Friday, April 13, 2018
7:45 a.m. to 3:00 p.m.
E-351 and CARE/Crawley Atrium

KEYNOTE:
Maura L. Gillison, MD, PhD
Professor, Division of Cancer Medicine
Department of Thoracic/Head and Neck Medical Oncology
University of Texas MD Anderson Cancer Center
Houston, TX

med.uc.edu/intmed/news/research-symposium
Cover Photo:
Verhoeff-van Gieson special stain for elastic fibers. Mouse lung (400X magnification).

Staining by Lori Pitstick
Imaging by Nikolaos Nikolaidis
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>7:45-8:45 a.m.</td>
<td>Round Table with Maura Gillison, MD, PhD, Professor, Department of</td>
<td>CARE Crawley 6870</td>
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<td>Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine,</td>
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<td>University of Texas MD Anderson Cancer Center, Houston, TX</td>
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<td>Moderated by Trisha Wise-Draper, MD, PhD</td>
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<td>Assistant Professor of Medicine, Division of Hematology Oncology, Head</td>
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<td>and Neck Oncology/Experimental Therapeutics, Medical Director of the</td>
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<td>UCCI Clinical Trials Office, University of Cincinnati Cancer Institute</td>
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<td>8:30-9:00 a.m.</td>
<td>Breakfast</td>
<td>Outside E351 (Main Conference Room)</td>
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<td>9:00-9:15 a.m.</td>
<td>Introductory Comments</td>
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<td>Carl Fichtenbaum, MD, Associate Chair for Translational Research,</td>
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<td>Professor, Division of Infectious Diseases</td>
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<td>9:15-10:15 a.m.</td>
<td>KEYNOTE SPEAKER: MAURA GILLISON, MD, PHD</td>
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<td></td>
<td>“HPV and the Epidemic of Oropharyngeal Cancer”</td>
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<td></td>
<td>Introduced by Trisha Wise-Draper, MD, PhD Division of Hematology</td>
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<td>Oncology</td>
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<td>10:30 a.m. – 12:30 p.m.</td>
<td>Planning for the Future of Research, Discovery &amp; Innovation in the DOIM</td>
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<td>Facilitated by Melanie T. Cushion, PhD, Senior Associate Dean for</td>
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<td>Research, University of Cincinnati College of Medicine</td>
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<td></td>
<td>• The Impact of Collaborative Research on the Cincinnati Metropolitan</td>
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<td>Statistical Area (25 min)</td>
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<td>Rita Alloway, PharmD, Research Professor of Medicine, Director,</td>
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<td>Transplant Clinical Research, Division of Nephrology/Kidney CARE</td>
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<td>Program</td>
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<td>• Collaborative Research that Changes the Landscape (25 min)</td>
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<td>Frank McCormack, MD, Gordon and Helen Hughes Taylor Professor and</td>
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<td>Director, Division of Pulmonary, Critical Care and Sleep Medicine</td>
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<td>• Building an Infrastructure and Culture to Foster and Nurture Research</td>
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<td>Kelly Niederhausen, Assistant Director, Research and Education, Sr.</td>
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<td>Business Administrator, Divisions of Infectious Diseases and Nephrology, Kidney, CARE Program, Office of Medical Education,</td>
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<td>Yolanda Wess, MEd, RN, BSN, Research Manager, Academic Research Services</td>
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<td>Carl Fichtenbaum, MD</td>
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<td>• Research Innovation Panel: What is the most important thing we can</td>
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<td>do to build and foster research? (45 min)</td>
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<td>Invited panelists: Gregory Rouan, MD, Gordon and Helen Hughes Taylor</td>
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<td>Professor, Chair of Internal Medicine; William Ball, MD, Christian</td>
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<td>R. Holmes Professor and Dean, College of Medicine, Senior Vice</td>
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<td>President for Health; Richard Lofgren, MD, MPH, President &amp; Chief</td>
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<td>Executive Officer, UC Health; and Karen Bankston, PhD, MSN, FACHE,</td>
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<td>Executive Director of the Child Poverty Collaborative, Adjunct</td>
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<td>Professor in the College of Nursing</td>
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<td>12:30-2:00 p.m.</td>
<td>Trainee Poster Session</td>
<td>CARE/Crawley Atrium</td>
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<td>Images in Medicine Gallery</td>
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<td>People’s Choice Voting 12:30 p.m. – 2:00 p.m.</td>
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<td>Emily Dobbs, MS, BA, Research Associate, Academic Research Services</td>
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<td>Lunch provided</td>
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<td>3:00-3:30 p.m.</td>
<td>Award ceremony for posters and images</td>
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<td>Carl Fichtenbaum, MD and Gregory Rouan, MD</td>
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Message from the Chair

This seventh annual 2018 Department of Internal Medicine Research Symposium plays an important role in supporting our tripartite mission of excellence in education, research and patient care and promotes cross-divisional and departmental collaboration among our divisions with other departments in the UC College of Medicine, Children's Hospital, the Cincinnati VAMC, and others throughout the nation. This has been fundamental to the execution of our strategic plan and under the direction of the Research Core Governance Committee (RGC).

Internal Medicine has long been a leader at the University of Cincinnati, consisting of nine divisions with more than 280 faculty clinicians and scientists. We are the largest unit of full-time geographic faculty in the college with responsibility for $80 million in research funding. We currently hold over 136 total awards, including 29 RO1’s from the NIH with $8.5 million in new awards during the 2017-18 academic year.

The Associate Chair of Research, Manoocher Soleimani, MD and Associate Chair of Translational Research, Carl Fichtenbaum, MD and other faculty and staff on the RGC deserve a great deal of credit for coordinating and preparing our Annual Research Symposium.

Our faculty have developed expertise that has helped advance our understanding of a diverse array of topics ranging from combating migraine to reviewing the usage of statins on heart patients to the treatment of pancreatic, brain and blood cancers, to name just a few areas of impact. This expertise is highlighted at the symposium and affords students, residents, fellows and faculty the opportunity to engage with our expert researchers and national leaders.

Very importantly, our support services provided by the Academic Research Services (ARS) office to our basic and translational scientists, has become extremely robust. This service has now been recognized as an exemplar regionally and nationally.

Thank you for joining us,

Sincerely,

GREGORY W. ROUAN, MD
Taylor Professor and
Chair of Internal Medicine
Message from the Associate Chairs for Research, Department of Internal Medicine

Welcome.

The Internal Medicine Research Symposium is one of the venues provided on an annual basis to assist the department in creating an environment that encourages, stimulates, and promotes research and researchers. This is our seventh year of hosting the symposium.

This all day event brings together researchers and trainees from the Academic Health Center and the larger research community at the University of Cincinnati.

The theme of the symposium is “Planning for the Future of Research, Discovery, and Innovation.” The symposium will begin with a keynote address by an internationally renowned scientist. The morning sessions will be devoted to panels discussing a range of topics including our transplantation programs, rare lung diseases program, the research initiative to support excellence (RISE-UC) program, and a panel discussion of research priorities, which will include input from the Dean of the College of Medicine, the CEO of UC Health, the Director of the Child Poverty Collaborative, and the Chairman of the Department of Medicine. These events will highlight some of our successes in team science and infrastructure to support and stimulate research.

The afternoon program will include our Trainees’ Poster Session. This year the symposium will also host a new image competition and gallery titled “Images in Medicine,” which includes photography featuring basic and clinical research. During the Trainees’ Poster Session, post-doctoral fellows, graduate students, residents, and interns will have the opportunity to discuss their ideas with investigators and junior faculty. They will use this opportunity to share their research techniques and develop future collaborations and mentoring relationships. Finally, we are very excited to collaborate with Alumni Weekend. We invite our alumni to join us throughout the day.

We hope you will enjoy attending this year’s symposium. We invite you to learn more about our cutting-edge research and how you can become involved in our research efforts.

Respectfully,

CARL FICHTENBAUM, MD
Professor of Clinical Medicine
Associate Chair for Translational Research

MANOOCHER SOLEIMANI, MD
James F. Heady Professor of Medicine
Associate Chair for Research
133 TOTAL GRANTS
21 percent are held by primary investigators with R01 awards

$80.9 million TOTAL FUNDING

OVER $13.1 million in NEW AWARDS IN FY2017

$4.7 million CLINICAL TRIAL REVENUE (FY2017)

> 25% INCREASE IN TOTAL FUNDING (FY2017)

up from 25% to 27% SUCCESS RECEIVING FUNDING

$246,000 INTRAMURAL FUNDING (FY2017)

We are cultivating a productive, innovative and growing research program that supports basic, clinical and translational research to make a difference in the health of our community.
Year at a Glance

2016

July

- $1.67M NIAID award (Fred Finkelman, MD)
- Two Senior Pilot Awards funded by DOIM (Laura Conforti, PhD and George Smulian, MD)
- One Distinguished Research Achievement award funded by DOIM (Ken Sherman, MD, PhD)
- One Rehn Family Research Award funded by DOIM (Phillip Owens, PhD)
- DOIM hire of Research Associate (Grant Writer, Eric Smith, MD) for faculty support within Academic Research Services (ARS)

September

- Twenty-one researchers in the department, receiving grants totaling $100,000 in direct and indirect costs per year, were highlighted as part of the College of Medicine’s Gallery of Awardees by the College of Medicine Research Recognition Award Program
- $1.37M NIDDK award (Jason Winnick, PhD)
- $2.67M NIH U01 award (Frank McCormick, MD)
- Research Governance Committee (RGC) redesign of monthly Research Conferences to be interactive and collaborative

October

- Lifetime Achievement Award, College of Medicine (Arnold Schwartz, PhD)
- DOIM transitioned to an electronic grant competition and awards program site (CCAPS) for submission of all intramural awards

November

- Trisha Wise-Draper, MD, PhD, appointed as Medical Director of the UC Cancer Institute Clinical Trials Office

2017

January

- Four Junior Pilot Awards funded by DOIM (Silvi Shah, MD; Moises Huaman, MD; Phillip Owens III, PhD; Dylan Steen, MD)

February

- Atsuo Sasaki, PhD, wins Innovator Award at Health Care Heroes Banquet
- Jack Rubinstein, MD, named Director of the Department of Veterans Affairs Medical Center Clinical Research Unit in Cincinnati
- Michael Tranter, PhD, chosen as the 2017 Research Rising Star in the College of Medicine.
- DOIM releases 2015-2016 Annual Research Report

March

- DOIM J-Club (Research Faculty Career Development Group for Junior Faculty) met for the first time
- Melanie Cushion, PhD, named recipient of the Antimicrobial Research Award presented by the American Society for Microbiology (ASM), at the 2017 ASM Microbe meeting

April

- Jack Rubinstein, MD, received the Emerging Entrepreneurial Achievement Award, presented at the 2017 University of Cincinnati Faculty Awards Ceremony

May

- George Deepe Jr., MD, professor in the Division of Infectious Diseases, honored as one of four recipients of the College of Medicine Daniel Drake Medal

June

- Sixth Annual DOIM Research Symposium and Trainee Grand Rounds expanded to 2 day format with 46 mentored trainee posters and 50 judges
- DOIM Academic Research Services (ARS) staff moved to new office space in MSB 6111
- IMSTAR graduates (first class of trainees): Dana Sall, MD; Matt Kelleher, MD; Ahsan Zafar, MD; and Kiran Afshan, MD
TAB 1
symposium
speakers
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Maura Gillison, MD, PhD

Professor, Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine
University of Texas MD Anderson Cancer Center
Houston, TX

Maura Gillison, MD, PhD, is Professor of Medicine and a CPRIT scholar at The University of Texas MD Anderson Cancer Center, recruited from Ohio State in March 2017. She is a head and neck medical oncologist and molecular epidemiologist. Her laboratory focuses on the role of human papillomavirus (HPV) infection in head and neck malignancies. Her work ranges from cohort studies of oral HPV infection to genetic indicators of response to chemoradiotherapy.

She is a physician scientist and has made significant contributions to the identification of human papillomavirus as a cause of a distinct subset of head and neck cancer, resulting in a paradigm shift in concepts for risk, diagnosis and therapy of head and neck cancer. As a doctorate-level trained molecular epidemiologist and medical oncologist with expertise in head and neck cancer, she currently investigate the implications of our findings for primary and secondary prevention strategies, diagnostics, prognostics, genomics, molecular therapeutics, clinical decision making and population-level cancer incidence trends in the United States and worldwide.

Dr. Gillison earned her MD from the Johns Hopkins School of Medicine, then served successively as a postdoctoral fellow at the Johns Hopkins Hospital, as a medical resident at Massachusetts General Hospital, and as a clinical fellow and later as a senior clinical fellow in oncology at Johns Hopkins before earning her PhD from that University's School of Hygiene and Public Health. She rose to the rank of Associate Professor on faculty at Johns Hopkins Schools of Medicine and Public Health prior to her departure.

Dr. Gillison is supported by grants from the National Institute of Health and CPRIT and has published extensively in such prestigious journals as The New England Journal of Medicine, Journal of the National Cancer Institute, and Journal of Clinical Oncology.
Symposium Speakers

**KEYNOTE SPEAKER:**

Maura L. Gillison, MD, PhD  
Professor, Division of Cancer Medicine  
Department of Thoracic/Head and Neck Medical Oncology  
University of Texas, MD Anderson Cancer Center

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Rita R. Alloway, PharmD  
Research Professor of Medicine  
Director, Transplant Clinical Research  
University of Cincinnati College of Medicine

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Carl Fichtenbaum, MD  
Professor of Clinical Medicine  
Associate Chair for Translational Research  
University of Cincinnati College of Medicine

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Francis X. McCormack, MD  
Taylor Professor and Director  
Division of Pulmonary, Critical Care and Sleep Medicine  
University of Cincinnati College of Medicine

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Kelly Niederhausen  
Assistant Director, Research and Education  
Sr. Business Administrator  
Division of Infectious Diseases  
Division of Nephrology, Kidney CARE Program  
Office of Medical Education  
University of Cincinnati College of Medicine

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Yolanda Wess, MEd, RN, BSN  
Research Manager, Academic Research Services (ARS)  
Department of Internal Medicine  
University of Cincinnati College of Medicine
Symposium Facilitators/Moderators

**Melanie T. Cushion, PhD**
Senior Associate Dean for Research
University of Cincinnati College of Medicine
Research Career Scientist, VAMC

**Trisha Wise-Draper, MD, PhD**
Assistant Professor of Medicine, Division of Hematology/Oncology
Head and Neck Oncology/Experimental Therapeutics
Medical Director of the UCCI Clinical Trials Office
University of Cincinnati Cancer Center
Panelists

William S. Ball, MD
Senior Vice President for Health Affairs
Christian R. Holmes Professor and Dean
University of Cincinnati College of Medicine

William Ball, MD, is the current Senior Vice President for Health Affairs and the Christian R. Holmes Professor and Dean of the College of Medicine for the University of Cincinnati (UC). He is the 51st dean of medicine since the college was founded as the Medical College of Ohio in 1819. He served as Interim and then Vice President for Research for UC from 2011-2016. In addition to chief executive officer for the College of Medicine, he is responsible for Academic Health Center strategic planning and the UC affiliations with UC Health, Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati Department of Veterans Affairs Medical Center and Shriner's Hospitals for Children.

A professor of radiology, biomedical engineering and pediatrics, Dr. Ball practiced as a pediatric neuroradiologist at CCHMC for 28 years, served as chief of the section in pediatric neuroradiology at Cincinnati Children's (1988 to 2001) and is the former chair of the Department of Biomedical Engineering (2001 to 2008). In 1992, he created the Imaging Research Center at CCHMC and served as its director until 2002. In 2011, he created the business plan for the creation of the UC Research Institute (UCRI) and served as its first CEO until 2012. He currently serves on the President’s Executive Committee, the President’s Cabinet and the President’s Strategic Advisory Committee.

Karen Bankston, PhD, MSN, FACHE
Executive Director, Child Poverty Collaborative
Adjunct Professor in the University of Cincinnati College of Nursing

With over 40 years in health care, Karen Bankston, PhD, MSN, FACHE, is the Executive Director of the Child Poverty Collaborative, Cincinnati, a collective impact organization designed to lead the community's planning and implementation of efforts to ameliorate poverty by providing guidance on public policy, employment, housing, transportation, education and health care concerns. Previously she held the role of Associate Dean for Clinical Practice, Partnership and Community Engagement of the College of Nursing at the University of Cincinnati. In that role, she was responsible for developing and maintaining partnerships with nursing and other disciplines, while engaging in community based research focused on student and parental success in the urban core.

Additionally, she is the president and CEO of KDB and Associates Consulting Service, a company she founded after completing 5 years as the senior vice president/CEO of Drake Center, Inc., part of UC Health. Dr. Bankston previously served as the senior vice president of external affairs for the Health Alliance responsible for local, state and federal government relations, community relations, marketing and public relations. She also served as the external affairs liaison to neighborhood councils, the Uptown Consortium, United Way and other community agencies, and oversaw the Health Alliance departments of community health and diversity.

Prior to that she held positions as vice president of operations/chief operating officer and vice president for patient care/chief nursing officer at University Hospital in Cincinnati. She served as associate dean of clinical services and clinical assistant professor at the University of Cincinnati College of Nursing and Health. She also held nursing and nurse manager positions at Western Reserve Care System in Youngstown, Ohio.

She is actively involved in numerous boards including the United Way of Greater Cincinnati, Legal Aid Society and The Children’s Home.
Richard P. Lofgren, MD, MPH, FACP

President and Chief Executive Officer
UC Health

Richard P. Lofgren, MD, MPH, FACP, is president and CEO of UC Health, the University of Cincinnati’s affiliated health system. UC Health, with more than 11,000 employees, physicians and advanced practice providers, comprises University of Cincinnati Medical Center, West Chester Hospital, Daniel Drake Center for Post-Acute Care, Lindner Center of HOPE and more than 30 outpatient service locations in three states.

Dr. Lofgren is a board-certified internal medicine physician and administrator with nearly 40 years of experience in health care with a particular interest health care delivery redesign, operational efficiencies, performance improvement and applied health services/quality research.

Dr. Lofgren previously served as senior vice president and chief clinical officer for University HealthSystem Consortium (UHC), now Vizient, and was responsible for helping UHC members improve the quality, safety, efficiency and effectiveness of their clinical services. Prior to UHC, he spent eight years at UK HealthCare, the University of Kentucky’s academic health system, joining as chief medical officer in 2004 and later becoming vice president for health care operations and chief clinical officer. Before joining UK HealthCare, Dr. Lofgren held various faculty and administrative posts throughout the Midwest including the Medical College of Wisconsin, the University of Pittsburgh (and the Pittsburgh VA Medical Center), the University of Minnesota (and the Minneapolis VA Medical Center) and Michigan State University.

He also serves on the boards of the Association of American Medical Colleges’ Council of Teaching Hospitals and Health Systems (COTH), Greater Cincinnati Urban League and the Cincinnati USA Regional Chamber.

Gregory W. Rouan, MD

Taylor Professor and
Chair of Internal Medicine
University of Cincinnati College of Medicine

Gregory W. Rouan, MD, has served as Chair of the Department of Internal Medicine and the Gordon and Helen Hughes Taylor Professor of Medicine at the University of Cincinnati College of Medicine since 2011. Previously he was associate chair for education of the department and program director. As an American College of Physicians (ACP) Teaching and Research Scholar, he completed a fellowship in Clinical Epidemiology at the Brigham and Women’s Hospital in Boston, MA.

Dr. Rouan has been the recipient of numerous teaching awards including the ACP Master Teacher Award and the ACGME Parker Palmer Teaching Recognition.

Dr. Rouan has been very active nationally with the Society for General Internal Medicine (SGIM), the Association of Program Directors in Internal Medicine (APDIM) and the ACP. He has chaired a variety of ACP regional and national committees, served as treasurer for the Ohio Chapter of the ACP, and the ACP Governor of the Ohio Chapter. He has been a fellow of the American College since 1988 and recently was elected as a master.

Dr. Rouan still has an extremely busy clinical practice in Cincinnati. He has been recognized as one of “The Best Doctors in America” and a “Top Doctor”. Additionally, he has served as President of the Cincinnati Society of Internal Medicine and is currently President of the Cincinnati Academy of Medicine. He is a member of the board of directors for UC Health, a trustee on the board of the University of Cincinnati Medical Center Fund and Chair of the UC Health Foundation Board.
TAB 2
“posters”
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## Trainees’ Research Grand Rounds
Friday, April 13, 2018

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<th>Title</th>
<th>Clinical or Clinical Case Reports</th>
<th>Poster</th>
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<tr>
<td>Haili Su, MD, PhD Cardiovascular Health and Disease</td>
<td>Kevin Haworth, PhD</td>
<td>Modulating the partial pressure of oxygen using acoustic droplet vaporization</td>
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<td>Hala Mualla, MD Endocrinology, Diabetes and Metabolism</td>
<td>Mercedes Falciglia, MD</td>
<td>Empagliflozin Effect on Weight Reduction and Glycemic Control in a Patient with Prader-Willi Syndrome</td>
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<tr>
<td>Hala Mualla, MD Endocrinology, Diabetes and Metabolism</td>
<td>Shailendra Patel, PhD</td>
<td>A Case of reversible adrenal suppression induced by Fluconazole in an HIV infected patient</td>
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<td>Anis Rehman, MD Endocrinology, Diabetes and Metabolism</td>
<td>Mercedes Falciglia, MD</td>
<td>Definitive Treatment of a Complicated Case of Amiodarone Induced Thyrotoxicosis</td>
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<td>Anis Rehman, MD Endocrinology, Diabetes and Metabolism</td>
<td>Mercedes Falciglia, MD</td>
<td>Doege-Potter Syndrome: Liver Solitary Fibrous Tumor with Insulin-like Growth Factor 2 mediated Non-Islet Cell Tumor Hypoglycemia with Incidental Findings of Adrenal Insufficiency and Differentiated Papillary Thyroid Cancer</td>
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<td>Susan Bal, MD “WITHDRAWN” Hematology Oncology</td>
<td>Mahmoud Charif, MD</td>
<td>Alteration in Red Cell Indices during Palbociclib Therapy</td>
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<td>Ihab Eldessouki, MD Hematology Oncology</td>
<td>John C. Morris, MD</td>
<td>Monitoring of clonoctypic immunoglobulin heavy chain sequences in plasma and outcome in patients with diffuse large B-cell lymphoma (DLBCL)</td>
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<td>Shuchi Gulati, MD Hematology Oncology</td>
<td>Trisha Wise-Draper, MD, PhD</td>
<td>A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation in patients with locally advanced head and neck squamous cell carcinoma</td>
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<td>Cindy Hochstetler, BS Hematology &amp; Cancer Biology</td>
<td>Yi Zheng, PhD</td>
<td>An Altered Bone Marrow Vascular Niche Impacts Normal Hematopoiesis and Tilts the Balance Between Myelopoiesis and Lymphopoiesis</td>
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<td>Yoshiti Ikeda, PhD Hematology Oncology</td>
<td>Atsuo Sasaki, PhD</td>
<td>Structure-based screening to identify inhibitor against GTP-sensor kinase, PISP4Kβ, for cancer therapy</td>
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<td>Donatien Kamdem Toukam, PhD Hematology Oncology</td>
<td>John C. Morris, MD</td>
<td>Vaccine Derived From Cancer Stem Cells Engineered To Express Interleukin-15 and its Receptor Inhibits Tumor Growth</td>
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<td>Vidhya Karivedu, MD Hematology Oncology</td>
<td>Trisha Wise-Draper, MD, PhD</td>
<td>Brain metastases treated with immune checkpoint inhibitors: A single center experience</td>
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<tr>
<td>Investigator and Department/Division</td>
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<td>Kara Wolfe, BS Hematology Oncology</td>
<td>Atsuo Sasaki, PhD</td>
<td>Localized GTP biosynthesis fuels renal cell carcinoma migration and metastasis</td>
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<td>Shinsmon Jose, PhD Infectious Disease</td>
<td>Rajat Madan, MD, PhD</td>
<td>Obesity-associated Gut Microbiota Enhances Clostridium difficile Infection in Mice</td>
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<td>Matthew Doers, MD Internal Medicine (General)</td>
<td>Ahsan Zafar, MD</td>
<td>Predictors of Stable Discharge from the ED Observation Unit in COPD Exacerbation</td>
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<td>Jose Gomez-Arroyo, MD, PhD Internal Medicine (General)</td>
<td>Jose F. Huizar, MD (external collaborator)</td>
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Cardiovascular Health and Disease

Richard C. Becker, MD
DIVISION DIRECTOR
Modulating the Partial Pressure of Oxygen Using Acoustic Droplet Vaporization

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BACKGROUND AND PURPOSE:
We have proposed modifying the oxygen partial pressure (pO2) to attenuate reperfusion injury. The purpose of this study is to modulate the pO2 with acoustic droplet vaporization (ADV) by varying ultrasound insonation parameters and droplet concentration.

METHODS:
Droplets were manufactured using high speed shaking and size-isolated to diameters between 1 and 6 μm. Droplets were diluted to volume concentrations between 4.61E-05 mL/mL and 4.45E-03 mL/mL and pumped through a flow phantom. The droplets were exposed to pulsed ultrasound at a center frequency of 5 MHz using either 5-cycle pulses at 4 MPa peak negative pressure or 20-cycle pulses at 5MPa peak negative pressure. A numerical model was used to predict the expected decrease in pO2. Agreement between predicted and observed pO2 values was evaluated. Multiple regression models were used to assess the association between change in pO2 and concentration with/without ADV.

RESULTS:
By adjusting the droplet concentration and ultrasound insonation parameters, the pO2 was reduced from an initial value of 154 mmHg without ADV to between 134 mmHg and 32 mmHg with ADV. For all conditions, predicted and observed pO2 values agreed (ICC=0.94, 95% CI: 0.88-0.97, p-value<0.0001; r=0.97, p-value<0.0001). Multiple regression models showed that the pO2 significantly decreased with increased droplet concentration (p-value < 0.001) as well as with increased ultrasound pressure amplitude and pulse duration (p-value = 0.014).

CONCLUSION:
The magnitude of pO2 reduction by ADV can be modified by adjusting the droplet concentration and/or ultrasound insonation parameters.
Empagliflozin Effect on Weight Reduction and Glycemic Control in a Patient with Prader-Willi Syndrome

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Division of Endocrinology, Metabolism and Diabetes,
University of Cincinnati College of Medicine

Clinical Case Presentation

BACKGROUND:
Prader-Willi Syndrome (PWS) is a rare genetic disorder (prevalence: 1/25000) with increased incidence of type 2 diabetes. Management of hyperglycemia and obesity in these patients is a challenge. We present a case report of a PWS patient who was successfully treated with Empagliflozin.

CASE REPORT:
A 26-year-old man with type 2 diabetes since age 20, obesity, hypertension, developmental delay, and hyperphagia presented for diabetes management. During work up, he was diagnosed with PWS. In 4/2017 empagliflozin was started: first with metformin, glimepiride and liraglutide (4/2017 to 7/2017) and then with metformin, liraglutide and insulin glargine (7/2017 to 10/2017). HbA1c decreased from 7.9% in 4/2017 to 6.6% in 7/2017, weight decreased from 167 pounds in 4/2017 to 151 pounds in 10/2017 and hyperphagia significantly improved.

DISCUSSION:
PWS is caused by a deletion in the paternal copy of the long arm of chromosome 15 and is associated with hyperphagia, obesity and type 2 diabetes. Empagliflozin was effective in our patient in lowering HbA1c and reducing weight. Empagliflozin has been associated with weight loss in type 2 diabetes patients, however this case indicates that it can have similar effects in PWS patients who are usually resistant to other weight loss medications. To the best of our knowledge this is the first report of its use in PWS patients.

CONCLUSION:
Empagliflozin improves glycemic control PWS patients with type 2 diabetes and may also be effective in weight loss in combination with other medications.
A Case of Reversible Adrenal Suppression Induced by Fluconazole in an HIV Infected Patient

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Division of Endocrinology, Diabetes and Metabolism,
University of Cincinnati College of Medicine
Clinical Case Presentation

BACKGROUND:
Adrenal dysfunction is frequently involved in patients with HIV. We report a case of reversible adrenal suppression induced by fluconazole in an HIV-infected patient.

CASE REPORT:
A 50-year-old man with HIV/AIDS with CD4 count of 97 cells/mm\(^3\) was admitted to the hospital with group A streptococcus pyogenes septic arthritis affecting multiple joints with progression to septic shock. Initially sodium level was normal. Patient was given fluconazole 200 mg for one dose then 100 mg daily for oral candidiasis. The next day sodium was at 130 mEq/L and gradually fell to 125 mEq/L. An ACTH stimulation test was performed and showed relatively flat cortisol levels of 13.4, 14.9 and 17.9 µg/dL at 0, 30, 60 minutes respectively, indicating adrenal insufficiency; he was started on hydrocortisone 15 mg in the morning and 10 mg in the afternoon. Fluconazole was discontinued on hospital day 14 and a repeat ACTH stimulation test on hospital day 18 was normal.

DISCUSSION:
Adrenal dysfunction is involved in patients with HIV. Causes are variable. Literature suggested a role of fluconazole in the suppression of steroidogenesis, although it remains debatable if fluconazole can cause adrenal insufficiency. We suspect that Fluconazole was a cause of the blunted cortisol response to ACTH stimulation. Clinicians should be aware of this potential effect of Fluconazole especially as it is widely used in the HIV patient group.

CONCLUSION:
Abnormal ACTH stimulation test in HIV patients can occur when receiving Fluconazole and this can be reversible after stopping this medication.
Definitive Treatment of a Complicated Case of Amiodarone Induced Thyrotoxicosis

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BACKGROUND:
Type 1 Amiodarone Induced Thyrotoxicosis (AIT) is commonly treated with thionamides as radioactive iodine (RAI) is typically ineffective. In cases of thionamide intolerance, thyroidectomy offers definitive treatment. However, thyroidectomy is ideally performed when the patient is euthyroid and correcting thyrotoxicosis without thionamides or RAI is challenging. We report a complicated case of type 1 AIT treated with lithium, glucocorticoids, and thyroidectomy.

CASE REPORT:
A 67 year old male with history of medication non-adherence and paroxysmal ventricular tachycardia requiring amiodarone for four years, presented in another city with thyrotoxicosis (TSH < 0.01uIU/mL, FT4 8.0 ng/dL, TT3 700 ng/dL). Because he developed hives with propylthiouracil, methimazole 30 mg daily was initiated. Within a week, liver enzymes increased and soon after the patient was lost to follow-up. He was admitted to our hospital 4 months later with agitation, excessive sweating, anxiety, heat intolerance, diarrhea and leg edema. Blood pressure was 162/70 mmHg with normal pulse, respiration, and temperature. No clinical or historical features suggested Graves’ disease and the thyroid gland was normal without palpable nodules. Admission labs included TSH <0.01 uIU/mL, FT4 > 8 ng/dL, TT3 574 ng/dL, normal liver enzymes. The diagnosis of type 1 AIT was made based on clinical presentation, correlation with amiodarone use and thyrotoxicosis lasting 14 weeks. The patient was started on methimazole 20 mg TID and labetalol. Although symptoms improved within 2 days, thyroid hormone levels after 5 days were unchanged, and AST and ALT rose to 152 U/L and 150 U/L respectively. Methimazole was discontinued and the patient refused PTU due to history of hives. Definitive treatment was the goal as the patient lived 2 hours away with a chronic history of medication non-adherence and adverse reaction to thionamides. Recent amiodarone use precluded RAI ablation. Thus the options for definitive treatment were limited to thyroidectomy which could only be performed safely after treatment of thyrotoxicosis.

The patient was started on lithium 300 mg TID and hydrocortisone. Within 2 days, TT3 and FT4 decreased to 299 and 7.32 ng/dL respectively and FT4 decreased further to 2.26 ng/dL in the next 7 days. Total thyroidectomy was performed without complications. Pathology showed multinodular thyroid hyperplasia. A week after discharge, the patient was started on levothyroxine replacement and is currently clinically and biochemically euthyroid.

CONCLUSION:
We describe a complicated case of type 1 AIT with limited treatment options and inability to use PTU, iodine or RAI. Methimazole could not be continued due to elevated transaminases and ineffectiveness despite high doses. We used lithium and glucocorticoids to decrease thyroid hormone levels for successful thyroidectomy in a patient with AIT.
Doege-Potter Syndrome: Liver Solitary Fibrous Tumor with Insulin-like Growth Factor 2 mediated Non-Islet Cell Tumor Hypoglycemia with Incidental Findings of Adrenal Insufficiency and Differentiated Papillary Thyroid Cancer

Anis Rehman, MD, Colin Carracher

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BACKGROUND:

Doege-Potter Syndrome (DPS) is a rare disease which is characterized by Insulin-like Growth Factor 2 (IGF-2) mediated Non-Islet Cell Tumor Hypoglycemia (NICTH) arising from a large Solitary Fibrous Tumor (SFT). NICTH is rare with around 290 cases reported. Three cases of NICTH have also been reported arising from metastatic thyroid cancer. We present an incidental finding of papillary thyroid cancer (PTC) as well as secondary adrenal insufficiency (AI) in a patient with DPS.

CASE REPORT:

A 56-year-old male with a history of hypertension presented with confusion and was found to have a fingerstick blood glucose (BG) of 24 mg/dL. CT abdomen/pelvis showed a 20 cm liver mass and multiple smaller liver lesions. Work-up included normal CSF studies, normal non-contrast brain MRI, normal echocardiogram, an EEG that showed cerebral slowing and a CT chest that showed thyroid nodules. Thyroid ultrasound confirmed three nodules, the largest being 4.2 cm in the right lobe with a hypoechoic halo and internal blood flow, but no microcalcifications. Liver biopsy confirmed SFT with pathognomonic gene fusion NAB2-STAT-6. Surgical oncology determined he was not a surgical candidate due to the presence of multiple liver lesions.

The patient was readmitted one month later for confusion and hypoglycemia of 33 mg/dL, corrected with an ampule of D50. BG dropped again to 59 mg/dL and he was started on an infusion of D10 1/2NS. Labs were normal including CBC, BMP, INR, TSH, LFT, UA and AFP. CT head was normal however 8AM cortisol was low at 6.3 µg/dL with an inappropriately normal ACTH of 19.60 pg/mL, suggesting AI. A 72-hour fasting test concluded within 3 hours when central BG dropped to 40 mg/dL. Labs included: insulin <2 (0 - 29.1 uIU/mL); proinsulin 1.6 (0.0 - 10.0 pmol/L); c-peptide 0.6 (0.9 - 7.1 ng/mL); beta-hydroxybutyrate 0.05 (0.02 - 0.27 mmol/L); insulin antibody <5.0 uU/mL; IGF binding protein-3 1400 (2133 – 5711 ug/L); negative sulfonylurea screen; cortisol 3.6 µg/dL. IGF-1 was 38 (54 – 194 ng/mL) and IGF-2 was 534 (333 – 967 ng/mL). The ratio of IGF-2 to IGF-1 was 14 (ref >10), strongly suggesting the hypoglycemia was IGF-2 mediated.

The diagnosis of DPS was made based on the simultaneous presence of a large SFT and IGF-2 mediated hypoglycemia, however AI can also cause hypoglycemia. The patient underwent embolization of the large SFT and was discharged on prednisone 30 mg PO daily. There were no further hypoglycemic events at follow-up. The right thyroid nodule was later evaluated for possible metastasis from SFT, however cytology suggested PTC. Total thyroidectomy was done with pathologic staging of pT3aN0Mx (5cm) PTC, follicular variant. He was then started on thyroid hormone replacement with levothyroxine 125 mcg/day.

CONCLUSION:

We report incidental findings of both AI and PTC in a patient with DPS. Evaluating hypoglycemia can be difficult, especially when several possible causes are present concurrently.

References:

Hematology Oncology

Pier Scaglioni, MD
DIVISION DIRECTOR
Alteration in Red Cell Indices During Palbociclib Therapy

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BACKGROUND:
Palbociclib is a CDK 4/6 inhibitor approved for treatment of metastatic hormone receptor positive breast cancer with hormone therapy. We noticed variations in red cell indices in patients on therapy and performed a retrospective review to systematically assess change in red cell indices in patients on Palbociclib.

METHODS:
We identified 46 patients with advanced hormone receptor (HR) positive, human epidermal growth factor receptor 2 negative breast cancer who were treated with Palbociclib at our institution from March 2015 to January 2018. The co-primary endpoint of our study was an increase in MCV greater than 10% and an increase in MCH greater than 10%. Secondary end points included increase in MCHC, RDW, assessment of progression free survival, correlation of de novo vs recurrent metastatic disease with change in MCV.

RESULTS:
34 patients were included in the analysis. Median age was 61.5 (33-83) years. 32 (94.11%) patients were female. 24 (70.58%) patients had recurrent disease while 10 (29.41%) patients had de novo metastatic disease. 20 (58.82%) patients received Palbociclib in first line setting. Both primary end points were met - mean delta MCV (18.07; t value 6.37; p <0.0001) and mean delta MCH (20.97; t value 6.39; p<0.0001) was statistically significant using T test. Mean increase in delta MCHC (2.38; p=0.0026) and RDW (8.20; p=0.0050) also reached statistical significance. No etiology of macrocytosis was apparent in the 9 patients tested. 24 (70.58%) patients were still on Palbociclib therapy without progression at the time of analysis. Four of the 10 patients who progressed had a decrease in MCV after discontinuation of Palbociclib (mean delta MCV –4.51%) suggesting reversal of macrocytosis with treatment discontinuation.

CONCLUSION:
Palbociclib therapy is associated with significant increase in red cell indices which seems to be reversible with treatment discontinuation. CDK 4/6 inhibition results in cell cycle arrest which may lead to discordance between cytoplasmic and nuclear maturation in erythroid precursors leading to macrocytosis. This can be a simple test of compliance to therapy on oral agents. Long term follow up is required to see if these changes correlate with response to therapy and/or survival.
Monitoring of Clonoctypic Immunoglobulin Heavy Chain Sequences in Plasma and Outcome in Patients with Diffuse Large B-Cell Lymphoma (DLBCL)

Ihab Eldessouki, Donatien Kamdem Toukam, Tahir Latif, Stephen C. Medlin, John C. Morris

Hematology Oncology (Trainee’s Division)

BACKGROUND:
Diffuse large B-cell lymphoma (DLBCL) is a type of high-grade non-Hodgkin’s lymphoma. Despite advances in treatment, long-term survival is approximately 40-50%. Recent studies have shown limited utility of routine surveillance imaging for DLBCL patients achieving remission. At the molecular level the junction between the immunoglobulin (Ig) variable, (diversity), and joining genes (J genes) provides a unique DNA clonotype that is shared by the malignant B-cells. Detection of residual disease by immunoglobulin heavy chain sequencing from peripheral blood may provide an alternate strategy for surveillance.

METHODS:
We prospectively evaluated this approach in 102 serial blood samples from 21 patients with DLBCL as they progressed through their treatment. Immunoglobulin heavy chain clonality was assessed by Sanger sequencing after amplification of extracted DNA. Assessment of Ig heavy(IgH) chain from cell-free DNA from peripheral blood plasma was compared to clinical outcomes at various time points and 26 FDG-PET/CT imaging.

RESULTS:
Clonoctypic immunoglobulin heavy chain rearrangements were detected in 100% of DLBCL patients in the peripheral blood either initially prior to treatment or upon relapse. Molecular detection of disease in the plasma often preceded PET/CT detection of relapse in patients initially achieving remission. During surveillance, time-points prior to relapse, plasma Ig heavy chain demonstrated improved specificity (100% vs. 54%, p<0.001) and similar sensitivity (32% vs. 56%, p=0.4) compared to PET/CT imaging. We were able to detect relapse 2-4 months prior radiological relapse by either PET or CT. Moreover, patients initially demonstrating 5 ng/ml or more of plasma free DNA had a poor outcome and appeared more resistant to first-line chemotherapy. (n=8).

CONCLUSIONS:
Immunoglobulin heavy chain analysis obtained from cell-free DNA in the plasma demonstrated higher specificity and equivalent sensitivity to PET/CT imaging, it may be used as a method for minimal residual disease assessment for DLBCL NHL.
A Phase I Dose-Finding Study of Metformin in Combination with Concurrent Cisplatin and Radiation in Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma

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¹ Division of Hematology Oncology

**BACKGROUND:**
Despite definitive cisplatin (Cis) based chemo-radiation (CRT), 3 year PFS/OS for locally advanced head and neck cancer (LAHNSCC) remain at 62%/73% respectively (RTOG 0522), underscoring the need for improved regimens. Metformin, hypothesized to suppress tumor cell growth by mTOR pathway inhibition, mediates PI3-kinase/Akt signalling pathway (frequently deregulated in HNSCC). Retrospective studies suggest that metformin improves survival in HNSCC patients. Therefore, we conducted a phase I open-label dose escalation study combining metformin with CRT in LAHNSCC.

**METHODS:**
Previously untreated LAHNSCC patients enrolled to receive escalating doses of metformin with a 7-14 day lead-in prior to CRT. Starting dose of metformin was 2000mg daily in addition to Cisplatin (100mg/m² days 1,22,43) and standard radiation (70Gy).

**RESULTS:**
20 patients enrolled, (2 replaced due to withdrawal of consent during lead-in period). Most common grade≥ 2 toxicities (CTCAE v4.03): nausea (25%), vomiting (25%), diarrhea (20%), AKI (15%). Dose limiting toxicity included Grade 3 diarrhea (cohort 3) and AKI (cohort 2). MTD established at 2550mg daily in combination with CRT. Patient characteristics: Median age 55(R46-65); 95% male, 95% Caucasians, 70% tobacco users, 70% HPV positive. After median follow up of 18 months (range 1-26), 1-year PFS/OS remain at 94%. 1 death reported (sudden cardiac, unrelated, occurred> 8 weeks after stopping metformin). Pharmacokinetic data showed that Cisplatin did not affect metformin steady-state

**CONCLUSIONS:**
For the first time, metformin is shown to be safe/tolerable with CRT with an impressive impact on survival in LAHNSCC pts; warranting further investigation in phase II trials, with established MTD of 2550 mg as recommended dose.
An Altered Bone Marrow Vascular Niche Impacts Normal Hematopoiesis and Tilts the Balance Between Myelopoiesis and Lymphopoiesis

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BACKGROUND AND PURPOSE:
Previous studies have demonstrated that an abnormality in the bone marrow (BM) niche can impact hematopoiesis and lead to the development of blood disorders. Bone marrow endothelial cells (BMECs) are critical constituents of the BM vascular niche. We hypothesize that an alteration in BMECs will compromise normal hematopoiesis. Our goal is to decipher how abnormal BMECs are impacting hematopoiesis.

METHODS:
We have generated an inducible Tie2-CreER/LSL-KRasG12D mouse model with a tdTomato reporter to introduce an oncogenic mutation in endothelial cells. The BM vasculature was visualized via confocal imaging. Complete blood counts and flow cytometry were used to evaluate cell counts and lineage composition. Spleens and bones were used in colony forming assays to investigate the colony forming potential of progenitor cells. Furthermore, we transplanted BM cells from syngeneic BoyJ mice into KRasG12D or WT recipients. Competitive transplant studies were performed to evaluate whether aberrant BMECs could affect the functional output of HSPCs.

RESULTS:
The Tie2-CreER/LSL-KRasG12D;tdTomato fluorescent reporter overlapped with the CD31 endothelial cell marker. Mice expressing endothelial KRasG12D (KRasG12D mice) had more leukocytes and increased myeloid cells in the blood and spleen. KRasG12D mice also had splenomegaly. Colony forming assays revealed that compared to controls, KRasG12D mice had greater colony forming potential. They also had a faster recovery rate after hematopoietic stress. Endothelial KRasG12D expression in recipient mice led to splenomegaly. Competitive transplantation showed that cells from donor KRasG12D mice (CD45.2) had lower CD45.2 donor chimerism.

CONCLUSION:
Endothelial KRasG12D compromised normal hematopoiesis and promoted a myeloproliferative phenotype.
Structure-Based Screening to Identify Inhibitor Against GTP-Sensor Kinase, PI5P4Kβ, for Cancer Therapy

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BACKGROUND AND PURPOSE:
PI5P4Kβ is an emerging target for cancer therapy. Recently, we have discovered that PI5P4Kβ is a novel type of kinase that utilizes GTP as a preferential substrate over ATP and acts as a cellular GTP sensor to regulate cellular metabolism and tumorigenesis (Molecular Cell, 2016). While pharmacological inhibition of the PI5P4Kβ kinase activity would provide an essential tool to study the roles of GTP sensing activity in cell functions and be a novel approach for cancer therapy, there has been no potent PI5P4Kβ inhibitor reported. This is partly due to the technical difficulty for assessing GTP-dependent kinase activity in a high throughput screening.

Towards this, we have developed a new screening strategy that consists of two unique steps to take advantage of our knowledge and strength: the first structure-based in silico screening was carried out using the crystal structure of PI5P4Kβ-GTP complex determined by ourselves, the second NMR-based screening directly assesses GTP dependent kinase activity.

RESULTS:
Through these screenings, we have identified two different classes of unique compounds that inhibit PI5P4Kβs activity. We have co-crystalized the identified compound with PI5P4Kβ for further optimization by a medicinal chemistry approach. Finally, we have combined the two different types of compounds, and the synthesized compounds dramatically increased the inhibitory activity against PI5P4Kβ, less off-target effect in vitro, and caused substrate accumulation in cells.

CONCLUSION:
Our data suggest that these novel PI5P4Kβ inhibitors will be critical tools to elucidate the mechanistic role of PI5P4Kβ regulating tumorigenesis and metabolism.
Vaccine Derived From Cancer Stem Cells Engineered To Express Interleukin-15 and its Receptor Inhibits Tumor Growth

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BACKGROUND AND PURPOSE:
Interleukin-15 (IL-15) is a powerful activator and inducer of NK and CD8+ cytolytic T cells. It activates and expands CD8+ memory T cells without stimulating immunosuppressive CD4+CD25+ T regulatory cells. As such, IL-15 may be useful as an immunotherapy for cancer. In an effort to enhance antitumor activity and reduce systemic side effects, we studied an approach using a vaccine enriched for cancer stem cells (CSCs) expressing murine (m) IL-15 and its receptor (mIL-15Ra).

METHODS:
Lentiviral vectors expressing the wild type or optimized (opt) cDNA sequences for mIL-15 and/or mIL-15Ra under the control of the human EF-1 promoter were generated and used to transduce TC1 mouse lung cancer cells. The TC1 cells were cultured under low serum conditions to generate tumor spheroids enriched for CSCs.

RESULTS:
The transduced TC1 cells demonstrated the expected mRNA transcripts. On flow cytometry only the cells transduced with mIL15Ra in combination with mIL-15opt showed surface expression of mIL-15, while cells transduced with mIL-15opt or mIL-15Ra constructs did not. When co-cultured with the transduced tumor spheroids or incubated with supernatants from these TC1 cells, CTLL-2 murine T cells demonstrated proliferation indicating that the cloned cDNAs were functional. The vector demonstrating the greatest stimulation of CTLL-2 cells expressed both the mIL-15Ra and mIL-15opt sequences and inhibited TC1 tumor growth in vivo.

CONCLUSION:
CSCs expressing mIL-15Ra and mIL-15 stimulated the proliferation of T cells and inhibited tumor growth. In vivo tumor vaccination studies are in progress.
Brain Metastases Treated with Immune Checkpoint Inhibitors: A Single Center Experience

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BACKGROUND:
We conducted a retrospective study to analyze the overall survival (OS) and progression free survival (PFS) among patients with brain metastases (BM) from Melanoma, Non-small cell Lung Carcinoma (NSCLC), Small cell lung cancer (SCLC), Head and neck squamous cell carcinoma (HNSCC) treated with immunotherapy (Nivolumab, Pembrolizumab, Ipilimumab or a combination, Atezolizumab, or Durvalumab).

METHODS:
After IRB approval, we retrospectively evaluated patients with BM treated at our institute from 2012-2017 who received either immunotherapy alone or immunotherapy and one or more of the following: stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), and/or surgery. Univariate analysis was utilized to analyze OS and PFS.

RESULTS:
A total of 51 patients were identified, median age at diagnosis of BM was 61 years (range 33-84). 32 (63%) patients were male. 43 (84%) patients had a good performance score (KPS 70-100) at the time of BM diagnosis. The median OS from the start of immunotherapy was 7.6, 7.2, 6.2 and 4 months for Melanoma, NSCLC, SCLC and HNSCC respectively. On univariate analysis, patients who received immunotherapy alone as primary BM treatment had worse survival compared to combination with radiotherapy or surgery (95% CI 0.03-0.95, p = 0.04) and patients who had partial intra cranial response with immunotherapy had better survival compared to those with stable disease (95% CI 1.77-239, p = 0.01).

CONCLUSIONS:
Immune check point inhibitors alone in treatment of BM is associated with worse survival outcomes compared to combination with radiotherapy or surgery. Further analysis is needed to validate these results.
Localized GTP Biosynthesis Fuels Renal Cell Carcinoma Migration and Metastasis

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BACKGROUND AND PURPOSE:
Despite nephrectomy and adjuvant treatments, over 30% of renal cell carcinoma (RCC) patients either have or develop distal metastasis to multiple organs, including the brain. Survival of metastatic RCC patients at 5-years is < 10% despite recent advances in therapeutics. There remains a clear need to develop more effective therapeutics and preventative measures for metastatic RCC and to understand the mechanisms behind RCC metastasis.

METHODS:
Utilizing cell-based immunohistochemistry, immunofluorescence, and wound healing assays in cells genetically or pharmacologically manipulated, we investigated the role of GTP metabolism in RCC migration.

RESULTS:
From two cohorts analyses on RCC patient tumor samples, we discovered high expression of the key enzyme for GTP biosynthesis, inosine 5’-monophosphate dehydrogenase II (IMPDH2), is significantly correlated with distal metastases. In wound healing assays, we found that genetic depletion of IMPDH by CRISPR/Cas9 as well as pharmacological inhibition of IMPDH activity lead to the significant suppression of RCC cell motility. At the molecular level, FRET-based analysis demonstrates RhoA activity is decreased in EGF-stimulated cells upon IMPDH inhibition. Furthermore, we found both IMPDH and the downstream biosynthetic enzymes, guanosine 5’-monophosphate synthase (GMPS) and nucleoside diphosphate kinase, localize to the leading edge of RCC cells during migration.

CONCLUSION:
Together, these results reveal a novel mechanism for concentrated GTP production at the leading edge, which is likely promoting the localized activation of RhoA and perhaps other cytoskeletal regulators for cell migration. Furthermore, our findings unveil a druggable pathway for the possible prevention of RCC metastasis.
Infectious Diseases

George Smulian, MD
DIVISION DIRECTOR
Obesity-associated Gut Microbiota Enhances Clostridium difficile Infection in Mice

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BACKGROUND AND AIMS:
Clostridium difficile is the leading cause of nosocomial infections in the U.S. Obesity, which is a modern-day epidemic, increases the risk of acquiring C. difficile and is also associated with clinically severe C. difficile infection (CDI). However, the mechanism(s) that increase CDI susceptibility in obese individuals and lead to worse clinical disease remain unknown.

METHODS:
We established a novel animal model of CDI in obesity by coupling a mouse model of high fat diet (HFD)-induced obesity with CDI. Obese and control (non-obese) mice pre-treated with antibiotics were challenged with C. difficile spores by oral gavage, and disease parameters such as weight loss, diarrhea, tissue damage and bacterial burden were studied.

RESULTS:
We show that compared to control mice, obese mice had longer duration of clinical disease (weight loss and diarrhea), inflammation and colonic tissue damage. Worse clinical disease in obese mice correlates with persistence of both C. difficile pathogen and toxins. During the early stages of infection, obese mice had lower toxin levels despite similar overall pathogen load, but the clearance of C. difficile bacteria and toxins was delayed in obese mice. Host gut microbiota and metabolic environment can influence C. difficile lifecycle (sporulation and germination). In fact, transfer of microbiota from obese mice increased diarrhea and mortality in control mice after CDI.

CONCLUSIONS:
Overall our data indicate that obesity-associated changes in commensal bacteria could alter dynamics of the C. difficile life cycle and thus impact clinical disease.
Predictors of Stable Discharge from the ED Observation Unit in COPD Exacerbation

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BACKGROUND AND PURPOSE:
Acute exacerbations of COPD (AECOPD) deleteriously affect mortality, quality-of-life, and healthcare cost. ED observation units (ED-Obs) allow 24 hour in-hospital care to determine the need for hospitalization. However, clinical and care-delivery variables that predict a stable discharge from ED-Obs for AECOPD have not been well studied.

METHODS:
We performed a retrospective cross-sectional study of consecutive patients with AECOPD who were admitted to ED-Obs from 4/2016-5/2017 at UCMC. The primary outcomes were ‘stable discharge’ vs ‘admitted or unstable discharge’. Predictor variables included patient demographics (age, gender, BMI, smoking status, comorbidities), COPD severity (FEV1, home inhalers, home oxygen use, frequency of hospitalizations and ED visits, past intubation), exacerbation severity (vitals on arrival and at 3 hours, laboratory test results, chest X-ray) and care-delivery variables (time to first steroid, time of ED presentation).

RESULTS:
133 patients were studied. After ED-Obs management, 62(46.6%) were hospitalized, 71(53.4%) were discharged home of whom 9(6.7%) returned to the ED in 7 days. Stable discharge occurred in 62(46.6%) patients. Hospitalization within the previous year was negatively associated with stable discharge (p=0.02). No other predictors were independently associated with stable discharge. Time to first steroid administration was similar in both groups (207 vs 224min, p=0.74).

CONCLUSION:
In patients with AECOPD admitted to ED-Obs, none of the studied bedside clinical variables predict stable discharge. Time to first steroid administration does not affect ED-Obs disposition. Hospitalization during the previous year negatively correlates with stable discharge from ED-Obs. Better prediction tools are needed to guide disposition planning for patients with AECOPD managed in ED-Obs.
Transcriptomic Profiling Reveals Key Molecular Pathways Associated with Preventricular Contraction-induced Cardiomyopathy

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BACKGROUND AND PURPOSE:
Left ventricular dysynchrony, as well as post-extrasystolic potentiation caused by premature ventricular contractions (PVCs) contribute to PVC-induced cardiomyopathy. We sought to characterize the molecular mechanisms whereby ventricular ectopy results in nonischemic cardiomyopathy.

METHODS:
We utilized a highly reproducible canine model of PVCs-induced cardiomyopathy. Using a premature pacing algorithm, bigeminal PVCs at coupling intervals of 200 ms were delivered from the epicardial right ventricular apex in previously healthy dogs for 12-weeks. Myocardial tissue from multiple regions of the LV free wall were harvested and total RNA was extracted. 16 ribo-depleted libraries were created including samples from 5 sham controls and 11 PVC-dogs. Paired-end massive parallel sequencing of cDNA (RNA-seq) was performed using an Illumina HiSeq platform. Gene models were defined using the UCSD/Broad CanFam3.1 assembly. Gene-level exploratory analysis and differential expression was performed using the DeSeq2 R-package. Gene ontology analysis was performed using NIH-DAVID v6.8.

RESULTS:
22,652 mapped reads with a >5 total read count were used for downstream analysis. 646 genes (2.9%) were significantly upregulated, whereas 470 (2.1%) were downregulated in PVC myocardium compared to sham controls (FDR <0.1). Gene ontology analysis revealed key molecular pathways associated with high PVCs burden including response to external stimulus, response to wounding, response to cytokine stimulus, inflammation response and response to stress. Indeed, several inflammation-related genes such as IL-33, IL-6, IL-4 receptor, NFKbeta subunits and the leukotriene B4 receptor, as well as genes encoding different tissue metalloproteinases (MMPs 8,9,3,24) were significantly upregulated. Conversely, pathways related to neuronal projection, axon guidance, muscle contraction and angiogenesis were significantly downregulated in PVCs hearts. Similarly, cation binding and metal ion binding biological processes were downregulated.

CONCLUSIONS:
Ventricular ectopy results in a highly specific molecular signatures associated with impaired LV function. Inflammation might occur in early stages of cardiomyopathy even before a heart failure syndrome is developed.
Derivation and Validation of a Simple Inflammation-Based Risk Score System for Predicting In-Hospital Mortality in Patients with Acute Coronary Syndrome

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BACKGROUND AND PURPOSE:
Inflammation is key in promoting and perpetuating acute coronary syndromes (ACS). However, current risk stratification tools do not account for systemic inflammation or utilize only single biomarkers such as C-reactive protein. We sought to derive and internally validate a simple inflammation-based risk score system to predict in-hospital mortality for the whole spectrum of ACS, based on high-sensitivity C-reactive protein (≥13.0 mg/L), white blood cell count (≥9.3 × 103/µL) and serum albumin level (≤3.6 g/dL) obtained at admission.

METHODS:
The study cohort included 7,396 Mexican-mestizo patients with ACS admitted to a referral center. We randomly assigned patients to an independent derivation (66.6%) or validation (33.4%) cohorts. The score was calculated based on the combination of three biomarkers of inflammation and were categorized into four categories of systemic inflammation: without, mild, moderate and severe inflammation.

RESULTS:
Unadjusted in-hospital mortality was significantly different across the four categories of inflammation in the derivation cohort (1.8%, 2.8%, 4.1% and 13.8% for without, mild, moderate and severe inflammation, respectively; P <0.0001). These results were similar in the validation cohort (1.1%, 2.9%, 5.2%, and 12.6%, respectively, P <0.0001). After multivariate adjustment, only the category of severe systemic inflammation was associated with a 3-fold increased risk of in-hospital mortality and was the most powerful predictor of mortality (C-statistic 0.71). After subsetting patients based on their GRACE risk score, we demonstrated that a higher inflammation risk score was associated with a significant increase of in-hospital mortality across all sub-groups. Most importantly, we demonstrate that systemic inflammation is associated with worse prognosis independently from other clinical variables included in other conventional risk scores such as GRACE.

CONCLUSION:
An inflammation risk score system, based on the combination of high-sensitivity C-reactive protein, white blood cell count and serum albumin levels at admission, independently predicts in-hospital mortality and identifies a subset of high-risk patients independently of their GRACE risk score. These findings could have clinical implications not only for risk stratification but also for management of ACS.
Gene Expression Signature after One Dose of Neoadjuvant Pembrolizumab Associated with Tumor Response in Head and Neck Squamous Cell Carcinoma (HNSCC)

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Division of General Internal Medicine (Trainee’s Division)

BACKGROUND AND PURPOSE:
Immune checkpoint inhibitors have been shown to induce durable tumor response in a subset of recurrent and/or metastatic HNSCC. Higher expression of PD-L1, INF-γ, and composite signatures such as “T cell-inflamed” profiles have been reported as biomarkers of response. However, prospective study of gene expression profiles after a single dose of Pembrolizumab compared to pre-treatment biopsy have not been reported. As a part of study “Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC” (NCT02641093), we have investigated gene expression changes associated with Pembrolizumab pathological response in HNSCC.

METHODS:
Total RNA was extracted from 11 paired samples of pre- and post- one dose of Pembrolizumab. Total RNA was subjected to a hybridization-based digital counting assay (Nanostring®), which measures mRNAs of 770 immune-related genes and controls. RNA counts were normalized and log-transformed. Gene expression comparison analysis was performed between pre- and post- Pembrolizumab treatment and between five responders and six non-responders. Response was defined as more than 10% of pathologic treatment effect.

RESULTS:
Higher expression of PD-L1, PD-L2, and INF-γ in pre-treatment samples were associated with tumor response after one dose of Pembrolizumab (Welch’s t-test, p=0.015, 0.021, 0.006). Existence of T cells, B cells, NK cells, macrophages, neutrophils in pre-treatment samples were not predictive with response. However, macrophages, T and B lymphocytes were increased in post-treatment samples of responders, implying that these were recruited effectors. There was no such difference in NK cells and neutrophils. INF-γ induced genes including CXCL9, OASL, IFI35, and IDO1 showed higher expression in responders (Welch’s t-test p=0.004, 0.005, 0.007, 0.01).

CONCLUSION:
Inflamed tumor microenvironment, evidenced by increased INF-γ irrespective of lymphocyte infiltration, is associated with pathological response after a single dose of Pembrolizumab in HNSCC.
Improving Adherence to Pulmonary Hypertension Screening in Patients with Systemic Sclerosis: Overcoming the Provider-Level Barriers

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BACKGROUND AND PURPOSE:
Pulmonary arterial hypertension (PAH) is a life-limiting complication in patients with systemic sclerosis (SSc). Current recommendations suggest a minimum screening of annual echocardiogram (TTE) and PFT. We hypothesize that several modifiable provider-level hurdles contribute to inadequate screening and can be alleviated.

METHODS:
Physicians in rheumatology and pulmonary clinics at University of Cincinnati were surveyed for knowledge and perceived barriers in PAH screening of SSc patients. We performed a longitudinal study of all SSc patients seen in pulmonary and/or rheumatology clinics between 8/2016-12/2017. Data were collected on the most recent TTE and PFT using electronic medical record (EMR). Appropriate screening was defined as TTE and PFT within last 18 months. Interventions were performed to improve appropriate screening rate to >90% goal. Annotated run-chart was used to measure screening adherence at monthly intervals.

RESULTS:
Eighteen physicians completed the survey. 67% knew minimal screening recommendations. 44% identified “difficulty ordering screening tests” as a barrier. Subsequent interventions were: 1) physician education through lecture series, 2) best practice alert in EMR to facilitate just-in-time ordering of screening tests in clinics. The longitudinal study included 166 SSc patients. Appropriate testing of TTE and PFT increased from 50% to 96% and from 45% to 93% respectively. Patients with combined appropriate TTE and PFT screening improved from 30% to 93%.

CONCLUSION:
Physician-level hurdles contribute to sub-optimal PAH screening in SSc patients. Lack of knowledge and difficulty in ordering tests were major barriers. Use of just-in-time decision-support aids can improve screening rates in this vulnerable population.
Nephrology, Kidney CARE Program

Charuhas Thakar, MD
DIVISION DIRECTOR
Potential Role of miRNAs in the Baseline Expression and Activity of Proximal Tubule Phosphate Transporter NaPi-IIa

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BACKGROUND:
The apical sodium-phosphate cotransporter (NaPi-IIa) controls phosphate balance by regulating the rate of inorganic phosphate reabsorption in the kidney proximal tubule. We have previously shown that the 3′-untranslated region (3′UTR) of NaPi-IIa mRNA transcript plays an important role in the post-transcriptional regulation of NaPi-IIa in response to estrogen. However, whether 3′UTR regulates the baseline expression of NaPi-IIa remains unknown.

METHODS:
We studied the role of 3′UTR in NaPi-IIa expression and activity using Opossum Kidney (OK) cells transfected with mammalian expression plasmids containing NaPi-IIa with or without 3′UTR. Further, we examined the role of four overlapping (~250bp) fragments (F1-F4 from stop codon) in 3′UTR function using Luciferase assay. Subsequently, we identified three common miRNAs in mouse and human NaPi-IIa 3′UTR and examined their potential role in the expression of mNaPi-IIa-3′UTR using both Luciferase assay and immunoblotting.

RESULTS:
3′UTR deletion caused a significant increase in the protein abundance of mouse and human NaPi-IIa. These findings were confirmed by 32P transport activity assay, which showed 50% increase in Pi transport in OK cells expressing 5′-ORF vs. ORF-3′UTR of mNaPi-IIa. Further, we observed an increase in luciferase activity of 3′UTR fragments F1 to F4 by 36%, 74%, 54% and 27%, respectively, compared to intact 3′UTR. We identified three miRNAs (miR-24, miR-377 and miR-485), which decreased luciferase activity and protein abundance of mNaPi-IIa.

CONCLUSION:
3′UTR regulates the baseline expression of mouse and human NaPi-IIa protein abundance and activity in OK cells. This phenomenon is mediated through a sequence specific post-transcriptional mechanism involving microRNAs.
The Development of Hyperglycemia Correlates with the Stimulation of Ammoniagenesis. An Early Contributing Factor to Renal Hypertrophy in Diabetes Mellitus

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**BACKGROUND:**  
Diabetes Mellitus (DM) is associated with early renal hypertrophy in humans and rodents, and ammonia (NH4+ + NH3) has been shown to induce renal cell hypertrophy in vitro. However, whether ammonia contributes to renal enlargement in DM remains elusive.

**METHODS:**  
Rats treated with streptozotocin (STZ) and Akita mice and their wild-type (Type I DM); ob/ob mice and their lean controls (Type II DM) were housed in metabolic cages for food and water balance studies. Urinary NH4+ excretion was analyzed and correlated with changes in kidney mass (kidney weight/BW). The role of metabolic acidosis in DM-induced ammoniagenesis was examined using acetazolamide treatment.

**RESULTS:**  
STZ-treated rats exhibited a significant increase in kidney mass, which correlated with a increase in urinary NH4+ excretion as early as 6 days of hyperglycemia. The stimulation of ammoniagenesis is corrected by insulin treatment in STZ model. Hyperglycemic Akita mice showed a 4-fold increase in NH4+ excretion at 4 weeks and kidney mass doubled at 9 weeks of age. Similarly, ob/ob mice exhibited a sharp hyperglycemia, which correlated with a 7-fold increase in NH4+ excretion with significant increase in kidney mass at 9 weeks of age. DM and ACTZ have an additive effect on the stimulation of ammoniagenesis.

**CONCLUSIONS:**  
The development of renal hypertrophy correlates with early hyperglycemia-induced ammoniagenesis in both type I and type II DM models. The stimulation of ammoniagenesis is not mediated via acidosis. Hence, ammoniagenesis likely contributes to the development of early renal hypertrophy, which subsequently progresses to kidney disease in diabetes mellitus.
Ca$^{2+}$ Fluxes in PD1 Positive Exhausted T Cells in Head And Neck Cancer

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BACKGROUND AND PURPOSE:
Several T-cell markers have been correlated with cancer immune evasion, being responsible of functional abnormalities of anti-tumor immune cells. Programmed Death-1 (PD1) is a negative regulator overexpressed by exhausted T-cells. T-cells are critically dependent on Ca$^{2+}$, which directs crucial events in T-cell activation and function. The relationship between Ca$^{2+}$ fluxes and PD1 expression in anti-tumor T cells remains unclear. Our purpose is to investigate intracellular Ca$^{2+}$ responses in HNC peripheral blood (PB) CD8+ T-cells according to their PD1 status.

METHODS:
Activated PB CD8+ T-cells derived from 3 HNC patients were stained with fluorescent anti-PD1 antibody in order to distinguish PD1 positive and PD1 negative cells. We then loaded the cells with Fura-2 (ratiometric Ca$^{2+}$ indicator) and recorded Ca$^{2+}$ fluxes elicited by thapsigargin (bypassing the TCR) and TCR stimulation in PD1+ vs PD1- cells. To determine if anti-PD1 antibody changed intracellular Ca$^{2+}$ fluxes, we compared Ca$^{2+}$ fluxes in anti-PD1 labeled and unlabeled Jurkat cells which overexpressed PD1 (Jurkat-PD1high).

RESULTS:
Anti-PD1 staining did not changed the Ca$^{2+}$ response of Jurkat-PD1high cells making a suitable method to distinguish PD1+ cells in live experiments. Ca$^{2+}$ response in HNC CD8+ T-cells was not influenced by the expression of PD1, given no robust difference between PD1 positive and PD1 negative cells.

CONCLUSION:
The PD1 status of HNC PB T cells does not alter their Ca$^{2+}$ fluxing abilities. Further investigations are required to show the influence of PD1 expression on Ca$^{2+}$ fluxes in tumor-infiltrating lymphocytes given their stronger PD1 expression.

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Belatacept and Tacrolimus Corticosteroid-Free Regimens Lead to Elevated Mycophenolic Acid Exposure at 1 and 3 Months After Kidney Transplantation

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BACKGROUND AND PURPOSE:
Mycophenolate mofetil (MMF) is generally administered as a fixed dose. Studies have shown relationships between MPA exposure (MPAAUC) and adverse effects in renal transplants (RT). No data evaluates this relationship in CNI/steroid-free regimens. Our objective was to evaluate the incidence of adverse events per MPAAUC in a prospective trial.

METHODS:
Prospective MPAAUC measurement protocol was implemented in recipients receiving CNI- or belatacept-based steroid-free regimens at 1 (MPAAUCM1) and 3 (MPAAUCM3) months post RT using the Pawinski equation (7.75+6.49C0+0.76C0.5+2.43C2). MPAAUC ranges were: low (< 30mg/L*h⁻¹), intermediate (30-60mg/L*h⁻¹) and high (AUC >60mg/L*h⁻¹). MMF dose was adjusted per MPAAUC, AEs (viremia, leukopenia, neutropenia, BPAR1yr), and provider discretion. An AE was considered associated with an MPAAUC when it occurred within 1 month of the measurement.

RESULTS:
101 patients were analyzed. Demographics, MPAAUCs, and AEs per IS group are included in Tables 1 and 2. Mean MPAAUCs were elevated (range 56-62.4mg/L*h⁻¹). Following MMF dosage decrease at month 1 in >30% of patients, mean MPAAUCM3 remains similar to MPAAUCM1. Figure 2 (panels A-D) represents the distribution of overall AEs at 1 and 3 months per MPAAUC groups and panels E-F the distribution of BPAR1yr.

CONCLUSION:
Regardless of concomitant IS, MPAAUCM1 was high in 1/3 of patients; low MPAAUC was rare. Despite similar MPAAUCM1, leukopenia occurred more frequently in belatacept vs. tacrolimus regimens. Similar MPAAUCM3 following dose decrease at 1 month indicates potential increase in MPA exposure over time post RT. As no relationship between MPAAUC and AEs has been observed, studies to determine optimal MPAAUC should be conducted.

(Figures on back)
# Table 1 – Demographics and MPA AUC exposure per baseline immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Belatacept (n = 76)</th>
<th>Tacrolimus (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, median (IQR)</strong></td>
<td>47 (29 - 61)</td>
<td>53 (40.5 - 63)</td>
</tr>
<tr>
<td><strong>Race – white/black, n (%)</strong></td>
<td>65 (85.5), 11 (14.5)</td>
<td>17 (68), 8 (32)</td>
</tr>
<tr>
<td><strong>Male Sex, n (%)</strong></td>
<td>50 (85.8)</td>
<td>13 (52)</td>
</tr>
<tr>
<td><strong>Transplant type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First transplant</td>
<td>72 (94.7)</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Second Transplant</td>
<td>4 (3.9)</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Deceased</strong></td>
<td>28 (36.8)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Living</td>
<td>48 (63.2)</td>
<td>16 (64)</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-ATG</td>
<td>41 (53.9)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>35 (46.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>MPA-AUC&lt;sub&gt;b&lt;/sub&gt;, mean (SD)</strong></td>
<td>59.8 (25.9)</td>
<td>62.4 (4.9)</td>
</tr>
<tr>
<td>High, n (%)</td>
<td>31 (40.8)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Intermediate, n (%)</td>
<td>39 (51.3)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Low, n (%)</td>
<td>6 (7.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Dose change after MPA-AUC&lt;sub&gt;b&lt;/sub&gt;, n (%)</strong></td>
<td>25 (32.9)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Increase</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decrease</td>
<td>24 (31.6)</td>
<td>7 (100)</td>
</tr>
<tr>
<td><strong>MPA-AUC&lt;sub&gt;sp&lt;/sub&gt;, mean (SD)</strong></td>
<td>56 (20.8)</td>
<td>60.4 (7.5)</td>
</tr>
<tr>
<td>High, n (%)</td>
<td>29 (38.2)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Intermediate, n (%)</td>
<td>42 (55.3)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Low, n (%)</td>
<td>5 (6.6)</td>
<td>3 (12)</td>
</tr>
<tr>
<td><strong>Dose change after MPA-AUC&lt;sub&gt;sp&lt;/sub&gt;, n (%)</strong></td>
<td>24 (31.6)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Increase</td>
<td>2 (2.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decrease</td>
<td>22 (28.9)</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>

# Table 2 – Comparative incidence of adverse event per baseline immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Belatacept (n = 76)</th>
<th>Tacrolimus (n = 25)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>30 (39.5)</td>
<td>7 (28)</td>
<td>0.347</td>
</tr>
<tr>
<td>At 3 month</td>
<td>39 (51.3)</td>
<td>14 (56)</td>
<td>0.818</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>57 (75)</td>
<td>15 (60)</td>
<td>0.202</td>
</tr>
<tr>
<td>Neutropenia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>3 (3.9)</td>
<td>1 (4)</td>
<td>1.000</td>
</tr>
<tr>
<td>At 3 month</td>
<td>30 (39.5)</td>
<td>7 (28)</td>
<td>0.350</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>41 (53.9)</td>
<td>10 (40)</td>
<td>0.256</td>
</tr>
<tr>
<td>Viremia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>8 (10.5)</td>
<td>2 (8)</td>
<td>1.000</td>
</tr>
<tr>
<td>At 3 month</td>
<td>10 (13.2)</td>
<td>5 (20)</td>
<td>0.517</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>29 (38.2)</td>
<td>9 (35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>9 (11.8)</td>
<td>6 (24)</td>
<td>0.192</td>
</tr>
<tr>
<td>At 3 month</td>
<td>11 (14.5)</td>
<td>0 (0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>31 (40.8)</td>
<td>8 (32)</td>
<td>0.485</td>
</tr>
<tr>
<td>BPAR at 1 year, n (%)</td>
<td>16 (21.1)</td>
<td>1 (4)</td>
<td>0.063</td>
</tr>
<tr>
<td>Time to first BPAR, days, range</td>
<td>8 - 341</td>
<td>338</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher’s exact test
PD1 Signaling Alters Store-Operated Ca$^{2+}$ Entry in Cytotoxic T Cells of Head and Neck Cancer Patients

Vaibhavkumar S. Gawali$^1$, Ameet Chimote$^1$, Trisha Wise-Draper$^2$, Laura Conforti$^1$

1 Division of Nephrology, Department of Internal Medicine, College of Medicine, University of Cincinnati.

2 Division of Hematology Oncology, Department of Internal Medicine, College of Medicine, University of Cincinnati.

BACKGROUND AND PURPOSE:
Head and neck cancer (HNC) shows high resistance to immunotherapy. The mechanism of action of recently approved immunotherapeutic anti-PD1 antibodies (Pembrolizumab) is poorly understood. PD1 and its ligand (PD-L1/PD-L2) interaction limits T cell function by reducing T cell receptor (TCR) stimulated Ca$^{2+}$ fluxes. Ca$^{2+}$ entry is mediated by ion channels (store-operated Ca$^{2+}$ entry, SOCE). It is unknown whether PD1 signaling involves ion channels. We hypothesize that Pembrolizumab improves T cell function by increasing SOCE.

METHODS:
We studied the effect of Pembrolizumab and PD-L1 in circulating CD8$^+$ T cells of HNC patients and healthy donors (HD) using thapsigargin (TG). TG allows the measurements of Ca$^{2+}$ fluxes through ion channels independently on TCR activation. Additionally, we tested the effect of Pembrolizumab on TCR-mediated Ca$^{2+}$ fluxes on PD1-expressing NFAT-reporter Jurkat cells.

RESULTS:
Pembrolizumab increased Ca$^{2+}$ influx by 55% ($p<0.02$) in HNC T cells (5/9 patients). SOCE was lower in HNC who positively responded to Pembrolizumab compared to untreated HD ($p<0.006$). PD-L1 reduced SOCE by 38% in HD T cells (3/6 donors). This inhibition was reversed by Pembrolizumab ($p<0.009$). Pembrolizumab increased the rate of Ca$^{2+}$ influx in HNC patients ($p<0.008$) and HDs ($p<0.03$). In PD1-expressing Jurkat cells, Pembrolizumab increased the number of cells (30%; $p<0.001$) that responded to TCR stimulation with a sustained increase in Ca$^{2+}$.

CONCLUSION:
Pembrolizumab enhances SOCE in T cells thus providing a role for ion channels in mediating its effect. This mechanism may contribute to the improved functionality of T cells in HNC patients undergoing immunotherapy.

Funding: (DoD CA160714; 2-R01-CA95286)
Optimization of Multiplex Immunofluorescent Staining of Paraffin Tumor Sections

Farhan Z. Ilyas1, Ameet A. Chimote1, and Laura Conforti1
1 Division of Nephrology, Department of Internal Medicine, University of Cincinnati, Cincinnati, OH.

BACKGROUND AND PURPOSE:
The composition and functionality of tumor infiltrating lymphocytes (TILs) affects tumor progression and therapy. The expression of ion channels in TILs marks their functional state. Immunofluorescent staining could be used to analyze CD8+/CD4+ T cells, ion channels (Kv1.3, KCa3.1, STIM1 and ORAI1) and functional markers (Ki67 and Granzyme B) in TILs, allowing for greater understanding of tumor composition. However, complex multi-color protein staining may require the use of primary antibodies raised in the same host. Herein we optimized a protocol for multi-protein staining using same host antibodies.

METHODS:
Paraffin tumor sections were deparaffinized, blocked and stained with different concentrations of anti-CD4/CD8/Ki67/STIM1/Granzyme B/ORAI1/Kv1.3/KCa3.1 antibodies alone or in combination with pancytokeratin (marker of tumor cells), and DAPI (nuclear marker). Staining of two proteins using same host primary antibodies was also performed.

RESULTS:
We optimized the concentrations of the different antibodies described above. We performed sequential staining of multiple proteins using antibodies generated in the same-host species by staining the first protein by saturating concentrations of a primary rabbit antibody, followed by a secondary anti-rabbit fluorophore X-conjugated antibody. After a series of washes, the second protein was stained with its corresponding primary rabbit antibody followed by a secondary anti-rabbit fluorophore Y-conjugated antibody. Optimal concentration of primary and secondary antibodies, exposure times, and wash times allowed specific staining. Non-specific staining of the first protein by the second secondary antibody was determined by omitting the second primary antibody.

CONCLUSION:
This optimized technique allows for the multi-protein staining of tumors and other tissues.

Funding: DoD CA160714; 2-R01-CA95286
Clinical Heterogeneity of Early Anamnestic Donor Specific Antibody Responses in Kidney Transplantation

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Division of Nephrology, Kidney CARE Program (Trainee’s division)

BACKGROUND:
Anamnestic donor specific antibody (DSA) responses may threaten renal transplants (RTx). We hypothesize earlier DSA detection may minimize RTx injury and enhance therapeutic responses.

METHODS:
Intensive DSA monitoring (IDM) was prospectively implemented in high-risk RTx. High-risk defined as: 1) previous txp, 2) female RTx with paternal Ag, 3) pre-transplant DSA, 4) slow graft function in patients (pts) with previous HLA exposure, 5) current cytotoxic PRA >25% or peak cytotoxic PRA >50%, or 6) positive T or B cell FXM. IDM included sampling on posttxp days 0, 1, 2, 3, 5, 7, 14, 30, 90, 180, and 360. Clustered SABs expressing donor antigens (CL-DSA) was evaluated by an HLA scientist.

RESULTS:
64 pts underwent IDM with 27 (42.2%) demonstrating progressive DSA increases. Multivariate analysis revealed pretransplant DSA was the strongest predictor of progressive DSA increases (40.2 fold increased odds). 10 pts with peak DSA values >5000MFI received AMR treatment with 6/10 showing >50% DSA decrease within 14d, with 5/10 pts showing DSA resolution. Pts with peak DSA values <5000MFI were treated at physician discretion. Of 13 pts with DSA peak <5000MFI were not treated, 9(69.2%) resolved spontaneously within 14d; 2 pts(11/13 total, 84.6%) eventually resolved without treatment. Of 4 pts with peak DSA <5000MFI and treated, three (75%) eliminated DSA by treatment. Five pts with early CL-DSA had biopsy-proven AMR.

CONCLUSIONS:
1) IDM with routine evaluation for CL-DSA allows early DSA detection;
2) DSA elevations <5000MFI may be observed without treatment with frequent spontaneous regression;
3) patients with progressive DSA increases >5000 MFI had treatment responses inferior to those whose MFI <5000. IDM and early DSA treatment may avert early AMR.
Selective Knockdown of A2AR in CD8+ T Cells Using CD8-Targeting Nanoliposomes

Hannah S. Newton¹, Michael J. Arnold¹, Ameet Chimote¹, Trisha Wise-Draper², Laura Conforti¹

¹ Department of Internal Medicine, Division of Nephrology and Hypertension, University of Cincinnati, Cincinnati, Ohio; ² Department of Internal Medicine, Division of Hematology Oncology, University of Cincinnati, Cincinnati

Pathobiology and Molecular Medicine (Trainee's division)

BACKGROUND AND PURPOSE:
Adenosine accumulates in the tumor microenvironment and contributes to the inhibition of T cell function via the A2A receptor (A2AR). Blockade of A2AR has been shown to rescue T cell function and decrease tumor burden. However, A2AR is present in variety of cells and a limitation of non-selective A2AR pharmacological blockers is the development of side effects. Our goal is to selectively knockdown the A2AR in cytotoxic CD8+ T cells through lipid nanoparticles (NPs) decorated with anti-CD8 antibody containing A2AR siRNAs.

METHODS:
Human peripheral blood T cells (PBTs) were isolated. Flow cytometry and RT-qPCR were used to determine A2AR knockdown in PBTs after nucleofection with A2AR or scramble siRNAs. A functional assay for IL-2 production (cytokine produced by activated PBTs and suppressed by the A2AR pathway) in PBTs treated with siRNAs and activated in the presence of CGS21680 (A2AR agonist) was used to verify A2AR knockdown.

RESULTS:
Nucleofection of PBTs with A2AR or scramble siRNAs downregulated mRNA and protein by 61% and 14-42%, respectively. PBT treatment with A2AR siRNAs prevents the CGS21680-induced inhibition of IL-2 production by 27%. Additionally, NPs were fabricated using biotinylated lipids as previously described (Hajdu et al., Biomaterials 2013) and labeled with anti-CD8 antibody. Flow cytometry revealed that CD8-labeled NPs are specific to CD4- PBTs and suggested that the NPs are subsequently internalized.

CONCLUSION:
These data indicate the feasibility of fabrication and potential efficacy of CD8-specific A2AR siRNAs-loaded NPs that should restore the functionality selectively in CD8+ tumor infiltrating lymphocytes—a potential targeted cancer therapy with limited side effects.
Fibrinogen Depletion Attenuates Angiotensin II-induced Abdominal Aortic Aneurysm


Nephrology, Kidney CARE Program (Trainee’s Division)

BACKGROUND:
Fibrinogen and fibrin provide physical and biochemical support to a developing clot and is defined as one of the most crucial independent risk factors for cardiovascular diseases (CVDs). In addition to clot formation, fibrinogen promotes wound healing and powerful inflammatory and immune responses by engagement of leukocytes. Increased circulating fibrinogen and fibrin degradation products are correlated with increased diameter and progression of abdominal aortic aneurysm (AAA). However, a causal link between fibrinogen and AAA has not yet been established. The objective of this study was to determine the role of fibrinogen depletion in a mouse model of AAA.

METHODS AND RESULTS:
To determine whether aneurysm resulted in a procoagulant environment, we examined plasma levels of thrombin generation by calibrated automated thrombography (CAT), thrombin anti-thrombin (TAT), and fibrinogen in control and AAA plasma from mice and humans. Patients and mice with AAA had significant elevations in thrombin generation, TAT, and fibrinogen versus saline controls (mice) and control patients (human). To determine the effect of fibrinogen, in vivo, low density lipoprotein receptor deficient (Ldlr-/-) mice were injected with scrambled anti-sense oligonucleotide (ASO) or β-fibrinogen ASO (30 mg/kg) 3 weeks prior to experimentation and throughout the study. Fibrinogen ASO treatment achieved > 90% depletion of fibrinogen. After 3 weeks, mice were fed a fat and cholesterol enriched diet (42% milk fat; 0.2% cholesterol) 1 week prior to and throughout infusion with angiotensin II (AngII; 1,000 ng/kg/day) for 28 days. Fibrinogen ASO attenuated abdominal diameter (33% decrease; P = 0.001), and inflammatory cytokines (>75% decreased IL-1 and IL-6; P = 0.001) versus scrambled ASO control. Further, fibrinogen depletion significantly attenuated aneurysm incidence and rupture-induced death (P < 0.05).

CONCLUSIONS:
Our results demonstrate that AAAs augment procoagulant markers in both humans and mice. Importantly, fibrinogen depletion attenuates AAA incidence, diameter, rupture-induced death, and inflammation. Therefore, reduction of plasma fibrinogen may be a novel treatment strategy in patients with AAA.
Impact of Elderly Donor Obesity on Long-Term Outcomes in Renal Transplant Recipients

Masaaki Yamada, MD, Silvi Shah, MD
Nephrology, Kidney CARE Program (Trainee’s Division)

BACKGROUND:
Over the last decade, the proportion of obesity has drastically increased in the United States (U.S.). Higher body mass index (BMI) and longer duration of obesity were related to multiple comorbidities. This obesity burden can further affect the quality of donor organs. Purpose of this study is to determine the impact of elderly donor obesity on long-term kidney allograft outcomes.

METHOD:
We performed a cohort study of 19,545 adult renal transplant recipients from elderly donors ≥60 years between 1/1/2000 and 12/31/2016, using US national transplant registry data to examine the effect of body mass index (BMI) in elderly donors on patient and allograft survival.

RESULTS:
In the primary analysis, elderly donor morbid obesity (BMI ≥40 kg/m²) was associated with higher recipient mortality (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.10-2.01, p <0.01) and death-censored allograft loss (OR, 1.23; 95% CI, 0.92-1.65, p = 0.16) at 1 year compared with elderly donor with BMI <40 (Table 1). The recipient survival with donor BMI ≥40 was statistically significantly worse than the survival of recipient with donor BMI <40, p <0.001 (Figure 1).

CONCLUSION:
Elderly donor obesity (BMI ≥40) was associated with higher risk of 1-year recipient mortality although not statistically significant influence in kidney graft survival at 1 year. Further investigation is needed to understand the cumulative impact and associated risk of elderly donor obesity.

Table 1

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>1-year death censored graft loss OR (95% CI), p value</th>
<th>Mortality at 1 year OR (95% CI), p value</th>
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<tbody>
<tr>
<td>18.5-24.9</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>25-29.9</td>
<td>0.93 (0.82-1.07), 0.32</td>
<td>1.1 (0.96-1.28), 0.16</td>
</tr>
<tr>
<td>30-34.9</td>
<td>0.99 (0.61-1.51), 0.93</td>
<td>1.1 (0.95-1.34), 0.18</td>
</tr>
<tr>
<td>35-39.9</td>
<td>0.79 (0.61-1.02), 0.07</td>
<td>1.3 (0.99-1.62), 0.06</td>
</tr>
<tr>
<td>≥40</td>
<td>1.23 (0.92-1.65), 0.16</td>
<td>1.5 (1.10-2.01), &lt;0.01</td>
</tr>
</tbody>
</table>
Figure 1

![Graph showing patient survival over days post-transplant for different BMI categories.](image)

Donor_BMI (kg/m²)
- < 40
- ≥ 40

<table>
<thead>
<tr>
<th>Donor_BMI</th>
<th>Number at risk</th>
<th>Days Posttransplant</th>
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<tr>
<td>&lt; 40</td>
<td>18981</td>
<td>17443</td>
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<tr>
<td>≥ 40</td>
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<td>491</td>
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</table>
The U.S. Experience of Octogenarian Donor Kidney Transplantation

Masaaki Yamada, MD, Silvi Shah, MD
Nephrology, Kidney CARE Program (Trainee's division)

BACKGROUND:
Although the total number of transplantation is increasing over the last 5 years, nearly 5,000 patients decrease while waiting for kidney transplantation. Despite critical shortage of donors, more than 85% of recovered kidneys from octogenarian donors are discarded and little is known about long-term outcomes of those kidneys.

METHODS:
Using U.S. national transplant registry data, a propensity-score matched 1:4 case-control study of adult kidney transplant recipients between 1/1/2000 and 12/31/2016 was performed to compare patient and allograft survival in patients who received a kidney from an octogenarian donor vs. non-octogenarian donor.

RESULTS:
Only 23 of 251,295 adult renal transplant recipients received kidney from octogenarian donors. The primary analysis revealed octogenarian donor kidney use was not related to a statistically significant difference in risk of patient death (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.12-1.8; p = 0.36) or death-censored graft loss (OR, 2.2; 95% CI, 0.43-8.9, p = 0.30). Kaplan-Meier curve is shown in figure 1. Mean wait list time and mean pretransplant dialysis duration were not statistically significantly different between octogenarian donor and non-octogenarian donor group: Mean wait list time (414 vs. 585 days, p=0.11) and mean dialysis duration (620 vs. 766 days, p=0.32).

CONCLUSION:
Octogenarian donor status did not impact patient and kidney allograft survival compared with non-octogenarian donor organs. Our study potentiates expansion of the organ donor pool with a careful organ selection in very old donors.

Figure 1. Kaplan Meier Survival Curve
Dynamics of Adaptive Natural Killer Cells in Longitudinal Analysis of CMV Vaccine Recipients

Ivayla E. Gyurova1,2, Heinrich Schlums3, David Bernstein4,5, Yenan Bryceson3, Stephen N. Waggoner1,2,5

1 Center for Autoimmune Genomics and Etiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
2 Pathobiology and Molecular Medicine Graduate Program, University of Cincinnati, Cincinnati, OH
3 Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden
4 Division of Infectious Diseases, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
5 Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

BACKGROUND AND PURPOSE:
Classical vaccine efforts focusing on the induction of B- and T-cell memory have proven ineffective in the protection against pathogens such as cytomegalovirus (CMV). Thus, CMV remains a significant public health threat. There is clear evidence that patients lacking natural killer (NK) cells suffer recurrent, severe infections with multiple herpesviruses, including CMV, highlighting the importance of NK cells in controlling this pathogen. In addition, several studies describe the expansion and persistence of phenotypically and functionally distinct murine (Ly49H+) and human (NKG2C+, FcRγneg, EAT-2neg, SYKneg) NK-cell subsets with putatively enhanced antiviral effector function upon CMV infection. Therefore, one potentially pioneering approach to creating an efficacious CMV vaccine would include the induction of such NK cell adaptations.

RESULTS:
To test this, we used longitudinal PBMC samples collected during a vaccine trial with HCMV gB in MF59 adjuvant administered to CMV negative adolescent females. We observed several patterns of transient and sustained elevations in the frequency of FcRγneg, EAT-2neg, and SYKneg subsets at various time points despite absence of detectable CMV infection in any trial participants.

Surprisingly, these patterns were apparent in participants regardless of administration of vaccine or placebo. In contrast to previous cross-sectional studies, we present evidence that these CMV-reactive adaptive NK cells exhibit continuous oscillations in the blood of CMV negative individuals, suggesting that they may react to unknown environmental or inflammatory cues.
The Role of Transcription Factor KLF2 in Regulating Th2 Responses

Shuo Huang, George Deepe, MD

Pathobiology and Molecular Medicine (Trainee’s division)

BACKGROUND AND PURPOSE:
Kruppel-like factor 2 (KLF2) is a transcription factor in the KLF protein family. It is highly expressed in leukocytes in the lung. The Deepe lab has previously described the role of KLF2 in inducing Th2 responses through Dendritic cell (DC)-T cell interaction, particularly, the Notch signaling pathway. Lyz2creKlf2fl/fl mice (KLF2 deficiency in myeloid cell lineage) infected with Histoplasma capsulatum (Hc) display a higher fungal burden, which is caused by increased IL-4 production from accumulated Th2 cells in the lung. The hypothesis is that KLF2 in DCs is the central regulator of Th2 immunity. We hypothesize that the elevated Th2 cell numbers in lungs is a result of increased production of Th2 chemoattractants by KLF2-deficient dendritic cells. We also postulate that one of the Notch receptors (NR1 and NR2) is more expressed on Th2 cells in the lung.

RESULTS:
KLF2 deficient mice expressed significantly higher CCL17 and CCL22 (Th2 chemoattractants), but not CXCL9, CXCL10 and CXCL11 (Th1 chemoattractants) on day 3 post-infection. A significant difference expression of NR1 and NR2 between KLF2 deficient mice and WT mice was observed on day 7 post-infection. The conclusion is that KLF2 in dendritic cells regulates Th2 cell accumulation by release of chemoattractants and Notch receptor expression on T cell.
Pulmonary, Critical Care and Sleep Medicine

Frank McCormack, MD
DIVISION DIRECTOR
Pulmonary Manifestations of Inflammatory Bowel Disease

M. K. Grewal¹, B. Collins², B. Yacyshyn³, N. Gupta¹

¹ Pulmonary & Critical Care, University of Cincinnati, Cincinnati, OH, United States
² Internal Medicine, University of Cincinnati, Cincinnati, OH, United States
³ Gastroenterology, University of Cincinnati, Cincinnati, OH, United States

RATIONALE:
The nature and frequency of pulmonary involvement in inflammatory bowel diseases (IBDs) such as Crohn’s Disease (CD) and Ulcerative Colitis (UC) is not well characterized.

METHODS:
We queried the University of Cincinnati’s electronic medical record to identify adult patients with UC or CD using ICD-9 and 10 codes. Computed tomography (CT) scans and pulmonary function tests (PFTs) were reviewed to determine the nature and prevalence of pulmonary involvement. Pulmonary involvement was further classified into subcategories based on CT findings, and chi-squared analysis was performed to compare the prevalence of these findings in UC versus CD.

RESULTS:
We identified 975 patients with a histopathologically confirmed diagnosis of UC (341, 35%) and CD (634, 65%). 185 patients with UC (54%) and 332 patients with CD (52%) had at least one abnormal finding on CT scan. Abnormalities were further characterized as parenchymal, airway, pleural, or vascular involvement. Parenchymal abnormalities were seen more commonly in patients with UC (145/185, 78%) as compared to patients with CD (168/332, 51%) (p<0.0001). Airway manifestations such as bronchiectasis and mosaic attenuation were more common in patients with CD as compared to UC (9/332, 2.7% versus 0/185, 0%) (p=0.02). 54 patients had PFTs of which 27 (50%) were abnormal. Isolated reduction in diffusion capacity was the most commonly identified PFT abnormality (26/54, 48%).

CONCLUSIONS:
Pulmonary manifestations were seen in over half of the patients with IBD and varied depending upon the underlying IBD, with parenchymal findings seen more commonly in UC and airway manifestations seen more commonly in CD.
Reducing Lab Testing in Medical ICU Through System Redesign Using Improvement Science: Project SMART

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BACKGROUND:
Excessive laboratory testing in critically-ill leads to high cost, unnecessary procedures and interventions.

Setting: UCMC MICU is 24-bed unit. At baseline 9.4 lab orders are performed/patient/day.

METHODS:
We performed a quasi-experimental, prospective study. We developed a multidisciplinary-team (physicians, nurses, respiratory-therapists, pharmacists) and analyzed the existing system through process-mapping and observation. We surveyed attending physicians to assess burden of non-value labs. SMART aim: decrease MICU lab volume by 25% from 9.4 to 7 labs/patient/day by April 2018 (outcome measure). We performed iterative Plan-Do-Study-Act (PDSA) cycles to test and implement changes. Based on identified opportunities, our key process-measure was % patients for whom a lab plan was discussed on rounds. We used control charts to track measures.

RESULTS:
Baseline system: Labs were non-value 34% times. Lab plan was discussed 30% of time with inconsistent documentation. Differences in protocol-driven labs and nurses-practices existed.

We performed multiple PDSA cycles to increase lab discussion on rounds. These included interventions for nurses, residents and pharmacists to increase team awareness and defining new roles. EMR note-templates were modified. Visual reminders on rounding computers were applied. Pharmacists on teams were tasked to collect data and remind if lab discussion was missed. The lab discussion and appropriate documentation increased from 30% to 95%. Visual flow charts were created and pasted in nurses work spaces to guide lab testing per protocols. The number of labs/patient/day (outcome measure) decreased from 9.4 to 8 with an ongoing trend towards 7.

CONCLUSION:
Engagement of multidisciplinary team, increasing team awareness, standardization of work and visual management were key interventions in reducing non-value labs tests in MICU. Ongoing efforts are needed for sustainability and reliability.
Tuberin Negatively Regulates Sphingolipid Metabolism in an mTOR-independent Manner in Tuberous Sclerosis Complex


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BACKGROUND AND PURPOSE: Tuberous Sclerosis Complex (TSC) is an autosomal dominant disorder with development of tumors in the brain, heart, lung, and kidneys. TSC is caused by TSC1 or TSC2 mutations, resulting in hyperactivation of mTORC1 and the aberrant cell growth. Sphingolipids are the major components of plasma membrane, where they maintain membrane integrity and integrate signal transduction events mediating survival and cancer progression. The purpose of this study is to investigate how TSC2 regulates sphingolipid metabolism.

METHODS: Mass-spectrometry was performed in patient-derived-TSC2-null cells, and plasma from patients with pulmonary lymphangioleiomyomatosis (LAM). mRNA and protein levels of acid ceramidase (AC), which catalyzes the conversion of ceramides to sphingolipids, were quantified using real-time RT-PCR, immunoblotting, and immunohistochemistry. AC gene was deleted using siRNA/shRNA. Cell survival was measured using MTT, flow cytometry, and colony formation. Xenograft models were developed using TSC2-null-luciferase AC-shRNA cells. Tumor progression were monitored using non-invasive bioluminescent imaging.

RESULTS: A significant increase in sphingosines was identified in TSC2-null cells. TSC2-null cells exhibited enhanced levels of AC mRNA, protein, and activity, which were insensitive to mTORC1 inhibition. LAM lesions and renal angiomyolipomas accumulated abundant AC protein relative to adjacent normal tissues. AC-knockdown decreased the proliferation and colony formation, and increased the death of TSC2-null cells. Treatment with AC inhibitors led to growth arrest of TSC2-null cells. The initiation of TSC2-null-ACshRNA xenografts was drastically delayed in vivo.

CONCLUSION: TSC2 negatively regulates sphingolipid metabolism via acid ceramidase (AC) in an mTORC1-independent manner. Targeting the sphingosine metabolism may have therapeutic benefit for TSC.
Primary Sjögren’s Syndrome-associated Interstitial Lung Disease

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BACKGROUND AND PURPOSE:
Sjögren’s syndrome (SS) is a chronic autoimmune inflammatory exocrinopathy. When it occurs independently of other connective tissue diseases, it is termed primary SS (pSS). Interstitial lung disease (ILD) is present in approximately 16% of patients with pSS. The natural history of pSS-associated ILD (pSS-ILD) is not well defined.

METHODS:
ICD-9 and ICD-10 codes identified adult patients with pSS and ILD seen at UCMC. Demographic data, diagnosis dates, imaging findings, clinical symptoms, lung biopsy results, and medical treatments were recorded.

RESULTS:
24 patients with pSS-ILD were included in our analysis. Our population was female predominant (88%, 21/24). ILD was the presenting manifestation of pSS in 4 patients, with pSS manifesting an average of 4 years later. In the remaining patients, the diagnosis of ILD was established with mean follow-up period of 8.2 years after the diagnosis of pSS.

Cough and dyspnea were the most common presenting symptoms seen in 83% and 79% of patients, respectively. Airway manifestations such as bronchiectasis were the most common CT abnormalities, seen in 63% (15/24) of patients.

At the most recent follow-up, 50% of patients reported improved symptoms compared to the time of diagnosis, and 59% of patients had improved or stable CT findings. Treatment of ILD led to a significant improvement in PFTs.

CONCLUSIONS
ILD is commonly seen in patients with pSS, and can be the presenting manifestation of pSS. Immune-modulating treatment can have a beneficial effect on symptoms, CT findings and PFTs.
ERK and Akt Integrate Pro-Survival Signals in Sirolimus-Induced Cytostasis in Lymphangioleiomyomatosis (LAM)

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BACKGROUND AND PURPOSE:
LAM is a devastating pulmonary disease affecting young women that is characterized by smooth muscle cell infiltration and emphysema-like lung remodeling. LAM is associated with mutations in the TSC2 gene resulting in constitutive activation of mTORC1. A seminal clinical trial showed that the mTORC1 inhibitor sirolimus suppresses lung function decline and improves symptoms while treatment continues. However, in all cases, progression resumes following drug cessation, consistent with a cytostatic rather than a cytocidal effect; continuous drug exposure is required for sustained benefit. Moreover, a subset of LAM patients are either refractory to sirolimus effects, or develop resistance. The purpose of this study is to develop novel combinatorial cytocidal treatments to eliminate LAM cells.

METHODS:
Single cell RNA-seq was performed with LAM-lung xenograft tumors of TSC2-null cells. Xenograft tumor progression was monitored by non-invasive bioluminescence imaging. Cell proliferation/arrest was monitored by cell number. Cell death/survival was measured by flow cytometry using LSRII and Attune, and data was analyzed using FlowJoX. Protein levels were assessed by immunoblot. Statistical analysis was performed using GraphPad PRISM-7.

RESULTS:
Sirolimus differentially induces acute and long-term compensatory effects on MAPK and PI3K/Akt signaling pathways. TSC2-null xenograft tumors of ELT3 and 621-101 cells become refractory to chronic sirolimus therapy, similar to that observed in sirolimus unresponsive LAM patients. scRNAseq data reveal that the expression of the mitogen-activated protein kinase kinase kinase 3 (MAPKKK3) gene is upregulated in cell cluster expressing LAM marker genes in sirolimus-treated LAM lung relative to that in the naïve LAM lung.

CONCLUSION:
Rapamycin integrates ERK and Akt-mediated pro-survival signals to prevent cell death in cytostatic TSC2-null tumor cells. Further investigation will be required for identifying the target genes promoting cell death in response to sirolimus treatment in LAM.
Correlation Between NK Cell Receptor Ligands and Severity of COPD

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Pulmonary, Critical Care, and Sleep Medicine (Trainee’s division)

BACKGROUND AND PURPOSE:
Recent studies in COPD have focused on the role of immune function in the role of COPD progression after viral exacerbations. Studies of murine COPD models and COPD patients have shown chronic cigarette smoking primes NK cell activation. The B7 family is a group of cellular receptors that provide both stimulatory and inhibitory signals to NK cells. We looked at B7H6, a direct activator of NK function, and its soluble ligand levels in never smoking controls and patients with varying degrees of COPD.

METHODS:
Serum samples were obtained from the COPD VA Cohort. ELISAs for B7H6 (N=73) were performed on samples including control patients, former and current smokers, and varying severities of COPD (based on GOLD classification). ELISAs performed according to manufacturer protocol. Results were analyzed with 5-parameter logarithmic regression.

RESULTS:
We measured serum levels B7H6 and evaluated based on correlation with control, current smokers, former smokers, and varying severities of COPD (GOLD I/II based on FEV1 >50% and GOLD III/IV based on FEV1 <50%). We found an inverse relationship between B7H6 levels and COPD severity. Compared with controls and smokers, COPD patients had significantly decreased B7H6 levels as disease severity progressed (p=0.041).

CONCLUSION:
Our study showed that soluble level of B7H6 was inversely correlated with disease progression. This finding fits with our expected theory of NK cell function and COPD progression. Ultimately the level of B7H6 soluble ligand may be useful as a clinical tool in patients with COPD exacerbations as it may aid in differentiating between viral illnesses and inflammatory exacerbations.
Novel Monitoring Tools for Predicting Stable Discharge from Emergency Department Observation Unit in Acute Exacerbation of COPD

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BACKGROUND AND PURPOSE:
ED-observation units (ED-Obs) provide an avenue for short-term inpatient care of COPD exacerbations (AECOPD) to reduce preventable hospitalizations. ED-Obs disposition decision remains subjective. Decision-support tools are needed to predict stable discharge from ED-Obs.

Setting:
UCMC ED-Obs unit with 16-beds, staffed by advanced practitioners under physician-supervision.

METHODS:
Respiratory therapists (RT) serially evaluated AECOPD patients triaged to ED-Obs using two measures, 1) Dyspnea Assessment Score (DAS), a novel tool based on vitals and clinical exam (range 4-16), 2) Resting BORG score (range 0-10). Assessment was performed at each treatment (every 2-4 hours) during ED-Obs stay until final disposition of discharge or hospitalization. Primary outcomes were ‘stable-discharge’ vs ‘admission or unstable-discharge (defined as discharge with revisit within 7-days)’. Predictor variables were: DAS and BORG scores, each of which was analyzed as: delta (Δ=first – last score), last score, %change (Δ/first score*100). Associations were performed using t-test (continuous variables) and chi-square (categorical variables). ROC-analysis was performed. P<0.05 was considered significant.

RESULTS:
25 patients were studied with mean (+SD) age, FEV1 %predicted, BMI and Charleston co-morbidity index of 57.6(9.6) years, 41(15) %, 28.1(8.4) kg/m2 and 2.5(1.4), respectively. ΔDAS, last BORG and %change in BORG were associated with stable-discharge (p<0.05). ROC AUC was greatest for %change of BORG(0.76), ΔBORG(0.72) and ΔDAS(0.71). A BORG-threshold (BT) (defined as ΔBORG > 2 and last BORG < 3) was 60% sensitive and 90% specific for stable-discharge (p=0.01).

CONCLUSION:
Novel measurements of serial resting BORG scores and BORG-threshold (BT) may complement clinical decisions-making in predicting stable discharge from ED-Obs and improve patient-safety and resource utilization.
Mechanisms of Microlith Clearance Induced by Dietary Phosphate Restriction in Pulmonary Alveolar Microlithiasis


Pulmonary, Critical Care and Sleep Medicine (Trainee's Division)

BACKGROUND AND PURPOSE:
Pulmonary alveolar microlithiasis (PAM) is an autosomal recessive disorder caused by deficiency of Npt2b, a sodium phosphate cotransporter that is required for phosphate export. Progressive calcium phosphate microlith deposition and macrophage rich inflammation and fibrosis often results in respiratory failure and death. Microlith burden in the Npt2b-/- murine model is reduced by dietary phosphate restriction. We investigated the upregulation of alternative phosphate transporters, osteoclastogenesis and osteoclast activation as mechanisms of dietary modulation.

METHODS:
Npt2b-/- and Npt2b+/+ mice were fed diets with typical (0.7% Pi), low (0.02%, 0.1% and 0.4% Pi) or high (2% Pi) phosphate content, denoted RPD, LPD and HPD, respectively. Phosphate metabolism markers and expression of related genes were measured.

RESULTS:
Npt2b-/- mice treated with LPD or HPD for 8 weeks decreased and increased stone burden and lung weights, respectively. LPD reduced serum levels of FGF-23 and PTH, increased serum 1,25(OH)Vit D levels and reduced BAL levels of phosphate and calcium. Alternative sodium-phosphate cotransporters, Pit1 and Pit2, were upregulated following LPD. Osteoclast related genes were upregulated in Npt2b-/- mice after LPD. Osteoprotegerin, and calcium and phosphate levels were increased in the BALF of Npt2b-/- mice on HPD.

CONCLUSION:
LPD prevents progressive microlith accumulation in young Npt2b-/- mice and reverses stone burden by a mechanism that includes upregulation of Pit1/Pit2, reduction of calcium and phosphate, and activation of osteoclastogenesis and osteoclastic function. HPD increases alveolar calcium, phosphate and osteoprotegerin levels. We conclude that dietary phosphate restriction may be a promising approach for the treatment of PAM.
Osteogenesis and Osteolysis in Pulmonary Alveolar Microlithiasis


Pulmonary, Critical Care and Sleep Medicine (Trainee’s Division)

BACKGROUND AND PURPOSE:
Pulmonary alveolar microlithiasis (PAM) is an autosomal recessive lung disease due to deficiency of the Npt2b-/- sodium-phosphate transporter, which results in accumulation of microliths in the alveolar space. Adoptive transfer of microliths into the lungs of wild type mice is followed by formation of macrophage-rich aggregates at 1wk and complete clearance of stones and inflammation by 1mo. We investigated the structure and composition of microliths, osteoclast differentiation and recruitment, and biomarkers.

METHODS:
The structural, proteomic and elemental composition analysis of microliths from Npt2b-/- mice and PAM patients was interrogated by scanning electron microscopy (SEM), energy dispersive X-ray spectrometry (EDX) and mass spectrometry (nanoLC-MS/MS). Microliths from Npt2b-/- mice were instilled into the lungs of wild type mice and CCR2-/- mice, and bronchoalveolar lavage (BAL) cells were collected.

RESULTS:
Microliths were composed of calcium and phosphate; SEM revealed highly spherical surfaces resembling trabecular bone. Proteomic analysis revealed hundreds of proteins, including osteopontin (OPN), Alpha-2-HS-glycoprotein and surfactant proteins A, B and D. Comparison of BAL cells revealed an osteoclast-related gene signature. Microliths adoptively transferred into Npt2b+/+ mice induced similar osteoclast differentiation in BAL cells, that resolved by 14d. In contrast, CCR2-/- mice that cannot recruit monocytes to the lung exhibited delayed microlith clearance after adoptive transfer.

CONCLUSION:
PAM microliths are composed of calcium phosphate crystals with a rich protein matrix, and induce inflammation, barrier dysfunction and osteoclast differentiation. Efficient clearance of microliths requires monocytes capable of replenishing the pulmonary osteoclast pool. OPN, one of the microlith components, is elevated, and is a promising biomarker.
Development of a Chronic Lung Remodeling Preclinical Model of Pulmonary Lymphangioleiomyomatosis

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**Pulmonary, Critical Care and Sleep Medicine (Trainee’s Division)**

**BACKGROUND AND PURPOSE:**
Lymphangioleiomyomatosis (LAM) is a devastating pulmonary disease affecting young women that is characterized by smooth muscle cell infiltration and emphysema-like airspace dilation. Mutations in the TSC1 or TSC2 lesions result in de-repressing of mTORC1 in LAM cells. Although mTORC1 inhibitors have been shown to impede lung function decline in LAM patients, there are many remaining challenges to optimizing therapy. The purpose of this study is to establish a mouse model that recapitulates LAM features.

**METHODS:**
LAM patient-derived cells expressing luciferase were intravenously inoculated into NSG mice. Lung tumor growth was monitored using non-invasive bioluminescent imaging. Two-dimensional chest x-ray images were obtained using In-Vivo Multispectral Imaging System. MicroCT scans were performed using Inveon with respiratory gating applied during image acquisition. Lung physiology was measured using a Flexivent system.

**RESULTS:**
Alveolar enlargement was prominent in mouse lungs, indicative of lung remodeling. MicroCT showed that dense nodular opacities were present in mice inoculated with TSC2-null cells, associated with 3-fold increase in lung density, indicative of tumor formation, consistent with lesions detected by bioluminescent imaging. Mice bearing lung lesions showed a restrictive physiologic defect. The elastance of mice bearing lung lesions was greater than control mice. These data indicate mice bearing established lung tumors and airspace enlargement exhibit impaired lung physiology.

**CONCLUSION:**
We have developed a novel chronic lung remodeling mouse model that mimics LAM including lung lesion formation, alveolar destruction, and lung function decline. We will apply this new model to test therapeutic responses in LAM.
Thank you!

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