European Respiratory Society
Annual Congress 2013

Abstract Number: 5335

Publication Number: P3933

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: ALI (Acute Lung Injury) **Keyword 2:** Inflammation **Keyword 3:** Anti-inflammatory

Title: Post-treatment with the heat shock protein 90 (hsp90) inhibitor, AUY-922, reduces lung hsp90 tyrosine (Y) phosphorylation and pulmonary inflammation in LPS-induced acute lung injury (ALI) in mice

Christiana 32307 Dimitropoulou cdimitro@gru.edu [1], Nektarios 32308 Barabutis nbarabutis@gru.edu [2], Haralmbos 32309 Birmpas hbirmpas@gru.edu [2] and John 32310 Catravas jcatravas@med.uoa.gr [2,3]. [1] Department of Medicine, Georgia Regents University, Augusta, GA, United States, 30912 ; [2] Vascular Biology Center, Georgia Regents University, Augusta, GA, United States, 30912 and [3] Laboratory of Experimental Pharmacology, University of Athens School of Medicine, Athens, Greece, 11527 .

Body: Pre-treatment with hsp90 inhibitors reduces the magnitude of LPS-induced ALI in mice. Because the most frequent use of any intervention would be after the onset of ALI/ARDS, we now tested the hypotheses that post-treatment with hsp90 inhibitors would also reduce the magnitude of LPS-induced ALI and would decrease hsp90 activation as reflected in hsp90 Y phosphorylation. 24h after the intratracheal instillation of vehicle or LPS (1.5mg/kg), mice were given either vehicle or the hsp90 inhibitor, AUY-922 ; i.p. 10mg/kg. 48h later, lung tissue was collected. LPS, but neither vehicle nor AUY-922, alone, increased 9-fold hsp90 Y phosphorylation, as detected in immunoprecipitation/immunoblotting experiments; when post-treated with AUY-922, hsp90 phosphorylation was significantly and dramatically reduced to near control levels. Furthermore, LPS produced a profound inflammatory response, characterized by an increase in alveolar septal thickness, hemorrhage and cellular infiltration, reflected in lung sections stained with H&E, as well as by neutrophil accumulation and capillary plugging, revealed immunocytochemically with anti-MPO (myleoperoxidase, an enzyme marker of granulocytes) antibody; inflammation was remarkably reduced in mice post-treated with auyAUY-922. Collectively these data reveal important reparative actions of hsp90 inhibitors when administered after the LPS insult and suggest that prevention of post-translational modifications of hsp90 may be an important therapeutic mechanism. Supported by NHLBI grants HL101902 and HL093460.