PI3Kyδ inhibition suppresses key disease features in a rat model of asthma

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Phosphoinositide 3-kinase (PI3K) has 4 isoforms; two of which, p110γ and p110d, are predominantly expressed in leukocytes which represents an attractive therapeutic target for asthma. The aim of this study was to assess the impact of administration of an inhaled PI3Kyδ inhibitor (AZD8154) in a rat model of asthma. To confirm specificity of AZD8154 for rat PI3K γ & δ kinases, cell-based assays were employed. Next, a DMPK experiment was performed, by dosing AZD8154 into the airways, to deduce a suitable exposure profile. Subsequently, a time-course study was conducted in a rat model of asthma, to assess lung phosphorylation (p) of Akt, a marker of PI3K activation. Lastly, target engagement, pathway specificity, airway inflammation and whole-body plethysmography performed to measure enhanced pause (penh) in the model and compared to a clinical comparator, budesonide. AZD8154 demonstrated target engagement with PI3K γ & δ isoforms in cells. Following allergen challenge, pAkt, pSTAT & NF-κB reach maximal activation 2hrs post-challenge, prior to peak inflammation & increased penh. Administration of AZD8154 caused a dose related suppression in pAKT activity 2hrs post-challenge in whole lung. Unlike with budesonide treatment, pSTATs and NF-kB pathway activation were not affected by AZD8154. Furthermore, AZD8154 administration was associated with an inhibition of airway inflammation and penh to a similar degree as budesonide. These data show that a dual PI3Kyδ inhibitor suppress key features of disease in a rat model of asthma to a similar degree as budesonide and indicate that dual PI3Kyδ inhibition may be an effective treatment for people suffering from asthma if an optimal safety profile can be achieved.