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Title: Inhibition of lung inflammation by a protein epitope mimetic (PEM) neutrophil elastase inhibitor, POL6014, in a sub-chronic tobacco smoke (TS) model in mice

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Body: Rationale: Neutrophil elastase (NE) plays a central role in inflammation and tissue degradation in airway diseases, e.g. alpha-1 antitrypsin deficiency, cystic fibrosis and chronic obstructive pulmonary disease. Its inhibition might therefore be of use to improve the current treatments for those diseases. Objective: The aim of the study was to evaluate the effect of a direct lung application of POL6014, a potent NE inhibitor, in a 4 day TS model in mice. Methods: POL6014 (0.1, 0.5, 2 and 10 mg/kg) or a positive control, p38 inhibitor (0.1 mg/kg) were intranasally administered daily 1 h before each TS exposure in C57BL/6j mice for 4 days. The bronchoalveolar lavage (BAL) fluid was collected 24 h after the end of the last TS exposure and the total and differential cell counts were determined. Plasma and lung compound levels were also measured. Results: POL6014 dose-dependently and significantly reduced the number of macrophages, epithelial cells, neutrophils and lymphocytes recovered in BAL. The maximum inhibition was reached at 2 mg/kg in reducing neutrophils by 65% ($p < 0.001$), epithelial cells by 68% ($p < 0.001$), macrophages by 33% ($p < 0.001$) and lymphocytes by 77% ($p < 0.001$). At 0.1 mg/kg POL6014 already showed significant inhibition on neutrophils by 50% ($p < 0.001$). POL6014 showed dose-related exposures with substantial lung and low plasma levels and no accumulation after repeated administration. Conclusion: POL6014 significantly and dose-dependently reduced TS-induced inflammation. It might provide a new therapeutic approach for the treatment of NE-driven lung diseases.