Title: Synthetic response of stimulated respiratory epithelium: Modulation by prednisolone and iKK2 inhibition

Dr. Lucy B. 29427 Woodman lw86@le.ac.uk ¹, Ms. Wing Yan Heidi 29428 Wan whw7@le.ac.uk ¹, Ms. Roberta 29429 Milone roby.ita@gmail.com ², Dr. Ken 29430 Grace ken.g.grace@gsk.com ², Dr. Ana 29431 Sousa ana.x.sousa@gsk.com ², Dr. Rick 29445 Williamson rick.a.williamson@gsk.com ² and Prof. Christopher 29461 Brightling ceb17@le.ac.uk MD ¹. ¹ Infection, Immunity and Inflammation, University of Leicester, Leicestershire, United Kingdom, LE3 9QP and ² Refractory Respiratory Inflammation DPU, GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom, SG1 2NY.

Body: Background: The airway epithelium plays a central role in wound repair & host defence & is implicated in the immunopathogenesis of asthma. Whether there are intrinsic differences between the synthetic capacity of epithelial cells derived from asthmatics & healthy controls & how this mediator release is modulated by anti-inflammatory therapy remains uncertain. Aims: We sought to examine the synthetic function of epithelial cells from different locations in the airway tree from subjects with & without asthma & to determine the effects of anti-inflammatory therapies upon this synthetic capacity. Methods: Primary epithelial cells were derived from 17 asthmatics & 16 controls. The release of 13 mediators from nasal & bronchial basal & air-liquid interface differentiated epithelial cells before & after stimulation with IL-1β, IL-1β & IFNγ or Poly-IC (TLR3 agonist) were measured using MSD or ELISA & the effects of prednisolone, rosiglitazone, & an inhibitor of nuclear factor K-β2 (IKK2i) were determined. Results: The pattern of release of cytokines & chemokines was significantly different between nasal & bronchial basal & differentiated epithelial cells, but not between health & disease. Stimulation of the epithelial cells caused marked up-regulation of most mediators which were broadly corticosteroid unresponsive, but attenuated by IKK2i. Conclusion: Synthetic capacity of primary airway epithelial cells varies between location & degree of differentiation, but is not disease specific. Activation of epithelial cells by pro-inflammatory cytokines & TLR3 agonism is attenuated by IKK2i, but not corticosteroids suggesting that IKK2i may represent an important novel therapy for asthma.