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Title: The role of bromodomain-containing protein 4 in the constitutive activation of nuclear factor-kappa B in endothelial cells from patients with pulmonary arterial hypertension

Dr. Natalia 16738 Gambaryan ngambaryan@gmail.com [1], Dr. Christophe 29140 Guignabert christophe.guignabert@inserm.fr [1], Mr. Ly 29141 Tu ly.tu@inserm.fr [1], Dr. Frederic 29142 Perros frederic.perros@gmail.com [1], Prof. Dr Ian 29143 Adcock ian.adcock@imperial.ac.uk [2], Prof. Dr Marc 29158 Humbert marc.humbert@abc.aphp.fr MD [1] and Dr. Stephen 29179 Wort s.wort@imperial.ac.uk MD [2]. [1] INSERM U999, Centre Chirurgical Marie Lannelongue, Université Paris-Sud 11, Le Plessis-Robinson, France, 92350 and [2] Department of Critical Care, National Heart and Lung Institute, Imperial College, London, United Kingdom .

Body: BACKGROUND Pulmonary arterial hypertension (PAH) is characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. Pulmonary endothelial cells (P-ECs) are well known as producers of cytokines and chemokines essential in the recruitment of inflammatory cells to the lungs, and a constitutive activation of the nuclear factor-kappa B (NF-κB) signaling pathway in P-ECs has been recently described in PAH. RelA lysine-310 acetylation of NF-κB generates a specific docking sites for bromodomain-containing protein 4 (Brd4). We hypothesize that Brd4 through an NF-κB-dependent mechanism contributes to the hyperproliferative and proinflammatory phenotype in P-ECs in patients with PAH. AIM The aim of the study was to evaluate the in vitro effect of Brd4 inhibition using the selective inhibitor JQ1 on proliferation and apoptosis in P-ECs. METHODS AND RESULTS The effect of JQ1 on P-ECs proliferation was established by assessing the incorporation of BrdU. We found a strong anti-proliferative effect of JQ1 in P-ECs (Fig. 1A). We also demonstrated that JQ1 induces caspase-3 activity in P-ECs resulting in increased apoptosis (Fig. 1B).

CONCLUSION Selective Brd4 inhibitors, such as JQ1, may represent novel therapeutic agents for the treatment of PAH. Further work is necessary to explore this hypothesis.