ENTELLIGENCE™
Young Investigators
Award Program

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

We are delighted to announce that in 2011, 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 and 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 30 promising researchers in the field of pulmonary hypertension have been funded.

Original basic and 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, 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. ENTELLIGENCE 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.

ENTEILLIGENCE 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: 6
Awards distributed: 34

Awarded 2011

Jana Bagerova, 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

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

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
Columbia University
College of Physicians and Surgeons
Mentor: Jahar Bhattacharya, MBBS, DPhil
Project Title: Targeting the MetAP2 Pathway in Pulmonary Arterial Hypertension

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
Boston Adult Congenital Heart Program
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

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 (Formerly, Stanford 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
Overview of ENTELLIGENCE Awards

Awarded 2008

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
Overview of ENTELLIGENCE Awards

Awarded 2007

Olga Rafikova, MD, PhD
Georgia Health Sciences University (Formerly, University of Pittsburgh)
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

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
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 attenuates signaling of...
Jana Bagarova, PhD

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...
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 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 from athymic rats with
Yon K. Sung, MD

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.

Eric Douglas Austin, MD, MSCI

Vanderbilt University Medical Center
Nashville, Tennessee

Sex Hormone Abnormalities in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive, fatal disease characterized by increased pulmonary vascular resistance and arterial pressure resulting in right heart failure and rapid death. Most types of PAH, including heritable (HPAH) and idiopathic (IPA), predominantly affect women for unknown reasons, and our preliminary laboratory data support the central hypothesis that sex hormone variation modifies disease expression in PAH, with metabolites that possess greater estrogenic effects in abundance compared to those with less estrogenic effects. To test our hypothesis, we will determine whether mediators of estrogen and androgen activity are associated with HPAH and IPA in females and males. We hypothesize that higher estrogen activity (e.g., as represented by a lower ratio of 2-hydroxyestrogens: 16α-hydroxyestrogens) will be associated with increased risk of disease and younger age at diagnosis. We expect this study to confirm and extend the PI’s preliminary studies demonstrating altered sex hormone levels in PAH patients, with implications for disease prevention and therapy.
Angela V. Ghatnekar, PhD
Medical University of South Carolina
Charleston, South Carolina

The Role of GATA-6 in Pulmonary Arterial Hypertension

Our recent data revealed that GATA-6, a zinc-finger transcription factor, is strikingly down-regulated at the mRNA and protein level in endothelial cells (ECs) lining all vessel types, both occluded and non-occluded, in idiopathic pulmonary arterial hypertension (PAH) patients, as well as systemic sclerosis-associated PAH patients. In addition, we have found that GATA-6 transcript levels are reduced in the lungs of the monocrotaline rat model of PAH at an early time point in disease onset. Furthermore, in vitro data suggest that loss of GATA-6 in ECs leads to a reduction in EC markers and an increase in markers of vascular remodeling. Based on our preliminary findings, we hypothesize that loss of GATA-6 after vessel injury may be an important component of EC activation/dysfunction. Moreover, reduction of GATA-6 may be an important early feature of PAH. To study the potential role of GATA-6 in PAH, we propose to investigate the functional consequences of reduced GATA-6 in ECs, both in cultured human pulmonary artery endothelial cells (HPAECs) and in mouse lungs in vivo. In specific aim 1, we will investigate changes in gene expression patterns in HPAECs with reduced GATA-6 using Human Endothelial Cell Biology PCR arrays. Putative direct transcriptional targets will be validated using quantitative RT-PCR, western blotting, and chromatin immunoprecipitation (ChIP) analysis. In specific aim 2, we propose to investigate the functional consequences of decreased GATA-6 levels in pulmonary endothelial cells in vivo using transgenic mice [Cre/loxP system] with conditional GATA-6 knockdown in endothelial cells. GATA-6 conditional knockout mice will be characterized by performing hemodynamic analyses and lung tissue analyses with respect to vascular abnormalities. Lung endothelial cells will also be isolated to check for differential expression of markers identified in Aim 1, which may be specifically altered in response to GATA-6 down-regulation. We expect that once these experiments are complete, they will provide us with novel insights about the molecular mechanisms contributing to vascular remodeling in PAH.
pulmonary hypertension; however, their role in neonatal PPHN is less well defined. We recently reported a role for ROCK2 in regulating angiogenesis in the developing lung and the finding that high ROCK activity contributes to impaired angiogenesis in PPHN. While the effect of ET-1 on angiogenesis in the developing lung remains unknown, ET-1 is an important regulator of ROCK activity and many of the effects of ROCK parallel those of ET-1. Gaining a better understanding of the mechanisms of ROCK and ET-1 interactions that produce vascular remodeling and impaired angiogenesis in severe neonatal PPHN will lay the foundation for the development of novel therapies that will improve outcomes in this setting.
Gene Therapy to Drive Endogenous Biosynthesis of Prostacyclin

The overall goal of this proposal is to design and test a gene therapy strategy for pulmonary arterial hypertension (PAH). PAH is a rare, deadly, and incurable disease with a mean survival of 2.8 years from onset of symptoms, if left untreated. Of the three classes of approved therapeutics, endothelin receptor antagonists, phosphodiesterase inhibitors, and prostacyclins, prostacyclin is the most effective therapy. However, complicated delivery systems and potential side effects associated with the present formulation of prostanoids (e.g., prostacyclin) have deterred some patients and caregivers from instituting this highly effective class of agents. The challenge to be addressed by this proposal is the need for a therapeutic regimen that allows for endogenous production of prostacyclin therapy within the patient’s own body, throughout the entire lifetime of the patient. Because prostacyclin can be produced endogenously through expression of the enzyme prostacyclin synthase (PGIS), gene therapy has previously shown proof-of-principle efficacy in animal models by enabling endogenous production of prostacyclin and reversal of experimental PAH. This proposal will build upon this concept, but will execute this strategy using newly developed gene transfer technology that obviates the viral gene delivery vectors used in prior studies. Viral vectors have been extremely useful in earlier studies, but have limited duration of expression, and, due to host immune response, cannot affect life-long therapy nor can they be re-dosed. Our gene delivery system, which uses ultrasound-induced microbubble cavitation to allow entry of non-viral DNA vectors into cells, is thought to evade host immune responses, theoretically allowing re-dosing of the PGIS therapeutic transgene as a periodic booster throughout the entire lifespan of the patient. An additional innovation of this proposal toward achieving the field-wide goal of endogenous prostacyclin production is the choice of the salivary glands as the therapeutic biosynthesis site. The salivary glands can be accessed through a bloodless, outpatient procedure, and contain a robust endocrine secretory pathway capable of secreting transgene products into the intravascular space. The encapsulated, fixed volume of the intraductal labyrinth of the salivary glands also allows precise control of the delivery system, making ultrasound-assisted gene transfer (UAGT) far more practical and consistent than has been observed in other organs (e.g., heart or pancreas). A final innovation of this proposal is the choice of the salivary glands as the therapeutic biosynthesis site. The salivary glands can be accessed through a bloodless, outpatient procedure, and contain a robust endocrine secretory pathway capable of secreting transgene products into the intravascular space. The encapsulated, fixed volume of the intraductal labyrinth of the salivary glands also allows precise control of the delivery system, making ultrasound-assisted gene transfer (UAGT) far more practical and consistent than has been observed in other organs (e.g., heart or pancreas). A final innovation of this proposal is the first in vivo application of a Cox-1/PGIS fusion protein that produces dramatically higher levels of prostacyclin than PGIS alone. In summary, this project seeks to innovatively test the enticing idea of PGIS-based gene therapy for PAH, aggregating three enabling technologies: 1) a practical, re-dosable gene delivery technique; 2) a novel biosynthesis site (salivary glands) that can be accessed through an outpatient procedure; and 3) a Cox-1/PGIS fusion protein transgene that produces superior levels of therapeutic prostacyclin. The efficacy of this gene therapy strategy will be tested in a highly relevant rat model of severe PAH.
Michael York, MD
Boston University Medical Center
Boston, Massachusetts

dsRNA Stimulates Toll-like Receptor-3 and Increases Endothelin-1 Production by Pulmonary Artery Endothelial Cells

We propose, in this work, that dsRNA stimulates toll-like receptor [TLR]3 on endothelial cells, causing endothelin-1 (ET-1)-mediated fibrosis, vasoconstriction, and inflammation, as a mechanism of relevance in immune-mediated causes of pulmonary arterial hypertension (PAH). Research will focus on investigating how the immune system causes endothelial cell dysfunction, a hallmark of systemic sclerosis (SSc), and how these events may lead to PAH, a frequent cause of mortality in SSc. We have shown that interferon (IFN)-regulated genes are expressed highly in SSc patients’ peripheral blood mononuclear cells and also have demonstrated that this can be replicated by nucleic acid-containing immune complexes stimulating TLRs. We have recently extended this finding to endothelial cells and hypothesize that the phenotype of SSc, particularly the vasculopathy, may be induced through extracellular dsRNA binding to a specific TLR on endothelial cells, called TLR3. TLR3 is unique among the family of TLRs in that it signals using a different adaptor protein, and also has both endosomal and cell surface expression in endothelial cells. Stimulation of endothelial cell TLR3 has been shown to be pro-inflammatory and inhibit blood vessel growth (antiangiogenesis). Our preliminary data demonstrate that dsRNA stimulates endothelial cells via a TLR3-dependent mechanism to produce the vasoactive and pro-fibrotic peptide, ET-1, a molecule strongly implicated in SSc pathogenesis. We also show that continuous infusion of dsRNA into mouse dermis leads to inflammation, marked up-regulation of IFN-regulated genes, increased ET-1 in the skin, lung, and serum, and increased dermal fibrosis. All of these effects are abrogated in mice deficient in TLR3 signaling. Therefore, we hypothesize that dsRNA, possibly contained in circulating immune complexes or in cellular debris, triggers TLR3 on endothelial cells, resulting in inflammation, endothelial cell dysfunction, and vasculopathy. To test our hypothesis, we will: 1) examine the role of TLR3 stimulation in pulmonary artery endothelial cell (PAEC) dysfunction and apoptosis; and 2) investigate the effects of prolonged infusion of dsRNA into mice and quantify endothelial cell activation, ET-1 production, and histologic changes.
Olga Rafikova, MD, PhD
Georgia Health Sciences University (Formerly, University of Pittsburgh)
Augusta, Georgia

Mentor
Stevan P. Tofovic, MD, PhD
Assistant Professor
Department of Medicine
University of Pittsburgh School of Medicine

Biochemical and Molecular Biology studies performed in the lab of
Stephen M. Black, PhD
Professor, Department of Obstetrics and Gynecology
Medical College of Georgia
Georgia Health Sciences University

Protein Nitration and Anti-remodeling Effects of Endothelin Receptor Antagonists in Pulmonary Hypertension

Background
Pulmonary arterial hypertension (PH) is a progressive and fatal disease, characterized by uncontrolled pulmonary vascular cell proliferation.(1) However, the molecular mechanisms and temporal pathological events in the development of PH are unresolved. A severe form of PH in humans is characterized by clustered proliferation of endothelial cells (ECs) in the lumen of the pulmonary artery resulting in concentric obliteration of the lumina and complex vascular structures known as plexiform lesions.(1,2) Three-dimensional analysis of vascular lesions revealed the existence of two EC phenotypes in severe PH: (i) normal quiescent, apoptosis-sensitive ECs, located in the peripheral area, that have a high expression of cell cycle inhibitory protein p27\(^{kip1}\), a marker of low growth potential and (ii) highly proliferative, apoptosis-resistant cells in the central core of the vascular lesion, that have low expression of p27\(^{kip1}\). Thus, the tumor-like proliferation of ECs may be the underlining process in severe PH.(3) A rat model of severe PH recently developed by Dr. Voelkel and colleagues is also characterized by marked pulmonary vascular lesions that are similar to those seen in humans with severe PH.(4,5) Therefore, it was important to examine the treatment effects of bosentan on pulmonary hemodynamic parameters and cardiac and vascular remodeling in a model of PH which mimics key alterations seen in the severe form of PH in humans. The aim of this study was to determine the role of endothelin receptors (ETRs) in the development of a human-like model of severe PH.

Methods
Female Sprague Dawley rats were assigned to normoxia or combination of chronic hypoxia and a single injection of SU5416 [200mg/kg] in the presence or absence of the non-selective ETR antagonist bosentan treatment [250mg/kg/day] started on day 10 of study:

- **Control (1):** Control SD rats.
- **CH-10d (SU 10d) (2):** Diseased time control group; animals examined after 10-day exposure to hypoxia and single injection of SU5416 [200mg/kg].
- **CH-21d (SU 21d) (3):** Diseased animals, rats exposed to hypoxia for 21 days + single dose of SU5416.
- **Bosentan (4):** Diseased animals treated with bosentan [250mg/kg mixed with rodent transgenic dough] starting from the 10th day of exposure to hypoxia.

On the 21st day of exposure to hypoxia, animals were anesthetized and instrumented for measurement of right ventricle (RV) and systemic blood pressure, then euthanatized. Measurements included superoxide levels in lung tissue, total superoxide dismutase (SOD) and manganese SOD (MnSOD) activities, nitrite content in plasma samples, total level of protein dityrosine formation, and levels of antigen CD34.
Results
PH was characterized by a significant continuous increase in RV peak systolic pressure (RVPSP) and RV hypertrophy in accordance with the duration of chronic hypoxia and a marked increase in the levels of both ETR (ETA and ETB) in the lung. The levels of oxidative stress and nitrative stress, i.e., total protein nitration and nitration of specific proteins (MnSOD and endothelial nitric oxide (NO) synthase (eNOS)), were also significantly higher. In contrast, NO bioavailability was markedly diminished. These changes correlated with the loss of MnSOD activity, eNOS uncoupling, and both lung endothelial and smooth muscle cell (SMC) proliferation. Bosentan treatment preserved RVPSP and RV hypertrophy and resulted in a decrease in ETA and ETB protein levels, reduced oxidative stress (Figure 1), decreased protein nitration, and markedly attenuated pulmonary endothelial and SMC proliferation.

Conclusion
The recently developed, unique, human-like model of severe PH reproduces the main histological changes associated with PH in humans (i.e., complex precapillary arteriolar lesions, which contain phenotypically altered SMCs and ECs). This model creates new opportunities in studying the underlying mechanisms of human-like disease in animals. However, this relatively new model is not completely characterized and the information concerning the development of endothelial dysfunction and changes in NO metabolism is insufficient. Nevertheless, those events are considered to play the critical role in idiopathic PH development.

There is an urgent necessity for an animal model that reproduces human-like endothelial dysfunction. Our results suggest the severe PH model, which combines chronic hypoxia with vascular endothelial growth factor (VEGF) receptor inhibition, mimics the alterations in NO metabolism known to be induced by PH in humans. This study represents data showing that

PH mediates the reduction in NO bioavailability due to inhibition of eNOS activity and increased production of superoxide, an active NO scavenger. Notably, the product of superoxide and NO reaction, peroxynitrite, induces a massive protein nitration also known to occur in lungs of patients with PH.[6] Thus, the severe PH model reproduces the situation seen in humans when active NO is diminished while the amount of deleterious peroxynitrite is increased, contributing to further oxidative stress development.

Bosentan is one of very few therapies that were found to be effective in complete prevention of PH progression in this model. These results provide a rationale for using bosentan to stop PH progression in patients

Figure 1. Levels of superoxide production in lung tissue of healthy controls and animals with severe PH, with and without bosentan treatment. (n=6) *P<0.05 vs. Control; †P<0.05 vs. SU 21d.
and also underline the role of up-regulated ET signaling and the particular ET mediated pathological mechanisms in PH development. Moreover, the data obtained from this study provide a good background for the improvement of present treatments or the creation of new strategies and therapies aimed to prevent and reverse PH development.

References

Results

Fibrocytes
Children with PH had significantly higher percentages of fibrocytes in peripheral blood compared to controls. No differences were observed in fibrocyte numbers among children with idiopathic PH compared to secondary PH. No differences were observed in fibrocyte numbers among female and male children with PH (mean 4.2% each). Children untreated or undergoing one treatment [Ca channel blockers, or sildenafil, or ambrisentan] had a mean fibrocyte count of 3.02%, while for children treated with two drugs it was 3.9%, and for children undergoing three or more treatments the fibrocyte count was 5.98%. The children with the most severe disease were those receiving three or more medications.

Fibrocyte numbers showed statistically significant correlation to mean pulmonary artery pressure, increasing age, and increasing duration of treatment (all p < 0.05). No correlations were found between fibrocyte numbers and any of: gender, six minute walk distance, plasma brain natriuretic peptide (BNP), or N-terminal pro-brain natriuretic peptide (NT-BNP).

MDSC:
We found that children with PH had significantly higher percentages of MDSC compared to controls. No differences were observed in MDSC numbers among children with idiopathic PH compared to secondary PH. Females with PH had higher MDSC compared to males with PH.

MDSC counts showed correlation to mean pulmonary artery pressure, increasing age, and duration of treatment in years (all p < 0.05).

Phospho-STAT3 was detected in MDSC sorted from blood of PH patients but not controls. Control MDSC had minimal Arg-1 gene expression and activity, while those from PH patients showed enhanced expression and activity of Arg-1.

Conclusion

Fibrocytes: We tested the hypothesis that fibrocytes would be increased in the circulation of patients with PH. We found a four-fold increase in circulating fibrocytes in pediatric patients with pulmonary hypertension compared with control individuals undergoing catheterization for arrhythmia. In addition, we found correlation between fibrocyte counts and mean pulmonary artery pressure as well as number and duration of PH therapies. Our data support the notion that the presence of these progenitor cells may contribute to pathological pulmonary vascular remodeling in the setting of inflammation. This is the first demonstration that children with PH harbor increased numbers of circulating fibrocytes, a cell type that has been identified in adults with chronic inflammatory disorders and is associated with poor prognosis, inflammation, and tissue remodeling in the lung. Our study might therefore represent the first step in understanding putative pathological roles of fibrocytes in the course of pediatric pulmonary hypertension.

MDSC: We have previously shown that cells (fibrocytes) of a mononuclear phagocytic origin accumulate in peribronchovascular regions in animal models of PH and likely contribute to vascular remodeling (1). Others have described immature myeloid cells in similar regions in humans and in animal models, often in proximity with T and B lymphocytes (2). Furthermore, observations of impaired dendritic cell function (3) and increases in Treg lymphocytes (4-5) convinced us to test whether MDSC would be elevated in patients with PH vs. controls. We demonstrate a 3.5-fold increase in circulating CD45+/CD33+/MHCII-/CD11b+ MDSC in PH patients compared with controls. We found correlation between MDSC counts and mean pulmonary artery pressure, age, and duration of treatment. Our finding of activated MDSC in PH blood supports the notion that their presence may contribute to pathological pulmonary vascular remodeling in the setting of PH. This is the first demonstration that children and young adults with PH harbor increased circulating...
activated MDSC, a potent immunomodulatory cell functionally implicated in the pathobiology of chronic inflammatory disorders, cancer, and immunosuppression phenomena.

References


response. We estimated the interaction between treatment assignment (ERA vs. placebo) and sex, and between treatment and white or black race, in terms of the change in six-minute walk distance (6MWD) from baseline to 12 weeks, the absolute walk-distance achieved, and the rates of occurrence of a composite measure of clinical events (death, hospitalization for right heart failure, initiation of an additional pulmonary vasodilator, or clinical worsening of right ventricular function).

### Results

Trials included 1130 participants with a mean age of 49 years; 21% were male, 74% were white, and 6% were black. The placebo-adjusted response to ERAs was 29.7m (95% CI: 3.7m, 55.7m) greater in women than in men (p = 0.03). The placebo-adjusted response was 43.6m (95% CI: -3.5m, 90.7m) greater in whites than in blacks (p = 0.07). Similar results were found in a series of sensitivity analyses, and in secondary analyses using absolute distance walked as the outcome. Rates of reduction in clinical events with ERAs vs. placebo were also greater for women than men and for whites than blacks, but these were not statistically significant due to small numbers of total events.

Aim I: Our primary hypotheses in this Aim, based on animal data and studies of the use of ERAs in essential hypertension in humans, were that (1) men would have greater placebo-adjusted responses to ERAs than women, and (2) blacks would have greater placebo-adjusted responses to ERAs than whites. We tested these hypotheses using generalized linear models (with study entered as a fixed effect) of all patients randomized to an ERA or placebo in one of the 7 placebo-controlled trials of ERAs. Because these trials were of differing duration [12-18 weeks], we chose change in 6MWD from baseline to 12 weeks as the primary endpoint, and change in 6MWD from baseline to the final measured 6MWD as a secondary endpoint. Variables forced into the model using the foregoing criteria were baseline hemoglobin, creatinine, sodium, cardiac index, and pulmonary capillary wedge pressure. Contrary to our hypotheses, we found that women have greater placebo-adjusted treatment responses to ERAs than do men [treatment-by-sex interaction: p = 0.043] and that there was no difference in the placebo-adjusted treatment responses among blacks and whites [treatment-by-race interaction: p = 0.58]. When we used final 6MWD to calculate change in 6MWD rather than 12-week 6MWD, the results were nearly identical. These results suggest that ERAs provide greater improvements in 6MWD among women than among men with PAH, and that their effects on blacks and whites are similar.

Aim II: Our primary hypotheses in this Aim were the same as in Aim I but now the outcome variable was the risk for a clinical event rather than change in 6MWD. We therefore used multivariable logistic regression, conditional on study, to complete these analyses. Similar variables were forced into this model as were forced into the models in Aim I, except that in this model, we also used baseline 6MWD as a covariate. We found a trend towards a reduction in clinical events associated with the use of ERAs vs. placebo (p = 0.063). There was no significant treatment-by-sex interaction (p = 0.50) or treatment-by-race interaction (p = 0.44), suggesting that ERAs provide similar, modest reductions in short-term risks for clinical events among men and women and among whites and blacks.

### Conclusions

Women and whites had greater response to ERAs than men and blacks with PAH. This heterogeneity in treatment response may reflect pathophysiologic differences between sexes and races or distinct disease phenotypes.
Biography

Ronald J. Oudiz, MD
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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.

Biography

Jocelyn Dupuis, MD, PhD
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Jocelyn Dupuis, MD, PhD, is Associate Professor of Medicine in the Department of Medicine at the University of Montreal. He is a Cardiologist at the Montreal Heart Institute and National Researcher of the Quebec Health Research Funds. He serves as President of the Pharmacology Committee at the Montreal Heart Institute in Montreal.

Dr. Dupuis earned a medical degree from the University of Montreal and a PhD in Experimental Medicine from McGill University. He completed an internship in Medicine at McGill University and post doctoral work in Internal Medicine and Cardiology at Sherbrooke University.

Dr Dupuis is a member of the editorial boards of the Journal of the American College of Cardiology, the American Journal of Pathology, and the Canadian Journal of Cardiology. He has been published in numerous peer-reviewed journals, including Circulation, Journal of the American College of Cardiology, Journal of Nuclear Medicine, Cardiovascular Research, and American Journal of Respiratory and Critical Care Medicine.
Biography

Harrison (Hap) Farber, MD
Professor of Medicine
Boston University School of Medicine
Director, Pulmonary Hypertension Center
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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.

Biography

Adaani E. Frost, MD
Professor of Medicine
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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.
Biography

Mardi Gomberg-Maitland, MD, MSc
Associate Professor of Medicine
Director, Pulmonary Hypertension Program
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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.

Biography

Maureen D. Mayes, MD, MPH
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Dr. Mayes graduated from Eastern Virginia Medical School and completed her Internal Medicine training and Rheumatology fellowship at the Cleveland Clinic. She received a Master’s in Public Health (MPH) in Epidemiology from the University of Michigan School of Public Health. She joined the University of Texas – 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.
Harold I. Palevsky, MD
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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.”

Ivan M. Robbins, MD
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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.