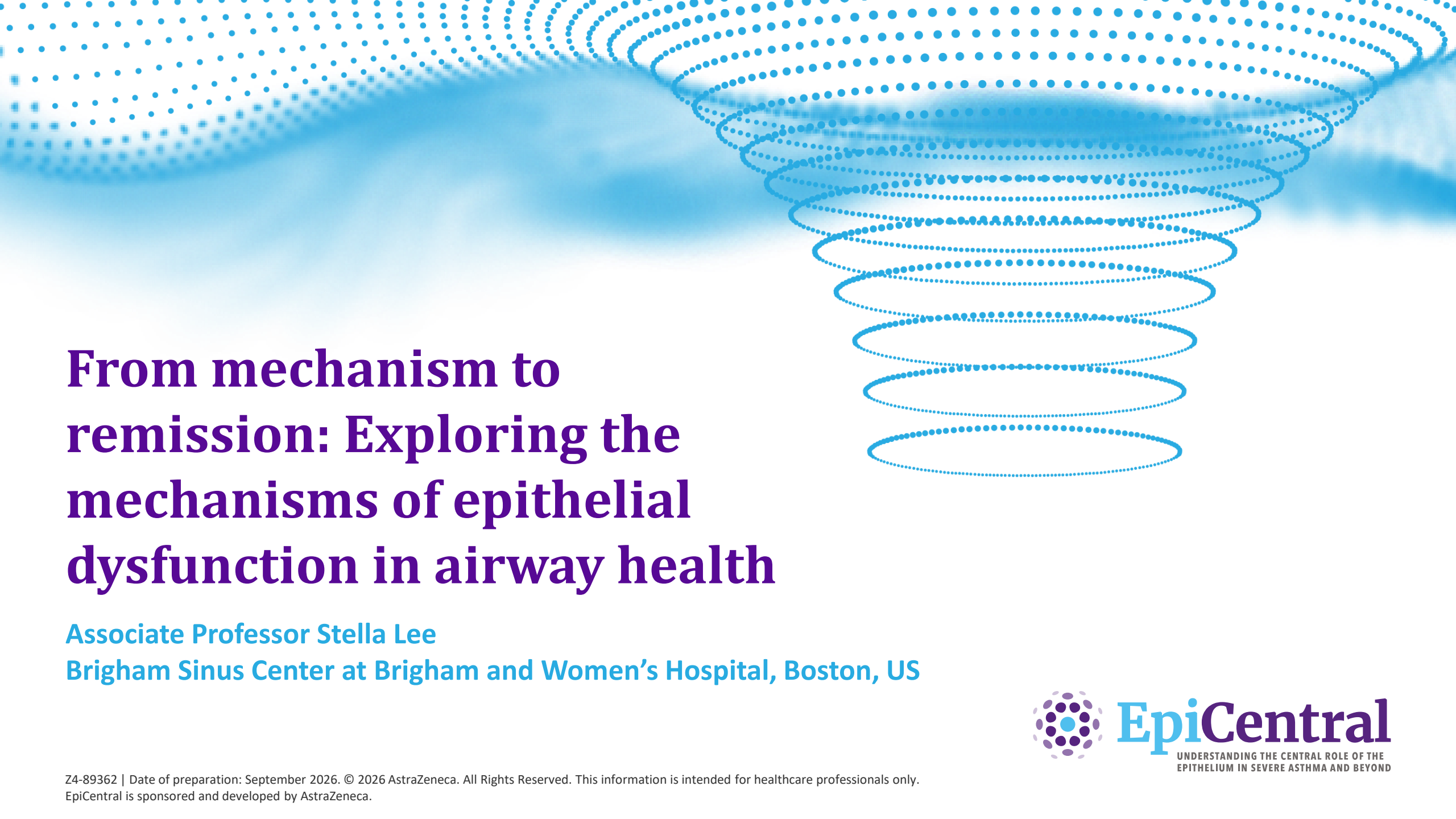
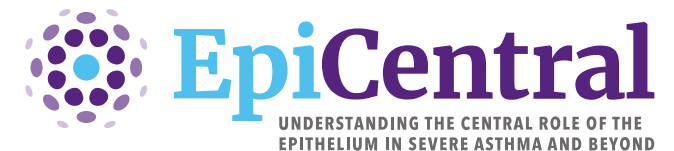




From mechanism to remission: Exploring the mechanisms of epithelial dysfunction in airway health

Associate Professor Stella Lee

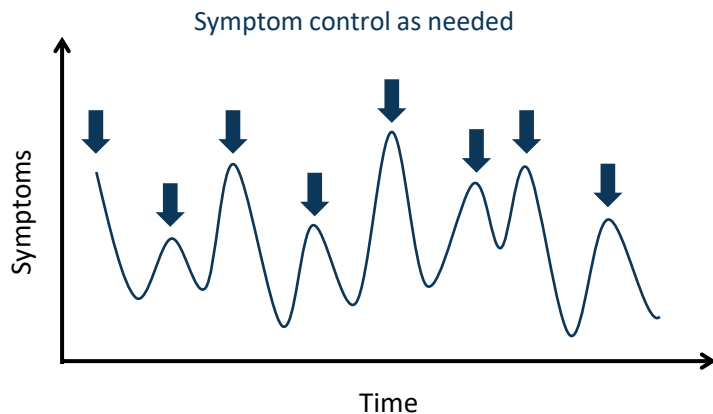
Brigham Sinus Center at Brigham and Women's Hospital, Boston, US



Greater understanding of airway disease mechanisms is transforming treatment goals in asthma and CRSwNP^{1,2}

Traditional management

Reactive disease control



‘One size fits all’, reactive treatment:^{1,2}

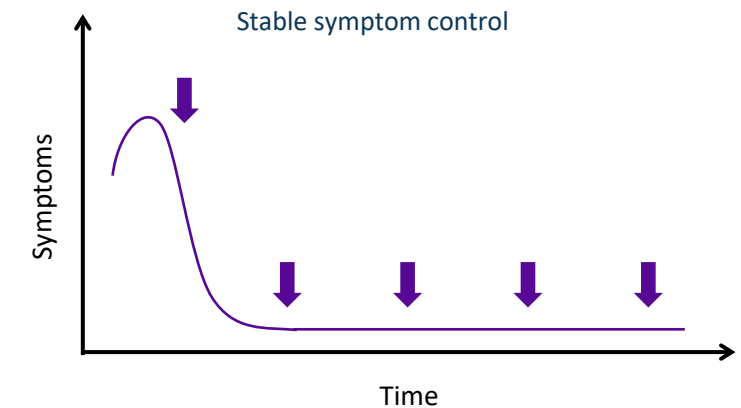
- Recurrent acute therapy
- Aimed to relieve symptoms
- Associated with major adverse effects

Increasing understanding of airway disease pathophysiology¹⁻⁷



Evolving biologic era

Targeted and proactive management



Individualised, proactive prevention:

- ‘Treat to target’¹
- Aims for disease modification and remission¹
- May reduce reliance on recurrent acute therapy⁷

CRSwNP, chronic rhinosinusitis with nasal polyps.

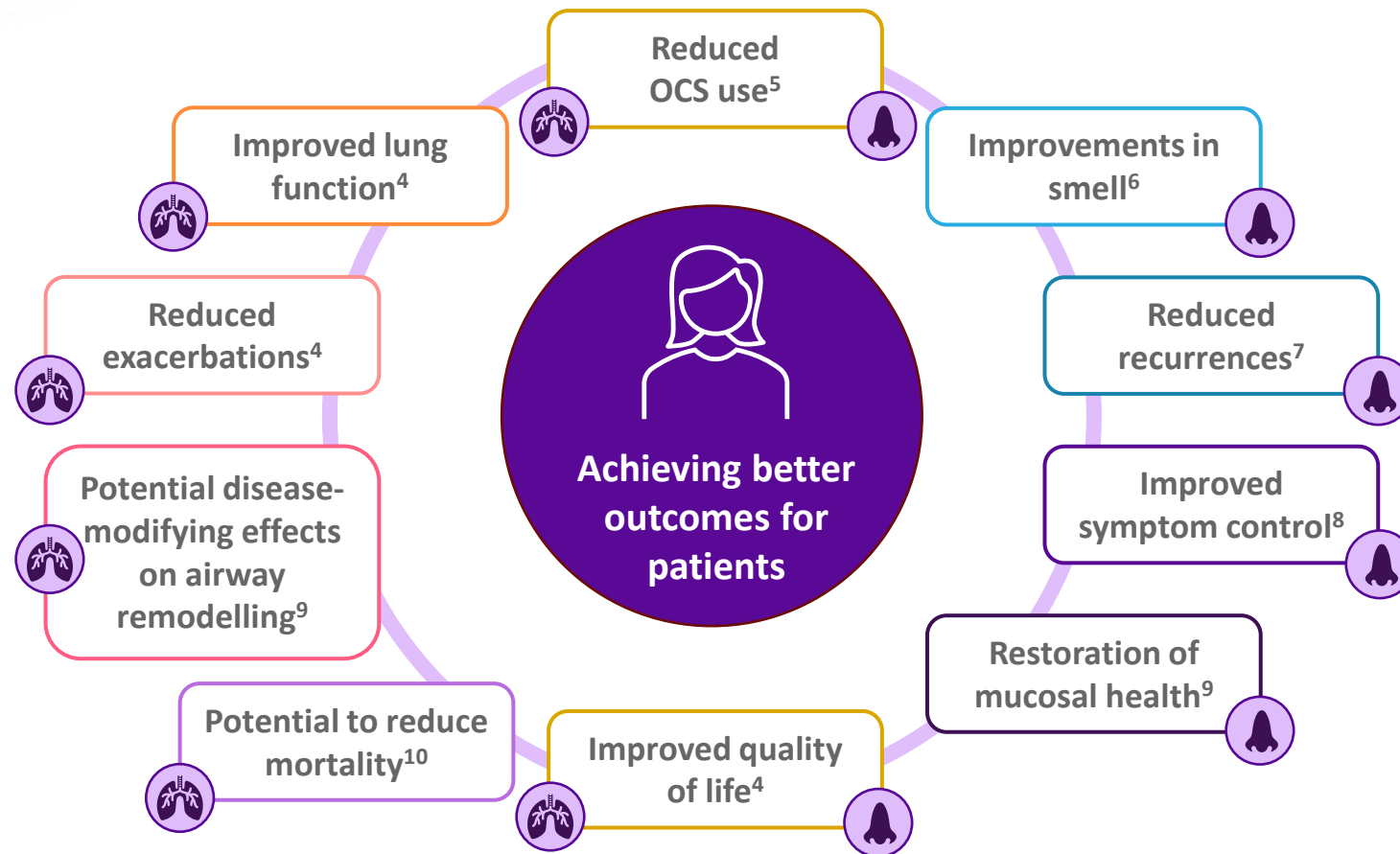
1. Lommatzsch M, et al. *Lancet*. 2022;399(10335):1664–8; 2. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4(4):565–72; 3. Howell I, et al. *J Exp Med*. 2023;220(7):e20221212; 4. Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180(5):388–95; 5. Wenzel SE. *Nat Med*. 2012;18(5):716–25; 6. Miller RL, et al. *J Allergy Clin Immunol*. 2021;148(6):1430–41; 7. Hellings PW, et al. *Allergy*. 2024;79(5):1123–33.

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Advances in biologic therapies are redefining treatment goals towards remission in airway disease¹⁻³

Biologic therapies targeting key inflammatory pathways have improved outcomes across airway diseases, making sustained disease control and clinical remission increasingly achievable goals¹⁻³



OCS, oral corticosteroids.

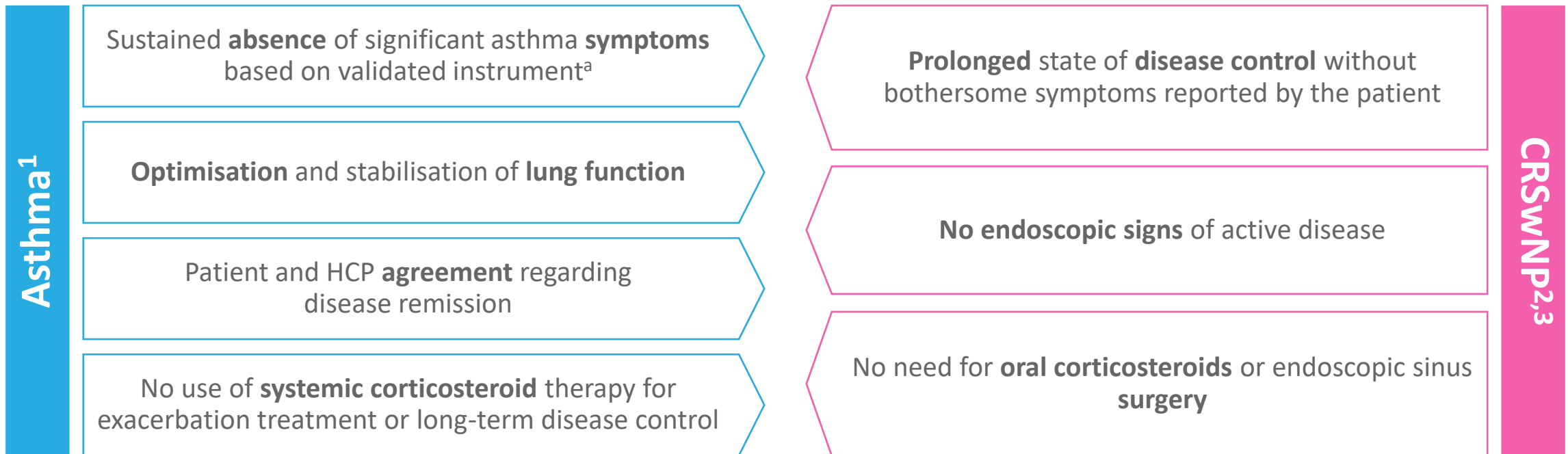
1. Lommatzsch M, et al. *Lancet*. 2022;399(10335):1664–8; 2. Hellings PW, et al. *Allergy*. 2024;79(5):1123–33; 3. McDowell PJ, et al. *Eur Respir J*. 2023;62(6):2300819; 4. Carr TF, et al. *Adv Ther*. 2024;41(7):2987-2990; 5. Wechsler ME, et al. *Lancet Respir Med*. 2022;10(7):650-660; 6. Tanase MI, et al. *Cureus*. 2025;17(1):e77804; 7. Patel GB and Peters AT. *Ear Nose Throat J*. 2021;100(1):44-47; 8. Pavord I, et al. *J Allergy Clin Immunol*. 2025;156(3S):S15-S19; 9. Varricchi G, et al. *Allergy*. 2022;77(12):3538-3552; 10. Caminati M, et al. *World Allergy Organ J*. 2021;14(2):100502

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As remission becomes an emerging treatment goal, expert groups are working to define remission across airway diseases^{1,2}

- ❖ In both asthma and CRSwNP, expert consensus has so far proposed a framework for remission as the following.
For ≥12 months:



^ae.g., Asthma Control Questionnaire or Asthma Control Test.

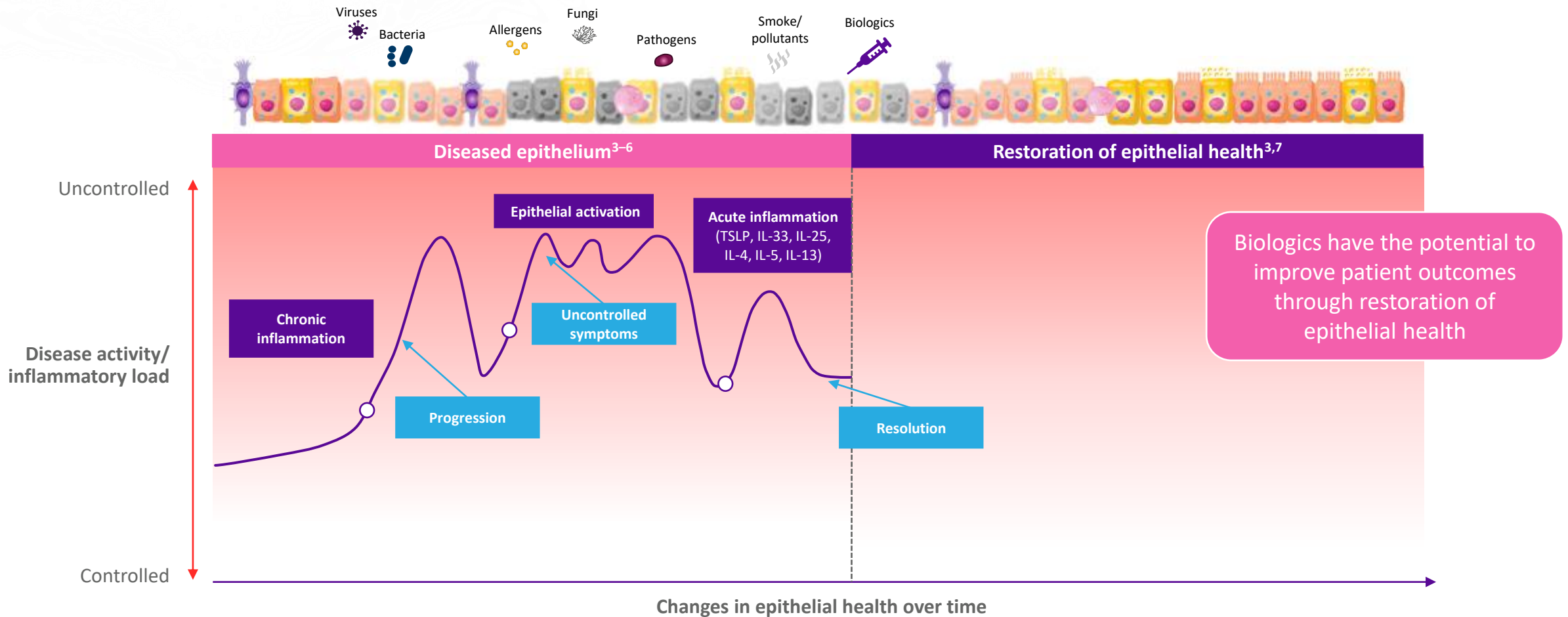
CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; HCP, healthcare professional.

1. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757–65; 2. Fokkens WJ, et al. *Rhinology.* 2024;62(3):287–98; 3. Heffler E, et al. *J Allergy Clin Immunol Pract.* 2026;14(4):937–51.

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Restoring epithelial health may be a critical step to achieving remission^{1,2}



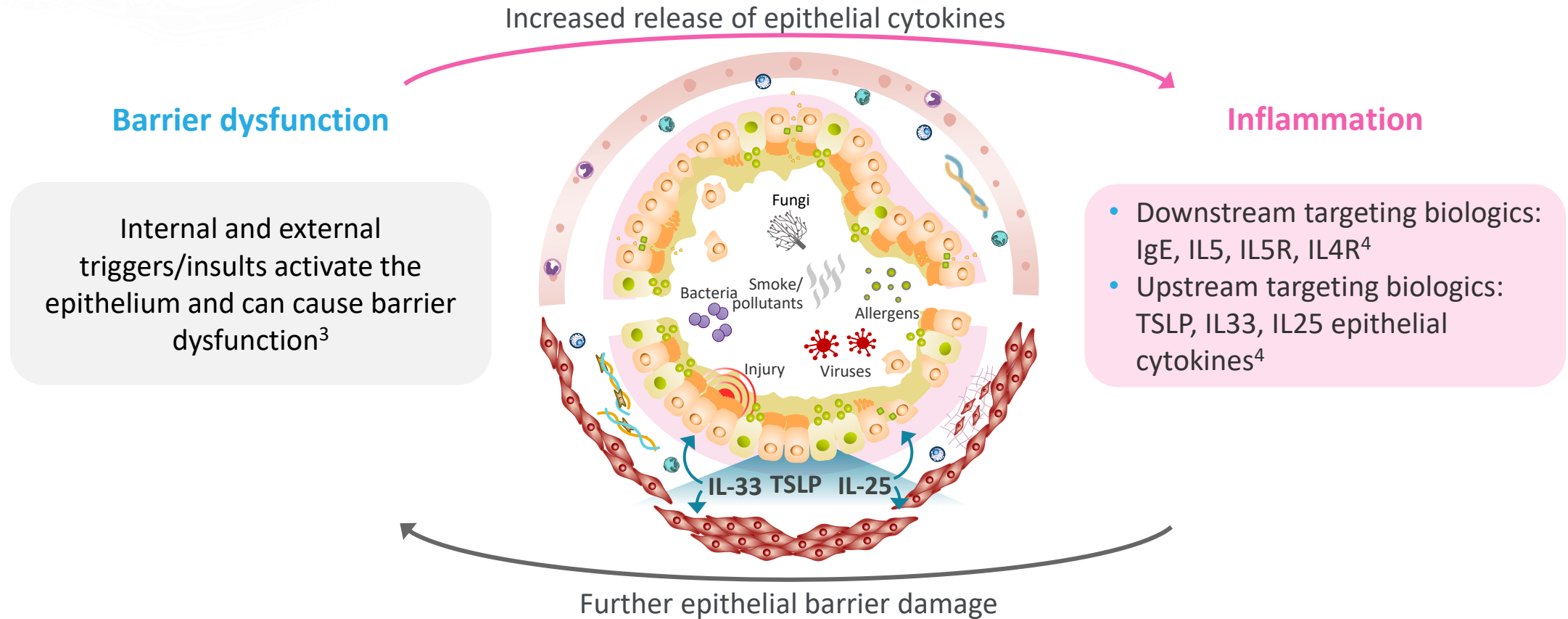
IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Menzies-Gow A, et al. *Respir Res.* 2020;21(1):268; 2. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24(8):777–92; 3. Russell RJ, et al. *Eur Respir J.* 2024;63(4):2301397; 4. Farokhi S, et al. *Immuno.* 2025;5(3):26; 5. Heijink IH, et al. *Allergy.* 2020;75(8):1902–17; 6. Porsbjerg C, et al. *Lancet.* 2023;401(10379):858–73; 7. Brightling CE, et al. *Eur Respir Rev.* 2024;33(174):240221.

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Targeting pathways of inflammation may help break the cycle of dysfunction and inflammation and lead toward remission^{1,2}



Refer to the Centre of Excellence in Severe Asthma. *Severe Asthma Toolkit*. 2018. <https://toolkit.severeasthma.org.au/severe-asthma/pathophysiology/> Accessed June 2026.

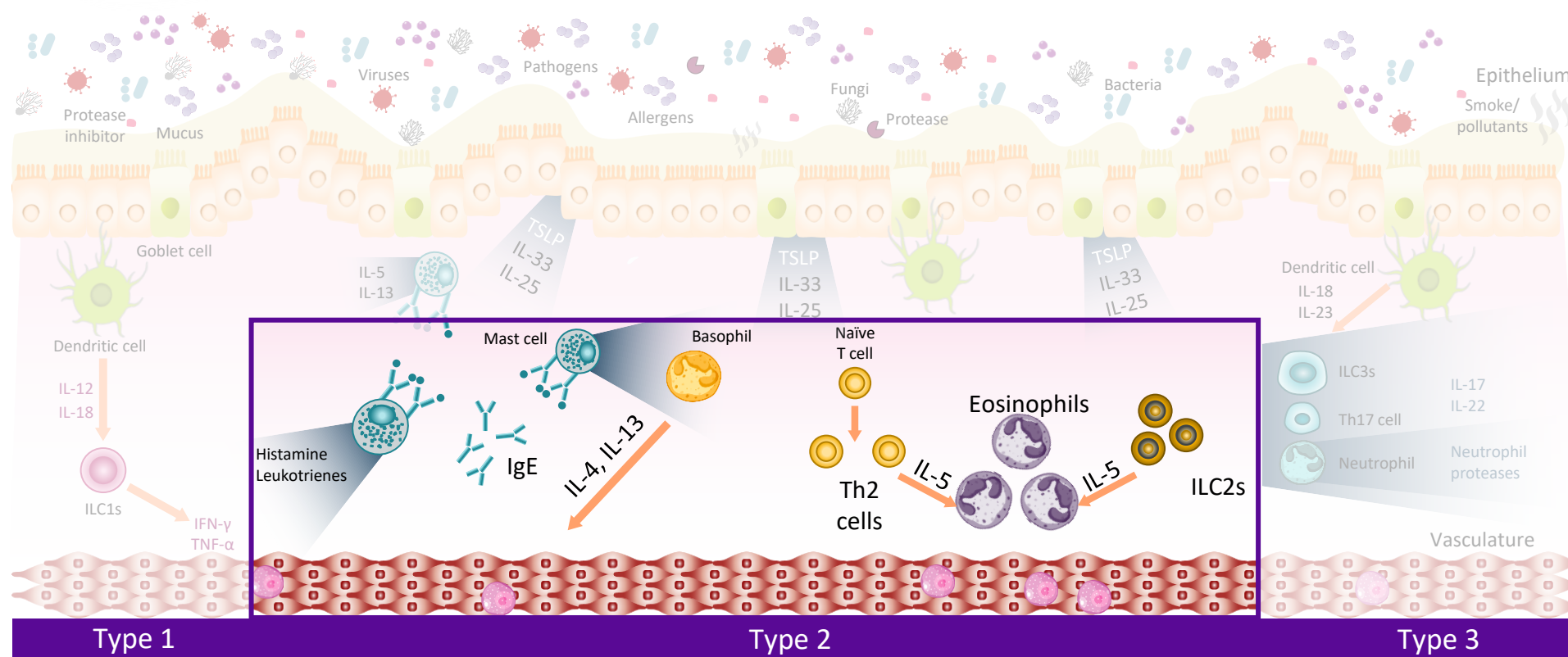
IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Menzies-Gow A, et al. *Respir Res*. 2020;21(1):268; 2. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24(8):777–92; 3. Hellings PW and Steelant B. *J Allergy Clin Immunol*. 2020;145(6):1499–509; 4. Porsbjerg CM, et al. *Eur Respir J*. 2020;56(5):2000260.

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Targeting downstream inflammatory pathways has improved patient outcomes, while highlighting the complexity of residual inflammation¹⁻⁴



Refer to Caminati M, et al. *Allergy*. 2024;79(5):1134–45.

CRSwNP, chronic rhinosinusitis with nasal polyps; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; T1, type 1; T2, type 2; T3, type 3; Th, T helper; TNF-α, tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

1. Porsbjerg CM, et al. *Eur Respir J*. 2020;56(5):2000260; 2. Caminati M, et al. *Allergy*. 2024;79(5):1134–45; 3. Fokkens WJ, et al. *Rhinol*. 2020;58(Suppl. S29):1–464; 4. Walsh GM. *Antibodies (Basel)*. 2025;14(4):101.

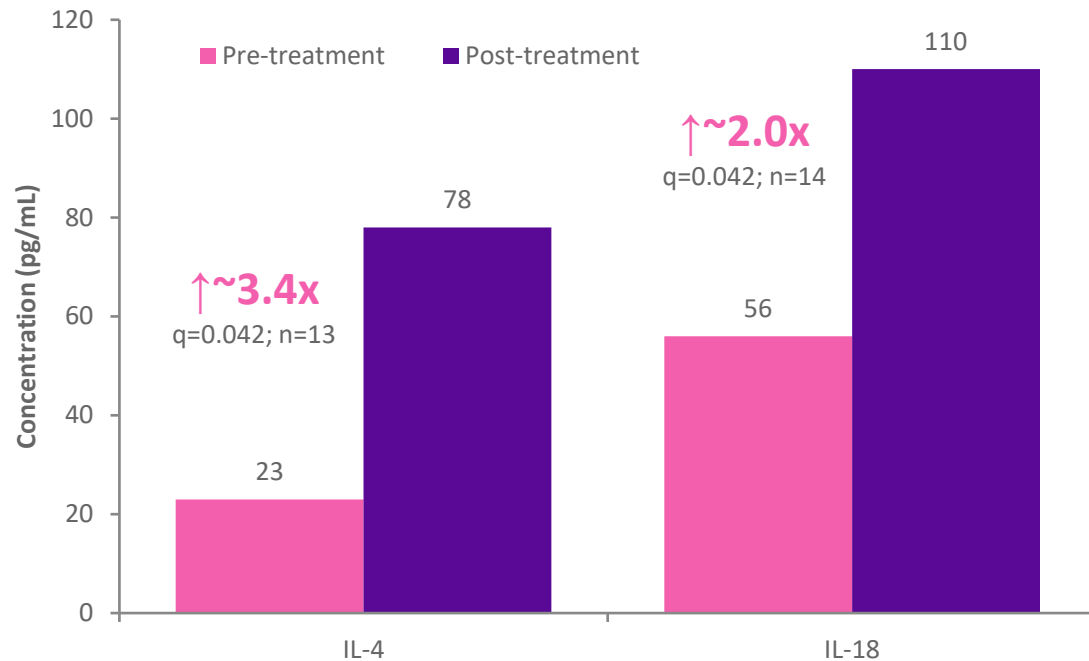
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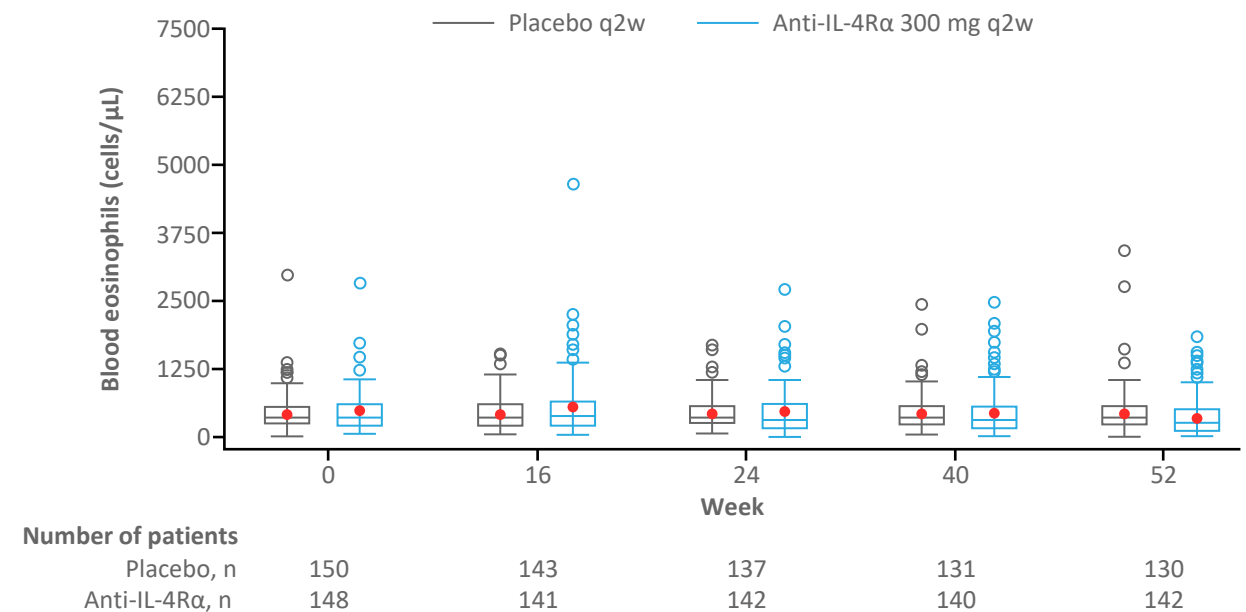
Biomarker changes after downstream T2 pathway blockade¹⁻³

IL-4 and IL-18 rose after anti-IL-4R α treatment in patients with CRSwNP^{a,b} 1

Paired nasal mucus, pre- vs post-treatment · Wilcoxon signed-rank · BH-adjusted q



Mean blood eosinophil counts may change after anti-IL-4R α treatment in patients with CRSwNP^{c,d} 3



Data presented are representative of a limited number of studies and require further validation to fully understand the mechanisms contributing to pathogenesis

Figure on the left refer to Morris J, et al. *Int Forum Allergy Rhinol.* 2022;12(10):1313–16. Figure on the right refer to Wechsler M, et al. *J Allergy Clin Immunol Pract.* 2022;10(10):2695–709.

^aValues are group means; SE in source table. Significance by Wilcoxon signed-rank test on paired ranks, Benjamini-Hochberg adjusted across nine analytes; ^bObservational translational study assessing cytokine changes in patients receiving dupilumab for type 2 inflammatory disease, using patient samples to evaluate treatment-associated changes in IL-4 and IL-18 production; ^cPost hoc analysis of Phase III LIBERTY NP SINUS-52 trial in patients with CRSwNP; ^dPost hoc analysis of dupilumab clinical trials across multiple type 2 inflammatory diseases, evaluating changes in blood eosinophil counts over time and eosinophilia-related treatment-emergent adverse events.

BH, Benjamini-Hochberg; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; q, q-value; q2w, every 2 weeks; SE, standard error; T2, type 2.

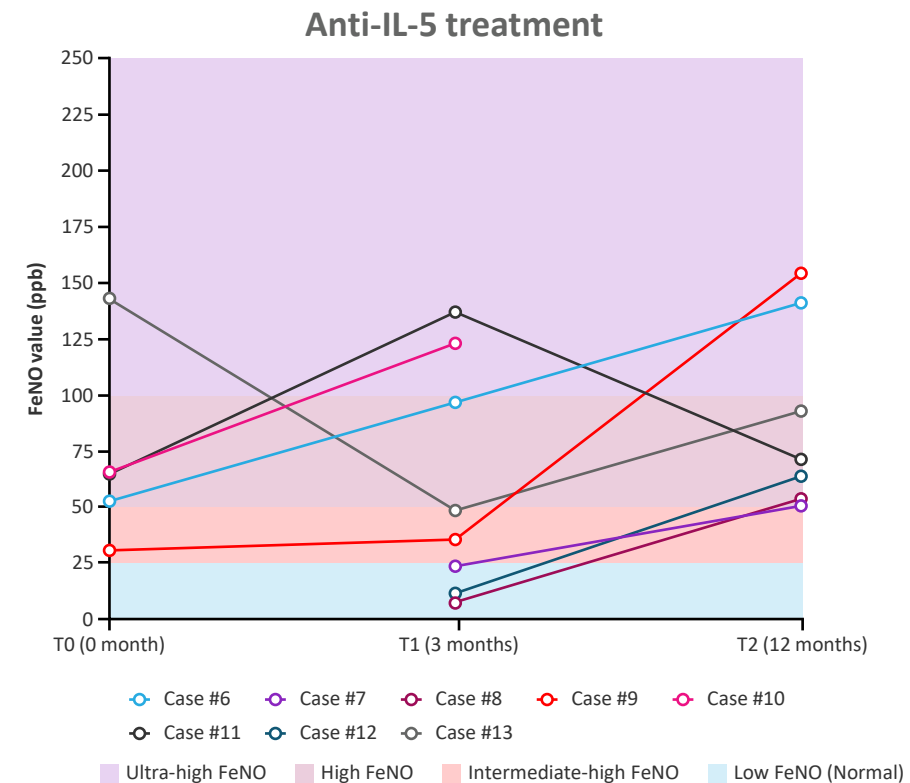
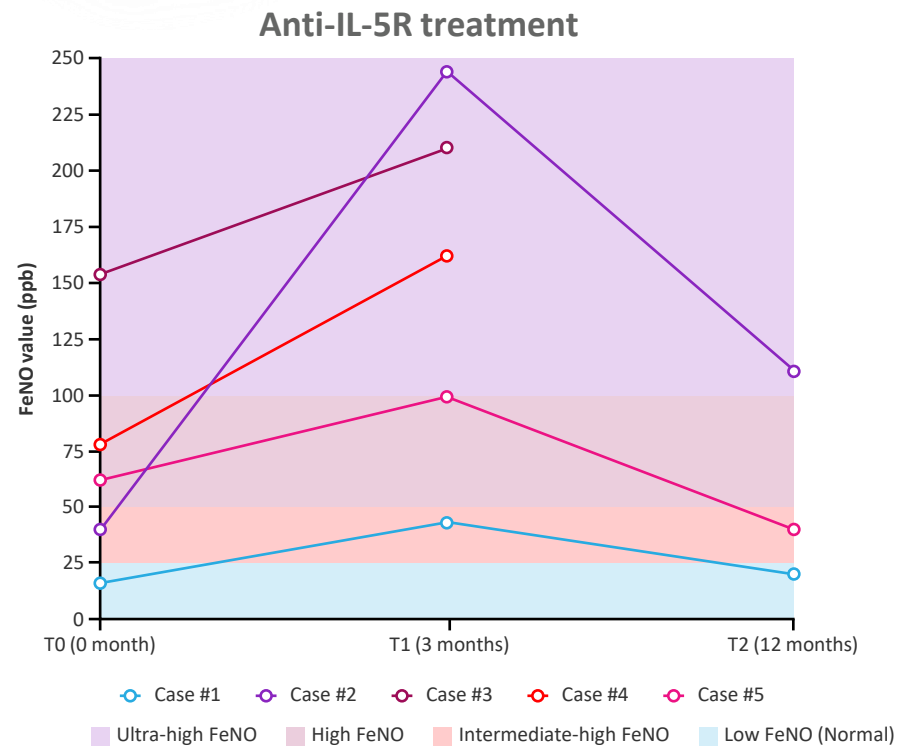
1. Morris J, et al. *Int Forum Allergy Rhinol.* 2022;12(10):1313–16; 2. Kremenevski I, et al. *Dtsch Arztebl Int.* 2022;119(6):88–95; 3. Wechsler M, et al. *J Allergy Clin Immunol Pract.* 2022;10(10):2695–709.

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Biomarker changes after downstream T2 pathway blockade¹⁻³

Retrospective case series observed significantly increased FeNO in patients with severe asthma treated with anti-IL-5/IL-5R treatment³



Data presented are representative of a limited number of studies and require further validation to fully understand the mechanisms contributing to pathogenesis

Refer to Pelletier G, et al. *J Asthma Allergy*. 2022;15:691–701.

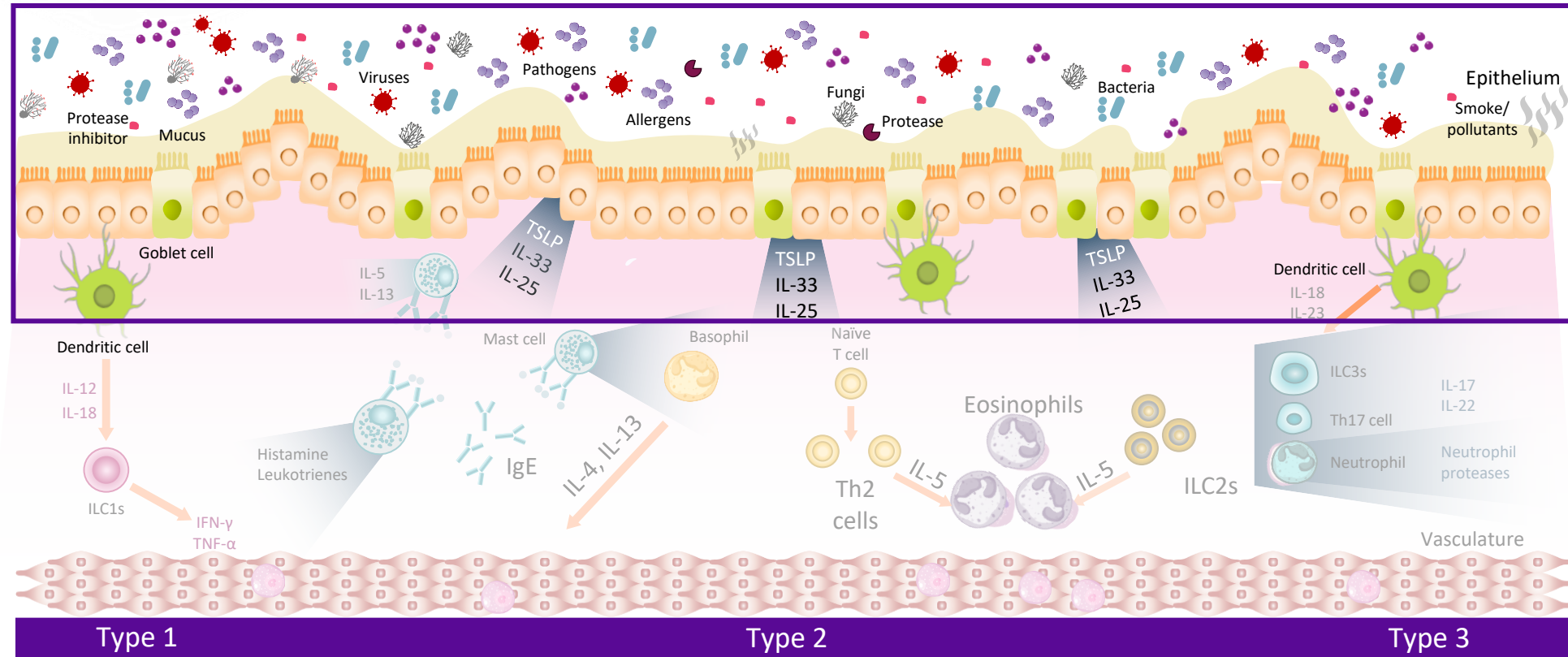
FeNO, fractional exhaled nitric oxide; IL, interleukin; ppb, parts per billion; T, type.

1. Dos Santos Sliva RA, et al. ERS, Vienna, 7–11 September 2024. Abstract PA3083; 2. Hekking PP, et al. *Allergy*. 2024;79(8):2244–7; 3. Pelletier G, et al. *J Asthma Allergy*. 2022;15:691–701.

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Targeting upstream epithelial cytokines offers an opportunity to address inflammation^{1,2}



Refer to Caminati M, et al. *Allergy*. 2024;79(5):1134–45.³

CRSwNP, chronic rhinosinusitis with nasal polyps; IFN- γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TNF- α , tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

1. Kato A and Kita H. *Nat Rev Immunol*. 2025;25(8):569–87; 2. Hellings PW and Steelant B. *J Allergy Clin Immunol*. 2020;145(6):1499–509; 3. Caminati M, et al. *Allergy*. 2024;79(5):1134–45.

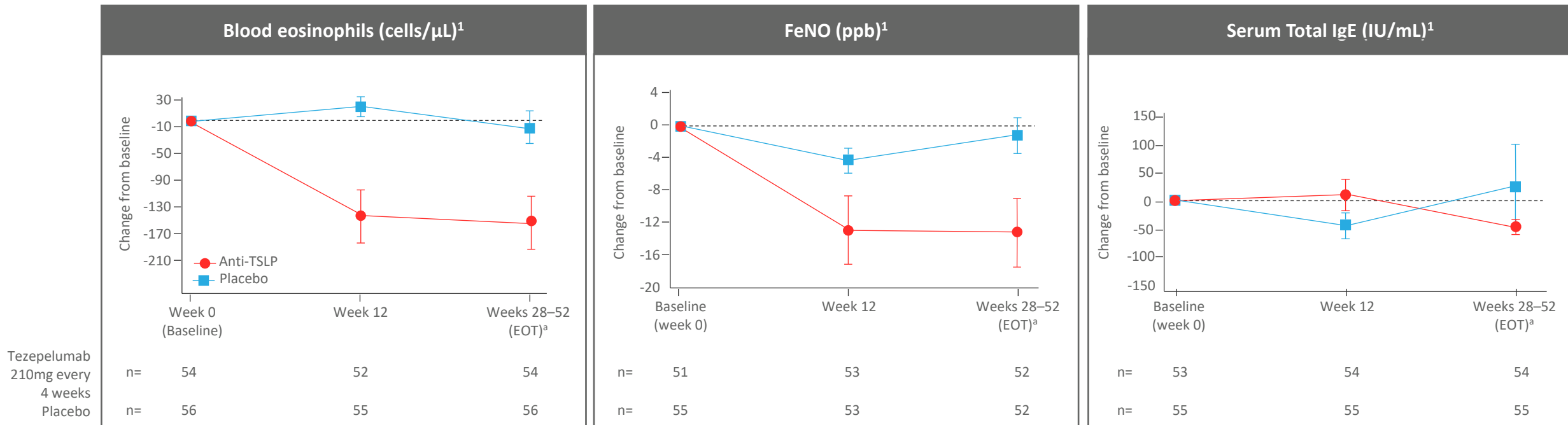
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Effect of TSLP blockade on downstream pathways^{1,2}



Change from baseline in biomarkers of T2 inflammation in patients with moderate-to-severe uncontrolled asthma¹



Results are descriptive only. The mechanism of action of anti-TSLP and the clinical significance of these outcomes and their impact on asthma have not been established.

Refer to Diver S, et al. *Lancet Respir Med.* 2021;9(11):1299-1312.

CASCADE was a phase 2, double-blind, randomised, placebo-controlled study evaluating tezepelumab's effects on airway inflammation and remodelling in adults with uncontrolled moderate-to-severe asthma.

^aTreatment was planned for 28 weeks; however, due to COVID-19-related protocol amendments, the treatment period was extended by up to 6 months (with dosing at weeks 28, 32, 36, 40, 44, and 48 as needed) to ensure that participants continued to receive study drug until circumstances allowed them to visit the study site for EOT assessments.

EOT, end-of-treatment; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoietin.

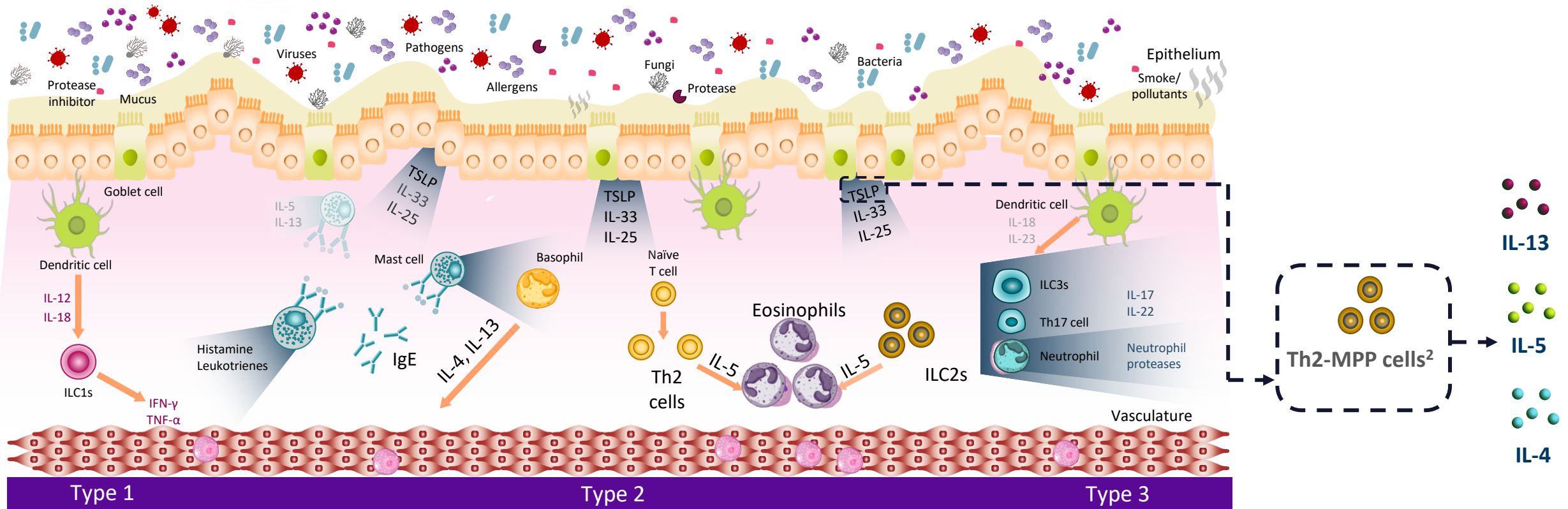
1. Diver S, et al. *Lancet Respir Med.* 2021;9(11):1299-1312; 2. Menzies-Gow et al. *N Engl J Med.* 2021;384:1800-1809.

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Emerging evidence demonstrates role of TSLP to drive persistent inflammation¹⁻³

Newly identified cell populations may promote persistent T2 inflammation²



Refer to Caminati M, et al. *Allergy*. 2024;79(5):1134–45.

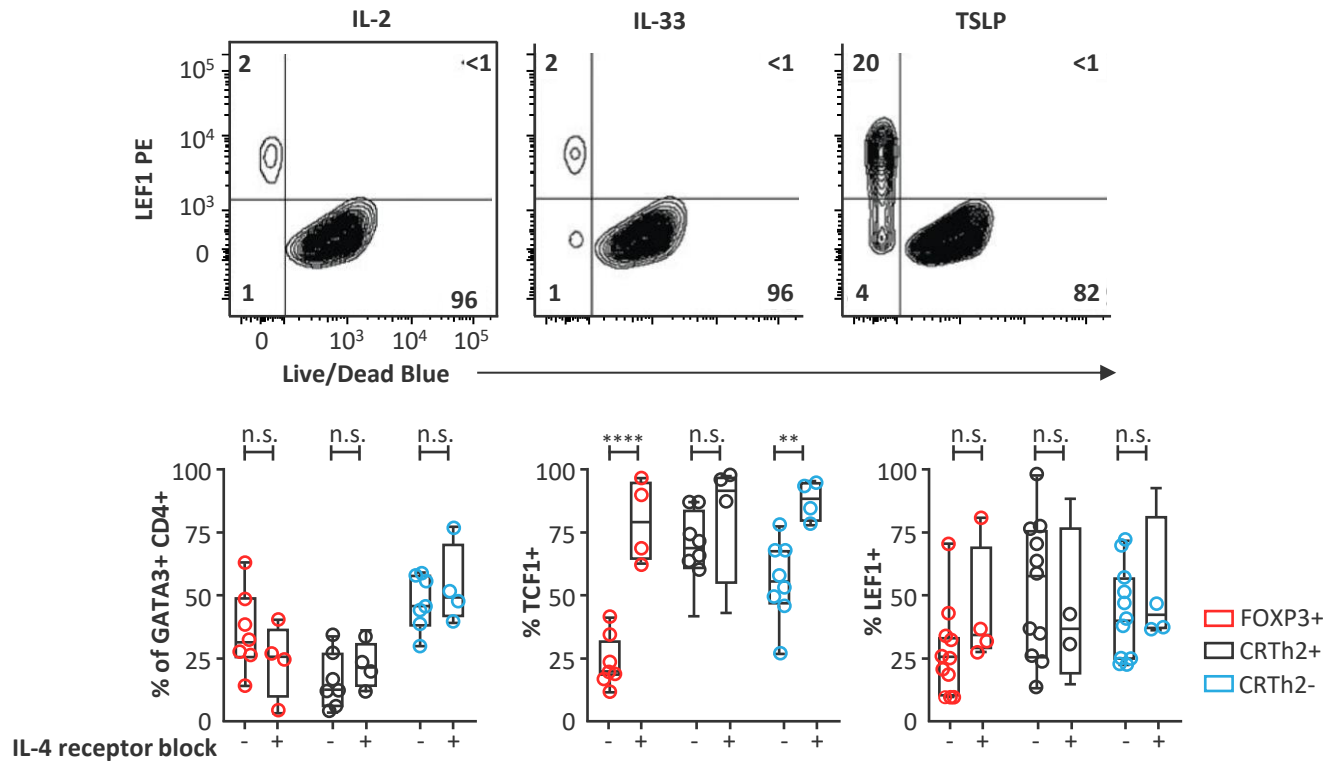
CRSwNP, chronic rhinosinusitis with nasal polyps; IFN- γ , interferon gamma; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; MPP, multipotent progenitor; T2, type 2; Th, T helper; TNF- α , tumour necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

1. Menzies-Gow A, et al. *Respir Res*. 2020;21(1):268; 2. Kratchmarov R, et al. *Nat Immunol*. 2024;25(5):902–15; 3. Sverrild A, et al. *Allergy*. 2024;79(3):656–66. Article and supporting appendix; 4. Caminati M, et al. *Allergy*. 2024;79(5):1134–45.

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Emerging evidence demonstrates role of TSLP to drive persistent inflammation¹⁻³



A study by Kratchmarov, et al 2024 demonstrated that compared with IL-2 and IL-33, TSLP drove survival and expansion of Th2-MPP cells in vitro²

The same study also demonstrated Th2-MPP cells persisted despite in vivo IL-4 receptor blockade²

Data presented are representative of a single study; additional studies are required to fully understand the role of epithelial and downstream cytokines on Th2-MPP cells and their respective impact on disease. The effect of TSLP blockade on Th2-MPP cells has not yet been established.

Refer to Kratchmarov R, et al. *Nat Immunol.* 2024;25(5):902–915.

CD4+, cluster of differentiation 4+; IL, interleukin; ILC, innate lymphoid cell; MPP, multipotent progenitor; Th, T helper; TSLP, thymic stromal lymphopoietin.

1. Menzies-Gow A, et al. *Respir Res.* 2020;21(1):268; 2. Kratchmarov R, et al. *Nat Immunol.* 2024;25(5):902–15; 3. Sverrild A, et al. *Allergy.* 2024;79(3):656–66.

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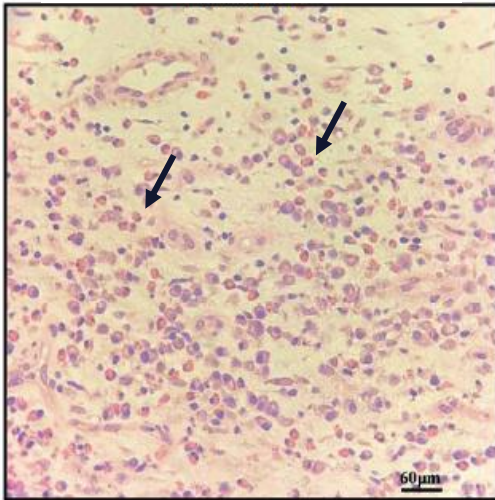
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Targeting IL-5 may help restore some aspects of epithelial health¹

Anti-IL-5 therapy reduced eosinophilic infiltration, subepithelial oedema,
and goblet cell hyperplasia in nasal polyp tissue¹

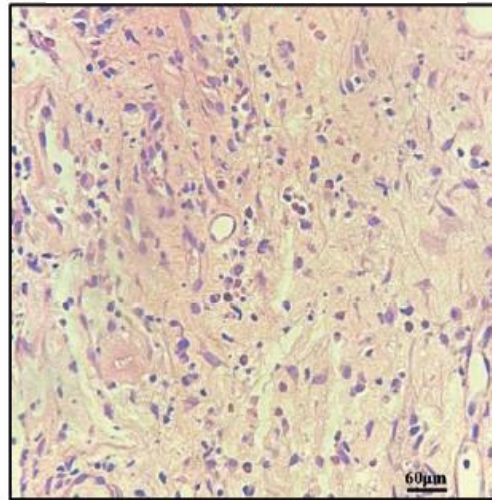
Representative nasal polyp tissue microscopic images of an individual patient before and after treatment with anti-IL-5 therapy

Pre-treatment with anti-IL-5



Eosinophilic infiltration (small arrows) prior to treatment

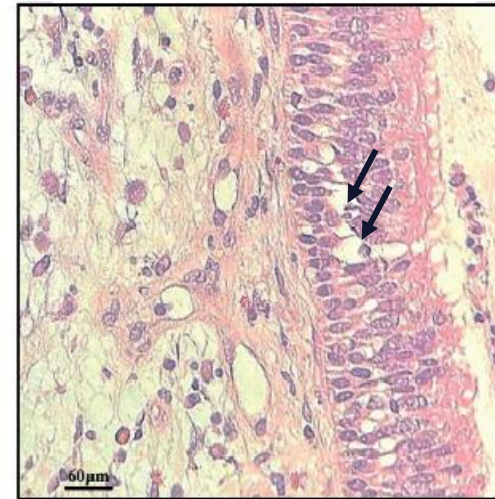
Post-treatment with anti-IL-5



Reduced eosinophilic infiltration after treatment

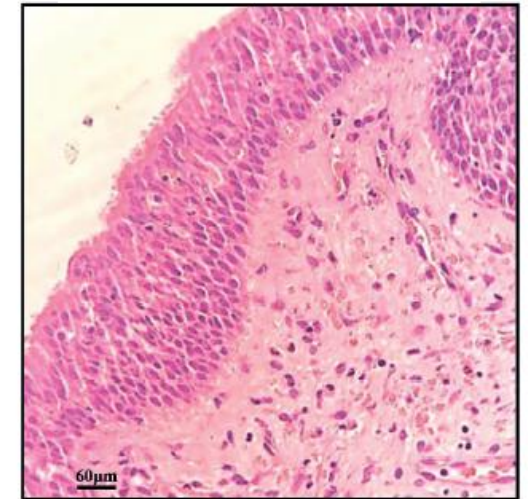
Effect of anti-IL-5 therapy treatment on goblet cell hyperplasia

Pre-treatment with anti-IL-5



Goblet cell hyperplasia (small arrows) prior to treatment

Post-treatment with anti-IL-5



Reduced goblet cell hyperplasia after treatment

Data presented are representative of a limited number of studies and require further validation to fully understand the mechanisms contributing to pathogenesis

Images: haematoxylin-eosin: magnification, ×40.

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin.

1. Matucci A, et al. *J Invest Allergol Clin Immunol*. 2026;36(4). doi: 10.18176/jiaci.1095.

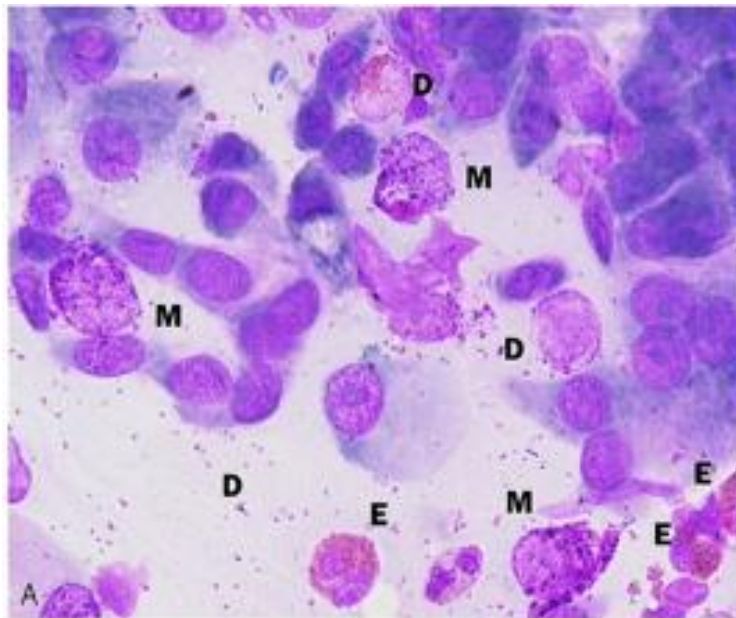
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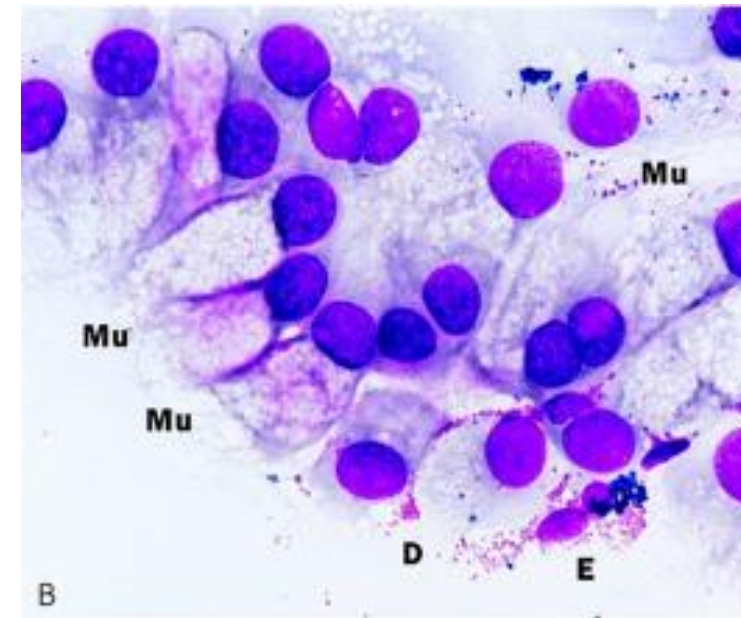
Targeting IL-4/IL-13 may help restore some aspects of epithelial health^{1,2}

Anti-IL-4R α therapy caused a reduction in the number of eosinophils and degranulation, an increase in goblet cells and the disappearance of mast cells²

Comparison of nasal cytology before and after 1 year of treatment²



Panel A:
Mixed eosinophil (E)
mast-cell (M) pattern
with massive
degranulation (D)



Panel B:
At 1 year of treatment,
nasal cytology shows
the presence of goblet
cells (Mu) and the
disappearance of
mast cells

Data presented are representative of a limited number of studies and require further validation to fully understand the mechanisms contributing to pathogenesis

MGG staining. Magnification 1000 $\times$.

CRSwNP, chronic rhinosinusitis with nasal polyps; E, Eosinophil; D, Degranulation; IL, interleukin; M, Mast cell; MMG, May Grunwald-Giemsa; Mu, Muciparous cell (goblet cell); Q2W, every two weeksT2, type 2.

1. Bachert C, et al. *Lancet*. 2019;394:1638–1650; 2. Gelardi M, et al. *Am J Otolaryngol*. 2024;45(4):104275.

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Targeting TSLP may help to restore some aspects of epithelial health¹

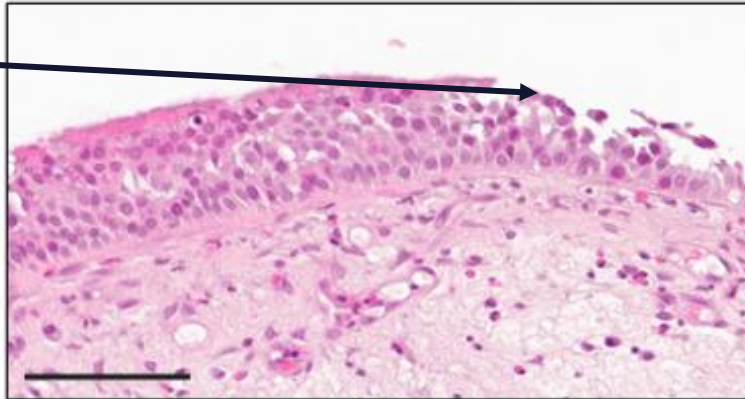
Blocking TSLP has been found to reduce eosinophils, FeNO and IgE versus placebo¹

Baseline

Week 52 of tezepelumab (EoT)

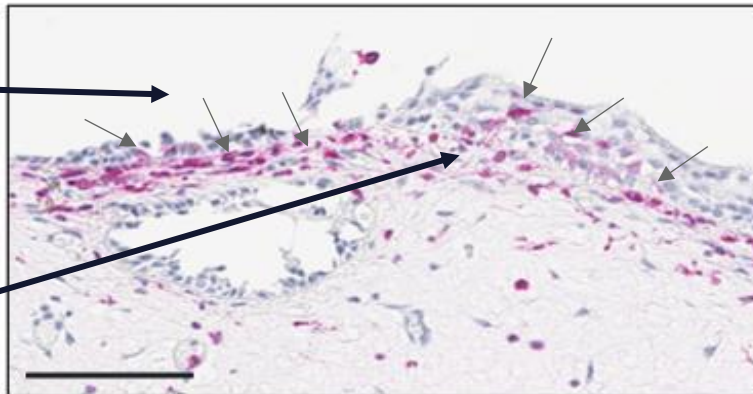
Patchy airway
epithelial
damage

H&E



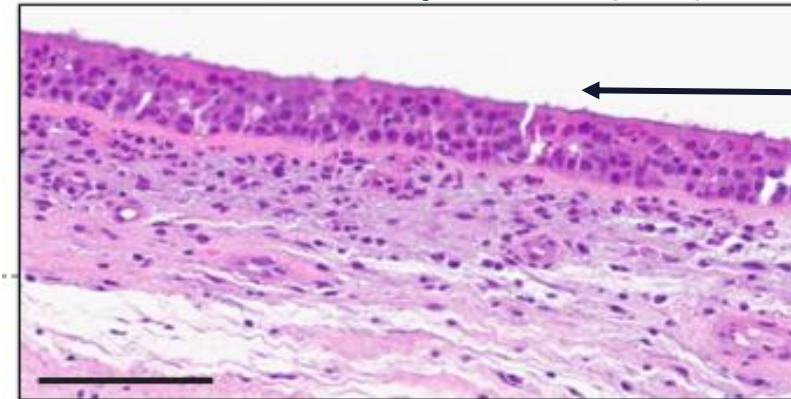
Large area of
epithelial
denudation

NP EDN

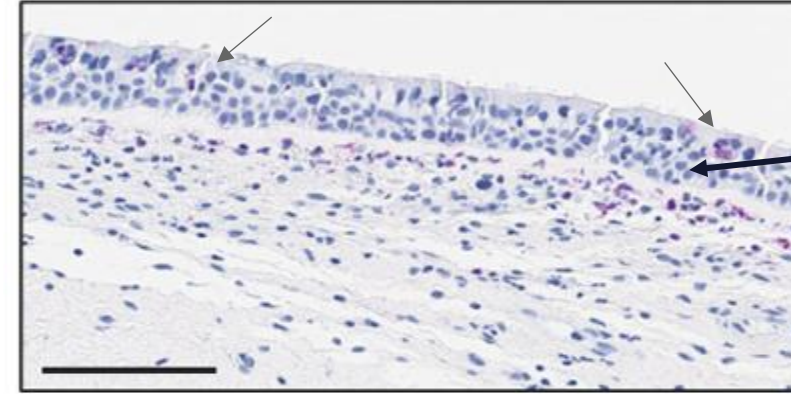


Area with partial
denudation (basal
cell layer present)

Lack of patchy
epithelium and
denudation



Improved
epithelial
integrity



Small arrows point to EDN

Representative images from one tezepelumab-treated patient at baseline and at EoT; the bar in the lower left of the images is equal to 100 μ M.

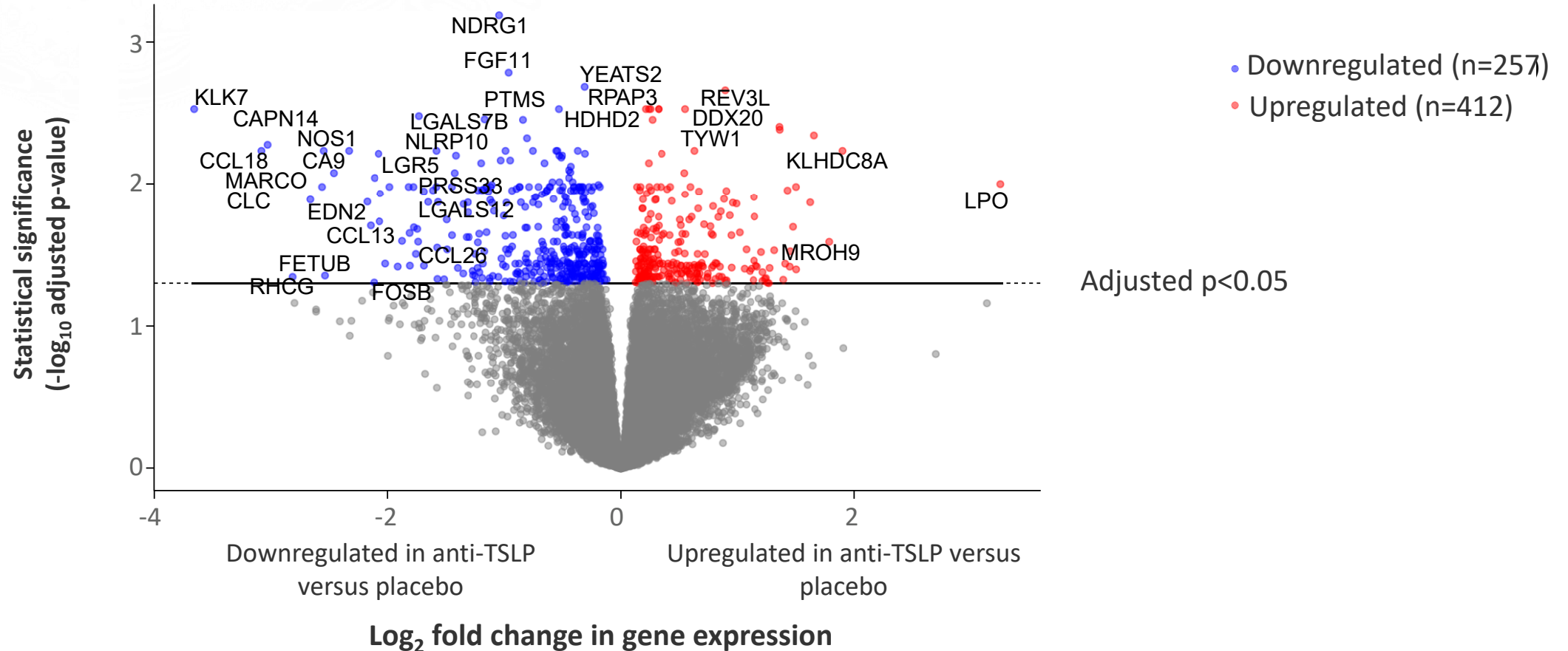
CRSwNP, chronic rhinosinusitis with nasal polyps; EDN, eosinophil-derived neurotoxin; EoT, end of treatment; H&E, haematoxylin and eosin; IgE, immunoglobulin E; NP, nasal polyp; TSLP, thymic stromal lymphopoietin.

1. Lipworth BJ, et al. ERS, Amsterdam, 27 September–1 October 2025. OA2336.

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Further analysis shows that targeting TSLP impacts broad gene expression pathways in nasal polyp tissue¹



These data suggest that targeting TSLP influences multiple biological pathways at the tissue level

Refer to Lipworth BJ, et al. AAAAI, Philadelphia, 27 February–2 March 2026. Poster 255.

TSLP, thymic stromal lymphopoietin.

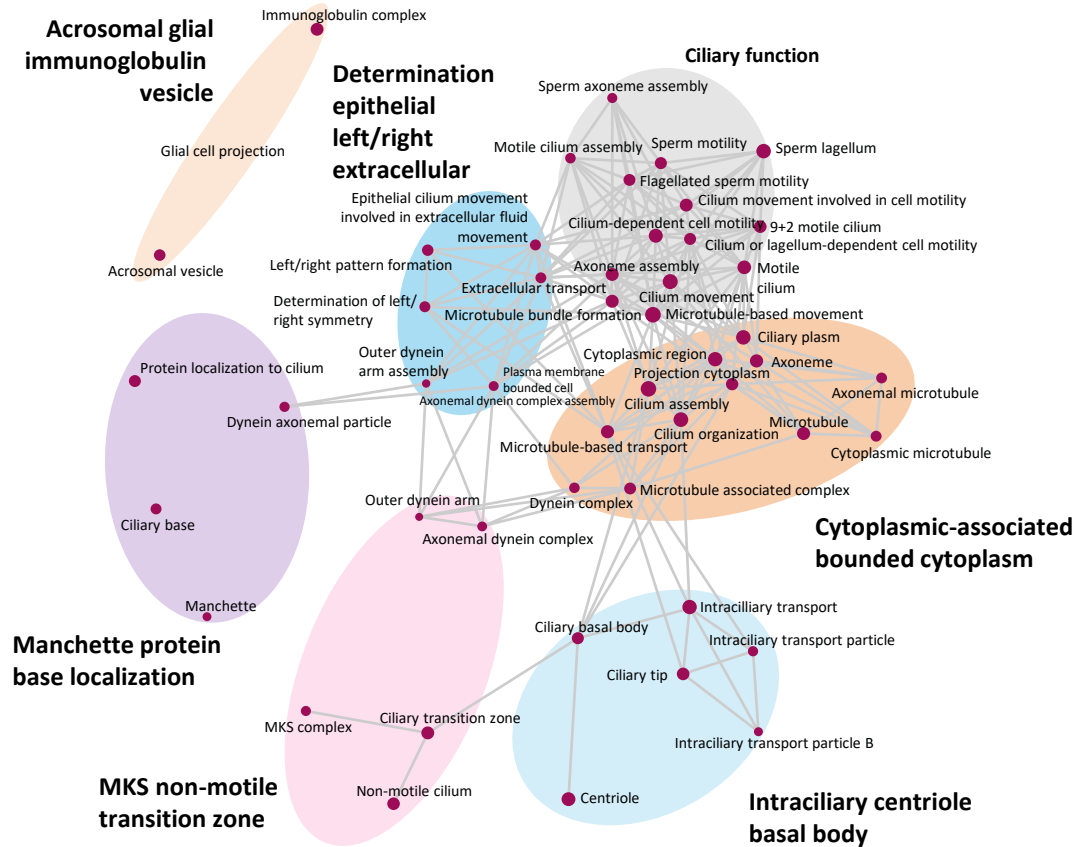
1. Lipworth BJ, et al. AAAAI, Philadelphia, 27 February–2 March 2026. Poster 255.

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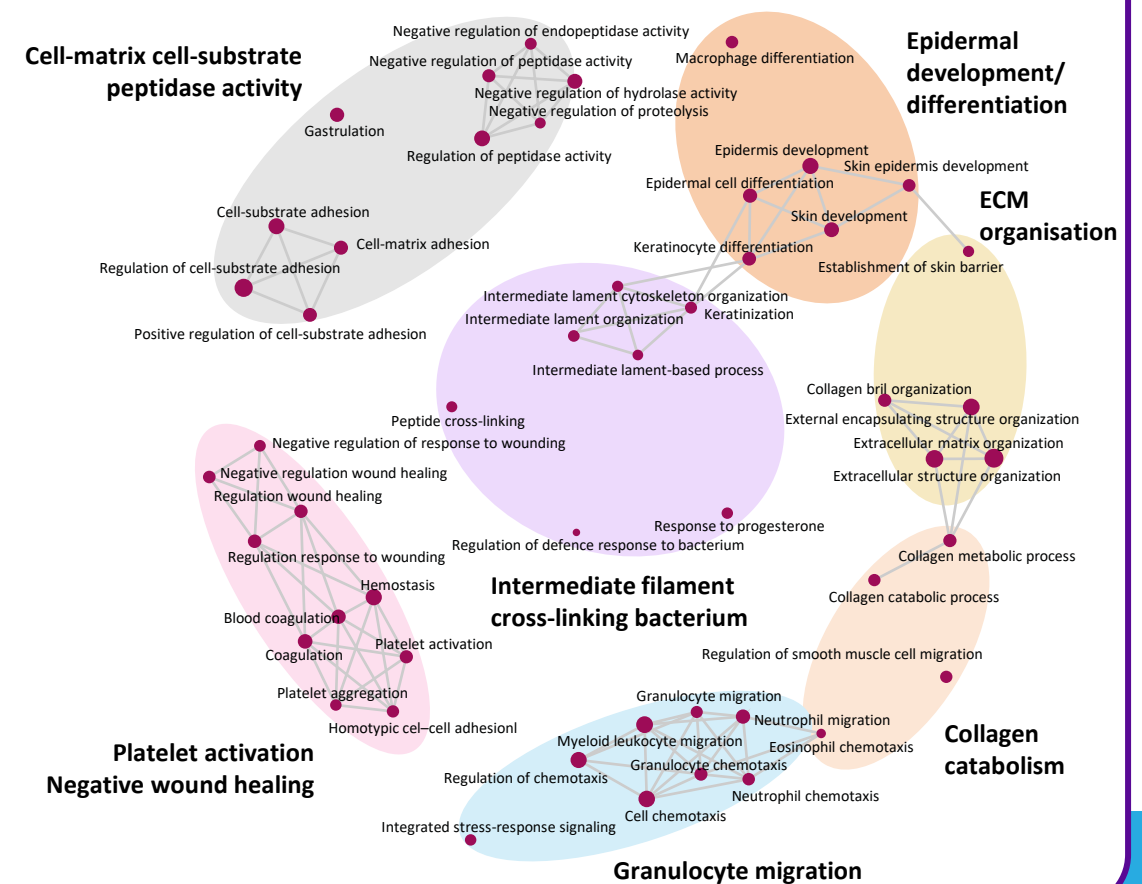
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Further analysis shows that targeting TSLP impacts broad gene expression pathways in nasal polyp tissue¹

Pathways upregulated with anti-TSLP versus placebo



Pathways downregulated with anti-TSLP versus placebo



Refer to Lipworth BJ, et al. AAAAI, Philadelphia, 27 February–2 March 2026. Poster 255.

ECM, extracellular matrix; MKS, Meckel-Gruber syndrome.

1. Lipworth BJ, et al. AAAAI, Philadelphia, 27 February–2 March 2026. Poster 255.

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Section summary



The use of biologics has transformed our understanding of airway disease biology and the treatment goals in asthma and CRSwNP^{1,2}



Remission is emerging as an aspirational treatment goal in asthma and CRSwNP^{3,4}



Achieving remission requires strategies that address the cycle of persistent inflammation and restore epithelial health and function^{5,6}



Emerging evidence indicates that inhibition of epithelial cytokines improves/modulates underlying gene expression associated with improvement in epithelial health and function^{7,8}

CRSwNP, chronic rhinosinusitis with nasal polyps.

1. Lommatzsch M, et al. *Lancet*. 2022;399(10335):1664–8; 2. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4(4):565–72; 3. Menzies-Gow A, et al. *J Allergy Clin Immunol*. 2020;145(3):757–65; 4. Fokkens WJ, et al. *Rhinology*. 2024;62(3):287–98; 5. Menzies-Gow A, et al. *Respir Res*. 2020;21(1):268; 6. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24(8):777–92; 7. Lipworth BJ, et al. ERS, Amsterdam, 27 September–1 October 2025. OA2336; 8. Lipworth BJ, et al. AAAAI, Philadelphia, 27 February–2 March 2026. Poster 255.

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