European Respiratory Society
Annual Congress 2013

Abstract Number: 5404

Publication Number: P555

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Infections **Keyword 2:** COPD - mechanism **Keyword 3:** Anti-inflammatory

Title: Endothelin receptor antagonists (ERAs) neutralize LPS-induced cytokine release from pulmonary vascular smooth muscle cells (PVSMCs) by down-regulation of CD14

Mr. David 31953 Jungck david.jungck@bergmannsheil.de MD [1], Ms. Maria 31954 Feldmann maria.feldmann@bergmannsheil.de [1], Mr. Chiara 31955 Wahl chiara.wahl@bergmannsheil.de [1], Prof. Juergen 31956 Behr juergen.behr@bergmannsheil.de MD [1], Prof. Erich 31957 Stoelben erich.stoelben@bergmannsheil.de MD [2], Dr. Juergen 31958 Knobloch juergen.knobloch@bergmannsheil.de [1] and Dr. Andrea 31959 Koch andrea.koch@bergmannsheil.de MD [1]. [1] Medical Clinic III for Pneumology, University Hospital Bochum-Bergmannsheil, Bochum, NRW, Germany, 44789 and [2] Department of Thoracic Medicine, Lungenklinik Merheim, Cologne, NRW, Germany, 51109 .

Body: Bacterial infections induce COPD exacerbations by enhancing airway inflammation. Inflammation-induced vascular remodeling might drive the development of pulmonary hypertension (PH) in COPD. ERAs are approved for PH but their utility in COPD exacerbations is unknown. Hypothesis: Bacterial endotoxin (LPS)-induced cytokine releases are reduced by ERAs in human PVSMCs. Human PVSMCs were pre-incubated with the endothelin-A-receptor (ETAR)-selective inhibitor ambrisentan (AMB), with the ETBR-specific inhibitor BQ788 or with the dual blocker bosentan (BOS) before stimulation with clinically relevant long/smooth LPS (S-LPS), short/rough LPS (Re-LPS) or a mixture (M-LPS). Cytokine- and LPS-receptor (TLR4, CD14) expression were analyzed via ELISA and/or qRT-PCR. All LPS forms induced IL-6-, IL-8- and GM-CSF-release (each $p<0.05$). BOS and BQ788 dose-dependently blocked M-LPS-induced release of all cytokines (each $p<0.05$) and soluble CD14 (sCD14) ($p<0.05$) but not TLR4 transcription. AMB blocked M-LPS-induced IL-6 release ($p<0.05$) but not IL-8, GM-CSF, TLR4 or sCD14. IL-8 induced by S-LPS, which requires CD14 to activate TLR4, was blocked by BOS and BQ788 (each $p<0.05$). IL-8 induced by Re-LPS, which CD14-independently activates TLR4, was insensitive to BOS and BQ788. PVSMCs contribute to infection-caused inflammation in COPD exacerbations. ETBR-blockade suppresses cytokines induced by smooth LPS due to sCD14 down-regulation. ERAs, particularly when targeting ETBR, might have therapeutic utility in COPD exacerbations with regard to attenuating inflammation-induced vascular remodeling. Funded by Actelion Pharmaceuticals, Germany.