

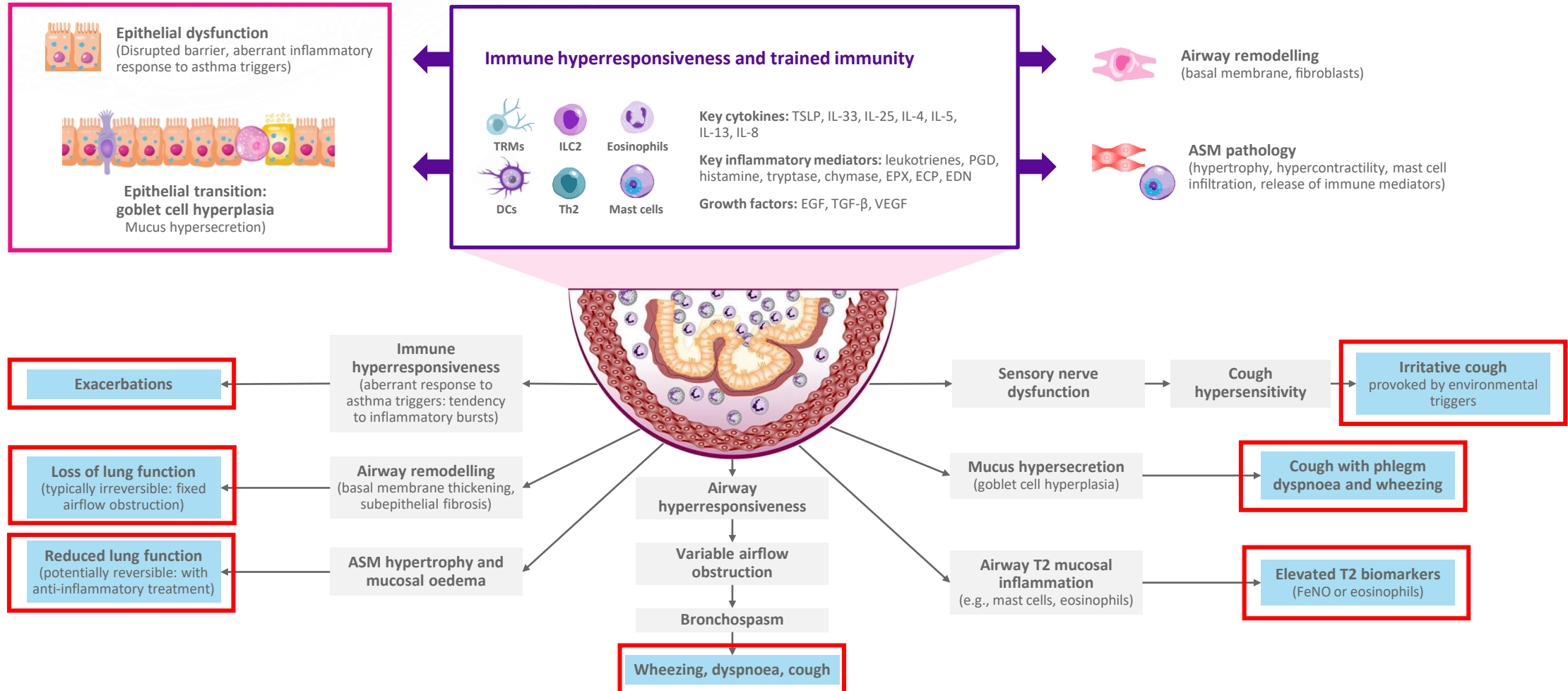
From biology to the clinic: epithelial health in patients

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Bispebjerg Hospital, Denmark



Epithelial dysfunction and immune hyperresponsiveness interact to drive airway remodelling and the clinical manifestations of asthma



Refer to Porsbjerg C, et al. *Lancet*. 2023;401:858–73.

ASM, airway smooth muscle; DC, dendritic cell; ECP, eosinophilic cationic protein; EDN, eosinophil-derived neurotoxin; EGF, epidermal growth factor; EPX, eosinophil peroxidase; FeNO, fractional exhaled nitric oxide; IL, interleukin; ILC, innate lymphoid cell; PGD, prostaglandins; T2, type 2; TGF, transforming growth factor; Th2, T2 helper cells; TRM, tissue-resident memory T cell; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

Porsbjerg C, et al. *Lancet*. 2023;401:858–73.

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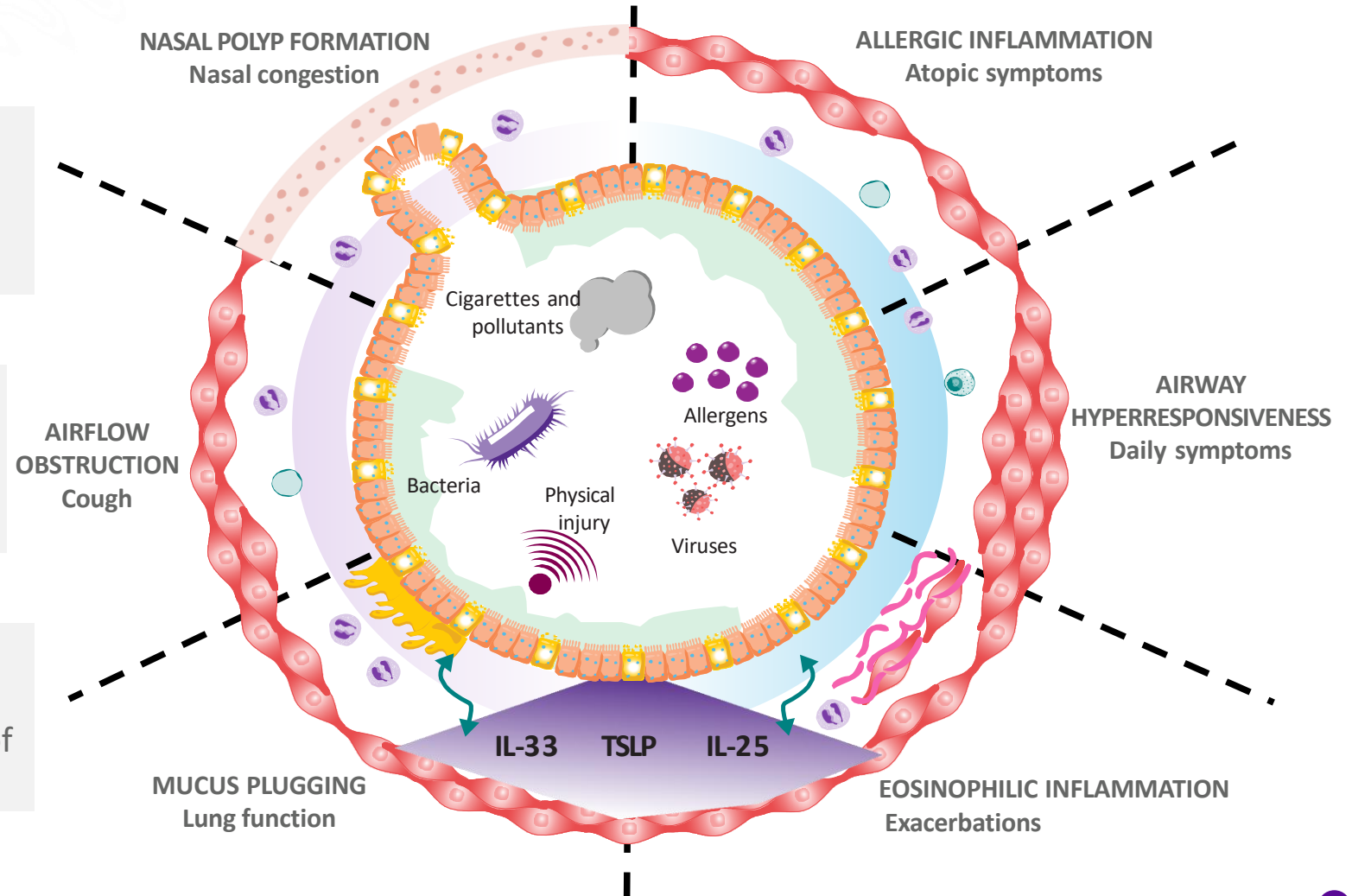
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Chronic airway diseases can be referred to as ‘epithelial-driven diseases’: the epithelium is responsible for initiation and amplification of downstream pathways

Epithelial activation is the **critical initiation step** for multiple diseases of the airway, orchestrating complex and overlapping immune pathways¹

Environmental triggers **activate the epithelium** and cause **barrier dysfunction** and **immune hyperresponsiveness**^{1,2}

Multiple triggers cause release of **epithelial cytokines** (TSLP, IL-33 and IL-25), which drive inflammatory pathways leading to a variety of clinical manifestations^{3,4}



Refer to Porsbjerg C, et al. *Lancet*. 2023;401:858–73.

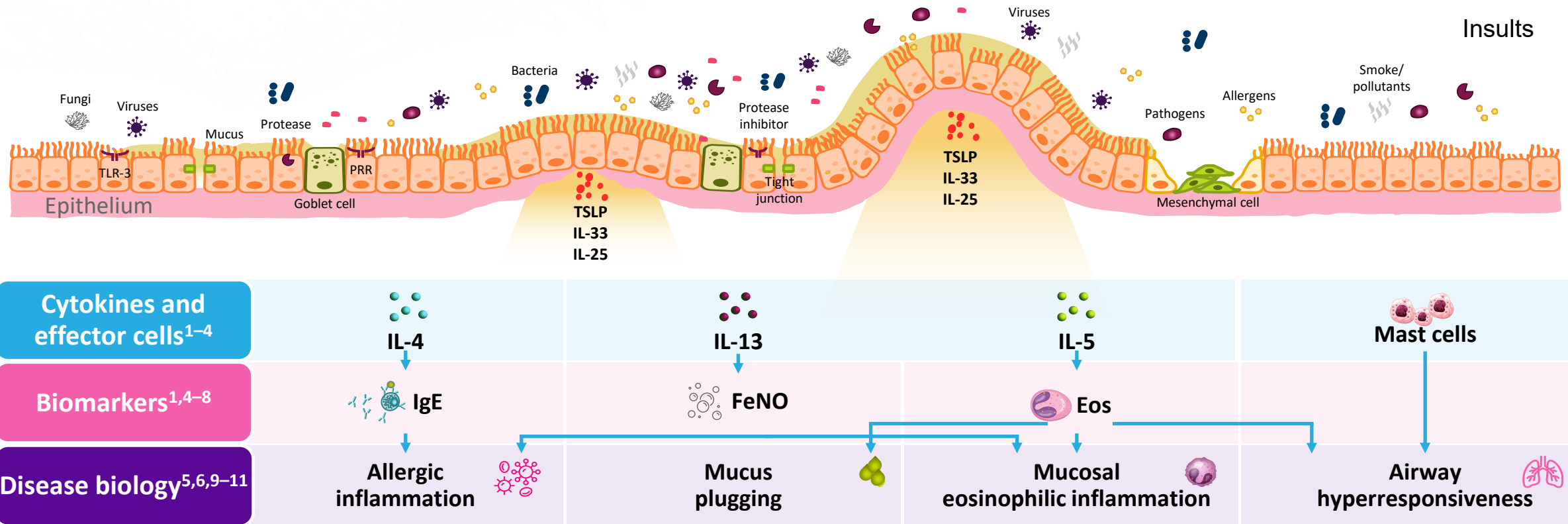
IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Hellings PW, Steelant B. *J Allergy Clin Immunol*. 2020;145:1499–509; 2. Porsbjerg C, et al. *Lancet*. 2023;401:858–73; 3. Roan F, et al. *J Clin Invest*. 2019;129:1441–51; 4. Mitchell PD and O’Byrne PM. *Chest*. 2017;151:1338–44.

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There are multiple drivers of disease biology in severe asthma



Eos, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; PRR, pattern recognition receptor; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin

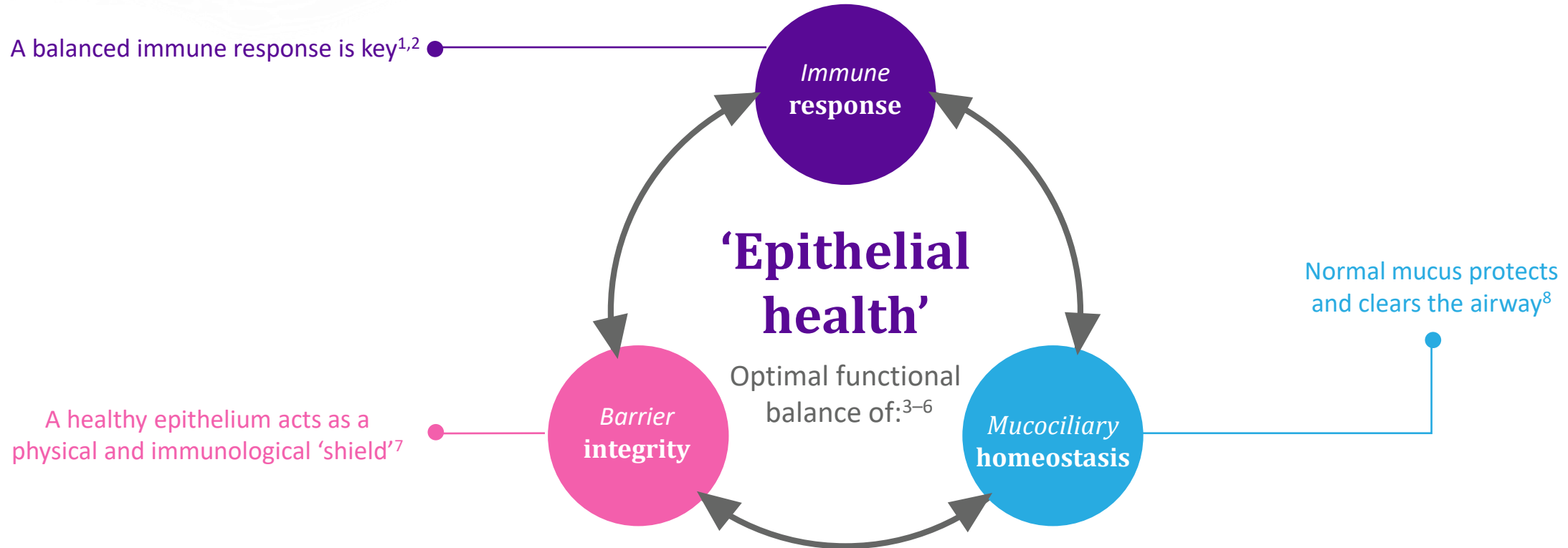
1. Sverrild A et al. *Eur Respir J*. 2022;59:2101296; 2. Gauvreau GM, et al. *N Engl J Med*. 2014;370:2102–10; 3. Diver S, et al. *Lancet Respir Med*. 2021;9:1299–312; 4. Menzies-Gow A, et al. *Respir Res*. 2020;21:266; 5. Chipps BE and Marshik PL. *Biotechnol Healthc*. 2004;1:56–61; 6. Pelaia C, et al. *Front Physiol*. 2019;10:1514; 7. Vatrella A et al. *Biomedicines*. 2022;10:2181; 8. Porsbjerg CM, et al. *Eur Respir J*. 2020;56:2000260; 9. Murugesan N, et al. *Diagnostics (Basel)*. 2023;13:1428; 10. Porsbjerg C, et al. *Ann Allergy Asthma Immunol*. 2007;98:44–50; 11. Chan R, et al. *J Allergy Clin Immunol Pract*. 2023;11:195–199.e2

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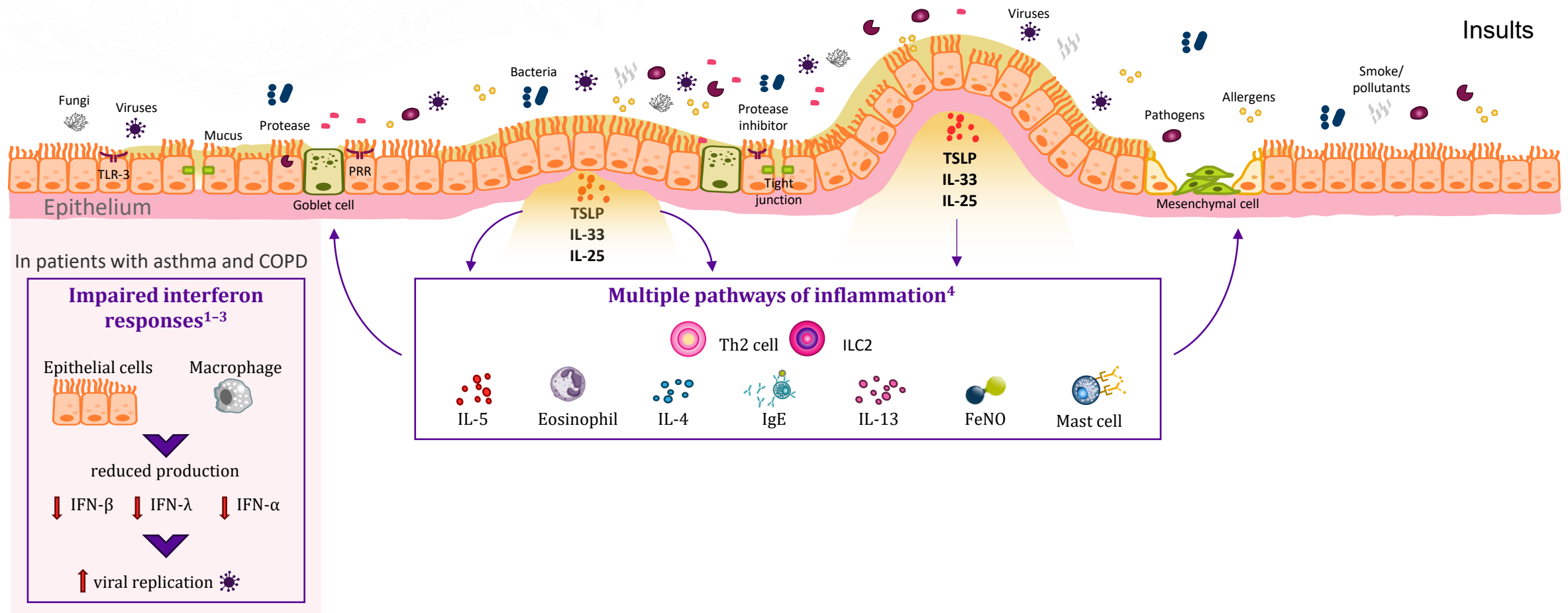
'Epithelial health' refers to the optimal structural integrity and functional balance of the airway epithelial layer

'Epithelial health' is maintained through three core domains



Restoring epithelial health may be a critical step towards clinical remission and disease modification

Impaired interferon response and immune hyperreactivity in response to environmental triggers in patients with airway diseases¹⁻⁴



The information presented in this image has been simplified for illustration purposes.

Refer to Caminati M et al. *Allergy*. 2024;79(5):1134–45. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/>. Accessed August 2026.

COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; PRR, pattern recognition receptor; Th2, type 2 helper T cells; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

1. Woehlk C, et al. *Am J Respir Crit Care Med*. 2023; 207(9):1161–70; 2. Zhu J, et al. *J Allergy Clin Immunol*. 2019;143(1):114–125.e4; 3. Johnston SL. *Am J Respir Crit Care Med*. 2020;201(1):9–11; 4. Caminati M et al. *Allergy*. 2024;79(5):1134–45. Z4-89374 | Date of preparation: September 2026. © 2026 AstraZeneca. All Rights Reserved. This information is intended for healthcare professionals only.

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Azithromycin strengthens epithelial IFN responses while reducing IL-33 after viral stimulation

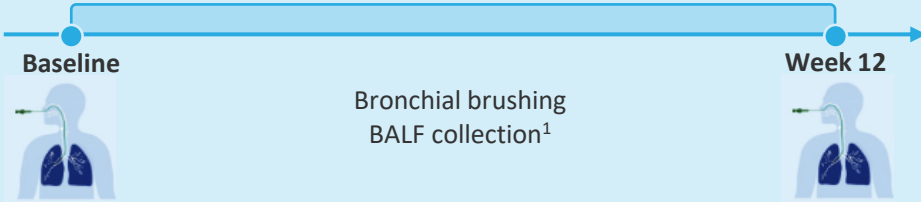
Study design¹

Adult patients with uncontrolled asthma¹

**Azithromycin 500 mg
three times/week¹**
n=16

AZIMUNE²
NCT04319705
Phase IV randomised,
double-blind, placebo-
controlled trial

Placebo¹
n=16



Methods¹

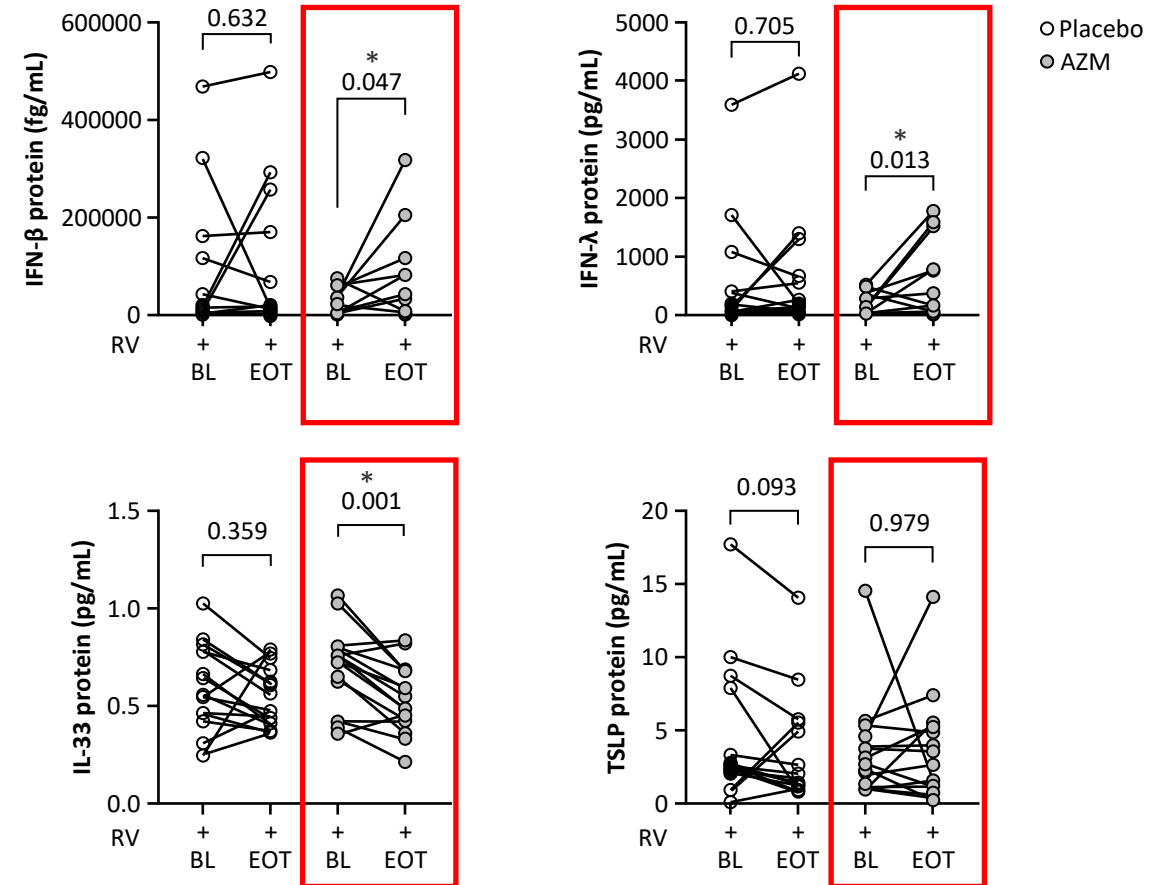
Stimulation of bronchial
epithelial cells with RV



1h
Exposure to RV1B,
MOI 0.05

48h
Incubation followed by
multiplex immunoassay

Effects of azithromycin on protein release of IFN- β , IFN- λ , IL-33 and TSLP in Poly (I:C-) and RV-stimulated BECs



Refer to Ghanizada et al. *Eur Respir J.* 2026;2502441.

Protein data are presented as absolute values. Two-tailed Wilcoxon t-test was used for paired comparisons and Mann-Whitney U test was used for unpaired comparisons.¹ *p<0.05.

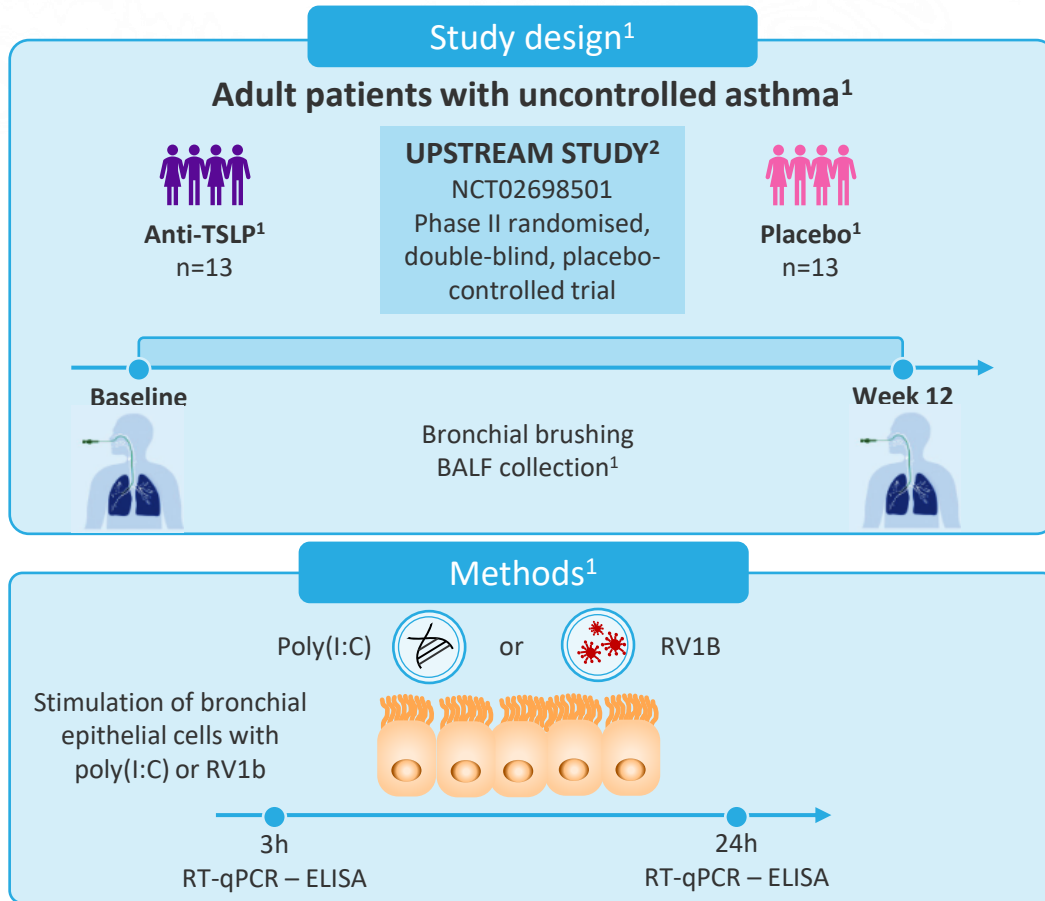
AZM, azithromycin; BALF, bronchoalveolar lavage fluid; BL, baseline; EOT, end of treatment; IFN, interferon; IL, interleukin; MOI, multiplicity of infection; RV, rhinovirus; RV1B, human rhinovirus 1B; TSLP, thymic stromal lymphopoietin.

1. Ghanizada et al. *Eur Respir J.* 2026;2502441; 2. ClinicalTrials.gov. NCT04319705. Accessed August 2026.

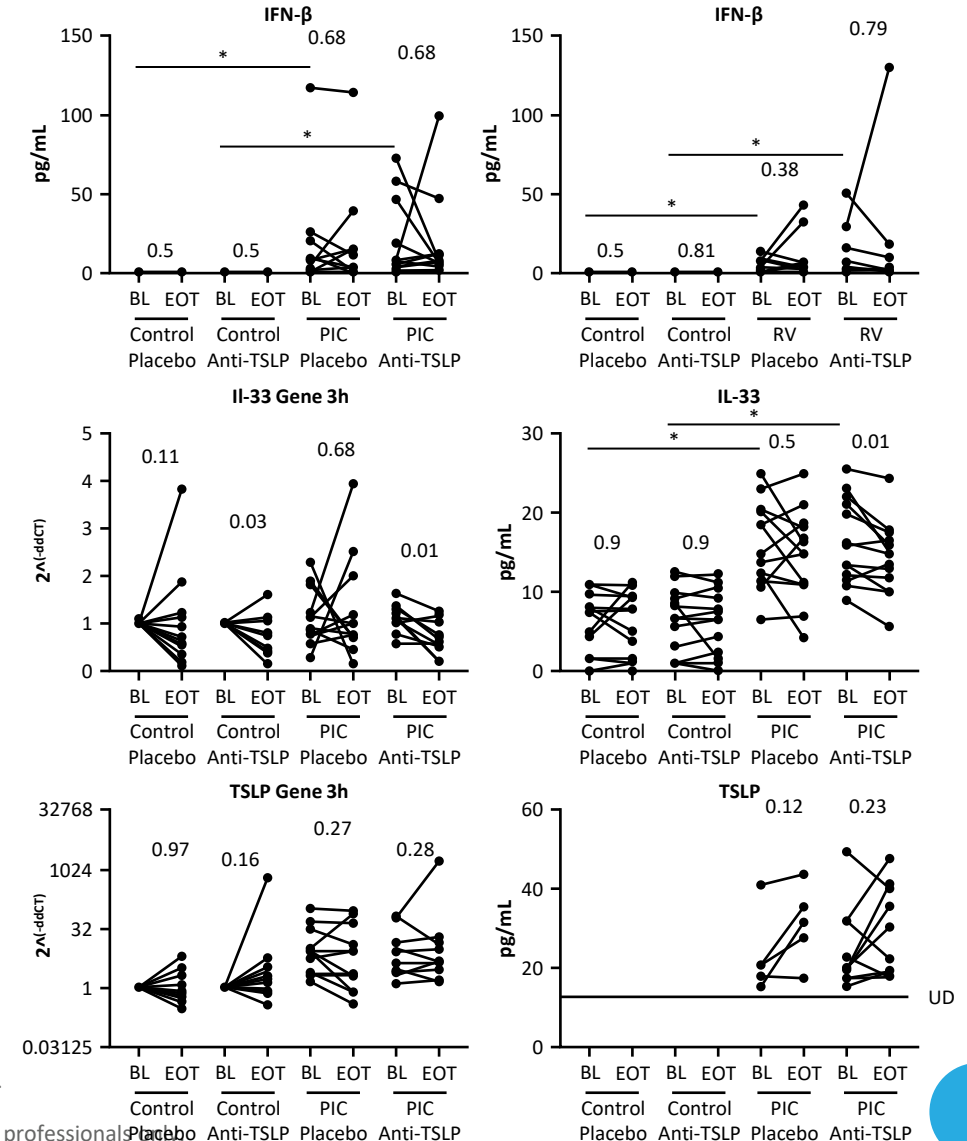
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Anti-TSLP reduces virus-induced epithelial IL-33 while maintaining antiviral IFN- β responses in uncontrolled asthma



Effects of anti-TSLP treatment on protein release of IFN- β , IL-33 and TSLP in Poly(I:C-) and RV-stimulated BECs



Refer to Sverrild et al. *Allergy* 2024; 79(3):656–66.

Gene data presented at BL and EOT are normalised toward the dCT of BL control (equal to baseline data without PIC stimulation) for each individual. Protein data are presented as absolute values. Two-tailed Wilcoxon t-test was used for paired comparisons and Mann–Whitney U test was used for unpaired comparisons.¹ *p<0.05.

BALF, bronchoalveolar lavage fluid; BEC, bronchial epithelial cell; BL, baseline; dCT, delta cycle threshold; ELISA, enzyme-linked immunosorbent assay; EOT, end of treatment; HDM, house dust mite; IFN, interferon; IL, interleukin; PIC, Poly(I:C); Poly(I:C), polyinosinic:polycytidylic acid; RT-qPCR, reverse transcription quantitative polymerase chain reaction; RV1B, human rhinovirus 1b; SLIT, sublingual immunotherapy; TSLP, thymic stromal lymphopoietin.

1. Sverrild et al. *Allergy* 2024; 79(3):656–66; 2. ClinicalTrials.gov. NCT02698501. Accessed August 2026.

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AIT strengthens bronchial epithelial antiviral immunity while maintaining epithelial cytokine responses in allergic asthma

Study design¹

Adult patients with asthma and HDM-induced rhinitis¹

HDM-SLIT 12-SQ daily¹
n=20

VITAL STUDY²
NCT04100902
Phase IV randomised,
double-blind, placebo-
controlled trial

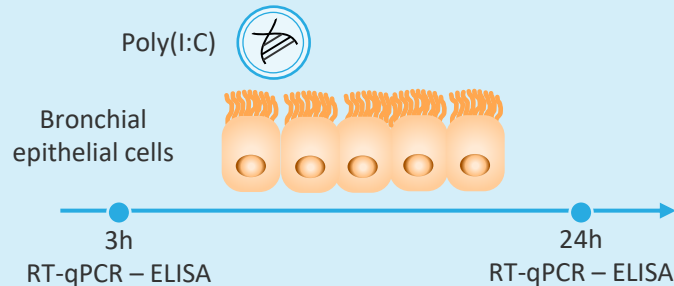
Placebo¹
n=19

Baseline

Week 24

Bronchial brushing
BALF collection

Methods¹



Refer to Woehlk C, et al. *Am J Respir Crit Care Med*. 2023; 207(9):1161–1170.

mRNA expression was normalised of control for each individual. Protein data are presented as absolute values. Two-tailed Wilcoxon t-test was used for paired comparisons and Mann–Whitney U test was used for unpaired comparisons.¹ *p<0.05.

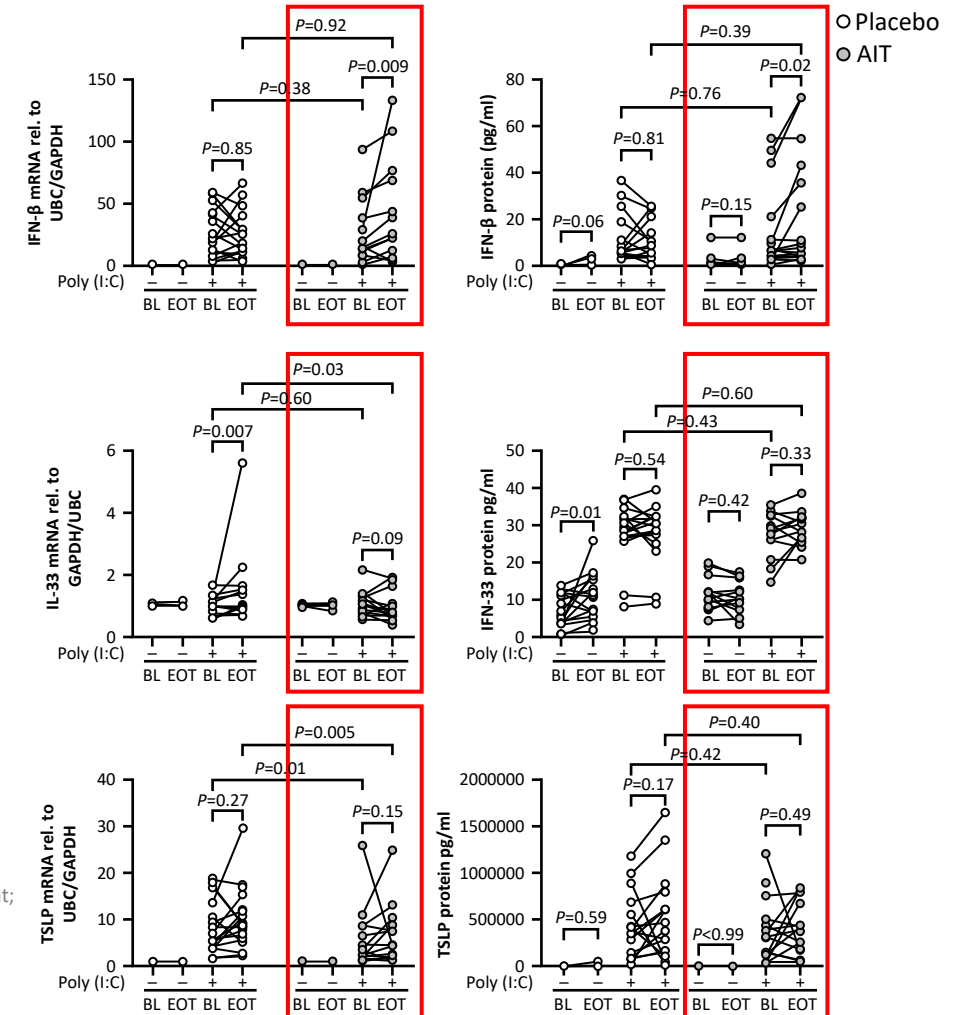
AIT, allergen immunotherapy; BALF, bronchoalveolar lavage fluid; BL, baseline; ELISA, enzyme-linked immunosorbent assay; EOT, end of treatment; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HDM, house dust mite; IFN, interferon; IL, interleukin; Poly(I:C), polyinosinic:polycytidylic acid; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SLIT, sublingual immunotherapy; SQ, standard quality; TSLP, thymic stromal lymphopoietin; UBC, ubiquitin C.

1. Woehlk C, et al. *Am J Respir Crit Care Med*. 2023; 207(9):1161–70; 2. ClinicalTrials.gov. NCT04100902. Accessed August 2026.

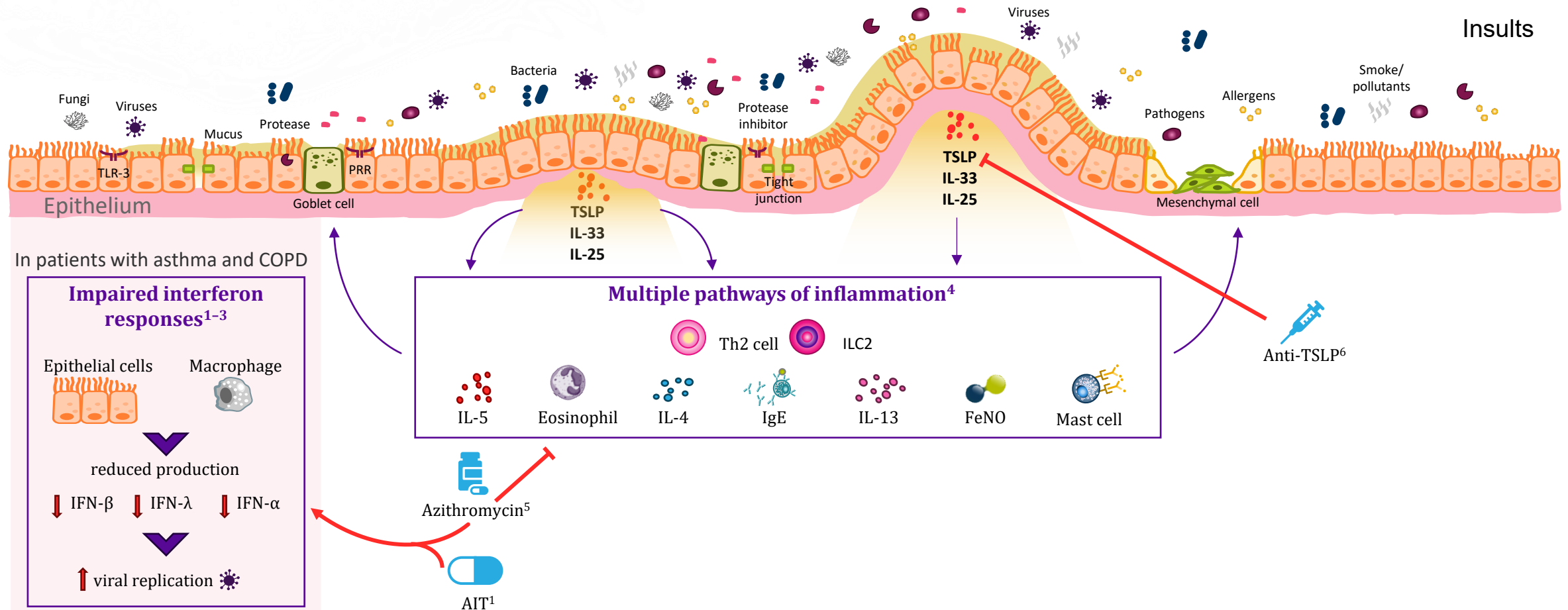
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Effects of AIT on the expression and protein release of IFN-β, IL-33 and TSLP in Poly (I:C)-stimulated human bronchial epithelial cells from patients with allergic asthma



Existing interventions for the management of asthma modulate antiviral and epithelial cytokine responses



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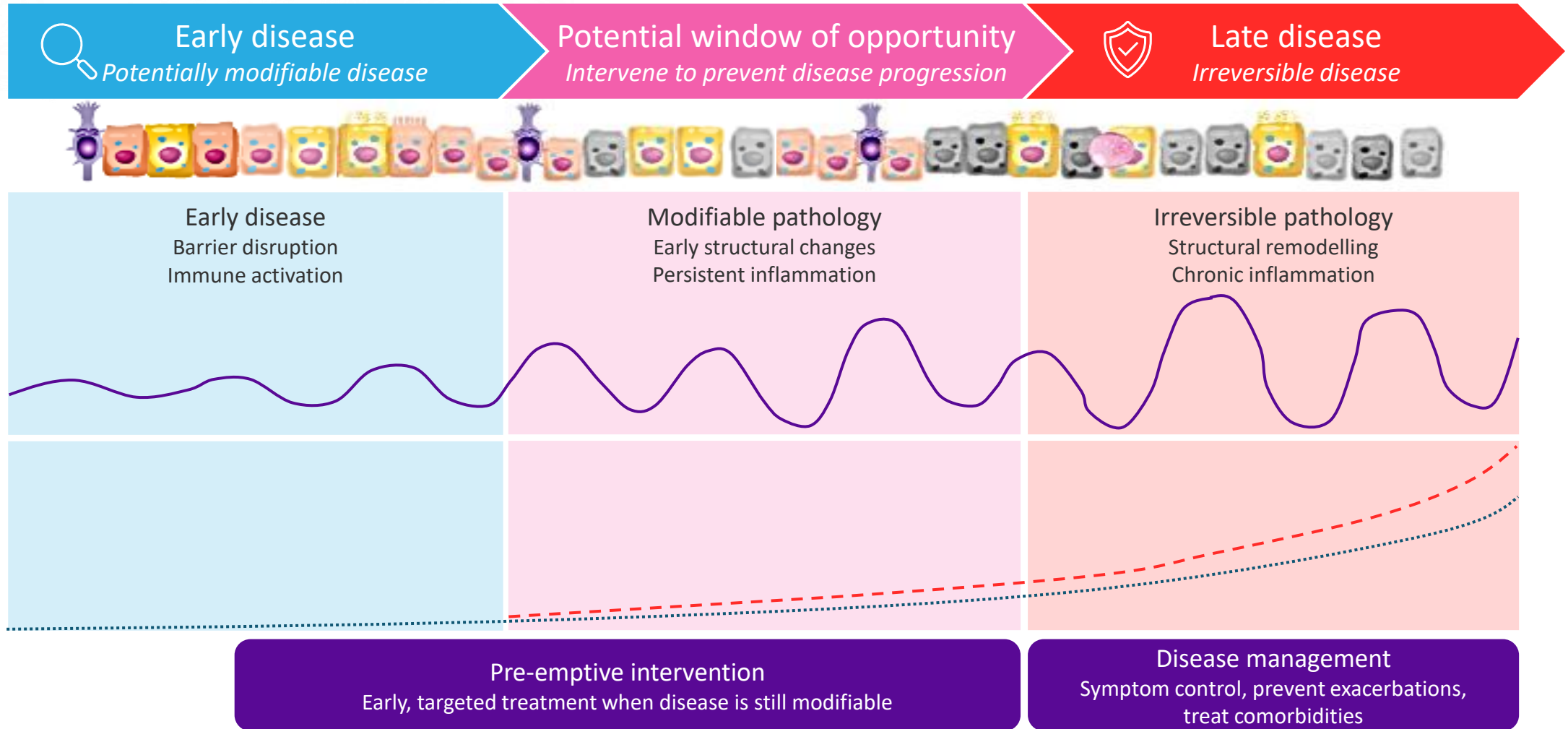
AIT, allergen immunotherapy; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; PRR, pattern recognition receptor; Th2, type 2 helper T cells; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

1. Woehlk C, et al. *Am J Respir Crit Care Med*. 2023; 207(9):1161–70; 2. Zhu J, et al. *J Allergy Clin Immunol*. 2019;143(1):114–125.e4; 3. Johnston SL. *Am J Respir Crit Care Med*. 2020;201(1):9–11; 4. Caminati M et al. *Allergy*. 2024;79(5):1134–45; 5. Ghanizada et al. *Eur Respir J*. 2026;2502441; 6. Sverrild et al. *Allergy*. 2024; 79(3):656–66.

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Early intervention during modifiable asthma pathology may help limit progression towards irreversible remodelling and greater disease burden



The figure is conceptual and is not intended to represent the relative magnitude or precise temporal relationship of individual disease processes.
Porsbjerg et al. *Lancet Respir.* 2025;13(11):1026–40.

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Recognition of the airway epithelium as a driver of airway disease is evolving

The airway epithelium is increasingly recognised as an active regulator of disease biology across upper and lower airway diseases, linking barrier integrity, immune response and mucociliary homeostasis with pathogenesis and progression^{1–6}

Ongoing research is now assessing how targeting epithelial cytokines may help restore the three domains of epithelial health and translate into meaningful outcomes^{7–11}

Tezebarrier⁸

An exploratory study evaluating the effect of **anti-TSLP treatment on the barrier function** of upper and lower airways in patients suffering from severe asthma with and without CRSwNP

3TR-ABC⁹

Multicentre observational prospective cohort study assessing **response to biological treatment** in patients with severe asthma and examining clinical characteristics, biomarkers, and immunological mechanisms related to response, including remission and non-response, that might be new targets or explanations for insufficient treatment

TezALL^{10,11}

Non-interventional study evaluating **anti-allergic effects of anti-TSLP** in patients with severe allergic asthma being treated with anti-TSLP

Better characterisation of epithelial biology may improve how disease progression and treatment response are measured across the united airway

ABC, asthma biologics cohort ; TSLP, thymic stromal lymphopoietin

1. Hallstrand TS, et al. *Clin Immunol.* 2014;151:1–15; 2. Davis JD and Wypych TP. *Mucosal Immunol.* 2021;14:978–90; 3. Porsbjerg C, et al. *Lancet.* 2023;401:858–73; 4. Calvén J, et al. *Int J Mol Sci.* 2020;21:8907; 5. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204; 6. Bousquet J, et al. *Nat Rev Dis Primers.* 2020;6:95; 7. Caminati M, et al. *Allergy.* 2024;79:1134–45; 8. ClinicalTrials.gov. NCT07046117. Accessed August 2026; 9. ClinicalTrials.gov. NCT06126692. Accessed August 2026; 10. Bergmann KC, et al. EAACI, Istanbul, 12–15 June 2026. Poster D1.111; 11. Paul-Ehrlich-Institut. Non-interventional study (observational study) NIS No. 774. www.pei.de/SharedDocs/awb/nis-0701-0800/0774.html. Accessed August 2026.

Restoration of 'Epithelial Health' could have a potential link to the wider goal of achieving disease modification and clinical remission

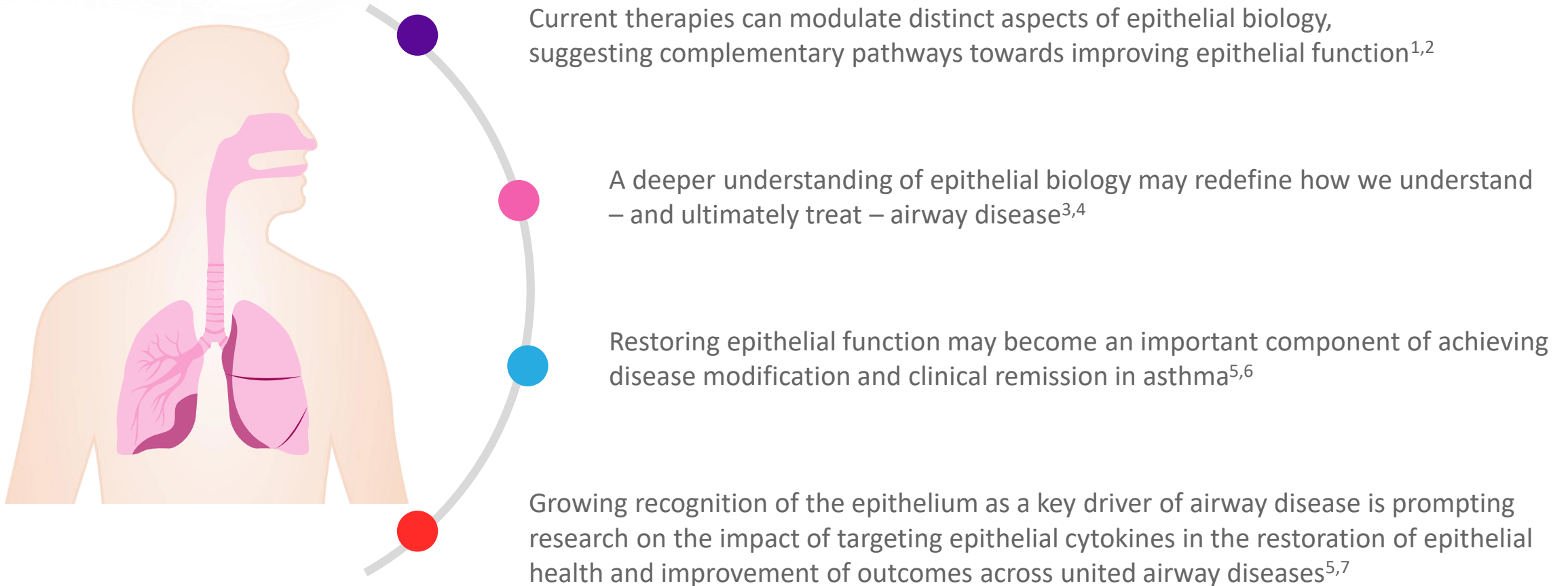
A clearer understanding of **epithelial dysfunction** and '**Epithelial Health**' could support the goal of achieving clinical remission for patients with **epithelial-driven disease**¹



To achieve clinical remission, the epithelium must be repaired and 'Epithelial Health' restored

OCS, oral corticosteroid

1. Brightling CE, et al. *Eur Respir Rev.* 2024;33:240221.



1. Sverrild A, et al. *Allergy*. 2024;79(3):656–66; 2. Ghanizada et al. *Eur Respir J*. 2026;2502441; 3. Hallstrand TS, et al. *Clin Immunol*. 2014;151(1):1–15; 4. Porsbjerg C, et al. *Lancet*. 2023;401(10379):858–73; 5. Brightling CE, et al. *Eur Respir Rev*. 2024;33:240221; 6. Porsbjerg C, et al. *Lancet Respir Med*. 2025;13(11):1026–40; 7. Fokkens W and Reitsma S. *Otolaryngol Clin North Am*. 2023;56(1):1–10.