European Respiratory Society
Annual Congress 2012

Abstract Number: 2298

Publication Number: 2805

Abstract Group: 5.1. Airway Pharmacology and Treatment

Keyword 1: Animal models **Keyword 2:** Anti-inflammatory **Keyword 3:** COPD - mechanism

Title: A comparison of anti-inflammatory compounds in a steroid-insensitive mouse tobacco smoke model

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Body: The effects of PDE4 and p38 inhibitors were compared to steroids in a robust model of lung inflammation induced by 4 days of exposure to tobacco smoke (TS). Methods Mice were exposed to either air or TS for 4d and were killed 24hr after the last exposure, the lungs lavaged and cells counted. Compounds were given at maximal efficacy doses as defined in a mouse LPS model. Steroids were dosed orally (Dexamethasone, 300µg/kg 1hr pre- and 6hr post- TS); or intra-nasally (fluticasone proprionate (FP), budesonide (BUD) 300µg/kg 1hr pre- TS). Roflumilast (ROF) was dosed either i.n. (0.1, 0.3, 1mg/kg) or orally (5 mg/kg) 1hr pre-TS. The inhaled p38i PF03715444 was dosed 100µg/kg i.n 1hr pre-TS. The p38i BIRB-796 was orally (1mg/kg) dosed 1hr pre- and 6hr post-TS. Results TS-exposure caused cellular infiltration into the lung which was reproducible across multiple studies. Oral or i.n. dosed steroids did not inhibit the inflammation ($p>0.05$ total cell and neutrophil (neut) count). Body weight significantly decreased over the 4d (FP 6%, BUD 11%, DEX 11%; all $p<0.05$) confirming steroid availability and efficacy. ROF reduced TS-induced inflammation when given i.n. (totals -50%, neuts -60%; both $p < 0.05$) or orally (totals -50%, neuts -66%; both $p < 0.05$). The p38 inhibitors were effective dosed orally (BIRB: totals -42%, neuts -55%) or i.n. (PF: totals -50%, neuts -61%; all $p < 0.05$). Conclusions TS-exposure for 4d induced a steroid-insensitive lung inflammation which was reproducibly inhibited by PDE4 and P38 inhibitors; although neither caused a total inhibition of the inflammation, suggesting that there is scope to investigate more efficacious mechanisms and combinations within this model.