

MD& PHD, Vice Professor

Department of Pulmonary Disease and Critical Care Medicine

Shanghai Ruijin Hospital

Shanghai Jiaotong University School of Medicine, China

- Vice Chairman, Youth Committee, Chinese Society of Allergy
- Vice Chairman, Shanghai Allergy Society
- General Secretary, Chinese Thoracic Society of Asthma





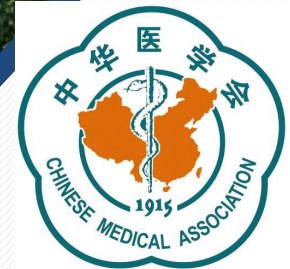
Epithelial cell derived cytokine - A new asthma endotype

Tang Wei

Department of pulmonary disease and Critical Care Medicine

Shanghai Ruijin Hospital

Jiaotong University School of Medicine





Asthma Phenotype and Endotype

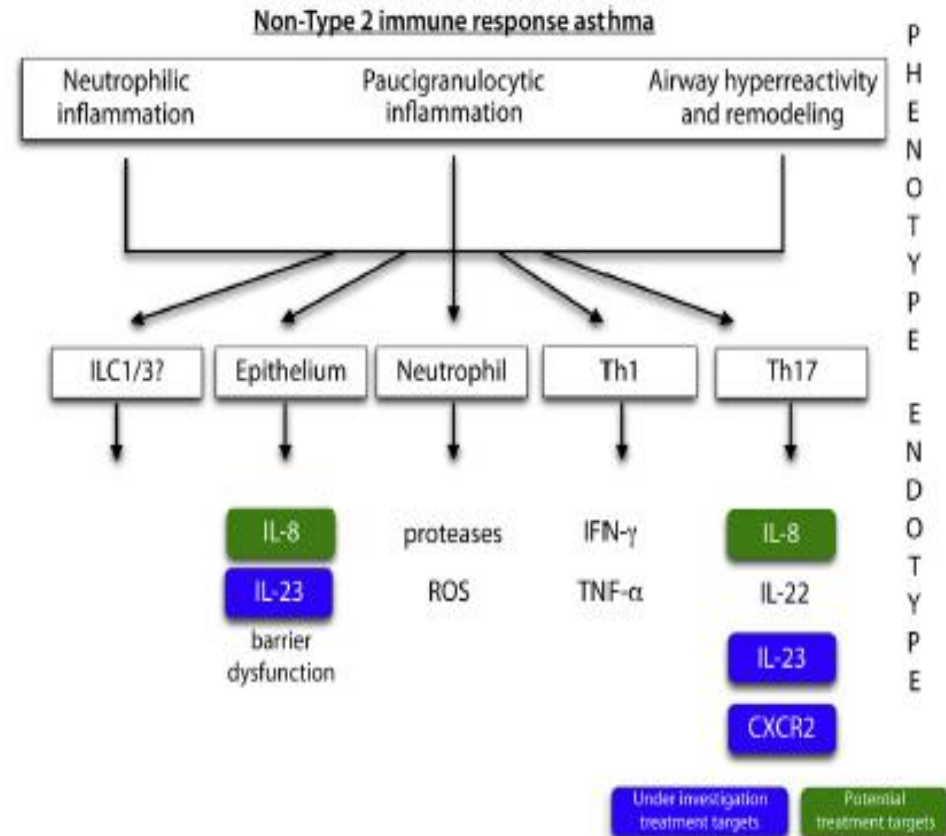
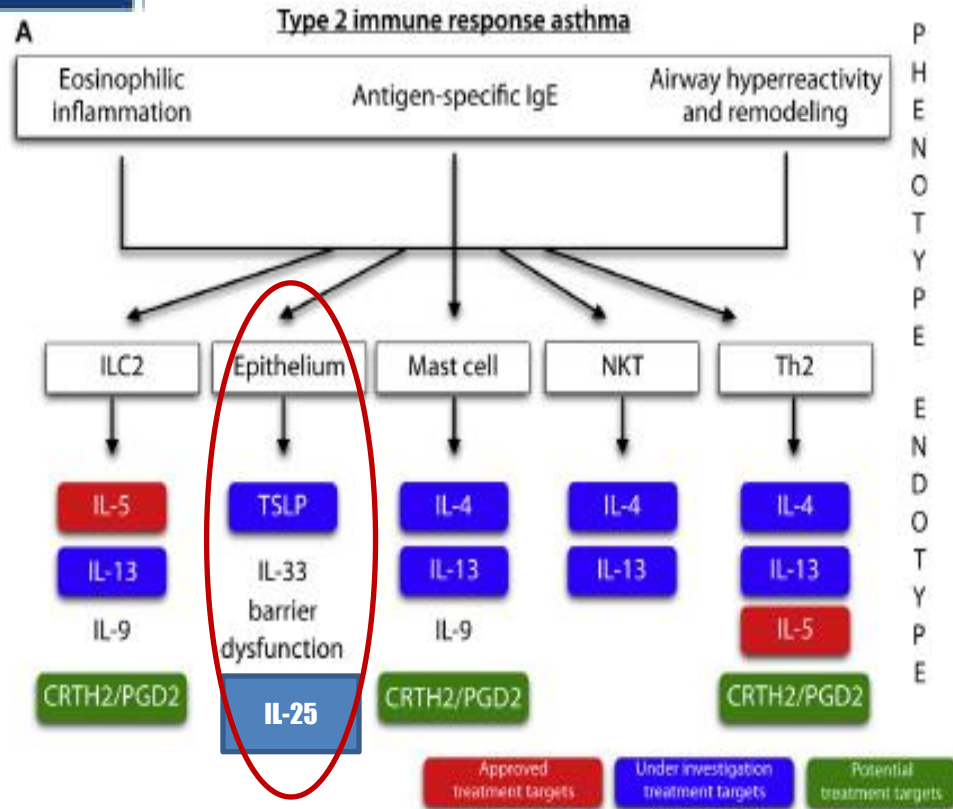
The heterogeneity of asthma in relation to patients' characteristics (phenotype), underlying pathogenic mechanisms (endotype), and clinically significant outcomes, including response to treatment, has been established beyond any doubt. Better asthma management needs a refined understanding of disease heterogeneity and mechanisms in relation to clinically significant outcomes.

Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology.
J Allergy Clin Immunol. 2016 May;137(5):1347-58





Asthma Phenotype and Endotype

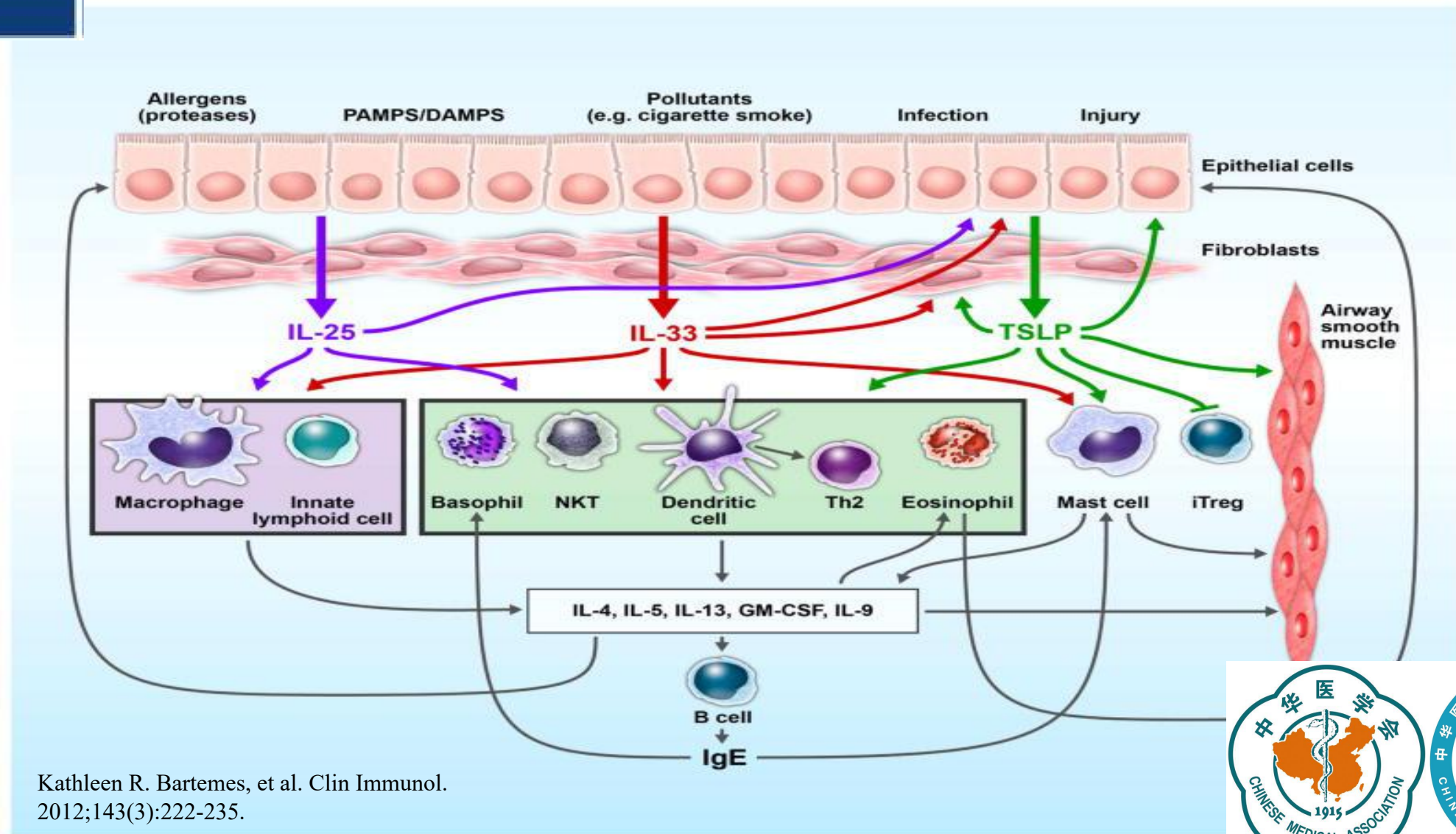


Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology.
J Allergy Clin Immunol. 2016 May;137(5):1347-58

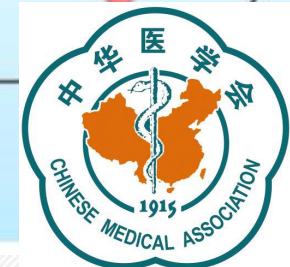




Epithelial Cell Derived Cytokine and Asthma

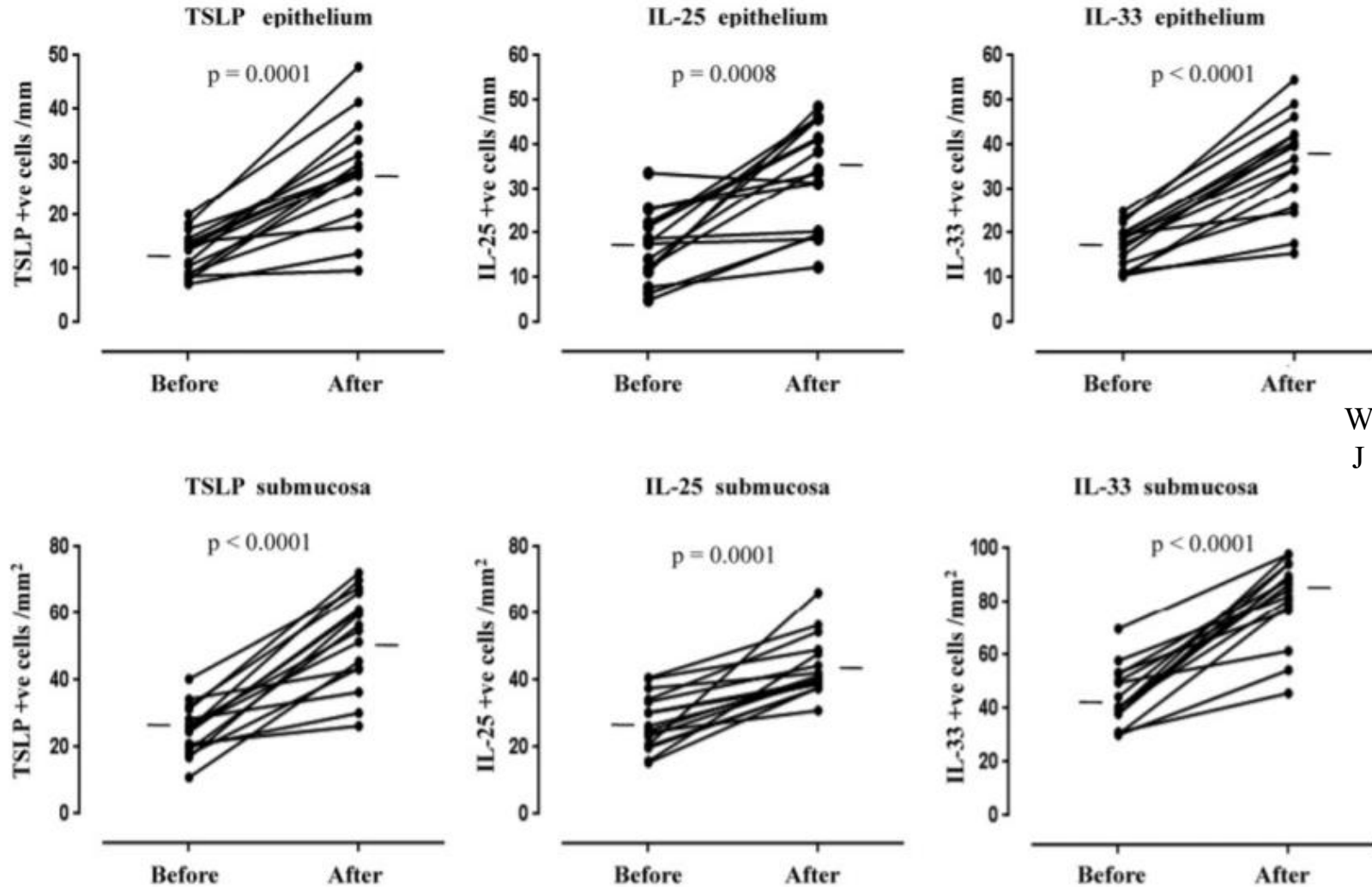


Kathleen R. Bartemes, et al. Clin Immunol. 2012;143(3):222-235.





Epithelial cell derived cytokine experssion after allergen challenge

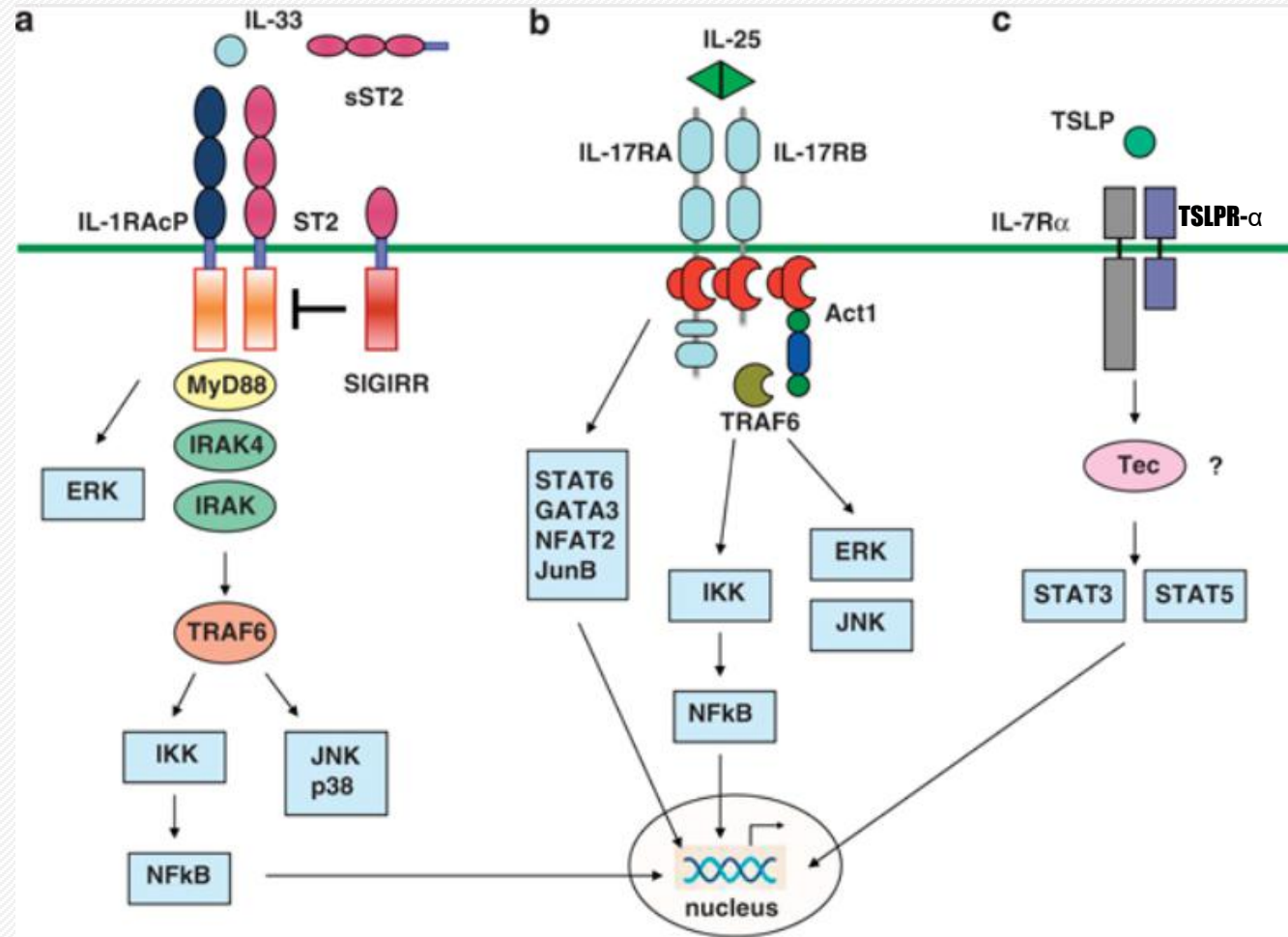


Wei Wang, Yan Li, Sun Ying.
J Immunol 2018; 201:2221-2231;





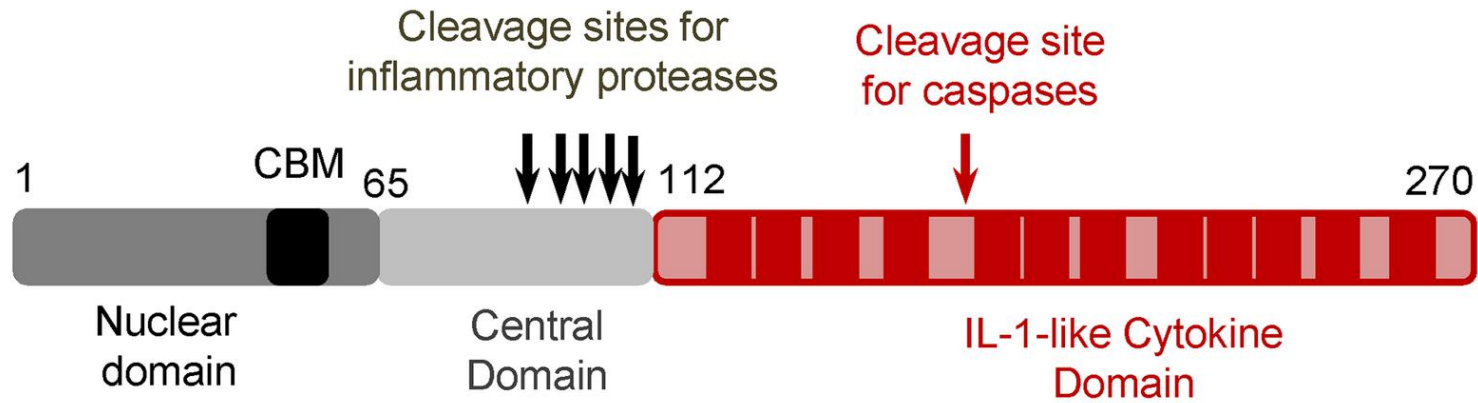
Epithelial cell derived cytokine and It's recetpor



IL-33



The human IL-33 protein



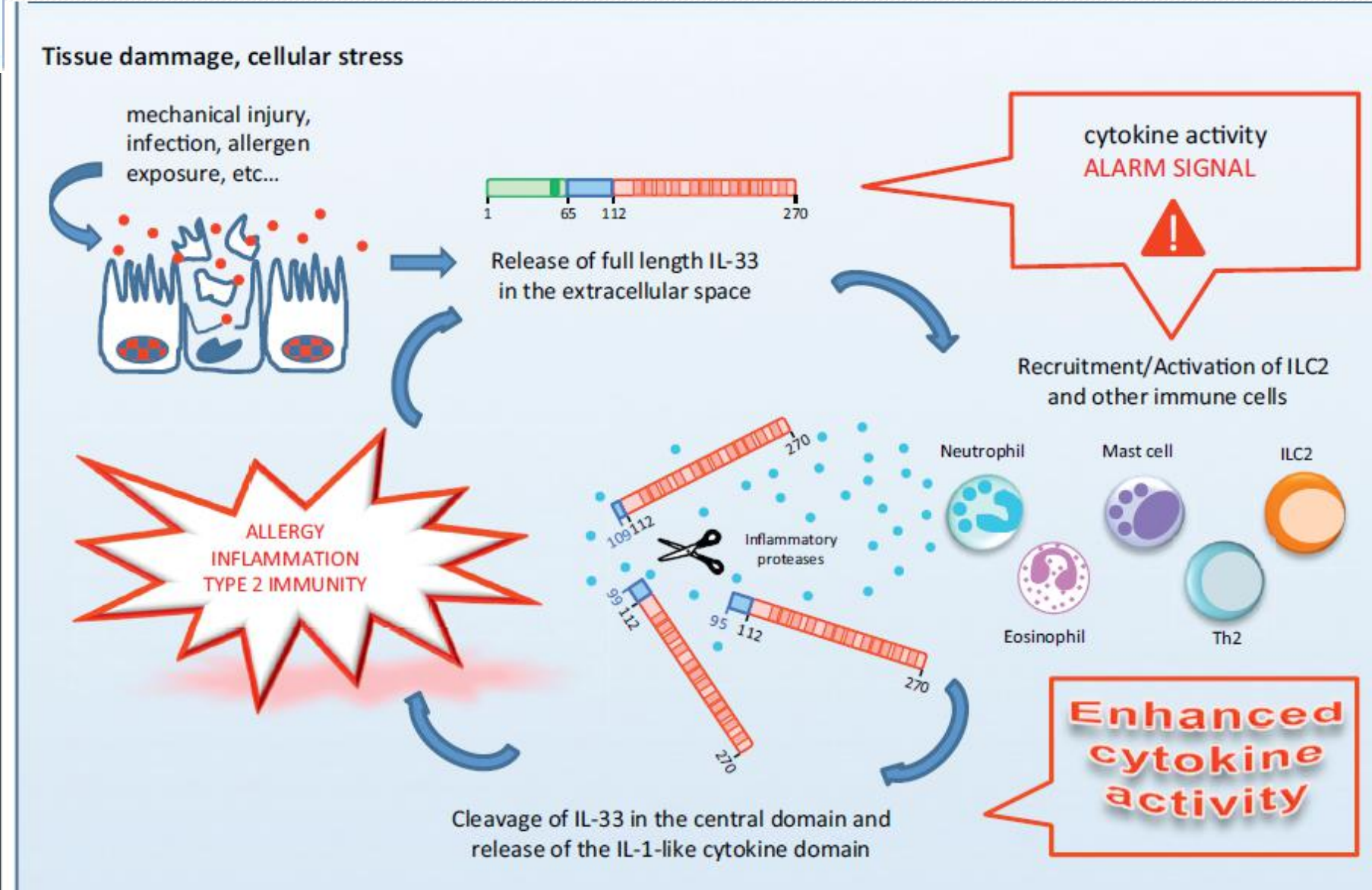
Cayrol C, et al. Immunol Rev. 2018;281(1):154-168

ST2

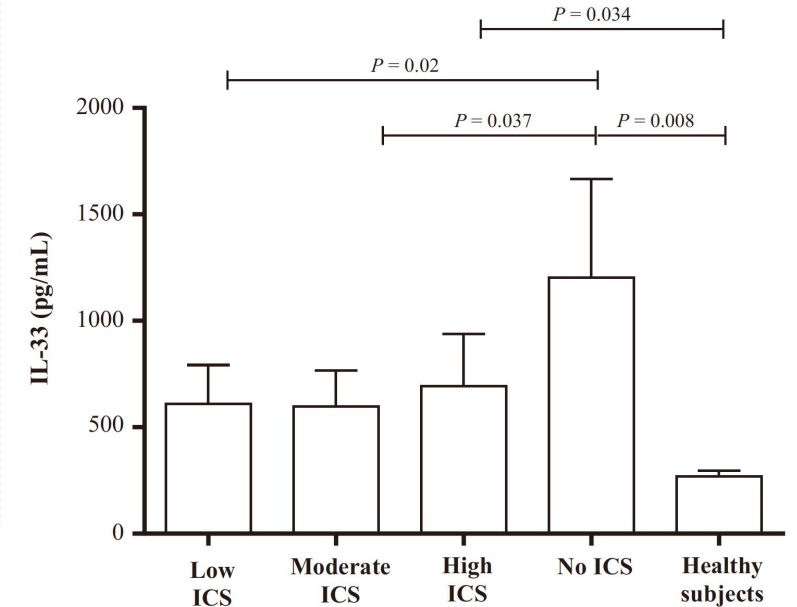
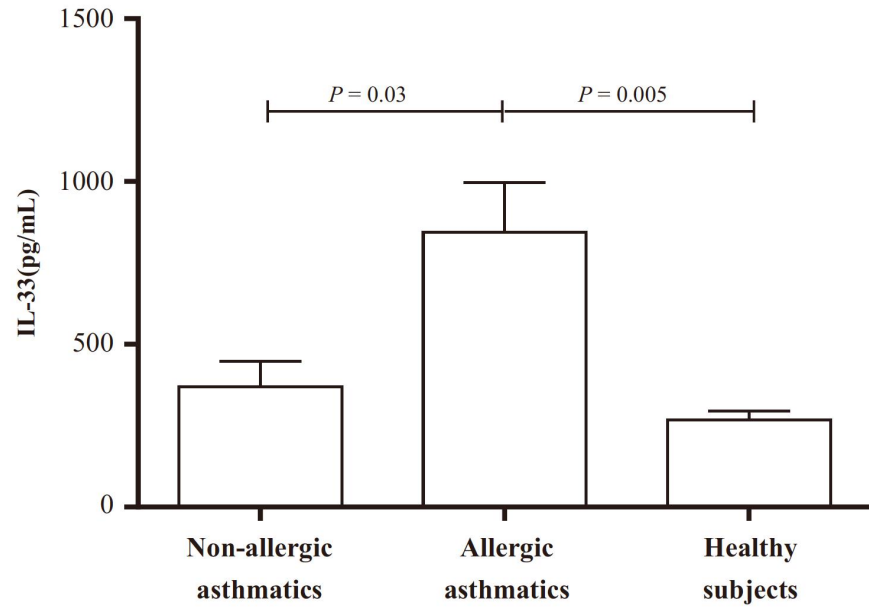




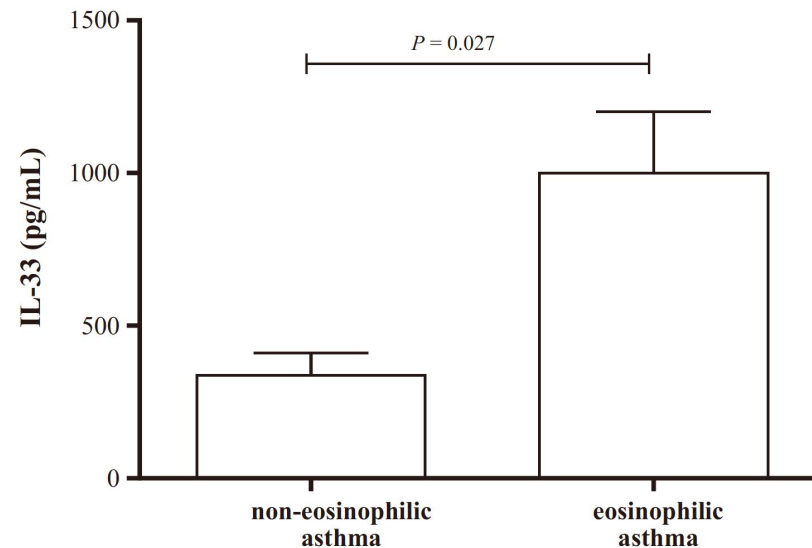
IL-33 Activation



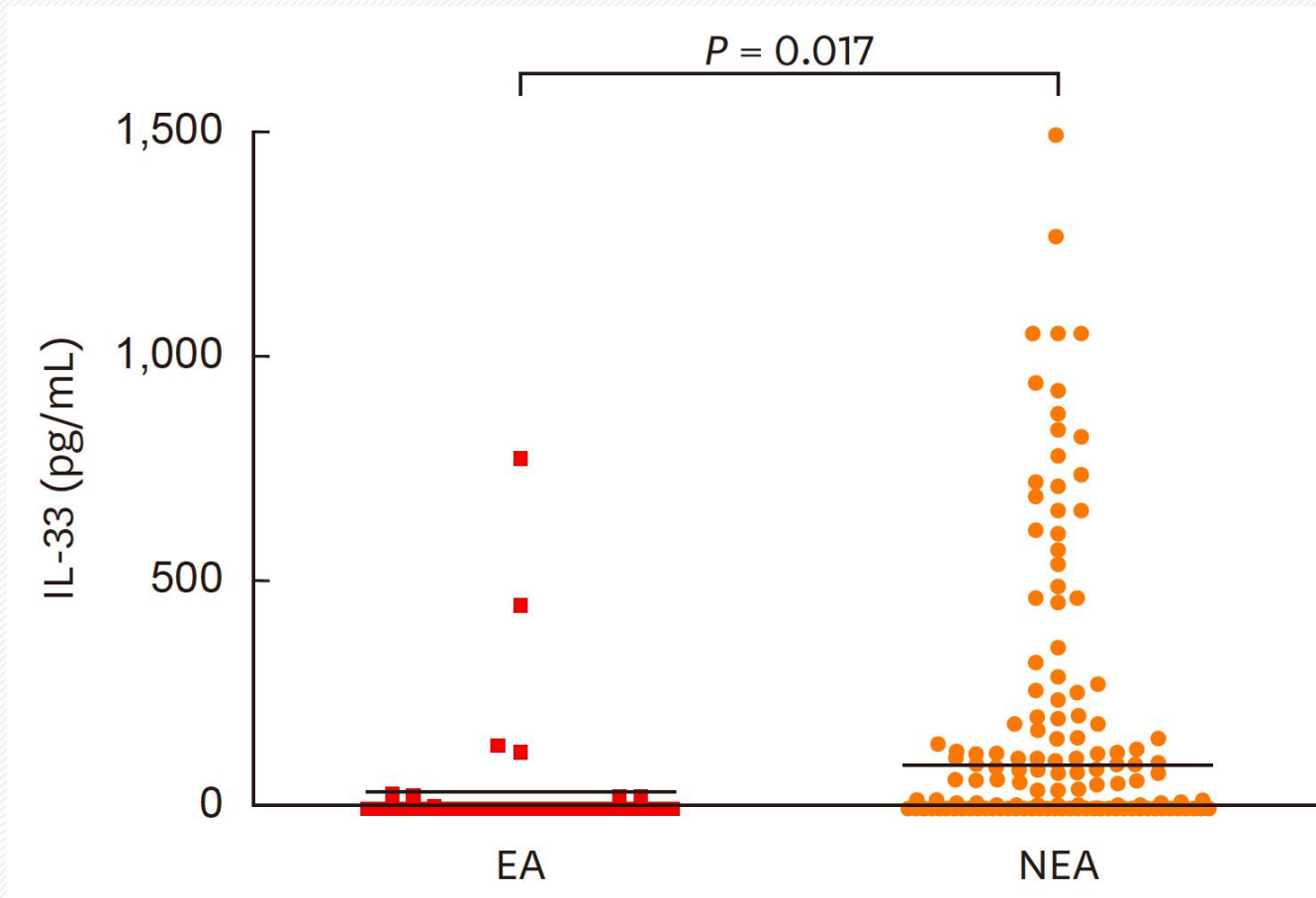
IL-33 and Asthma



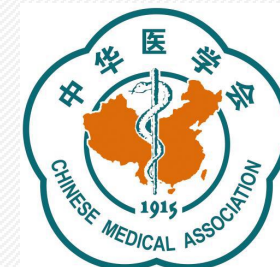
Gasiuniene et al. Scand J Immunol. 2019;89:e12724



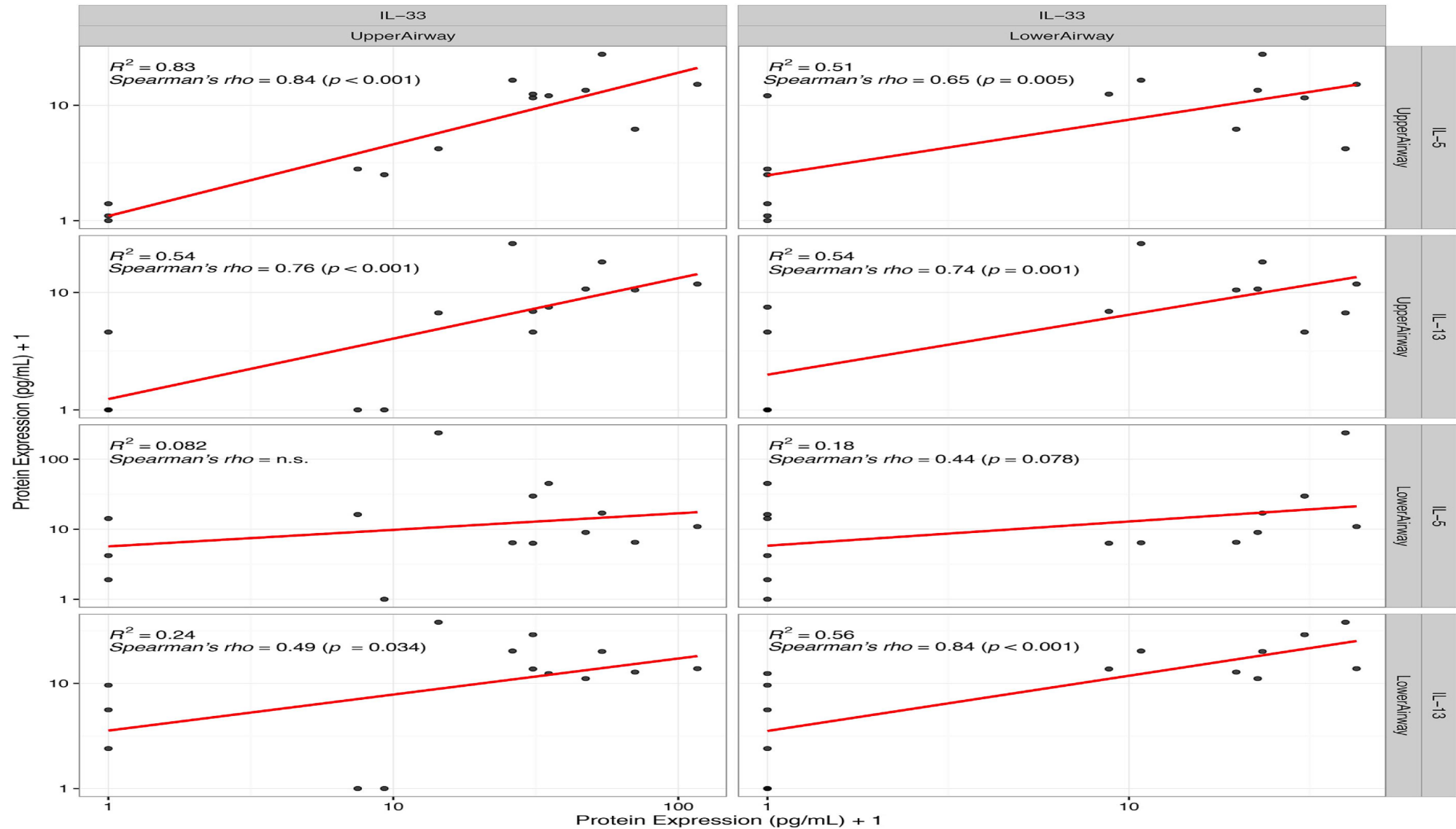
IL-33 and Asthma



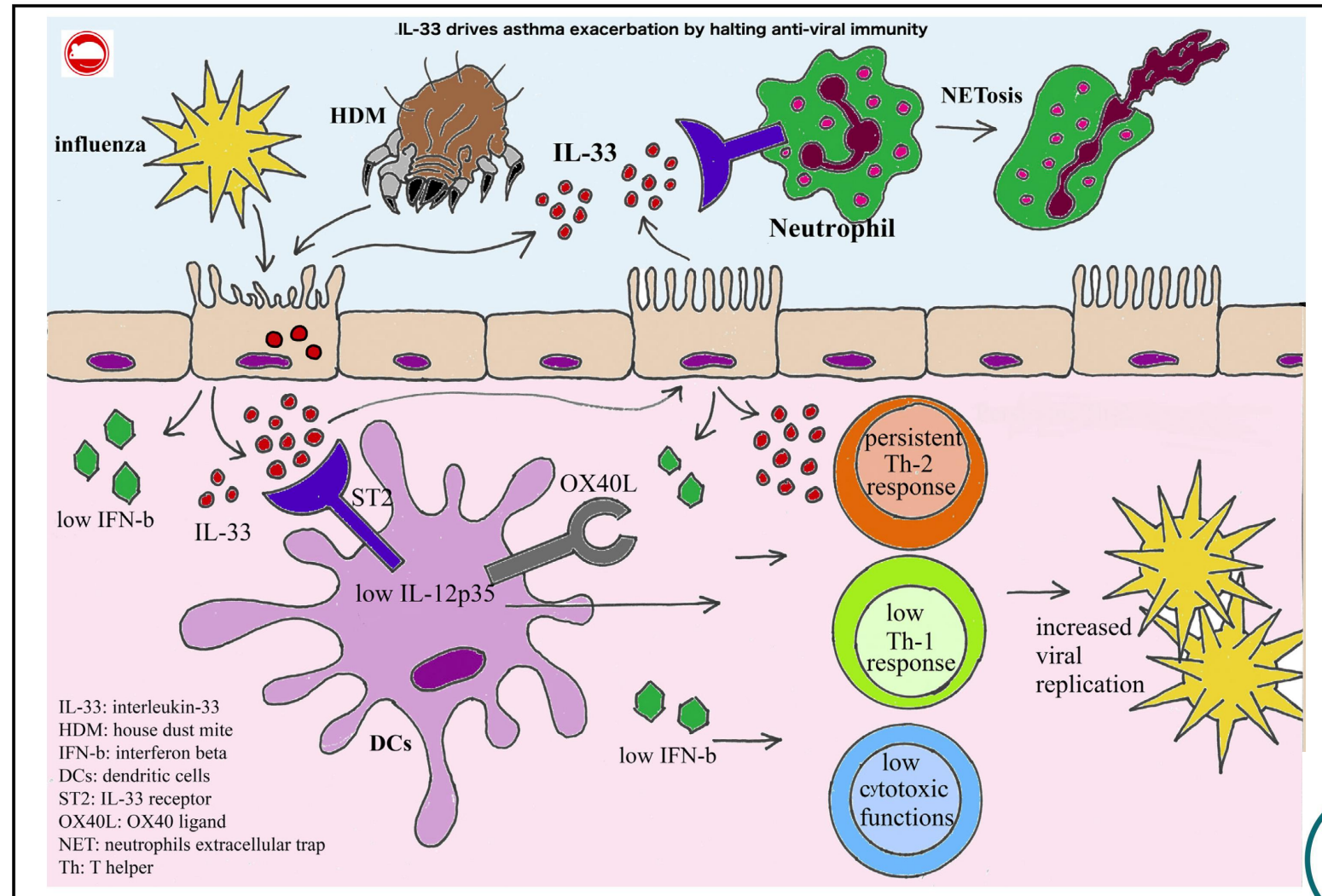
EA, elderly asthma
NEA, non-elderly asthma



IL-33 and asthma exacerbation



IL-33 and Asthma exacerbation



Clinical Trail

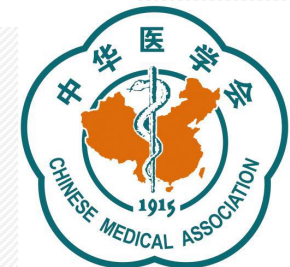


- IL-33 receptor antibody--NCT03207243
- moderately severe asthma
- 33wks
- 148 subjects

Actual Study Start Date : September 14, 2017

Estimated Primary Completion Date : February 28, 2019

Estimated Study Completion Date : May 23, 2019





IL-25 and asthma

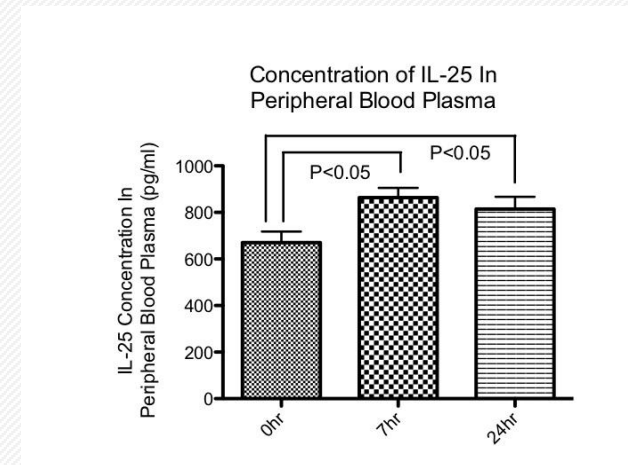
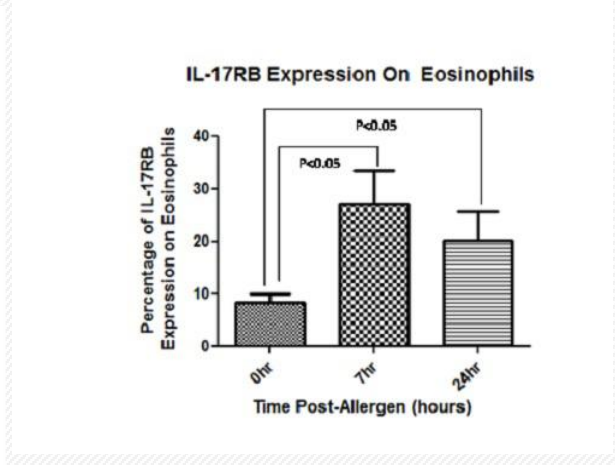
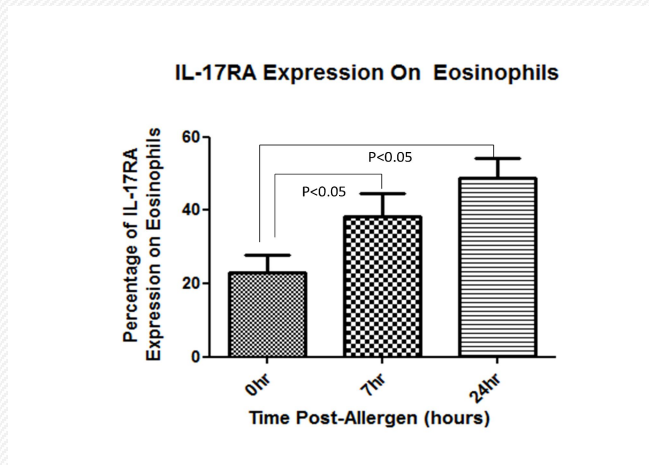
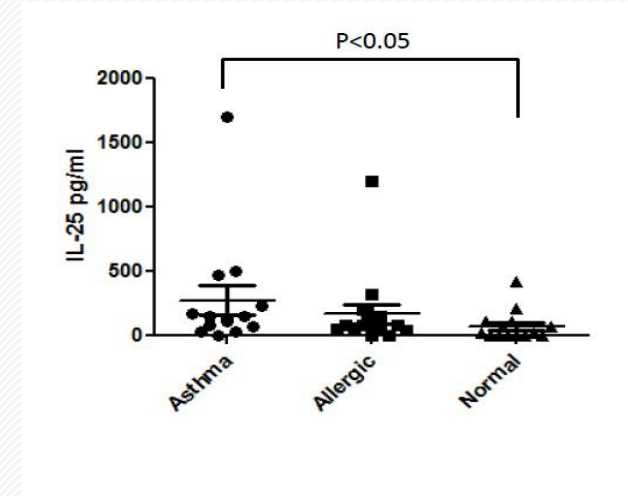
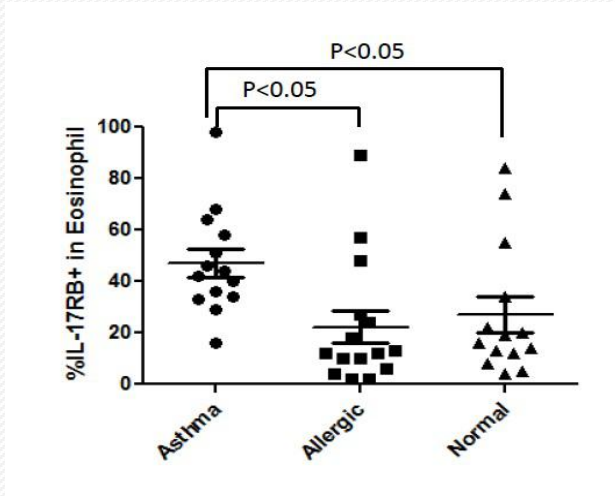
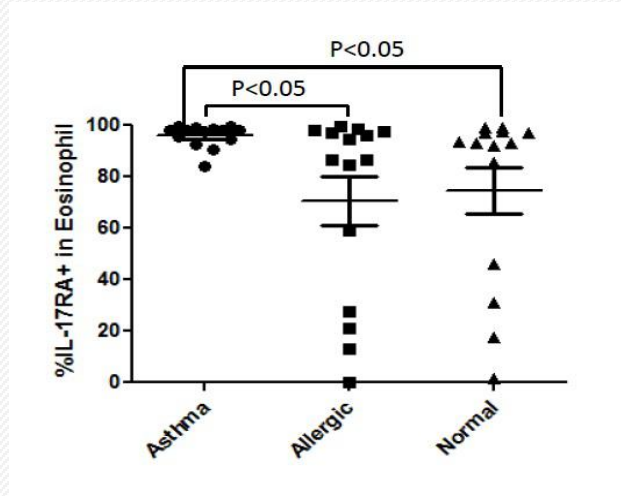
639

Table 1 Potential cellular sources and targets of interleukin (IL)-25

Cell type	IL-25-producing cells	IL-25 responder cells (IL-17RB/RA expressing cells)
Innate immune cells	Human/Murine mast cells ^{12,19} Murine alveolar macrophages ¹³ Human eosinophils and basophils ^{18,19}	Human basophils and eosinophils ^{19,21,22} Human mast cells ¹⁸ Murine type 2 myeloid cells ^{23,24} Murine NKT cells ^{25,26} Murine macrophage ²⁷ Murine dendritic cells ²⁸ Murine non-T/non-B (NBNT) lineage: multipotent progenitor cell (MPP) type2 cells, ^{29,30} innate helper type 2 (ih2) cells, ³¹ natural helper cells (NHC), ³² nuocyte ^{33,34}
Adaptive immune cells	Murine Th2 cells ¹⁰	Human CD4 ⁺ T memory cells ^{14,19,35} Murine Th9 cells ³⁶
Structural cells	Human and murine epithelial cells ^{15,16,20,37} Human and murine endothelial cells ¹⁷⁻¹⁹	Human epithelial cells ³⁷ Human primary lung fibroblasts ³⁸ Human vascular endothelial cells (HUVEC) ^{18,19,39}

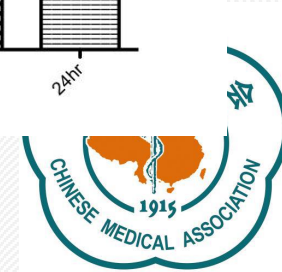


IL-25 and Asthma(eosinophil)



Tang W, Int Arch Allergy Immunol 2013; 163(1):5-10

Tang W, et al. Int Arch Allergy Immunol. 2016 Sep 30;170(4):234-242.





IL-25 and Asthma(DC&Basophil)

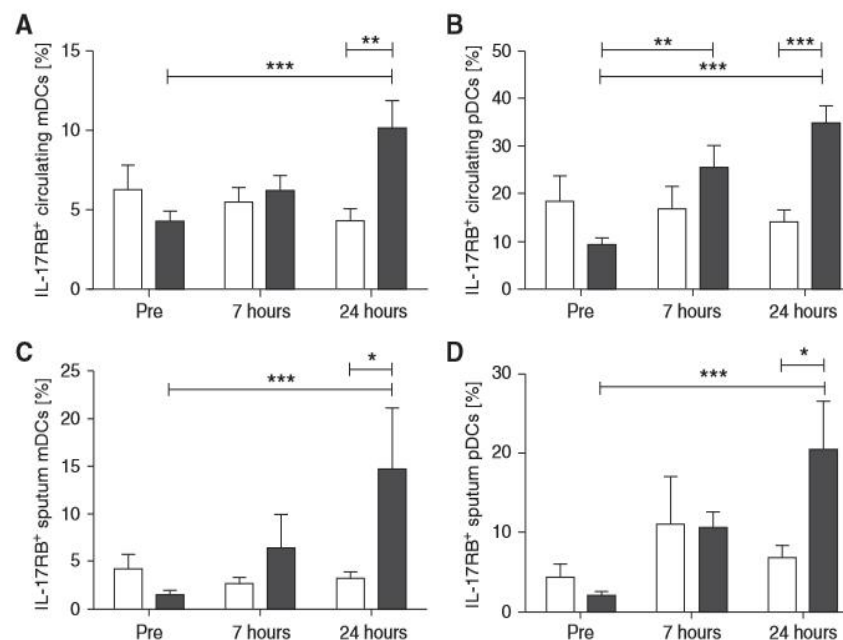
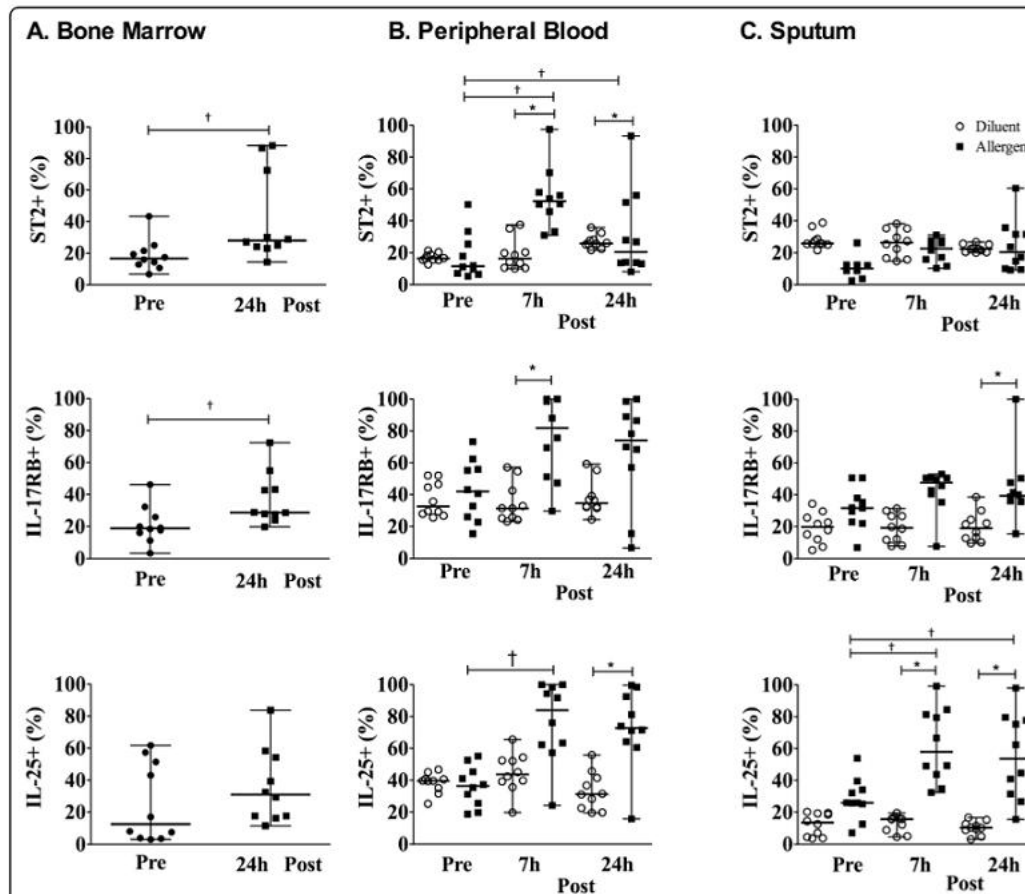


Figure 3. The percentage of blood and sputum IL-17RB⁺ myeloid (A and C) and plasmacytoid dendritic cells (B and D) before and 7 and 24 hours after diluent (open bars) and allergen (solid bars) inhalation. Data are mean ± SEM (n = 13 for blood and n = 10 for sputum). *P < 0.05; **P < 0.01; ***P < 0.001. IL-17RB = IL-25 receptor; mDCs = myeloid dendritic cells; pDCs = plasmacytoid dendritic cells.

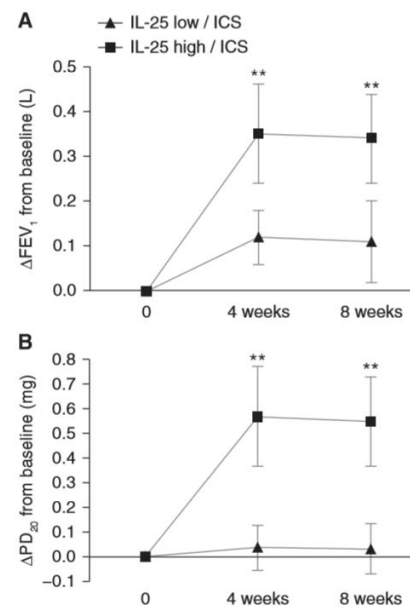
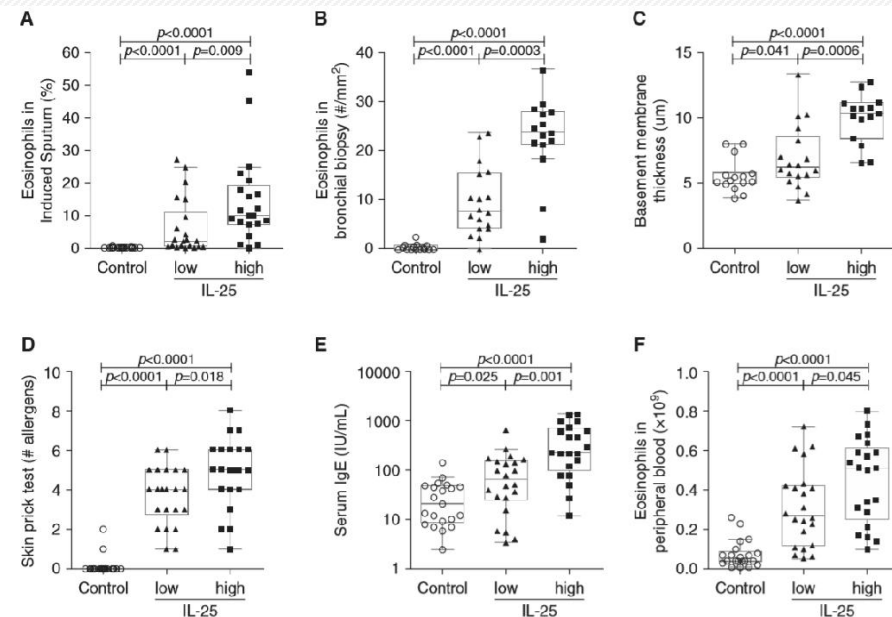
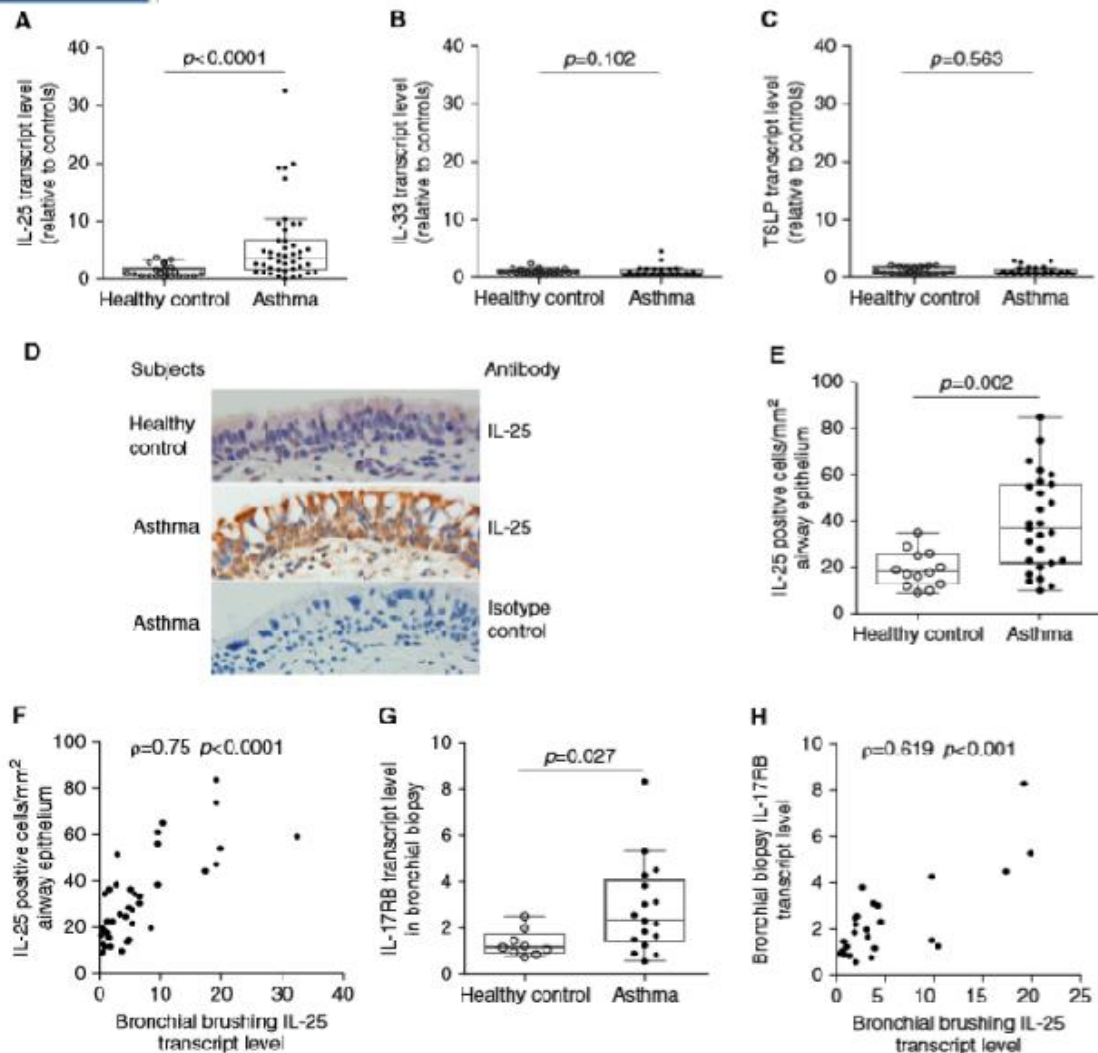


Salter et al. Respiratory Research (2016) 17:5
Tworek, Smith, Salter, et al. Am J Respir Crit Care Med. 2016 957–964

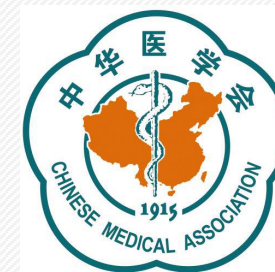




IL-25 and Asthma



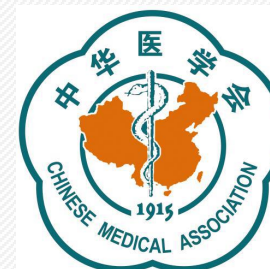
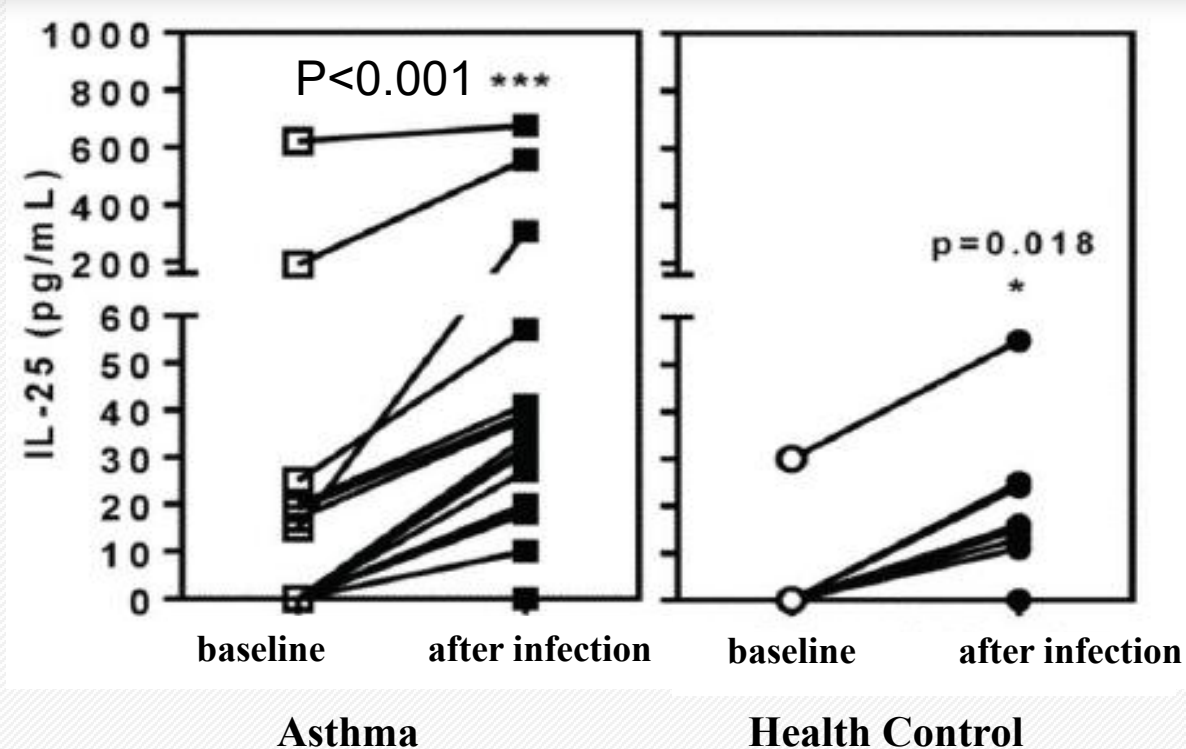
Zhen GH, et al. Am J Respir Crit Care Med. 2014. 190(6)639-648










Rhinovirus induced IL-25 in asthma exacerbation drives type-2 immunity and allergic pulmonary inflammation

Janine Beale^{#1,2,3}, Annabelle Jayaraman^{#1,2,3}, David J. Jackson^{#1,2,3,4}, Jonathan D. R. Macintyre^{1,2,3,4}, Michael R. Edwards^{1,2,3}, Ross P. Walton^{1,2,3}, Jie Zhu^{1,2,3}, Yee Man Ching^{1,2,3}, Betty Shamji⁵, Matt Edwards⁵, John Westwick⁵, David J. Cousins^{2,6}, You Yi Hwang⁷, Andrew McKenzie⁷, Sebastian L. Johnston^{#1,2,2,4}, and Nathan W. Bartlett^{#1,2,3,~}

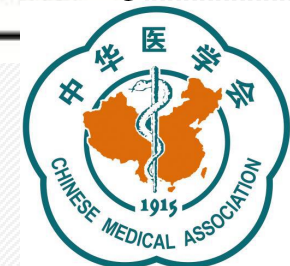




TSLP

Cellular sources of TSLP	Cellular targets of TSLP	Actions
Epithelial Cells 	Dendritic Cells	↑ Co-stimulatory molecules, Th2 priming
	CD4 ⁺ T Cells	↑ Proliferation, Th2 differentiation
Fibroblasts 	Mast Cells	↑ Cytokine production
	Eosinophils	↑ Extracellular trap formation, cytokine production
Dendritic Cells 	Basophils	↑ Expansion, cytokine production
	Treg Cells	↓ Suppressive activity
Basophils 	Treg Cells	↓ Suppressive activity
	Lung natural helper innate type 2 cells	↑ Th2 cytokine production (with IL-33)
Mast Cells 		

Drug Discov Today Dis Mech. 2012 Dec 1; 9(3-4)



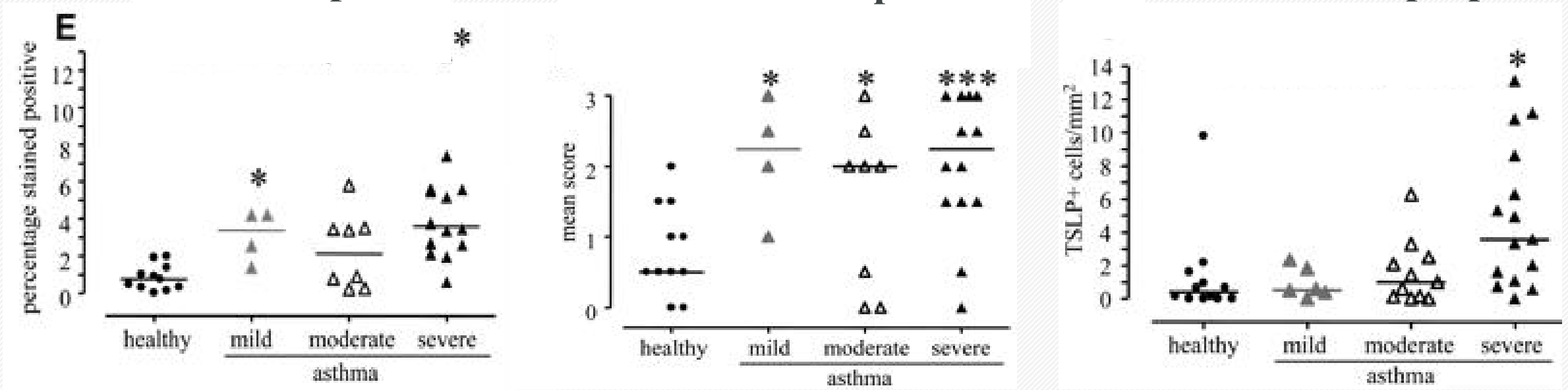


Translational Science Studies

TSLP % epithelium

TSLP scored epithelium

TSLP lamina propria



TSLP protein is increased in asthma patients (bronchial biopsy)

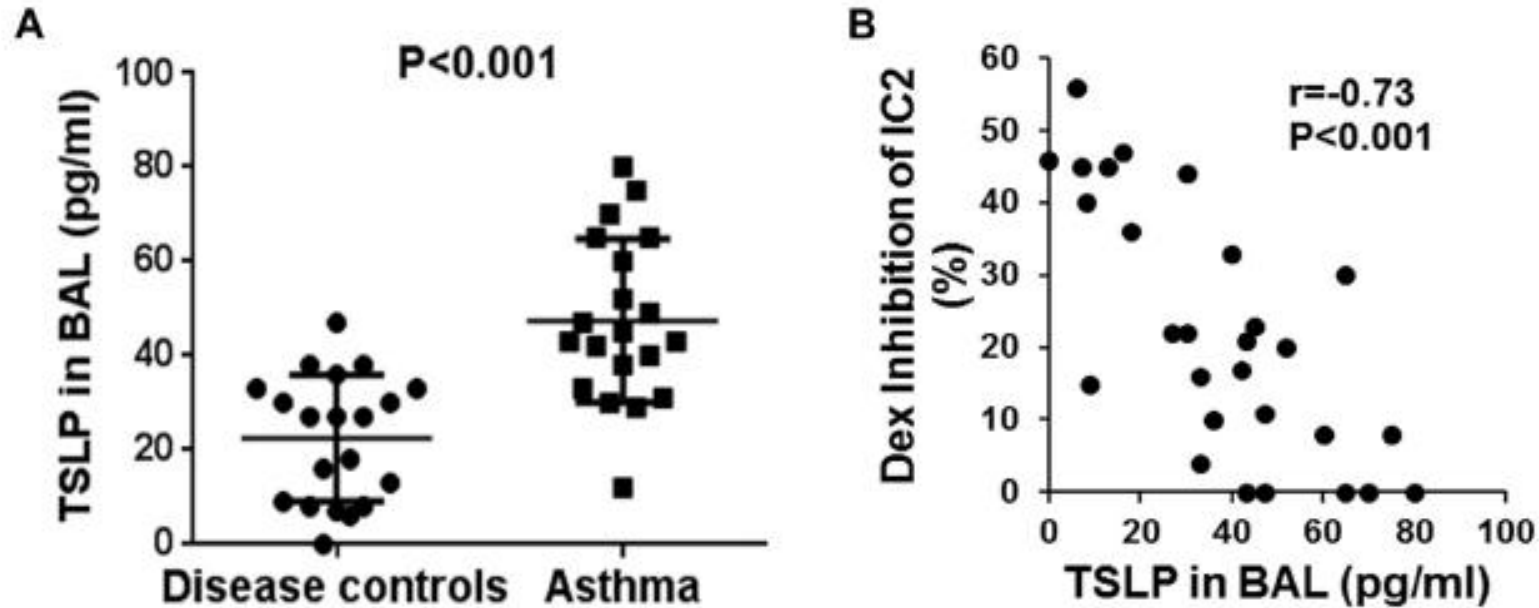
Reannotated from Shikotra A et al J. Allergy Clin. Immunol. 2012; 129: 104-111

Amgen- AZ C





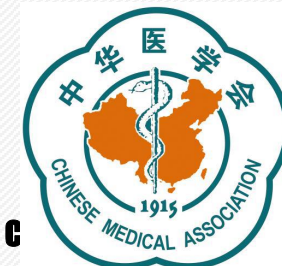
Translational Science Studies



TSLP protein is increased in BAL from severe asthma patients and negatively correlated with dexamethasone inhibition of IL5 +ve immune cells

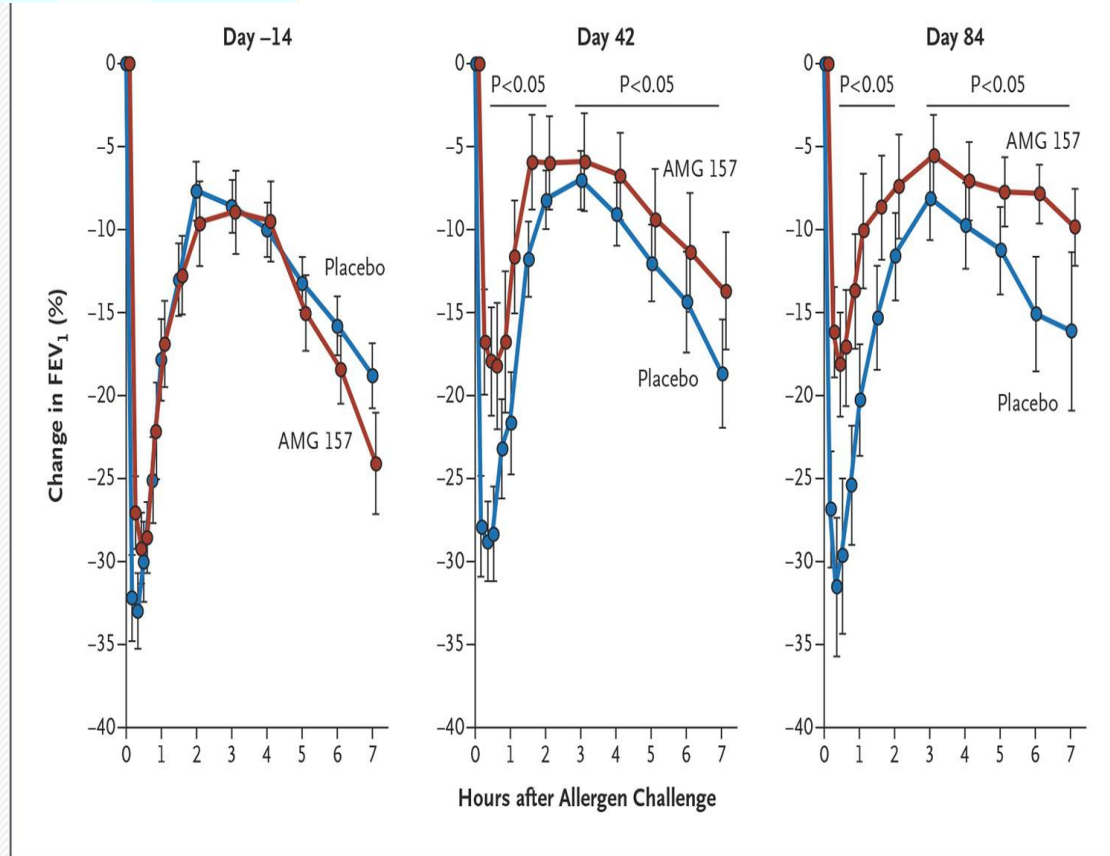
Liu et al J Allergy Clin Immunol. 2018 Jan;141(1):257-268

Amgen- AZ C

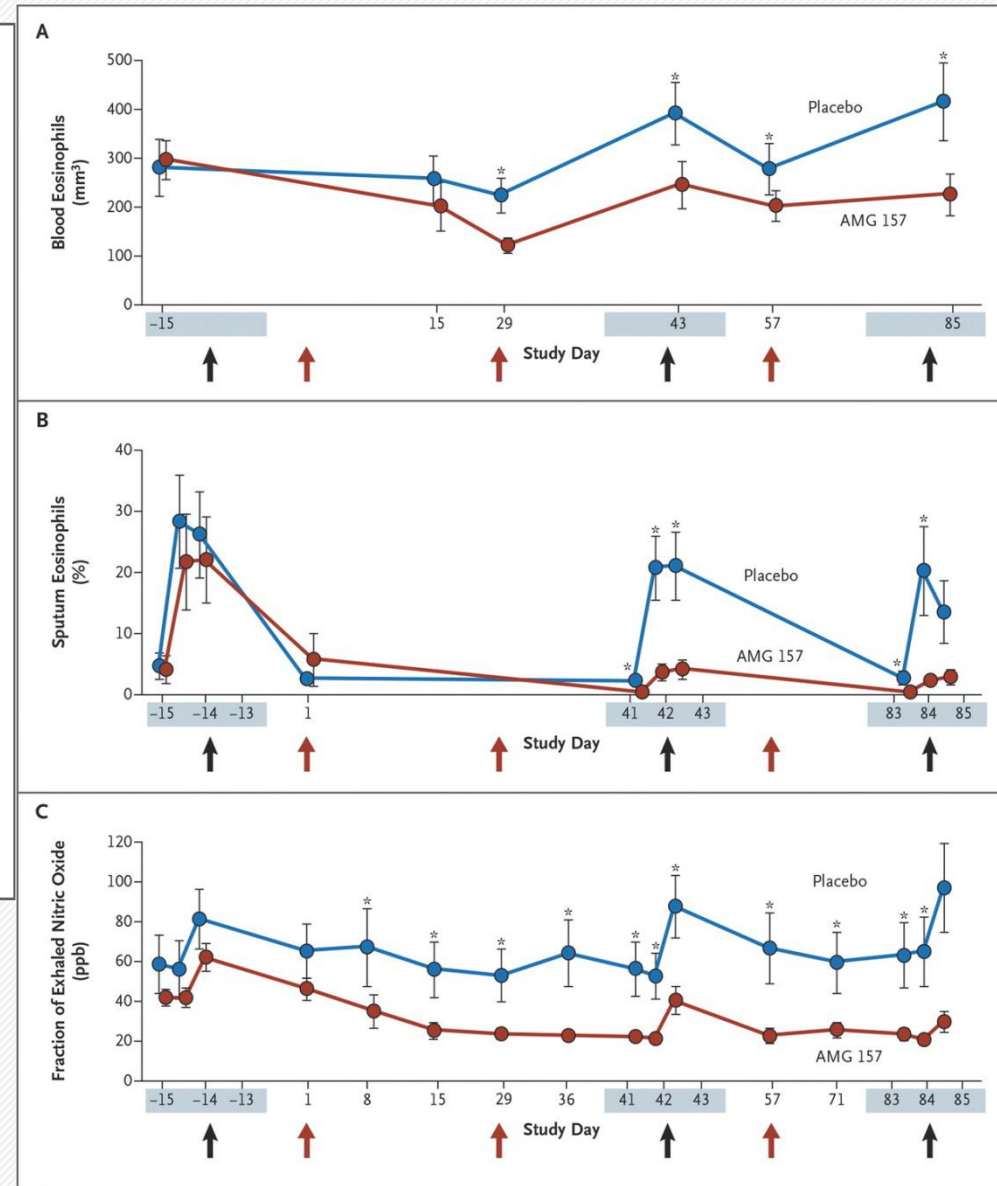




Target therapy——TSLP Antibody (Tazalizumab)



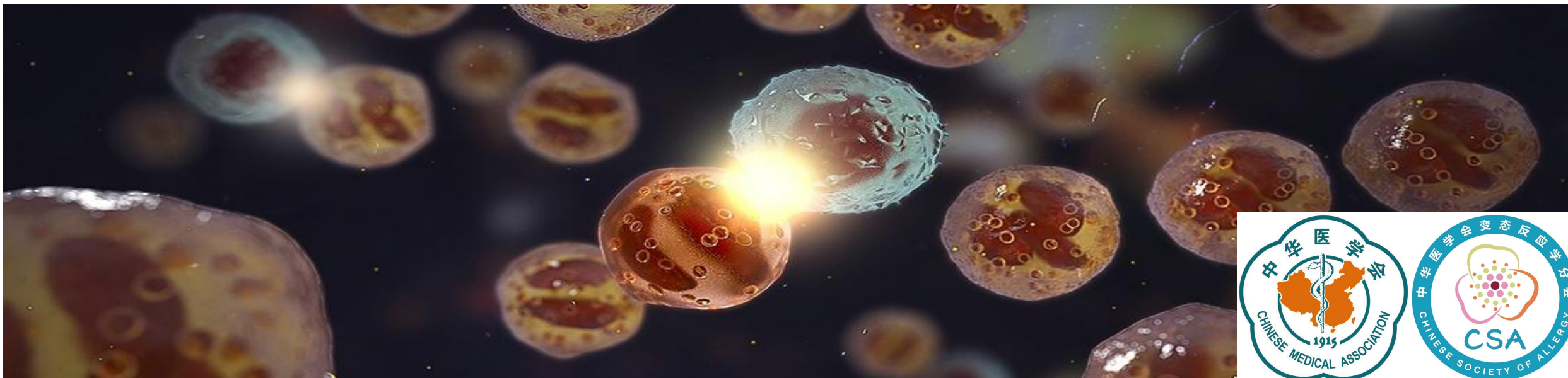
Effects of an anti-TSLP antibody on allergen-induced asthmatic responses
N Engl J Med.2014 May 29;370(22):2102-10

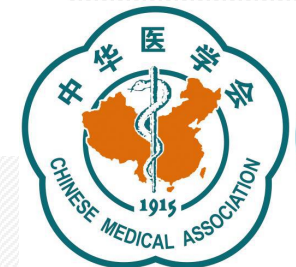
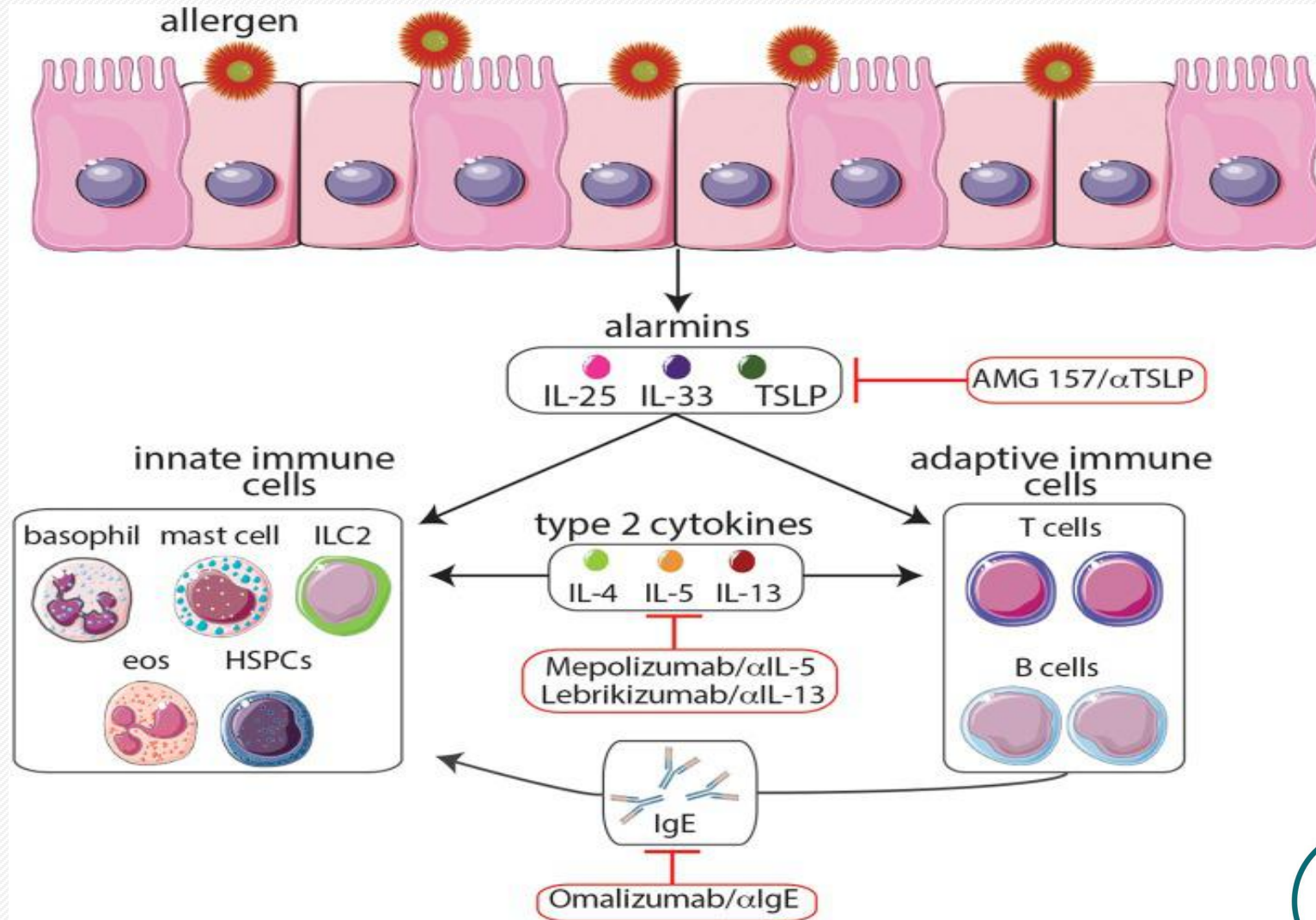




**A multinational, multicenter, randomized, double-blind, placebo-controlled, parallel, phase III study
To evaluate the efficacy and safety of Tezepelumab in adults with poorly controlled severe asthma**

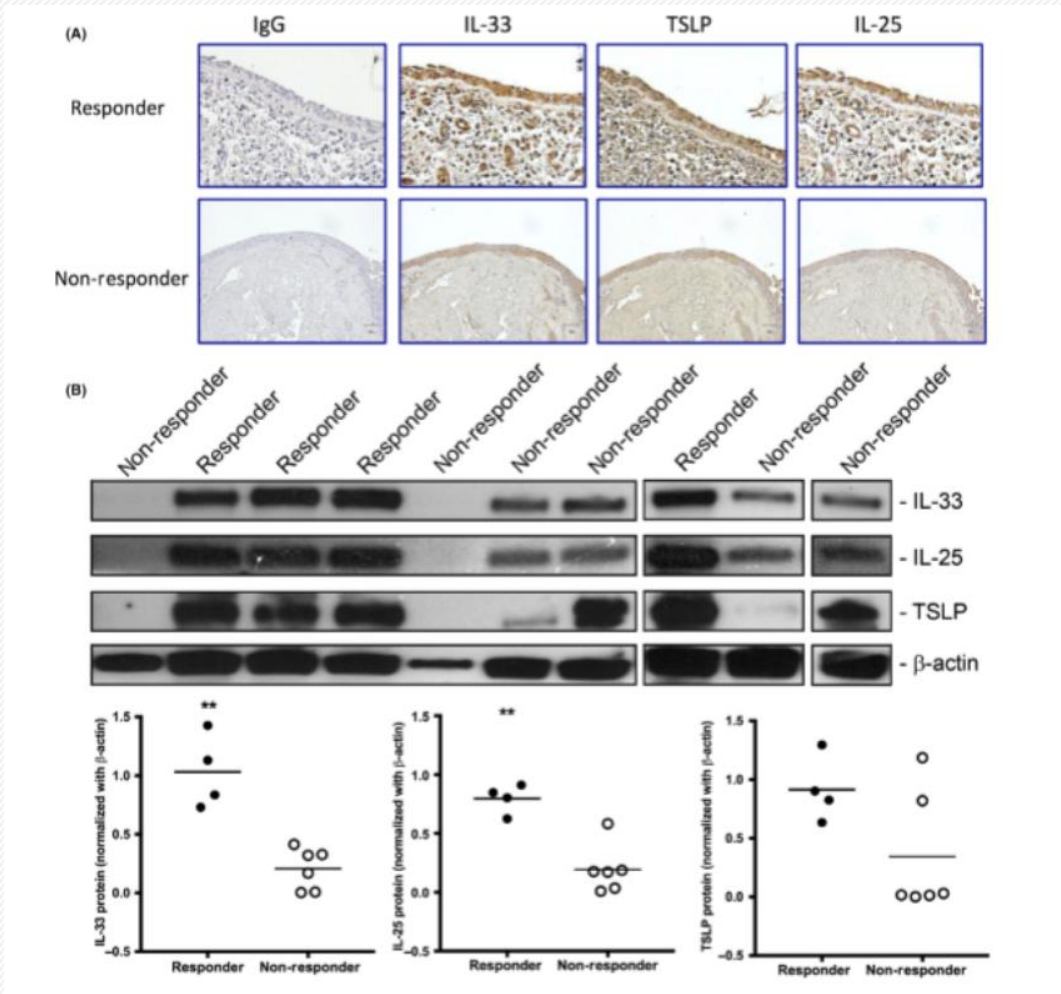
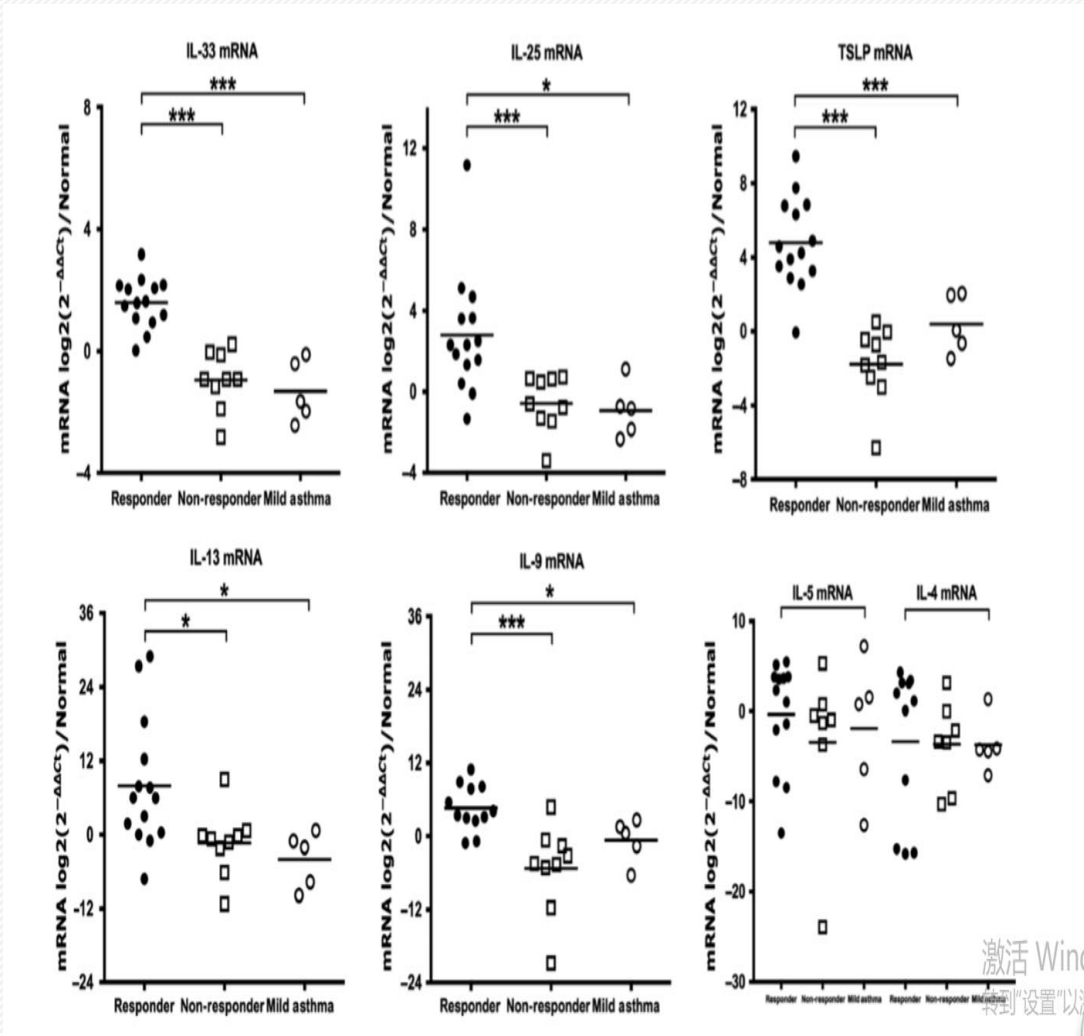
Study No. D5180C00021







Omalizumab Treatment in Epithelial cell derived cytokine endotype asthma





IL-33

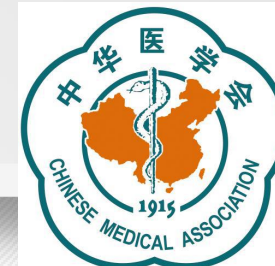
- Airway epithelium is not only the victim of asthma inflammation but also asthma initiator and precedent. Epithelial derived cytokines endtype composed in various phenotypes of asthma, especially in allergic asthma.

IL-25

- At present, studies on epithelial derived cytokines endtype asthma mainly from animal model, vitro and pre-vivo studies. The exact definition of epithelial derived cytokine endtype is still unclear.

TSLP

- The clinical trial of target therapy to epithelial derived cytokine asthma is ongoing.



Thank you

