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 2015, the ENTELLIGENCE™ Young Investigator Program chose four new young investigators to receive ENTELLIGENCE awards based on their outstanding pulmonary vascular disease-related research proposals. 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 10 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 40 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 20 peer-reviewed journals, including American Journal of Physiology, American Journal of Respiratory and Critical Care Medicine, Chest, Circulation, 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, and visit the newly redesigned ENTELLIGENCE website at www.entelligencemd.org.

ENTEILLIGENCE thanks Dr. Adaani Frost (Baylor) for her outstanding contributions to the program as a Steering Committee member and welcomes Dr. Kurt Stenmark (University of Colorado) as a new Steering Committee member!

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: 10
Awards distributed: 50
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

Marshaleen Henriques-Forsythe, 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

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: D. Dunbar Ivy, MD
Project Title: Non-invasively derived vascular and ventricular markers predict invasively derived hemodynamic data in children with pulmonary hypertension
Overview of ENTELLIGENCE Awards

Awarded 2014

**Evan Brittain, MD**
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

**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

**Clyde J. Wright, MD**
University of Colorado School of Medicine
**Mentor:** Kurt R. Stenmark, MD
**Project Title:** Role of Macrophage ET-1 Expression in the Pathogenesis of Persistent Pulmonary Hypertension of the Newborn (PPHN) Caused by Perinatal Inflammation
  • Presented at 2015 Western Society for Pediatric Research Annual Meeting and 2014 Neonatal Cardiopulmonary Biology Young Investigators Forum

**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 meetings
  • Published in American Journal of Physiology-Lung Cellular and Molecular Physiology, 2014
Overview of ENTELLIGENCE Awards

2014 Award Winners

From left: Ronald J. Oudiz, MD [Program Chair], Evan Brittain, MD, Clyde J. Wright, MD, and R. Blair Dodson, PhD
Missing: Joshua M. Diamond, MD
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 2014 Keystone Symposium on Molecular and Cellular Biology
• Published in FASEB Journal, 2015 and Journal of Heart and Lung Transplantation, 2015 (under revision)

Michael L. O’Byrne, MD
Children’s Hospital of Philadelphia
Co-Investigators: Brian D. Hanna, MD, PhD; Steven M. Kawut, MD, MS; and Russell T. Shihohara, 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 (in press); American Journal of Cardiology, 2015; Catheterization Cardiovascular Intervention, 2015; Congenital Heart Disease, 2014; Journal of Thoracic and Cardiovascular Surgery, 2014; and Pediatric Cardiology, 2014

Tien Peng, MD
Hospital of the University of Pennsylvania
Mentor: Edward Morrisey, PhD
Project Title: The Role of Sonic Hedgehog (Shh) Signaling in Pulmonary Arterial Hypertension

Keivan Zandinejad, MD
Case Western Reserve University
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 and American Journal of Respiratory Cell and Molecular Biology, 2013

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 Conferences and 2012 American Heart Association meeting
  • Published in Chest, 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
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 meeting

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 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 Pulmonary Circulation, 2011 and 2013, and Biology of Sex Differences, 2012
- Published abstracts: American Journal of Respiratory and Critical Care Medicine, 2011 and 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

**Jason Gien, MD**
University of Colorado Health Sciences Center
**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 meetings
- Published in American Journal of Physiology Lung Cellular and Molecular Physiology, 2013 and 2014 and Pediatric Research, 2013 and 2014

**Michael J. Passineau, PhD**
Allegheny Health Network
**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 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
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 Conferences
• Published in PLoS One, 2012

Sean E. McLean, MD
University of North Carolina at Chapel Hill
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: D. 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 meeting 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
University of Pennsylvania School of Medicine
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
• 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 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
John A. Burns School of Medicine
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
UAB School of Medicine
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
  • 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 meeting
  • Published in American Journal of Physiology: Lung Cellular and Molecular Physiology, 2010

Yerem Yeghiazarians, MD
University of California, San Francisco
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 European Respiratory Journal, 2008
  • Published abstracts: Circulation, 2008 and 2010; American Thoracic Society (ATS) meeting, 2007; and ATS International Conference, 2007

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 of Heart and Lung Transplantation meeting

Giuseppe Valacchi, PhD
University of Siena
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 School of Medicine
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
Genetic and sex determinants of hyper-responsiveness to SU5416 alone producing severe pulmonary arterial hypertension in a sub-strain of Sprague Dawley rats

Introduction:
Pulmonary arterial hypertension (PAH) is a progressive disease with unclear etiology characterized by increases in mean pulmonary arterial pressure (>25 mmHg) leading to right ventricular hypertrophy and heart failure, and ultimately death. While pharmacotherapy can slow the progression of the disease, there is no cure.

Background:
PAH is a multifactorial disease with a strong genetic component. Mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene account for a substantial proportion of hereditary and sporadic disease, but the penetrance is low (~20%). A multitude of environmental factors have also been implicated in PAH, including exposure to toxins, anorexigens, high shear stress and viral infections; however, the exact pathobiology still remains unclear. Recently, a new animal model has been introduced that better reproduces the salient pathological features of human PAH, involving the injection of a single dose of the VEGFR2 antagonist, SU5416 (SU), followed by a 3-week exposure to chronic hypoxia (CH). SU is believed to cause lung endothelial cell apoptosis that, together with CH as a “second hit,” results in the emergence of growth dysregulated, quasi-neoplastic vascular cells that form characteristic plexiform-like arterial lesions. Our lab has studied strain differences in the SU/CH model of PAH. Interestingly, we observed that a specific sub-strain of the Sprague Dawley rats obtained from a Canadian supplier was hyper-responsive to SU and developed a progressive severe PAH phenotype in response to a single SU injection, even in the absence of CH. The hyper-responsive phenotype was seen in 70-75% of the male rats; whereas only 25-30% of the female rats were responsive to SU alone. Furthermore, crossing non-responsive male and female animals markedly decreased the proportion of hyper-responsiveness in the F1-generation (male: 15%; female: 0%), highly suggestive of a genetic basis for the hyper-responsive phenotype.

Hypothesis and Objectives:
We hypothesize that hyper-responsiveness to SU alone is conferred by as yet unknown genetic determinant(s). Moreover, the influence of this genetic determinant(s) is importantly modified in a sex dependent manner, likely by the action of female sex hormones.

Specific Aim 1:
To identify genetic determinant(s) in the SU hyper-responsive Sprague Dawley rats using the exome sequencing or the whole genome sequencing in collaboration with the STAR rat genome consortium. This work could uncover novel genetic factors associated with PAH.

Specific Aim 2:
To explore the role of sex hormones in modifying the SU hyper-responsive phenotype using surgical (e.g. oophorectomy/castration) or pharmacological (e.g. hormone replacement or inhibition) manipulations.

Specific Aim 3:
To explore the mechanistic relevance of “modifier” genes identified in Aim 1 in the pathogenesis and treatment of PAH using human material (DNA, lung tissue, vascular cells and blood) available from patients with idiopathic and hereditary PAH.
The Prevalence and Pathogenesis of HIV-Associated Pulmonary Arterial Hypertension among Underserved Urban Populations

Introduction:
Pulmonary arterial hypertension (PAH) is a non-infectious complication of HIV which has become increasingly important as HIV survival has increased. Although HIV is an 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.

Background:
The three-year survival for HIV-PAH is significantly higher for persons diagnosed as New York Heart Association (NYHA) functional classes I & II (~85%) compared to patients diagnosed as NYHA functional classes III & IV (~30%). Unfortunately, HIV-PAH is associated with non-specific symptoms; thus, it is often diagnosed late, leading to the need for more expensive therapeutic options and a greater health burden. African-Americans may have an escalating risk for developing HIV-PAH given the rapid increase in HIV infection among African-American women. In addition, studies suggest that the prevalence of preclinical HIV-PAH may be higher than that of clinically diagnosed HIV-PAH. If this is true, routine PAH screening should be considered for persons with HIV, given the poor prognosis of HIV-PAH when diagnosed late or left untreated. This study will use targeted screening to determine the prevalence of HIV-PAH among African-Americans in Atlanta with a view to developing screening guidelines for this high-risk population.

The HIV protein Nef has been implicated in HIV-PAH pathogenesis, but the exact mechanism is unknown. Additional studies are needed to explore the role of Nef in HIV-PAH pathogenesis among humans. This study will 1) investigate the relationship between HIV-PAH and exosomal Nef and 2) determine if exosomal Nef has predictive or prognostic value with regards to the development and progression of HIV-PAH, respectively. Knowledge gained regarding exosomal Nef’s role in HIV-PAH pathogenesis may prove useful in developing screening guidelines and may identify pathways that could be targeted to intervene in HIV-PAH pathogenesis.

Hypothesis and Objectives:
We hypothesize that: 1) targeted screening for HIV-PAH among an urban underserved community will improve the early detection of PAH; and 2) there is a relationship between HIV-PAH and the levels of exosomal Nef.

Specific Aim 1:
To determine whether targeted screening for HIV-PAH among an urban underserved community improves early detection of PAH.

Specific Aim 2:
To determine whether there is a correlation between PAH and HIV Nef-driven exosome-linked factors.
Introduction:
Pulmonary arterial hypertension is a disease characterized by the vascular remodeling of the pulmonary arterioles, leading to increased pulmonary vascular resistance and right ventricular failure. A number of microRNAs have emerged as promising therapeutic targets, but significant hurdles remain before they can be pursued in clinical studies.

Background:
Pulmonary arterial hypertension (PAH) is a disease of exceedingly high mortality with limited therapeutic modalities. Work from the Chun (mentor) laboratory and others have identified key microRNAs involved in the disease pathogenesis, including miR-424, miR-503, miR-204, miR-130, miR-301, miR-21, miR-145, and miR-124. Although these studies have all identified novel pathways in experimental models with strong translational applicability to human disease, a number of limitations prevent advancement of a microRNA based therapeutic strategy in PAH. First, there is currently no standardized delivery strategy for the microRNA mimics or antagonists to the pulmonary vascular cells. Second, although each of these studies has demonstrated varying degrees of therapeutic efficacy for the specific microRNAs of interest, a direct comparison of efficacy using a standardized delivery technique and disease model has never been investigated. The current proposal will identify an effective delivery strategy for oligonucleotide based therapy to the pulmonary vasculature. It will then utilize this strategy to compare the efficacy of targeting candidate microRNAs known to be involved in the pathogenesis of PAH, to identify the best therapeutic targets for development of early clinical trials. We will utilize novel, vascular targeting nanoparticle based delivery strategies, in conjunction with robust experimental rodent models of pulmonary hypertension, to pursue these studies.

Hypothesis and Objectives:
We hypothesize that a nanoparticle based approach for delivery of microRNA mimics or antagonists is an effective strategy for treatment of pulmonary arterial hypertension. We will determine the most effective delivery strategy and identify the strongest microRNA candidate(s) with the goal of developing early clinical studies.

Specific Aim 1:
Develop and identify the optimal nanoparticle composition and delivery strategy for targeting oligonucleotides to the pulmonary vasculature. We will test the efficacy of modified nanoparticle compositions to achieve selective delivery of microRNA mimics or antagonists in vitro to primary cells of the pulmonary vascular cells.

Specific Aim 2:
Identify the microRNA targets with the most effective therapeutic efficacy in rescuing preclinical models of pulmonary hypertension. We will utilize the optimal nanoparticle composition identified in Specific Aim 1 to test the efficacy of targeting multiple microRNA candidates in vivo, using the monocrotaline and the SU-5416/hypoxia models of pulmonary hypertension.

Specific Aim 3:
Evaluate the feasibility of combining microRNA targets to augment therapeutic efficacy. We will determine if a combination of the best microRNA mimics/antagonists (identified in Aim 2) can achieve an additive or synergistic effect to augment therapeutic efficacy.
Introduction:
Prognosis in childhood pulmonary hypertension (PH) remains poor. Research efforts in pediatrics are complicated by the disease’s multifactorial nature and potential risks posed on subjects. The single, standard diagnostic measure is pulmonary vascular resistance. This is only one of many factors predictive of mortality and does not reflect ventricular dysfunction.

Background:
Ventricular-vascular coupling (VVC) is critical in understanding the interaction between the pulmonary vasculature and the myocardial function in pulmonary hypertension (PH). The gold standard for determining VVC is cardiac catheterization. The invasive nature of this procedure has led clinicians to look towards non-invasive imaging modalities. Recently, studies have demonstrated that VVC can be estimated with CMR in PH. This can reduce radiation and anesthesia exposure to PH children requiring longitudinal monitoring. We have previously shown that VVC by CMR has high predictability for vascular acute reactivity in pediatric PH. In a more recent study, we prospectively recruited 46 pediatric PH and 26 normotensive controls to evaluate VVC by CMR. Bivariable analysis indicated significant correlation between VVC and current WHO score (p=0.02), WHO score progression over the past year (p<0.01), and the current use of intravenous/subcutaneous therapy (the most intensive forms of PH therapy) (p<0.01). The subject group in this recent study is small and is a significant limitation to the interpretation of these data. That, however, does not negate the importance of our findings and is the stepping stone to posing the question for clinicians: can serial catheterization in children with PH be avoided if non-invasive imaging can provide accurate and adequate cardiovascular data for the management of these patients? This can potentially open wide the door for facilitating increased research in a vulnerable population that is unique from the adult population in whom the majority of PH research has been done.

Hypothesis and Objectives:
Furthermore, CMR-derived ventricular-vascular coupling correlates with hemodynamic data by cardiac catheterization and 0-D computational model. VVC is predictive of future clinical deterioration, including WHO progression and escalation of medicinal needs.

Specific Aim 1:
VVC correlated with hemodynamic data. VVC has been shown in adults, excluding those with congenital heart disease, to correlate well with hemodynamic data, including pulmonary vascular resistance. Our aim is to evaluate VVC with hemodynamic data, including PVR, pulmonary vascular stiffness, transpulmonary gradient, and right ventricular end-diastolic pressure.

Specific Aim 2:
VVC by CMR in PH children has predictive value in disease progression and outcomes. We will correlate VVC to future WHO classification progression, future medicinal requirements, and progression of 6-minute walk. This will determine predictive value of VVC and its role in understanding maladaptive ventricular vascular remodeling in pediatric PH.

Specific Aim 3:
VVC by CMR correlated with a validated 0-D right ventricular-pulmonary artery computational model to assess differences in right ventricular-pulmonary response to altered hemodynamics. The 0-D model will allow the reconstruction of 2 pressure-volume loops: one at baseline and one that corresponds to a challenge condition, similar to the catheterization laboratory.
Dysregulation of Lipid Metabolism and Right Ventricular Function in Pulmonary Arterial Hypertension

Introduction
Right ventricular (RV) failure is the predominant cause of death in pulmonary arterial hypertension (PAH). No RV-specific therapies are available, in part because the underlying mechanisms of RV dysfunction are poorly understood. The development of RV-specific therapeutic targets would represent a major advance in the treatment of PAH.

Preliminary Data
We have found: 1) Elevated circulating free fatty acids (FAs) in PAH patients compared to age, gender, and BMI matched controls. 2) Elevated long-chain acylcarnitines in peripheral blood in PAH patients. 3) Decreased expression of enzymes involved in carnitine shuttling in pulmonary microvascular endothelial cells with BMPR2 mutation. 4) Decreased myocardial acylcarnitines associated with worse RV function and myocardial steatosis in a murine model of PAH. 5) Marked RV lipid deposition detected in vivo in patients with PAH and in explanted hearts from humans with PAH. 6) Successful trans-cardiac blood sampling and possible decreased trans-cardiac FA consumption in PAH patients compared to control.

We hypothesize that defects in FA metabolism are common in PAH and contribute to RV failure.

We propose to test this hypothesis with the following specific aims:
1. To test the hypothesis that defects in FA metabolism are common in PAH and are associated with insulin resistance, RV function, and exercise capacity. We will perform metabolomics analysis focusing on the long-chain acylcarnitine oleoylcarnitine – the most abundant acylcarnitine in our preliminary data – in 30 patients with idiopathic PAH (IPAH) and 30 matched controls.
2. To test the hypothesis that trans-cardiac metabolic profiling will demonstrate decreased uptake of FA metabolites and increased glycolysis. In this aim, we will interrogate in vivo FA metabolism by measuring trans-cardiac (pulmonary artery wedge to coronary sinus) metabolite gradients to determine the relationship between substrate metabolism and RV function. We will prospectively sample trans-cardiac FA and glucose metabolite gradients in 20 PAH patients undergoing right heart catheterization and same-day cardiac magnetic resonance imaging (MRI).
Clinical and Biomarker Risk Evaluation of Pulmonary Hypertension in Lung Transplantation

Pulmonary arterial hypertension (PAH) is a severe, progressive disorder with a median survival of 2.8 years if left untreated. While certain therapies are effective, these treatments do not cure PAH and do not appear to benefit patients with pulmonary hypertension (PH) secondary to parenchymal lung disease (WHO Group 3). Lung transplantation remains the only available therapeutic option for PAH refractory to treatment and severe WHO Group 3 PH.

Unfortunately, PH related to either PAH or parenchymal lung disease significantly increases the risk of post-lung transplant primary graft dysfunction (PGD), a form of acute lung injury that is the major cause of early post-transplant morbidity and mortality. Patients with severe PH have double the risk of PGD after transplant compared with those without PH, and those with PAH have more than three times the risk of PGD. Despite the enormous adverse impact of PH on transplant, there is poor understanding of the clinical predictors and biochemical mechanisms linking PH to PGD, preventing the institution of potential preventative or treatment strategies before or early after surgery.

Long pentraxin-3 (PTX3) is produced by macrophages and dendritic cells as a result of interleukin-1 (IL-1) and toll-like receptor (TLR) signaling pathways, and indicates activation of innate immunity. We have preliminary data showing that higher plasma PTX3 in PH may increase the risk of PGD in these patients. We have demonstrated that elevated post-transplant plasma complement levels are associated with PGD and higher post-transplant plasma PTX3 levels are associated with increased risk of PGD. We have also found that genetic variation in PTX3 is associated with PGD risk.

Furthermore, a recent case-control study demonstrated higher mean plasma PTX3 concentrations in patients with PAH compared to control subjects, suggesting that PTX3 levels may serve as an effective diagnostic biomarker for PAH. The clinical and biochemical risk factors that determine which patients with PH (including PAH and PH with parenchymal lung disease) will develop PGD will be the focus of this application.
Intrauterine Hemodynamic Stress Mechanisms of Fetal Pulmonary Vascular Injury

Biomechanical forces are essential for normal fetal pulmonary vascular growth and development, but increased hemodynamic stress in utero contributes to the pathogenesis of neonatal pulmonary hypertension (PPHN). Impaired endothelial function results from high pulmonary vascular resistance in PPHN, but mechanisms through which hemodynamic stress causes the PPHN remain uncertain. At birth, rapid physiologic adaptation is required for the lung to assume its essential postnatal role of gas exchange. The normal transition of the pulmonary circulation includes hemodynamic changes of immediate and progressive fall in pulmonary vascular resistance (PVR) allowing an eight-fold increase in pulmonary blood flow. Increased oxygen tension, ventilation, and shear stress are factors that contribute to the fall in PVR at birth, largely through the release of endothelium-derived vasodilators, including nitric oxide (NO) and prostacyclin, and decreased production of vasoconstrictors, such as endothelin-1 (ET-1). Failure to develop or sustain this drop in PVR at birth leads to hypoxemia and constitutes clinical syndrome of PPHN. Successful transition of the pulmonary circulation from prenatal to postnatal life requires precise and highly responsive vascular adaption to changes in hemodynamics as well as diverse growth factors and signaling. Previous models of PPHN from our laboratory have shown that chronic hemodynamic stress alters endothelial cell phenotype as characterized by abnormal vascular tone, growth, and structure, with decreased NO production and up-regulation of ET-1. In addition, fetal pulmonary artery endothelial cells (PAEC) from PPHN sheep have persistent abnormalities of growth, angiogenesis and production of vasoactive mediators. However, biomechanical mechanisms that disrupt normal vascular development and contribute to the pathogenesis of PPHN are incompletely understood.

1) Normal fetal PAECs will exhibit a phenotype similar to PPHN PAECs in vitro—increased vasoconstriction ET-1 but reduced vasodilator NO—in pathologic shear stress environment.

2) Hypoxia will augment the adverse effect of hemodynamic stress to increase production of increased vasoconstrictors but decreased vasodilators.

3) ET-1 blockade through SiRNA or bosentan will preserve fetal PAEC phenotype in hemodynamic stress and hypoxia.
Role of Macrophage ET-1 Expression in the Pathogenesis of Persistent Pulmonary Hypertension of the Newborn (PPHN) Caused by Perinatal Inflammation

PPHN affects 2-6% of births and is the most common cause of cardiopulmonary failure in the neonate. Of these patients, >40% fail medical therapy and need ECMO or die. Although exposure to inflammation (chorioamnionitis, sepsis) causes 30% of the cases of PPHN, the specific cells and signaling pathways mediating this response are poorly understood. The significance of this proposal is that we will identify novel therapeutic targets for these critically ill neonates by defining the mechanistic link between perinatal inflammatory stress and PPHN.

Whether inflammatory stress-induced ET-1 expression contributes to PPHN, and whether the use of ET receptor antagonists is indicated in these patients remains largely unexplored. Although the pulmonary endothelium has been considered the primary source of ET-1, macrophages secrete ET-1 in response to pro-inflammatory stimuli. With inflammatory stress, there is a massive influx of macrophages into the fetal lung. Additionally, the rate-limiting step of ET-1 bioavailability is gene transcription.

Determining the transcriptional regulation of inflammatory-stress induced ET-1 expression may identify additional therapeutic targets. The dimeric transcription factor NFκB regulates the cellular response to inflammatory stress, and the ET-1 promoter is known to have NFκB binding sites. We hypothesize that antenatal inflammation causes PPHN in part due to NFκB regulated ET-1 expression from fetal lung macrophages.

Specific Aims:
1) Demonstrate that TLR4-NFκB signaling drives LPS-induced macrophage ET-1 expression.
   Lipopolysaccharide (LPS)-stimulated macrophages will be tested for NFκB activation and ET-1 expression. The effect of attenuated TLR4/NFκB signaling on LPS-induced ET-1 expression will be tested.
2) Establish that antenatal inflammation induces NFκB-regulated ET-1 expression in fetal lung macrophages.
   The effect of antenatal inflammation (intraamniotic LPS) on pulmonary macrophage NFκB activation, ET-1 expression and PPHN will be determined. Mice with macrophage-specific disrupted TLR4/NFκB signaling will be assessed.
3) Test whether pharmacologic NFκB or ET receptor blockade will attenuate antenatal inflammation induced PPHN.
   The effect of postnatal ETA or nonselective ET receptor blockade on PPHN will be compared to global NFκB inhibition in newborn mice exposed to IA LPS.
Complement Activation as a Novel Mechanism of Endothelial Activation in PH

Background
Pulmonary hypertension (PH) is a fatal disease with high mortality. Its pathogenesis involves vasoconstriction and pulmonary vascular remodeling due to endothelial dysfunction as defined by 1) upregulation of adhesion molecules, 2) platelet activation and aggregation, 3) endothelial cell apoptosis, and 4) increased thrombogenicity. Obstruction of the pulmonary vasculature leads to resistance rising progressively over time to promote right heart failure and death. Current therapies target this constrictive phenotype aiming to improve vasodilation, but with only limited success. The presence of immune cells has been observed in lung lesions of PH patients in addition to case studies showing a benefit to the treatment with anti-inflammatory drugs. Our group focuses on the still largely unexplored role the immune system plays in PH. The importance of the complement system as part of the innate immune system is well established and studied in many immune diseases (systemic lupus). We recently observed increased complement deposition in lung sections from patients with idiopathic PH and showed that activation of the complement system contributes to its development in mice.

With several reports on a role for complement in acute lung injury little is known in regard to PH. One study observed elevated complement levels in PH patients. We recently showed that genetic ablation of complement in mice leads to decreased platelet activation attenuating the development of hypoxia-induced PH. Preliminary data further suggest that recombinant CR2-Crry, an inhibitor of complement activation, may limit the development of hypoxia-induced PH. The success of CR2-Crry has already been shown in models of ischemic reperfusion injury, stroke, collage-induced arthritis, and acute lung injury.

Specific Aim 1: Is the pulmonary endothelium activated by complement in vitro and in vivo in hypoxia-induced PH? 1A: Endothelial activation will be assessed in human pulmonary endothelial cells after addition of activated complement by a) flow cytometry using P-selectin, E-selectin, VCAM, Tissue Factor as markers b) Tunel staining for apoptosis. 1B: Wildtype and complement deficient mice will be exposed to a time course of hypoxia with endpoint measurements of right ventricular pressures, right ventricular hypertrophy, pulmonary vascular remodeling, platelet activation, and endothelial activation.
Specific Aim 2: Can the complement inhibitor CR2-crry halt or reverse the development of hypoxia-induced PH? 2A: Preliminary data show that a trial dose of CR2-crry partially attenuates hypoxia-induced PH. 2B: The potential of CR2-crry as therapeutic will be studied by testing if it can halt the progression or reverse already established PH. Endpoints for this aim include measurements of right ventricular pressures, RV hypertrophy, pulmonary remodeling, platelet activation, and endothelial activation.

Results
Complement activation is a highly evolutionary conserved innate immune mechanism. Here we proposed to study PH as an inflammatory proliferative disease. While our experimental PH model is based on chronic hypoxic exposure, we here focused on early initiating events corresponding to the common fast response of complement activation.

We exposed wildtype mice to hypoxia (10% O₂) over a 6 hr time-period, and harvested the organs/blood for evaluation of innate immune markers. We observed a robust and significant increase at 6 hrs of the soluble complement component C5a, a complement marker often missed due to its short lifetime. Other common inflammatory markers (IL-6, ET-1, IL-2, INFϒ) remained unchanged.

We already reported that complement C3 contributes to the development of hypoxia-induced PH. In the classical view C3 activation leads to activation of C5 downstream. Others recently also described C5 activation independent of C3. We thus exposed C5 null mice to chronic hypoxia. As expected, complement C5 contributes at least in part to experimental PH, since its lack attenuated right ventricular systolic pressures, interestingly with no significant changes in RV hypertrophy. Treatment with the complement CR2-crry also attenuated hypoxia-induced PH.

We previously reported on the contributory role of the innate immune receptor toll-like receptor 4 (TLR4) in PH. Murine lungs were stained for complement deposition. Interestingly, pulmonary arterioles (<150 microns) showed minimal, if any, complement deposition in the hypoxic TLR4 null mice (green: autofluorescence, blue: nuclear stain).

While complement causes in vitro platelet activation, it is significantly blunted in platelets isolated from TLR4 null mice. These results further emphasize the complexity within the innate immune system and its various factors ranging from cellular immunity (platelets), to humoral immunity (complement), and to ligand-receptor activation, (TLR4).

Conclusion
PH is a complex disease. Funding of this proposal allowed us to better understand the role of the complement system in PH. Our lab focuses mainly on the innate immune system and these studies allowed us to find new connections between various players: the complement system, TLR4, the coagulation cascade and platelets. Maybe combination therapy targeting not just the vasodilatory pathways but also the immune system will finally allow us to stop and reverse this fatal disease.

This was my first monetary award in my academic career and has been a wonderful, productive experience. It allowed me to successfully apply and obtain further funding, including a scientist development grant from the AHA.
Idiopathic pulmonary fibrosis (IPF) is a terminal disease characterized by progressive fibrosis and respiratory insufficiency and a median survival of 2.5 to 5 years (1). IPF has an incidence of approximately 163 cases/million (2). The prevalence of pulmonary hypertension (PH) in patients with IPF has been reported to range between 32-85% (3) and is a marker of increased morbidity and mortality (3). Despite the strong association of PH and mortality, there are currently no effective treatments for this disorder, in part due to our poor understanding of the underlying mechanisms that lead to PH in IPF (3). Research and therapeutic efforts have largely focused on idiopathic pulmonary arterial hypertension (IPAH), a form of PH lacking lung interstitial involvement with an incidence of 2-4 cases/million (4).

Increased knowledge of the mechanisms that lead to PH in patients with IPF is needed to support the development of novel therapies for this fatal disease.

PH is defined by a mean pulmonary arterial pressure ≥ 25 mmHg diagnosed by right-heart catheterization. This increased pressure is caused by extensive remodeling of the vasculature resulting from enhanced proliferation of pulmonary artery endothelial and smooth muscle cells (PASMC), muscularization of previously non-muscular arteries, increased vascular tone, and formation of complex vascular lesions (5). However, the mechanisms that lead to the development of PH, particularly that associated with chronic diseases of the lung remain elusive. Altered extracellular matrix (ECM) turnover is a feature of several pulmonary diseases including acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and IPF (6). Hyaluronan (or hyaluronic acid) is an abundant component of the lung extracellular matrix (7). Hyaluronan is synthesized by one of three hyaluronan synthases (HAS 1, 2, or 3). The most prevalent form of hyaluronan is the 1,000 kDa high-molecular-weight (HMW-HA) (8) and is thought to modulate protective effects (9). However, degradation of this 1,000 kDa HMW-HA to low-molecular-weight (LMW-HA) fragments by hyaluronidases can promote deleterious effects that contribute to disease (9). Increased levels of hyaluronan have been observed in IPF patients and in remodeled vessels of patients with IPAH (10). Despite these independent observations in IPF and IPAH, the role of hyaluronan in the development of PH secondary to IPF has not been examined. Our hypothesis is that elevated hyaluronan leads to the development of PH in IPF.

The following key aims were tested:

1) Examine whether components of the hyaluronan system are altered in PH secondary to IPF. Transcript and protein analysis will be performed to identify changes in expression of hyaluronan synthases and hyaluronidases in lung explants from patients with IPF with and without PH.

2) Examine the effect of hyaluronan-synthesis inhibition in a model of lung fibrosis and PH. The hyaluronan synthase inhibitor 4-methylumbellifluorone (4-MU) will be tested in a mouse model of PH secondary to lung fibrosis. Consistent with previously published results in patients with COPD and PH (11) we report an increased deposition of hyaluronan in remodeled vessels of patients with IPF and PH (Figure 1A). We also demonstrate a significant correlation between HAS2 and HAS3 expression levels and mPAP values for patients diagnosed with IPF with and without PH (Figure 1B, C). These observations suggest a pathological role for increased hyaluronan synthesis through elevated HAS2 expression in patients with IPF + PH.
The Role of Hyaluronan in Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis (IPF) (continued)

Furthermore, experiments using isolated 1ary pulmonary arterial smooth muscle cells from normal controls or patients with PH secondary to COPD show increased HAS2 expression, in particular for the activated dimer of HAS2 (Figure 1D). Taken together, these observations point at increased hyaluronan and activation of HAS2 in PASMCs as a main driver of elevated hyaluronan synthesis, in patients with IPF + PH. Furthermore, we identified a significant correlation between hyaluronidase 2 (HYAL2), an enzyme responsible for the breakdown of hyaluronan and NRF2 a marker of oxidative stress that can also contribute to the generation of pathogenic smaller fragments of hyaluronan, that suggest breakdown of HMW-HA to pathogenic LMW-HA fragments.

In order to study the effects of inhibition of hyaluronan synthesis in a model of PH secondary to lung fibrosis, we exposed C57BL/6 mice to BLM as described previously (12). On day 15 of BLM exposure, mice were treated with chow containing the hyaluronan synthesis inhibitor 4-Methylumbelliferone (4MU) or control chow. Our results show that BLM exposed 4MU-treated mice were able to show reduced right ventricle systolic pressures (RVSP) compared to BLM-exposed mice (Figure 2A). These results were accompanied by reduced evidence of right ventricle hypertrophy (RVH), assessed using the Fulton index, in 4MU-treated, BLM-exposed mice (Figure 2B). In line with these observations, we report reduced arterial oxygenation, a measure of alveolar gas exchange, measured by SpO\textsubscript{2} in BLM-treated mice that were inhibited in 4MU-treated-BLM-exposed mice (Figure 2C). Immunohistochemistry (IHC) for hyaluronan revealed increased deposition in BLM-exposed mice that was reduced in BLM-exposed but 4MU treated mice (Figure 2D). Double immunofluorescence (IF) for α-smooth muscle actin (αSMA) and HAS2 revealed increased αSMA deposition consistent with vascular remodeling following BLM exposure, that co-expressed for HAS2 (Figure 2E). These results are consistent with our studies in human PASMC where increased HAS2 expression was observed in cells from a patient with COPD + PH. Treatment with 4MU was able to inhibit expression of HAS2 and was consistent with reduced deposition of αSMA (Figure 2E). In line with these observations, we report reduced expression of HAS2 transcript levels in 4MU-treated-BLM-exposed mice compared to BLM-exposure (Figure 2F). Taken together, our results show that treatment with 4MU can be useful for the treatment of PH in a model of PH secondary to lung fibrosis. Interestingly, our results did not show significant differences in fibrotic parameters between BLM-exposed-vehicle-treated mice and BLM-exposed-4MU-treated mice that suggest differential mechanisms in the pathogenesis of PH and fibrosis.

Taken together, our results point at a pathological role of hyaluronan in the development of PH secondary to lung fibrosis and suggest that therapies targeting hyaluronan could be used for the treatment of PH secondary to lung fibrosis.
The Role of Hyaluronan in Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis (IPF) (continued)

References:

Figure 2. RVSP (A), Fulton index (B), SpO2 levels (C), IHC for HA (blue- D), IF for αSMA (red), HAS2 (green) or αSMA/HAS2 merge (E) and HAS2 transcript levels from mice exposed with BLM or PBS and treated with control chow (vehicle) or chow with 4MU. * P≤ 0.05 between PBS and BLM (vehicle). # P≤ 0.05 between BLM + Vehicle and BLM + 4MU Scale bar represent 200µm (D) or 100 µm (E).
Background
Pulmonary hypertension (PH) affects 2.1-3.7 children per million (1-3), but remains an extremely morbid condition with a five-year survival of 65-75% (1, 2, 4-6). Hemodynamic measurement obtained via right heart catheterization is an important tool in the diagnosis, classification, and longitudinal care of these patients (7, 8). However, cardiac catheterization in children with PH carries a risk of cardiac arrest of 4.5-5.7 per hundred (9, 10), which is over ten times the risk of catheterization in children with other diagnoses and in adults with PH (11-20). The determinants of peri-procedural morbidity and mortality are not well defined, particularly in children. Relatively small procedural volumes at single centers and differences in practice at different centers are obstacles to the study of outcome in children with PH. Identification of risk factors for adverse outcomes could provide an opportunity to intervene and improve safety of catheterization in children with PH and to define high-quality care and identify centers of excellence in the field.

Aims:
We performed a multi-center retrospective cohort study assessing risk factors for catastrophic adverse events using the Pediatric Health Information Systems (PHIS) database, an administrative database. We hypothesized that patient level risk factors, such as age, etiology of PH and indicators of severity of illness would influence the peri-procedural risk of death and catastrophic outcome.

Methods:
Data Source: The PHIS is an administrative database that contains data from inpatient, emergency department, ambulatory surgery, and observation encounters from 43 not-for-profit, tertiary care pediatric hospitals affiliated with the Children’s Hospital Association (Overland Park, KS) in the United States.

Study Population: We included children and adults, age 0-21 years carrying a diagnosis of PH as identified by International Classification of Disease, ninth revision code (ICD-9). We excluded subjects from centers 1) reporting fewer than 25 cardiac catheterization procedures per year or 2) not reporting cardiac catheterization procedures in at least 4 of 6 years during the study period to insure that only centers with stable reporting practices were included. Subjects for whom the date of catheterization was missing were also excluded as were those undergoing electrophysiology studies or cardiac catheterization on mechanical circulatory support.

Study Measures: Data were extracted from the PHIS database by direct query using ICD-9 codes for diagnoses and procedures as well as Clinical Transaction Codes for pharmaceutical products. The primary outcome was a composite of death or initiation of mechanical circulatory support (extracorporeal membrane oxygenation, percutaneous ventricular assist device, or balloon pump) within 1 day of cardiac catheterization. Sub-classification of PH was limited in this data set to 1) idiopathic pulmonary arterial hypertension (IPAH), 2) pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD), 3) PH with cardiomyopathy, 4) PH in the context of a heart transplant, and 5) chronic thromboembolic pulmonary hypertension (CTEPH). Diagnoses are based on ICD-9 codes extracted by coders at member institutions based on physician documentation and are directly sent to CHCA. Further detail regarding
Adverse Outcomes Associated with Cardiac Catheterization in Children with Pulmonary Arterial Hypertension (continued)

diagnoses and clinically relevant data such as oximetry, pressure data, laboratory, and imaging data are not available in the dataset. Procedural data included whether a trans-catheter intervention was performed during the case.

Statistical Analysis: Descriptive statistics were expressed as mean ± standard deviation, median (range and inter-quartile range (IQR)), and percentages and counts as appropriate. Multiple catheterizations were performed on individual subjects over the study period. All eligible procedures were included, and all statistics are reported per procedure except where noted. The association between patient level characteristics and composite outcome was assessed using mixed-effects multivariate generalized linear models (with logistic link) (22). To account for covariance within centers and between multiple procedures performed in a single individual, random intercepts were added to the model for each center and patient(23). Based on previous research(24), an interaction term for age category and history of prematurity was included. All analysis was performed using Stata MP v13 (Statacorp, College Station TX). Threshold for statistical significance was set at p<0.05.

Results:

Study population: The study population and observed outcomes are summarized in Table 1.

Multivariate model for risk factors associated with death or mechanical circulatory support within 1 day of cardiac catheterization

Table 2 shows the results of a mixed effects multivariate regression model of the risk factors for death or mechanical circulatory support within 1 day after catheterization. Using conditional standardization for other covariates, the adjusted risk of composite primary outcome within one day of catheterization was 3.3% (95% CI: 1.9-5.5%). Several factors were independently associated with an increased risk. Neonates with history of prematurity (OR: 4.95, p=0.02) and infants without prematurity (OR: 1.61, p=0.007) were associated with an increased risk of the composite outcome relative to subjects between 1 and 8 years of age. Similarly, older children (age 8-18) had a reduced risk of the composite outcome (OR: 0.45, p=0.02). Age greater than 18 years was not associated with a significant change in the risk of adverse events. In terms of diagnosis, relative to IPAH there were no significant differences in risk of composite outcome for subjects with APAH-CHD, cardiomyopathy, or chronic thromboembolic pulmonary hypertension. PH after heart transplant, however, was associated with significantly increased risk (OR: 2.78, p=0.005).

Several aspects of pre-procedural medical care were independently associated with the risk of catastrophic adverse outcome. Hemodialysis was associated increased risk (OR: 19.40, p<0.001), as was receipt of systemic vasodilators (OR: 1.85, p=0.007). Receipt of any PH medications was associated with reduced risk of adverse outcome (OR: 0.38, p<0.001). Mechanical ventilation and receipt of inotropes were not associated with risk of composite outcome.

Conclusion:
The risk of catastrophic adverse outcome following cardiac catheterization in children with PH is significantly higher than in children with other diagnoses. Younger age, pre-procedural systemic vasodilators, and cardiac operation within the same admission all increase the risk of an adverse event, while treatment with PH medications was associated with reduced risk. Further study is necessary to determine how these factors interrelate and whether a predictive model based on these factors would be useful to improve outcomes of children and young adults undergoing cardiac catheterization for PH.
### Table 1: Study Population

<table>
<thead>
<tr>
<th>Catheterization Procedures (n)</th>
<th>6,339</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Patients (n)</td>
<td>4,401</td>
</tr>
<tr>
<td>Age (years)</td>
<td>2.2 (IQR: 210 days–9.5 years Range: 2 days-21 years)</td>
</tr>
<tr>
<td>Age categories:</td>
<td></td>
</tr>
<tr>
<td>Neatone with prematurity</td>
<td>0.3% (21)</td>
</tr>
<tr>
<td>Neatone without prematurity</td>
<td>3.3% (207)</td>
</tr>
<tr>
<td>Infant (30 days to 1 year)</td>
<td>3.7% (236)</td>
</tr>
<tr>
<td>Infant (30 days to 1 year) without prematurity</td>
<td>28% (1,827)</td>
</tr>
<tr>
<td>1-8 years</td>
<td>36% (2,279)</td>
</tr>
<tr>
<td>8-18 years</td>
<td>24% (1,503)</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>4.2% (266)</td>
</tr>
<tr>
<td>Male sex % (n)</td>
<td>51% (3,236)</td>
</tr>
<tr>
<td>Race % (n)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62% (3,920)</td>
</tr>
<tr>
<td>Black</td>
<td>14% (917)</td>
</tr>
<tr>
<td>Asian</td>
<td>3% (216)</td>
</tr>
<tr>
<td>Other</td>
<td>16% (998)</td>
</tr>
<tr>
<td>Missing</td>
<td>5% (288)</td>
</tr>
<tr>
<td>Payor % (n)</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>38% (2,430)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>43% (2,716)</td>
</tr>
<tr>
<td>Other</td>
<td>19% (1,193)</td>
</tr>
<tr>
<td>Diagnosis % (n)</td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>21% (1,304)</td>
</tr>
<tr>
<td>APAH-CHD</td>
<td>69% (4,357)</td>
</tr>
<tr>
<td>Cardiomyopathy with PH</td>
<td>6% (359)</td>
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<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>1% (49)</td>
</tr>
<tr>
<td>PH with orthotopic heart transplant</td>
<td>4% (270)</td>
</tr>
<tr>
<td>Genetic syndrome % (n)</td>
<td>18% (1,126)</td>
</tr>
<tr>
<td>Non-cardiac congenital anomaly</td>
<td>12% (752)</td>
</tr>
<tr>
<td>Mechanical ventilation prior to catheterization</td>
<td>16% (1,038)</td>
</tr>
<tr>
<td>Medications prior to catheterization</td>
<td></td>
</tr>
<tr>
<td>PDE-5 inhibitors</td>
<td>10% (624)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>5% (335)</td>
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<tr>
<td>Prostacyclin analogues</td>
<td>1.1% (77)</td>
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<tr>
<td>ETA antagonists</td>
<td>6% (349)</td>
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<tr>
<td>Inhaled nitric oxide</td>
<td>0.1% (5)</td>
</tr>
<tr>
<td>Inotropic agents</td>
<td>13% (817)</td>
</tr>
<tr>
<td>Systemic vasodilators</td>
<td>10% (641)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.2% (15)</td>
</tr>
<tr>
<td>Cardiothoracic operation prior to catheterization during the same hospitalization</td>
<td>5% (324)</td>
</tr>
<tr>
<td>Trans-catheter intervention during catheterization</td>
<td>23% (1,441)</td>
</tr>
<tr>
<td>Outcomes % (n)</td>
<td></td>
</tr>
<tr>
<td>Composite outcome within 1 day</td>
<td>3.5% (222)</td>
</tr>
<tr>
<td>Death within 1 day</td>
<td>0.3% (17)</td>
</tr>
<tr>
<td>ECMO within 1 day</td>
<td>3.3% (206)</td>
</tr>
<tr>
<td>Composite outcome on day of catheterization</td>
<td>1.0% (61)</td>
</tr>
<tr>
<td>Death on day of catheterization</td>
<td>0.1% (9)</td>
</tr>
<tr>
<td>ECMO on day of catheterization</td>
<td>0.8% (52)</td>
</tr>
</tbody>
</table>

### Table 2: Multivariate model of risk factors for combined outcome (random intercept, with interaction between age category and prematurity) Adjusted risk of composite outcome is 3.3% (95% CI:1.9-5.5%).

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 30 days with prematurity</td>
<td>4.95</td>
<td>1.30-18.86</td>
</tr>
<tr>
<td>0-30 days without prematurity</td>
<td>1.63</td>
<td>0.84-3.17</td>
</tr>
<tr>
<td>30 days to 1 year with prematurity</td>
<td>0.99</td>
<td>0.45-2.20</td>
</tr>
<tr>
<td>30 days to 1 year without prematurity</td>
<td>1.61</td>
<td>1.14-2.28</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>0.71</td>
<td>0.44-1.17</td>
</tr>
<tr>
<td>Asian</td>
<td>0.75</td>
<td>0.32-1.76</td>
</tr>
<tr>
<td>Other</td>
<td>0.86</td>
<td>0.56-1.31</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>White</td>
<td>1 n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>0.71</td>
<td>0.44-1.17</td>
</tr>
<tr>
<td>Asian</td>
<td>0.75</td>
<td>0.32-1.76</td>
</tr>
<tr>
<td>Other</td>
<td>0.86</td>
<td>0.56-1.31</td>
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<td>Payor</td>
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<tr>
<td>Private insurance</td>
<td>0.63</td>
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<td>Public insurance</td>
<td>0.81</td>
<td>0.53-1.24</td>
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<td>Diagnosis</td>
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<td>IPAH</td>
<td>1 n/a</td>
<td>n/a</td>
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<tr>
<td>APAH-CHD</td>
<td>1.32</td>
<td>0.82-2.12</td>
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<tr>
<td>PAH with cardiomyopathy</td>
<td>1.52</td>
<td>0.75-3.12</td>
</tr>
<tr>
<td>PAH with orthotopic heart transplant</td>
<td>2.62</td>
<td>1.28-5.35</td>
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<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>0.95</td>
<td>0.12-7.34</td>
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<td>Genetic syndrome</td>
<td>0.93</td>
<td>0.65-1.33</td>
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<tr>
<td>Non-cardiac structural anomaly</td>
<td>1.06</td>
<td>0.71-2.91</td>
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<tr>
<td>Cardiovascular operation prior to catheterization</td>
<td>2.57</td>
<td>1.28-5.35</td>
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<tr>
<td>Pre-procedural care</td>
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<tr>
<td>Mechanical ventilation</td>
<td>0.79</td>
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<td>Hemodialysis</td>
<td>19.40</td>
<td>5.50-68.40</td>
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<td>Inotropic agents</td>
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<td>Systemic vasodilators</td>
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<td>1.18-2.91</td>
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<td>Pulmonary vasodilators</td>
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<td>Intervention during procedure</td>
<td>0.69</td>
<td>0.48-0.99</td>
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</table>
Adverse Outcomes Associated with Cardiac Catheterization in Children with Pulmonary Arterial Hypertension (continued)

References:
The ENTELLIGENCE Steering Committee

Biography

Ronald J. Oudiz, MD
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

Ronald J. Oudiz, MD, FACP, FACC, FCCP is Professor of Medicine, David Geffen School of Medicine at UCLA and is the Director of the Pulmonary Hypertension Center and Faculty Cardiologist at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Southern California. Dr. Oudiz received his medical school training at the University of Southern California in Los Angeles, his Internal Medicine training at the University of California, San Diego, and his training in Cardiovascular Diseases at Harbor-UCLA Medical Center in Torrance, CA. He is board-certified in Internal Medicine and Cardiovascular Diseases.

Dr. Oudiz is a past holder of scientific research awards from the American Heart Association and the National Institutes of Health. He has authored several papers in pulmonary hypertension and has presented his research at national and international seminars. Dr. Oudiz is the past Editor-in-Chief of the scientific publication Advances in Pulmonary Hypertension.

He has participated in several trials of innovative medical treatments for pulmonary hypertension (PH), many of which are still ongoing. Dr. Oudiz’s recent 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.
The ENTELLIGENCE Steering Committee

Biography

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

Dr. Harrison W. 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.

Dr. Farber 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.
Dr. Adaani Frost is Professor of Medicine in the Pulmonary and Critical Care Section of Baylor College of Medicine in Houston, TX.

She undertook her postgraduate training in pulmonary and critical care, including a fellowship in lung transplantation, in the Toronto Hospital System and McGill University.

She was Medical Director of the Lung Transplant Program at both the Methodist Hospital and St. Luke’s Episcopal Hospital from 1990 to 2001 and developed the Pulmonary Hypertension and Advanced Lung Disease Service at Baylor. Currently, she is involved in clinical management and clinical research on patients with end stage lung disease, predominantly in pulmonary hypertension, and pulmonary fibrosis.

Dr. Frost was on the Scientific Advisory Council of the Pulmonary Hypertension Association until 2009 and on the steering committee of REVEAL (a US-based registry of more than 3500 pulmonary hypertensive patients). She has authored numerous papers on pulmonary hypertension, and is a participant in multiple new and ongoing studies in the treatment of pulmonary hypertension.
The ENTELLIGENCE Steering Committee

Biography

Mardi Gomberg-Maitland, MD, MSc
Associate Professor of Medicine
Director, Pulmonary Hypertension Program
University of Chicago Medical Center
Chicago, IL

Mardi Gomberg-Maitland, MD, MSc, is Associate Professor of Medicine and Director of the Pulmonary Hypertension Program at the University of Chicago Medical Center in Chicago, IL.

Dr. Gomberg-Maitland earned her undergraduate degree at Yale University, her medical degree at the Albert Einstein College of Medicine and completed a residency at New York Presbyterian Hospital-Weill/Cornell Medical Center and a fellowship at Mount Sinai Medical Center. She earned a Masters in Clinical Epidemiology at Harvard School of Public Health.

Dr. Gomberg-Maitland is an expert clinician and researcher in the field of pulmonary heart disease. In recent years, she has participated in dozens of multicenter, multinational research trials to explore new therapies for pulmonary hypertension. She is currently focusing on pulmonary arterial, pulmonary venous hypertension/diastolic dysfunction, and biomarker development.

A fellow of the American College of Cardiology, American College of Chest Physicians, and American Heart Association, and a member of the International Society of Heart and Lung Transplantation, American Thoracic Society, and Pulmonary Hypertension Association, Dr. Gomberg-Maitland has published numerous articles in peer-reviewed journals, including Circulation, Journal of the American College of Cardiology, Clinical Pharmacology and Therapeutics, Chest, European Respiratory Journal, and the American Journal of Respiratory and Critical Care Medicine.
Maureen D. Mayes, MD, MPH
Professor of Internal Medicine
Elizabeth Bidgood Chair in Rheumatology
Division of Rheumatology and Clinical Immunogenetics
University of Texas – Houston 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 – Houston Medical School faculty in 2002 and subsequently established the Scleroderma Clinic. Dr. Mayes is the recipient of many distinctions, awards and grants for the study and treatment of scleroderma. She is the author of over 180 published manuscripts, 26 reviews, 9 book chapters and 2 full length 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 currently the Principal Investigator of the NIH/NIAMS funded ‘Genome-Wide Association Study in Systemic Sclerosis’ that has the objective of identifying genes that influence disease susceptibility and severity; and PI 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.
The ENTELLIGENCE Steering Committee

Biography

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.

Recently, 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

Harold I. Palevsky, MD, 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.”
Richard M. Silver, MD
Distinguished University Professor of Medicine and Pediatrics
Director, Division of Rheumatology & Immunology
Medical University of South Carolina
Charleston, SC

Dr. Richard Silver serves as Director of the Division of Rheumatology & Immunology at the Medical University of South Carolina (MUSC).

He joined the faculty at MUSC in 1981, where he is a Distinguished University Professor of Medicine and Pediatrics. In 2007, MUSC’s Board of Trustees named him a “Master Teacher” and bestowed the University’s highest academic recognition, Distinguished University Professor. Also in 2007, the Scleroderma Foundation named him their “Doctor of the Year.”

Dr. Silver’s major research interest is interstitial lung disease associated with systemic sclerosis.
The ENTELLIGENCE Steering Committee

Biography

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

Dr. Stenmark is Professor of Pediatrics, Medicine, and Anesthesiology at the University of Colorado Anschutz Medical Campus in Aurora, CO. He is also the Division Head of Pediatric Critical Care Medicine and Director of the Cardiovascular Pulmonary Research Laboratory.

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.

An Associate Editor for American Journal of Physiology: Lung Cellular and Molecular Physiology, Dr. Stenmark serves 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, Scleroderma Foundation PeerReview, and Pulmonary Vascular Research Institute (PVRI) Steering and Scientific committees.

A featured speaker at numerous conferences, Dr. Stenmark has been published in many peer-reviewed journals, including the New England Journal of Medicine, Science, Journal of Clinical Investigation, Circulation Research, and American Journal of Physiology.
The ENTELLIGENCE Steering Committee

Biography

Jason X-J Yuan, MD, PhD
Professor of Medicine
Associate Vice President for Translational Health Sciences
University of Arizona
Director, Division of Translational and Regenerative Medicine
Department of Medicine
University of Arizona College of Medicine
Tucson, AZ

Dr. Jason Yuan is Professor of Medicine and Associate Vice President for Translational Health Sciences at the University of Arizona in Tucson, AZ. He is also Director of the Division of Translational and Regenerative Medicine in the Department of Medicine at the University of Arizona College of Medicine. 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 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. He is currently Chair of the Pulmonary Circulation Assembly of the American Thoracic Society, Editor-in-Chief of the journal Pulmonary Circulation, and Associate Editor of the American Journal of Physiology-Cell Physiology.