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Title: The histone-deacetylase-8 selective inhibitor PCI-34051 enhances IFN-λ production in vitro and reduces inflammation in mouse models of rhinoviral infection and rhinovirus-induced exacerbations of asthma in vivo

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Body: An impaired immune response to viral infection, in particular reduced production of type I and III interferons (IFN), is considered to be an important mechanism of greater susceptibility of asthmatic patients to respiratory infections. Therefore, novel therapies aimed at replacing or augmenting deficient IFN production are being investigated. According to the literature, histone-deacetylase-8 (HDAC8) is a negative regulator of innate antiviral responses since it functions as a repressor for IFN-β gene expression. Consequently, HDAC8 silencing increases IFN-β mRNA levels. The aim of this work was to validate HDAC8 as a pharmacological target by using PCI-34051, HDAC8 selective inhibitor, as a tool compound. We have shown that PCI-34051, HDAC8 selective inhibitor (IC_{50} 10nM) with >200-fold selectivity over the other HDAC isoforms, enhanced IFN-λ production in human bronchial cells from normal and asthmatic donors after rhinovirus (RV1B and RV16) infection. In vivo, PCI-34051 reduced cell counts in bronchoalveolar lavage fluid (BALF) and viral load in lung tissue of mice infected with RV-1B. Finally, the compound was also effective at reducing BALF cell counts and cytokine concentration in a mouse model of rhinovirus-induced exacerbation of allergic airway inflammation. Taken together, these findings indicate that inhaled selective HDAC8 inhibitors could be useful as a novel treatment for rhinovirus-induced exacerbations of asthma.