

# European Respiratory Society Annual Congress 2012

**Abstract Number:** 367

**Publication Number:** P2125

**Abstract Group:** 5.1. Airway Pharmacology and Treatment

**Keyword 1:** COPD - management **Keyword 2:** Immunology **Keyword 3:** Lung injury

**Title:** Statins worsen pulmonary fibrosis through enhancing NLRP3 inflammasome activation

Prof. Jin-Fu 2168 Xu [jfxucn@gmail.com](mailto:jfxucn@gmail.com) MD <sup>1,2</sup>, Dr. George R. 2169 Washko [jfxu@ymail.com](mailto:jfxu@ymail.com) MD <sup>2</sup>, Prof. Hui-Ping 2170 Li [lihuiping1958@yahoo.com.cn](mailto:lihuiping1958@yahoo.com.cn) MD <sup>1</sup>, Prof. Augustine M.K. 2171 Choi [amkchoi@partner.org](mailto:amkchoi@partner.org) MD <sup>2</sup> and Prof. Gary M. 2172 Hunninghake [gmhunninghake@partner.org](mailto:gmhunninghake@partner.org) MD <sup>2</sup>. <sup>1</sup> Department of Pulmonary Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China and <sup>2</sup> Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States .

**Body:** The role of statins is controversial. To evaluate the association between statin use and ILD. We used regression analyses to evaluate the association between statin use and interstitial lung abnormalities (ILA) in a large cohort of smokers from COPDGene. Next, we evaluated the effect of statin pretreatment on bleomycin-induced fibrosis in mice and explored the mechanism behind these observations in vitro. In COPDGene, 38% of subjects with ILA were taking statins compared to 27% of subjects without ILA. Statin use was positively associated in ILA (odds ratio [OR] 1.60, 95% confidence interval [CI] 1.03-2.50, P=0.04) after adjustment for covariates including a history of high cholesterol or coronary artery disease. This association was modified by the hydrophilicity of statin and the age of the subject. Next, we demonstrate that statin administration aggravates lung injury and fibrosis in bleomycin-treated mice. Statin pretreatment enhances caspase-1-mediated immune responses in vivo and in vitro; the latter responses were abolished in bone marrow-derived macrophages (BMDM) isolated from *Nlrp3*<sup>-/-</sup> and *Casp1*<sup>-/-</sup> mice. Finally, we provide further insights by demonstrating that statins enhance NLRP3-inflammasome activation by increasing mitochondrial reactive oxygen species generation in macrophages. Statin use is associated with ILA among smokers in the COPDGene study and enhances bleomycin-induced lung inflammation and fibrosis in the mouse through a mechanism involving enhanced NLRP3-inflammasome activation. Our findings suggest that clinicians should be aware that radiological evidence of ILD can develop in some COPD patients treated with statins.