

# The first Keystone Symposia Conference on pulmonary vascular disease and right ventricular dysfunction: Current concepts and future therapies

**Scientific Organizers: Georg Hansmann, Stephen L. Archer, and Margaret R. MacLean**  
**Portola Hotel and Spa, Monterey, California, September 10-15, 2012**

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of pulmonary arterioles leading to increased pulmonary vascular resistance, right heart failure, and death in 30-60% of PAH patients five years after diagnosis. Although PAH is primarily a vascular disease, patients die from right ventricular failure. PAH is a panvasculopathy with key abnormalities evident in the blood, endothelium, smooth muscle cells, and fibroblasts. While the pathology in PAH is mainly evident in the resistance arteries, there are also abnormalities in the large pulmonary arteries and in the right ventricular microcirculation that accompany the syndrome. There is a component of vasoconstriction in many PAH patients; however, recent research suggests a substantial role for excessive proliferation, migration, and resistance to apoptosis of vascular cells. It is also evident that PAH is characterized by proliferative-inflammatory responses mediated by blood and fat cells as well as lymphoid tissue within the lung.

When the NIH registry for primary pulmonary hypertension (PH Category 1) was published in 1987, there were no approved therapies. In 2012, PH is classified into five groups in the WHO classification system. Group 1 PH (i.e., PAH) has a number of approved medical therapies (including calcium channel blockers, prostanoids, endothelin receptor antagonists, inhibitors of phosphodiesterase 5). There are also effective surgical therapies for Group 4 PH (chronic thromboembolic PH), namely pulmonary endarterectomy.

However, despite more than 15 published randomized clinical trials (RCT) that demonstrated moderate effectiveness in improving exercise capacity, the four classes of approved PH drugs have not led to a cure or substantial increase in survival for PAH. Hence, basic science and translational research focusing on the discovery of novel pathways in pulmonary vascular disease (PVD) and right ventricular dysfunction (RVD), new drug targets,

development of novel therapeutic paradigms, cell-based and pharmacotherapies, and their translation into RCTs, is urgently needed.

The first Keystone Symposia Conference on PVD and RVD, organized by Georg Hansmann, Stephen Archer, and Mandy MacLean, gathered 127 basic and clinical researchers working in the field of PVD, right ventricular dysfunction, vascular biology, and lung development, and was held in Monterey, California, in September 2012. Affiliation of the participants was as follows: Academia/research institute (83.33%), industry (4.76%), government (3.17%), other non-profit organizations (3.17%), and unknown (5.56%). Primary job positions were as follows: Student (15.87%), post-doc (16.78%), early-stage investigator (11.11%), established or senior investigator (41.95%), and unknown (3.97%). There were 26 plenary speakers, > 50 oral (short, long) and 70 interactive poster presentations. The session topics are shown in Table 1.

The **full conference report** including brief summaries of each oral presentation can be found in the **Online Supplement**. Several oral presentations have been recorded as **webinars**, and can be found on the website of the Pulmonary Hypertension Association <http://www.PHAOnlineUniv.org/KeystoneSymposium>

The focus of this conference was on basic science with an emphasis on (1) our understanding of this fatal disease, and (2) discoveries with great potential to be translated into clinical practice in the near future. Late-breaking and emerging clinical studies on novel PAH therapies were also presented, underlining the translational, interdisciplinary spirit of this meeting. The Monterey Symposium 09/2012 was the first PH meeting in the Keystone series.

This Keystone meeting addressed new genetic and

**Table 1 : Session Topics of the First Keystone Symposia Conference on PVD and RVD (09/2012):**

- The Role of Stem Cells, Progenitor and Differentiated Blood Cells in Pulmonary Vascular Disease and Repair
- Workshop 1: How to Translate Basic Research Findings into Improvement of Patient Care – The Role of Industry
- Growth Factors, TGF- $\beta$ /BMP Signaling and Pulmonary Vascular Disease
- Metabolic Regulators in Pulmonary Vascular Disease
- Workshop 2: MicroRNAs and iPS Cells – Novel Tools and Targets in Cardiovascular Biology and Pulmonary Vascular Research
- The Right Ventricle in Pulmonary Hypertension: Cardiomyocyte Function and Hemodynamic Performance
- MicroRNAs in Proliferative Vascular Disease
- Innovative Clinical PAH Trials
- Pulmonary Hypertension in Parenchymal Lung and Thromboembolic Diseases
- Workshop 3: Vascular Metabolomics and Proteomics: Where Are the Novel Biomarkers for Pulmonary Vascular Diseases?
- Pulmonary Arterial Hypertension – Current Concepts and Future Therapies

epigenetic mechanisms (e.g., BMPR2 mutations, microRNA-mediated gene regulation, epigenetic silencing of SOD2) of PH, which while intriguing, have yet to be exploited as therapeutic or diagnostic tools. The epigenetic mechanisms suggest new means of inheritance and may underlie gene-environment interactions that promote PAH. In addition, the role of the RV in determining the prognosis in PH is increasingly recognized. Chronic pressure overload in PH stimulates RV hypertrophy (RVH) in an attempt to compensate for the increased afterload and maintain cardiac output. However, RVH is rarely fully compensatory and may come at the price of creating RV ischemia and maladaptive metabolic changes. As such, RVH can eventually lead to RV failure (RVF). The cellular signaling mechanisms in RVH and RVF are two of many areas in which research is required to overcome knowledge gaps. The sessions hopefully inspired researchers to unravel the mysteries of the right ventricle.

This Keystone Symposia meeting addressed several important paradigm shifts in the field of pulmonary hypertension:

1. PVD relates in large part to increased cell proliferation, resistance to apoptosis, and inflammation (with a smaller contribution from vasoconstriction).
2. The right ventricle is the key determinant of prognosis in PAH and thus an important therapeutic target.
3. Stem cells, progenitor, and differentiated blood cells play important roles in PH.

We believe that the strength of this meeting's design was its comprehensiveness (four days, 10 sessions, three workshops), its multidisciplinary nature, and educational mission, and the creation of an interface between both junior and senior scientists as well as academia and industry. The post-hoc evaluation of this first Keystone Symposia Conference in PVD and RVD was excellent and above the average score of the 55 Keystone Symposia of the preceding cycle. The overall scientific content at this PVD/RVD meeting was ranked "excellent" or "very good" by 98% of the participants versus 92% for the according Keystone mean score of the preceding conference cycle 2011-2012. The major results of the conference evaluation survey are shown in Table 2.

From our perspective, the aims of this PVD/RVD Keystone Symposia conference were as follows:

1. To bring together basic researchers, physician scientists, and clinicians, as well as regulatory and funding agencies (FDA, NIH, industry) to improve our current understanding of pulmonary hypertension.
2. To present cutting edge technologies, innovations, and discoveries with great potential to be translated into clinical practice in the near future.
3. To present and discuss late breaking clinical studies on novel PAH therapies, and to develop future strategies to cure this fatal disease.
4. To engage experts from outside the PAH field to benefit from the cross-fertilization of important new concepts that may be new to the PH community.
5. To provide a platform for graduate students, post-doctoral fellows, and early career investigators to present their work, and offer specific workshops addressing emerging knowledge, strategic, and technical questions in hot topic areas of PVD and RVD research.

## CURRENT CONCEPTS AND FUTURE THERAPIES

This Keystone Symposia conference offered a forum for addressing new "big ideas" in PH:

1. Can we adopt similar therapeutic strategies that apply to cancer, in which there is increased proliferation and impaired apoptosis, for the treatment of PAH?
2. Can the RV be therapeutically targeted in PAH, independent of effects on the lung vasculature?
3. Can we exploit epigenetics in understanding PAH and/or developing therapies?
4. How can investigators' promising therapeutic agents realistically be moved to clinical trials?
5. Can the glycolytic shift in metabolism that has been observed in the pulmonary vasculature and right ventricle in human and experimental PH be treated through metabolic strategies?
6. Are cell-based therapies or epigenetic manipulation ready for prime time as potential therapies, and if so, should they have priority over other therapies?

**Table 2: Post-hoc evaluation of the Keystone symposia conference on pulmonary vascular disease and right ventricular dysfunction (09/2012) by participants**

Scientific content	Ranking	PVD and RVD (09/2012). Total survey responses: 44	Average of all 55 Keystone symposia (10/2011-05/2012). Total survey responses: 4035
Overall rating for scientific content	Excellent	65.91	57.30
	Very good	31.82	34.72
	Good	2.27	6.29
	Fair	0	0.94
	Poor	0	0.15
	No response	0	0.6
Overall quality of plenary speakers' presentation content	Excellent	72.73	52.81
	Very good	27.27	38.54
	Good	0	7.19
	Fair	0	0.87
	Poor	0	0.12
	No response	0	0.47
Overall workshop quality and content	Excellent	50.00	21.51
	Very good	36.36	30.16
	Good	13.64	11.57
	Fair	0	1.96
	Poor	0	0.4
	N/A	0	34.4
Overall panel quality and content	Excellent	47.73	N/A
	Very good	40.91	N/A
	Good	11.36	N/A
	Fair	0	N/A
	Poor	0	N/A
	No response	0	N/A
Overall scientific quality of posters/abstracts	Excellent	43.18	35.99
	Very good	52.27	49.47
	Good	4.55	12.34
	Fair	0	1.09
	Poor	0	0.12
	No response	0	0.99

Figures are in percentage (%); The above evaluation is based on a post-meeting, web-based survey response from 44 participants. Affiliation of all participants ( $n=127$ ) were: Academia/research institute (83.33%), industry (4.76%), Government (3.17%), other non-profit organizations (3.17%), and unknown (5.56%). Primary job positions were: Student (15.87%), post-doc (16.78%), early-stage investigator (11.11%), established or senior investigator (41.95%), and unknown (3.97); **PVD**: pulmonary vascular disease; **RVD**: right ventricular dysfunction; **N/A**: not applicable

7. Can strategies for the treatment of Class I pulmonary hypertension (i.e., PAH) be applied to PH Classes 2-5 (non-PAH)?

Hot topics such as progenitor and stem cell biology, novel tools such as inducible pluripotent stem cells (iPS) and microRNA, metabolic regulators, metabolomics/proteomics/new biomarkers, and future clinical trial design were presented and discussed in separate, in-depth sessions with broader relevance and impact on our understanding of cardiovascular pathobiology. This and future Keystone meetings will be instrumental in addressing the key questions necessary to cure the disease within the next 20 years.


Having preceded the most recent PH World Symposium (02/2013) by six months, this Keystone Symposium has been timely indeed. Future four-day Keystone meetings on PVD and the right ventricle may be held in between PH World Symposia, i.e., every three to five years. We hope you will be able to attend such future meetings.

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*Alexander von Gise, Stephen L. Archer, Margaret R. MacLean, and Georg Hansmann*

Email: hansmann.georg@mh-hannover.de

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