

## INTRODUCTION

# The 4th World Symposium on Pulmonary Hypertension

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The 4th World Symposium on Pulmonary Hypertension (PH) took place in Dana Point, California, in February 2008. This 4-day summit of international experts in PH, which highlighted the findings of 11 scientific working groups, was an occasion for looking backward and for looking ahead. Thirty years ago, adults diagnosed with pulmonary arterial hypertension (PAH) could expect to live less than 3 years, and the therapeutic armamentarium was limited to nonselective vasodilators. By 2003, however, when the 3rd World Symposium was held in Venice, Italy, much more was known about the pathologic changes seen in PAH and PH, and several important therapies had been shown to be effective. Today, our selection of therapeutic modalities is broader still, and more than 15 large randomized clinical trials have provided reliable evidence for their benefit. The purpose of the 4th World Symposium was to review the progress we have made in diagnosing and treating PH and PAH; redefine and, when appropriate, reclassify the disease itself; better understand the rationale for ongoing research; and formulate proposals for new investigative paths that may translate into a brighter future for our patients.

The Dana Point meeting opened with an update on the natural history of PH. We learned that the vascular remodeling characteristic of PH may have its origins in disruptions or alterations that take place in lung circulation as early as embryonic and fetal development and certainly plays a role in pediatric lung disease. These early alterations in developmental physiology may determine the likelihood of developing PH in adult life. We now understand that inflammatory processes also contribute to PH, particularly in connective tissue diseases and chronic obstructive pulmonary disease, and inflammation is involved in all of the mechanisms of vascular remodeling.

Pulmonary arterial hypertension is characterized by cellular changes in the walls of pulmonary arteries. Building on the discussion of endothelial dysfunction at the Venice meeting, at Dana Point, we further explored the key role of the endothelium in PAH. In addition, we examined the strong association between mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) gene and PH: such mutations have been found in approximately 80% of families with PAH and 25% or less of families with idiopathic PAH. The *BMPR2* mutation was discovered in 2000, not long before the Venice meeting; other genetic markers have been discovered in the intervening years.

With the development of new therapeutic options, early and accurate diagnosis of PH becomes increasingly important. One working group at Dana Point examined optimal modalities for diagnosing the disease and predicting outcomes. These include hemodynamic and echocardiographic measures, as well as biomarkers such as brain natriuretic protein.

An increasing number of agents, including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, continue to provide effective treatment options. One working group at Dana Point developed an algorithm that reflects the best evidence currently available for the appropriate treatment of patients who can benefit from these agents. At the same time, surgical treatment for PH was reviewed, including pulmonary thromboendarterectomy, currently the only cure for chronic thromboembolic PH; atrial septostomy, which decompresses the failing right ventricle; and finally, for those for whom other options are not viable, heart and lung transplantation.

An increase in the number of therapeutic strategies brings new opportunities but also new challenges. Thus, there is a need for well-designed clinical trials with appropriate end points that will enable reliable interpretation of the benefit-to-risk profile of all current and emerging therapies. Consequently, 1 working group dedicated itself to an in-depth examination of the benefits and drawbacks of a variety of clinical trial end points and designs to determine the most interpretable and clinically relevant.

Most often the cause of death from PH is right ventricular failure, and the effect of treatment on right ventricular function is currently under study. Likewise, therapeutic

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antiremodeling strategies are under investigation. Dysregulated proliferation of endothelial and smooth muscle cells in PH, along with increased expression of growth factors, have led to the use of antineoplastic drugs, which have shown promise in patients with PH.

Thus, despite the fact that a cure for PAH remains elusive, we concluded the Dana Point meeting with a feeling of optimism. Today, we can improve life expectancy, functional class, and quality of life for many patients with PAH. Tomorrow, as we increase our understanding of specific disease pathways, we will be able to develop targeted therapies that will further improve outcomes.

One of the takeaway lessons from Dana Point is the need for collaborative efforts that will ultimately lead to improved

treatment for all patients with PH. Large international registries can help us understand and assess patterns of treatment. Despite complex regulatory complications, we need to establish multi-institutional networks for tissue banking. Multicenter collaboration will also be needed to conduct statistically meaningful genome studies. Such collaborative efforts will be invaluable in providing the necessary resources to help us successfully navigate the road ahead.

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