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 2019, 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 14 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 65 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
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: 14
Awards distributed: 67
Overview of ENTELLIGENCE Awards

Awarded 2019

Mark Dodson, MD, PhD
Intermountain Medical Center
Murray, UT
Mentors: Gregory Elliott, MD, and Lisa Cannon-Albright, PhD
Project Title: Identifying Genetic Risk Factors for Chronic Thromboembolic Pulmonary Hypertension

Jonathan Edwards, MD
Children’s Hospital of Philadelphia
Philadelphia, PA
Mentors: Zoltan Arany, MD, and Laura Mercer-Rosa, MD
Project Title: Investigating Altered Right Ventricular Myocardial Gene Expression and Biomarkers Patterns Associated with Adaptive and Maladaptive Remodeling in Diverse Human Models

Andrea Frump, PhD
Indiana University School of Medicine
Indianapolis, IN
Co-Investigator: Mark Geraci, MD
Mentors: Tim Lahm, MD, and Micheala Aldred, PhD
Project Title: Identification of the Apelin-mediated Transcriptome in Right Ventricular Failure using Single Cell RNA-Seq

Victor Tseng, MD
Emory University
Atlanta, GA
Mentors: C. Michael Hart, MD, and Eva Grayck, MD
Project Title: Hyaluronan Drives Pathologic Vascular Metabolism in Pulmonary Hypertension
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

2018 Award Winners

From left: Daniel Lachant, DO; Meghan Bernier, MD; Catherine Avitabile, MD; and Stephen J. Coleman, MS, PhD
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 and 2019 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
  • Published in American Journal of Respiratory Cell and Molecular Biology, 2019

**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
  • Presented at American Society of Nuclear Cardiology, 2018
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 N. Henriques King, MD, MSc
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: MATCH-uPP - MRI and catheterization hemodynamics in pediatric 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, MSCI**  
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 Annals of the American Thoracic Society, 2019; 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 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*
- 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
University of Toronto
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 Respirology, 2019; 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; Arteriosclerosis, Thrombosis, and Vascular Biology, 2011; and Journal of Heart and Lung Transplantation, 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
Identifying Genetic Risk Factors for Chronic Thromboembolic Pulmonary Hypertension

Introduction and Background:
Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating condition caused by chronic obstruction of the pulmonary arteries by thromboembolic material arising from incomplete resolution of pulmonary embolism (PE). Existing data suggest that the majority of CTEPH cases go undiagnosed, and when a correct diagnosis of CTEPH is made there is often an unacceptably long diagnostic delay. There are two major reasons for this. First, CTEPH occurs in only a small percentage of PE survivors (approximately 3%), making screening of all PE survivors for subsequent development of CTEPH inefficient. Second, the mechanisms leading to incomplete thrombus resolution after acute PE are not well understood, and thus no clinically useful biomarkers of future risk of CTEPH have been identified.

The goal of this proposal is to identify genetic markers associated with CTEPH risk. These genetic markers could ultimately be integrated into a risk prediction model for CTEPH, which may improve case recognition by allowing for the triage of high-risk patients to more intensive surveillance for CTEPH after acute PE. In a recently published manuscript, our group has used the Utah Population Database (UPDB), a unique genealogical database that includes a majority of families in the state of Utah, to show that patients with CTEPH are significantly more related than would be expected by chance. These data provide the strongest evidence to date that genetic factors influence CTEPH risk. In this proposal, we aim to use unique Utah genetic resources to gain further insight into the types of genetic variants that are associated with CTEPH, and then use both candidate-based and unbiased screening methods to identify CTEPH predisposition genetic variants.

Hypothesis:
The unifying hypothesis of this proposal is that genetic factors influence CTEPH risk, and that these genetic factors are distinct from the common inherited thrombophilias that influence the risk of acute uncomplicated VTE. We hypothesize the existence of a set of genetic variants that specifically predispose to VTE events that do not resolve and thus predispose to CTEPH. This set of genetic variants contrasts with the common inherited thrombophilias (including the Factor V Leiden mutation), which we hypothesize predispose to VTE events that are likely to resolve and thus unlikely to lead to CTEPH.

Specific Aim 1:
Determine the frequency of the Factor V Leiden mutation in patients with CTEPH and in carefully matched patients with acute uncomplicated PE in whom CTEPH is not suspected.

Specific Aim 2:
Use the UPDB to determine whether CTEPH high risk pedigrees are also VTE high risk pedigrees, and whether probands from these pedigrees carry common inherited thrombophilias.

Specific Aim 3:
Use a powerful pedigree-based whole genome sequencing approach to identify and validate novel candidate genetic variants underlying CTEPH risk in Utah high risk CTEPH pedigrees.
Jonathan Edwards, MD
Children's Hospital of Philadelphia
Philadelphia, PA

Investigating Altered Right Ventricular Myocardial Gene Expression and Biomarkers Patterns Associated with Adaptive and Maladaptive Remodeling in Diverse Human Models

Introduction and Background:
The mechanisms of adaptive remodeling and pathologic right ventricular (RV) remodeling, which lead to preserved RV function (pRV) or RV failure (RVF) respectively, are poorly understood despite RVF being the primary cause of hospitalization and mortality in PAH. The molecular mechanisms that drive adaptive and pathologic RV remodeling in PAH have remained incompletely characterized due to lack of tissue availability, particularly for pRV. However, given that previously implicated pathways in RV remodeling appear to be involved in multiple etiologies, we will use the availability of RV tissue from left ventricular failure (LVF) to our advantage. From more than 150 ischemic (ICM) and 200 dilated cardiomyopathy (DCM) patients in the Penn Human Heart Tissue Bank, we will identify pRV and RVF using preexplant hemodynamics and compare to nonfailing (NF) controls as a discovery cohort. We will leverage ongoing bulk RNAseq to identify representative age, gender, and ethnicity-matched DCM-pRV, DCM-RVF, ICM-pRV, and ICM-RVF samples to assess using a single nuclear RNAseq method sNucDrop-seq. sNucDrop-seq will provide unique insight into cell population source for differential gene expression, the role of cardiomyocyte and noncardiomyocyte heterogeneity in adaptive and pathologic remodeling, and uncover the role of noncardiomyocyte cell populations that can be averaged out at the bulk RNAseq level.

Next, novel RV remodeling targets will be tested against clinically used and recently identified biomarkers of ventricular remodeling (NT-proBNP, MMP1, MMP9, and GAL3) using echocardiographic indices of RV remodeling and function in two pediatric cohorts. The first will be comprised of Nice classification group 1 PAH serum and the second will be comprised of serial tetralogy of Fallot (TOF) preoperative serum, RV tissue collected at surgery, and serum at one year follow up.

Hypothesis:
Through these studies, we hope to identify novel prognostic and therapeutic targets of RV remodeling, which will have broad applicability across multiple etiologies and demographics groups, and will ultimately lead to improved clinical outcomes for all patients with RVF.

Specific Aim 1:
Determine the cell-specific transcriptional signature of RV myocardium in pRV and RVF in the setting of LVF as a discovery cohort.

Specific Aim 2:
Test novel, cardiomyocyte and non-cardiomyocyte RV remodeling expression targets and biomarkers in pediatric PAH and TOF.
Introduction and Background:
RV function is the primary prognostic factor for both morbidity and mortality in PH, but despite this importance, no RV-directed therapies exist. Furthermore, patients with more common cardiopulmonary diseases such as chronic obstructive pulmonary disease, pulmonary fibrosis, sleep disordered breathing and left heart disease are at major risk for developing PH and/or RV failure. Intriguingly, despite increased susceptibility to PH, women have better RV function and survive longer with PH than men. Therefore, there is an unmet, scientific need to identify the sex- and cell-specific pathways driving RV failure, and to target those pathways to prevent, delay or reverse RV failure. We hypothesize that apelin-mediated signaling will promote a prolonged adaptive remodeling response in the pressure-overloaded RV. The goal of this proposal is to identify the hitherto unknown molecular, sex and cell-specific targets of apelin during the progression of RV failure and how it may be used to prevent or delay RV failure, which would allow for the development of novel, RV-targeted therapies (an area that has been identified as a critical need in PH therapy).

Apelin is a secreted peptide that plays a critical role in cardiac development, angiogenesis, pro-survival signaling, inflammation, and pro-contractile signaling. Our hypothesis is based on preliminary data demonstrating that decreased RV apelin expression in rats with RV failure and in PH patients is a hallmark of maladaptive (decompensated), but not adaptive (compensated) RV remodeling. Furthermore, we found that apelin enhances pro-survival signaling in RV-specific endothelial cells (ECs) and cardiomyocytes (CMs).

Upon completion of this project, we will have leveraged the power of single cell RNA-Seq to identify the cell-specific changes to the male and female transcriptome and provided the first molecular characterization and cellular targets of apelin signaling during the progression of RV failure. This work will lay the foundation for the development of personalized RV-directed therapies for male and female patients with PH.

Hypothesis:
Our compelling data led us to hypothesize that apelin-mediated signaling will promote a prolonged adaptive remodeling response in the pressure-overloaded RV. This proposal will decipher apelin's role in the progression of RV failure and, by using a single cell RNASeq approach, identify novel cell-specific targets of apelin-mediated signaling.

Specific Aim 1:
To investigate whether apelin treatment preserves vascular density, contractile function and abrogates the progression of RV failure. We hypothesize that long-term apelin treatment will delay the development of RV failure by stimulating pro-angiogenic and pro-contractile signaling.

Specific Aim 2:
To identify the apelin-mediated transcriptional profile during RV failure development using single cell RNA-Seq. We hypothesize that apelin mediates cell-specific, sex-specific and time-dependent protective responses that delay progression of RV failure.
Introduction and Background:
Pulmonary hypertension (PH) is a complex and incurable cardiovascular disorder that is both deadly and morbid. Contemporary treatment rests upon supportive care and maximal relief of pulmonary vasoconstriction. However, disease-modifying therapies that can halt or reverse vascular remodeling, a cardinal feature of PH, are lacking. Mounting evidence indicates that vascular remodeling in PH involves crosstalk between metabolically defective vascular wall cells and their abnormal extracellular matrices.

This basic and translational study examines the impact of hyaluronan (HA), the extracellular matrix glycan, on aberrant vascular metabolism and growth responses in pulmonary hypertension (PH). This project will confront a critical gap in knowledge about the interface between cellular and matrix metabolism in pulmonary vascular biology. The biochemical foundation for this proposal is found in the structure of HA, which is formed by the linear polymerization of aminosugars generated through the hexosamine biosynthetic pathway (HBP). The HBP directly connects to and orchestrates glucose, glutamine, fatty acid, and nucleotide metabolism. Derangements in these metabolite families have been implicated in the pathogenesis of PH.

Hypothesis and Objectives:
The proposed studies explore the hypothesis that excessive HA synthesis and HBP activation exacerbate metabolic reprogramming and proliferation of pulmonary artery smooth muscle cells to drive PH. Three main objectives test this hypothesis. The first objective will define the dynamics and key regulators of HA synthesis and HBP in human samples and rodent models of PH. The second objective will elucidate the impact of HA on cellular bioenergetics, and the third objective will test the therapeutic potential of a pharmacologic HA inhibitor in experimental PH.

Specific Aim 1:
Establish the contribution of the HA-HBP axis to PH pathogenesis and progression.

Specific Aim 2:
Define the impact of the HA-HBP axis on PASMC bioenergetics and phenotype.

Specific Aim 3:
Evaluate the therapeutic potential of HA blockade on experimental PH.
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.
Introduction:
The actin cytoskeleton is a key component of endothelial structure and function, and alterations may effect 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.
Extracellular vesicles as a marker of vascular disease activity in PAH

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 vasodilator therapy changes miRNA in ECV. Correlate miRNA from ECV with PAH risk profiles.
**Background**

The natural history of pulmonary vascular disease (PVD) associated with congenital heart disease (CHD) reveals the differential, or perhaps incremental, effects of increased pulmonary blood flow and increased pulmonary arterial pressure. In patients with increased blood flow alone as occurs in pre-tricuspid valve lesions, the development of PVD is uncommon and presents late, among 5-15% of patients by the fourth decade of life. In contrast, PVD associated with post-tricuspid lesions is common, progressive, and develops early in life. Although PH due to systemic-to-pulmonary shunt is preventable with early closure of most defects, the global burden of PH associated with CHD and the vulnerable perioperative period in these patients continue to underline the importance of understanding the pathologic mechanisms whereby mechanical forces translate into characteristic pulmonary vascular lesions.

**Aims**

We utilized lamb models of congenital heart disease (CHD) with either a fetally implanted aortopulmonary shunt (increased pulmonary artery pressure and blood flow) or fetal left pulmonary artery (LPA) ligation (increased pulmonary blood flow) to determine differential gene expression related to differing mechanical forces associated with CHD and to investigate their underlying mechanisms. We hypothesized that increased flow and pressure would induce differential changes in gene expression that contribute to the differing risk of developing PVD in CHD. This study was organized according to **two specific aims:** (1) to determine the effect of mechanical forces—flow and pressure vs. flow alone—on pulmonary artery vascular tone and endothelial cell function (2) to characterize and compare differential gene expression patterns associated with exposure to differential mechanical forces in the setting of CHD.

**Results:** After establishing our surgical models, we defined the morphology of the three models in juvenile lambs (3 weeks of age) using computed tomography angiography (CTA, Figure 1.) CTA of control animals demonstrates the expected size ratio between aorta and pulmonary artery with a normal vascular arborization pattern. In contrast, the CTA of the fetal LPA ligation lamb shows an expected complete absence of the left pulmonary artery and left distal vasculature with mild dilation of the remaining right main pulmonary artery and branches. Finally, CTA of the shunt lamb demonstrates marked dilation of the main pulmonary artery segment with dilation and extended recruitment of distal vessels, compared to control.

When lambs from each model system were 4-6 weeks of age, they underwent hemodynamic study and in vivo pulmonary vascular reactivity testing. As expected, both LPA and shunt lambs had significantly higher pulmonary artery blood flow (PBF), compared to controls, although PBF was 2-fold control in LPA lambs, and 3-fold control in shunts. While LPA lambs had modest increases in mean PA pressure (PAP) compared to controls, shunt lamb PAP was significantly higher, compared to both control and LPA lambs. Further, shunt lambs had increased pulmonary pulse pressure—the difference between diastolic and systolic pressure—compared to both control and LPA lambs, while pulmonary pulse pressure was similar in control and LPA lambs. This
physiologic difference has important pathologic consequences, given the increase in cyclic stretch associated with pulse pressure.

Having established baseline hemodynamics, we next administered pulmonary vasoconstricting stimuli and assessed differing responses in the intact animals. In response to hypoxia, shunt lambs significantly increased mean PAP, compared to both control and LPA lambs. Next, we administered the thromboxane A2 mimic U46619 to induce pulmonary vasoconstriction. LPA lambs had a greater rise in mean PAP than did control lambs, but PAP increased most in shunt lambs. Isolated PA rings from shunt lambs, compared to control and LPA, had exaggerated vasoconstriction in response to norepinephrine. Together, these data suggest that shunt animals have exaggerated pulmonary vasoreactivity, compared to controls, and that LPA ligation lambs have an intermediate phenotype. Further, shunt lambs also had increased pulmonary artery muscularization, compared to both control and LPA ligation groups.

Having defined physiologic responses differing chronic hemodynamic forces in our model, we next sought to examine the gene expression profile of pulmonary artery endothelial cells (PAECs) which are primarily affected by both shear (increased pulmonary blood flow) and cyclic stretch (increased pulmonary pressure.) We first performed RNA sequencing on PAECs derived from control, LPA, and shunt lambs. Principle clustering analysis (Figure 2A) demonstrated excellent differentiation between PAECs derived from each model, as did unsupervised hierarchical clustering heat map analysis (Figure 2B.) We next visualized comparisons between each individual group using volcano plots representing the relationship between fold change and significance. Volcano plots are shown in Figure 2 for control vs. LPA (2C) control vs. shunt (2D) and LPA vs. shunt (2E.) These data provide visualization for transcriptome-level differences between models. Although important differences exist, the LPA ligation model (increased PA flow only) is the most similar to control, while shunt lambs (increased PA pressure and flow) have more differences in RNA expression. Taken together, these data confirm that our observations of different physiologic responses are also evident at the transcriptional level in PAECs derived from these models.

We next defined the functional characteristics of PAECs derived from these different lamb models. We first utilized a tube formation assay in growth factor restricted Matrigel to characterize angiogenesis. PAECs from LPA ligation animals had a greater rate of angiogenesis compared to controls after 72 h in Matrigel, as quantified by the number of branch points and tube length. However, PAECs derived from shunt animals had an even greater rate of angiogenesis than did either control or LPA. Next, we quantified apoptosis, utilizing TUNEL staining following tumor necrosis factor-alpha (TNF-α) stimulation to induce apoptosis. Control PAECs had the greatest percentage of apoptotic cells, followed by LPA PAECs, with shunt PAECs exhibiting the greatest resistance to apoptosis. Then, we quantified PAEC proliferation from each model and demonstrated greater proliferation in PAECs derived from shunt animals, compared to both control and LPA ligation. Consistent with other models of pulmonary vascular disease, these data collectively demonstrate that PAECs derived from shunts are more proliferative, apoptosis-resistant, and prone to angiogenesis than PAECs derived from either control or LPA ligation lambs, although PAECs derived from LPA ligation lambs do have an intermediate phenotype, compared to control and shunts, in their resistance to apoptosis and propensity for angiogenesis.

Conclusion

The natural history of pulmonary vascular disease associated with congenital heart disease suggests distinct pathophysiologic consequences of different hemodynamic insults to the pulmonary vasculature. In this study, we establish the first fetal cardiac surgical model of increased pulmonary blood flow alone (LPA ligation), and compare that new model with our established CHD model of increased pulmonary pressure and flow (shunt lambs). These studies demonstrate substantial differences between the animals with normal physiology, those with increased pulmonary blood flow (LPA), and those with increased pulmonary pressure and flow (shunt) both in whole animal physiologic responses to vasoactive stimuli and the pulmonary artery endothelial cell transcriptome. These large animal models represent a seminal development in our ability for preclinical studies of PVD associated with CHD as we characterize responses in the intact animal as well as endothelial cells derived from primary cell culture. Notably, the LPA ligation model demonstrates
Translating the natural history of pulmonary vascular disease secondary to congenital heart disease into basic mechanisms and therapeutic targets (continued)

a primed or intermediate phenotype in endothelial function, which may reflect chronic effects of flow-mediated shear stress. This intermediate phenotype is consistent with clinical experience, which suggests that the stimulus of increased pulmonary blood flow alone is not sufficient to develop significant, rapidly progressive pulmonary vascular disease, but these patients may be more vulnerable to "second hits" such as predisposing genetic conditions, environmental hypoxia due to living at altitude or lung disease, or diseases leading to vascular inflammation.

In conclusion, through the introduction of a new model of congenital heart disease with increased pulmonary blood flow alone (fetal LPA ligation), we are able to investigate the differential and additive effects of common hemodynamic alterations in the pulmonary vasculature – increased pulmonary blood flow and increased pulmonary arterial pressure – as a consequence of congenital heart disease. Given the significant burden of PVD among patients with CHD particularly in the pediatric population, a fundamental understanding of the differing mechanisms leading to vascular pathology associated with different CHD lesions provides an essential tool in tailoring therapy to these patients.

Figure 1.

Figure 2.
Background
Augmentation of cyclic guanosine monophosphate (cGMP) signaling through inhibition of specific phosphodiesterase (PDE) enzymes is a cornerstone of therapy in pulmonary arterial hypertension (PAH). Cyclic GMP plays a critical role in the regulation of endothelial, vascular smooth muscle, and cardiac myocyte function. Activation of downstream signaling promotes vaso-relaxation and myocardial contractility while preventing hypertrophy and proliferation. Nitric oxide (NO) and natriuretic peptides (NP) initiate cGMP-dependent signaling by activating soluble (NO) and particulate (NP) guanylate cyclase isoforms. Activation of specific PDE isoforms leads to hydrolysis of cGMP, down-regulating cGMP-dependent signaling.

In the pulmonary circulation, NO-dependent cGMP signaling promotes vasodilatation and may regulate vascular remodeling. Clinically, this pathway is promoted through specific inhibitors of PDE5, though a number of well described counter-regulatory mechanisms may reduce NO bioavailability and limit efficacy. PDE9A has the highest affinity for cGMP of all known PDE isoforms and is expressed in heart and lung tissue. Myocardial PDE9A is upregulated in heart failure and in an animal model of chronic left ventricular pressure overload, and PDE9A deficiency or inhibition reduced myocyte hypertrophy and improved myocardial function. Importantly, PDE9A functions through inhibition of NP-dependent (not NO-dependent) cGMP signaling and is not dependent on NO bioavailability. As NP levels are routinely elevated in human PH, we hypothesized that NP-dependent cGMP signaling may similarly limit RV or pulmonary vascular remodeling in PH, and that PDE9A deficiency would augment these effects. We tested this hypothesis in a murine model of chronic hypoxic PH (CH-PH).

Aims
1. To determine whether PDE9A inhibits RV and/or lung cGMP-dependent signaling during CH-PH.
2. To measure the effects of PDE9A deficiency on CH-PH induced RV and pulmonary vascular remodeling.

Results
CH-PH is associated with increased circulating ANP
After 3 weeks, CH-PH caused RV hypertrophy and increased right ventricular systolic pressure (RVSP) in C57 BL/6 mice, as anticipated. Serum ANP levels increased 5-fold after 3 weeks of CH (136 ± 36 pg/mL vs. 27 ± 8 pg/mL; P < 0.0001). ANP levels correlated robustly with body-weight normalized RV mass (r = 0.78, R²=060; P = 0.0007). Increases in serum ANP were associated with a four-fold reduction in lung neprolysin-3 receptor (Npr3) transcription but were not associated with increased RV Nppa transcription, suggesting that serum ANP levels are up-regulated primarily through decreased NP clearance in the model.

CH-PH induced increases in ANP are not associated with increased cGMP production or VASP phosphorylation
Cyclic GMP has several well-characterized roles in cardiac myocyte, vascular
SMC, and EC biology, primarily mediated via activation of downstream signaling through protein kinase G (PKG). In addition, cGMP-PKG signaling leads directly to phosphorylation of the actin-binding protein VASP (vasodilatory-stimulated phosphoprotein). Baseline levels of cGMP in RV homogenates were extremely low in normoxic mice, and did not increase with CH-PH. Baseline cGMP levels were considerably higher in normoxic lung homogenates, but did not increase after 3 weeks of CH-PH. Similarly, phosphorylation of VASP was not increased in either RV or lung homogenates from mice exposed to CH-PH. Taken together, these observations suggest that CH-PH-induced increases in circulating ANP are not associated with measurable activation of cGMP-dependent signaling in lung or RV tissues.

CH-PH induced increases in circulating ANP are not associated with increased expression or activity of cGMP-specific phosphodiesterases Cyclic-GMP dependent activation of specific PDE isoforms that catabolize cGMP may attenuate protective effects of cGMP-dependent signaling in lung and RV tissues. We hypothesized that ANP-dependent increases in PDE9 or PDE5 activity may explain the lack of observed cGMP-dependent signaling in the model. CH-PH did not increase transcription of Pde9 or Pde5 in RV or lung tissue. Lung (but not RV) PDE5 protein levels were significantly increased by CH-PH, and this was associated with a modest, non-significant increase in lung PDE5 activity (fluorescence polarimetry). CH-PH did not increase lung PDE9 activity or total PDE activity.

PDE9A deficiency is not associated with attenuated lung or RV remodeling in CH-PH To determine whether PDE9 is necessary for CH-PH induced lung or RV remodeling, we exposed mice lacking PDE9 expression (Pde9a−/−) to CH-PH and compared lung and RV remodeling, hemodynamics, VASP phosphorylation, and PDE expression and activity between knockout mice and wild-type littermates (Pde9a+/+). We hypothesized that if PDE9 was required for suppression of cGMP-dependent signaling downstream of ANP in the CH-PH model, that knockout animals would have increased cGMP-dependent signaling and attenuated pulmonary hypertension. As shown in Figure 1, PDE9A deficiency did not attenuate CH-PH induced increases in RVH, RVSP, dP/dt max, or dP/dt min. Sex did not alter this relationship. Furthermore, Pde9a−/− mice did not show increased VASP phosphorylation under baseline or CH-PH conditions when compared to Pde9a+/+ littermate controls (Figure 2). These negative findings were not secondary to upregulation of PDE5 expression or activity in the knockout; there was no difference in baseline or CH-PH induced PDE5 transcription, protein expression, or activity between genotypes.

Conclusions In sum, our study demonstrates that murine CH-PH is associated with increased circulating natriuretic peptide levels, driven (at least in part) through down-regulation of pulmonary Npr3 expression. These observations are similar to previous reports in mice and rats. However, in our study, increased ANP was not associated with increased cGMP or PKG activation in lung or RV homogenates, and this was not due to up-regulation of cGMP-specific PDE activity, including PDE9. Most importantly, PDE9A deficiency was not associated with increases in cGMP activity or attenuation of CH-PH in C57 BL/6 mice.

Taken together, our findings do not support a definitive role for PDE9A in the regulation of murine CH-PH. Previous studies demonstrate that ANP deficiency promotes lung and RV remodeling in CH-PH, and ANP over-expression attenuates the phenotype. However, downstream effectors and regulators remain unclear. Observed increases in endogenous ANP levels in our mice (similar to previous reports) were up to two orders of magnitude less than protective levels obtained by overexpression. It is certainly possible that the largely negative findings in our study are a function of the tested model, which yields limited pulmonary vascular and RV remodeling when compared to other models. We have performed some preliminary experiments in RV samples from rats with Su5416/CH-induced PH and observed significant increases in PDE9 (but not PDE5) activity, supporting the need for further analyses in this model.
PDE9A in right ventricular and pulmonary vascular remodeling (continued)

Figure 1.
RV remodeling and hemodynamics for Pde9−/− mice and Pde9+/+ littermates are shown after 3 weeks of CH-PH. Males and females are included in each group. RVH = right ventricular hypertrophy; RV/LV+S = RV mass divided by mass of LV/septum; RVSP = right ventricular systolic pressure; RV/BW = RV mass divided by body weight; LV+S/BW = LV/septum mass divided by body weight. Interaction \( P \) = 2-way ANOVA; *=\( P \)<0.05, **=\( P \)<0.01, ***=\( P \)<0.001, ****=\( P \)<0.0001.

Figure 2.
Effects of PDE9A deficiency on PKG activity during CH-PH. Lung and RV VASP phosphorylation (ser239) are shown for Pde9a KO mice (PDE9−−) and wild-type littermates (PDE9+/+) after 3 weeks of normoxia (red) or CH-PH (blue; \( N=3 \)/group). AU = arbitrary units; Norm = normoxia; CH = CH-PH. Interaction \( P \) = 2-way ANOVA; there were no statistically significant post-hoc comparisons among groups.
Background

Pulmonary hypertension (PH) is a progressive disease with no cure. Despite therapeutic advances, survival remains poor. PH affects both adults and children, with an annual incidence of adult PH estimated to be 50 per million and pediatric PH estimated to be 63 per million. While there are some similarities between adult and pediatric pathophysiology, the disease may be more severe with worse survival in children. This higher severity in youth is due to differences in underlying causes, presence of congenital heart disease, effects of maturation, and differences in clinical symptoms leading to diagnosis in later stages. Despite significant differences from adult PH, clinical management for children is heavily guided by studies in adults and from the non-evidence-based experiences of pediatric practitioners. There is absolutely a paucity of pediatric PH research, to the detriment of childhood PH survival and quality of life. In particular, there has been a steady rise in research interest in vascular and ventricular function and interaction in adult PH, while the pediatric knowledge continues to lag behind. Cardiac catheterization is the gold standard for establishing the diagnosis as well as for determining disease severity and response to therapy in PH. However, serial catheterizations expose children to repeated anesthesia and excessive radiation over their lifetime. In one study, 6% of children undergoing catheterization under anesthesia required resuscitation or died. Catheterization itself carries risks, with about 3% of children undergoing catheterization for PH having significant adverse events. These numbers are staggering and pose the question: is it time to monitor these children differently, especially with the upsurge in advances in cardiovascular imaging? Cardiac magnetic resonance imaging (MRI) is the single imaging modality that allows assessment of both the ventricle and the vasculature involved in PH pathophysiology, without radiation exposure, or anesthesia exposure in older children. MRI is the gold standard for measuring ventricular volume, mass, function, and evidence of myocardial fibrosis. It also can evaluate measures of vascular function, including flow patterns, flow velocity, wall shear stress (WSS) and ventricular-vascular coupling ratio (VVCR).

We have directly measured pulmonary WSS by MRI in children and have a long-standing interest in measurement of total right ventricular (RV) afterload. We plan to evaluate proximal vascular function and cardiac function to better predict PH outcomes in the pediatric population using noninvasive MRI with advanced computational technology.

Specific Aims

1. (Vascular index) Determine the ability of non-invasively derived proximal WSS to predict the gold standard, invasively derived hemodynamic data.

2. (Vascular and ventricular index) Determine the ability of non-invasively derived VVCR to predict the gold standard, invasively derived hemodynamic data.

Results/Conclusions

We enrolled 14 subjects, mean age of 12.7 years (5–20 years). Eleven of fourteen were female (78%). Our recruitment represented 80% success in
enrollment of subjects who met inclusion criteria. This success was attributed to the relationship that our PH team has with the families. The female gender represented a larger percentage in this pediatric group than larger published datasets. Similar to published data, 64% of the subjects had idiopathic PAH. Twenty-one percent was attributed to congenital heart disease: all were associated with atrial septal defects.

**Wall shear stress**

We combined the data derived from this prospective study with our retrospective data to further understand the role of WSS. In total, forty pediatric PAH patients and 26 age- and size-matched controls underwent magnetic resonance imaging (MRI) studies in order to compute time-resolved wall shear stress (WSS), oscillatory shear index (OSI), and vascular strain as measured by relative area change (RAC), and RV volumetric and functional parameters.

WSS$_{sys}$ and WSS$_{TA}$ were strongly statistically decreased in the PAH group, in both vessel segments (all $P < 0.0001$). Peak flow metrics did not differ in analyzed segments, except $Q_{avg}$, which was significantly larger in the RPA of PAH group. The OSI was significantly larger in PAH in the MPA ($P < 0.05$) but not in the RPA. The peak velocity $V_{max}$ measured through the described planes was significantly higher in the RPA of controls compared to PAH subjects (104.5 cm/s vs. 83.2 cm/s, $P < 0.05$) but interestingly this difference was not present in the MPA. Similarly, the average velocity $V_{avg}$ was significantly higher in both the RPA as well. The PC-MRI derived hemodynamic metrics did not show significant differences between the PAH WHO I and WHO II subgroups.

MPA WSS$_{sys}$ also displayed a positive logarithmic association with RVEF ($r = 0.65, P < 0.0001$) (see Figure 1). Strain in the MPA also positively correlated logarithmically with RVEF ($r = 0.63, P < 0.0001$). The formerly introduced trends existed between the RPA measured markers as well but without statistical significance. Also, the WSSSys measured in both vascular segments significantly correlated with indexed pulmonary vascular resistance in negative exponential fashion (Figure 2). The regression analysis in MPA ($r = -0.66, P < 0.001$) was more significant than in RPA ($r = -0.59, P < 0.01$).

We concluded that the WSS is reduced in pediatric PAH patients concomitantly with vascular strain, indicating stiffness within the proximal pulmonary vasculature. These results were also followed by increased OSI in MPA, which further has a potential to accelerate stiffness process. Furthermore, these vascular parameters have important association with RV myocardial function. The non-invasively computed WSS can be used as good marker of stiffness and cardiac function. The vascular characterization in proximal pulmonary conduit could provide important insights to pathogenesis and therapeutic effects in pediatric PAH population.

**Ventricular vascular coupling ratio.**

The mean VVCR from our group was $1.0 \pm 0.39$. Using SAS, we determined the beta value of VVCR to the 3 main RHC parameters, mainly PVR, mPAP, and PVR:SVR. Unfortunately, we did not find any significant relationship among our subjects.

We then combined our data with Gronigen Pulmonary Hypertension team—a national referral center for the Netherlands. We identified 31 PAH patients who had catheterization and CMR within 90 days were included from two specialized PH centers. VVCR$_{m}$ (defined as VVCR estimated by MRI) and VVCR$_{s}$ (single-beat method) were compared using regression analysis and Bland-Altman plots. Both were correlated to disease severity (PVRi, mPAP, CI) and adverse outcome (death, lung transplantation, atrial septostomy and intravenous medication). The area under the receiver operating characteristic curve (AU-ROC) and hazard ratios (HR) from Cox regression determined their value in predicting adverse outcome.

In the 31 patients included (17 from CHC and 14 from UMCG), median age was 14 years (0.3 – 23), median PVRi was 7.6 WU × m$^2$ (2.1 – 32). VVCR$_{m}$ and VVCR$_{s}$ were strongly correlated ($r = 0.78, p < 0.001$) with a mean difference of 0.2 and 95% of the differences between -0.3 and 0.7. Both had comparable significant correlations with disease severity and adverse outcome. Also, both VVCR$_{m}$ and VVCR$_{s}$ were shown to be of good prognostic value with AU-ROCs of respectively 0.84 and 0.90 and HRs (95%-CI) of 0.82 (0.70 – 0.96) and 0.69 (0.53 – 0.90).

We concluded that VVCR$_{m}$ and VVCR$_{s}$ are comparable in pediatric PAH. Furthermore, VVCR by MRI is a good predictor of outcome.
In summary, we found promising evidence that pulmonary vascular parameters have significant correlation with RHC derived parameters. This is consistent with our prior description of decreased WSS in the proximal vessels in pediatric PH. WSS studies throughout the literature have shown that both qualitative and quantitative descriptors play major roles in endothelial function and vascular tissue response. While the majority of these studies have been focused on the systemic circulation, the functional changes within the pulmonary endothelial lining are no less important and exhibit similar shear stress dependent changes. We believe that dilation of proximal conduit vessels decreases WSS and may be the principle driving mechanism through which mechano-transduction promotes vascular stiffness. While VVCR did not correlate with RHC parameters in our cohort, a larger cohort suggested otherwise. Although interesting, we understand the limitations of combining data from 2 institutions with different protocols. Nonetheless, VVCR is critical for understanding right ventricular adaptation in PH. With a larger dataset, we will be able to explore the relationship between WSS and VVCR, and how this relates to disease outcome. We surmise that vascular markers of function in pediatric PH will be the key factors in predicting RHC parameters.

Figure 1.
Regression analysis of peak WSS with systolic marker right ventricular ejection fraction. Positive logarithmic trend between two markers showed significant relationship. Based on observed trend between strain and the WSS, this relation suggests that cardiac systolic performance is affected by stiffening of the proximal pulmonary vasculature as well.
Figure 2. Regression analysis of peak WSS with right heart catheterization derived PVRi in MPA (left panel) and RPA (right panel). Both trends showed negative significant exponential relationships despite considerable mean period (236 days) between catheterization and CMR evaluation.
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Biographies

Ronald J. Oudiz, MD
ENTEELLIGENCE Steering Committee Chair
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LA Biomedical Research Institute at Harbor-UCLA Medical Center
Professor of Medicine
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Dr. Oudiz 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
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Dr. Farber has focused on research into pulmonary arterial hypertension (PAH) and the clinical care of PAH patients for over 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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Mardi Gomberg-Maitland, MD, MSc
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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
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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 200 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 multi-center, 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.
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Evangelos D. Michelakis, MD
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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
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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.”
Dr. Silver is a graduate of the University of Tennessee and Vanderbilt University School of Medicine. Dr. Silver completed training in Internal Medicine at the University of North Carolina at Chapel Hill. He trained in Pediatric Rheumatology with Dr. Barbara Ansell at London's Northwick Park Hospital, followed by training in Adult Rheumatology with Dr. Nathan Zvaifler at the University of California at San Diego. Dr. Silver joined the MUSC faculty in 1981, and served as Director of the Division of Rheumatology & Immunology from 1995 to 2018. In 2007, MUSC’s Board of Trustees named him a “Master Teacher” and bestowed the University’s highest academic recognition, “Distinguished University Professor”. He was named the 2007 “Doctor of the Year” by the Scleroderma Foundation. Dr. Silver’s research interests include the pathogenesis and treatment of scleroderma interstitial lung disease, as well as environmental exposures and the risk of systemic sclerosis. He maintains an active practice specializing in all aspects of scleroderma.

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 is currently Deputy Editor of Pulmonary Circulation and Associate Editor of Cardiovascular Research and on the editorial boards of several journals, including American Review of Respiratory and Critical Care Medicine and Circulation Research. 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 National and International conferences, Dr. Stenmark has published over 335 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. He has received continuous funding for his research from the NIH since 1984.
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Biographies

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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, Associate Editor of the American Journal of Physiology-Cell Physiology, and a regular member of the NIH Vascular Cell and Molecular Biology study section.