The ENTELLIGENCE™ Young Investigator Program is supported through an educational grant from Actelion Pharmaceuticals US, Inc.
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Dear Colleagues,

We are delighted to announce that in 2018, the ENTELLIGENCE™ Young Investigator Program chose four new young investigators to receive ENTELLIGENCE awards based on their outstanding pulmonary vascular disease-related research proposals. This year, we received extremely high quality, competitive submissions, and we are proud to recognize these four young leaders. These awards provide support to individual young investigators at universities and research institutes in the US and Canada to conduct basic science, translational, and/or clinical research through a 12-month mentored grant. For the past 13 years, members of the independent Steering Committee have selected cutting-edge projects that are scientifically relevant, original, and applicable to the problem of pulmonary vascular disease. More than 60 promising researchers in the field of pulmonary vascular disease have been awarded to date.

Funded studies have targeted pulmonary vascular disease in the areas of pathophysiology, pharmacology, treatment, genetics, diagnosis, and epidemiology. Results from many of these projects have been presented at numerous key scientific meetings such as the American Thoracic Society, the American Heart Association, and the European Respiratory Society, and have been published in more than 50 peer-reviewed journals, including American Journal of Physiology, American Journal of Respiratory and Critical Care Medicine, Chest, Circulation, Nature, and Pulmonary Circulation. ENTELLIGENCE awardees have also advanced their careers in pulmonary vascular disease, with many becoming Assistant and Associate Professors of Medicine, Directors, Section Leaders, and mentors for up-and-coming young investigators.

The ENTELLIGENCE Young Investigator Program will soon begin another cycle of competition, continuing its commitment to advancing the understanding of pulmonary vascular disease and promoting the career development of young investigators planning an academic career in pulmonary vascular disease research. Please see important dates shown in the timeline below, visit the ENTELLIGENCE website and follow ENTELLIGENCE on social media:

On behalf of the ENTELLIGENCE Steering Committee, I would like to express our appreciation to Actelion Pharmaceuticals US, Inc. for making the ENTELLIGENCE Program possible.

Best regards,

Ronald J. Oudiz, MD
Program Overview

The ENTELLIGENCE Young Investigator Program
Supporting young investigators

The ENTELLIGENCE Young Investigator Program, established in 2005, provides opportunities for promising young investigators to promote quality medical care and enhance patients’ lives by supporting research (basic science, clinical, or translational) in the area of pulmonary hypertension (PH), specifically related to expanding knowledge of pulmonary vascular pathobiology pathways. The ENTELLIGENCE program is led by a Steering Committee comprised of leaders in the field of PH who award 12-month mentored grants of up to $100,000 to conduct basic science and clinical research. Grants are based on scientific merit, originality, feasibility, and applicability to the diagnosis and treatment of PH, conditional upon supervision by an appropriate mentor, and conducted at a university or research institute in the US or Canada. The program is consistent with Actelion’s commitment to basic science and clinical research in the area of PH.

The ENTELLIGENCE program is funded by an independent grant from Actelion Pharmaceuticals US, Inc. All decisions to fund protocols are solely decided by the ENTELLIGENCE Steering Committee and the receipt of a grant in no way requires the recipient, nor implies that the recipient is obligated to, recommend or prescribe any Actelion product.

How to submit

Applicants are invited to submit original basic or clinical investigations specifically targeting pulmonary vascular disease in the following areas: Pathophysiology, Pharmacology, Treatment, Genetics, Diagnosis, and Epidemiology. Applications are submitted electronically as a Letter of Intent. Submitted applications are reviewed by the Steering Committee and selected applicants are invited to submit full proposals. The timelines, submission procedure, and submission forms are available on the ENTELLIGENCE website www.entelligencemd.org.

Review cycles completed: 13
Awards distributed: 63
Overview of ENTELLIGENCE Awards

Awarded 2018

Catherine Avitabile, MD
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA
Mentors: Stephen Paridon, MD, and Babette Zemel, PhD
Project Title: The association between skeletal muscle deficits and exercise performance in pediatric pulmonary hypertension patients

Meghan Bernier, MD
The Johns Hopkins University School of Medicine
Baltimore, MD
Co-Investigator: Larissa Shimoda, PhD
Mentor: Lewis Romer, MD
Project Title: Endothelial to mesenchymal transition in pulmonary hypertension: Formin a new identity

Stephen J. Coleman, MS, PhD
Colorado State University
Fort Collins, CO
Mentor: Milton Thomas, PhD
Project Title: Investigation of calcium regulatory processes and their role in a natural large animal model of altitude-associated pulmonary hypertension sensitivity leading to heart failure

Daniel Lachant, DO
University of Rochester Medical Center
Rochester, NY
Mentor: R. James White, MD
Project Title: Extracellular vesicles as a marker of vascular disease activity in PAH
Overview of ENTELLIGENCE Awards

Awarded 2017

Nadine Al-Naamani, MD, MS
University of Pennsylvania
Philadelphia, PA
Co-Investigator: David Lederer, MD
Mentor: Steven Kawut, MD
Project Title: Exploring the association of visceral intrathoracic fat with vascular stiffness in pulmonary hypertension
• Presented at 2018 American Thoracic Society Conference

Jonathan Davies, MD
Baylor College of Medicine
Houston, TX
Mentor: Michael Blackburn, PhD
Project Title: The role of adenosine signaling in pulmonary hypertension associated with bronchopulmonary dysplasia

Rebecca Kameny, MD
University of California, San Francisco
San Francisco, CA
Mentor: Jeffrey Fineman, MD
Project Title: Translating the natural history of pulmonary vascular disease secondary to congenital heart disease into basic mechanisms and therapeutic targets
• Presented at 2018 PVRI World Congress and 2018 Pediatric Academic Societies Meeting

Stephanie Thorn, PhD
Yale University
New Haven, CT
Mentors: Hyung Chun, MD, and Albert Sinusas, MD
Project Title: Pilot study to engage the Apelin-MEF2 signaling axis for myocardial preservation in a large animal model of right ventricle failure
• Accepted for presentation at American Society of Nuclear Cardiology, 2018
Overview of ENTELLIGENCE Awards

2017 Award Winners

From left: Nadine Al-Naamani, MD, MS; Rebecca Kameny, MD; Jonathan Davies, MD; and Stephanie Thorn, PhD
Overview of ENTELLIGENCE Awards

Awarded 2016

Olivier Boucherat, PhD
Québec Heart and Lung Institute Research Centre
Québec, QC, Canada
Mentor: Sébastien Bonnet, PhD
Project Title: Impact of mitochondrial heat shock protein
90 inhibition in pulmonary arterial hypertension
• Presented at 2017 American Thoracic International Conference; 2017 PVRI
World Congress; and 2016 American Heart Association Scientific Sessions
• Published in American Journal of Respiratory and Critical Care
Medicine, 2018

Vitaly O. Kheyfets, PhD
University of Colorado Denver
Denver, CO
Co-investigator: Shelley Miyamoto, MD
Mentors: Robin Shandas, PhD, and Dunbar Ivy, MD
Project Title: Inter-ventricular decoupling is an overlooked
contributor to right ventricular myocardial stress and dysfunction
in pediatric pulmonary hypertension

Todd M. Kolb, MD, PhD
Johns Hopkins University
Baltimore, MD
Co-investigator: David Kass, MD
Mentor: Paul Hassoun, MD
Project Title: PDE9A in right ventricular and pulmonary
vascular remodeling

Jeffrey C. Robinson, MD
University of Colorado
Aurora, CO
Mentor: Rubin Tuder, MD
Project Title: Iron deficiency and hypoxic signaling in
pulmonary hypertension
• Presented at 2017 PVRI World Congress

Haiyang Tang, PhD
University of Arizona
Tucson, AZ
Co-Investigator and Mentor: Jason Yuan, MD, PhD
Project Title: Differential role of mTORC1 and mTORC2 in hypoxic
vasoconstriction and the development of pulmonary hypertension
• Presented at 2018 American Thoracic Society Conference and 2017 American
Heart Association Scientific Sessions
• Published in American Journal of Physiology - Lung Cellular and Molecular
Physiology, 2018 and British Journal of Pharmacology, 2017
Overview of ENTELLIGENCE Awards

Awarded 2015

Ketul R. Chaudhary, PhD
Ottawa Hospital Research Institute
Ottawa, ON, Canada
Mentor: Duncan J. Stewart, MD
Project Title: Genetic and sex determinants of hyper-responsiveness to SU5416 alone producing severe pulmonary arterial hypertension in a sub-strain of Sprague Dawley rats
• Published abstracts: American Journal of Respiratory and Critical Care Medicine, 2015, 2016 and 2017; Canadian Journal of Cardiology, 2015 and 2016; and Circulation, 2015 and 2016

Marshaleen King, MD
Morehouse School of Medicine
Atlanta, GA
Mentors: Vincent Bond, PhD, and Harrison Farber, MD
Project Title: The prevalence and pathogenesis of HIV-associated pulmonary arterial hypertension among underserved urban populations
• Presented at 2016 American Thoracic Society Conference
• Published abstracts: American Journal of Respiratory and Critical Care Medicine, 2016

Alan R. Morrison, MD, PhD
Yale University
New Haven, CT
Mentor: Hyung J. Chun, MD
Project Title: Development of microRNA-based therapeutic strategies for pulmonary arterial hypertension

Uyen T. Truong, MD
Children’s Hospital Colorado
Denver, CO
Co-investigator: Robin Shandas, PhD
Mentor: Dunbar Ivy, MD
Project Title: Non-invasively derived vascular and ventricular markers predict invasively derived hemodynamic data in children with pulmonary hypertension
• Presented at 2015 and 2016 American Heart Association Scientific Sessions; 2016 Society of Cardiac Magnetic Resonance Scientific Sessions; 2016 American Thoracic Society Conference; and 2016 UCSF Pulmonary Hypertension Conference
• Published in European Heart Journal - Cardiovascular Imaging, 2017 and 2018; Pediatric Cardiology, 2018; The Journal of Heart and Lung Transplantation, 2018; Circulation: Cardiovascular Imaging, 2017; and Oxidative Medicine and Cellular Longevity, 2017
Overview of ENTELLIGENCE Awards

**Awarded 2014**

**Evan L. Brittain, MD, M SCI**  
Vanderbilt University Medical Center  
**Co-Investigator:** Thomas J. Wang, MD  
**Mentor:** Anna R. Hemnes, MD  
**Project Title:** Dysregulation of lipid metabolism and right ventricular function in pulmonary arterial hypertension  
- Presented at 2016 American Society of Clinical Investigation Annual Meeting and 2015 American Heart Association Scientific Sessions  
- Published in American Journal of Respiratory and Critical Care Medicine, 2016; Circulation, 2016; Journal of the American College of Cardiology, 2016; and Pulmonary Circulation, 2016

**Joshua M. Diamond, MD**  
University of Pennsylvania  
**Co-Investigator:** Harold I. Palevsky, MD  
**Mentor:** Steven M. Kawut, MD, MS  
**Project Title:** Clinical and biomarker risk evaluation of pulmonary hypertension in lung transplantation  
- Presented at 2015 American Thoracic Society Conference and 2015 International Society for Heart & Lung Transplantation  
- Published abstracts: Journal of Heart and Lung Transplantation, 2015 and American Journal of Respiratory and Critical Care Medicine, 2015

**R. Blair Dodson, PhD**  
University of Colorado Denver Anschutz Medical Center  
**Mentor:** Steven H. Abman, MD  
**Project Title:** Intrauterine hemodynamic stress mechanisms of fetal pulmonary vascular injury  
- Presented at 2014 and 2015 Pediatric Academic Societies Meeting  
- Published in American Journal of Physiology - Lung Cellular and Molecular Physiology, 2014

**Clyde J. Wright, MD**  
University of Colorado School of Medicine and Children’s Hospital Colorado  
**Mentor:** Kurt R. Stenmark, MD  
**Project Title:** Role of macrophage ET1 expression in the pathogenesis of persistent pulmonary hypertension of the newborn  
- Presented at 2015 Society for Pediatric Research Annual Meeting; 2015 Western Society for Pediatric Research Annual Meeting; and 2014 Neonatal Cardiopulmonary Biology Young Investigators Forum  
- Published in Journal of Immunology, 2015
Overview of ENTELLIGENCE Awards

Awarded 2013

Harry Karmouty-Quintana, PhD
The University of Texas Health Science Center at Houston
Mentor: Michael R. Blackburn, PhD
Project Title: The role of hyaluronan in pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF)
  • Presented at 2015 and 2016 American Thoracic Society Conference; 2015 European Respiratory Society Congress; and 2014 Keystone Symposium on Molecular and Cellular Biology

Michael L. O'Byrne, MD
Children's National Heart Institute
Co-Investigators: Brian D. Hanna, MD, PhD; Steven M. Kawut, MD, MS; and Russell T. Shinohara, PhD
Mentor: Jonathan J. Rome, MD
Project Title: Adverse outcomes associated with cardiac catheterization in children with pulmonary arterial hypertension
  • Published in American Heart Journal, 2015; American Journal of Cardiology, 2015; Catheterization Cardiovascular Intervention, 2015; Journal of the American College of Cardiology, 2015; Congenital Heart Disease, 2014; Journal of Thoracic and Cardiovascular Surgery, 2014; and Pediatric Cardiology, 2014

Tien Peng, MD
UCSF School of Medicine
Mentor: Edward Morrisey, PhD
Project Title: The role of sonic hedgehog (Shh) signaling in pulmonary arterial hypertension
  • Published in Nature, 2015

Keivan Zandinejad, MD
Case Western Reserve University School of Medicine
Mentor: Jonathan S. Stamler, MD
Project Title: S-Nitrosylation therapy to treat hypoxia-induced pulmonary arterial hypertension
Overview of ENTELLIGENCE Awards

Awarded 2012

**Eileen Bauer, PhD**  
University of Pittsburgh School of Medicine  
**Co-Investigator:** Stephen Tomlinson, PhD  
**Mentors:** Philip M. Bauer, PhD, and Timothy R. Billiar, MD  
**Project Title:** Complement activation as a novel mechanism of endothelial activation in PH

**Joshua P. Fessel, MD, PhD**  
Vanderbilt University Medical Center  
**Mentor:** James D. West, PhD  
**Project Title:** The role of sirtuins and lysine acetylation in pulmonary arterial hypertension  
• Presented at 2013 and 2014 American Thoracic Society Conference  
• Published in American Journal of Respiratory and Critical Care Medicine, 2014; American Journal of Respiratory Cell and Molecular Biology, 2013; and Pulmonary Circulation, 2013  
• Book chapter published in Pulmonary Hypertension, Basic Science to Clinical Medicine, 2016

**Kenny Schlosser, PhD**  
Ottawa Hospital Research Institute  
**Mentor:** Duncan J. Stewart, MD  
**Project Title:** Role of extracellular circulating microRNAs in idiopathic pulmonary arterial hypertension  
• Presented at 2013 and 2014 American Thoracic Society Conference and 2012 American Heart Association Scientific Sessions  
• Published in Pulmonary Circulation, 2017 and 2018; Theranostics, 2018; Scientific Reports, 2016; Chest, 2015; PLoS One, 2015; and American Journal of Respiratory and Critical Care Medicine, 2013

**Kelly J. Shields, PhD**  
Allegheny Health Network  
**Co-Investigator:** Joseph M. Ahearn, MD  
**Mentor:** Raymond L. Benza, MD  
**Project Title:** The role of perivascular adipose tissue in pulmonary arterial hypertension  
• Presented at 2014 American Thoracic Society Conference  
• Published in Pulmonary Circulation, 2016 and 2017
Overview of ENTELLIGENCE Awards

Awarded 2011

Jana Bagarova, PhD
Massachusetts General Hospital and Harvard Medical School
Mentor: Paul Yu, MD, PhD
Project Title: BMP9-mediated regulation of endothelin-1 expression in vascular endothelial cells
• Presented at 2011 American Heart Association Scientific Sessions

Marco Mura, MD, PhD
Western University of Canada
Co-Investigator: Marc de Perrot, MD, MSc
Mentor: John Granton, MD
Project Title: Osteopontin in idiopathic pulmonary arterial hypertension, a biomarker and therapeutic target
• Presented at 2013 International Society for Heart & Lung Transplantation Annual Meeting and 2013 Canadian Respiratory Conference
• Published in PLoS One, 2014 and Chest, 2012

Salah Najm, MD
University Hospitals, Case Medical Center
Mentor: Kingman Strohl, MD
Project Title: Vascular reactivity in response to acute hypoxia: defining features and mechanisms
• Presented at 2012 American Thoracic Society Conference

Yon K. Sung, MD
Stanford University School of Medicine
Mentor: Mark Nicolls, MD
Project Title: The role of antibodies in the pathogenesis of pulmonary arterial hypertension
Overview of ENTELLIGENCE Awards

Awarded 2010

Eric D. Austin, MD, MSCI
Vanderbilt University School of Medicine
Mentor: James E. Loyd, MD
Project Title: Sex hormone abnormalities in pulmonary arterial hypertension
• Published in Circulation, 2016; Pulmonary Circulation, 2011 and 2013; and Biology of Sex Differences, 2012

Angela V. Ghatnekar, PhD
Medical University of South Carolina
Mentor: Richard M. Silver, MD
Project Title: The role of GATA-6 in pulmonary arterial hypertension
• Published in American Journal of Pathology, 2013

Jason Gien, MD
University of Colorado School of Medicine
Mentor: Steven H. Abman, MD
Project Title: ET-1-Rho-kinase interactions in the pathogenesis of neonatal pulmonary hypertension
• Presented at 2010, 2011, and 2013 Pediatric Academic Societies Meeting
• Published in American Journal of Physiology - Lung Cellular and Molecular Physiology, 2013 and 2014; and Pediatric Research, 2013 and 2014

Michael J. Passineau, PhD
Drexel University College of Medicine
Mentor: Raymond L. Benza, MD
Project Title: Gene therapy to drive endogenous biosynthesis of prostacyclin
• Presented at 2012 American Society of Gene and Cell Therapy Annual Meeting
• Published in Human Gene Therapy, 2017
• Published abstract: Molecular Therapy Supplement, 2012

Michael York, MD
Boston University Medical Center
Mentor: Harrison Farber, MD
Project Title: dsRNA stimulates toll-like receptor-3 and increases endothelin-1 production by pulmonary artery endothelial cells
• Published in Current Opinion in Rheumatology, 2011; Expert Review in Clinical Immunology, 2011; Annals of the Rheumatic Diseases, 2010 and 2011; and Journal of Investigative Dermatology, 2010
Overview of ENTELLIGENCE Awards

Awarded 2009

Daniel J. Kass, MD
University of Pittsburgh
Co-Investigator: Hunter C. Champion, MD, PhD
Mentor: Mark Gladwin, MD
Project Title: Targeting the MetAP2 pathway in pulmonary arterial hypertension
• Presented at 2010 and 2011 American Thoracic Society Conference
• Published in PLoS One, 2012

Sean E. McLean, MD
University of North Carolina at Chapel Hill School of Medicine
Mentor: Cam Patterson, MD, MBA
Project Title: Smooth muscle cell related vascular remodeling in pulmonary hypertension in congenital diaphragmatic hernia

Alexander R. Opotowsky, MD, MPH
Boston Children's Hospital
Mentor: Michael J. Landzberg, MD
Project Title: The epidemiology and determinants of hospitalization for pulmonary hypertension in the United States
• Presented at 2013 American College of Cardiology Meeting

Michael E. Yeager, PhD
University of Colorado School of Medicine
Mentor: Dunbar Ivy, MD
Project Title: Circulating mesenchymal precursors in severe PAH and the role of endothelin-1 in their recruitment and differentiation into fibrocytes
• Published in Chest, 2012 and European Respiratory Journal, 2012
Overview of ENTELLIGENCE Awards

Awarded 2008

Gaurav Choudhary, MD
Alpert Medical School at Brown University
Mentor: James Klinger, MD
Project Title: Role of endothelin-induced PKC delta activation in right ventricular hypertrophy

Hyung J. Chun, MD
Yale University School of Medicine
Mentor: Thomas Quertemous, MD
Project Title: Role of the apelin-APJ pathway in endothelin-1 signaling and pulmonary arterial hypertension
  • Presented at 2009 American Heart Association Scientific Sessions and 2009 American Thoracic Society Conference
  • Published in Circulation, 2015; Circulation Research, 2013; Nature Medicine, 2013; and Arteriosclerosis, Thrombosis, and Vascular Biology, 2011

Scott D. Halpern, MD, PhD
Perelman School of Medicine at the University of Pennsylvania
Mentor: Brian Strom, MD
Project Title: Racial differences in responsiveness to endothelin receptor antagonists in pulmonary arterial hypertension

Sayyed A. Hamidi, MD
State University of New York, Stony Brook
Mentor: Sami I. Said, MD
Project Title: A new combination therapy for pulmonary arterial hypertension: bosentan and VIP
  • Presented at 2010 American Thoracic Society Conference; 2010 Aspen Lung Conference; and 2010 European Respiratory Society Congress
  • Published in Respiratory Research, 2011
  • Published abstracts: American Journal of Respiratory and Critical Care Medicine, 2010 and European Respiratory Journal Supplement, 2010

Sanjiv Shah, MD
Northwestern University Medical Center
Mentor: John Varga, MD
Project Title: Genetic risk factors for connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH)
  • Published in Arthritis Research & Therapy, 2015; Journal of Investigative Dermatology, 2013; Clinical and Experimental Rheumatology, 2012; and Current Rheumatology Reports, 2009

Venkataramana Sidhaye, MD
Johns Hopkins University
Mentor: Larissa Shimoda, PhD
Project Title: Endothelin-1 mediated pulmonary smooth muscle migration is mediated by AQP1
  • Published in American Journal of Physiology - Lung Cellular and Molecular Physiology, 2012

Ari L. Zaiman, MD, PhD
Johns Hopkins University
Mentor: Hal Dietz, MD
Project Title: Role of endothelin abrogation of TGF signaling in the vascular endothelium attenuates hypoxia induced pulmonary hypertension
  • Presented at 2010 American Thoracic Society Conference
Overview of ENTELLIGENCE Awards

Awarded 2007

Yabing Chen, PhD
UAB School of Medicine
Mentor: Raymond Benza, MD
Project Title: PAI-1 regulates vascular remodeling in hypoxia-induced pulmonary hypertension

Christopher Fiack, MD
The Queens Medical Center
Mentor: Harrison Farber, MD
Project Title: Pulmonary hypertension due to left ventricular dysfunction

Anna R. Hemnes, MD
Vanderbilt University School of Medicine
Mentor: John Newman, MD
Project Title: The role of endothelin-1 in right ventricular response to pressure overload
  • Presented at 2008 American Thoracic Society Conference

Jeffrey C. Horowitz, MD
University of Michigan Health System
Mentor: Victor J. Thannickal, MD
Project Title: Regulation of myofibroblast resistance to apoptosis by endothelin-1
  • Published in American Journal of Respiratory Cell and Molecular Biology, 2009

Meredith A. Preuss, PhD
University of Alabama at Birmingham
Mentor: David Curiel, MD
Project Title: Downstream redox regulation of endothelin B receptor in the pulmonary endothelium
  • Published in Virology, 2013 and The Open Gene Therapy Journal, 2008

Olga Rafikova, MD, PhD
Georgia Health Sciences University
Mentor: Steven P. Tofovic, MD, PhD
Project Title: Protein nitration and anti-remodeling effects of endothelin receptor antagonists in pulmonary hypertension
  • Presented at 2010 European Respiratory Society Congress; 2009 American Thoracic Society Conference; and 2009 Pittsburgh International Lung Conference
  • Published in Free Radical Biology and Medicine, 2013
  • Published abstracts: European Respiratory Society Congress, 2010; American Thoracic Society Conference, 2009; and Pittsburgh International Lung Conference, 2009

Megha H. Talati, PhD
Vanderbilt University
Mentor: Barbara Meyrick, PhD
Project Title: Effect of BMPR2 mutation in FPAH on ET-1 and ET-1 receptors and Smad/MAPK activation by ET-1 receptors in lung ECs and PASMCs in the mouse model of PAH
  • Presented at 2009 American Thoracic Society Conference
  • Published in American Journal of Physiology - Lung Cellular and Molecular Physiology, 2010

Yerem Yeghiazarians, MD
UCSF School of Medicine
Mentor: Teresa DeMarco, MD
Project Title: Effect of endothelin receptor blockade on circulating endothelial microparticle levels in patients with pulmonary hypertension
Overview of ENTELLIGENCE Awards

Awarded 2006

Joel Glasgow, PhD
UAB School of Medicine
Mentor: David Curiel, MD
Project Title: Gene delivery for pulmonary hypertension

Zhigang Hong, MD, PhD
University of Chicago
Mentor: Kenneth Weir, MD
Project Title: Endothelin-induced increase in pulmonary vascular smooth muscle calcium; the role of calcium channels
- Published in Journal of Molecular Medicine, 2014 and European Respiratory Journal, 2008

Peter Oishi, MD
UCSF School of Medicine
Mentor: Jeffrey Fineman, MD
Project Title: Endothelin-1 reactive oxygen species interactions in pulmonary hypertension
- Presented at 2007 Pediatric Academic Societies Meeting
- Published in American Journal of Physiology - Heart and Circulatory Physiology, 2008
- Book chapter published in Congenital Diseases in the Right Heart, 2009

Rajni Rao, MD
UCSF School of Medicine
Mentor: Yerem Yeghiazarians, MD
Project Title: Quantitative and qualitative properties of endothelial progenitor cells in patients with pulmonary hypertension
- Presented at 2007 International Society for Heart & Lung Transplantation Meeting

Giuseppe Valacchi, PhD
University of Ferrara
Mentors: Carol Cross, MD, and Gian Paolo Pessina, Professor
Project Title: Does tocopherol homeostasis play a role in endothelin mediated endothelial dysfunction?

Roham Zamanian, MD
Stanford University Medical Center
Mentor: Ramona Doyle, MD
Project Title: The effect of endothelin A and B antagonism on insulin resistance and outcomes in patients with pulmonary arterial hypertension
Catherine Avitabile, MD
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

The association between skeletal muscle deficits and exercise performance in pediatric pulmonary hypertension patients

Introduction:
Exercise intolerance is common in patients with pulmonary hypertension (PH) and affects quality of life and prognosis. Exercise physiology in PH is complex, with many cardiopulmonary factors contributing to intolerance. Skeletal muscle atrophy and muscle dysfunction are associated with worse performance on 6-minute walk test (6MWT) in adults with PH. Muscle deficits have not been described in pediatric PH patients, yet pediatric patients have risk factors for low muscle mass and poor strength. The impact on exercise performance is unknown.

Background:
Pediatric PH is associated with various vascular, cardiac, pulmonary, and systemic conditions. While therapies have improved in recent years, long-term outcomes remain poor. Exercise intolerance is common in PH patients, and improved performance on 6MWT is a common therapeutic target. Exercise physiology in PH is complex, with many cardiopulmonary factors contributing to intolerance. Association between peripheral skeletal muscle dysfunction and worse performance on 6MWT has recently been recognized in adult PH patients. Findings of skeletal muscle atrophy, impaired peripheral oxygen extraction, and reduced muscle contractility suggest that PH patients exhibit a generalized “myopathy” similar to patients with heart failure. Exercise training can improve exercise performance, quality of life, and functional class in adult PH patients and was beneficial in a pilot study of pediatric PH patients. But the mechanisms underlying this improvement continue to be investigated. Skeletal muscle deficits have not been described in pediatric PH patients, yet patients are potentially at risk due to inadequate physical activity, poor nutrition, vitamin D deficiency, chronic inflammation, low cardiac output, hypoxemia, and treatment with certain medications. The applicant previously described skeletal muscle deficits in association with worse exercise performance in children with complex, single ventricle congenital heart disease. Pediatric PH patients have similarities to this patient population. Characterization of skeletal muscle mass and strength in pediatric PH patients could improve understanding of modifiable determinants of exercise performance and open new therapeutic avenues in this high risk population.

Hypothesis and Objectives:
Pediatric PH patients have lower muscle mass and strength compared to healthy reference participants. If muscle deficits are identified, with or without association with exercise performance, the study will provide clinically significant targets for future interventions to improve functional capacity in this population.

Specific Aim 1:
To characterize skeletal muscle mass (as indicated by leg lean mass on densiometry) and muscle strength in pediatric PH patients (WHO Diagnostic Groups 1, 2, and 3) and to identify risk factors for decreased muscle mass and strength.

Specific Aim 2:
To explore the associations between muscle mass/strength and measures of exercise performance (on 6MWT, cardiopulmonary exercise test, and exercise cardiac MRI) in order to predict impediments to performance in pediatric PH patients.
**2018 Abstracts**

Meghan Bernier, MD  
The Johns Hopkins University School of Medicine  
Baltimore, MD

*Endothelial to mesenchymal transition in pulmonary hypertension: Formin a new identity*

**Introduction:**
The actin cytoskeleton is a key component of endothelial structure and function, and alterations may affect monolayer integrity. The transformation of endothelial cells to mesenchymal cells, and ultimately proliferation increasing vessel stiffness and creating obliterative lesions, is a hallmark of pulmonary hypertension. Cytoskeletal influence on this process is unknown.

**Background:**
Investigations into the pathogenesis of pulmonary hypertension (PH) have defined multiple pathways including inflammation, fibrosis, smooth muscle cell proliferation, and endothelial cell (EC) injury and dysfunction. EC and monolayer functions are abnormal in PH with altered apoptosis, increased cellular migration, and augmented vascular stiffness. A prominent component of this EC dysfunction is the formation of plexiform lesions. The origin is thought to be EC in nature with the transformed cells showing phenotypic variations consistent with hyperproliferation, resistance to apoptosis, and a mesenchymal-like phenotype. Pathways underlying endothelial to mesenchymal transition (EndMT) are not well understood, but an early step in transformed EC migration is the loss of vascular endothelial cadherin (VE-cad), a key component of EC adherens junctions. VE-cad, through β-catenin, is linked to the actin cytoskeleton and alterations in the cytoskeletal arrangement can change the organization of the adherens junction. Formins are integral in actin cytoskeleton polymerization and maintenance. Two in particular, the mammalian Diaphanous-related formin 1 (mDia1) and formin-like protein 3 (FMNL3) accelerate actin nucleation and bundles filaments and localizes to EC junctions, respectively. Decreased or absent formin activity is associated with increased cell migration and invasiveness. Isolated rat pulmonary microvascular endothelial cells from the Sugen-Hypoxia model show evidence of EndMT with co-expression of the endothelial markers von Willebrand Factor and Griffonia simplicifolia II with the smooth muscle cell markers smooth muscle α-actin and myosin heavy chain. Additionally, these cells show an altered spindle like form and exhibit enhanced migration, proliferation, and altered endothelial nitric oxide synthase levels.

**Hypothesis and Objectives:**
We hypothesize that cytoskeletal-organizing formins have a critical functional impact on pulmonary vascular endothelium that is lost in PH, and our objectives are to determine the impact of formins on endothelial form and function in human cells, the Sugen-Hypoxia animal model, and in patients affected with PH.

**Specific Aim 1:**
Determine the role of formin mDia1 in pulmonary endothelial adherens junction formation via epifluorescence and super resolution microscopy.

**Specific Aim 2:**
Analyze the effect of formin mDia1 inhibition on endothelial monolayer barrier function.

**Specific Aim 3:**
Characterize the role of formins mDia1 and FMNL3 in endothelial to mesenchymal transition in the microvasculopathy of pulmonary hypertension in the Sugen-Hypoxia animal model and in patients with PH.
Investigation of calcium regulatory processes and their role in a natural large animal model of altitude-associated pulmonary hypertension sensitivity leading to heart failure

Introduction:
Polygenic in nature, the pathophysiological development of pulmonary hypertension (PH) creates a gap in knowledge between the pathology and genes involved in response to hypoxia. We will utilize a natural animal model to investigate the role intra- and extracellular calcium gene expression differences of PH susceptibility at high altitude.

Background:
Pulmonary hypertension (PH) resulting in heart failure not only occurs in humans, but also in cattle and represents a significant burden for the beef cattle industry. Heart failure as a result of PH commonly occurs in beef cattle herds at high altitude (> 1,500 m), with mortality rates of 3 to 5%. Cattle share parallel pathologic mechanisms of pulmonary hypertension with humans and can serve as a natural model to study development and progression of the disease. Typically in beef cattle, we evaluate ontogeny (changes with age or growth of the animal). This model offers unique opportunities to investigate mechanisms of pulmonary vascular pathology, such as end-arterial remodeling and large artery stiffening that are not accessible in humans. Previous research suggests a putative role for calcium in PH sensitivity. Calcium is a key mediator of the physiology of the heart, including myocardial depolarization involved with contraction and relaxation. Parathyroid hormone modulates calcium availability affecting cardiovascular inotropic and chronotropic actions. Gene expression results from RNA-sequencing and genome-wide association data comparing cattle with high and low pulmonary arterial pressures identified genes with functional roles in calcium signaling, homeostasis, and utilization. Differentially expressed genes including solute carrier family 8 member A1, troponin I, calcium/calmodulin dependent protein kinase, and ATPase sarcoplasmic reticulum Ca2+ transporting 1 were identified in multiple functional pathways associated with cardiac and pulmonary vascular physiology. Limited knowledge exists regarding the role of calcium regulatory processes in determining susceptibility to PH and their influence on the development and progression of the disease.

Hypothesis and Objectives:
Intra- and extracellular calcium availability and usage plays a role in the development and susceptibility of an individual to PH. The identification of tissue-specific genes pre- or –post-transcriptionally regulated by calcium will aid in differentiation of cattle susceptible to pulmonary hypertension, as well as ontogeny-associated expression differences.

Specific Aim 1:
Characterize and compare the ontogeny of gene expression (RNA-seq) related to calcium signaling, homeostasis, and utilization in the regulation of PH susceptibility in cattle.

Specific Aim 2:
Determine if ontogeny-related differences in available and (or) utilized calcium exists with PH sensitivity by examining blood-based biomarkers and their association with tissue-specific expression changes.
Introduction:
Pulmonary arterial hypertension (PAH) is a progressive, fatal disease characterized by disorganized vascular proliferation, inflammation, and thrombosis. Extracellular vesicles (ECV) are 30 nm – 1000 nm in size and influence thrombosis, inflammation, and angiogenesis. Although extensively studied in other systemic vascular disease, ECV research in PAH is in its infancy.

Background:
Extracellular vesicles (ECV) consist of exosomes (30-100 nm), microparticles (100-1000 nm), and apoptotic bodies (>1000 nm). ECV are released during normal cellular homeostasis, cellular injury and activation, and apoptosis. ECV cargo includes nucleic acids, proteins, and enzymes to facilitate intercellular communication. Platelets produce the majority of ECV in healthy people with some released by leukocytes (monocytes) and endothelium. ECV have been studied in cardiovascular disease, malignancy, and sepsis. There have been limited data on ECV in patients with pulmonary arterial hypertension (PAH). Procoagulant microparticles shed from endothelial cells have been identified in the circulating blood of PAH patients. Other studies have concluded that larger microparticles are increased relative to healthy controls. Unfortunately, it is hard to draw conclusions or make comparisons between studies as they used different blood sample preparation techniques and different flow cytometers (typically limited in identifying ECV <400 nm); studies were generally isolated to a single blood draws. NanoSight is a technology complimentary to flow cytometry which can identify and count particles between 10 nm – 1000 nm analyzing Brownian motion. The ISTH published a consensus statement in 2012 (Lacrois et al., J Thromb Haemost, 10: 437-446) to help standardize processing of ECV and therefore allow for multi-site clinical research and cross laboratory comparison. Using Malvern Nanosight N300 and NTA software we have established a standardized protocol (camera and NTA settings) using samples from humans to allow for consistent analysis.

Hypothesis and Objectives:
We hypothesize that serial evaluation of ECV could be used as a biomarker of pulmonary vascular disease activity: 1) ECV changes (total number and origin) reflect disease activity and treatment response in the pulmonary vasculature; 2) ECV cargo, specifically miRNA, will be a marker of vascular health and response to therapy.

Specific Aim 1:
Characterize ECV concentration and stability/change over time with the NanoSight in male and female PAH research participants (10 treatment naïve PAH initiating therapy; 20 treated PAH with a low-risk phenotype, no change in therapy; 10 treated PAH with high-risk phenotype intensifying therapy; 20 matched healthy controls)

Specific Aim 2:
Characterize ECV cellular origin using Immunodepletion to isolate various fractions of ECV from blood already collected in Aim 1. Determine whether this distribution changes with therapy or disease activity.

Specific Aim 3:
Evaluate ECV miRNA from blood already collected in Aim 1. Determine whether vasoconstrictor therapy changes miRNA in ECV. Correlate miRNA from ECV with PAH risk profiles.
Exploring the association of visceral intrathoracic fat with vascular stiffness in pulmonary hypertension

Introduction:
Pulmonary arterial stiffness plays a crucial role in right ventricular dysfunction in pulmonary hypertension (PH) and has been shown to be a strong predictor of mortality in various forms of PH. We propose to study the role of obesity in pulmonary vascular disease, particularly focusing on the impact of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) on pulmonary arterial stiffness.

Background:
Adult obesity rates in the United States are increasing; a third of incident and prevalent patients with PH are obese. In the systemic vasculature, obesity is an important risk factor for vascular stiffness; specifically, abdominal VAT is linked to an increased risk of cardiovascular disease. While most adipokines secreted from adipose tissue are associated with atherogenesis, apoptosis, and inflammation, apelin, vaspin and C1q/tumor necrosis factor related protein (CTRP) are produced by VAT and have anti-inflammatory, anti-atherosclerotic, and anti-apoptotic effects. The effect of VAT on pulmonary hemodynamics, particularly thoracic VAT, whose lymphatics drain directly into the pulmonary circulation, has not been studied. The objective of this proposal is to study the role of obesity in pulmonary vascular disease, particularly focusing on the impact of thoracic VAT and SAT on pulmonary arterial stiffness in patients with PH. The proposal will utilize data from the Lung Transplant Body Composition (LTBC) Study, which is an NIH-funded, prospective, multicenter cohort study focused on primary graft dysfunction that has previously measured adipose tissue compartments using computed tomography (CT) of the chest in 540 individuals with advanced lung disease (ALD), assayed plasma cytokine and adipokine levels, and collected VAT biopsies (from explants) in patients undergoing lung transplantation (LTx).

Hypothesis and Objectives:
We propose to examine the association of VAT/SAT with pulmonary vascular disease in patients with ALD from the LTBC study. Specifically, we hypothesize that lower thoracic VAT/SAT will be associated lower plasma levels of apelin, vaspin and CTRP and lower pulmonary arterial capacitance, higher pulmonary vascular resistance and lower cardiac output, independent of measures of age, sex, race/ethnicity, and severity of lung disease as indicated by lung function. Results from this analysis will provide critical preliminary data for future studies investigating the role of body fat composition modification through diet and exercise on pulmonary hemodynamics in patients with PH.

Specific Aim 1:
To determine the associations of intrathoracic VAT and SAT volumes from quantitative chest CT with pulmonary hemodynamics in patients with ALD evaluated for LTx.

Specific Aim 2:
To determine the associations of VAT and SAT volumes with plasma adipokine levels (apelin, CTRP and vaspin) in patients with ALD listed for LTx.

Specific Aim 3:
To identify the gene expression signature of intrathoracic VAT in patients with PH.
The role of adenosine signaling in pulmonary hypertension associated with bronchopulmonary dysplasia

Introduction:
Bronchopulmonary dysplasia (BPD) is one of the most important morbidities in premature infants. Pulmonary hypertension (PH) is a complication of BPD and is a significant cause of morbidity and mortality in patients with BPD. This study will determine the role of adenosine signaling in the development of PH in BPD.

Background:
BPD occurs in 1/3 of extremely low birth weight infants (<1000 grams) and remains a significant cause of mortality and morbidity in premature neonates. PH is recognized as one of the most important complications of BPD, occurring in 20-40% of patients with BPD. The presence of PH is associated with a four-fold increase in mortality for patients with BPD as well as increased morbidities, including longer initial hospitalization and higher medical costs in the first two years of life. The key regulatory pathways that lead to the development of BPD and PH remain unknown. There is a critical need to identify these signaling pathways to provide a foundation for the development of effective targeted therapies to prevent BPD associated PH and improve long term morbidity and mortality in premature neonates.

One key regulatory pathway of lung development and pulmonary vascular remodeling is the adenosine signaling pathway. Lung injury is associated with increased extracellular adenosine and the activation of adenosine receptor-mediated signaling pathways. Sustained adenosine signaling contributes to the development of PH in chronic adult lung diseases. Additionally, our preliminary studies have demonstrated that activation of adenosine pathways contributes to ongoing inflammation and disruption of alveolar development in an animal model of BPD. However, the contribution of adenosine to disrupted vascular development and remodeling in BPD remains unknown. The goal of this project is to determine the extent to which the activation of adenosine signaling pathways contributes to the development of PH in BPD.

Hypothesis and Objectives:
We hypothesize that elevated levels of extracellular adenosine that result from hyperoxic lung injury activate specific adenosine-receptor signaling pathways in the developing lung to disrupt alveogenesis and inhibit normal pulmonary vasculogenesis. The combined effects of adenosine on alveolar and vascular development in the neonatal lung is the underlying cause for the development of PH in BPD.

Specific Aim 1:
To identify the pathways regulating extracellular adenosine production and signaling during hyperoxic lung injury in the developing neonatal lung. 1.1. Are transcript and protein levels of adenosine signaling mediators CD73, ENT, and adenosine receptors altered in an experimental model of BPD? 1.2. What is the effect of oxygen on adenosine signaling mediators in pulmonary vascular endothelial cells?

Specific Aim 2:
To determine the role of adenosine signaling in the disruption of pulmonary angiogenesis, vascular remodeling and development of PH in BPD. 2.1. Does decreasing extracellular adenosine levels in the lung improve pulmonary vascular density and attenuate vascular remodeling in a hyperoxia BPD model? 2.2. Will decreasing adenosine signaling decrease right ventricular systolic pressures in adult mice exposed to hyperoxia after birth?
Introduction:
The development of pulmonary vascular disease (PVD) is the most important complication for children with congenital heart defects (CHD) that result in increased pulmonary blood flow and pressure. Although the natural history of the development of PVD is well characterized for differing lesions, the mechanisms for these differences are not understood.

Background:
Beginning immediately after birth, the pulmonary vasculature in patients with common CHD, such as large ventricular septal defects, is subjected to pathologic mechanical forces, including increased shear stress and stretch, resulting in early functional abnormalities of the vascular endothelium. These aberrations include impaired nitric oxide (NO) signaling, increased endothelin1 (ET1) expression, and increased oxidative stress. Natural history studies clearly demonstrate that different lesions have differing risks and time frames for the development of PVD. For example, truncus arteriosus, a lesion that results in direct exposure of the pulmonary vasculature to both high blood flow and pressure, has a 100% incidence of developing PVD occurring within the first two years of life. However, pre-tricuspid valve lesions, such as atrial septal defects, expose the pulmonary vasculature to only high flow (without the direct pressure stimulus) and have only ~10-20% incidence of developing PVD, which does not occur until the third-fourth decades of life. Utilizing fetal cardiac surgical techniques, we have previously created an ovine model of CHD that induces postnatal increases in pulmonary blood flow and pressure (aortopulmonary window) which recapitulates human disease including early aberrations in endothelial function. More recently, we have created a model of increased pulmonary blood flow to the right lung with normal pressure (left pulmonary artery ligation). RNA sequencing data comparisons of pulmonary endothelial cells from juvenile lambs with normal flow and pressure, increased flow and pressure, and increased flow and normal pressure, demonstrate novel differences in gene expression related to these differing mechanical forces.

Hypothesis and Objectives:
The objective of these studies is to characterize the differential gene expression related to differing mechanical forces and investigate their mechanisms. We hypothesize that increased flow and pressure induce differential changes in gene expression that contribute to the differing risk of developing PVD in CHD.

Specific Aim 1:
To characterize and compare differential gene expression patterns (RNAseq) in endothelial cells and tissue isolated from juvenile lambs with either: normal flow and pressure, increased flow and pressure, or increased flow and normal pressure.

Specific Aim 2:
Utilizing an Ibido system, that allows endothelial cells and tissue rings to be exposed to shear stress and/or cyclic stretch, we will investigate the mechanisms for the changes in gene expression demonstrated in Aim 1.
Stephanie Thorn, PhD
Yale University
New Haven, CT

Pilot study to engage the Apelin-MEF2 signaling axis for myocardial preservation in a large animal model of right ventricle failure

Introduction:
Current therapies for pulmonary arterial hypertension (PAH) have largely neglected the role of right ventricular (RV) preservation in improving clinical outcomes associated with the disease. This proposal will utilize a highly innovative and translational large animal model to investigate the therapeutic efficacy of a novel strategy to preserve the RV function in PAH.

Background:
Despite the existence of multiple FDA approved therapies for PAH, along with a wide body of literature demonstrating therapeutic efficacy of various molecular targets in small animal experimental models of PAH, there remains a clear, unmet need for novel strategies in our clinical management of disease, based on the fact that: 1) mortality remains remarkably high (up to 45% at 3 years after diagnosis), and 2) rodent based experimental models face a significant hurdle in translating to human efficacy. Moreover, the preservation of RV function, which in many aspects is the ultimate determinant of clinical outcome in PAH, is not targeted by any of the existing therapies. A number of molecular therapeutic targets have been identified through the use of experimental models and human patient samples. One such pathway is that represented by the GPCR pathway involving the ligand apelin and its receptor APLNR, and its downstream activation of the transcription factor myogenic enhancer factor-2 (MEF2). With respect to apelin, 1) circulating levels of apelin have been demonstrated to be decreased in multiple cohorts of PAH subjects, 2) apelin knockout mice develop worsening PAH, and 3) exogenous apelin can effectively rescue multiple models of PAH. Studies on MEF2 have also identified it to be a critical transcription factor that is impaired in PAH, and importantly, its activation can be achieved by either exogenous apelin, or by selective inhibitors of class IIa histone deacetylases (HDAC), which serve as negative regulators of MEF2 via direct protein-protein interaction. In particular to the RV, apelin expression has been found to be remarkably downregulated in RV failure, while mice with genetic deletion of either APLNR or MEF2 develop spontaneous RV failure, supporting a key potential role of augmenting this pathway as a strategy to preserve RV function.

Hypothesis and Objectives:
We hypothesize that engagement of the apelin-MEF2 signaling axis will achieve preservation of RV function in PAH. In this highly innovative, translational project, we will utilize a unique and clinically relevant pulmonary artery (PA) banding model in pigs to investigate the feasibility and efficacy of pharmacologically engaging the apelin-MEF2 axis to preserve RV function, perfusion and hemodynamics.

Specific Aim 1:
Establish the efficacy of PA banding in promoting RV failure in a chronic pig model.

Specific Aim 2:
Investigate the efficacy of liposomal nanoparticle encapsulated apelin in the preservation of RV function and perfusion.

Specific Aim 3:
Determine the efficacy of activating MEF2 via HDAC class IIa inhibition in RV preservation.
The prevalence and pathogenesis of HIV-associated pulmonary arterial hypertension among underserved urban populations

Background

Pulmonary arterial hypertension (PAH) is a non-infectious complication of HIV that has become increasingly important as HIV survival has increased. Though HIV is an established independent risk factor for PAH, the pathogenesis of HIV-associated PAH (HIV-PAH) is largely unknown, and specific prevalence data for minority populations have not been investigated. The decrease in HIV mortality following the advent of anti-retroviral therapy has been accompanied by a rise in the non-infectious complications of HIV such as PAH. Although the pathological changes in HIV-PAH are very similar (almost identical) to those seen in idiopathic PAH (IPAH), the prevalence of HIV-PAH (0.5%) is significantly higher than that of IPAH (0.003 to 0.005%) suggesting that the virus may potentiate this condition. Of interest to this proposal, prevalence data for HIV-PAH in certain sub-groups of HIV-infected individuals, such as minority populations, do not exist. The African-American/Black population in Georgia, specifically black women, may have an increased risk for developing HIV-PAH due to the rapid increase in HIV infection in this population. Moreover, recent studies suggest a higher prevalence of HIV-PAH than previously reported. If true, PAH screening guidelines should be considered for high risk populations because of the poor prognosis of this condition if untreated. Lastly, studies have implicated the HIV protein, Nef, in development of HIV-PAH; however, the mechanism(s) by which this protein influences the pulmonary vasculature are not yet clear.

To address these issues, we hypothesize that: 1) there is a higher than reported level of PAH in specific populations; and 2) there is a relationship between HIV-PAH and the levels of exosomal Nef.

Specific Aims

1. To determine the prevalence of PAH among HIV-infected individuals in an underserved urban population.
2. To determine whether there is a correlation between PAH and HIV Nef-driven exosome-linked factors.

Results

Summary of Study Results and Preliminary Experimental Data.

A. Five out of Six RHCs confirmed PH, one of which included confirmation of PAH. Our pilot study in Atlanta (unpublished data) suggests that the prevalence of HIV-PAH may be higher than previously reported. We recruited 95 HIV-infected individuals during our pilot study, 80 of whom underwent echocardiography. Twenty (25%) of the HIV-infected persons who underwent transthoracic echocardiography (TTE) had findings suggestive of PH while 20 (25%) had findings that were borderline for PH, warranting further investigation to confirm PH by right heart catheterization (RHC). We are still in the process of obtaining RHCs for participants with suspected PH on TTE.

Six participants
among our HIV cohort have undergone RHC at this point, five of whom were confirmed to have PH, including one individual confirmed to have PAH (HIV-PAH).

Based on the RHC data thus far, the prevalence of HIV-PAH for our African American cohort is at least 1.25%. Our pilot study supports our hypothesis that the prevalence of HIV-PAH is higher for our African American cohort than previously reported; however, given the small size of our cohort, a larger study is needed to confirm this finding. We intend to expand the study and recruit a larger cohort from multiple sites to validate our pilot study.

B. RANTES and possibly MCP3 may be predictive of HIV PAH

We conducted experiments to characterize exosomal Nef and measure biomarkers in our study cohort versus a group of healthy controls. During our pilot study, levels of 51 cytokines were measured in the exosomes and plasma of HIV infected individuals using human cytokine 23-plex and 27-plex magnetic bead kits. Cytokines analyzed included 18 selected a priori, based on a review of available literature, and 33 exploratory cytokines. The cohort screened included three groups of individuals:

(i) 18 HIV-infected individuals with TTE findings suggestive of PH
(ii) 6 HIV-infected individuals with TTE findings not suggestive of PH
(iii) 10 healthy controls

ANOVA tests were used to compare cytokine levels among the three groups. Our findings suggest that levels of MCP326 and RANTES37 in the exosomes and plasma of HIV seropositive individuals are potential biomarker candidates that could predict development of PAH in these individuals (Figure 1).

Particularly of interest, RANTES levels were significantly lower in the exosomes and plasma of HIV-infected individuals with TTE findings suggestive of PAH compared to individuals without TTE findings to suggest PAH. Our findings may indicate that high RANTES levels would serve to protect HIV-infected individuals from developing PAH or alternatively, lower levels of RANTES would predispose HIV-infected individuals to higher inflammation levels and PAH. RANTES may therefore have predictive value in determining which HIV-infected individuals are at greater risk and/or are in the process of developing HIV-PAH. Given the small sample size, however, additional studies are warranted. We plan to investigate our experimental AIMs further during our expansion study.

Conclusions

In summary, our pilot study revealed that the prevalence of HIV-PAH for our African American cohort in Atlanta (at least 1.25% thus far and likely to approximate 4%) is higher than the previously published prevalence (0.5%). In addition, our experimental studies indicate that RANTES may serve as a predictive biomarker for HIV-PAH.
The prevalence and pathogenesis of HIV-associated pulmonary arterial hypertension among underserved urban populations (continued)

Figure 1.

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The prevalence and pathogenesis of HIV-associated pulmonary arterial hypertension among underserved urban populations (continued)

Figure 2.
Iron deficiency and hypoxic signaling in pulmonary hypertension

Background
Observational studies reveal increased rates of iron deficiency in patients with both idiopathic pulmonary arterial hypertension (PAH) as well as scleroderma-associated PAH. Further, in both of these populations, iron deficiency is associated with increased morbidity and mortality independent of anemia, suggesting that iron availability may play an important role in the pathobiology of PH, though the mechanistic details of how iron affects pulmonary vasoreactivity and remodeling remains largely unknown.

While the majority of iron (60-70%) serves for oxygen transport in the hemoglobin, iron is also a necessary cofactor for over 1000 different proteins in eukaryotic organisms. Given iron’s foundational cellular roles and its highly reactive nature, a rich homeostatic system has evolved to tightly regulate iron metabolism. Within the machinery of iron homeostasis, there are critical intersections with hypoxic signaling pathways that are important in the pathobiology of PAH; namely the hypoxia inducible factors and iron regulatory proteins.

Our goal is to more completely and mechanistically understand the relationship of iron deficiency and its affects upon hypoxic signaling within the context of PH pathobiology using murine models of the disease

Specific Aims
1. To determine that low iron availability in chronic hypoxic PH increases renal HIF2α stability via decreased PHD activity, resulting in increased serum EPO levels.
2. To determine that increased circulating EPO results in attenuated pulmonary hypertension.
3. To demonstrate that increased EPO signaling in hypoxic PH leads to enhanced pulmonary vascular eNOS activity

Results
Iron deficient exposure results in low systemic and tissue-level iron availability in hypoxic PH.
To assess iron availability after exposure to iron deficient conditions, multiple analyses were undertaken. First, hepatic iron stores were evaluated via Prussian blue staining hypoxia-exposed mice under normal and iron deficient conditions, demonstrating reduced iron stores with low iron exposure. Next, systemic iron availability was assessed by quantification of serum ferritin levels, which were significantly reduced in low iron exposure mice in both normoxia and hypoxia.

Iron deficiency results in attenuated experimental pulmonary hypertension
To assess the effect of low iron availability on the development of experimental PH, mice were exposed to 10% normobaric hypoxia for 4 weeks with concurrent exposure to either normal or low iron conditions. Iron deficiency had no effect on right ventricular hemodynamics in normoxia, while iron deficiency resulted in attenuation of the increased RVSP that was seen with hypoxic exposure.
Iron deficiency and hypoxic signaling in pulmonary hypertension (continued)

Low iron availability leads to significant increase in renal-derived EPO expression
Renal tissue expression of canonical HIF target gene EPO demonstrated significantly increased levels in the setting of experimental hypoxic PH and low iron availability. This was confirmed to occur at the level of transcription via quantification of mRNA transcripts. Finally, increased serum EPO levels were confirmed via ELISA of experimental groups.

Blockade of endogenous erythropoietin activity with soluble erythropoietin receptor restores pulmonary hypertension in the setting of iron deficiency
Given prior studies demonstrating a protective role of erythropoietin in the development of experimental PH, we sought to block the downstream signaling of the increased endogenous erythropoietin in animals with experimental PH with low iron exposure. To do this, recombinant soluble EPO receptor was utilized, which was administered intraperitoneally weekly throughout the 4-week exposure period. With this, it was found that we achieved blockade of EPO activity as hematocrits were significantly reduced in the treated animals compared to vehicle controls. Examination of the right ventricular hemodynamics showed a restoration of the PH phenotype that was observed in the animals exposed to 4 weeks of hypoxia with normal iron availability.

Conclusions
We have demonstrated that in experimental PH induced by exposure to hypoxia, the associated pulmonary hypertension is blunted from a hemodynamic standpoint by inducing iron deficiency. Given the multiple intersections of iron and hypoxic signaling, we sought to examine the effect of reduced iron availability on hypoxic signaling targets, finding that there was a significant upregulation of renal-derived erythropoietin.

We identified that the combination of hypoxia with low iron availability resulted in increased renal expression of EPO, potentially through further impairment of PHD-mediated HIF degradation. Further, there was increased systemic availability of EPO with significant increase in serum levels. Importantly, this finding is recapitulated in the human data available, and increased plasma EPO levels were noted in patients with idiopathic PAH with concomitant iron deficiency relative to subjects that were iron replete. Erythropoietin is increasingly noted to have pleiotropic effects beyond its regulation of erythroid cells, including cardioprotection, alteration of cellular energetics, and vasculoprotection via increased eNOS activity.

Specific to pulmonary hypertension, several prior studies have found that administration of exogenous erythropoietin results in attenuated experimental PH. Further, when mice lacking EPO receptors in the cardiovascular system but not in the hematopoietic system are exposed to hypoxia, they have accelerated development of PH related to wild-type controls. This work indicates that there likely is an important role of endogenous EPO/EPO receptor activity that regulates the development of pulmonary vascular disease.

Erythropoietin receptors are expressed upon pulmonary endothelial cells and are in fact upregulated in one study of tissue from patients with PAH. In vitro work utilizing endothelial cells has shown that stimulus of these receptors results in a signaling cascade resulting in increased eNOS activity, which represents a potential mechanistic explanation for our findings.

The present work demonstrates that the combined effects of experimental hypoxic PH with iron deficiency results in an upregulation of erythropoietin which is associated with attenuated RVSP. We further explored using a novel method of manipulating endogenous erythropoietin signaling via treatment with a recombinant soluble erythropoietin receptor. While iron deficiency is associated with worsened morbidity and mortality in IPAH and Scl-PAH, causation remains unclear. The present study highlights the myriad of biological roles that iron is involved in, and that there may be ways in which iron deficiency would be either protective or harmful depending upon the underlying biologic impetus, stage of development, and concomitant exacerbating factors (hypoxia, for example) of pulmonary vascular disease. By carefully parsing the mechanisms by which altered iron availability alters the pathobiology of pulmonary hypertension, there is potential for a more targeted therapeutic approach to the disease.
In murine hypoxic PH, (A) low iron availability leads to increased renal-derived EPO expression. (B) Blockade of endogenous erythropoietin activity with a soluble EPO receptor restores the PH phenotype that is attenuated by iron deficiency.
Differential role of mTORC1 and mTORC2 in hypoxic vasoconstriction and the development of pulmonary hypertension

Background

Idiopathic pulmonary arterial hypertension (IPAH) is a rare, progressive and fatal disease that predominantly affects women, while pulmonary arterial hypertension (PAH) associated with inflammatory cardiopulmonary diseases (e.g., scleroderma, sarcoidosis, HIV infection) is also progressive and significantly increases mortality of the patients. If not diagnosed and treated early, it will eventually lead to heart failure and premature death. In patients with IPAH and associated PAH (APAH), the increased PVR is the major cause for the elevated pulmonary arterial pressure (PAP). Sustained pulmonary vasoconstriction and excessive pulmonary vascular remodeling, characterized by concentric pulmonary vascular wall thickening and intimal lesions due to increased cell proliferation, are two major causes that directly increase PVR (and thus PAP) in patients with idiopathic and associated PAH and animals with experimental pulmonary hypertension (PH). Pulmonary arterial smooth muscle cell (PASMC) contraction results in pulmonary vasoconstriction, while PASMC proliferation is a key contributor to the development and progression of pulmonary vascular remodeling in PAH. The cellular and molecular mechanisms involved in the increased PASMC proliferation are, however, still poorly understood. One of the critical signaling pathways involved in cell proliferation is the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway, which can be activated by various growth factors as well as by chronic exposure to hypoxia.

There is significant research being conducted in understanding the role of mTOR, as a common component in both mTORC1 and mTORC2, in the development of hypoxia-induced PH by promoting PASMC proliferation. The individual protein complexes of mTOR have different upstream and downstream regulators. mTORC1 is a master growth regulator that promotes cell proliferation in response to growth factors, extracellular nutrients and amino acids; whereas mTORC2 promotes cell survival by activating AKT, regulates cytoskeletal dynamics by activating PKCα, and controls ion transport and cell growth via SGK1 phosphorylation. A relatively new topic of research in the field of pulmonary vascular disease that seems to be interesting and challenging is to understand the individual or differential roles of mTORC1 and mTORC2 in PASMC proliferation and the development and progression of PH. We previously reported that conditional and inducible knock-out (KO) of mTOR in smooth muscle cells almost completely prevented mice from the development of experimental PH. These data provide compelling evidence that the PI3K/AKT1/mTOR signaling pathway in PASMC plays an important role in the development and progression of PH. Specifically targeting signaling proteins and kinases in the PI3K/AKT1/mTOR cascade may help develop novel therapeutic approaches for idiopathic and associated PAH, as well as PH associated with hypoxia and lung diseases.
In this study, we aimed at examining whether mTORC1 and mTORC2 might potentially play a differential role in the development and progression of PH. We generated i) SM-specific Raptor KO mice (Raptor\textsuperscript{SM−/−}) to inhibit mTORC1 function in PASMC and ii) SM-specific Rictor KO mice (Rictor\textsuperscript{SM−/−}) to inhibit mTORC2 function in PASMC. Then we conducted and compared in vitro and in vivo experiments in WT, Raptor\textsuperscript{SM−/−} and Rictor\textsuperscript{SM−/−} mice using combined techniques of in vitro cell and molecular biology, and in vivo hemodynamic measurement in intact mice to define whether mTORC1 and mTORC2 are differentially involved in the development and progression of experimental PH.

Specific Aims

1. To determine the roles of mTORC1 and mTORC2 in the cell proliferation, migration, smooth muscle cells phenotypic switching under hypoxia conditions, and endothelial-mesenchymal transition using pharmacologic and genetic approaches.

2. To investigate whether mTORC1/mTORC2 complexes regulated hypoxic pulmonary vasoconstriction and the development of vascular remodeling in hypoxia-induced pulmonary hypertension models.

3. To determine whether dual inhibition of mTORC1/mTORC2 complexes prevent and/or reverse the development of hypoxia-induced pulmonary hypertension.

Results

In this project, we first conducted a series of in vivo experiments using WT and various KO mice to examine whether SM-specific KO of mTOR (mTOR\textsuperscript{SM−/−}), Raptor (Raptor\textsuperscript{SM−/−}) and Rictor (Rictor\textsuperscript{SM−/−}) exerted protective effects on experimental PH. Then, we conducted in vitro Western blot experiments using pulmonary artery (PA) isolated from WT and KO mice to examine whether functional disruption of mTORC1 in mTOR\textsuperscript{SM−/−} and Raptor\textsuperscript{SM−/−} mice or mTORC2 in mTOR\textsuperscript{SM−/−} and Rictor\textsuperscript{SM−/−} mice affects protein expression of PDGFRα and PDGFRβ in isolated PA. Finally, we examined and compared the level of phosphorylated AKT (pAKT), a downstream signaling protein of mTORC2 and an upstream signaling protein of mTORC1, in PA isolated from WT and KO mice and in PASMC isolated from normal subjects and IPAH patients. The results are listed below.

1. Conditional and inducible KO of mTOR in PASMC significantly inhibits the development of experimental PH.

2. Conditional and inducible deletion of Raptor in PASMC significantly inhibits the development of experimental PH.

3. Conditional and inducible deletion of Rictor results in increased basal RVSP and negligibly affects the development and progression of HPH.

4. Isolated pulmonary artery or PASMC from Rictor\textsuperscript{SM−/−} mice exhibit upregulation of PDGF receptors (PDGFRα and PDGFRβ).

5. Pharmacological inhibition of mTORC2 upregulates the expression of PDGFRα and PDGFRβ in human PASMC.

6. Pharmacological inhibition of mTORC2 increases the nuclear FOXO3a level in PASMC.

Conclusion

The data from this study indicate that the activated GPCR and/or TKR in PASMC activate the PI3K/Akt1/mTORC1 signaling pathway to stimulate cell proliferation and growth. The receptor-mediated Akt1 phosphorylation and the increase of mTORC1 kinase activity are critical in transferring the extracellular proliferative or mitogenic signals to the nucleus of PASMC, which plays an important and critical pathogenic role in the development and progression of pulmonary vascular remodeling and PH. Downregulation or inhibition of mTOR (required for the function of mTORC1 and mTORC2), Raptor (required for the function of mTORC1) and Rictor (required for the function of mTORC2) significantly attenuates the experimental PH in mice. Downregulation of Rictor or inhibition of mTORC2, however, also upregulates PDGF receptors in PASMC, and Rictor\textsuperscript{SM−/−} mice exhibit spontaneous PH. Since the inhibition of mTORC2 results in a paradoxical effect of experimental PH, we suggest that therapeutic regimen using inhibitors of the PI3K/AKT/mTOR signaling cascade for treatment of PH and PAH should include an inhibitor of PDGF receptor due to the upregulation of PDGFRα and PDGFRβ induced by mTORC2 inhibition.
Differential role of mTORC1 and mTORC2 in hypoxic vasoconstriction and the development of pulmonary hypertension (continued)

Figure 1. Conditional and inducible deletion of mTOR attenuates hypoxia-induced pulmonary hypertension (HPH) in mTOR\textsuperscript{SM−/−} mice. A. Schematic Strategy for the generation of mTOR\textsuperscript{SM−/−} mice. B. Timeline indicating the time conditional mTOR KO, hypoxic exposure for inducing PH and for experimental measurements. C. Representative immunofluorescence images showing cell nuclei (DAPI, blue), smooth muscle cells (SMA, red) and mTOR (green) in the cross-section of small pulmonary artery (PA) in lung tissues from WT and mTOR\textsuperscript{SM−/−} mice. It is noted that the mTOR (green) expression is almost abolished in SMA-positive PA wall in mTOR-Tam mice, but preserved in the mTOR-Oil mice. D. Representative record of right ventricular pressure (RVP) in WT and mTOR\textsuperscript{SM−/−} mice exposed to normoxia and hypoxia. E and F. Summarized data showing the peak value of right ventricular systolic pressure (RVSP) and Fulton Index [RV/(LV+S) ratio] in WT and mTOR\textsuperscript{SM−/−} mice exposed to normoxia and hypoxia. G and H. Representative H&E images of the cross-section of small PA and summarized data showing the PA wall thickness in WT and mTOR\textsuperscript{SM−/−} mice under normoxic and hypoxic conditions. I. Summarized data showing the number of red blood cells (RBC), hemoglobin concentration (HGB g/dl) and hematocrit percentage (HCT %) in WT and mTOR\textsuperscript{SM−/−} mice exposed to normoxia and hypoxia.
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Biographies

Ronald J. Oudiz, MD
ENTEELLIGENCE Steering Committee Chair
Director, Liu Center for Pulmonary Hypertension
LA Biomedical Research Institute at Harbor-UCLA Medical Center
Professor of Medicine
The David Geffen School of Medicine at UCLA
Torrance, CA

Dr. Oudiz, Professor of Medicine, David Geffen School of Medicine at UCLA, is Director of the Pulmonary Hypertension Center and is a Faculty Cardiologist at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. He is a past holder of scientific research awards from the American Heart Association and the National Institutes of Health. Dr. Oudiz received the Pulmonary Hypertension Association (PHA) Award of Excellence in Pulmonary Arterial Hypertension (PAH) Care in 2011, the PHA Legacy Award in 2015, and in 2015 he was named a PHA Periwinkle Pioneer for his contributions to the pulmonary hypertension (PH) field. He has authored several papers in the field of PH and has presented his research at national and international seminars. Dr. Oudiz has been on task forces for the past four World Symposia on Pulmonary Hypertension, covering clinical endpoints, diagnostic testing, and right ventricular function and physiology. He is currently the Chair of the American College of Chest Physicians Pulmonary Vascular NetWork, and is Chair-Elect of the PHA's Scientific Leadership Council (SLC). Dr. Oudiz is also a past Editor-in-Chief of the journal Advances in Pulmonary Hypertension. He has participated in several trials of innovative medical treatments for PH, many of which are still ongoing. His research focus has been to describe the physiologic abnormalities that are caused by PH, using measurements of lung gas exchange during exercise, and to study exercise rehabilitation as a treatment modality for patients with PH.

Harrison W. Farber, MD
Professor of Medicine
Boston University School of Medicine
Director, Pulmonary Hypertension Center
Boston Medical Center
Boston, MA

Dr. Farber is a Professor in the Department of Medicine and the Director of the Pulmonary Hypertension Center at Boston University. He has focused on research into pulmonary arterial hypertension (PAH) and the clinical care of PAH patients for approximately 20 years. Dr. Farber has received numerous grants (both basic science and clinical) and has an extensive publication record in this area, including articles in peer reviewed journals such as Circulation, New England Journal of Medicine, and Chest. He serves on many panels for the development of clinical recommendations in PAH, has participated in large multicenter clinical trials, and was on the Steering Committee of the REVEAL Registry (Registry to Evaluate Early and Long Term PAH Disease Management), the largest registry of PAH patients ever created. His research interests include endothelial cell biology, in particular, the response of the pulmonary vasculature to injury. After earning a medical degree at George Washington University School of Medicine, Dr. Farber completed an internship and residency at the Medical College of Virginia and a fellowship at Boston University.
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Biographies

Mardi Gomberg-Maitland, MD, MSc
Director of RV Failure, HFpEF, and Cardio-Oncology Programs
Co-Director of the Pulmonary Vascular Disease Program
Inova Heart and Vascular Institute
Falls Church, VA

Dr. Gomberg-Maitland earned her medical degree, with special distinction for research in cardiovascular medicine, from the Albert Einstein College of Medicine. She served her residency in internal medicine at New York Presbyterian Hospital/Weill-Cornell Medical Center, and a fellowship in cardiovascular diseases at the Mount Sinai Medical Center. During this fellowship, she was also a visiting fellow in critical care medicine at New York Presbyterian Hospital/Weill-Cornell Medical Center and earned a Master’s degree in clinical epidemiology from the Harvard School of Public Health. Her research focus is in understanding the epidemiology of pulmonary hypertension (PH) and development of novel therapeutics and biomarkers. By designing and implementing the largest single center database, tracking all the patients in the PH clinic, she identified new predictors of survival using simple tests (such as serum creatinine and treadmill testing) and developed a new survival equation to better predict prognosis. She is on multiple international trial steering committees, the lead on drug development at the Pulmonary Hypertension World Congress (JACC publication 2013), and on novel early development trials in early and late phase development in PH. She has over 100 publications in top tier medical journals, including CHEST, Circulation, Circulation Heart Failure, European Respiratory Journal, Journal of American College of Cardiology (JACC), JACC Heart Failure, JAMA-Internal Medicine, and the New England Journal of Medicine. She is a Section Editor at JACC and an Associate Editor at both CHEST and the European Respiratory Journal.

Maureen D. Mayes, MD, MPH
Professor of Internal Medicine
Elizabeth Bidgood Chair in Rheumatology
Division of Rheumatology and Clinical Immunogenetics
University of Texas – McGovern Medical School
Houston, TX

Dr. Mayes graduated from Eastern Virginia Medical School and completed her Internal Medicine training and Rheumatology fellowship at the Cleveland Clinic. She received a Master’s in Public Health (MPH) in Epidemiology from the University of Michigan School of Public Health. She joined the University of Texas – McGovern Medical School faculty in 2002 and subsequently established the Scleroderma Clinic and research program. Dr. Mayes is the recipient of many distinctions, awards and grants for the study and treatment of scleroderma. She is the author of over 190 published manuscripts, 28 reviews, 11 book chapters and 3 books. Her clinical interests include the treatment of scleroderma and its multiple complications. She participates in several multicenter, national trials of new agents for this disease. Her research interests include the identification of susceptibility genes and disease severity genes in scleroderma and related autoimmune diseases. She is the founder and director of the Scleroderma Family Registry and DNA Repository, which serves as a national resource to supply genetic material to other investigators to study this disease.
Biographies

Evangelos D. Michelakis, MD
Professor of Medicine, Division of Cardiology
Vice Chair (Research) – Department of Medicine
Director, Pulmonary Hypertension Program
University of Alberta
Canada Research Chair in Applied Molecular and Mitochondrial Medicine
Edmonton, AB, Canada

Dr. Michelakis was born in Greece, where he went to Medical School at the University of Patras. He completed training in Vascular Biology, Internal Medicine, and Cardiology at the University of Texas (Galveston), Yale University, and the University of Minnesota. He joined the faculty of the University of Alberta in 1998, where he is now a full Professor and a Vice Chair (Research) in the Department of Medicine. Dr. Michelakis founded and has directed the Pulmonary Hypertension Program and clinic at the University of Alberta since 2001; this multidisciplinary clinic is open 5 days a week and treats patients referred from Alberta, Northern BC, Saskatchewan and Manitoba. He is also a vascular biologist and runs an active laboratory with several graduate students and technicians, focusing on the discovery of novel therapies for pulmonary hypertension. He is the Canada Research Chair in Applied Molecular and Mitochondrial Medicine and the Chair of the Cardiopulmonary, Critical Care, Perioperative and Resuscitation (3CPR) Council of the American Heart Association, and he serves on the editorial boards of both Circulation and Circulation Research. Dr. Michelakis has discovered intriguing similarities in the biology of pulmonary hypertension and cancer, which have led him into an exciting translational research program in cancer as well.

Harold I. Palevsky, MD
Professor of Medicine
Perelman School of Medicine of the University of Pennsylvania
Chief, Pulmonary, Allergy and Critical Care
Director, Pulmonary Vascular Disease Program
Penn Presbyterian Medical Center
Philadelphia, PA

Dr. Palevsky is a Professor of Medicine at the Perelman School of Medicine of the University of Pennsylvania. He is also Chief of the Pulmonary, Allergy and Critical Care Division and Director of the Pulmonary Vascular Disease Program at the Penn Presbyterian Medical Center in Philadelphia. The Pulmonary Vascular Disease Program is a multi-disciplinary program focusing on the diagnosis and treatment of pulmonary vascular disease, pulmonary arterial hypertension, and pulmonary thromboembolic disease, both acute and chronic. Dr. Palevsky earned a medical degree from the Medical College of Virginia. He completed an internship and residency in internal medicine, and a fellowship in pulmonary and critical care medicine at the Hospital of the University of Pennsylvania, where he worked with Alfred P. Fishman, MD. His clinical and research interests include unexplained dyspnea, pulmonary vascular disease, pulmonary hypertension, and thromboembolic disease. Dr. Palevsky has been published in numerous peer-reviewed journals, including the Annals of Internal Medicine, JAMA, and Circulation. He has been recognized as one of Philadelphia’s “Top Docs” and is included in national lists such as “The Best Doctors in America” and the “Guide to America’s Top Physicians.”
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**Biographies**

**Richard M. Silver, MD**  
Distinguished University Professor  
Director, Division of Rheumatology & Immunology  
Medical University of South Carolina  
Charleston, SC

Dr. Silver serves as Director of the Division of Rheumatology & Immunology at the Medical University of South Carolina (MUSC). He is a graduate of the University of Tennessee–Knoxville and earned his MD from Vanderbilt University School of Medicine. Dr. Silver completed training in Internal Medicine at the University of North Carolina-Chapel Hill and in Rheumatology at London’s Northwick Park Hospital and at the University of California-San Diego. He joined the faculty at the Medical University of South Carolina in 1981, and has served as Director of the Division of Rheumatology & Immunology since 1995. MUSC’s Board of Trustees named him a “Master Teacher” and bestowed the University’s highest academic recognition, Distinguished University Professor. The Scleroderma Foundation named him their “Doctor of the Year” in 2007. Dr. Silver’s major research interest is interstitial lung disease associated with systemic sclerosis.

**Kurt R. Stenmark, MD**  
Professor of Pediatrics, Medicine, and Anesthesiology  
Section Head, Pediatric Critical Care Medicine  
Director, Cardiovascular Pulmonary Research Laboratories  
University of Colorado Anschutz Medical Campus  
Aurora, CO

Dr. Stenmark is a Professor of Pediatrics, Medicine, and Anesthesiology at the University of Colorado Anschutz Medical Campus in Aurora, CO. He is also the Section Head of Pediatric Critical Care Medicine and Director of the Cardiovascular Pulmonary Research Laboratories. Dr. Stenmark earned his medical degree at the University of Colorado, Denver and completed his internship and residency at the University of Colorado Health Sciences Center (UCHSC), where he was the Pediatric Chief Resident. He completed a Pediatric Critical Care fellowship at The Children’s Hospital and a Cardiovascular Pulmonary Research fellowship at UCHSC. Dr. Stenmark’s clinical and research interests include cellular and molecular mechanisms that contribute to structural remodeling of the pulmonary vasculature and to right heart dysfunction in the setting of pulmonary hypertension. He has served as an Associate Editor for the American Journal of Physiology - Lung Cellular and Molecular Physiology, and on the editorial boards of several journals, including American Review of Respiratory and Critical Care Medicine, Circulation Research, and Pulmonary Circulation. He is a member of the ATS Scientific Advisory Council, Scleroderma Foundation Peer Review, and Pulmonary Vascular Research Institute (PVRI) Steering and Scientific committees. A featured speaker at numerous conferences, Dr. Stenmark has published book chapters and over 289 manuscripts in peer-reviewed journals, including, but not limited to, the New England Journal of Medicine, Science, Journal of Clinical Investigation, Circulation Research, and the American Journal of Physiology.
Dr. Yuan is Professor of Medicine and Physiology, and Associate Vice President for Translational Health Sciences at The University of Arizona in Tucson, AZ. He is also Chief of the Division of Translational and Regenerative Medicine in the Department of Medicine at The University of Arizona College of Medicine in Tucson. Dr. Yuan received his medical school training at Suzhou Medical College (China), his PhD at Peking Union Medical College (China), and his postdoctoral training at the University of Maryland School of Medicine. His pulmonary vascular disease research propels the field on pathogenic roles of membrane receptors and ion channels in the development of pulmonary arterial hypertension and provides a new research direction for developing therapeutic approaches for the disease. Dr. Yuan is a Fellow of the American Heart Association, the American Association for the Advancement of Science, and the American Physiological Society. He is an elected Member of the American Society for Clinical Investigation and the Association of American Physicians. Dr. Yuan has served on many advisory committees and editorial boards, including Chair of the Respiratory Integrative Biology and Translational Research study section of the National Institutes of Health (NIH) and Chair of the Pulmonary Circulation Assembly of the American Thoracic Society. He is currently Editor-in-Chief of the journal Pulmonary Circulation, Deputy Editor of the American Journal of Physiology-Cell Physiology, and a regular member of the NIH Vascular Cell and Molecular Biology study section.