

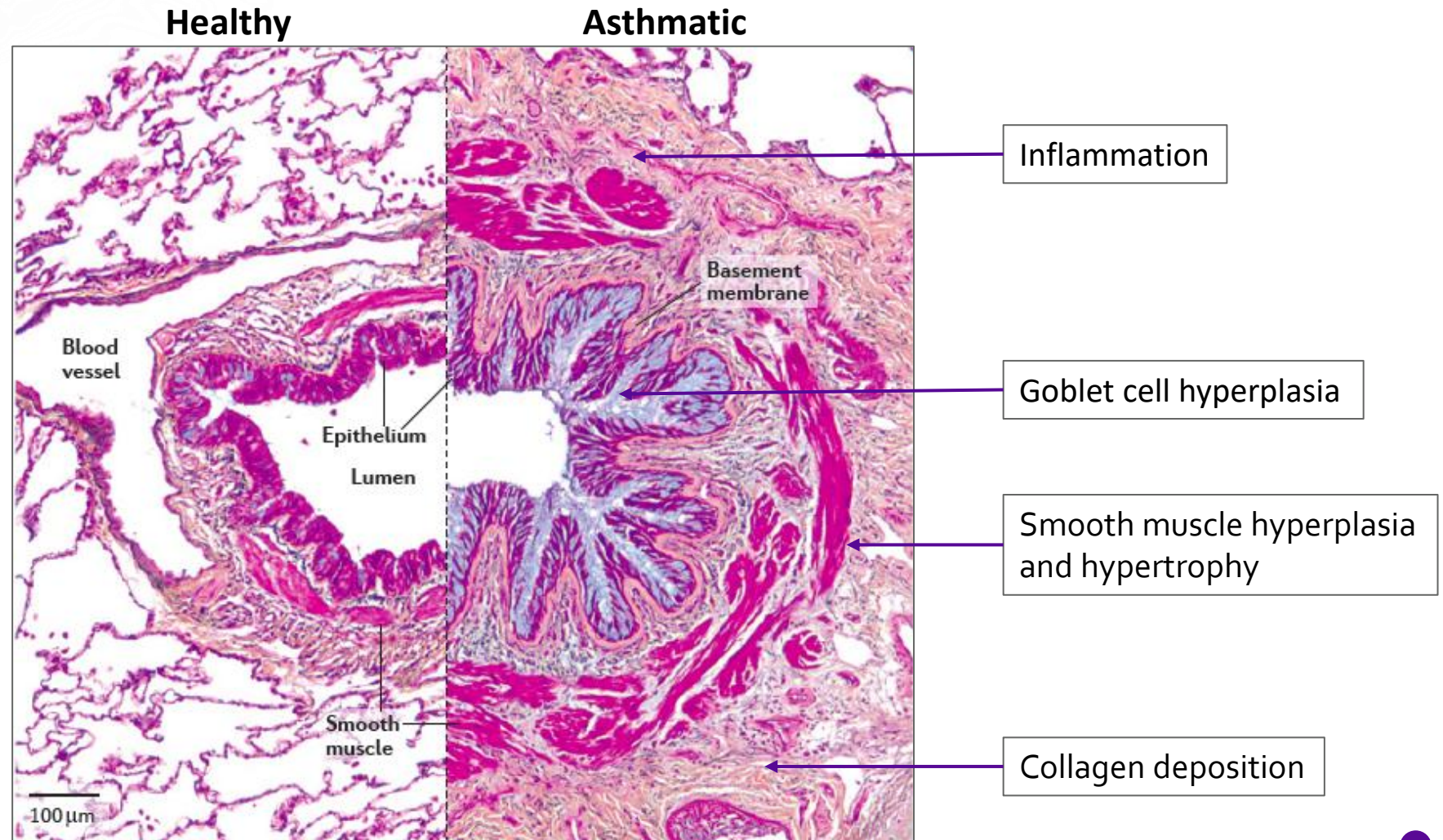
Mucus homeostasis: restoring airway defence and function

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Airway dysfunction arises from a failure to return to epithelial health following disease or insult



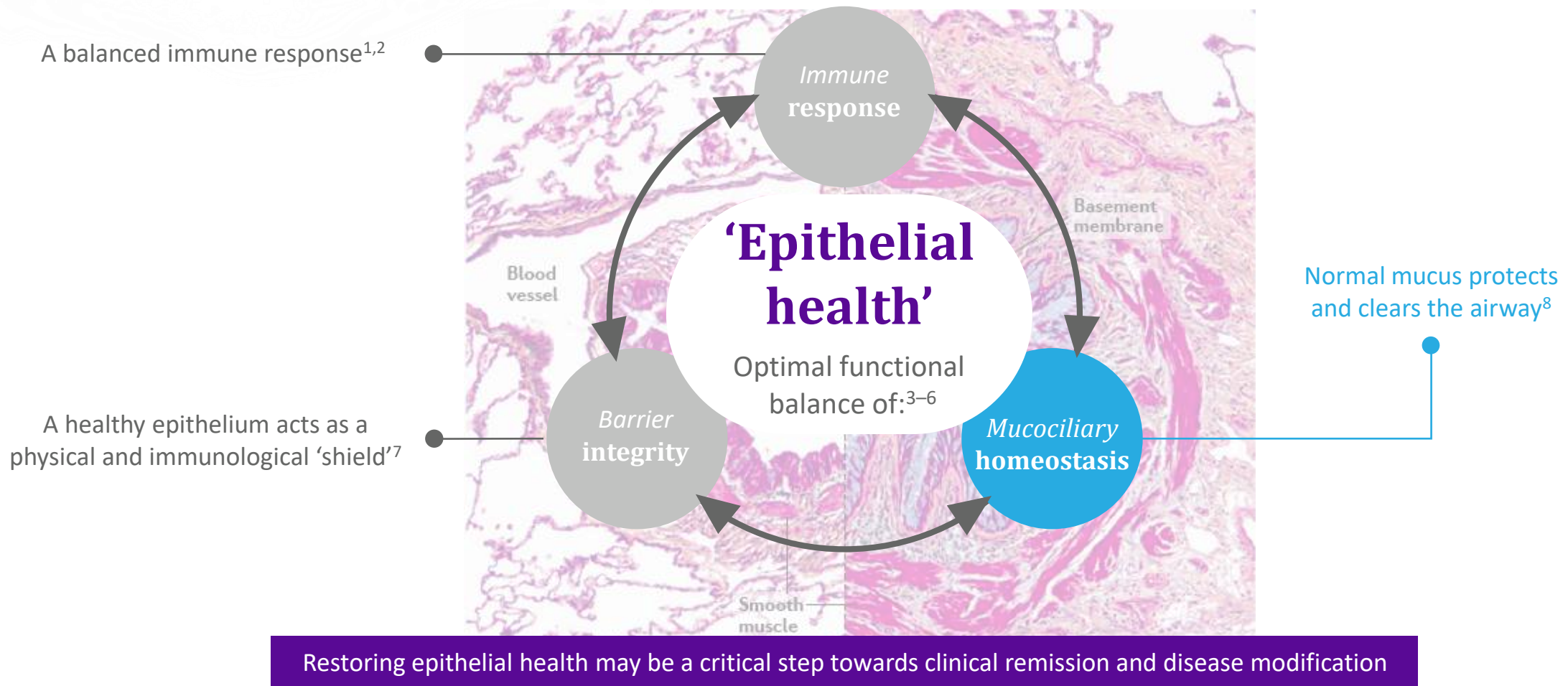
Refer to Wadsworth S, et al. *J Asthma Allergy*. 2011;4:77–86.

Lambrecht BN, et al. *Immunity*. 2019;50(4):975–91.

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Airway dysfunction arises from a failure to return to epithelial health following disease or insult



Refer to Wadsworth, et al. *J Asthma Allergy*. 2011;4:77–86.

1. Hallstrand TS, et al. *Clin Immunol*. 2014;151(1):1–15; 2. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol*. 2020;8:204; 3. Porsbjerg C, et al. *Lancet*. 2023;401(10379):858–73; 4. Calvén J, et al. *Int J Mol Sci*. 2020;21(23):8907; 5. Bousquet J, et al. *Nat Rev Dis Primers*. 2020;6(1):95; 6. MacNee W. *Proc Am Thorac Soc*. 2005;2(4):258–66; 7. Davis JD and Wypych TP. *Mucosal Immunol*. 2021;14(5):978–90; 8. Whitsett JA. *Ann Am Thorac Soc*. 2018;15(Suppl. 3):S143–S148.

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Mucus dysfunction leads to mucus plugging

Mucus
dysfunction

Mucus plugs are sticky, tenacious, persistent airway obstructions

Mucus
homeostasis

Normal mucus protects
and clears the airway²



Mucus plugs retrieved by bronchoscopy
from a patient with ABPA¹



Mucus plugs in a fatal asthmatic^{3,4}

Plugs result from a change in quality of mucus, as well as the quantity

Refer to Aegerter H, et al. *medRxiv*. 2025;26:25341000 and Dr Yale Rosen Atlas of Pulmonary Pathology.

ABPA, allergic bronchopulmonary aspergillosis.

1. Aegerter H, et al. *medRxiv*. 2025;26:25341000; 2. Whitsett JA. *Ann Am Thorac Soc*. 2018;15(Suppl. 3):S143–S148; 3. Dr Yale Rosen Atlas of Pulmonary Pathology. Bronchial mucous plug. 2010.

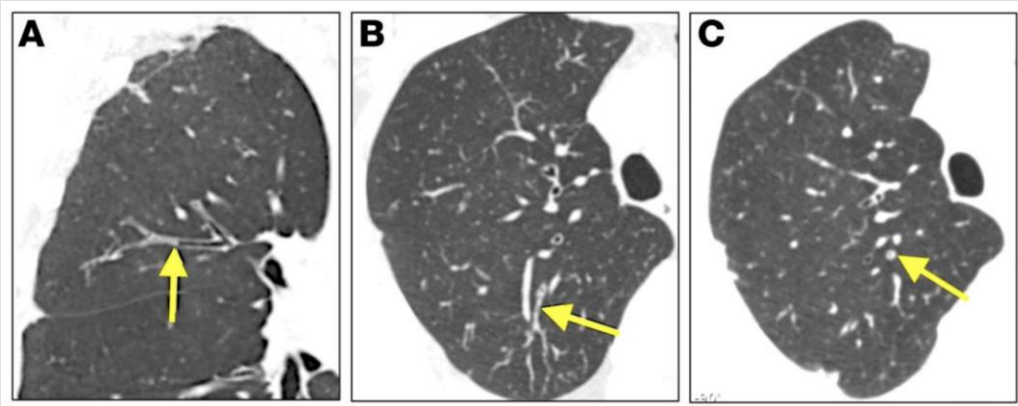
https://www.flickr.com/photos/pulmonary_pathology/. Accessed August 2026. Licenced under CC BY-SA 2.0; 4. Statement represents the knowledge of the presenter based on their professional experience.

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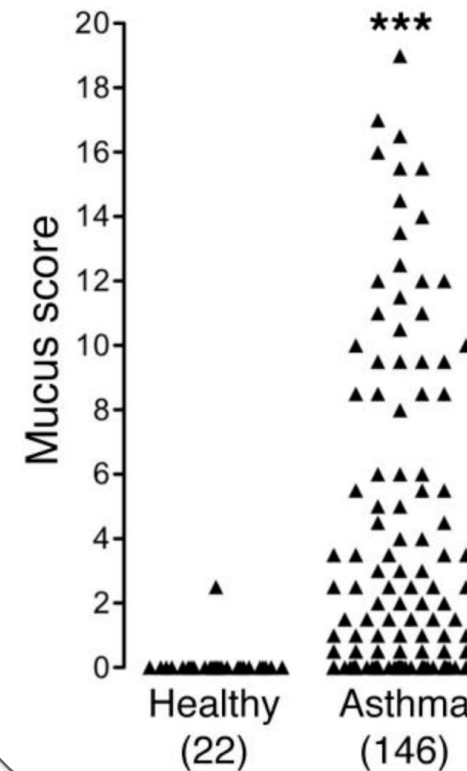
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Mucus plugs are identifiable by CT scans

Mucus plug with branching in patients with asthma



The mucus score is calculated by examining each bronchopulmonary segment and counting the number of segments containing at least one mucus plug



Segment score in healthy patients and patients with asthma^a

Refer to Dunican EM, et al. *J Clin Invest.* 2018;128:997–1009.

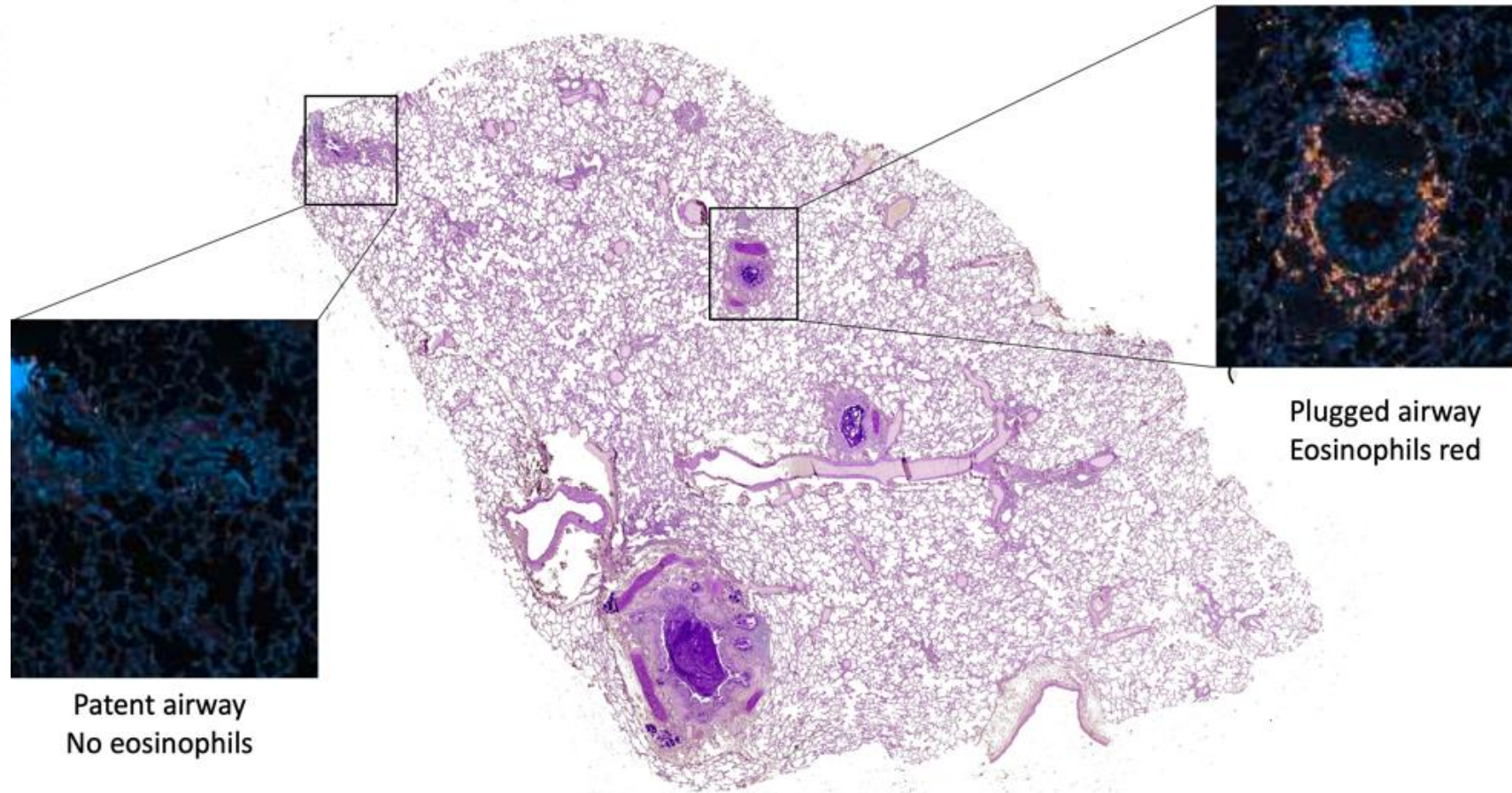
^aSegment score was generated by examining each bronchopulmonary segment of the lungs for mucus plugs, counting the segments with ≥ 1 mucus plug and then generating a score. CT, computed tomography.

Dunican EM, et al. *J Clin Invest.* 2018;128:997–1009.

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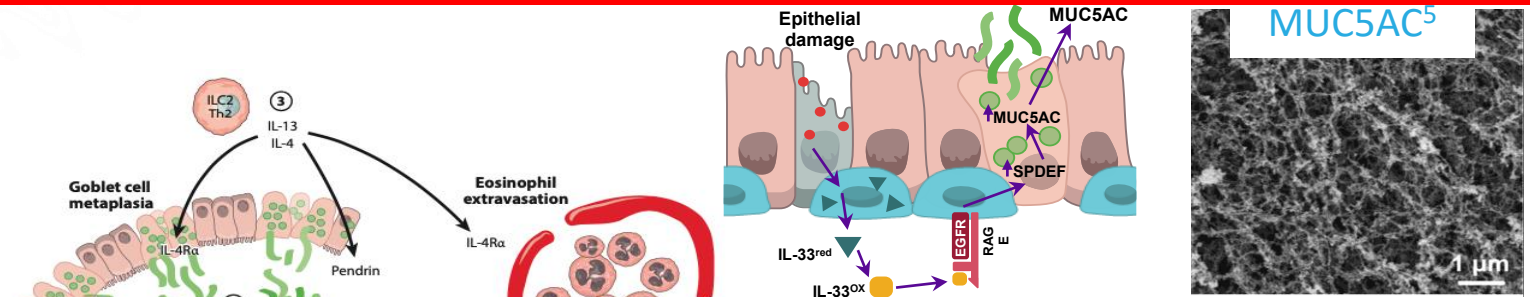
Mucus plugs are 'hotspots' of disease



Mechanisms driving mucus plug development

Alterations at the epithelial level^{1,2}

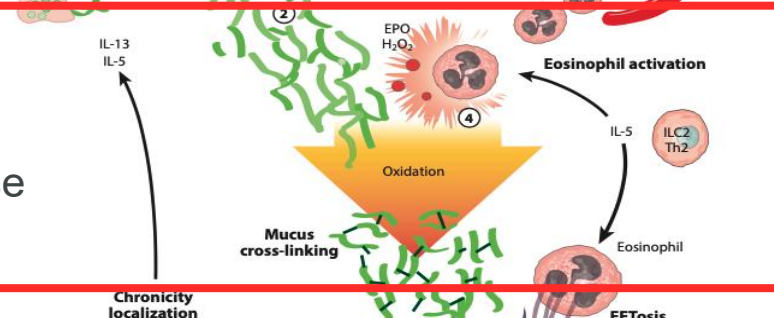
Upregulation of MUC5AC is induced by interleukins such as IL-13 and IL-33OX



Alterations of mucus^{1,3,4}

Mucin crosslinking

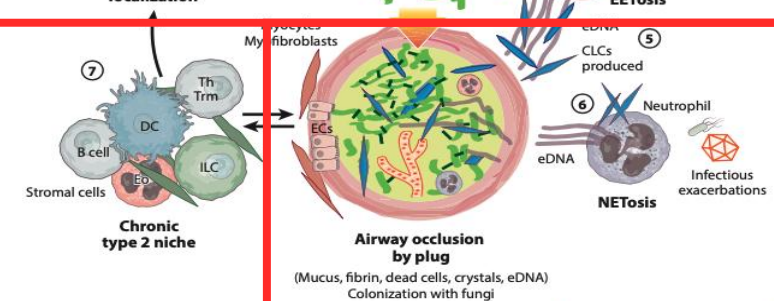
- Oxidation via eosinophil peroxidase, thyroid peroxidase, myeloid peroxidase



Granulocyte activation¹

Production of extracellular traps

Production of Charcot–Leyden crystals



Dead cells¹

Fibrin¹

Bacteria/viruses/fungi¹

Refer to Aegerter H and Lambrecht BN. *Annu Rev Pathol.* 2023;18:387–409.

CLC, Charcot–Leyden crystal; DC, dendritic cell; EC, epithelial cell; eDNA, extracellular DNA; EET, eosinophil extracellular trap; IL, interleukin; ILC, innate lymphoid cell; MUC5AC, mucin 5AC; NET, neutrophil extracellular trap; SPDEF, SAM pointed domain-containing ETS transcription factor; Trm, tissue-resident memory T cell.

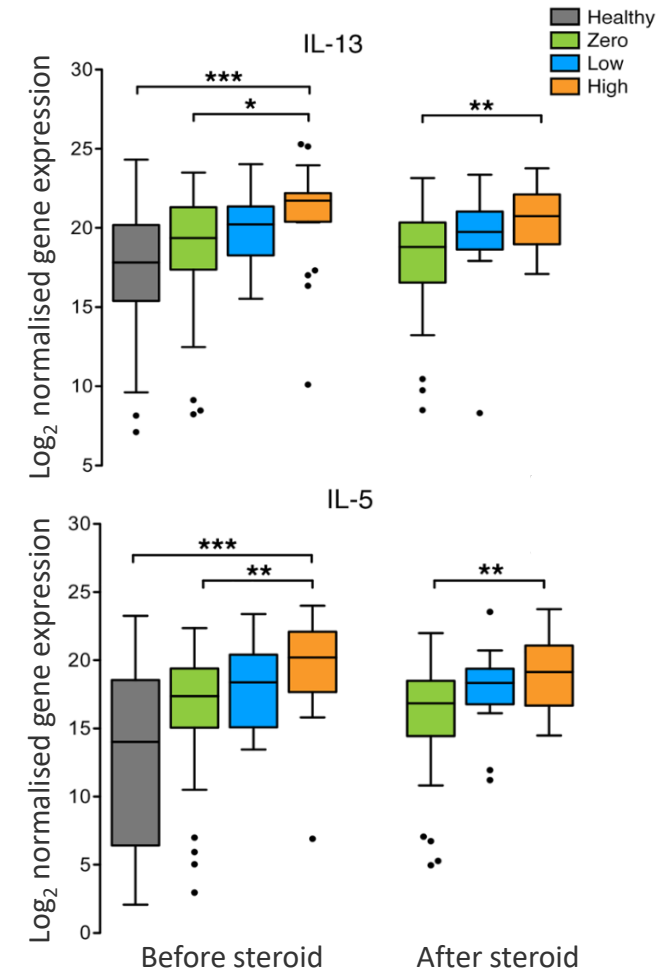
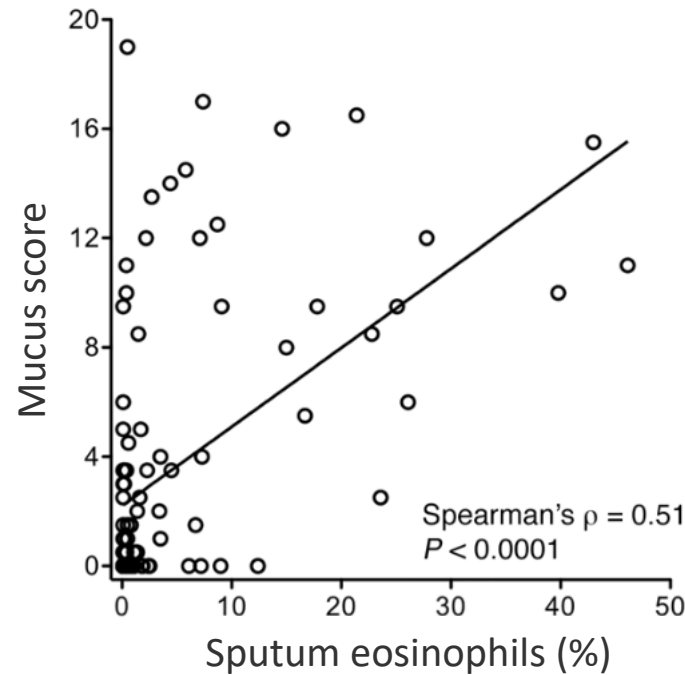
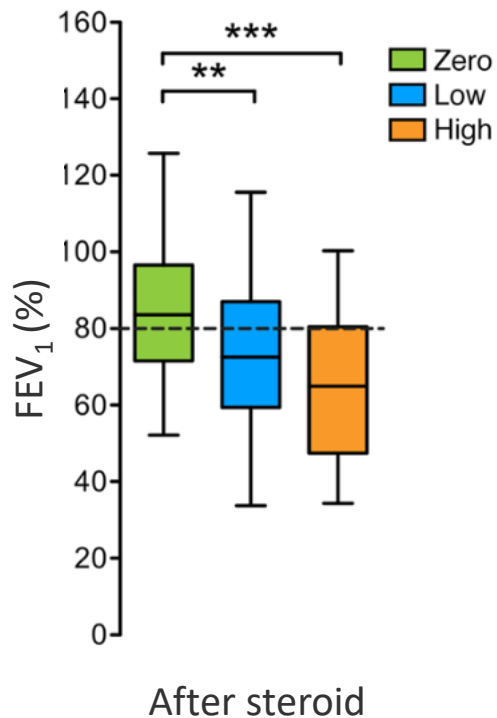
1. Aegerter H and Lambrecht BN. *Annu Rev Pathol.* 2023;18:387–409; 2. Strickson S, et al. *Eur Respir J.* 2023;62:2202210; 3. Liegeois MA, et al. *JCI Insight.* 2024;9:e181024; 4. Yuan S, et al. *Sci Transl Med.* 2015;25:7:276ra27 5. Carpenter J, et al. *Proc Natl Acad Sci U.S.A.* 2021;118(39):E2104490118.

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Mucus plugs correlate with features of type 2 inflammation in asthma

High mucus score is associated with markers of type 2 inflammation



Refer to Dunican EM, et al. *J Clin Invest.* 2018;128:997–1009.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

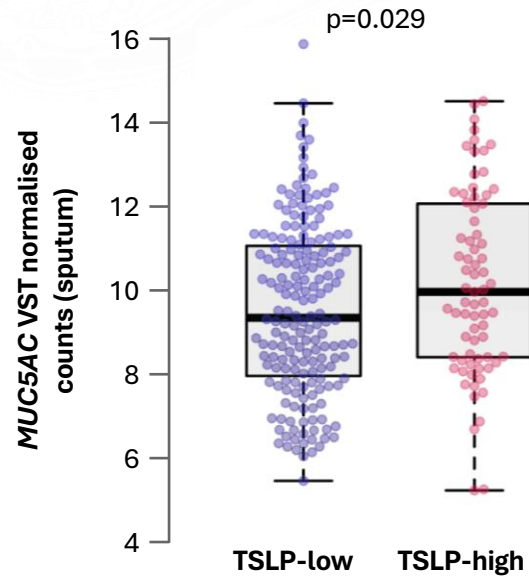
FEV₁, forced expiratory volume in 1 second; IL, interleukin.

Dunican EM, et al. *J Clin Invest.* 2018;128:997–1009.

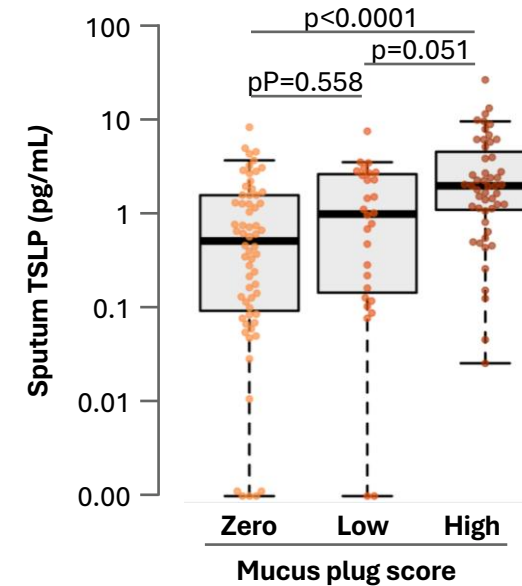
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In asthma, patients with elevated TSLP demonstrated increased expression of the *MUC5AC* and higher scores for mucus plugging



In sputum samples from patients with moderate-to-severe asthma (n=253), **TSLP-high asthma had higher *MUC5AC* gene expression than TSLP-low asthma** (p=0.029)



In sputum samples from patients with moderate-to-severe asthma (n=143), **TSLP levels were higher in patients with a high mucus plug segment score (score >4) than in patients with no plugs (mucus plug segment score of zero; p<0.0001)**

Equivalent data on IL-33 and IL-25 in mucus plugging in patients with asthma and/or CRSwNP are not available.

Refer to Khanna K, et al. *J Allergy Clin Immunol.* 2026;157:616–26.

Patients were categorised into three mucus-plug subgroups based on a mucus plug segment score: zero (score = 0), low (score >0 to <4) and high (score >4)

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; MUCA5AC, mucin 5AC; TSLP, thymic stromal lymphopoietin; VST, variance stabilising transformation

Khanna K, et al. *J Allergy Clin Immunol.* 2026;157:616–26.

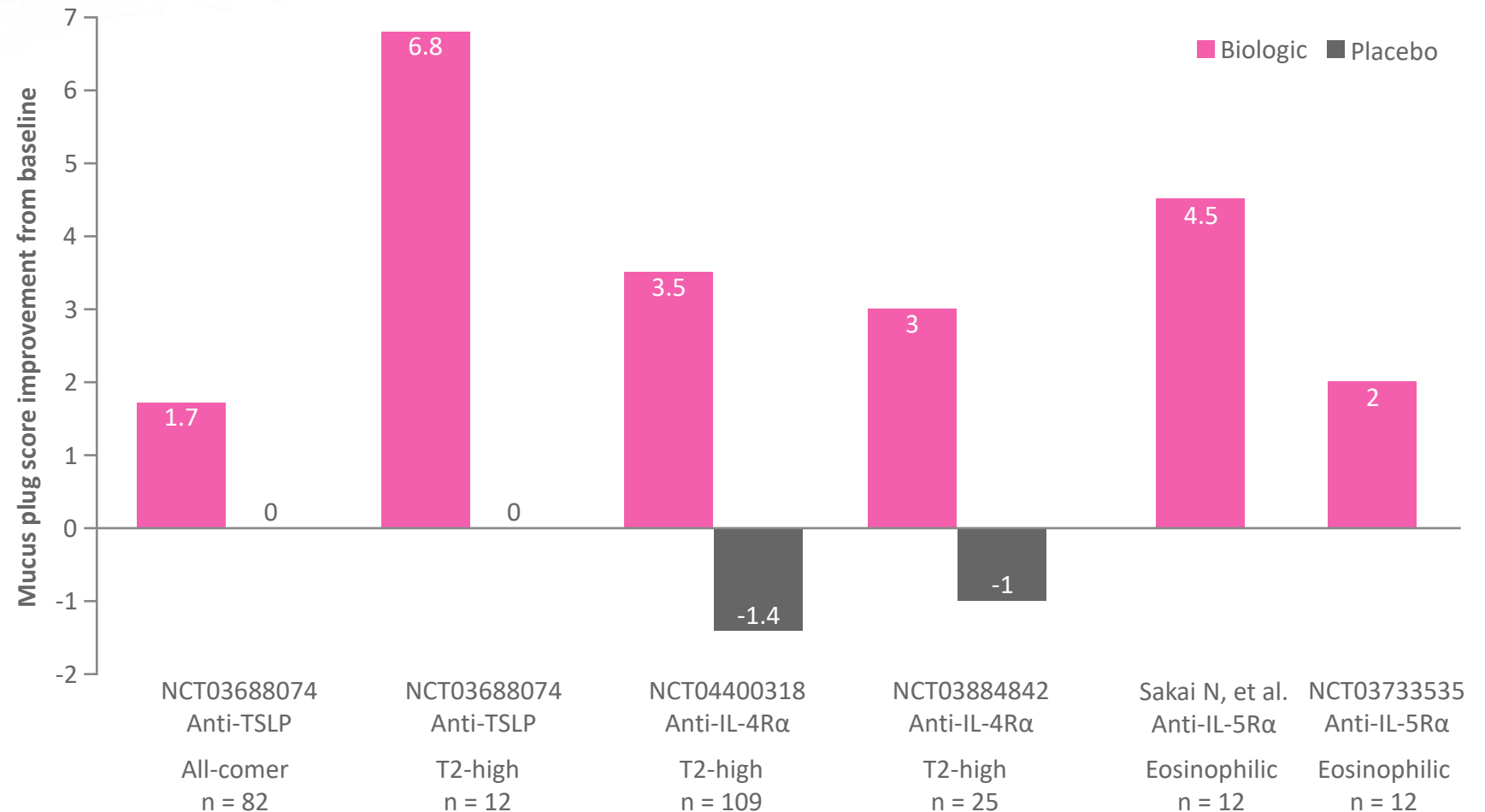
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Biologic studies show improvements in mucus plug burden in patients with uncontrolled moderate-to-severe asthma

Randomised, placebo-controlled trials

Single-arm studies



Change from baseline in mucus plug score following biologic treatment, based on a literature review of three randomised, placebo-controlled trials and two single-arm observational studies

Refer to Aegerter H, et al. *Respir Res.* 2026;27(1):69.

IL, interleukin; R, receptor; T2, type 2; TSLP, thymic stromal lymphopoietin.

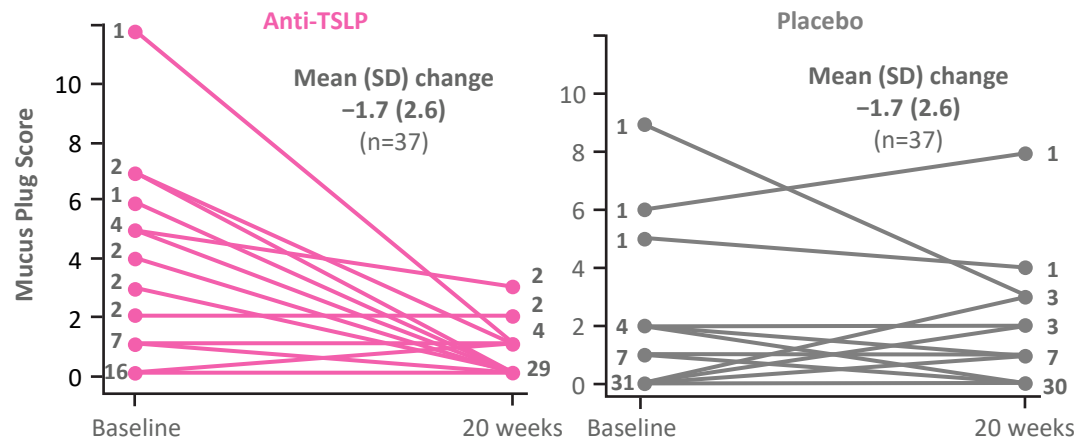
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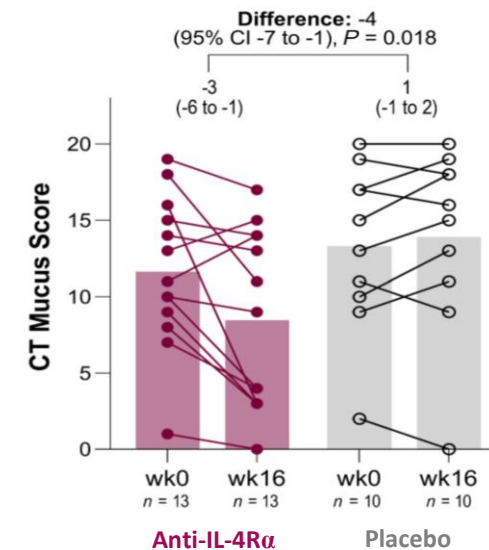
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Individual variability should be considered when interpreting mucus plug outcomes^{1,2}

Individual changes in mucus plug score from baseline to EOT (20 weeks) in adult patients with moderate-to-severe asthma receiving anti-TSLP or placebo in the randomised, placebo-controlled NCT03688074 trial¹



Individual changes in CT mucus score from baseline to EOT (16 weeks) in adult patients with uncontrolled moderate-to-severe asthma receiving anti-IL-4R α or placebo in the randomised, placebo-controlled NCT03884842 trial²



Individual responses to treatment varied, with most patients demonstrating reductions in mucus plug burden, although the magnitude of improvement differed between patients

These findings highlight the heterogeneity of mucus plugging and the importance of considering individual patient responses when interpreting treatment outcomes

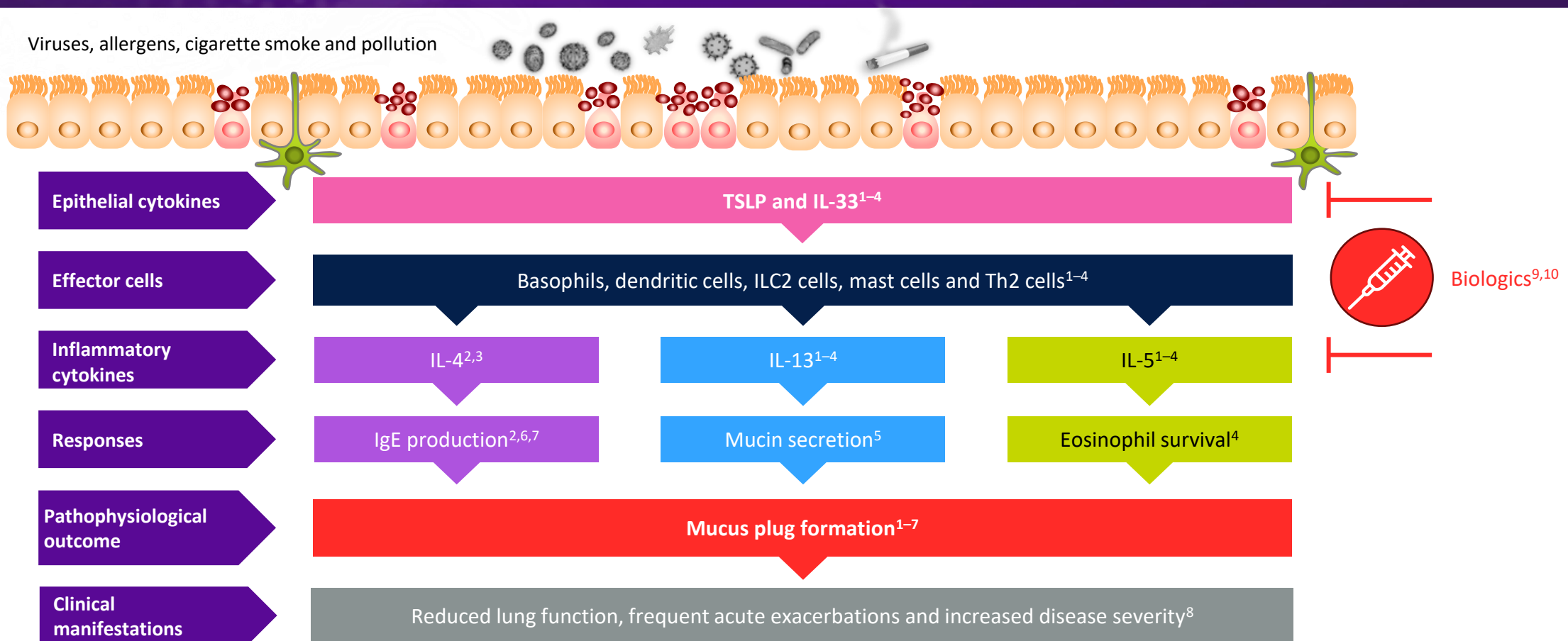
Refer to Nordenmark LH, et al. *NEJM Evid.* 2023;2:EVIDoA2300135 and Svenningsen S, et al. *Am J Respir Crit Care Med.* 2023;208:995–97.

CT, computed tomography; EOT, end of treatment; IL, interleukin; R, receptor; SD, standard deviation; TSLP, thymic stromal lymphopoietin; wk, week.

1. Nordenmark LH, et al. *NEJM Evid.* 2023;2:EVIDoA2300135; 2. Svenningsen S, et al. *Am J Respir Crit Care Med.* 2023;208:995–97.

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To achieve clinical remission, the epithelium must be repaired and epithelial health restored

IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Toki S, et al. *Allergy*. 2020;75:1606–1617; 2. Lambrecht BN, et al. *Immunity*. 2019;50:975–91; 3. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24:777–92; 4. Schuijs MJ, et al. *J Exp Med*. 2024;221:e20240103; 5. Dunican EM, et al. *Ann Am Thorac Soc*. 2018;15:S184–S191; 6. Kim Y and Yoo KH. *Allergy Asthma Immunol Res*. 2022;14:151–2; 7. Chan R, et al. *J Allergy Clin Immunol Pract*. 2023;11:195–199.e2; 8. Ueki S, et al. *J Allergy Clin Immunol Pract*. 2026;14:575–82;

9. Nordenmark LH, et al. *NEJM Evid*. 2023;2:EVIDoa2300135; 10. Svenningsen S, et al. *Am J Respir Crit Care Med*. 2023;208:995–97.

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