ENTELLIGENCE™
Young Investigators Award Program
2012

The ENTELLIGENCE program is supported through an educational grant from Actelion Pharmaceuticals US, Inc. The ENTELLIGENCE program is run as a nonprofit program.
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Foreword

Ronald J. Oudiz, MD
Chairman of the ENTELLIGENCE Steering Committee

Dear Colleagues,

We are delighted to announce that in 2012, the Actelion ENTELLIGENCE™ Young Investigators Award Program awarded four new pulmonary hypertension-related research projects. 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. Since 2005, members of the independent Steering Committee have selected cutting-edge projects that are scientifically relevant, original, and applicable to the problem of pulmonary hypertension. More than 35 promising researchers in the field of pulmonary hypertension have been funded.

Original basic, translational, and/or clinical investigations target pulmonary vascular disease in the areas of pathophysiology, pharmacology, treatment, genetics, diagnosis, and epidemiology. Results from many of these projects are presented at key scientific meetings such as the American Thoracic Society and published in peer-reviewed journals, including Chest, American Journal of Respiratory and Critical Care Medicine, and American Journal of Physiology.

Continuing its commitment to advancing the understanding of pulmonary hypertension and promoting the career development of young investigators planning an academic career in pulmonary hypertension research, the Young Investigators Award Program will soon begin another cycle of competition, with relevant dates announced later this year.

On behalf of the ENTELLIGENCE Steering Committee, I would like to express our gratitude to Actelion for their generous gifts to the pulmonary hypertension research community and their ongoing commitment to basic science and clinical research in this arena.

Best regards,

Ronald J. Oudiz, MD
The ENTELLIGENCE™ Young Investigators Award Program

Supporting young investigators

The ENTELLIGENCE Young Investigators Award 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: 7
Awards distributed: 38

Overview of ENTELLIGENCE Awards

Awards 2012

Eileen Bauer, PhD
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
Co-Investigator: Stephen Tomlinson, PhD
Mentors: Philip M. Bauer, PhD, 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
Nashville, Tennessee
Mentor: James D. West, PhD
Project Title: The Role of Sirtuins and Lysine Acetylation in Pulmonary Arterial Hypertension

Kenny Schlosser, PhD
Ottawa Hospital Research Institute
Ottawa, Canada
Mentor: Duncan J. Stewart, MD
Project Title: Role of Extracellular Circulating MicroRNAs in Idiopathic Pulmonary Arterial Hypertension

Kelly J. Shields, PhD
Allegheny Singer Research Institute
Pittsburgh, Pennsylvania
Co-Investigator: Joseph M. Ahearn, MD
Mentor: Raymond L. Benza, MD
Project Title: The Role of Perivascular Adipose Tissue in Pulmonary Arterial Hypertension
Awarded 2011

**Jana Bagarova, PhD**
Massachusetts General Hospital and Harvard Medical School
Boston, Massachusetts
Mentor: Paul Yu, MD, PhD
*Project Title: BMP9-Mediated Regulation of Endothelin-1 Expression in Vascular Endothelial Cells*

**Marco Mura, MD, PhD**
University of Toronto
Toronto, Ontario
Co-Investigator: Dr. Marc de Perrot
Mentor: John Granton, MD
*Project Title: Osteopontin in Idiopathic Pulmonary Arterial Hypertension, a Biomarker and Therapeutic Target*

**Salah Najm, MD**
University Hospitals, Case Medical Center
Cleveland, Ohio
Mentor: Kingman Strohl, MD
*Project Title: Vascular Reactivity in Response to Acute Hypoxia: Defining Features and Mechanisms*

**Yon K. Sung, MD**
Stanford University School of Medicine
Palo Alto, California
Mentor: Mark Nicolls, MD
*Project Title: The Role of Antibodies in the Pathogenesis of Pulmonary Arterial Hypertension*
Awarded 2010

**Eric Douglas Austin, MD, MSCI**  
Vanderbilt University Medical Center  
Mentor: James E. Loyd, MD  
*Project Title: Sex Hormone Abnormalities in Pulmonary Arterial Hypertension*  
Presented at 2011 Grover Conference  
Accepted for publication in 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*  

**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*  

**Michael J. Passineau, PhD**  
Allegheny General Hospital  
Mentor: Raymond L. Benza, MD  
*Project Title: Gene Therapy to Drive Endogenous Biosynthesis of Prostacyclin*  
Abstract submitted to 2012 American Society of Gene and Cell Therapy Annual Meeting

**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*  

Awarded 2009

**Daniel J. Kass, MD**  
University of Pittsburgh  
Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease  
Co-Investigator: Hunter C. Champion, MD, PhD  
Mentor: Mark Gladwin, MD  
*Project Title: Targeting the MetAP2 Pathway in Pulmonary Arterial Hypertension*  
Presented at American Thoracic Society Conferences, 2010 and 2011

**Sean E. McLean, MD**  
UNC 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**  
Children’s Hospital Boston  
Brigham and Women’s Hospital Boston Adult Congenital Heart and Pulmonary Hypertension Service  
Mentor: Michael J. Landzberg, MD  
*Project Title: The Epidemiology and Determinants of Hospitalization for Pulmonary Hypertension in the United States*  

**Michael Eric 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 European Respiratory Journal, 2012 and Chest, 2011
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*  
Published in Arteriosclerosis, Thrombosis, and Vascular Biology, 2011  
Presented at 2009 American Heart Association meeting and 2009 American Thoracic Society Conference

**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 abstracts: American Journal of Respiratory and Critical Care Medicine, 2010 and European Respiratory Journal Supplement, 2010  
Published in Respiratory Research, 2011

**Sanjiv Shah, MD**  
Northwestern University Medical Center  
Mentor: John Varga, MD  
*Project Title: Generic Risk Factors for Connective Tissue Disease (CTD)-Associated Pulmonary Arterial Hypertension (PAH)*  
Published in 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*

**Ari Lev 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
Awarded 2007

Yabing Chen, PhD
UAB, Molecular and Cellular Pathology, 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 the 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

Awarded 2007

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

Megha H. Talati, PhD
Vanderbilt University Medical Center
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
Published in the American Journal of Physiology: Lung Cellular and Molecular Physiology, 2010
Presented at 2009 American Thoracic Society meeting [travel funded by Cardiovascular Medicine Research and Education Fund]

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, PhD, MD
University of Chicago
Mentor: Kenneth Weir, MD
Project Title: Endothelin-Induced Increase in Pulmonary Vascular Smooth Muscle Calcium; The Role of Calcium Channels

Peter Oishi, MD
UCSF School of Medicine
Mentor: Jeffrey Fineman, MD
Project Title: Endothelin-1 Reactive Oxygen Species Interactions in Pulmonary Hypertension

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, FCCP
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
Eileen Bauer, PhD
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Complement Activation as a Novel Mechanism of Endothelial Activation in PH

Recent data from our laboratory demonstrate a role for the complement system, a major humoral component of innate immunity, in the pathogenesis of pulmonary hypertension (PH). However, the mechanisms by which complement promotes PH are poorly understood. This proposal aims to test the novel hypothesis that genetic deletion of complement components C3 or C5, or inhibition of activated complement, prevents and/or halts the progression of PH by inhibiting endothelial activation. To test this hypothesis I have proposed two specific aims. Aim 1 will explore if activated complement directly causes activation of pulmonary artery endothelial cells in vitro, and will establish a timeline of endothelial activation in vivo in our animal model of hypoxic exposure. Genetic deletion of complement components C3 or C5 will establish a role for complement in mediating endothelial activation in vivo. Aim 2 will focus on determining the therapeutic potential of the complement inhibitor CR2-crry in PH. Preliminary data show promising results when CR2-crry is administered to mice at the beginning of the disease course suggesting that complement inhibition can attenuate chronic hypoxia-induced PH. The first component of this aim will focus on further refinement of the dosage and timing interval to optimize CR2-crry delivery. Based on these results, inhibitor studies will be performed using mice with established PH to test the inhibitor’s therapeutic potential. Completion of the proposed research will give us a stronger foundation upon which to 1) further investigate the role of innate immunity in PH and 2) further explore the therapeutic potential of drugs targeting the complement system.

Joshua P. Fessel, MD, PhD
Vanderbilt University Medical Center
Nashville, Tennessee

The Role of Sirtuins and Lysine Acetylation in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension [PAH] is a progressive, incurable, and fatal disease of the lung vasculature characterized by increasing pulmonary vascular resistance (PVR) that ultimately leads to right ventricular failure and death. Although the gene responsible for the majority of cases of heritable PAH – bone morphogenetic protein receptor type 2 (BMPR2) – was identified over a decade ago, and despite creation of a robust transgenic mouse model, the precise molecular etiologies of PAH remain unclear. Increasingly, disrupted metabolic processes have been implicated as being key pathologic processes leading to PAH. Decreased insulin sensitivity, impaired glucose homeostasis, and increased aerobic glycolysis have all been demonstrated in PAH in cell culture, in animal models, and in patients with disease. We have recently analyzed the entire metabolome of human pulmonary endothelial cells expressing disease-causing BMPR2 mutations and have shown that many interconnected metabolic pathways are disrupted in PAH. These widespread and interconnected changes suggest the possibility of one or more master regulators that coordinate the balance of cellular metabolic flux and that may be dysfunctional in PAH. Sirtuins are class III lysine deacetylases that have been shown to regulate inflammation, transcriptional activation, and cellular metabolism. Many of the specific pathways regulated by sirtuins align very closely with the metabolic changes we and others have observed in PAH. We thus hypothesize that lysine hyperacetylation resulting from decreased sirtuin function drives the
Joshua P. Fessel, MD, PhD

metabolic defects underlying PAH. The proposed studies will demonstrate decreased sirtuin function in cell culture, in transgenic mouse models of PAH, and in cells and tissues from PAH patients. These studies will also use manipulation of sirtuin function [e.g., using knockout mice, caloric restriction, and nutrient excess] to show that sirtuins directly impact disease course in PAH. Demonstration of a causative role for decreased sirtuin function would allow for targeting sirtuins and the downstream metabolic defects to have a potentially disease-modifying effect.

Kenny Schlosser, PhD
Ottawa Hospital Research Institute
Ottawa, Ontario, Canada

Role of Extracellular Circulating MicroRNAs in Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by a deterioration of the underlying structure of the lung vasculature, and the resulting increase in pulmonary vascular resistance leads to right heart failure and premature death. Despite improvements in treatment, the overall prognosis for IPAH remains poor with no known cure. Although the precise cause of IPAH remains unclear, there is increasing interest in small non-coding RNA molecules known as microRNAs (miRNAs). MiRNAs associate with specific protein complexes and control gene expression by directing the translational inhibition or degradation of target messenger RNAs. To date, over 1000 highly conserved mammalian miRNAs have been annotated, and many have been shown to act as key regulators of fundamental biological processes, including cell proliferation, apoptosis, and inflammation; these processes have all been implicated as possible pathobiologic mechanisms of IPAH. MicroRNAs have traditionally been thought to exist and function exclusively within cells; however, stable extracellular miRNAs have recently been discovered in the blood, which has led to speculation of an entirely new type of paracrine and/or hormonal function. These circulating miRNAs have been isolated from blood plasma under both normal and pathophysiological conditions, including various cancers and cardiovascular disease, but their identification and functional significance in lung vascular diseases like IPAH have not been investigated. We hypothesized that IPAH is associated with aberrant levels of circulating miRNAs which reflect disease-specific mechanisms of vascular injury and/or remodeling. We aim to 1) characterize the global plasma miRNome...
Kenny Schlosser, PhD

of a cohort of IPAH patients, 2) identify specific plasma miRNAs with aberrant expression patterns that are conserved between human IPAH and the SU5416/hypoxia rat model, and 3) determine if these miRNAs play a causal, adaptive, or bystander role in the development of PAH, by evaluating the effects of both miRNA inhibition and supplementation in the experimental PAH model. The characterization of these circulating miRNAs may provide new biomarkers of PAH, insight into novel mechanisms underlying the pathobiology of this disease, and potential targets for therapeutic intervention.

Kelly J. Shields, PhD

Allegheny Singer Research Institute
Pittsburgh, Pennsylvania

The Role of Perivascular Adipose Tissue in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare disease characterized by ever increasing pulmonary vascular resistance and significant vascular remodeling. Although the classic indicators of PAH progression are well recognized, the initiating factors involved in the pathogenesis of PAH are not well understood. Perivascular inflammatory cells have been shown to influence plexiform lesion development, leading to growing interest in the relationship between perivascular inflammation and pulmonary artery (PA) remodeling. Smaller visceral adipose depots are receiving increased attention for their localized inflammatory role in cardiovascular disease. We previously found complement proteins C3 and C4 (C3/C4) deposited at the external elastic lamina of the descending aorta extending through the perivascular adipose tissue (PVAT) in the absence of luminal deposition or plaque development. We determined that C3/C4 bind to collagen and elastin within the vascular wall of murine aorta, suggesting that complement may play a critical role in the pathogenesis of vascular stiffness and atherosclerosis through a mechanism initiated at the adventitia or the PVAT rather than the endothelial surface. The same pro-inflammatory environment may exist surrounding the PAs, contributing to PAH.

We hypothesize that the vascular remodeling due to PAH progression is associated with dysfunctional PA PVAT. We propose that a PAH rat model will have a greater volume of PA PVAT with more extensive C3/C4 deposition and pro-inflammatory protein expression than a control model.

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2012 Abstracts

Kelly J. Shields, PhD

First we will quantify the volume of PA PVAT using microCT and correlate these findings with the extent of vascular remodeling and PA PVAT hypertrophy due to PAH progression as measured through morphological changes using scanning electron microscopy. Second, we will characterize the deposition of C3/C4 in the PA vascular wall and PA PVAT using established immunohistochemistry and histology techniques while evaluating the association with vascular remodeling. Finally, we will identify unique and novel pro-PAH proteins and inflammatory cell populations found in the PA PVAT using proteomics and molecular histology and we will correlate these findings with vascular remodeling at specified time intervals.

2011 Abstracts

Jana Bagarova, PhD

Massachusetts General Hospital and Harvard Medical School Boston, Massachusetts

BMP9-Mediated Regulation of Endothelin-1 Expression in Vascular Endothelial Cells

Pulmonary arterial hypertension (PAH) is a highly morbid condition characterized by abnormal pulmonary vasoreactivity and pulmonary angiopathy leading to progressively increased pulmonary resistance, and frequently culminating in right heart failure and death. The molecular basis of PAH has yet to be fully elucidated, although dysregulated bone morphogenetic protein (BMP) signaling due to loss-of-function mutations in BMPR2, encoding the BMP type II (BMPRII) receptor, have been implicated in several forms of PAH. Recent reports also indicate that BMP9, a BMPRII ligand, regulates transcription of the potent vasoconstrictor endothelin-1 [ET-1], an important mediator of PAH. BMP9 appears to function as a circulating vascular quiescence factor that promotes endothelial survival while inhibiting angiogenesis. We found that BMP9 activates both canonical BMP and TGF-β pathways via their respective effector molecules, SMAD1/5/8 and SMAD2/3. Blocking either BMP or TGF-β signaling pathways using small molecule receptor kinase inhibitors or recombinant receptor ectodomains prevents the induction of ET-1 by BMP9, suggesting a requirement for the coordinated activity of these two pathways. Preliminary ET-1 promoter analysis revealed distinct cis-regulatory elements involved in BMP9- and TGF-β-mediated activation of ET-1 transcription, suggesting a novel BMP-responsive regulatory element as well as cooperativity between BMP9 and TGF-β pathways. We previously found that ablation of BMPRII does not disrupt BMP signaling in vascular cells, but instead augments signaling for some BMP ligands, and

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attenuates signaling of other BMP ligands via transduction by Activin type II receptor (ActRIIa). Thus, the loss of BMPRII function has the potential to either disrupt or augment BMP9-induced regulation of ET-1, with potential consequences for pulmonary vascular tone in PAH associated with BMPR2 mutations. In this proposal we investigate the molecular mechanisms by which BMP9 and BMPRII contribute to the regulation of ET-1 in endothelial cells, using a combination of small molecule, recombinant protein, and molecular genetic approaches. We test the hypothesis that impaired BMPRII function dysregulates BMP9-induced ET-1 expression and may thereby contribute to abnormalities in vascular tone and/or remodeling in PAH.

Marco Mura, MD, PhD
University of Toronto
Toronto, Ontario

Osteopontin in Idiopathic Pulmonary Arterial Hypertension, a Biomarker and Therapeutic Target

Proliferation of smooth muscle cells (SMCs) and pulmonary arterial remodelling are key mechanisms in the pathogenesis of idiopathic pulmonary arterial hypertension (IPAH). Osteopontin (OPN) is a pleiotropic cytokine involved in the proliferation of vascular SMCs. We recently discovered that OPN is upregulated in the lungs of patients with pulmonary hypertension (PH) associated with pulmonary fibrosis (PF), suggesting that the lung tissue is a source of OPN. Genome-wide RNA expression profiling experiments demonstrated a significant elevation of OPN in lungs of rats with hypoxic PH. Circulating OPN levels are significantly higher in IPAH patients compared to healthy subjects, they independently predict survival and are associated with a higher NYHA class. In vitro, the OPN expression level is highly related to the proliferative state of arterial SMCs, promoting adhesion and chemotaxis of vascular cells. However, the expression level and the cellular sources of OPN in the lungs of IPAH are unknown. The correlation between OPN levels and hemodynamics has also never been studied. We hypothesize that there is a high expression of OPN in the lungs of IPAH patients, and that there is a significant correlation with circulating OPN and hemodynamic parameters. Ultimately we hope to provide further rationale for OPN as a biomarker and therapeutic target. To do this, we will compare the OPN gene expression (microarray analysis) in the lung tissue of patients with IPAH who underwent lung transplantation (LTx) with normal controls. To validate the microarray results, we will analyze

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Marco Mura, MD, PhD

the molecular expression level of OPN in the lung tissue with real-time RT-PCR, and measure OPN levels in the peripheral blood from the same patients. As heart catheterization is routinely performed immediately before starting LTx, we will study the relationship between OPN lung expression, circulating OPN and hemodynamic parameters. To investigate the cellular sources of OPN, we will perform OPN immunohistochemistry on the histological slides obtained from the native lungs of IPAH patients and normal controls.

Salah Najm, MD
University Hospitals, Case Medical Center
Cleveland, Ohio

Vascular Reactivity in Response to Acute Hypoxia: Defining Features and Mechanisms

Exposure to chronic hypoxia is a frequently used model for pulmonary arterial hypertension (PAH). However, it is clear that states of chronic hypoxia such as chronic obstructive pulmonary disease and obstructive sleep apnea, as well as high altitude exposure, do not uniformly lead to the development of PAH. This disparity may be due, in part, to genetic predisposition, yet it remains incompletely defined. The impact of acute hypoxia is even less well defined but may have significant clinical relevance. Increasing evidence suggests that acute and chronic hypoxemia responses may be related. Aldashev (2002) showed that the hyper-responsiveness, defined as 50% increase in pulmonary artery pressure to acute hypoxia at sea level, is predictive of the development of PAH in native highlanders (~3000m above sea level). We propose to systematically study the relationship between the dose-response to acute hypoxia and the development of PAH using a defined rat hemodynamic model created in our laboratory. We hypothesize that the acute hemodynamic response to brief hypoxia can be used as an indicator of the predisposition to develop chronic pulmonary hypertension and as an assay for testing the genetic predilection, mechanisms and new therapies. The aims of this application are: 1) to establish a new assay metric [dose-response] quantifying the acute effects of brief hypoxia [30 seconds] on the vasculature using in vivo recordings of hemodynamic variables; and 2) to define the relationship between acute and chronic hypoxemia in the development of PAH using genetically divergent strains.

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Salah Najm, MD

of rats. We will define these differences in dose-response curves with drug intervention [L-NAME: L-Nitro-Arginine Methyl Ester] and investigate potential mechanisms through which nitric oxide mediates this acute response. Thorough investigation of the vascular response of both the systemic and pulmonary circulation, as proposed by these studies, will lead to a better understanding of the mechanisms and genetics of hypoxia induced pulmonary hypertension. This work will form the foundation of a potential screening model for drug development in the area of PAH.

Yon K. Sung, MD

Stanford University School of Medicine
Palo Alto, California

The Role of Antibodies in the Pathogenesis of Pulmonary Arterial Hypertension

While the pathogenesis of pulmonary arterial hypertension (PAH) is likely multifactorial, there is increasing evidence that inflammation and immune dysregulation play a role in pulmonary vascular injury and remodeling. Previous studies have shown that athymic rats, which lack T cells, injected with the vascular endothelial growth factor receptor-2 (VEGFR-2) blocker, SU5416, develop severe PAH in normoxia and are characterized by perivascular infiltration of B cells and deposition of antibodies on the endothelium as seen in clinical disease. Preliminary data suggest that the susceptibility of these rats to PAH may be due to the lack of regulatory T cells. Hence, it has been postulated that loss of immune regulation leads to proliferation of autoreactive B cells. Pilot studies have shown that B cell depletion with an anti-CD20 antibody in athymic rats attenuates PAH, right ventricular hypertrophy (RVH), and pulmonary vascular remodeling. This proposal will evaluate the role of antibodies in the pathogenesis of PAH. The primary hypothesis is that the pathogenic property of the autoreactive B cell is its ability to produce autoantibodies against lung endothelial antigens which leads to persistent vascular injury, pulmonary vascular remodeling, and PAH. Furthermore, demonstration of this hypothesis will provide evidence that PAH may be considered an autoimmune disease. This premise will be addressed in two ways. First, the euthymic rat, which does not develop PAH with SU5416 injection in normoxia, will be used. Serum or purified antibodies

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Yon K. Sung, MD

from athymic rats with severe PAH will be transferred to euthymic rats after SU5416 injection. If antibodies are pathogenic, it is anticipated that these animals will develop elevated right ventricular pressures, RVH, and perivascular inflammation. Next, the pathogenicity of autoantibodies will be tested by depletion of antibodies by plasma exchange in athymic rats after SU5416 injection. It is anticipated that removal of pathogenic autoantibodies will attenuate PAH and vascular remodeling in these rats.

Angela V. Ghatnekar, PhD
Postdoctoral Scholar
Medical University of South Carolina
Charleston, South Carolina

Mentor
Richard M. Silver, MD
Distinguished University Professor of Medicine and Pediatrics
Director, Division of Rheumatology & Immunology
Medical University of South Carolina
Charleston, South Carolina

The Role of GATA-6 in Pulmonary Arterial Hypertension
Awarded 2011

Background

Pulmonary arterial hypertension (PAH) is characterized by an increase in pressure in the pulmonary artery (PA) or lung vasculature. Manifestations of PAH occur mainly in small PAs and include vasoconstriction, intimal proliferation, fibrosis, in-situ thrombosis, and plexogenic lesions. These vascular alterations are largely due to endothelial dysfunction, which is reflected by imbalances between vasoconstrictors and vasodilators, mitogens and growth inhibitors, and prothrombotic and antithrombotic factors. It is believed that pulmonary endothelial cell (EC) injury and/or activation is most likely the root cause of these homeostatic imbalances; however, the initial trigger leading to changes in ECs and the molecular mechanisms underlying activation of ECs remain poorly understood.

Recent studies in our laboratory suggest that GATA-6, a zinc-finger transcription factor, may be one of the critical regulators of vascular homeostasis. Based on our preliminary observations, we hypothesize that
Final Report

downregulation of GATA-6 is a critical pathological event that leads to EC dysfunction during PAH. To study the role of GATA-6, we propose to investigate the functional consequences of reduced GATA-6 in ECs, both in cultured cells and in mouse lungs in vivo.

Aims

Specific Aim 1: To investigate the hypothesis that reduction of GATA-6 in PAECs will lead to changes in gene expression patterns responsible for EC activation/dysfunction.

Specific Aim 2: To investigate the hypothesis that conditional knockdown of GATA-6 in ECs in vivo will lead to pulmonary vascular remodeling.

Results

GATA-6 regulates expression of genes involved in vascular remodeling

We found 18 genes to be differentially expressed in the GATA-6 deficient ECs. Among them, we were able to confirm that 11 were indeed altered after suppression of GATA-6 (Figure 1). Interestingly, this preliminary screen identified genes involved in vessel tone and permissibility, EC activation, and EC injury. In addition, we confirmed our previous findings in MVECs that matrix remodeling genes are upregulated after knockdown of GATA-6 by siRNA. We also demonstrated differential expression of several putative target genes at the protein level.

These data strongly suggest that GATA-6 may play a role in PAH by regulating genes that promote vascular remodeling and dysfunction. GATA-6 occupied one or more sites on the promoters of 8 genes, indicating that GATA-6 is a direct regulator of these genes.

GATA6 deficiency enhances vascular remodeling in hypoxic mice

Systolic blood pressure, diastolic blood pressure, mean pressure, heart pulse rate, and blood volume appeared to be no different in the Gata6ΔEC mice compared with controls. To investigate the effect of decreased GATA-6 levels on pulmonary vascular remodeling, the degree of muscularization and the medial wall thickness of intra-acinar PAs (20-70 μm in diameter) were analyzed. Morphometric analysis revealed there was no difference between Gata6ΔEC mice and control animals under normoxic conditions; however, enhanced PA muscularization was observed in Gata6ΔEC mice subjected to hypoxia. The analysis revealed significantly more fully muscularized vessels in the Gata6ΔEC mice and dramatically less non-muscularized vessels. In addition, the medial wall thickness was significantly increased in Gata6ΔEC mice under hypoxic conditions. Lastly, hypoxic mice also had significantly larger right ventricles as compared to control littermates. Right ventricular size appeared to be no different in the Gata6ΔEC mice housed in normoxic conditions.

These data suggest that loss of GATA-6 in combination with an environmental insult may be an important contributor in the pathogenesis of PAH.

Conclusion

Based on our data, reduction of GATA-6 in the ECs leads to enhanced muscularization of small PAs in mice under hypoxia. During PAH, a downregulation of GATA-6 in the endothelium leads to an increase in MMPs, which in turn contribute to extracellular matrix remodeling and release of matrix bound growth factors that stimulate smooth muscle cell (SMC) proliferation. Loss of GATA-6 expression in ECs may also contribute to a reduction in eNOS, contributing to a loss in the NO pathway and an increase in the potent vasoconstrictor EDN-1. This ultimately results in enhanced vasoconstriction and SMC proliferation. Lastly, a decrease in GATA-6 expression in the endothelial barrier leads to an increase in the chemokine CX3CL1, a known chemoattractant for T cells and monocytes. Furthermore, soluble CX3CL1 is linked to the phenotypic switching and proliferation of SMC in the muscularization of lung vasculature.1

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In conclusion, these data indicate that loss of GATA-6 may be an important component of EC activation and dysfunction. Further studies focusing on the functional consequences of its loss may provide insights into the molecular mechanisms underlying the pathogenesis of PAH and implications for the development of new therapies.

Reference
Final Report

Measurements:
All groups of rats were subjected to the following measurements, 3 weeks after the date of the single injection of MCT.

- **Hemodynamic Measurements.** Right ventricular (RV) systolic pressure was recorded as a measure of PAH.
- **Histologic & Morphometric Analyses:** Total vessel area [μm²], luminal area [μm²], and inner circumference [μm] were measured. Medial area [μm²] was calculated as the difference between total and luminal areas. Standard medial thickness [μm] was calculated as the ratio of medial area to inner circumference.
- **Assessment of RV Hypertrophy:** The RV/(left ventricular wall [LV]+septum) weight ratio was calculated as an index of RV hypertrophy.
- **Lung Inflammation:** Inflammation was graded 0, 1, 2, 3, or 4, based on the intensity and extent of perivascular and peribronchiolar inflammatory cell infiltrates.
- **Survival:** Mortality data were compared among the 3 experimental groups, by the log-rank test, and Kaplan-Meier curves were generated.

Results:

**Pulmonary vascular remodeling:** Small pulmonary arterioles from MCT-treated rats had thicker media (20.4 ± 1.1 μm vs. 8.5 ± 0.5 μm, n=10, P<0.001), and narrower lumen than control vessels of similar diameter (70-80 μm). The corresponding ratio of medial area to luminal area was 3.9 ± 0.51 vs. 0.8 ± 0.07 (n=10, P<0.001). In rats treated with either VIP or bosentan alone, the ratio of medial area to luminal area was significantly lower than in MCT-treated rats (1.97 ± 0.32, and 1.46 ± 0.11, respectively, n=7, P<0.001); the ratio of medial area to luminal area in the VIP-treated group was statistically no different from the bosentan-treated group. Rats receiving a combination of VIP and bosentan had a significantly much lower ratio of medial area to luminal area (n=8, P<0.05) compared to each drug alone, almost the same as control untreated rats (0.9 ± 0.09 vs. 0.8 ± 0.07, respectively).

**RV Hypertension:** MCT-treated rats had significantly elevated RV systolic pressure relative to control untreated rats (61.4 ± 4.8 vs. 24.3 ± 2.4 mm Hg, n=5, P<0.001). In rats treated with either VIP or bosentan, RV systolic pressure was significantly lower than in MCT-treated rats (33 ± 0.5 and 39 ± 1.2 mm Hg, respectively, n=5, P<0.001); RV systolic pressure in the VIP-treated group was statistically no different from control untreated rats. Rats receiving a combination of VIP and bosentan had much lower RV systolic pressure, almost the same as in control untreated rats (26.0 ± 1.2 vs. 24.3 ± 2.4 mm Hg, n=5, P<0.001).

**RV Hypertrophy:** The RV/(LV+septum) weight ratio in MCT-treated rats was significantly higher than in control untreated rats (0.56 ± 0.03, n=10, vs. 0.26 ± 0.01, n=12, P<0.001). This ratio was reduced in both bosentan- and VIP-treated groups, but the reduction was not statistically significant. In animals treated with a combination of bosentan and VIP, however, the degree of RV hypertrophy was significantly reduced (0.34 ± 0.02, n=8, P<0.05), and the ratio in the latter group was no different from that in normal, untreated animals. (Figure 1).

**Lung Inflammation:** Lungs from MCT-treated rats showed perivascular and peribronchiolar inflammatory cells infiltrates, predominantly mononuclear (inflammation score: 3.6 ± 0.4, n=10), compared to lungs from control untreated rat lungs (0.20 ± 0.2, n=10, P<0.001). Both the intensity and extent of inflammatory cell infiltrates were reduced to a minimal value by treatment with VIP, bosentan, and a combination of both drugs, no different from that in normal, untreated animals.

**Survival:** All MCT-treated rats were dead within 3–5 weeks after MCT injection. All groups that received additional treatment were observed for 6 weeks after MCT injection. Treatment with either bosentan or VIP...
alone significantly reduced mortality in MCT-treated rats (P< 0.0001). No mortality was observed during the same period of time in the rats that received both bosentan and VIP.

Conclusions:
RV hypertrophy was reduced, but not significantly, in MCT-injected animals co-treated with either bosentan or VIP alone. This reduction was pronounced and statistically significant in animals treated with a combination of bosentan and VIP. Treatment with either bosentan or VIP alone significantly reduced mortality in MCT-treated rats. No mortality was observed during the same period of time in MCT-injected rats that received both bosentan and VIP.

Figure 1. Right ventricular hypertrophy in animal groups.

Targeting the MetAP2 Pathway in Pulmonary Arterial Hypertension
Awarded 2009

Background and Hypothesis
Pulmonary hypertension (PH) is characterized by elevations in pulmonary arterial pressures leading to hypoxemia and right ventricular (RV) dysfunction; PH complicates and worsens the prognoses of many pulmonary and systemic diseases. Current therapies for PH enhance survival modestly\(^1\,^2\) but do not significantly reverse the accumulation of smooth muscle cells (SMCs) and endothelial cells (ECs). Therapies that reverse the proliferation of these cells would be predicted to impact positively both quality-of-life and survival in PH.

Methionine aminopeptidase-2 (MetAP2) is a metalloprotease that cleaves the initiator methionine off polypeptides, a process necessary for many downstream, post-translational modifications of certain proteins. Fumagillin is a fungal metabolite\(^3\) that irreversibly inactivates the enzymatic activity of MetAP2\(^4\,^5\).

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which has been implicated in the regulation of cell proliferation.\textsuperscript{6,7} Fumagillin and its analogues potently inhibit the proliferation of SMCs\textsuperscript{8} and ECs.\textsuperscript{9} We propose that inhibition of MetAP2 by fumagillin will attenuate the proliferation of SMCs and ECs and reverse pulmonary artery remodeling in animal models of PH.

Aims

Specific Aim 1: Determine the relative expression of MetAP2 in human lungs from patients with primary pulmonary arterial hypertension (PAH, WHO-Class I) and PH secondary to idiopathic pulmonary fibrosis (WHO-Class III) vs. normal controls.

Specific Aim 2: Determine if inhibition of MetAP2 by fumagillin will attenuate the development of PH in monocrotaline (MCT)-injured rats after PH is established, 14-28 days after MCT injury.

Specific Aim 3: Determine if inhibition of the MetAP2 pathway in two animal models of PH secondary to pulmonary fibrosis can decrease both fibrosis and PH. [These experiments are now underway.]

Methods:

1. Quantitative RT-PCR: Primers specific for human MetAP2 and the endogenous control PPIA were obtained.

2. MCT-Induced PH: A single subcutaneous injection of MCT (60 mg/kg) or vehicle control was administered on day 0 to male rats. Fumagillin (0.5 mg/kg) was administered by inhalation beginning at 3d [EARLY] or 14d [LATE] after MCT.


4. Measurement of Hemodynamics and Echocardiography: Five weeks after MCT injury, RV ejection fraction, end-diastolic pressure, and right ventricular-arterial coupling [Ees/Ea] were evaluated.

5. Measurement of Cardiomyocyte Cross-Sectional Area and Vessel Thickness: Pulmonary vessels <250 μm were identified by morphological features and their proximity to airways.

6. Immunostaining of Rat and Human Lung: Human lung tissues from patients with idiopathic PAH [IPAH, WHO-Class I] or normal controls were obtained and immunohistochemistry was performed for Ki67, MetAP2, and von Willebrand Factor. Immunostaining for CD45 was performed on cryosections of lungs from rats.

7. Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling (TUNEL): TUNEL+ cells were counted as the number of positively-staining nuclei per high power field.

Results

Specific Aim I: No significant difference in MetAP2 gene expression was detected between IPAH and normal controls.

Specific Aim II: Delivery of fumagillin beginning 14d after MCT injury (LATE) failed to prevent PH, but surprisingly, inhibited RV hypertrophy in the presence of PH. This inhibition of RV remodeling was clearly associated with improved health in these animals:

1. MCT-injured animals treated with fumagillin lost less weight than vehicle-treated controls (Figure 1).

2. Early, but not late, treatment with fumagillin prevented MCT-induced PH.

3. Late treatment with fumagillin prevented MCT-induced RV remodeling despite the presence of PH.

4. Early treatment with fumagillin preserved RV function in MCT-injured animals. Late treatment provided intermediate protection between vehicle-treated and early fumagillin-treated animals.

5. Both early and late treatment with fumagillin inhibited cardiac myocyte hypertrophy.

6. Fumagillin treatment did not prevent MCT-induced neoangiogenesis in the heart.
7. Fumagillin treatment significantly reduced apoptosis in the RVs of MCT-injured rats.

8. Fumagillin treatment was associated with a mild reduction in inflammatory cells in the lungs of MCT-injured animals.

Conclusions

Early treatment with fumagillin prevented MCT-induced PH, but the protective mechanism of fumagillin in MCT injury is far more complex than a simple effect on SMC proliferation.

Animals treated early with fumagillin exhibited decreased vessel thickness. We uncovered an anti-inflammatory effect of fumagillin following MCT injury, as we found fewer CD45+ leukocytes in the lungs of MCT-injured, fumagillin-treated animals compared to controls. Perhaps our most surprising observation was that late treatment of MCT-injured animals with fumagillin disconnected RV remodeling from PH.

The MCT-injured, late fumagillin-treated animals exhibited both decreased RV mass and decreased RV cardiac myocyte cross-sectional area compared to the MCT-injured vehicle controls. No clear difference was detected between the numbers of capillaries in MCT-injured animals treated with fumagillin late or the vehicle, suggesting that the effect of fumagillin in the heart was not a result of altered neoangiogenesis.

Apoptosis was significantly reduced in the hearts of MCT-injured animals treated with fumagillin compared with the vehicle controls. We suggest that the effect of fumagillin on the myocardium is at least partially protective. MCT-injured rats treated with fumagillin beginning 14d after injury exhibited decreased weight loss compared to the vehicle controls. Our data support a growing body of literature suggesting that RV failure in PH is not solely explained by RV pressure afterload.10,11

References

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 immediate 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.
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Dr. Harrison (Hap) 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 is 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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Dr. Adaani Frost is Professor of Medicine in the Pulmonary and Critical Care Section of Baylor College of Medicine, Houston, Texas. 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 has since 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, is on the steering committee of REVEAL (a US-based registry of more than 3500 pulmonary hypertensive patients), has authored numerous papers on pulmonary hypertension, and is a participant in multiple new and ongoing studies in the treatment of pulmonary hypertension.
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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, Illinois. 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.

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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 – 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 100 published manuscripts, 19 reviews, 5 book chapters and 1 full length book. 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 ‘Two-Stage Genome-Wide Association Study in Scleroderma’ that has the dual objectives to identify genes that influence disease susceptibility and severity, as well as to serve as a national resource to supply genetic material to other investigators to study this disease.
Evangelos D. Michelakis, MD, FACC, FAHA

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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 Pulmonary Hypertension and the Chair-Elect of the 3-CPR 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.

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Harold I. Palevsky, MD, is a Professor of Medicine at 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, lung transplant evaluation, 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.”
Biography

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Ivan M. Robbins, MD, is Associate Professor of Medicine, Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine and Director of the Pulmonary Vascular Center at Vanderbilt University Medical Center.

Dr. Robbins earned a medical degree from Case Western University School of Medicine, completed an internship and residency at Metrohealth Medical Center, and pursued a Pulmonary and Critical Care fellowship from Vanderbilt University School of Medicine.

An internationally recognized expert in the field of pulmonary vascular disease, Dr. Robbins’ research interests include the mechanisms of action of epoprostenol and the role of oxidant stress in pulmonary arterial hypertension. He has been published in numerous peer-reviewed journals, including Circulation, American Journal of Respiratory and Critical Care Medicine, and the Journal of the American College of Cardiology.

Biography

Richard M. Silver, MD
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Dr. Richard Silver serves as Director of the Division of Rheumatology & Immunology at the Medical University of South Carolina (MUSC). He was born in Tennessee and graduated from the University of Tennessee-Knoxville. After graduating from Vanderbilt University School of Medicine in 1975, Dr. Silver completed training in Internal Medicine at the University of North Carolina-Chapel Hill, and then in Rheumatology at London’s Northwick Park Hospital and at the University of California-San Diego. He joined the faculty at MUSC in 1981, where currently he is Professor of Medicine and Pediatrics and is the Director of the Division of Rheumatology and Immunology. 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.