Pulmonary arterial hypertension (PAH) is a lethal vasculopathy characterized by enhanced pulmonary artery (PA) smooth muscle cell (PASMC) proliferation and suppressed apoptosis. BRD4 (bromodomain-containing protein 4), a member of the BET (bromodomain and extra-terminal motif) family, has been identified as a critical epigenetic driver for cardiovascular diseases. We investigate the role of BRD4 in PAH pathogenesis and assess the therapeutic potential of clinically available BET inhibitors in a multicentric preclinical setting.

BRD4 is upregulated in the remodeled pulmonary vasculature of patients with PAH, where it regulates FoxM1 and PLK1, proteins implicated in the DNA damage response. In vitro, molecular (silencing RNA) and pharmacological (BET inhibitor) inhibition of BRD4 normalized the hyperproliferative, apoptosis-resistant, and inflammatory phenotype of microvascular endothelial cells and smooth muscle cells isolated from patients with PAH. In Vivo, oral treatment with BET inhibitors reversed vascular remodeling and improved pulmonary hemodynamics in 3 independent trials in Sugen5416 + hypoxia-PAH and in monocrotaline + shunt-PAH. BET inhibitors treatment also supported the pressure-loaded RV in pulmonary artery banding rats.

Conclusion BRD4 plays a key role in the pathological phenotype in PAH. BET inhibitors in vivo reversed established PAH in multiple preclinical models of the disease. Together, these data support the establishment of a clinical trial with BET inhibitors in patients with PAH.