.

Methods: Single-cell RNA sequencing (scRNA-seq) was performed to profile the transcriptome of malignant lymphocytes from skin biopsies of 5 patients with advanced-stage CTCL and 4 healthy donors. Biopsy samples were digested, cell suspensions loaded into the Chromium instrument (10X Genomics), and the resulting barcoded cDNAs were used to construct libraries. RNA-seq performed on each sample yielded approximately 200 million reads/sample. Cell-gene UMI counting matrices were generated and analyzed using Seurat software to identify distinct cell populations and were hierarchically clustered using Cluster 3.0. Immunohistochemistry and confocal immunofluorescence microscopy were employed to determine protein expression of identified genes by CTCL skin tumors.

Results: Transcriptome analysis at the single-cell level of CTCL skin tumors demonstrated T-cell heterogeneity between patient skin tumors as well as within each tumor. The analysis also identified novel gene expression related to functional pathways associated with malignant phenotype of CTCL. Furthermore, highly proliferating tumor cells were identified within a discrete subset of each tumor by the expression of the TOX gene (thymus high-mobility group box - a known marker of malignant CTCL lymphocytes) as well as genes implicated in cell cycle progression.

Conclusion: Our single-cell analyses of CTCL skin tumor samples provide new insight into CTCL disease pathogenesis and progression and establishes the basis for a new tool to gauge the efficacy of treatment and open avenues for tailoring therapy to specific patients.

112-B Poster: RNA-Sequencing of Inducible Pluripotent Stem Cell Derived Endothelial Cells Carrying BMPR2 Mutations Identifies SCUBE1 as a Putative Pathogenic Effector in Pulmonary Arterial Hypertension

Presenter: Wei Sun, Fellow
Cardiology

Research Interest: Translational

Mentors: Stephen Chan MD

Funding Source: R01 and HVI fellow grant

Authors: Wei Sun MD, Seungchan Kim , Adam Handen , Gil Speyer , Stephen Chan MD

Introduction: Pulmonary arterial hypertension (PAH) is a deadly disease characterized by progressive remodeling of the pulmonary vasculature, increased pulmonary pressures and right heart failure. Mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in over 70% heritable cases of PAH. It is thought that deficiency of BMPR2 and alterations of downstream signaling can drive endothelial dysfunction, vascular remodeling, and vasoconstriction. However, the exact molecular mechanisms driving PAH pathogenesis downstream of BMPR2 remain unclear. In comparison to artificial BMPR2 manipulation in cell culture, pathogenic BMPR2 mutations specifically and uniquely alter endothelial gene expression relevant to BMPR2 signaling in pulmonary endothelium. Genomic screening from endothelial cells derived directly from patients with BMPR2-specific hereditary PAH provides an approach to identify novel molecules and pathways in the pathogenesis of PAH.

Methods: As previously reported, skin fibroblasts were isolated from 11 individuals in 3 heritable PAH families, including 3 wild type controls, 3 BMPR2 mutation carriers, and 5 BMPR2 mutation PAH patients. The fibroblasts were induced into inducible pluripotent stem cells (iPSCs) and re-differentiated into iPSC-ECs. Our group re-analyzed the results of RNA-Sequencing (RNA-Seq) and screened for significant alterations of gene expression comparing mutant versus control cells. Such gene expression changes were confirmed via RT-PCR and immunoblotting in cultured human pulmonary arterial ECs (PAECs).

Results: RNA-Seq revealed 17 differentially expressed genes related to BMPR2 mutation. Among these genes, the expression of Signal Peptide CUB-EGF-Domain Containing Protein 1 (SCUBE1) was upregulated by 11.6±3.1 folds ($p<0.05$) in BMPR2 mutant cells as compared with control. As a known BMP co-receptor, SCUBE1 contains BMP1 and EGF domains, is considered a promising candidate for further analysis. By RT-PCR and immunoblotting, SCUBE1 was expressed substantially in PAECs but was undetectable in smooth muscle cells and fibroblasts. Interleukin-6 (IL-6), a known cytokine involved in PAH pathogenesis, increased SCUBE1 expression by 2.5±0.3 folds ($p<0.05$) in PAECs.

Conclusion: RNA-Seq in iPSC-ECs from PAH patients identified SCUBE1, a known BMP co-receptor, is significantly upregulated with BMPR2 deficiency or treated with IL-6. These results suggest SCUBE1 as a putative candidate molecule involved in pathogenic alterations of BMPR2 signaling in PAH.

113-B Poster: Idiopathic Pulmonary Fibrosis after Lung Transplantation: Shortened Telomere Length, the DNA Damage Response, and Immune Senescence

Presenter: Spencer Winters, Fellow Pulmonary, Allergy and Critical Care Medicine

Research Interest: Translational

Mentors: John McDyer MD

Funding Source: N/A

Authors: Spencer Winters MD, Aki Hoji PhD, Iulia Popescu PhD, Mary Armanios MD, John McDyer MD

Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and incurable lung disease and is now the leading indication for lung transplantation in North America. The pathogenesis of IPF has been linked to the shortening of telomeres, tandem DNA repeat sequences at the end of all chromosomes which protect chromosomes from deterioration and DNA damage. The histone variant H2AX becomes phosphorylated in the setting of double-stranded DNA breakage and helps to recruit ataxia telangiectasia mutant protein (ATM). ATM, after autophosphorylation, becomes an important activator of the DNA damage checkpoint machinery. The aim of this study is to determine if the presence of phospho-H2AX (?H2AX) and pATM is associated with shortened telomere length (TL), impaired cytomegalovirus (CMV)-specific CD8+γ proliferative response, and expression of the cell senescence marker CD57+ in IPF lung transplant recipients when compared to age-matched non-IPF LTRs.

Methods: Telomere length was measured on peripheral blood mononuclear cells (PBMCs) by flow cytometry and fluorescence in situ hybridization and compared to validated age-adjusted nomograms. PBMC samples underwent surface-staining with fluorochrome-labeled antibodies to CD3, CD4, CD8, CD57, and CMV-specific dextramer. Live/Dead staining was used for gating on viable cells. After fixation and permeabilization, PBMCs were stained with antibodies against ?H2AX and pATM. In certain experiments, proliferation was assessed by CSFE dilution assay. Flow cytometry data were analyzed using FlowJo software (Tree Star). Mann-Whitney testing was used for comparison between groups.

Results: 10 LTRs (6 IPF and 4 non-IPF) are included at this time. During acute CMV infection, IPF LTRs with TL <10th percentile had less CD8+γ proliferative response to the CMV-specific antigen pp65 (4.5% vs 60%, $p<0.01$) and to the superantigen staphylococcal enterotoxin B (8.3% vs 72%, $p<0.01$). IPF LTRs with TL < 10th percentile had more CD8+γH2AX+ (3.0% vs 1.0%, $p=0.03$) and CD8+γH2AX+pATM+ cells (1.66% vs 0.16%, $p=0.05$). Among all patients, 72.5% (95%CI: 43-94%) of CD8+γH2AX+ cells were CD57+.

Conclusion: IPF LTRs with shortened TL <10th percentile have impaired CMV-specific and SEB-stimulated CD8+γ proliferative responses when compared to age-matched, non-IPF LTRs. The presence of increased CD8+γH2AX+pATM+ cells suggests that IPF LTRs with short TL have increased DNA damage and subsequent activation of the pATM cell cycle checkpoint pathway leading to the impaired CD8+γ proliferative responses. Further research is required to evaluate the association between the increased expression of the replicative senescence marker CD57+ and the CD8+γH2AX+ compartment.

114-B Poster: A HIF-2a-long noncoding RNA Epigenetic Axis Modulates Histone Methylation and Mitochondrial Metabolism in Hypoxia: Implications for the Pathogenesis of Pulmonary Hypertension

Presenter: Qiujun Yu, Post-Doctoral Fellow Cardiology

Research Interest: Translational

Mentors: Stephen Chan PhD

Funding Source: RO1

Authors: Qiujun Yu PhD, Ying Tang MS, Miranda Tai MS, Jingsi Zhao MS, Vinny Negi PhD, Gil Speyer PhD, Catherine G. Corey BS, Frances Belmonte PhD, Bing Wang PhD, Brett Kaufman PhD, Sruti Shiva PhD, Stephen Chan PhD

Introduction: Long noncoding RNAs (lncRNAs) are expressed extensively in the mammalian vasculature, yet their potential involvement in regulating the hypoxic response and pathogenesis of pulmonary hypertension (PH) is unknown. We hypothesize that specific lncRNAs control the dysregulated metabolic and proproliferative states of endothelial cells induced by hypoxia and are central to the development of PH.

Methods: Transcriptomic profiles were generated by next generation RNA sequencing (Illumina), and differential expression analysis was performed in SU5416+hypoxia induced PH mouse lung versus controls. ChIP-qPCR was performed to analyze enrichment of HIF binding motifs at the KMT2E-AS1 promoter and methylated histone at the HIF-2a promoter. Cell apoptosis was measured by caspase-3/9 activity assay and proliferation capability was evaluated by BrdU incorporation. Mitochondrial oxygen consumption and glycolytic flux were measured by Seahorse assay.

Results: RNA sequencing revealed increased expression of the lncRNA 5031425E22RIK in PH mouse lung, which was further confirmed by its increased expression in cultured mouse PAECs exposed to hypoxia. Its human ortholog KMT2E-AS1, an antisense gene of a hypoxia-dependent histone lysine(K)-specific methyltransferase, also exhibited elevated expression in hypoxic human PAECs and in lung tissues of PH patients. Knockdown of a master transcription factor of hypoxia, HIF-2a, but not HIF-1a, prevented upregulation of KMT2E-AS1 in hypoxia, whereas overexpression of a constitutively active HIF-2a promoted its expression in normoxia. Luciferase assay and ChIP-qPCR verified HIF-2a-induced enrichment of HIF binding motifs in the KMT2E-AS1 promoter. More importantly, KMT2E-AS1 directly interacted with and up-regulated the expression of KMT2E and other KMT2 family members in hypoxia and controlled histone H3 lysine 4 trimethylation (H3K4Me3). More importantly, KMT2E-AS1 knockdown reduced H3K4Me3 enrichment at the HIF-2a promoter site, and increased expression of prolyl hydroxylase2 and UBE2D, two factors in the hydroxylase-ubiquitin pathway controlling HIF inactivation. RNA sequencing further revealed that KMT2E-AS1 knockdown inhibited hypoxia-activated HIF signaling with downstream reprogramming of metabolic genes controlling oxidative phosphorylation and glycolysis. Correspondingly, gain- and loss-of-function analysis suggested that KMT2E-AS1 is both necessary and sufficient to promote glycolytic flux, repress mitochondrial oxidative metabolism, and thus induce a hyperproliferative state in hypoxic PAECs.

Conclusion: In hypoxic PAECs, mouse lncRNA 5031425E22RIK and its human ortholog KMT2E-AS1 engage in an epigenetic regulatory feedback loop with HIF-2? to control histone methylation, leading to metabolic reprogramming and a proproliferative endothelial phenotype. These biological functions may play critical roles in the pathogenesis of pulmonary hypertension.

Acknowledgements

The Office of Academic Affairs of the Department of Medicine produced this program.

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

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

Project Manager and Editor
Jimette Gilmartin
Academic Affairs Project Coordinator

Project Coordinator
Amy Flaugh
Program Administrator, Center for Medicine and the Microbiome

Cover Photo
D. Hunter Todd
Higher Education Management Intern