European Respiratory Society
Annual Congress 2012

Abstract Number: 2817

Publication Number: P3711

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Asthma - mechanism **Keyword 2:** Inflammation **Keyword 3:** Pharmacology

Title: TNFα-induced glucocorticoid resistance: Effect of steroidal and non-steroidal GR agonists, formoterol and inhibition of inflammatory signalling

Mr. Christopher 3847 Rider cfrider@ucalgary.ca [1], Mr. Suharsh 3848 Shah svshah@ucalgary.ca [1], Dr. Anna 3849 Miller-Larsson Anna.Miller-Larsson@astrazeneca.com [2], Dr. David 3850 Proud dproud@ucalgarly.ca [1], Dr. Malcolm 3851 Johnson malcolm.x.johnson@gsk.com [3], Dr. Mark 3852 Giembycz giembycz@ucalgary.ca [1] and Dr. Robert 3853 Newton rnewton@ucalgarly.ca [1]. [1] Airway Inflammation Research Group, University of Calgary, AB, Canada, T2N 4Z6 ; [2] AstraZeneca R&D, AstraZeneca, Mölndal, Sweden, S-431 83 and [3] Respiratory Science, GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom, UB6 0HE .

Body: Inhaled glucocorticoids (GCs) w/wo long-acting β_2-adrenoceptor agonists (LABA) are the most effective treatment for asthma. However, GC insensitivity is a facet of severe asthma and COPD. We have examined TNFα-induced resistance to GC-dependent transcription by steroidal and non-steroidal GC receptor (GR) ligands in the absence and presence of a LABA, formoterol. METHODS: GC-dependent transcription was modeled by a simple 2×GRE-luciferase reporter in human bronchial epithelial BEAS-2B cells treated with TNFα (10 ng/ml) for 1 h prior to addition of GR ligands, and harvested after 6 h for luciferase assay. RESULTS: TNFα reduced by 43-54% the ability to drive 2×GRE-dependent transcription by dexamethasone, budesonide, fluticasone propionate or fluticasone furoate. The GCs des-ciclesonide, GW870086X, RU24858 and the non-steroidal GR agonist, GSK9027, all showed reduced maximal responses (E_{max}) with intrinsic activities 0.5-0.77 relative to dexamethasone. In each case, TNFα reduced E_{max} by a further 39-55%. Conversely, formoterol enhanced GRE-dependent transcription by each ligand and rescued the resistance induced by TNFα; these effects were proportional to the E_{max} of each drug. Statistically significant reversal of TNFα-induced resistance was observed with the c-jun N-terminal kinase inhibitor, JNK8, and PS-1145, an IκB kinase 2 (IKK2) inhibitor. CONCLUSIONS: TNFα induces GC resistance to steroidal GR ligands that are both full and partial agonists, as well as to a non-steroidal GR agonist. This effect is rescued by the addition of formoterol. It is possible that inhibition of inflammatory signalling may also reduce GC resistance.