European Respiratory Society
Annual Congress 2013

Abstract Number: 1222
Publication Number: 4877

Abstract Group: 3.2. Airway Cell Biology and Immunopathology
Keyword 1: COPD - mechanism **Keyword 2:** Molecular pathology **Keyword 3:** Cell biology

Title: The oncogene c-Src plays a crucial role in the pathogenesis of COPD

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Body: Activation of the tyrosine kinase c-Src promotes tumor invasion, loss of cell-cell adhesion, increased cell-matrix adhesion, and formation of focal adhesions. Cigarette smoke is known to activate c-Src kinase in a cancer phenotype, however little is known about the activation status of c-Src in non-cancerous lung diseases such as emphysema. The objective of this study was to examine whether c-Src is cigarette smoke activated and contributes to COPD progression. Increased c-Src activity was observed in small airway epithelial (SAE) cells and mouse lungs exposed to smoke and in advanced human emphysema lungs (Gold 3 or greater) compared to age matched control lungs. Cigarette smoke activated raf-1, ERK, JNK and p38 in a c-Src dependent manner in both SAE cells and mouse lung. Given these observed effects, A/J mice were orally administered the specific Src inhibitor AZD0530 while they were exposed to 2 months of cigarette smoke. Treatment with AZD0530 blocked c-Src activation and prevented the smoke-mediated influx of macrophages in the lung. In addition, inhibiting Src in these mice countered Raf, ERK, JNK, p38 activation, blocked the induction of MMP-9 and IL-17 and prevented the development of air space enlargement in the lung. Furthermore, it was determined that cigarette smoke directly triggers Src to phosphorylate EGFR and thereby activate MAPK pathways that have been implicated in the disease pathogenesis. Together, these results indicate that inhibition of c-Src activity represents a novel approach to prevent cigarette smoke induced inflammation and injury.