

Pathogenesis and Drug Development for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a chronic disorder that results in narrowing of the small pulmonary arteries and arterioles leading to elevation of pulmonary artery pressure, subsequent right ventricular failure, and if untreated, death. Advances in the treatment of PAH in the past two decades have dramatically improved symptoms and survival of the patients with PAH. The availability of new treatments has increased awareness of the condition.

Currently approved therapies for PAH include endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin pathway agents, that have been developed based on the assumption that PAH is caused by imbalance of vasoactive mediators of pulmonary arteries.

The description of the genetic features of PAH is accelerating, with novel mutations, such as potassium two-pore domain channel subfamily K member 3 (*KCNK3*) and caveolin 1 (*CAV1*), adding to the list of more established mutations in genes associated with bone morphogenetic protein receptor type 2 (*BMPR2*) or *SMAD9*. These insights have supported a paradigm shift in pathogenesis and treatment strategies from simply addressing the imbalance of vasoactive mediators observed in PAH towards tackling more directly the structural remodeling of the pulmonary artery.

In this symposium, the changing clinical and molecular landscape of PAH will be summarized. I will highlight novel therapeutic strategies that are in various stages of clinical development, targeting cell proliferation, metabolic, inflammatory/immune and *BMPR2* dysfunction, and the challenges around developing these treatments.