

Preface

Receptors, channels, and transporters play a critical role in vascular signal transduction and are key elements in the pathogenesis of pulmonary vascular disease. They provide front-line mechanisms for regulation of normal smooth muscle, for endothelial and inflammatory cellular homeostasis, and for responding to the extracellular environment and external mediators. Pathophysiological perturbations in their function and expression are associated with profound alterations in cellular function and make significant contributions to the development and progression of disease. As they are in the main situated in the plasma membrane and their molecular nature is often conducive to modulation of function by relatively highly specific agents, receptors, channels, and transporters are potentially key targets for novel therapeutics. Indeed, a high proportion of currently available therapeutic agents function as channel or transporter modulators or receptor antagonists and agonists.

Over the last few years, there have been significant advances in our understanding concerning the expression and function of novel channels, receptors, and transporters in the pulmonary circulation. Since the last Grover conference on the role of ion flux in pulmonary vascular control in 1992, several entirely new molecular classes of ion channels (e.g., transient receptor potential [TRP] channels and two-pore domain K^+ channels) have been identified and have more recently been shown to play key roles in pulmonary vascular function and the development of pulmonary arterial hypertension. In addition, the advent of enhanced molecular techniques, gene knockout models, and the Human Genome Project has provided new insight into the molecular identity and role of K^+ and Cl^- channels, water channels (aquaporins), and intracellular Ca^{2+} channels in pulmonary vascular function and disease.

One of the major advances in the research field of pulmonary arterial hypertension has been the identification of an association between disease development and genetic mutations in the bone morphogenetic protein receptor II (BMPR-II) and related pathways. New evidence suggests that there are significant interactions between bone morphogenetic protein and serotonin signaling and indeed modulation of ion channel expression and function. These and other similar interrelationships are likely to define a significant proportion of the altered vascular function and modeling of the pulmonary circulation in disease.

We therefore saw a need for a forum where these mechanisms and pathways can be discussed together, so identifying and highlighting the potential therapeutic

opportunities that this apparent convergence of pathways may reveal. This book presents the proceedings of the 2008 Grover Conference (Lost Valley Ranch and Conference Center, Sedalia, CO; September 3–7, 2008), which provided a forum for experts in the fields of those receptors, channels, and transporters that have been identified as playing key roles in the physiology and pathophysiology of the pulmonary circulation. The book rigorously addresses (1) recent advances in our knowledge of receptors, channels, and transporters and their role in regulation of pulmonary vascular function; (2) how modulation of expression and function of receptors, channels, and transporters and their interrelationships contribute to the pathogenesis of pulmonary vascular disease; and (3) the therapeutic opportunities that may be revealed by enhancing our understanding of this area.

The overall goal was to explore the mechanisms by which specific receptors, channels, and transporters contribute to pulmonary vascular function in both health and disease and how this knowledge may lead to novel interventions in lung dysplasia, pulmonary edema, lung injury, and pulmonary and systemic hypertension to reduce and prevent death from lung disease.

The book is divided into six parts. Part I (“Ion Channels in the Pulmonary Vasculature: Basics and New Findings”) is designated for basic knowledge and recent findings in the research field of ion channels in pulmonary circulation. There are five chapters in Part I discussing the function, expression, distribution, and regulation of various ion channels present in pulmonary vascular smooth muscle cells and how these channels are integrated to regulate intracellular Ca^{2+} and cell functions. Part II (“TRP Channels in the Pulmonary Vasculature: Basics and New Findings”) is composed of five chapters that are exclusively designed to discuss the role of a recently identified family of cation channels, transient receptor potential (TRP) channels, in the regulation of pulmonary vascular tone and arterial structure. Part III (“Pathogenic Role of Ion Channels in Pulmonary Vascular Disease”) presents four chapters that discuss how abnormal function and expression of various ion channels contribute to changes in cell functions and the development of pulmonary hypertension. Part IV (“Receptors and Signaling Cascades in Pulmonary Arterial Hypertension”) consists of five chapters devoted to the role of bone morphogenetic protein receptors, Notch receptors, serotonin receptors, Rho kinase, and vascular endothelial growth factor receptors in the development of pulmonary arterial hypertension. Part V (“Receptors and Transporters: Role in Cell Function and Hypoxic Pulmonary Vasoconstriction”) has four chapters designed to illustrate the potential mechanisms involved in oxygen sensing and hypoxia-induced pulmonary vasoconstriction and hypertension. Part VI (“Targeting Ion Channels and Membrane Receptors in Developing Novel Therapeutic Approaches for Pulmonary Vascular Disease”) consists of five chapters that discuss the translational research involving membrane receptors, channels, and transporters, including their potential as novel drug targets.

We hope that this book will allow readers to foster new concepts and new collaborations and cooperation among investigators to further understand the role of receptors, channels, and transporters in lung pathophysiology. The ultimate goal is to identify new mechanisms of disease as well as new therapeutic targets for pulmonary vascular diseases. An additional outcome should be enhanced understanding of the

role of these entities in systemic vascular pathophysiology since the conference included researchers and clinicians with interests in both pulmonary and systemic circulations.

The book could not have been completed without the support and encouragement of our families (Ayako Makino, Dolores) as well as our mentors, colleagues, and students at the University of California, San Diego (La Jolla, CA) and the King's College (London, UK). We are especially grateful to Ms. Mindy Okura-Marszycki for her instruction for compiling the book, to Dr. Carmelle V. Remillard for her diligence in preparing the figures and editing the text, and to all the contributors and speakers for their patience and conscientiousness in writing the manuscripts and presenting at the conference (Fig. 1). In addition, we thank the staff of the American Thoracic Society for their excellent help in running the conference and all our sponsors for supporting it. Finally, we would like to take this opportunity to thank Dr. Robert F. Grover and his wife, to whom this book is dedicated.



Fig. 1 Grover Conference 2008. *Front row (left to right):* Andrea Olszewski, Chandran Nagaraj, Angel Cogolludo, Tom Resta, Michelle Connolly, Donna Cioffi, Robert Grover, Karen Fagan, Ming-Yuan Jian, Konstantin Birukov, and Phillip Aaronson. *Middle rows (second and third row) (left to right):* Liliana Moreno-Vinasco, James Sham, Lih Chyan Ng, Usha Raj, Christina Barry, Charles Hales, Carmelle Remillard, Nikki Jernigan, Claudie Hecquete, Sabine Lange, Michael Sanderson, Larissa Shimoda, Francisco Perez-Vizcaino, Gaurav Choudhary, Normand Leblanc (inside the car), Ken Weir, Liz Weir, Allison Gurney (inside the car), Elise Grover, Mary Townsley, Mark Evans, Patricia Thistlethwaite, Gregory Knock, Eloa Adams, Navdeep Chandel, Rich Minshall, Norbert Weissmann, Zhigang Hong, Troy Stevens. *On the car (left to right):* John Westwick, Marlene Rabinovitch, Jeremy Ward, Jason Yuan, David Cornfield, Jens Lindert, Jessica Snow, Ralph Schermuly. *Absent from picture:* Steve Abman, Stephen Archer, David Clapham, Mark Gillespie, Brian Hanna, Joseph Hume, Landon King, Margaret MacLean, Asrar Malik, Ivan McMurtry, Dolly Mehta, Nicholas Morrell, Kurt Stenmark, Matt Thomas, and James West

History of the Grover Conference

The Grover Conferences on the Pulmonary Circulation were initiated in 1984 by Drs. John T. Reeves and E. Kenneth Weir in recognition of the many contributions of Dr. Robert F. Grover (Fig. 2) to our understanding of the physiology and pathophysiology of the pulmonary vasculature. His studies of brisket disease in cattle at high altitudes were among the first (1960) and were certainly the most complete descriptions of chronic pulmonary hypertension. He initiated or participated in investigations into factors influencing acute and chronic hypoxic pulmonary hypertension, including species differences, sympathetic activity, prostaglandins, endotoxins, calcium antagonists, mast cells and histamine, acetylcholine, unilateral pulmonary arterial ligation, ethyl alcohol, platelets, genetic factors, and cold exposure.

Dr. Grover conducted the initial studies showing a reversible component in pulmonary hypertension in congenital heart disease (1961) and the presence and reversibility of pulmonary hypertension in normal North American residents at high altitude (1963, 1966). He was involved in the first measurements of pulmonary vascular reactivity in pregnant women and in persons susceptible to high-altitude pulmonary edema and in investigations of high-altitude pulmonary edema in children of Leadville, Colorado.

These conferences provide North America's only ongoing forum dedicated to the pulmonary circulation. The conferences have been held in Deckers, Colorado, every second year (with one extra interpolated conference in 1991). The first in 1984 focused on pulmonary reactivity; the second on lipid mediators in the pulmonary circulation; the third on the control of cellular proliferation in the pulmonary vascular wall; the fourth on the diagnosis and treatment of pulmonary hypertension; and the fifth on the pathophysiology of the pulmonary circulation and gas exchange. The sixth in 1992 applied the knowledge of ion channels and transporters to the

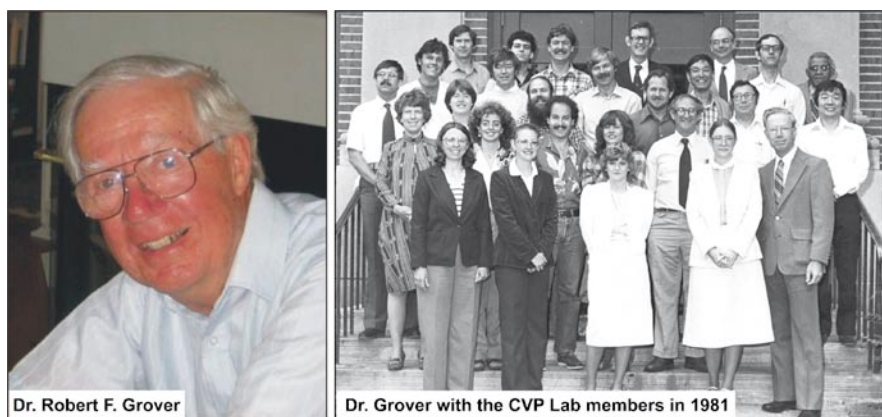


Fig. 2 Robert F. Grover, MD, PhD (*left*), and members of the Cardiovascular Pulmonary (CVP) Research Laboratory (in 1981, *right*)

Table 1 The Grover Conferences held in 1984–2008

Year	Title	References
1984	Pulmonary vascular reactivity	Chest 88:199S–272S, 1985 Clin Resp Physiol 21:583–590, 1985
1986	Lipid mediators in the pulmonary circulation	Am Rev Respir Dis 136:196–224, 455–491, 762–788, 1987
1988	The control of cellular proliferation in the pulmonary circulation	Am Rev Respir Dis 140:1092–1135, 1446–1493, 1989
1990	The diagnosis and treatment of pulmonary hypertension	Weir EK, Archer SL, Reeves JT (eds) The diagnosis and treatment of pulmonary hypertension. Futura, New York, 1992
1991	The pulmonary circulation and gas exchange	Wagner WW Jr, Weir EK (eds) The pulmonary circulation and gas exchange. Futura, New York, 1994
1992	The role of ion flux in pulmonary vascular control	Weir EK, Hume JR, Reeves JT (eds) Ion flux in pulmonary vascular control. Plenum, New York, 1993
1994	Nitric oxide and oxygen radicals in the pulmonary vasculature	Weir EK, Archer SL, Reeves JT (eds) Nitric oxide and radicals in the pulmonary vasculature. Futura, New York, 1996
1996	Pathogenesis and treatment of pulmonary edema	Weir EK, Reeves JT (eds) Pulmonary edema, Futura, New York, 1998
1998	Control mechanisms in the fetal and neonatal pulmonary circulations	Weir EK, Archer SL, Reeves JT (eds) The fetal and neonatal pulmonary circulations. Futura, New York, 2000
2000	Interactions of blood and the pulmonary circulation	Weir EK, Reeve HL, Reeves JT (eds) Interactions of blood and the pulmonary circulation. Futura, New York, 2002
2002	Pro-inflammatory signaling mechanisms in the pulmonary circulation	Bhattacharya J (ed) Cell signaling in vascular inflammation. Humana, Totowa, New Jersey, 2005
2004	Genetic and environmental determinants of pulmonary endothelial cell function	
2006	Rho family GTPases in pulmonary vascular pathophysiology	
2008	Membrane receptors, channels and transporters in pulmonary circulation: role in the development of pulmonary vascular disease	Yuan JX-J, Ward JPT (eds) Membrane receptors, channels and transporters in pulmonary circulation. Humana Press-Springer, Totowa, New Jersey, 2009

pulmonary vasculature; the seventh studied the role of radicals; the eighth examined the pathogenesis and treatment of pulmonary edema; the ninth discussed the fetal and neonatal pulmonary circulations; the tenth explored the interactions of the blood and the pulmonary circulation; the eleventh looked at proinflammatory signaling mechanisms; the twelfth covered genetic and environmental determinants of

pulmonary endothelial cell function; the thirteenth was devoted to Rho family guanosine triphosphatases (GTPases); and the last in 2008 returned again to the theme of ion channels and transporters (Table 1).

The proceedings of the first conference was published in *Chest* and the second and third in the *American Review of Respiratory Disease*, and the subsequent conferences have been published as books by Futura Publishing Company, Plenum Press, Humana Press, or Humana Press-Springer (Table 1). Thirteen eminent investigators in the field have been selected by the Grover Conference Committee to give the Estelle Grover Lecture (established in 1992), Terry Wagner Lecture (established in 2004), and John Reeves Lecture (established in 2006) (Table 2). In 2008, the Grover Conference Committee and the Program Committee of the American Thoracic Society Pulmonary Circulation Assembly established the Young Investigator Award to recognize outstanding young and new investigators in the research fields of pulmonary circulation, pulmonary vascular biology, and pulmonary vascular disease (Table 2). In addition to invited speakers in the conference, the committee also selected the authors of five abstracts to give oral presentations on their research findings.

In Grover Conference 2008, Dr. Margaret R. MacLean from the University of Glasgow (Glasgow, UK) presented the Estelle Grover Lecture, Dr. Ivan F. McMurtry from the University of South Alabama (Mobile, AL) presented the Terry Wagner Lecture, and Dr. Nicholas W. Morrell from the University of Cambridge (Cambridge, UK) presented the John Reeves Lecture (Fig. 3). Dr. Navdeep S. Chandel from Northwestern University (Chicago, IL) and Dr. Larissa A. Shimoda from Johns Hopkins University (Baltimore, MD) were Young Investigator Awardees in Grover Conference 2008 (Fig. 3).

We encourage you to participate in future Grover Conferences by coming to the meetings as well as by taking part in planning and development of new subjects for the meetings.

Table 2 The named lectures and awards given at the Grover Conferences during 1984–2008

Year	Estelle Grover Lecture	Terry Wagner Lecture	John Reeves Lecture
1992	John A. Bevan, MD		
1994	Edward R. Block, MD		
1996	Timothy W. Evans, MD, PhD		
1998	John T. Reeves, MD		
2000	Wiltz W. Wagner Jr, PhD		
2002	E. Kenneth Weir, MD		
2004	Norbert F. Voelkel, MD	Mark N. Gillespie, PhD	
2006	Barry L. Fanburg, MD	Jeremy P.T. Ward, PhD	Avril V. Somlyo, PhD
2008	Margaret R. MacLean, PhD	Ivan F. McMurtry, PhD	Nicholas W. Morrell, MD

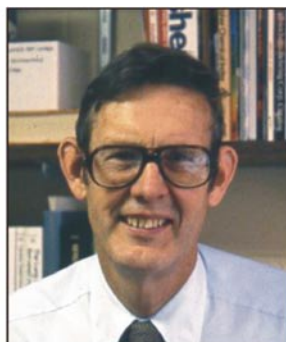
Year	Young Investigator Award
2008	Navdeep S. Chandel, PhD (Northwestern University Feinberg School of Medicine, Chicago, IL) Larissa A. Shimoda, PhD (Johns Hopkins University School of Medicine, Baltimore, MD)



Estelle Grover, 1919-1990



Terry Wagner, 1949-2002



Dr. John T. Reeves, 1928-2004



Dr. Margaret R. MacLean
Estelle Grover Lecturer, 2008



Dr. Ivan F. McMurtry
Terry Wagner Lecturer, 2008



Dr. Nicholas W. Morrell
John Reeves Lecturer, 2008



Dr. Navdeep S. Chandel
Young Investigator Awardee, 2008

Grover Conference



2008



Dr. Larissa A. Shimoda
Young Investigator Awardee, 2008

Fig. 3 Estelle Grover (1919–1990), Terry Wagner (1949–2002), and John T. Reeves (1928–2004), as well as the named lecturers and young investigator awardees at Grover Conference 2008

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