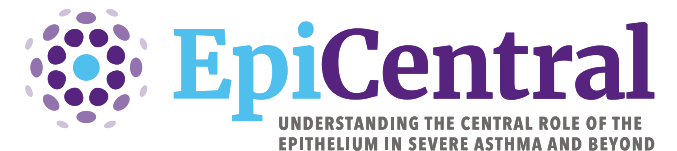
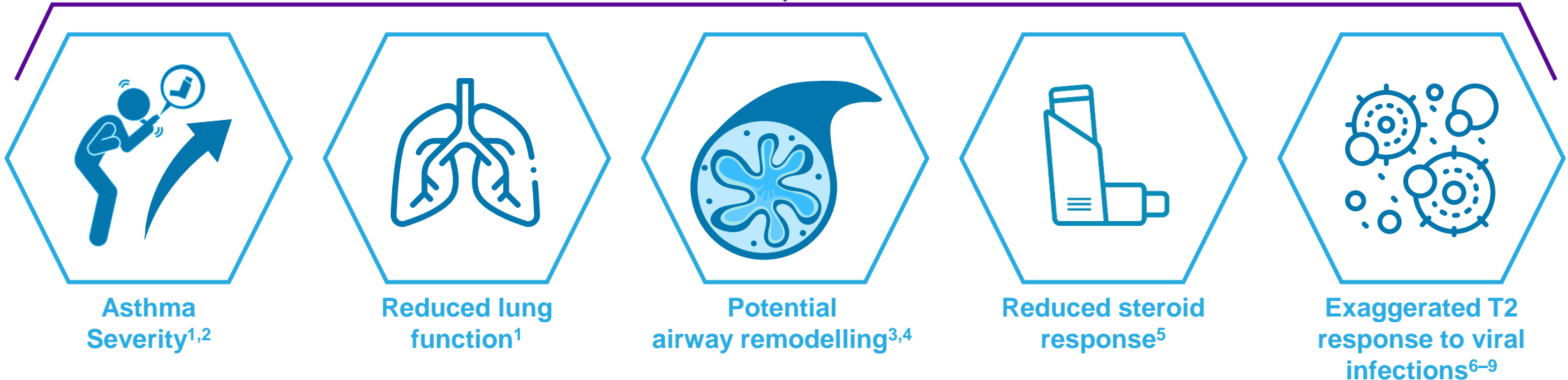


How epithelial cytokines correlate the clinical features of asthma



Multiple clinical features of asthma are associated with epithelial cytokines¹⁻⁹

Epithelial cytokines



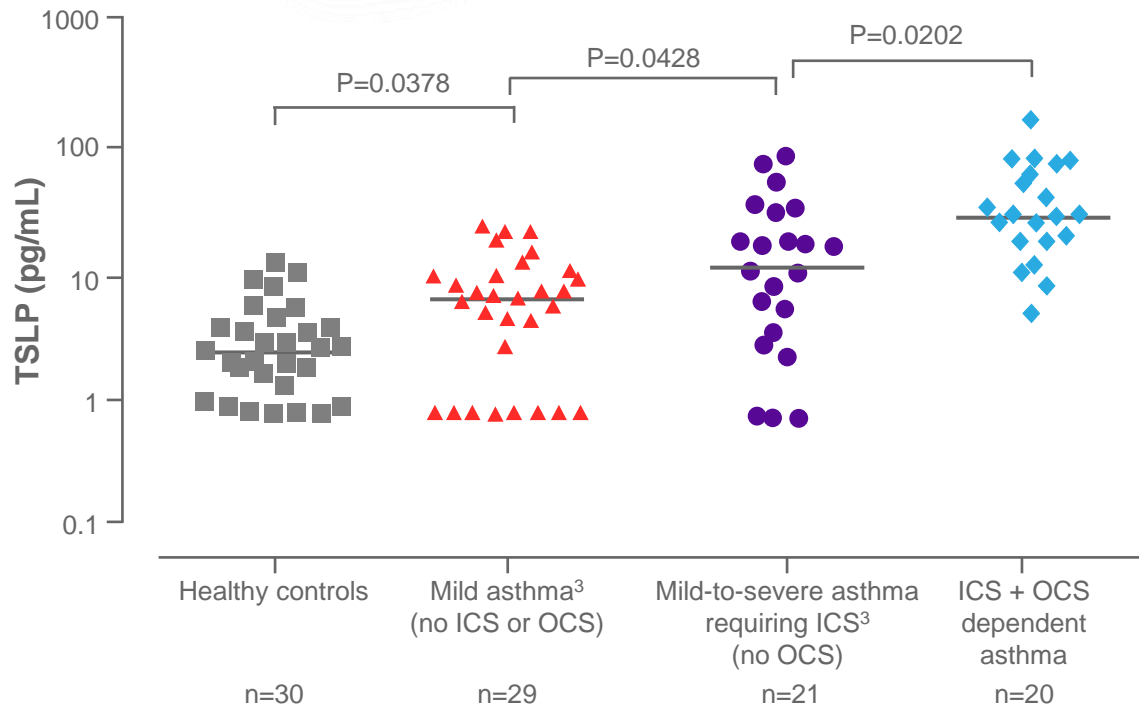
T2, type 2

1. Li Y, et al. J Immunol 2018;200:2253–2262; 2. Shikotra A, et al. J Allergy Clin Immunol 2012;129:104–111; 3. Cao L, et al. Exp Lung Res 2018;44:288–301; 4. Wu J, et al. Cell Biochem Funct 2013;31:496–503; 5. Liu S, et al. J Allergy Clin Immunol 2018;141:257–268; 6. Lee HC, et al. J Allergy Clin Immunol 2012;130:1187–1196; 7. Uller L, et al. Thorax 2010;65:626–632; 8. Kato A, et al. J Immunol 2007;179:1080–1087; 9. Beale J, et al. Sci Transl Med 2014;6:256ra134

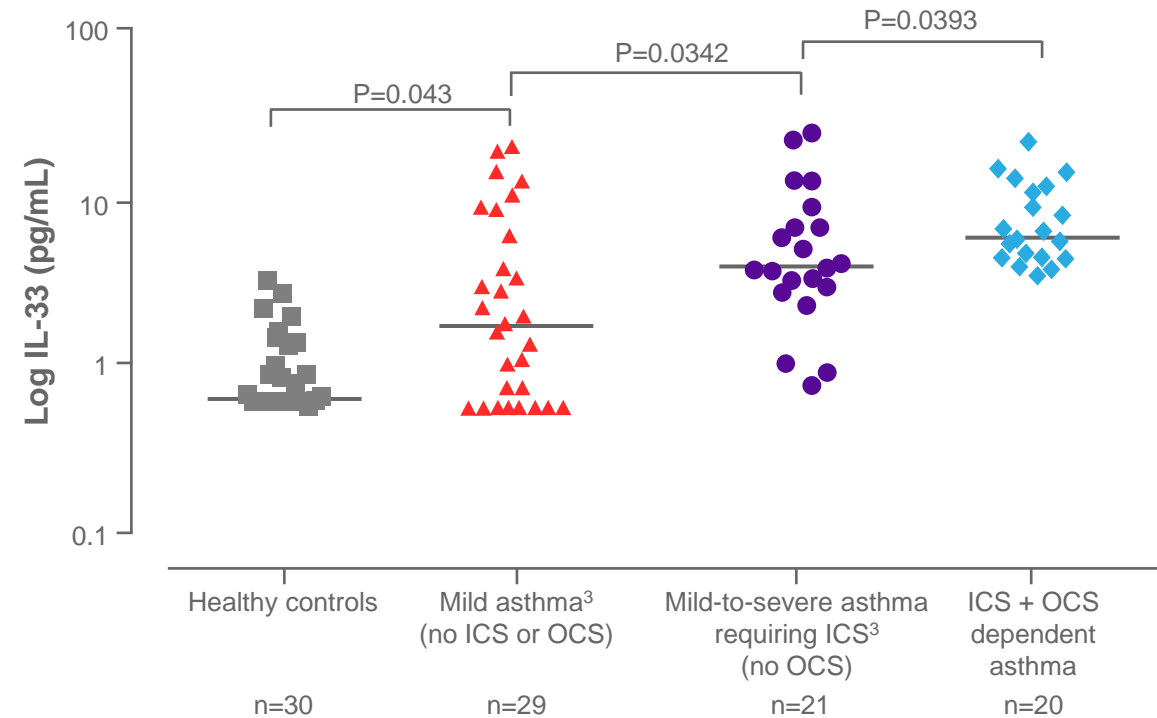
Veeva ID: Z4-39011; date of preparation: January 2022. © 2022 AstraZeneca. All Rights Reserved. This information is intended for healthcare professionals only. EpiCentral is sponsored and developed by Amgen and AstraZeneca.

Airway epithelial cytokine expression increases with disease severity in patients with asthma^{1,2}

TSLP expression increased with asthma severity^{1*}



IL-33 concentration increased with asthma severity^{1*}



Figures adapted from Li Y, et al. J Immunol 2018;200:2253–2262

Note: In-house ELISA platforms developed by Novartis, with lower limits of detection of 1 and 2 pg/mL, were used to analyse TSLP in BALF. Normal control patients were healthy, lifelong non-smoking volunteers who had no history of lung disease¹

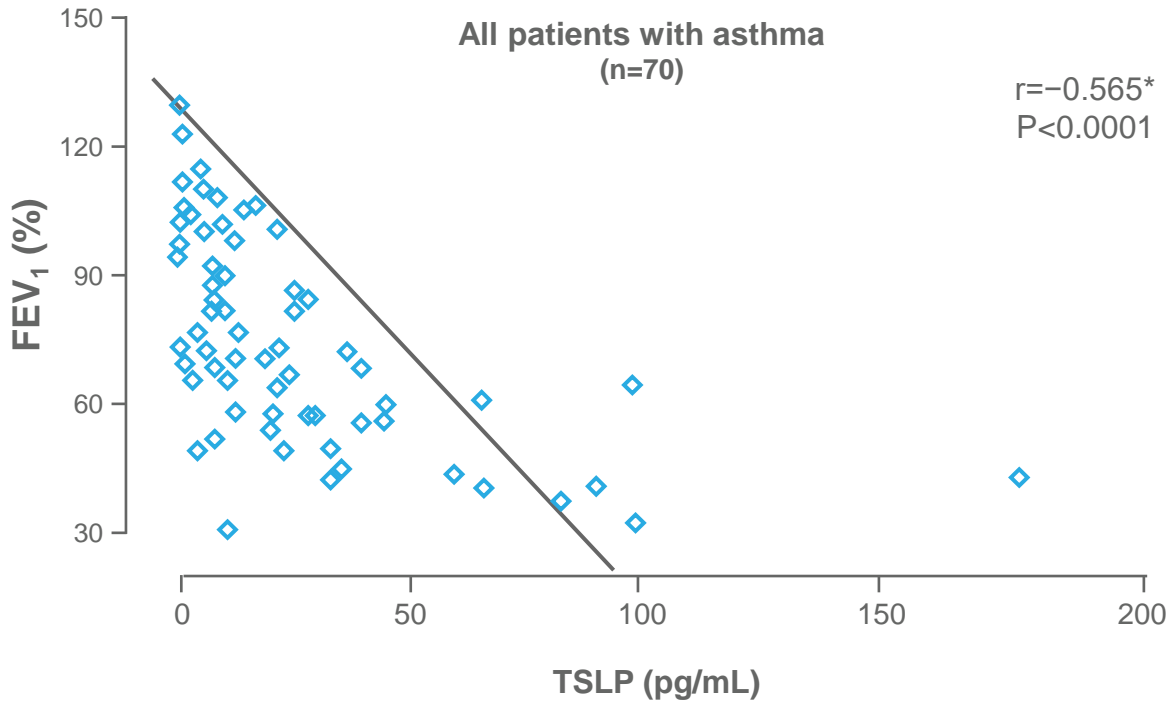
*BALF was used to measure the concentrations of TSLP or IL-33 (patients with asthma, n=70; controls, n=30)¹

BALF, bronchoalveolar lavage fluid; ELISA, enzyme-linked immunosorbent assay; ICS, inhaled corticosteroid(s); IL, interleukin; OCS, oral corticosteroid(s); TSLP, thymic stromal lymphopoietin

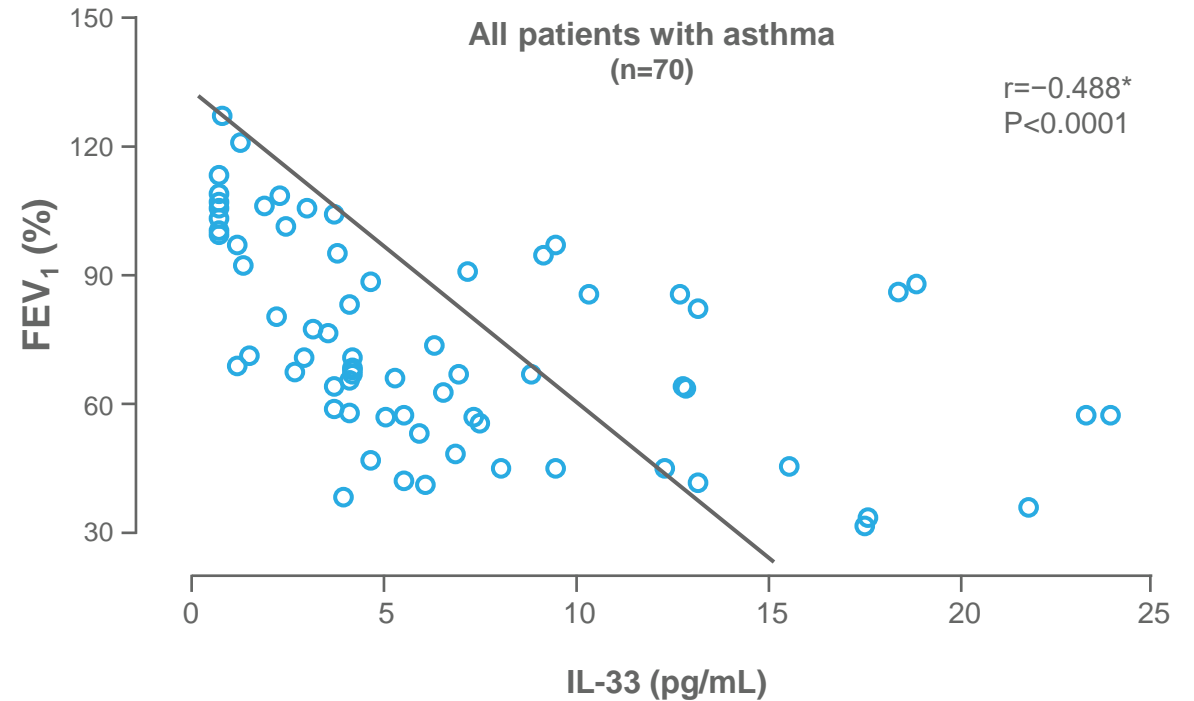
1. Li Y, et al. J Immunol 2018;200:2253–2262; 2. Shikotra A, et al. J Allergy Clin Immunol 2012;129:104–111; 3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2021. Available from: https://ginasthma.org/wp-content/uploads/2021/04/GINA-2021-Main-Report_FINAL_21_04_28-WMS.pdf (Accessed 13 December 2021)

Airway epithelial cytokine expression correlates with reduced lung function in patients with asthma¹

Higher TSLP expression correlated with reduced FEV₁¹



Higher IL-33 expression correlated with reduced FEV₁¹



Figures adapted from Li Y, et al. J Immunol 2018;200:2253–2262

BALF was used to measure the concentrations of TSLP and IL-33. Spearman rank-order method with correction for tied values was used to obtain correlation coefficients

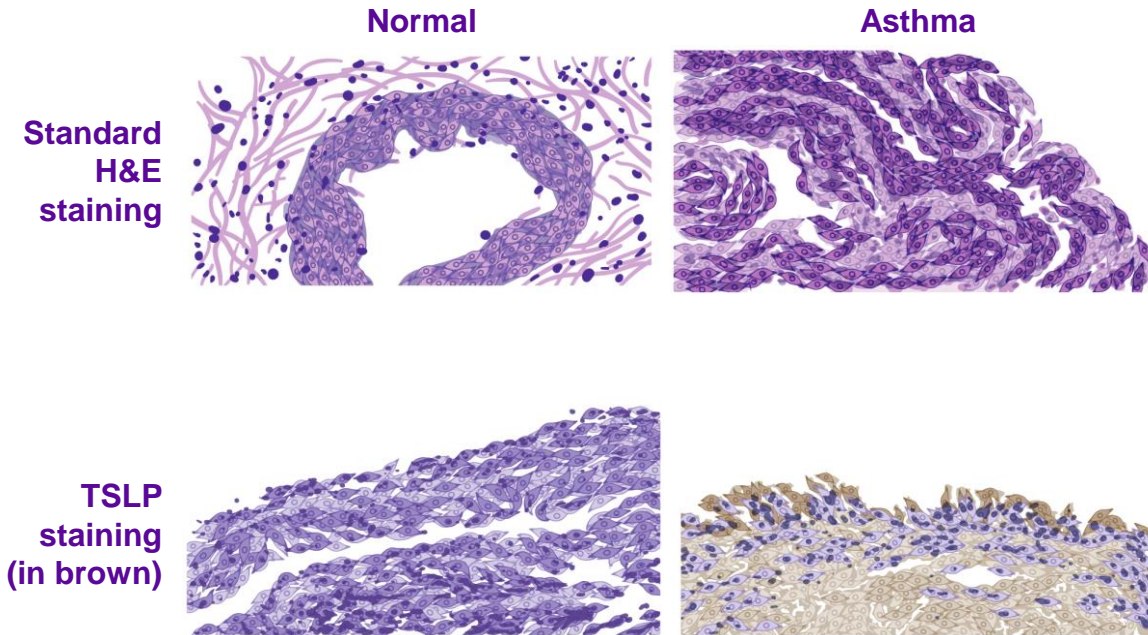
*Spearman rank-order correlation coefficient

BALF, bronchoalveolar lavage fluid; FEV₁, forced expiratory volume in 1 second; IL, interleukin; TSLP, thymic stromal lymphopoietin

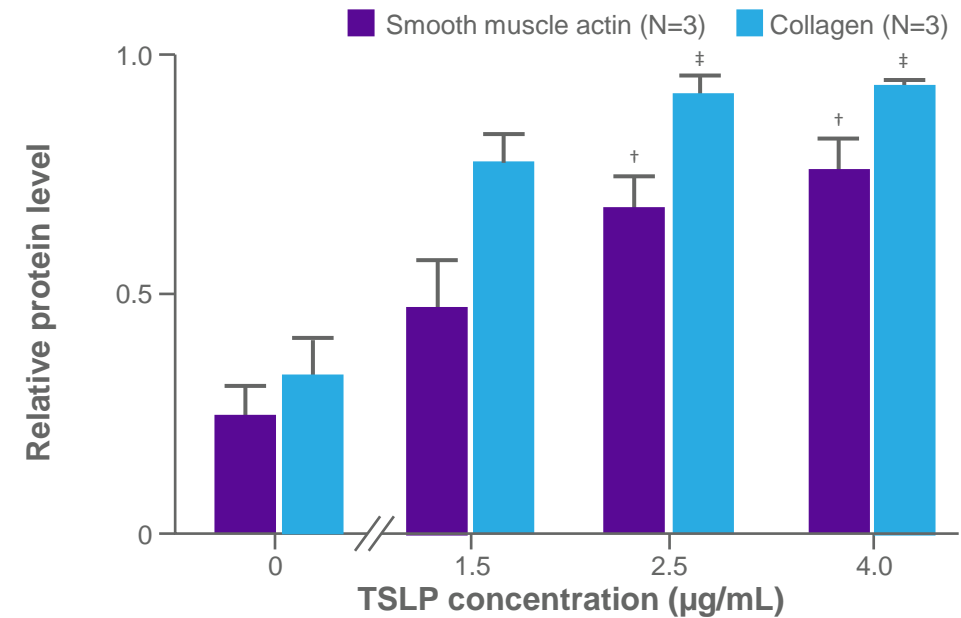
1. Li Y, et al. J Immunol 2018;200:2253–2262

TSLP may contribute to airway remodelling in patients with asthma^{1,2}

Bronchial airway epithelial cells in asthma versus healthy controls¹



In human lung fibroblasts, TSLP increased expression of collagen and smooth muscle actin in a concentration-dependent manner ($P < 0.05^*$)^{1,2}



Figures adapted from Cao L, et al. Exp Lung Res 2018;44:288–301

Human bronchial epithelial cells were stained with H&E or Masson Trichrome

*vs GAPDH control; [†] $P < 0.05$ vs GAPDH control (smooth muscle actin); [‡] $P < 0.05$ vs GAPDH control (collagen)

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; H&E, haematoxylin and eosin; TSLP, thymic stromal lymphopoietin

1. Cao L, et al. Exp Lung Res 2018;44:288–301; 2. Wu J, et al. Cell Biochem Funct 2013;31:496–503

IL-33 and IL-25 may promote airway remodelling in patients with asthma¹⁻⁴

In human lung fibroblasts, IL-33 increased expression of fibronectin 1 and type I collagen *in vitro*²

In human bronchial biopsies, RBM thickness was greater in patients with asthma and high IL-25 versus low IL-25 (P=0.0006)⁴

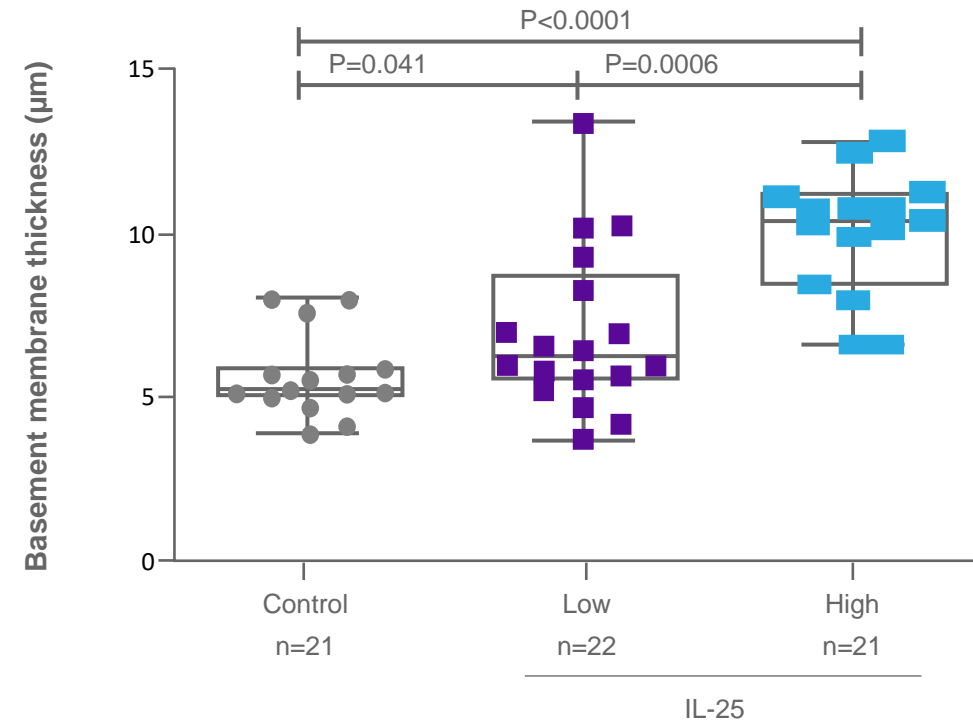
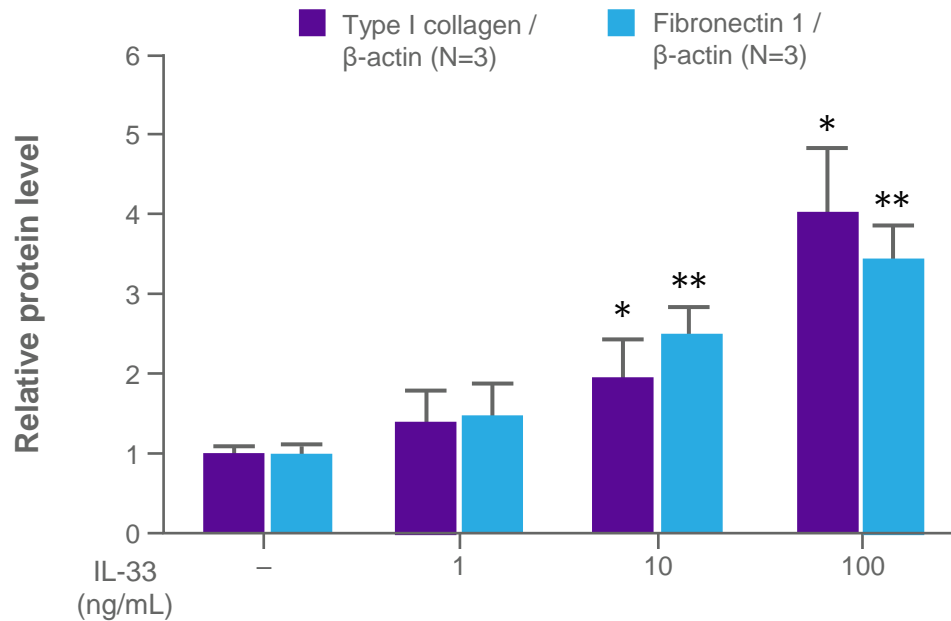


Figure adapted from Guo Z, et al. J Asthma 2014;51:863–869 and Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

*P<0.05 vs controls; **P<0.01 vs controls

IL, interleukin; RBM, reticular basement membrane thickness

1. Saglani S, et al. J Allergy Clin Immunol 2013;132:676–685; 2. Guo Z, et al. J Asthma 2014;51:863–869; 3. Préfontaine D, et al. J Immunol 2009;183:5094–5103;

4. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

Some epithelial cytokines may be associated with corticosteroid resistance in patients with asthma¹⁻⁴

- Blood and BALF ILC2s exposed to **TSLP** were resistant to steroids^{1*}
- Steroid resistance correlated with higher airway **TSLP** expression, higher BALF and blood eosinophils, and lower FEV₁ (P≤0.003)¹
- **IL-33** expression levels remained elevated after treatment with steroids in human bronchial biopsies² and ASMCS³
- ICS significantly improved lung function in patients with high plasma **IL-25** versus low plasma IL-25^{4†}
- Plasma **IL-25** was significantly decreased after 4 weeks of ICS treatment, demonstrating sensitivity to steroids^{4‡}

In patients with asthma, TSLP levels correlated with reduced steroid response¹

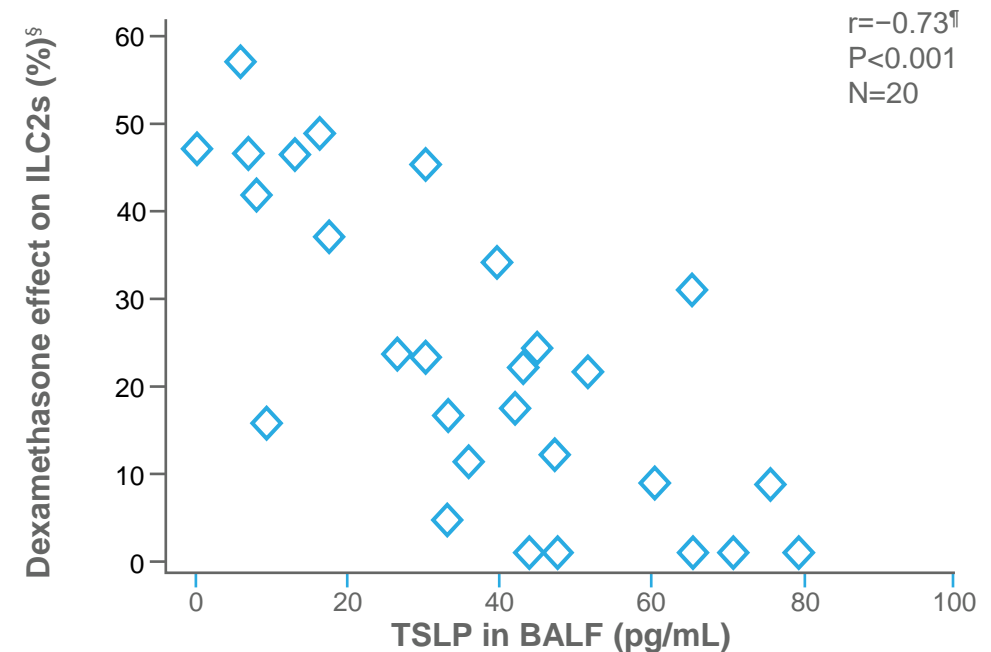


Figure adapted from Liu S, et al. J Allergy Clin Immunol 2018;141:257–268

*Resistance to steroids meant a lack of inhibition of T2 cytokine expression by ILC2s; †high plasma IL-25 threshold, >55 pg/ml and low plasma IL-25 threshold, ≤55 pg/ml; ‡decrease of IL-25 was mainly observed in IL-25-high patients; §BALF ILC2s in patients with asthma were examined (n=50). Controller medications were maintained (SCS and ICS medications); ¶Pearson correlation coefficient
ASMC, airway smooth muscle cell; BALF, bronchoalveolar lavage fluid; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IL, interleukin; ILC2, type 2 innate lymphoid cell; SCS, systemic corticosteroid(s); T2, type 2; TSLP, thymic stromal lymphopoietin

1. Liu S, et al. J Allergy Clin Immunol 2018;141:257–268; 2. Saglani S, et al. J Allergy Clin Immunol 2013;132:676–685; 3. Préfontaine D, et al. J Immunol 2009;183:5094–5103;

4. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648

Epithelial cytokine release following viral infection drives T2 response in patients with asthma^{1,2}

Following viral infection, TSLP release is increased from bronchial epithelial cells of patients with asthma^{1*}

24 hours post-viral infection, IL-25 release is increased from bronchial epithelial cells of patients with asthma^{2†}

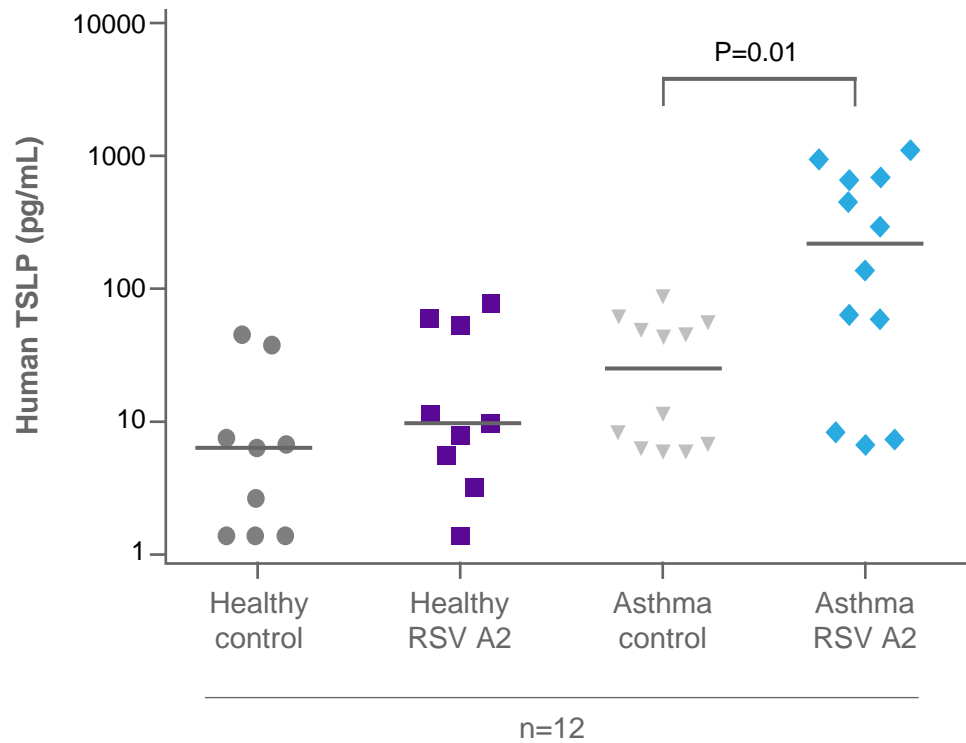


Figure adapted from Lee H-C, et al. J Allergy Clin Immunol 2012;130:1187–1196

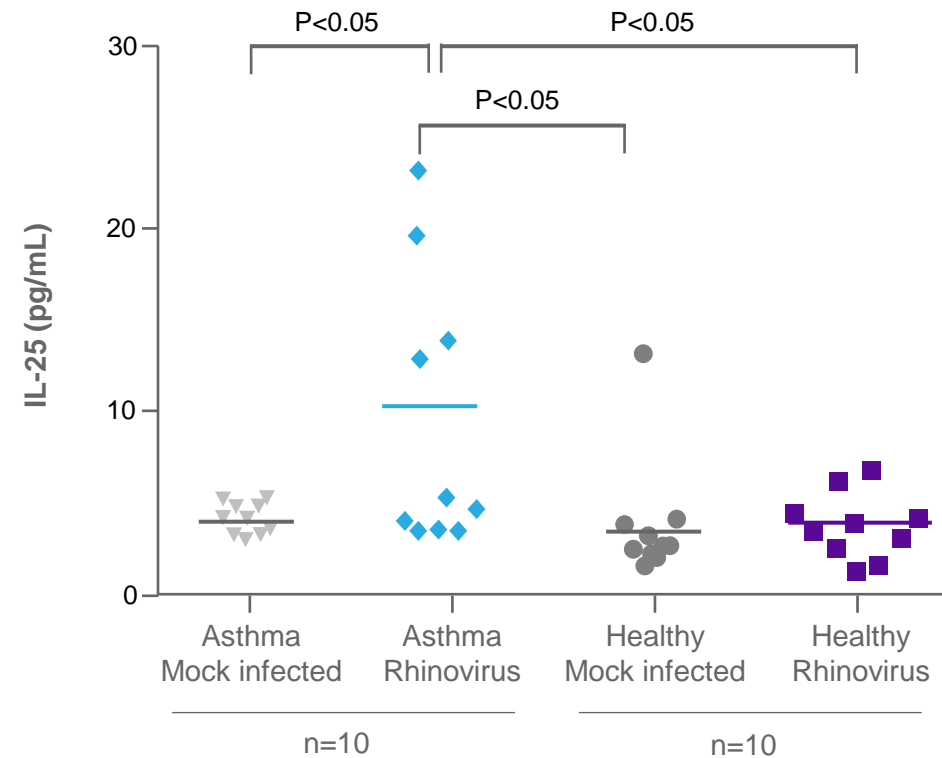


Figure adapted from Beale J, et al. Sci Transl Med 2014;6:256ra134

*n=12 patients for all groups; †bronchial epithelial cells were obtained from 10 patients with moderate atopic asthma and 10 non-atopic, non-asthmatic healthy volunteers

IL, interleukin; RSV, respiratory syncytial virus; T2, type 2; TSLP, thymic stromal lymphopoeitin

1. Lee H-C, et al. J Allergy Clin Immunol 2012;130:1187–1196; 2. Beale J, et al. Sci Transl Med 2014;6:256ra134