

# IL-33–Dependent Type 2 Inflammation during Rhinovirus-induced Asthma Exacerbations In Vivo

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Journal club “Current Topics in Applied Immunology “

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## Introduction



- **Rhinoviruses** have single-stranded positive sense RNA genomes
- **Rhinovirus infections** are
  - The most common trigger for asthma exacerbations
  - The predominant cause of the common cold
- **IL-33** is an epithelial cell–derived cytokine, and its receptor (ST2) is expressed on both Th2 cells and ILC2s (Type 2 Innate Lymphoid Cells)
- **IL-33** potently drives production of T helper-2 (Th2)-associated cytokines (IL 4, IL 5, IL 13)
- **IL-33** is expressed on a wide variety of cell types:
  - fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells

## Available Knowledge



Immune responses to **viral infections** -->

CD4<sup>+</sup> IFN- $\delta$ -producing *Th1* cells, regarded as the archetypal effector cell of antiviral immunity.

### *In contrast*

*Th2* cells, which secrete IL-4, IL-5, and IL-13, are regarded as critical effector cells in **allergic asthma**.

## Objective



- Does rhinovirus induce a type 2 inflammatory response in asthma in vivo ?
- Does IL-33 have a role in this pathway?

## Study Design



**Table 1. Baseline Characteristics of Study Volunteers**

Characteristics	Healthy (N = 11)	Asthma (N = 28)	P
Age, yr	31 ± 12	36 ± 11	NS
Sex			
Female, n (%)	4 (36)	15 (54)	NS
Male, n (%)	7 (74)	13 (46)	
Baseline FEV <sub>1</sub> , % predicted	104 ± 8	86 ± 12	<0.001
Baseline histamine PC <sub>20</sub> , mg/ml	>16	1.26 ± 2.01	—
ICS use, n (%)	—	15 (53.6)	—
ICS daily dose, beclomethasone/equivalent, µg*	—	427 ± 71	—
IgE, IU/ml, median (IQR)	16 (14–19)	139 (70–448)	<0.001
BAL fluid eosinophilia, %, median (IQR)	0 (0)	0.5 (0–1.7)	0.002

**Study volunteers: (n=46)**

**Asthma patients: (n=32)**

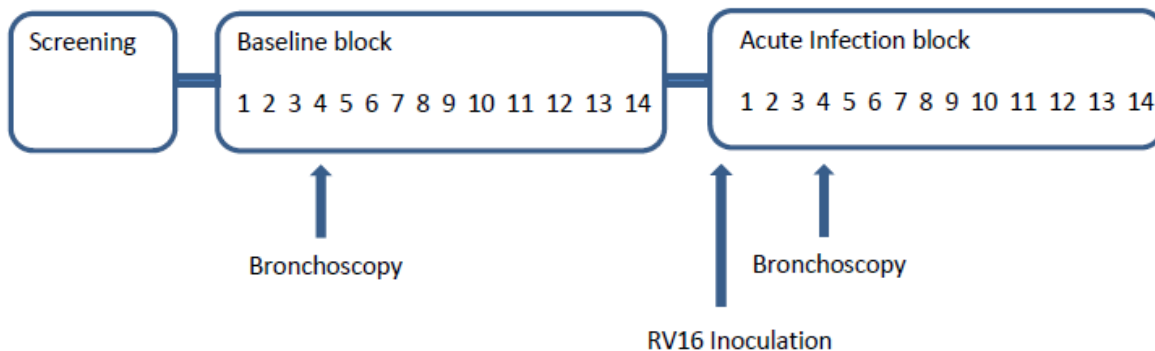
- nonsmoking
- with mild or moderately severe asthma

**Healthy individuals: (n=14)**

- nonsmoking,
- nonatopic

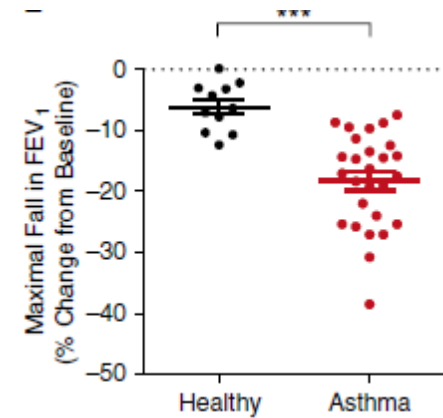
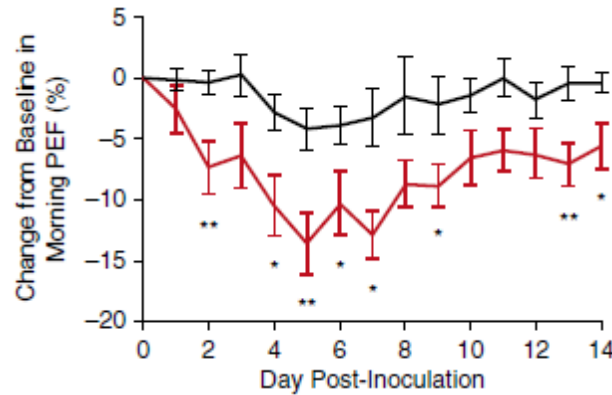
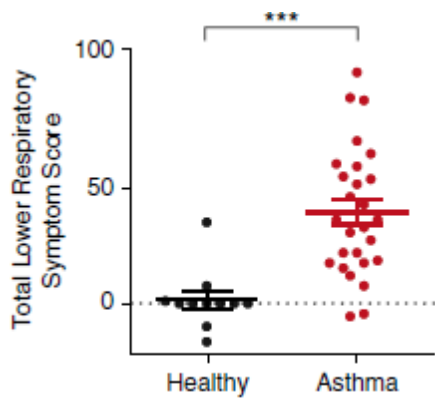
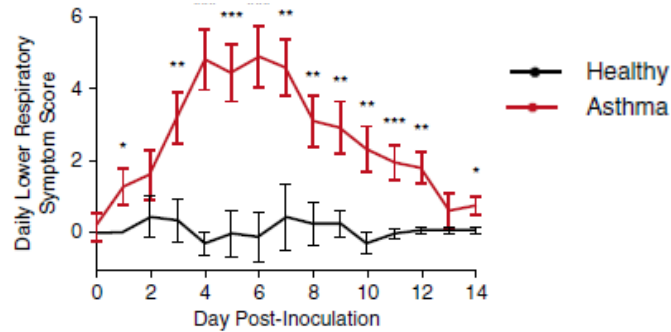
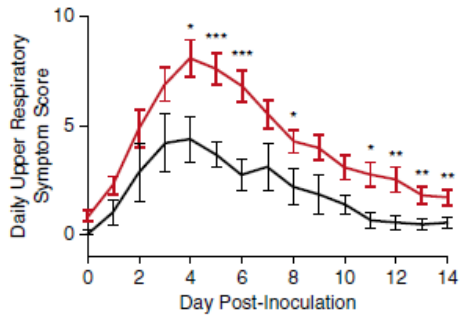
**Age:**  
18–55 years

**NO** recent viral illness or serum neutralizing antibodies to rhinovirus 16 (RV16) at screening.



## Patients with Asthma:

### ↑ Rhinovirus-induced Respiratory Morbidity

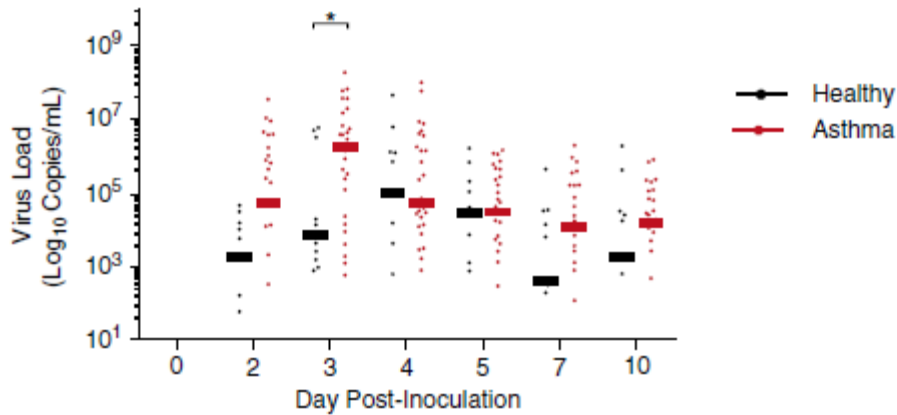


FEV<sub>1</sub>: Forced Expiratory Volume in 1 Second

PEF: Peak expiratory flow

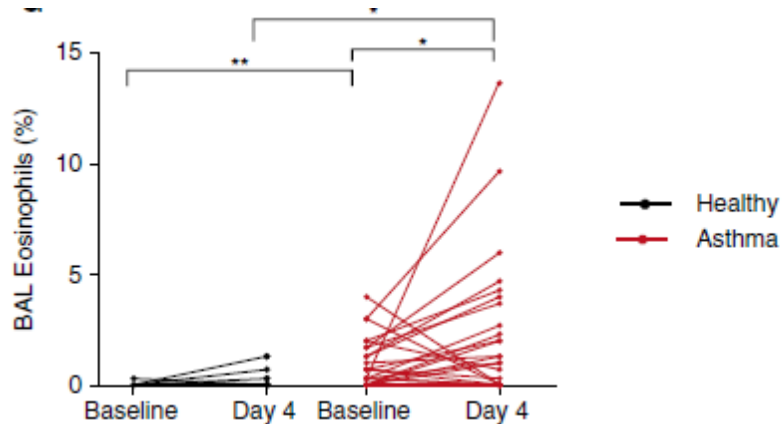
## Patients with Asthma:

↑ Viral Load than Healthy Subjects



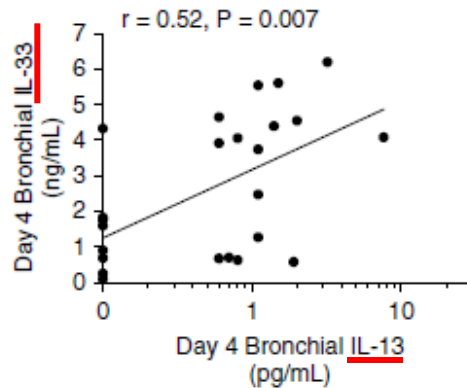
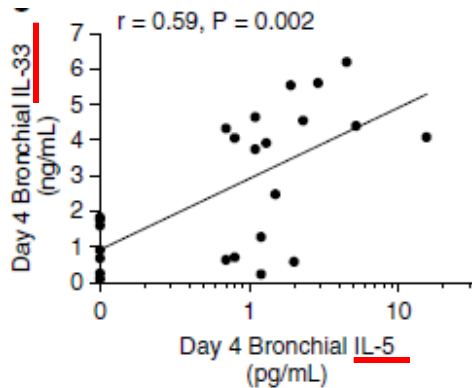
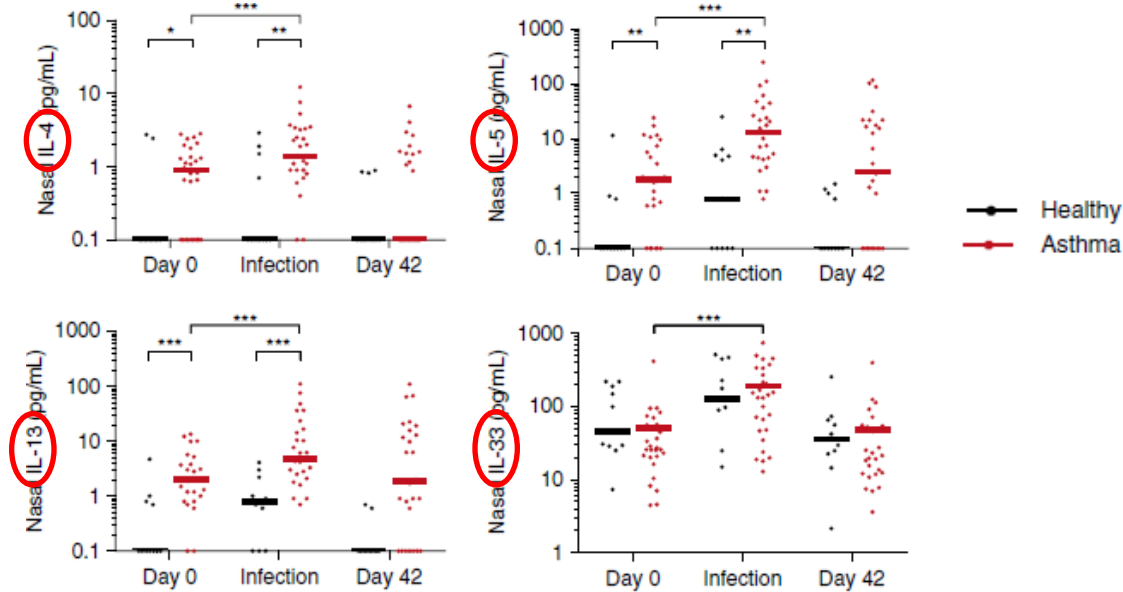
## Patients with Asthma:

↑ Virus-induced Lower Airway Eosinophilia



this is the first time a significant rhinovirus-induced eosinophilia has been demonstrated in asthma.

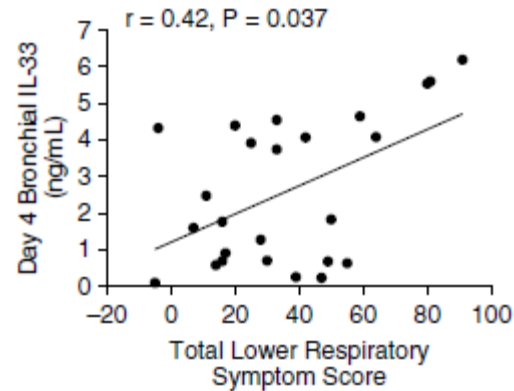
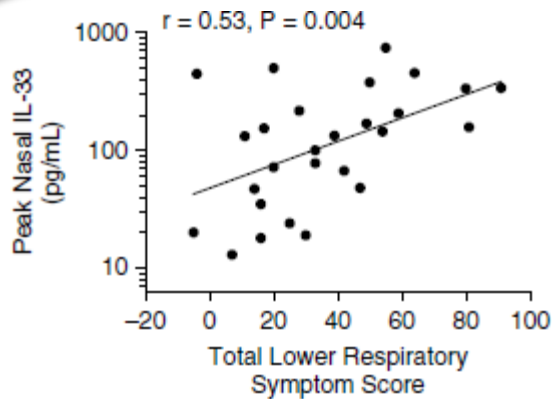
Rhinovirus infection in asthma:  
→ induction of IL-33 and type 2 cytokines in vivo



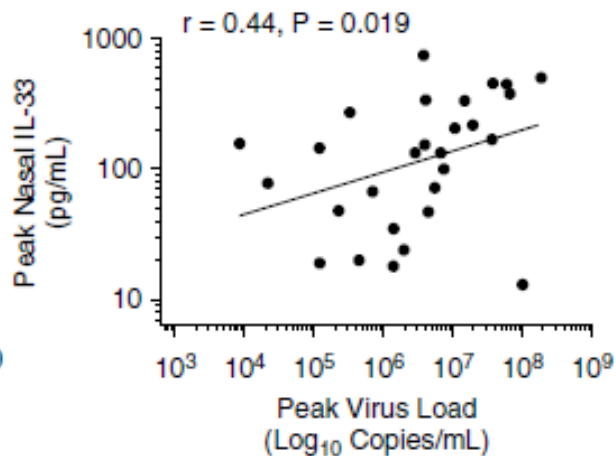
significant correlations  
between bronchial IL-33 and  
both IL-5 and IL-13 in Asthma  
subjects



## Type 2 Cytokines and IL-33 Correlate with Clinical Outcomes and Viral Load

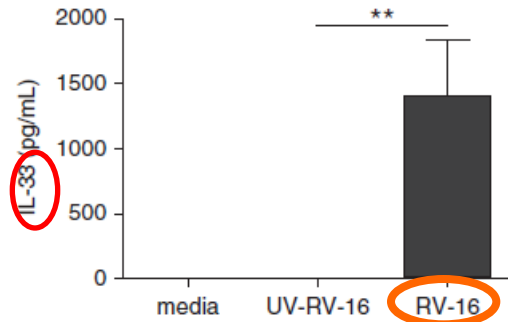


In asthma, IL-5 and IL-13 levels during infection both positively correlates with respiratory symptom severity

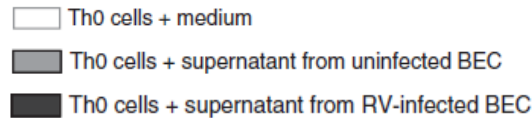


The IL-33 level correlates with viral load  
=> respiratory epithelium being both the site of infection and the source of IL-33.

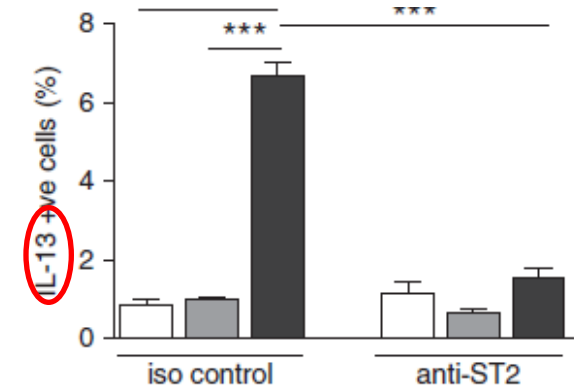
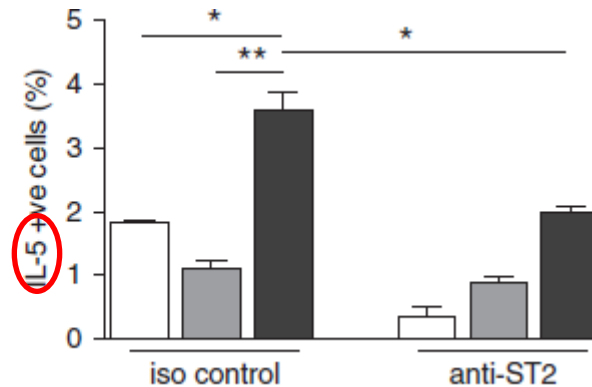
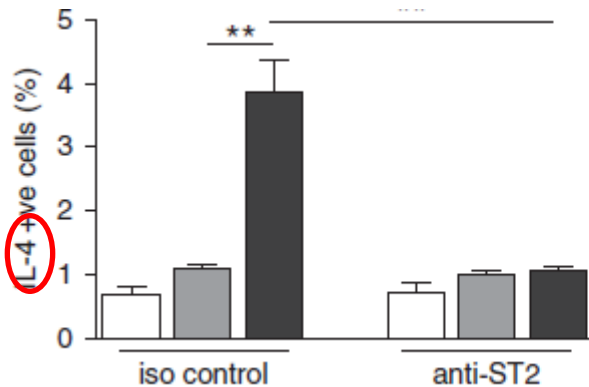
## Rhinovirus Infection of Primary Human BECs Ex Vivo



Rhinovirus infection of the bronchial epithelium leads to the release of large amounts of IL-33



## Functional role of IL-33 in inducing Th2 responses



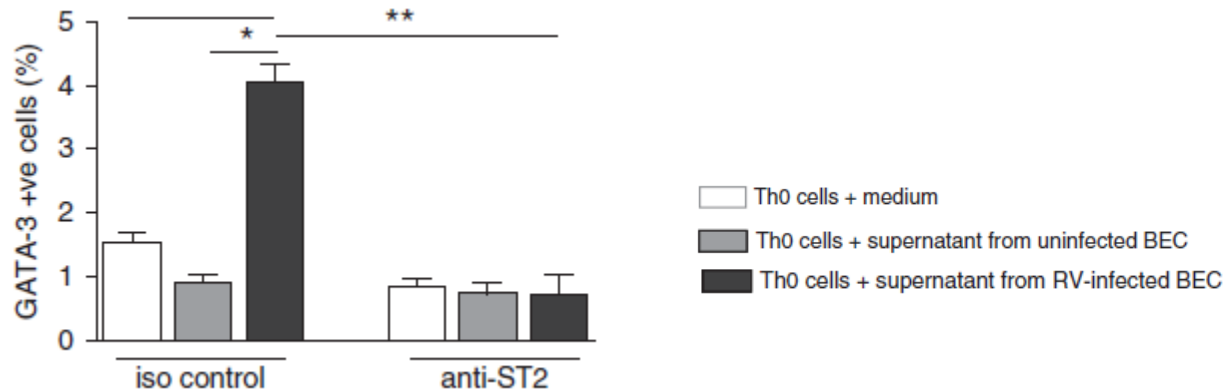
activated, nonpolarized human CD4<sup>+</sup> T cells (Th0 cells) were cultured with media alone and with supernatants from rhinovirus infected or uninfected BECs.



The Th0 cells cultured with supernatants from rhinovirus-infected BECs had significantly higher frequencies of IL-4<sup>+</sup>, IL-5<sup>+</sup>, IL-13<sup>+</sup> cells

## Rhinovirus Infection of Primary Human BECs Ex Vivo

### Functional role of IL-33 in inducing Th2 responses



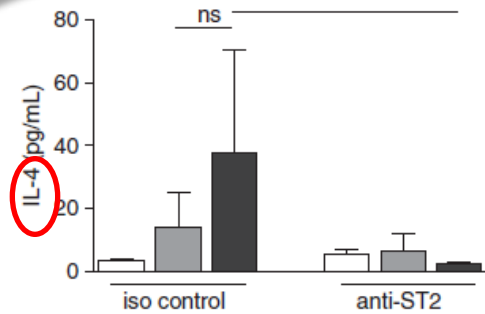
GATA3 → transcription factor

- Promotes secretion of IL-4, 5, 13
- Induces differentiation of Th0 cells to Th2
- Suppresses differentiation to Th1

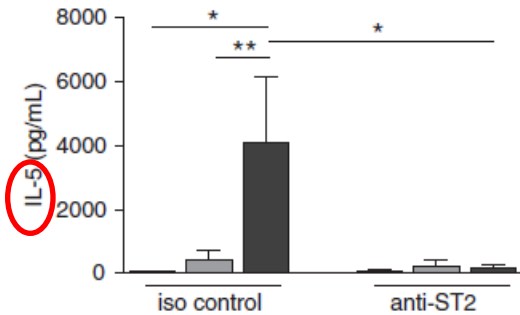
induction of Th2 responses was dependent on IL-33, as it was completely inhibited by pretreatment of the Th0 cells with anti-ST2 monoclonal antibody

## Rhinovirus Infection of Primary Human BECs Ex Vivo

### IL-33 activates human ILC2s to produce type 2 cytokines

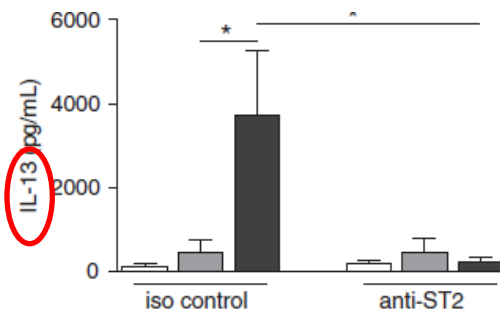


ILC2s + medium  
 ILC2s + supernatant from uninfected BEC  
 ILC2s + supernatant from RV-infected BEC



Critically, IL-5 and IL-13 induction was again completely blocked by anti-ST2 treatment

**⇒ IL-33 is the key factor in this pathway**



Rhinovirus trigger of IL-33 is therefore likely to drive an early and robust type 2 response via these innate cells.

## Summary



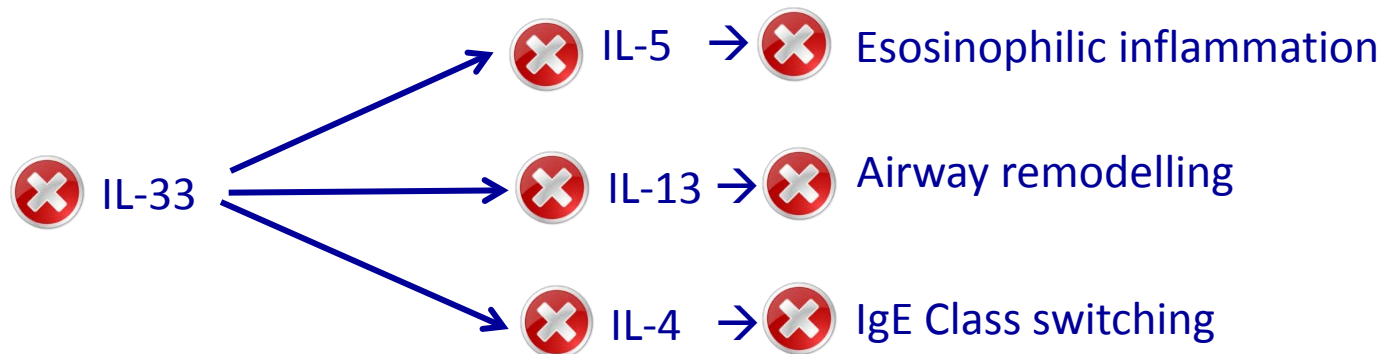
- Patients with Asthma Experience Greater Rhinovirus-induced Respiratory Morbidity and Viral Load than Healthy Subjects
- Virus-induced Lower Airway Eosinophilia is increased in Asthma
- IL-33 Is Induced by Rhinovirus infection In Vivo and is Related to Type 2 Responses
- Type 2 Cytokines and IL-33 Correlate with Clinical Outcomes and Viral Load
- IL-33 Present in Rhinovirus-infected BEC Supernatants
  - Induces Th2 responses in human T Cells
  - Induces IL-5 and IL-13 production by human ILC2s

## Conclusion



Virus-induced **IL-33** and IL-33–responsive T cells and ILC2s are key mechanistic links between **viral infection** and **exacerbation** of asthma.

IL-33 inhibition is a novel therapeutic approach for asthma exacerbations.





Thank you for  
your attention