Bi- and Tri-Specific Antibodies
The Wave of the Future in Severe Asthma?

Ayobami Akenroye, MBChB MPH PhD
Assistant Professor of Medicine,
Harvard Medical School
PI, Drug U.S.E. Lab
Division of Allergy and Clinical Immunology
Channing Division of Network Medicine
Brigham and Women's Hospital

COI

- I have no relevant conflicts to disclose

Objectives

- Aimed towards evidence and potential future uses of:
  Targeting two or more pathways in asthma treatment
  - Case for this approach
  - Biologics in the pipeline

Why this question matters

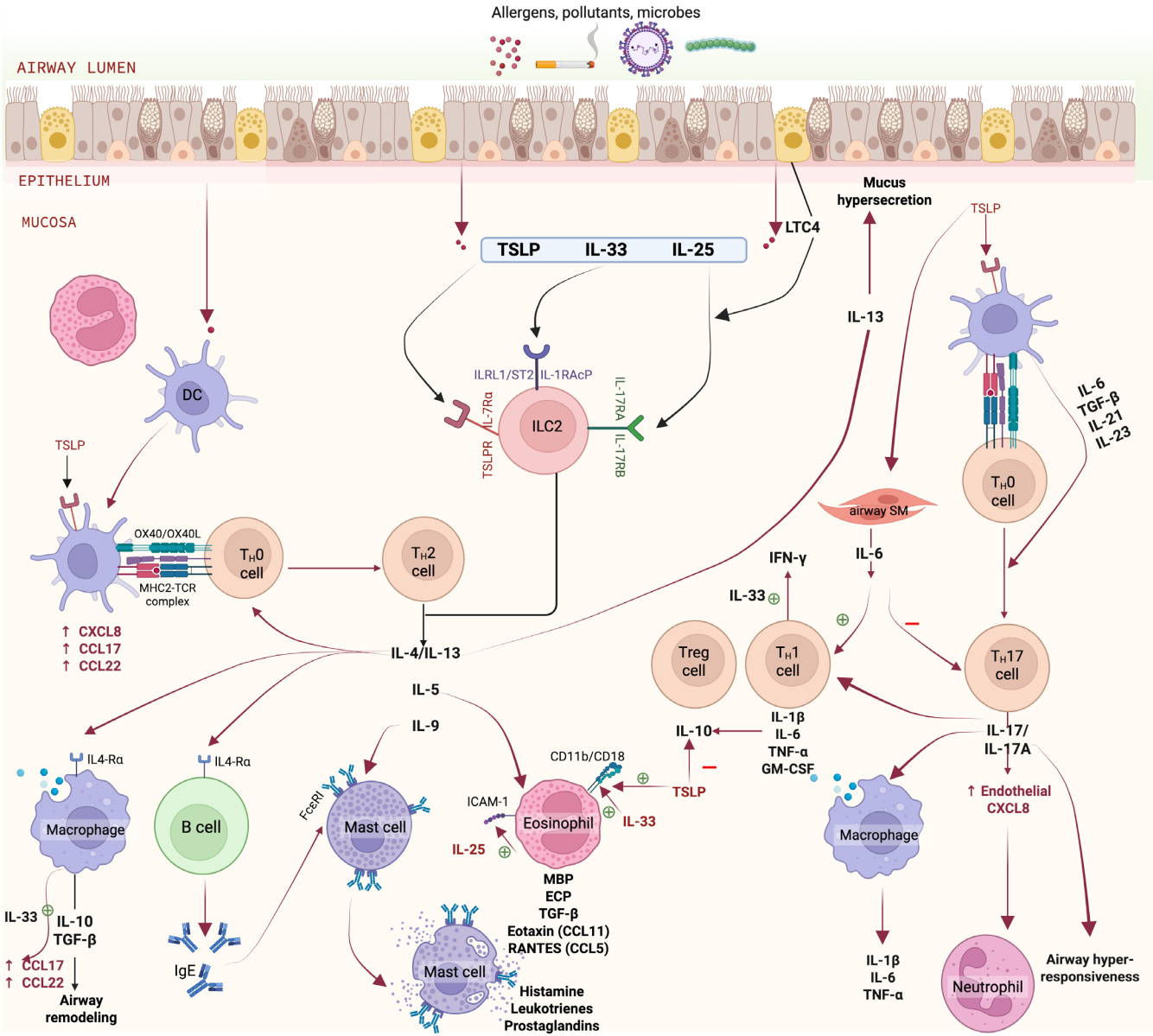
The unmet need persists even in the biologic era

- Biologics have transformed severe asthma, especially for T2-high disease
- Because current biologics work well, but not well enough for everyone.
- Many patients remain partial responders, need switching, or belong to multiple biomarker-defined categories or phenotypes.

---Asthma phenotypes are not mutually exclusive

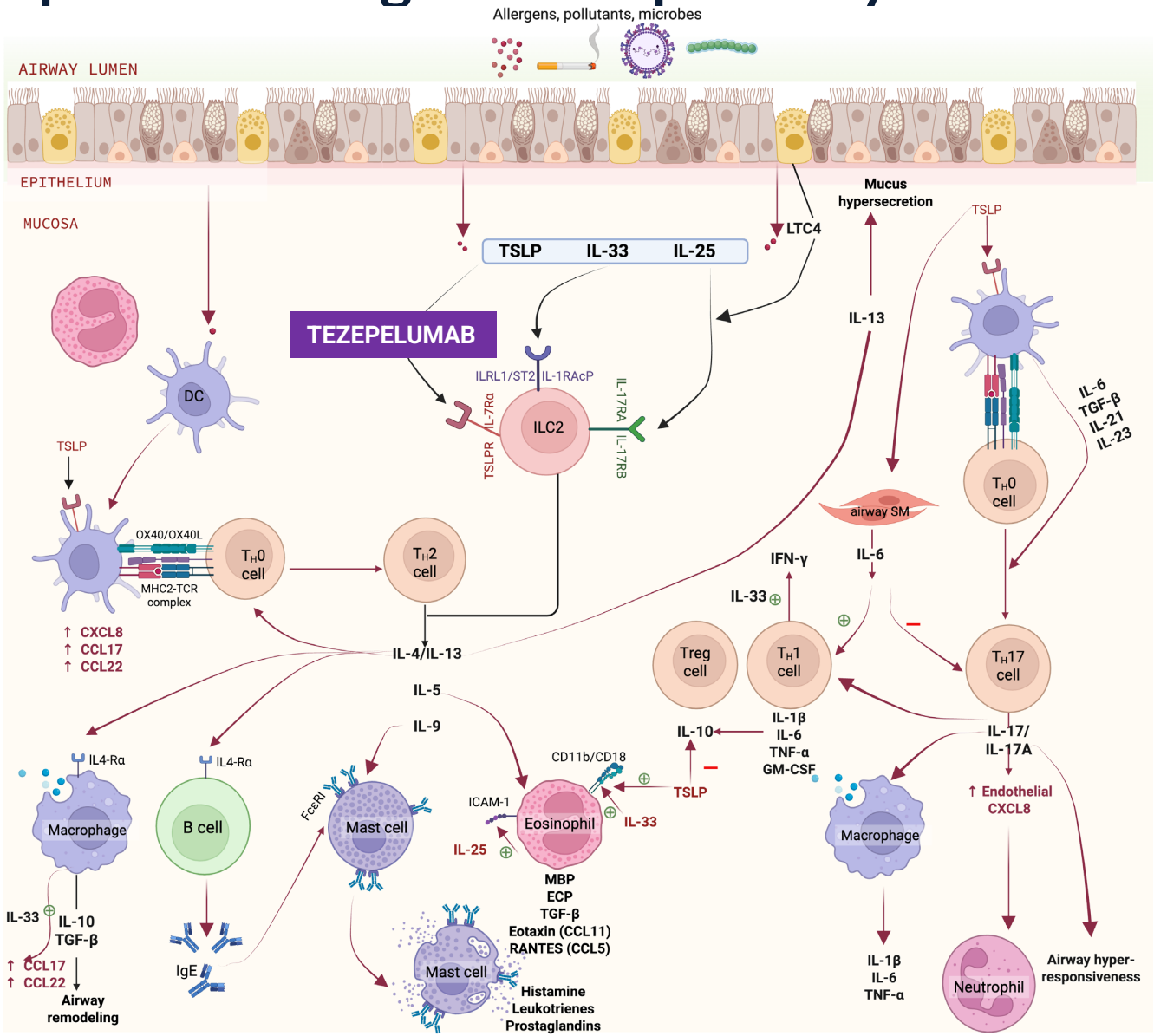
---Multiple pathways are dysregulated in asthma

Multiple pathways are dysregulated in asthma



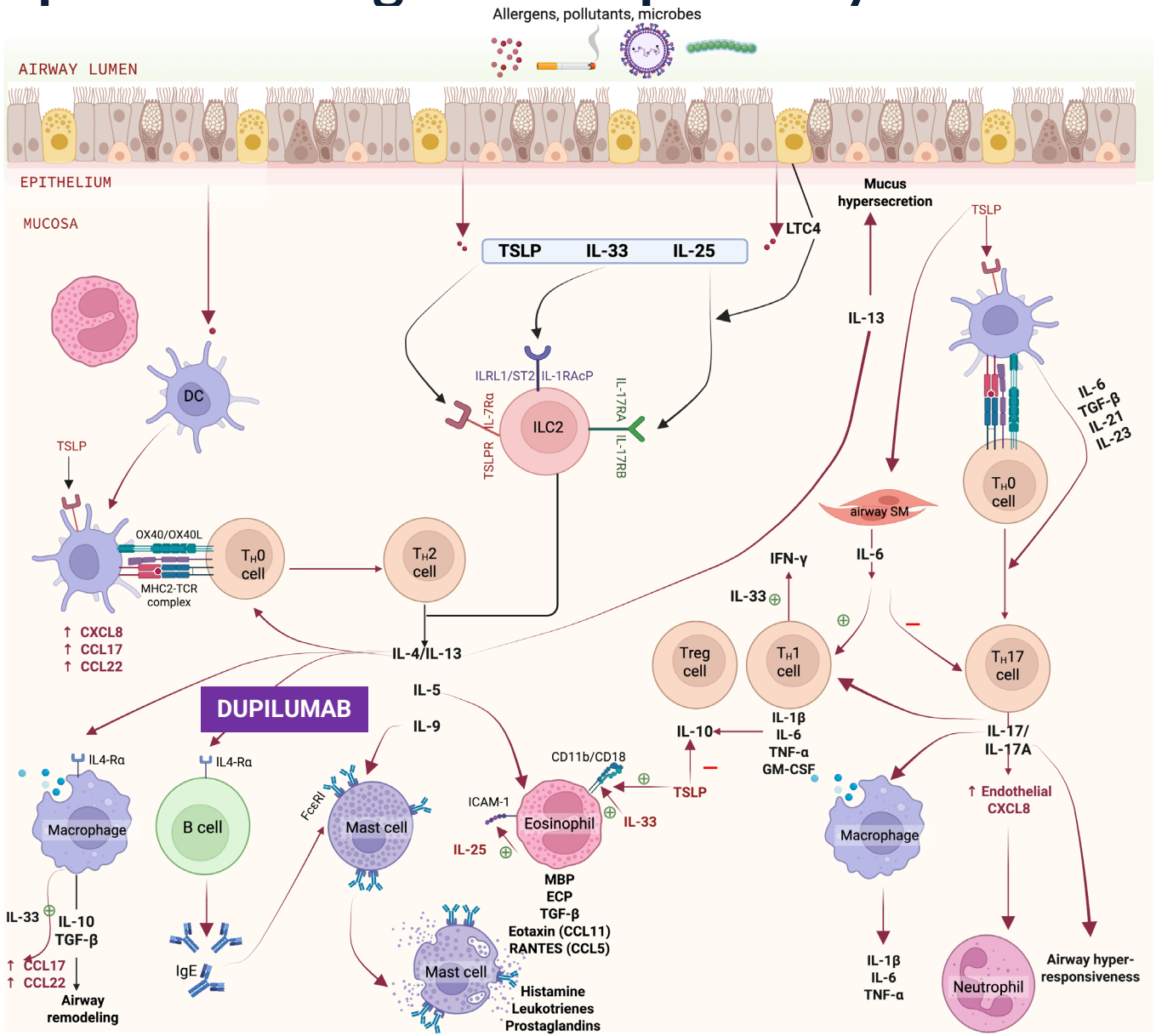
Adopted from: Akenroye, Boyce, & Kita, JACI 2025

Various therapies now target these pathways



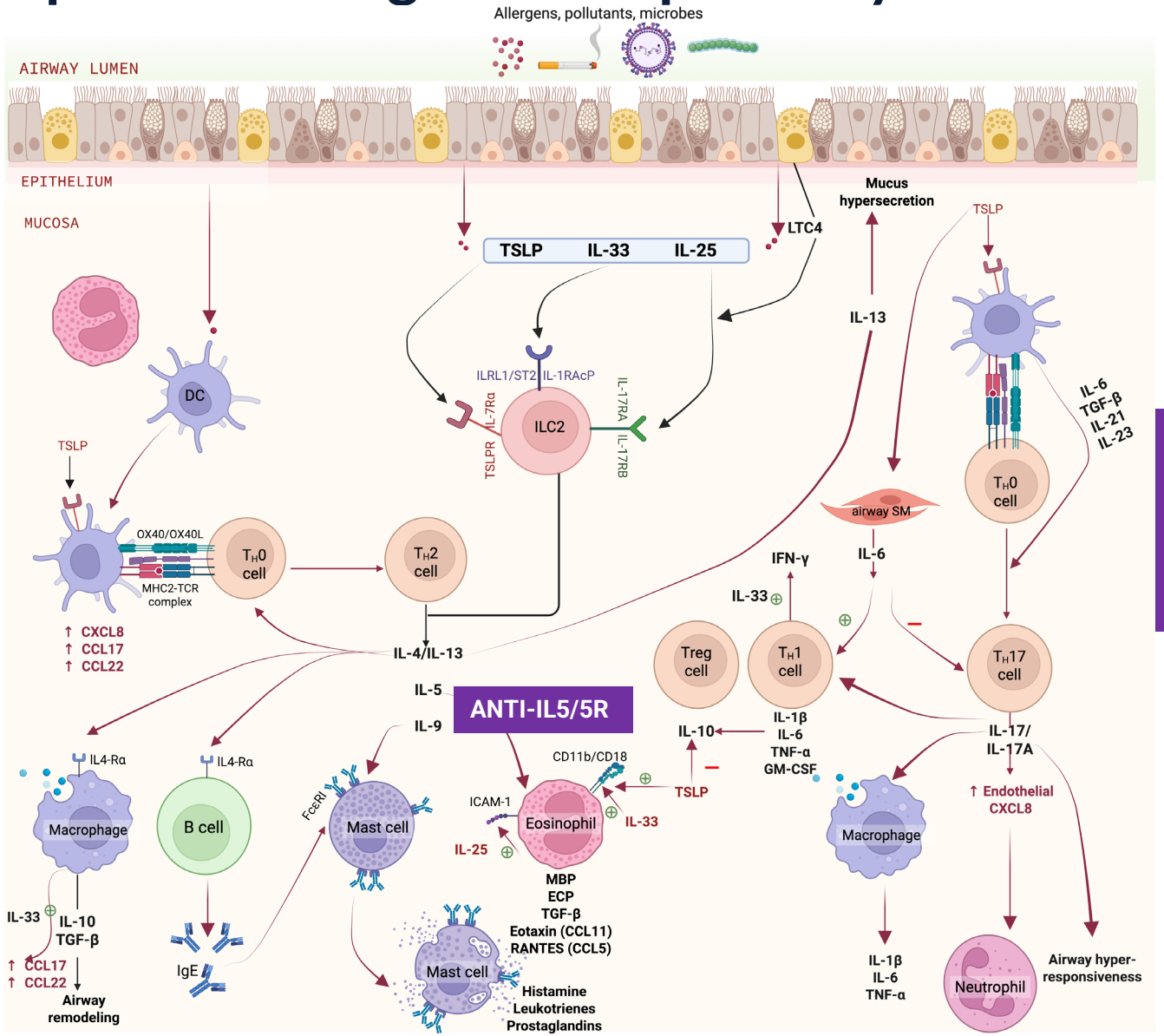
Adopted from: Akenroye, Boyce, & Kita, JACI 2025

Various therapies now target these pathways



Adopted from: Akenroye, Boyce, & Kita, JACI 2025

Various therapies now target these pathways

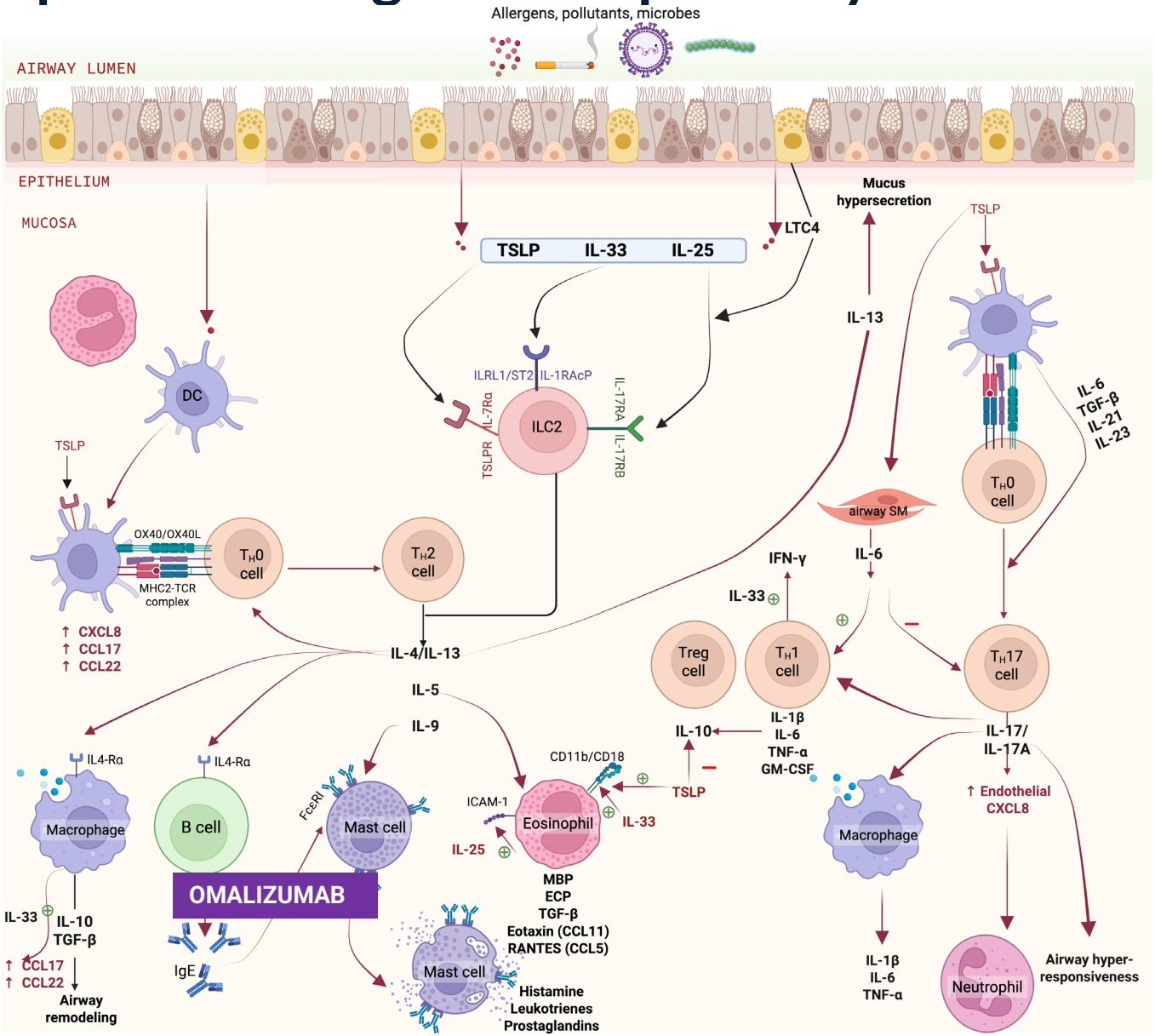


ANTI-IL5
MEPOLIZUMAB
RESLIZUMAB
DEPEMOKIMAB

ANTI-IL5R
BENRALIZUMAB

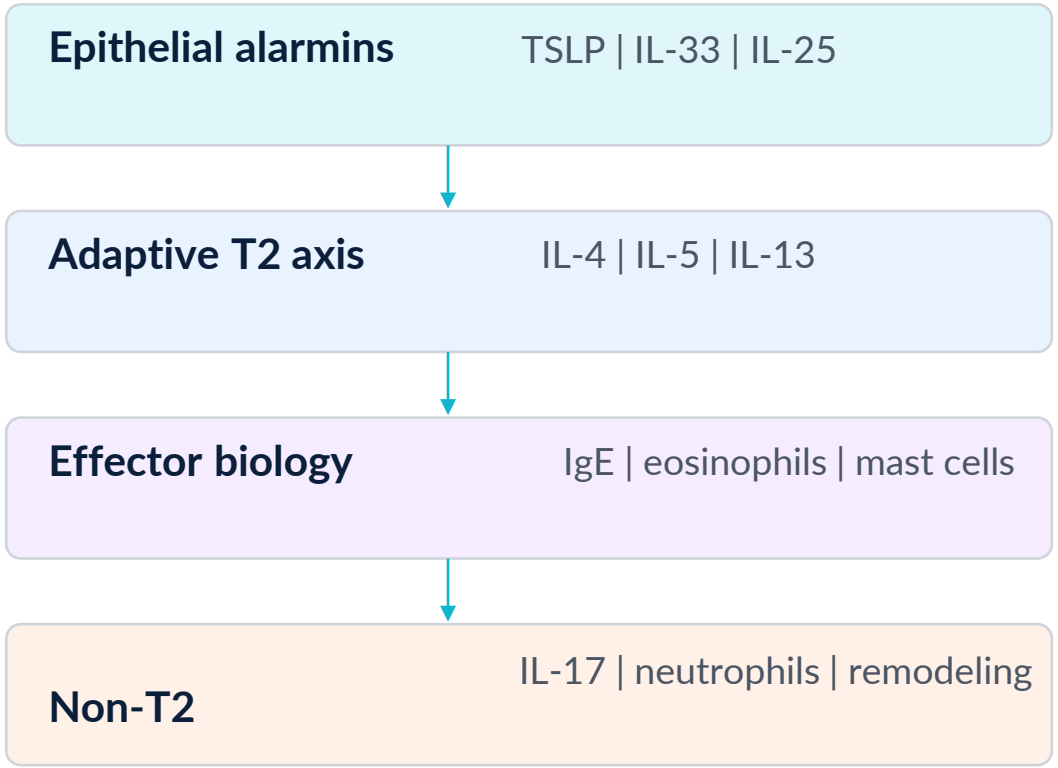
Adopted from: Akenroye, Boyce, & Kita, JACI 2025

Various therapies now target these pathways



Adopted from: Akenroye, Boyce, & Kita, JACI 2025

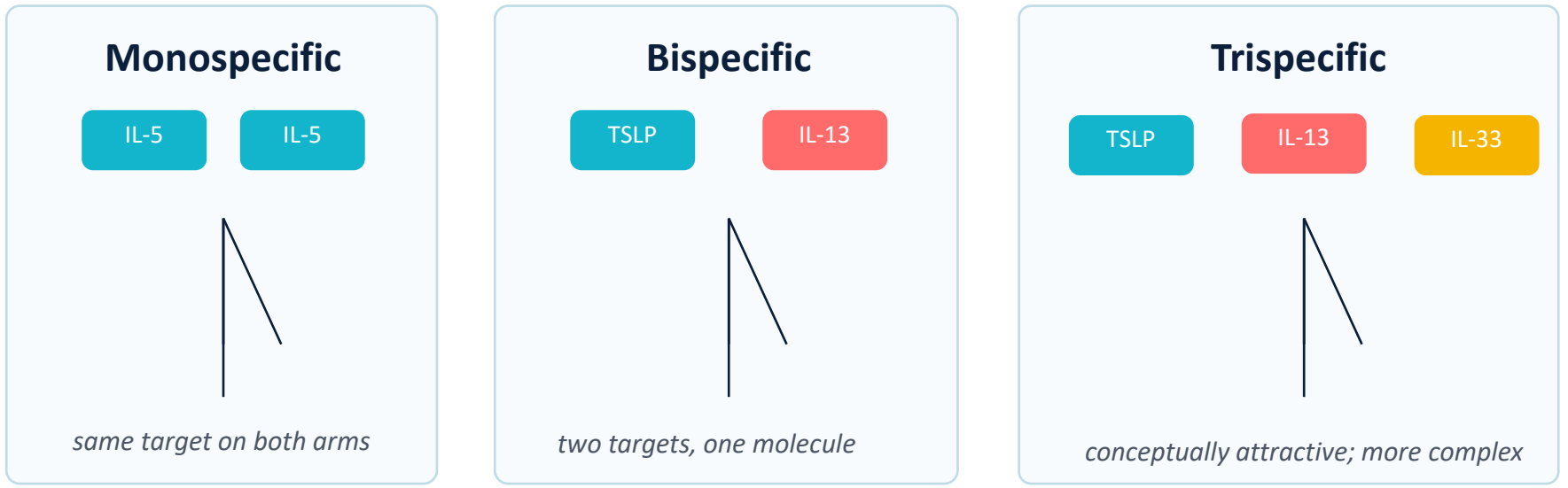
What is the ceiling of single-target therapy?



- Blocking a single pathway may leave **biologic redundancy** intact.
- Insurance companies rarely approve two biologics **except** eligible for different indications
- Sequential biologic trials are slow, expensive, and frustrating for patients and clinicians.
- A rational multispecific should target either: **upstream + downstream biology**, or two complementary inflammatory axes.

Brusselle, Koppelman, NEJM Jan 2022
Seluk et al, Annals A/I, Jan 2025
Akenroye, Boyce, Kita, JAC 2025l

What do we mean by bi- and tri-specific?



- A **bispecific** is one engineered molecule that binds two distinct targets; a **trispecific** binds three.

The **potential advantages:**

- No need to use two different biologics. One PK profile, lower administration burden.

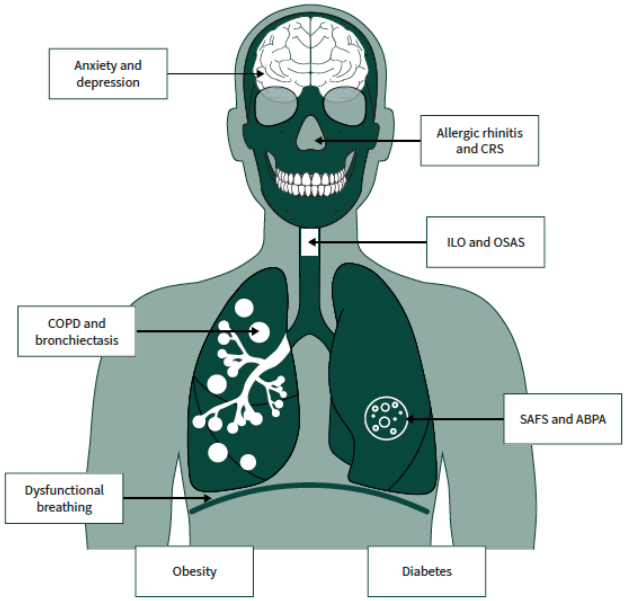
The **trade-off** is:

- need to choose the right target pair, manufacturing complexity, and immunogenicity.

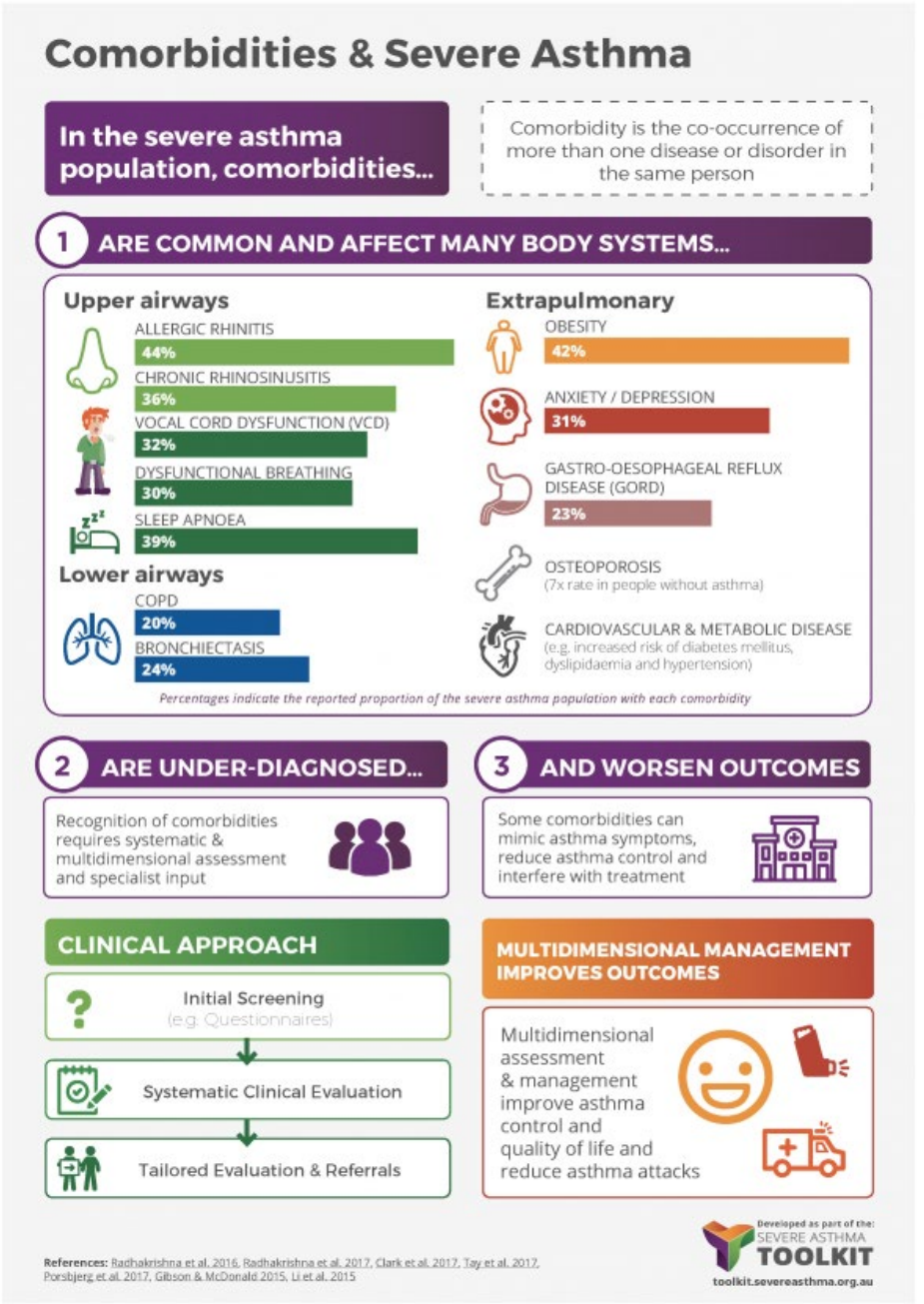
Carter & Rajpal, Cell, 2022
Kassem, Lam, & Khalili, RSC Pharm. Jul 2025

Why this question matters

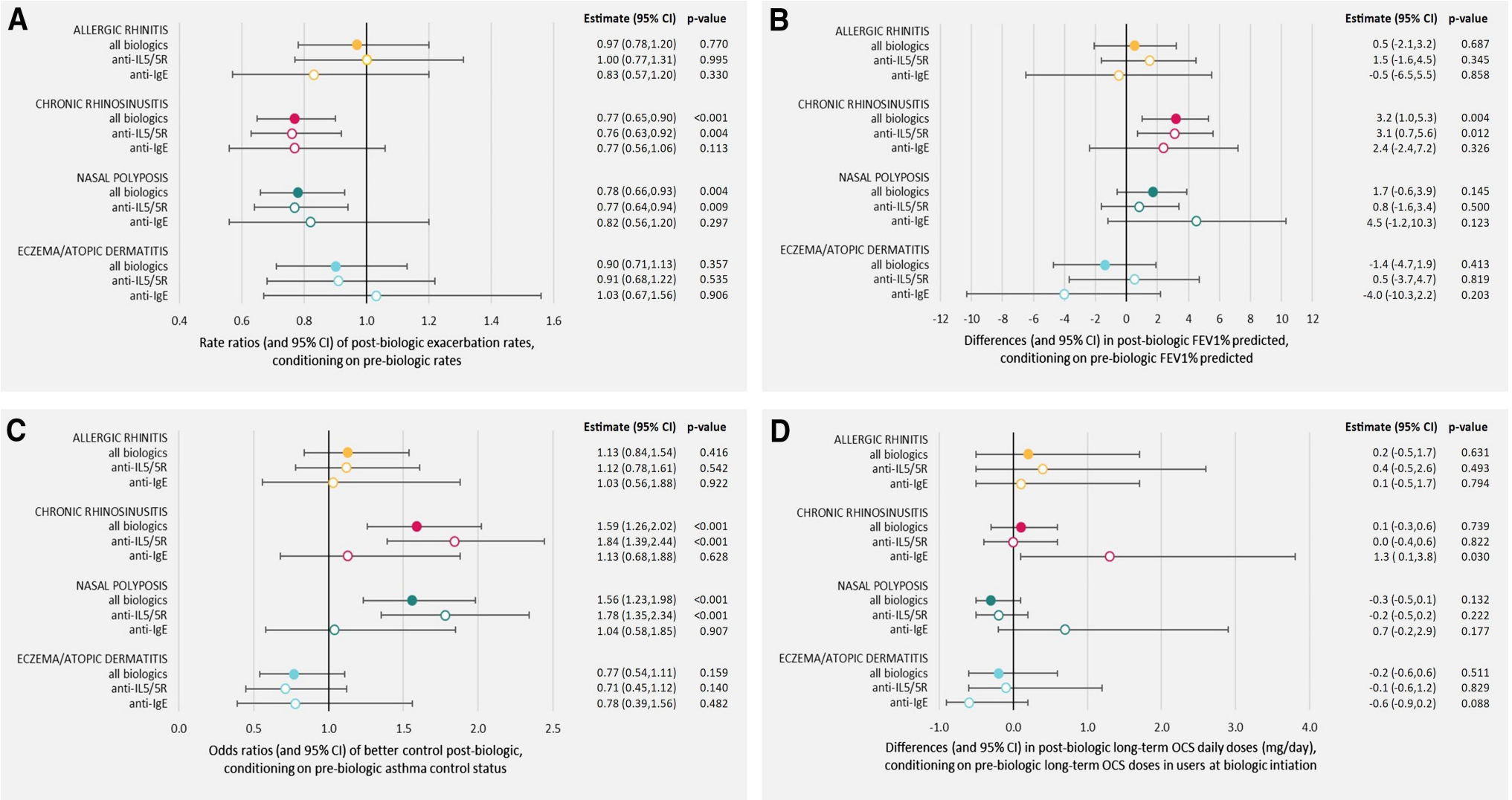
- Airway inflammation is often **complex**
- Dysregulated pathways **overlap** and/or **compensate** for each other.



- Most asthma patients have another **comorbidity** that could be targeted simultaneously----both T2-high and non-T2 comorbidities



These comorbidities are often modifiers of biologics' efficacy



Am J Respir Crit Care Med, Volume 209, Issue 3, February 2024, Pages 262–272, https://doi.org/10.1164/rccm.202305-0808OC

State of the pipeline:
True multispecifics in asthma or related conditions

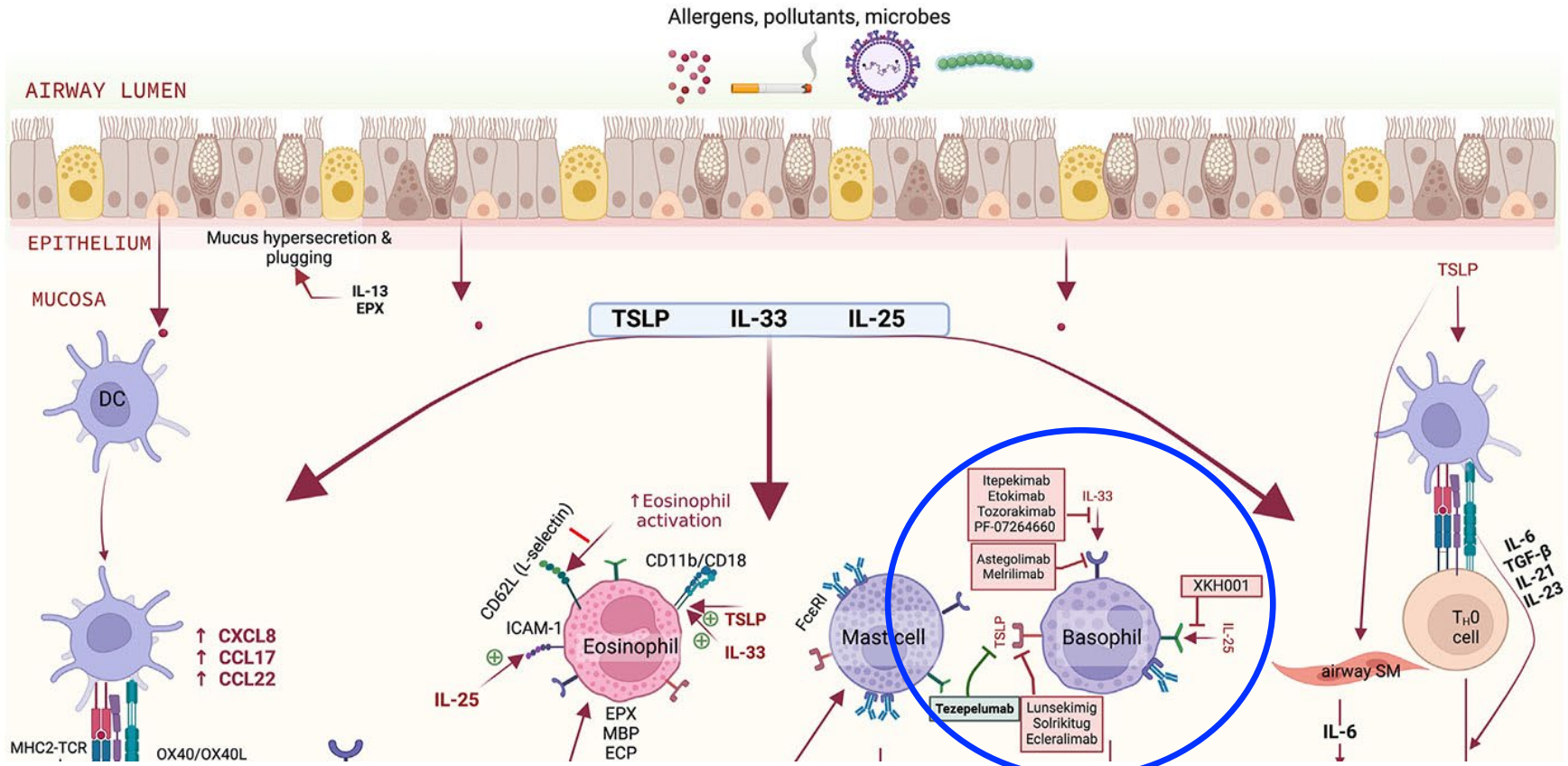
Program	Targets	Company	Asthma status / trial	Comment
Lunsekimig	TSLP × IL-13	Sanofi	Phase 2b AIRCULES NCT06102005; Phase 2 AIRLYMPUS NCT06676319	Lead clinical asthma bispecific; eos-COPD, CRSwNP
IL-13 × TSLP bsAb	IL-13 × TSLP	Tavotek Biotherapeutics	Phase 1 first patient dosed Mar 2026	Early, but directly relevant asthma program (AD)
BITS7201A	IL-13 × IL-17	Genentech/Roche	Phase 1 completed 2018 (NCT02748642)	Mixed T2/T17 concept; high ADA limited development
HXN-1013	TSLP × IL-33	Helixon Therapeutics	Preclinical / conference abstract	Dual-alarmin concept, Asthma/COPD
ZW1528	IL-4Rα × IL-33	Zymeworks	Preclinical respiratory program	COPD
AK139	IL-4Rα × ST2	Akeso	Phase 2 NCT07436221	7 indications: COPD, asthma, CSU, AR, CRSwNP, AD, and PN
PF-07275315	anti–IL-4/13/33 and anti–IL-4/13/TSLP	Pfizer	Trispecifics; NCT05995964	AD

Why the TSLP + IL-13 pairing is so attractive

Trigger allergen/virus/irritant → **TSLP alarmin** → **Th2 / ILC2 activation** → **IL-13 effector** → **Mucus, AHR, FeNO, dysfunction**

upstream block

downstream block



Akenroye, Boyce, & Kita, JACI 2025

15

Clinical spotlight: Lunsekimig is the lead asthma bispecific

What it is

- Nanobody VHH construct targeting TSLP and IL-13.
- Designed to pair an alarmin block with a downstream T2 effector block.
- First-in-human study in healthy volunteers showed acceptable PK/PD and supported further development.

Why people care

- In mild-to-moderate asthma, a single dose was well tolerated and significantly reduced FeNO and blood T2 biomarkers.
- Numerical lung-function improvements were seen, especially in participants with worse baseline function.

Where it is now

- AIRCULES: phase 2b dose-ranging trial in moderate-to-severe asthma (NCT06102005).
- AIRLYMPUS: phase 2 study in high-risk asthma initiated in Q4 2024 (NCT06676319).
- Sanofi said the AIRCULES readout is anticipated in 2026.

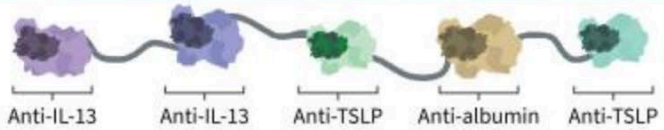
Clinical takeaway

- It is the closest to clinical translation
- Will likely be the benchmark against which newer respiratory bispecifics will be judged.

Lunsekimig (anti-TSLP/IL-13)

A. A first-in-human, single and multiple dose study of lunsekimig, a novel anti-TSLP/anti-IL-13 NANOBODY® compound, in healthy volunteers
B. Phase 1B

Lunsekimig, a novel bispecific NANOBODY construct, antagonises the function of two cytokines, TSLP and IL-13



- NANOBODY building blocks are highly stable, high-affinity (nM–pM) variable domains, ~10 times smaller than monoclonal antibodies, that can be fused together in a mix-and-match manner to generate multivalent, multispecific molecules

Phase 1b, single-dose, randomised (2:1), double-blind, proof-of-mechanism study

Participants
- 36 adults aged 18–60 years with controlled mild-to-moderate asthma for ≥12 months as defined in the GINA 2020 guidelines
- Elevated F_{ENO} (≥25 ppb)
- FEV_1 ≥60% predicted
- ICS-naive or on stable treatment (≥3 months) with low- or medium-dose ICS

Two sites
- Germany
- UK

Single subcutaneous injection of lunsekimig 400 mg or placebo

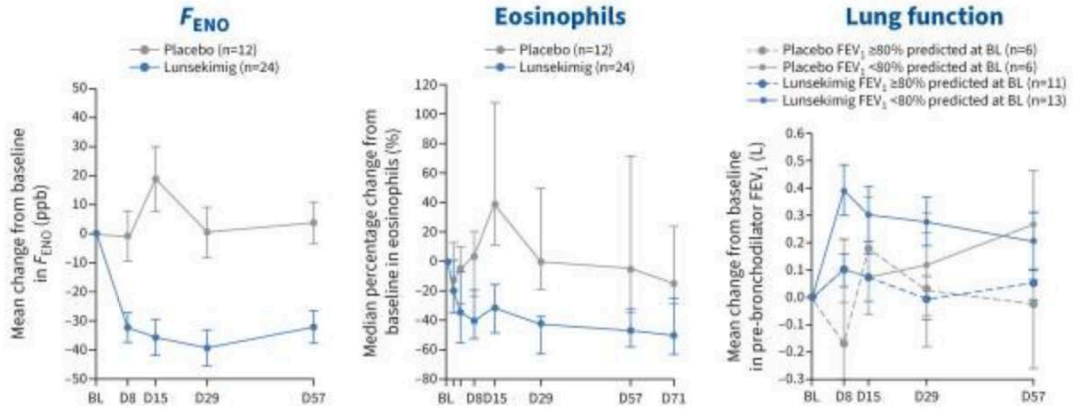
Screening	Admission	Discharge					Visits					EOS visit
D–28 to D–2	D–1	D1	D2	D3	D4	D5	D6	D8	D15	D29	D57	D71

- **Primary end-point**: Safety and tolerability through day 71
- **Main pharmacodynamic secondary end-point**: Change from baseline in F_{ENO} at day 29

Results

Safety
- A single dose of lunsekimig was well tolerated, with no serious TEAEs
- TEAEs were reported in 75% of participants in both treatment groups; all were mild or moderate in severity

Most common TEAEs (>10%) (n (%))	Lunsekimig 400 mg (n=24)	Placebo (n=12)
Nasopharyngitis	7 (29.2)	4 (33.3)
Headache	5 (20.8)	4 (33.3)
Injection site reaction	5 (20.8)	0



- Lunsekimig reduced F_{ENO}
- Lunsekimig reduced the type 2 asthma blood biomarkers eosinophils, IL-5, eotaxin-3/CCL26, TARC/CCL17 and IgE
- Lunsekimig improved lung function and small airway dysfunction in those with impaired lung function at baseline

Clinical Translational Sci, Volume: 17, Issue: 6, First published: 24 June 2024, DOI: (10.1111/cts.13864)
Eur Respir J. 2025 Apr 24;65(4):2401461. doi: 10.1183/13993003.01461-2024

CAUTION: The Itepekimab story

- Would/Should all combination therapy work?

Anti IL-33
1. Wechsler et al. NEJM Oct 2021

Phase 2 study

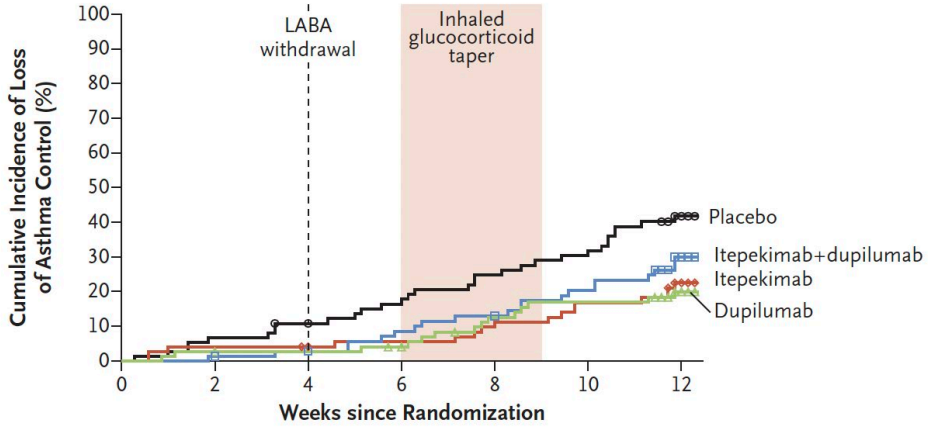
- Itepekimab in moderate to severe asthma
- Randomized to
  - Itepekimab 300 mg SC biweekly x 12 weeks
  - Itepekimab 300 mg + Dupilumab 300 mg
  - Dupilumab 300 mg
  - Placebo

- 18 to 70-year-old on medium to high dose ICS + LABA use at baseline x 3 months
  - Patients with a wide range of eosinophil counts at baseline
    - Median eosinophil in entire population 280 cells per microliter
    - Median IgE: 161 IU/ml, FeNO 20 ppb
  - LABA stopped at week 4
  - ICS tapered off from weeks 6-9

Anti IL-33
1. Wechsler et al. NEJM Oct 2021

Itepekimab (and dupilumab) was effective in improving exacerbations

- Combination of itepekimab + dupilumab was not significantly different from placebo

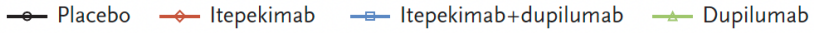


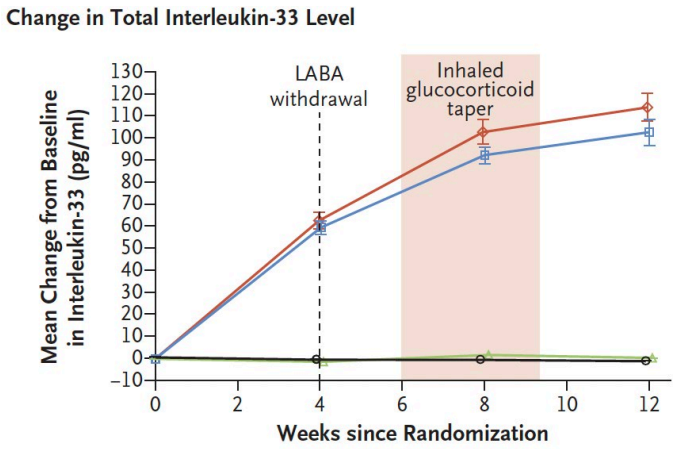
No. of Patients							
Placebo	74	69	65	60	54	50	31
Itepekimab	73	70	69	67	64	59	48
Itepekimab+dupilumab	74	73	68	63	60	54	32
Dupilumab	74	72	71	69	61	58	43

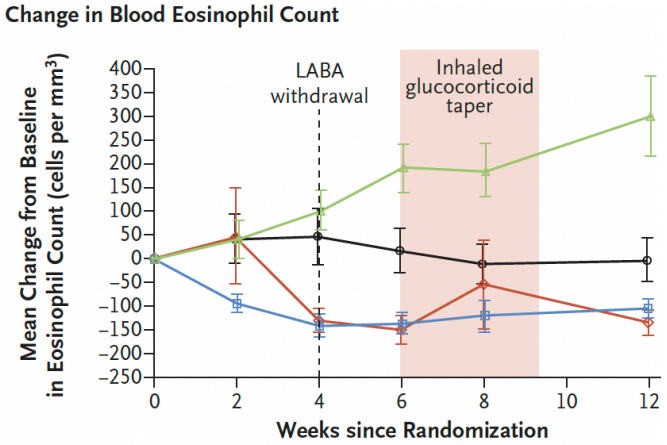
Take-away point.
Individually, an anti-IL-33 and anti-IL4/13 improved asthma-related outcomes. However, they were not effective when used in combination.

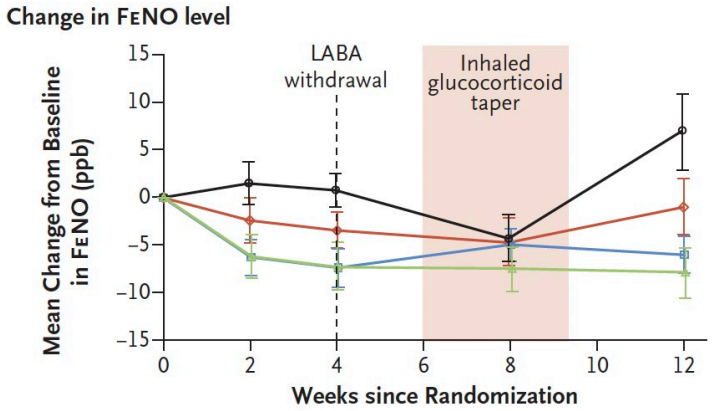
Anti IL-33

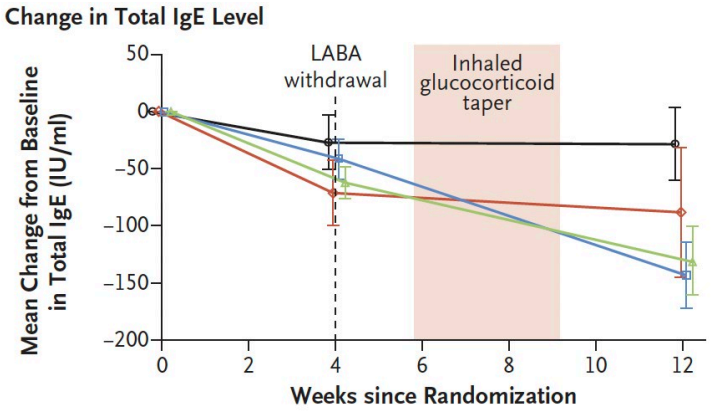
1. Wechsler et al. NEJM Oct 2021











Take-away points.
Itepekimab increased IL-33 levels (sST2 was stable), decreased eosinophil count, FeNO, and IgE levels.

Anti IL-33
1. Wechsler et al. NEJM Oct 2021

End Point	Placebo (N=74)	Itepekimab (N=73)	Itepekimab plus Dupilumab (N=74)	Dupilumab (N=74)
Secondary end points				
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.05	0.10±0.05	0.06±0.05	0.12±0.05
Least-squares mean difference vs. placebo (95% CI)		0.14 (0.01 to 0.27)	0.10 (−0.03 to 0.23)	0.16 (0.03 to 0.29)
Patients with baseline eosinophils <300 cells per mm^3 — no.	19	32	30	31
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	0.03±0.07	0.06±0.06	0.02±0.06	0.02±0.06
Least-squares mean difference vs. placebo (95% CI)		0.03 (−0.14 to 0.20)	−0.01 (−0.18 to 0.16)	−0.01 (−0.18 to 0.15)
Patients with baseline eosinophils ≥300 cells per mm^3 — no.	22	26	19	25
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.07	0.18±0.07	0.15±0.08	0.30±0.08
Least-squares mean difference vs. placebo (95% CI)		0.22 (0.02 to 0.41)	0.19 (−0.01 to 0.40)	0.34 (0.14 to 0.54)
Other end points				
Change in ACQ-5 score from baseline to wk 12	−0.54±0.12	−0.96±0.11	−0.86±0.11	−1.00±0.11
Least-squares mean difference vs. placebo (95% CI)		−0.42 (−0.73 to −0.12)	−0.32 (−0.63 to −0.01)	−0.46 (−0.76 to −0.15)

Take-away points.
Itepekimab improved ACQ-5 and led to greater improvements in prebronchodilator FEV1 in patients with eosinophils ≥300 cells per microliter.

Why trispecifics are attractive — & why they are not here yet

The attraction

- In theory, a trispecific could hit an upstream alarmin plus two effectors — for example TSLP + IL-13 + IL-33, or IL-4/13 + IL-33 via an IL-4Rα-containing design.
- That could better match the messy biology of severe asthma and reduce the need for sequential switching.

The barrier

- Every added specificity increases engineering, stability, CMC, and safety complexity.
- The clinic usually moves one step behind the idea: first validate the pair, then think about the trio.

My pragmatic read

- Near term: bispecifics are the realistic next wave in asthma.
- Mid term: trispecifics may emerge first in preclinical respiratory platforms or adjacent immune diseases---AD now

Translation test

Does the extra target meaningfully improve outcomes more than it complicates the drug?

Potential advantages — and the main concerns

Why they could be better

- Broader pathway suppression
- One drug instead of a sequence of switches
- Potentially more robust biomarker suppression

Who might benefit most

- Mixed or overlapping inflammatory signatures
- Patients not fully captured by a single biomarker
- Patients needing simpler dosing logic

Key concerns

- Infection/host-defense trade-offs
- Immunogenicity and ADA risk
- Manufacturing and cost if complexity outweighs benefit

Clinical proof still needed

- Head-to-head vs best single biologic?
- Which biomarkers predict response?
- Can broader biology still remain safe long term?

How might these agents fit into real severe-asthma practice?

1 Today

Choose among validated single-target biologics using phenotype, biomarkers, exacerbations, steroid burden, and comorbidity profile.

2 Near future

Use a bispecific when biology is overlapping, the response to a single biologic is partial, or one mechanism does not adequately explain the disease.

3 Later

Reserve trispecifics or broader immune modulators for highly selected endotypes (going beyond T2 vs nonT2) once proven effective

4 What will decide it

Not novelty alone: the winner will be the molecule that clearly improves exacerbations, function, steroid sparing, and practical use.

Take-home messages

- The biological rationale for multispecifics in severe asthma is strong
- Lunsekimig is the clearest current clinical leader among asthma bispecifics; Tavotek's IL-13 × TSLP program shows the space is still expanding.
- Broader immune regulation, rather than bi-specifics, may also compete for the same future treatment space.
- For now, bispecifics closer to clinical translation in asthma than trispecifics. However, the winning programs will need to prove not just elegant biology, but superior clinical value.

Biology Pipeline Practicality

Thank you!

https://druguselab.bwh.harvard.edu/
Email: aakenroye@bwh.harvard.edu