

Airway remodeling in Asthma

- Assessment and Treatments

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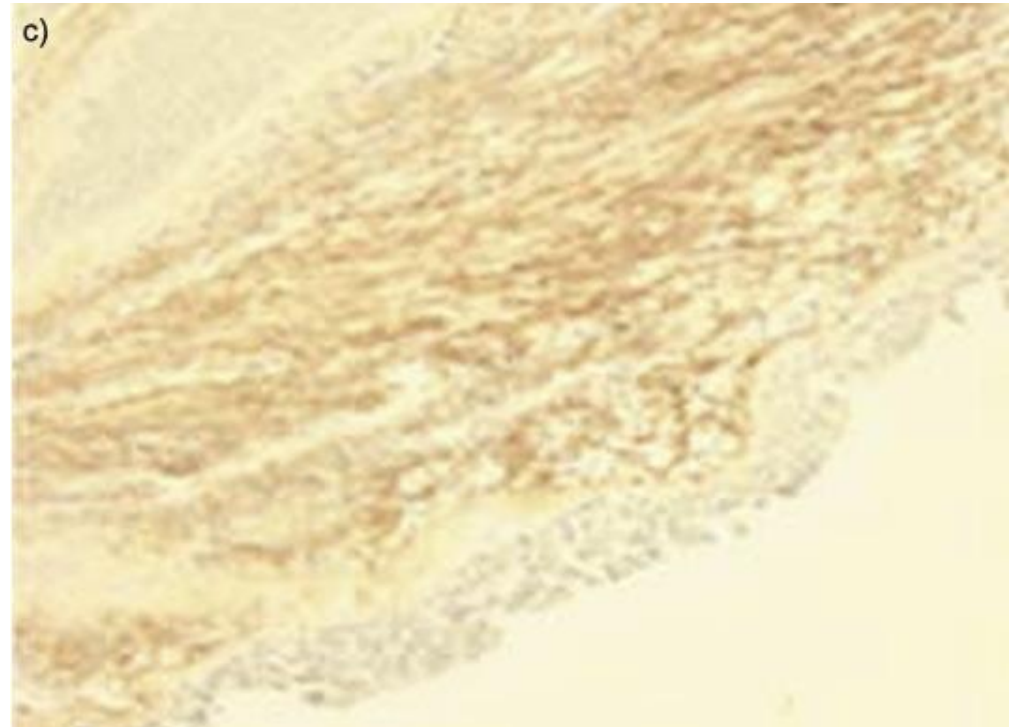
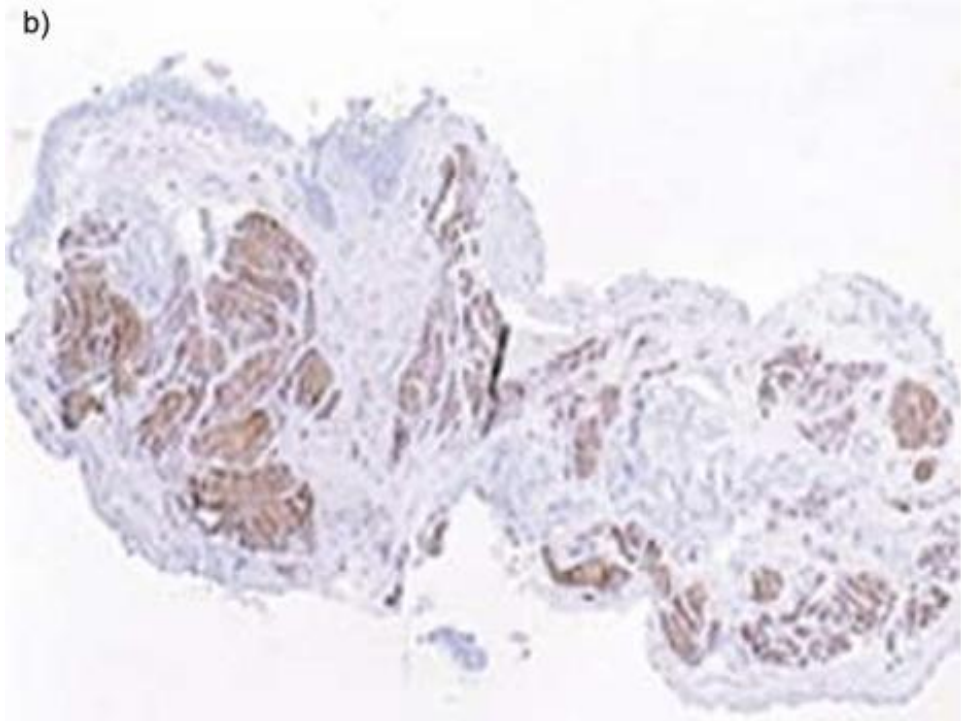
Assessment to airway remodeling

Airway remodelling = structural changes

- The characteristics of structural changes
 - increased thickness of the subepithelial reticular basement membrane (RBM)
 - increased airway smooth muscle (ASM) mass
 - goblet cell and submucosal gland enlargement
 - increased airway vascularity

Method for assessment of airway remodelling

- **Direct assessment : airway tissues**
 - Post mortem and surgical lung specimens
 - Endobronchial biopsies
 - Transbronchial biopsies

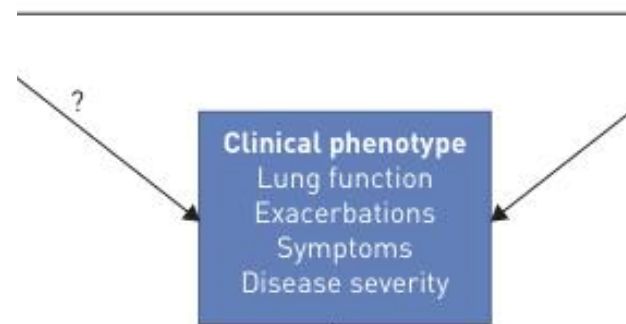


Method for assessment of airway remodelling

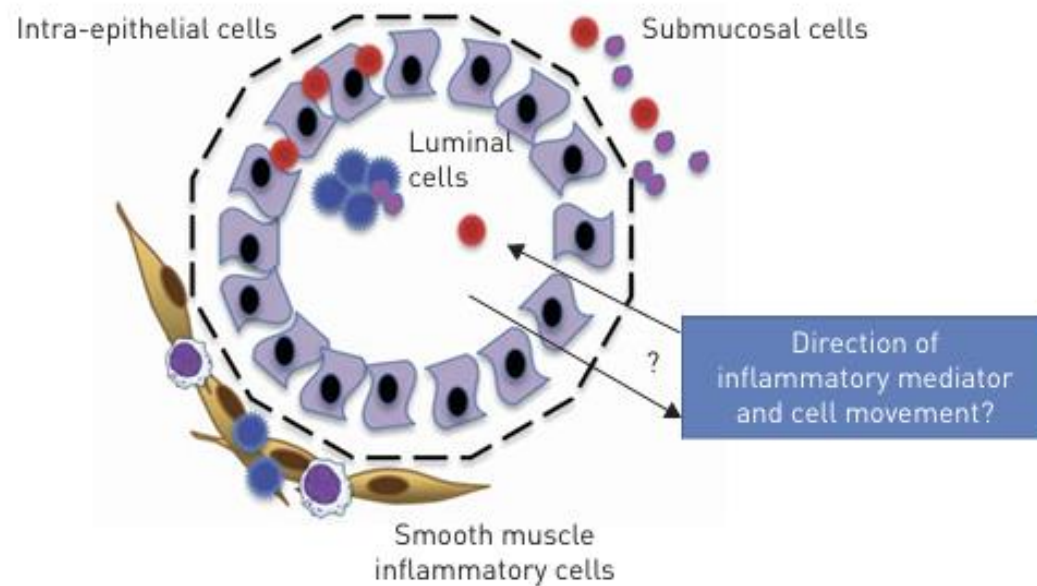
- **Indirect assessment : body fluids**
 - Bronchoalveolar lavage
 - Induced sputum
 - Exhaled breath condensate
 - Blood
 - Urine

Method for assessment of airway remodelling

- **Radiological** assessment
 - High-resolution computed tomography
 - Endobronchial ultrasound
- **Physiological** assessment
 - Lung function

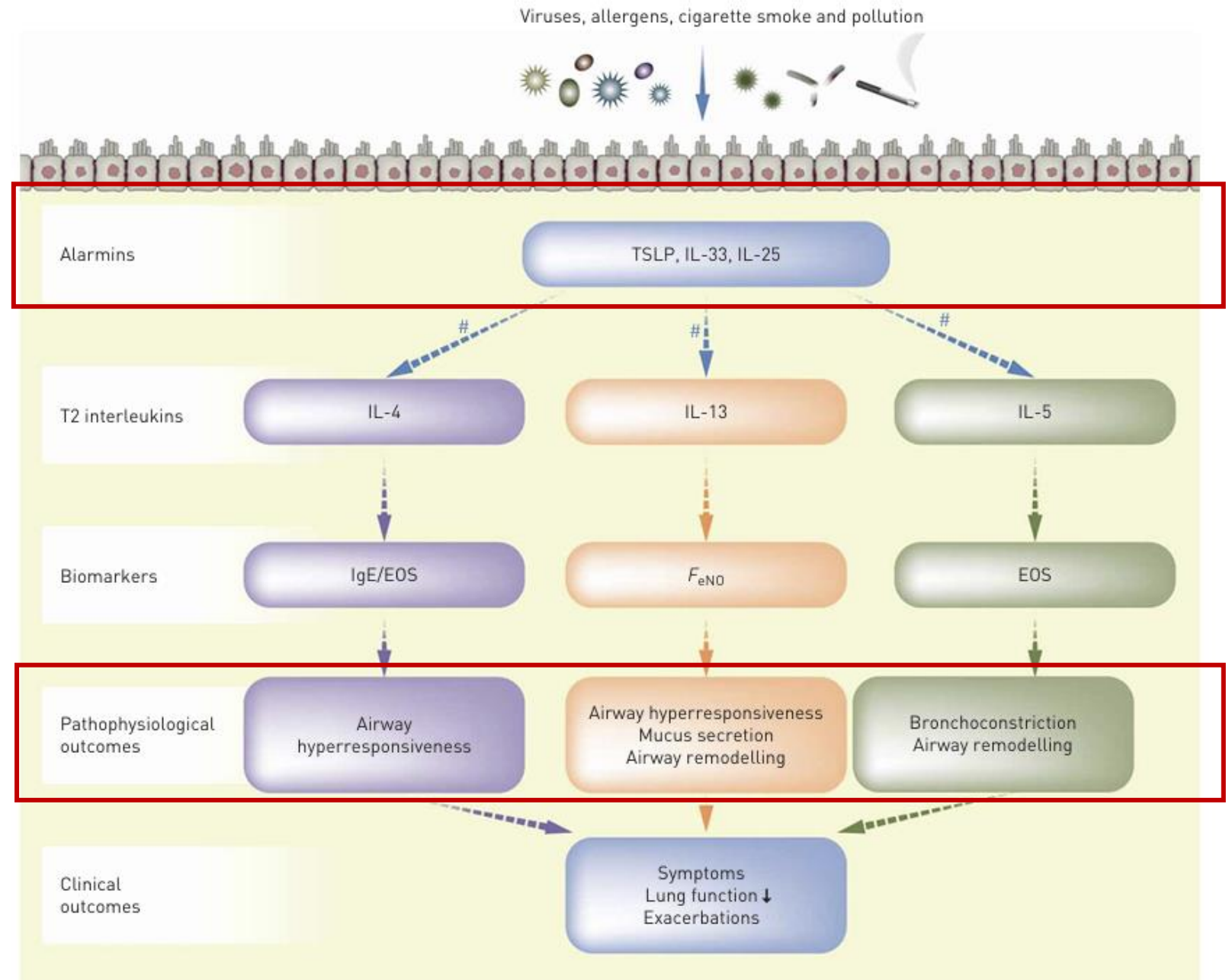


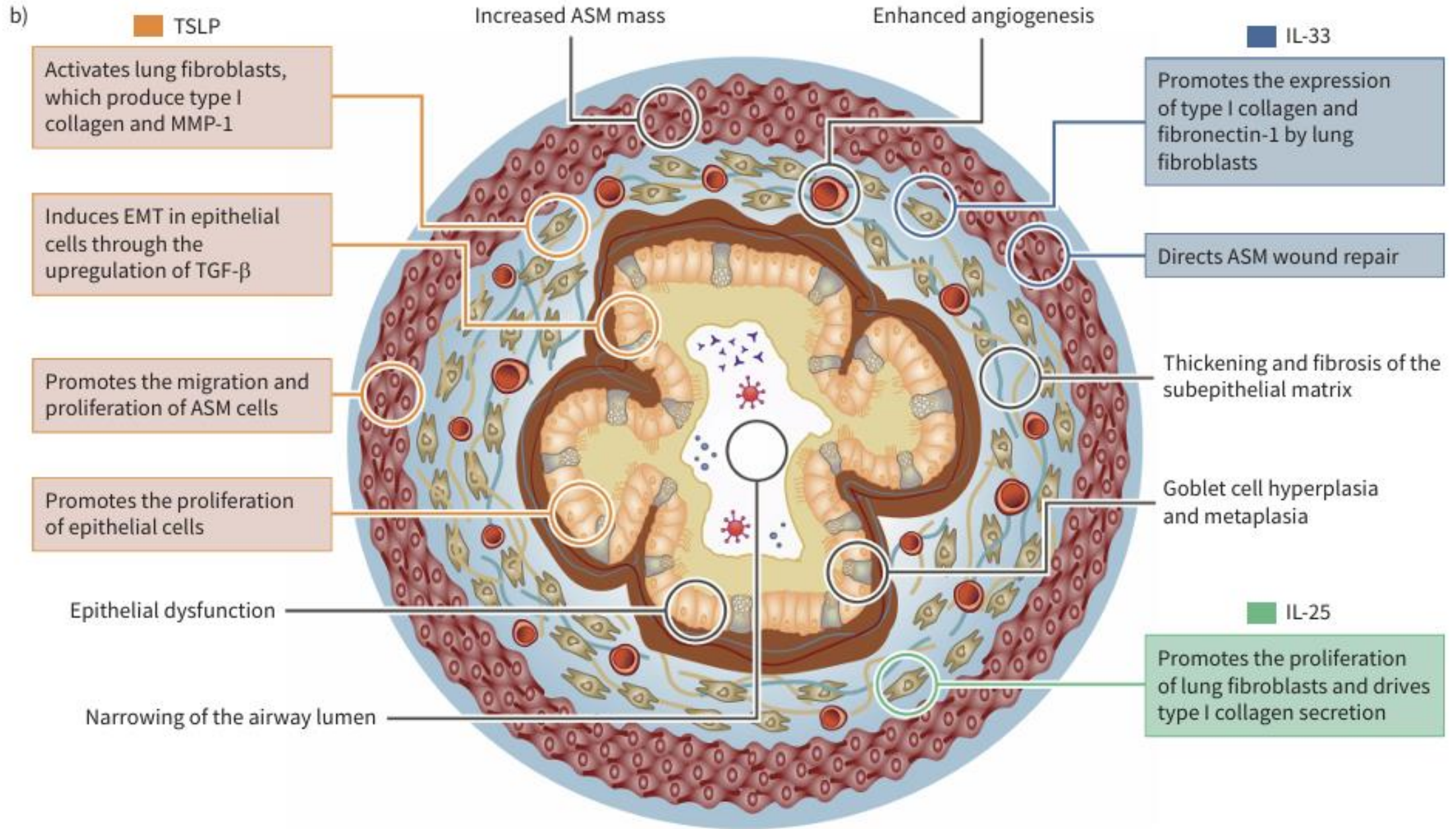
Location, position and interaction of structural and inflammatory cells



Airway epithelium

plays a critical role in the pathophysiology of asthma, acting as a structural and immunological barrier to the external environment



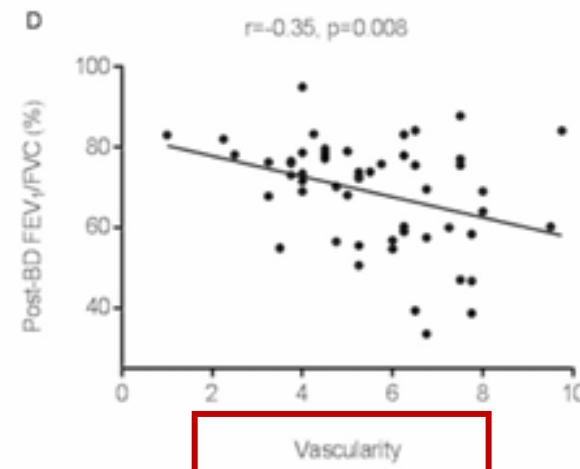
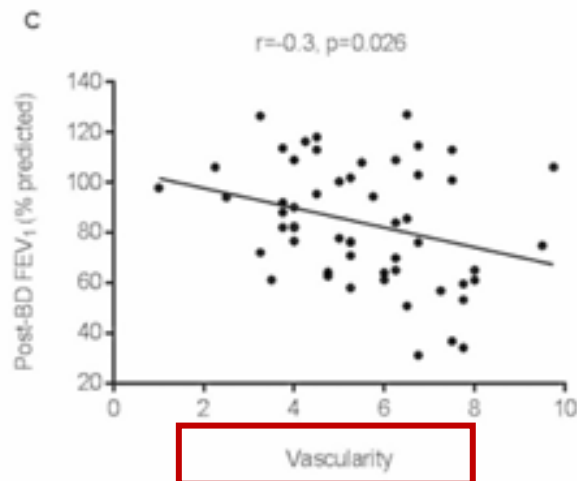
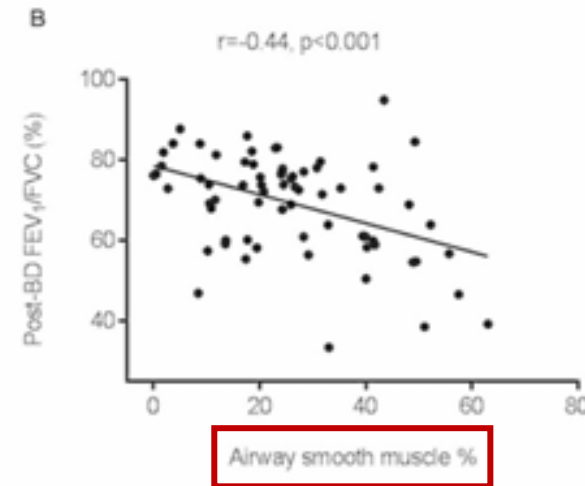
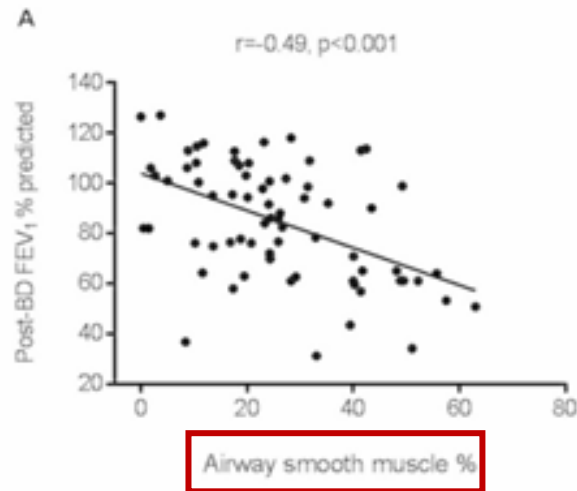


Structural changes with airway remodelling

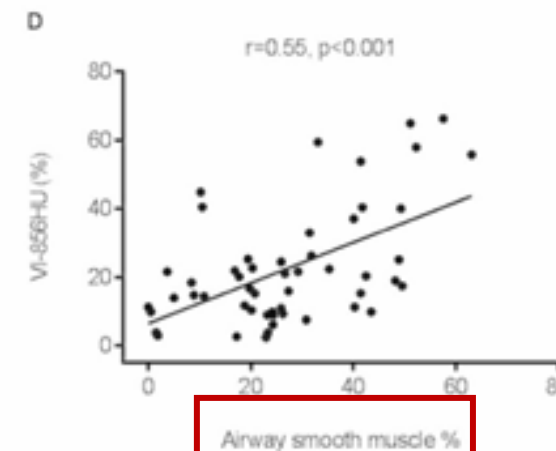
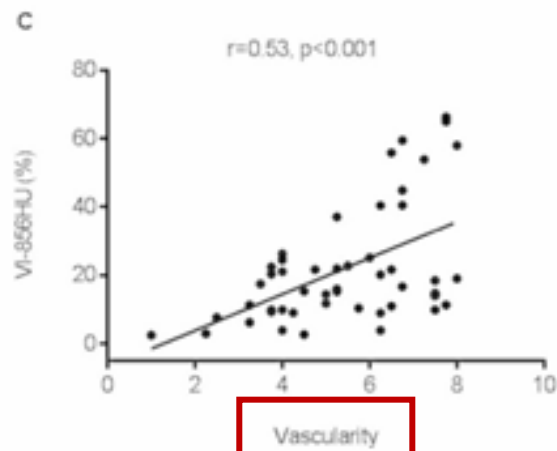
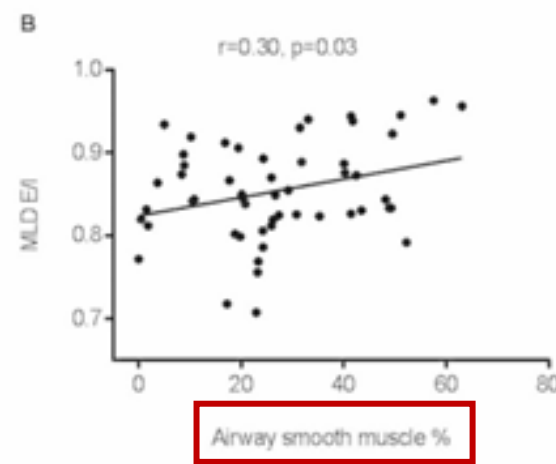
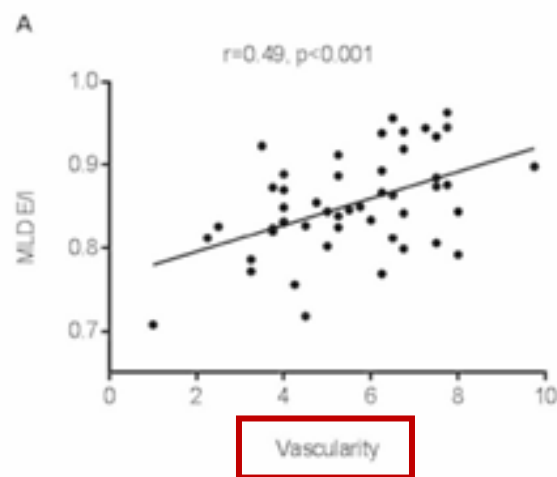
- The ultrastructural changes associated with airway remodelling
 - **altered airway geometry** : airway wall thickening and luminal narrowing
 - **ventilation defects** : mucus plugging and airway obstruction

Associations in asthma between Q-CT and bronchial biopsy-derived airway remodelling

- Subjects were recruited into either test (n=70) or replication (n=24) groups at two independent centres UK and USA.
- Were underwent Bronchial Bx. and chest CT.



Characteristic	All patients (n = 56)	Post-bronchodilator FEV ₁ <80% (n =29)	Post-bronchodilator FEV ₁ ≥80% (n = 25)	p-value
<i>CT-derived quantitative morphometry</i>				
Mean segmental bronchial lumen area/BSA (mm ² /m ²)	10.4 (2.3)	9.7 (2.2)	11.0 (2.3)	0.047
Mean segmental bronchial wall area/BSA (mm ² /m ²)	17.0 (2.6)	16.5 (2.9)	17.5 (2.4)	0.133
Mean segmental bronchi wall area %	63.0 (2.2)	63.6 (2.0)	62.5 (2.1)	0.039
<i>CT-derived measures of air-trapping</i>				
MLD E/I	0.85 (0.06)	0.89 (0.05)	0.83 (0.05)	<0.001
VI-856HU (%)	22.6 (17.0)	32.2 (19.8)	15.5 (10.1)	<0.001



Redefining airway remodelling from quantitative CT

- Computed tomography (CT)–assessed proximal airway remodeling and air trapping in asthmatic patients might provide new insights into underlying disease mechanisms. The aim of this study was to explore novel, quantitative, CT-determined asthma phenotypes
- Sixty-five asthmatic patients and 30 healthy subjects** underwent detailed clinical, physiologic characterization and quantitative CT analysis.

TABLE II. RB1 dimensions of asthmatic patients and healthy subjects

	Patients with severe asthma (n = 48)	Patients with mild-to-moderate asthma (n = 17)	Healthy control subjects (n = 30)	Significance (P value)
Inspiratory				
Wall area/BSA (mm ² /m ²)	18.2 (5.5)	18.5 (3.7)	18.7 (5.2)	.9
Lumen area/BSA (mm ² /m ²)	11.3 (4.4)	11.7 (3.0)	13.7 (5.2)	.08
Total area/BSA (mm ² /m ²)	29.5 (9.7)	30.2 (6.4)	32.3 (10.3)	.4
Wall area (mm ²)	34.8 (10.6)	35.6 (8.0)	36.1 (10.7)	.8
Lumen area (mm ²)	21.6 (8.4)	22.6 (6.5)	26 (10.3)	.06
Total area (mm ²)	56.4 (18.7)	58.2 (14.2)	62.6 (20.8)	.4
Length (mm)	12.8 (2.7)	11.8 (2.4)	13.7 (4.4)	.2
Wall volume (mm ³)	437.6 (144.0)	412.9 (88.5)	496.3 (222.1)	.2
LV (mm ³)	272.3 (112.6)	259.0 (53.3)	366.4 (195.3)	.007*†
Total volume (mm ³)	709.9 (252.4)	672.0 (134.9)	862.8 (414.6)	.05
Wall volume (%)	62.4 (3.6)	61.4 (2.9)	58.5 (3.6)	<.0005*†

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TABLE III. Densitometric indices in asthmatic patients and healthy subjects

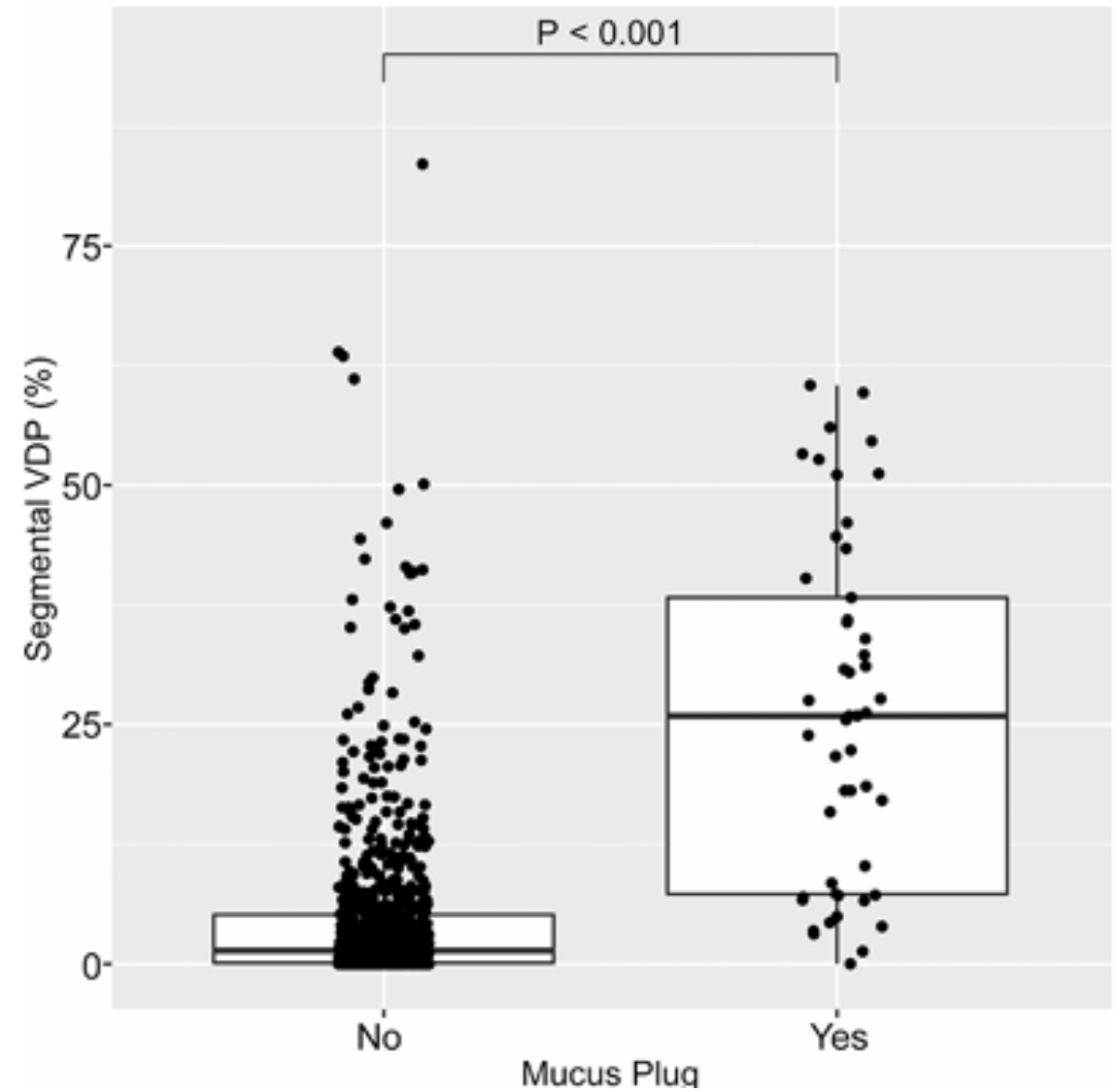
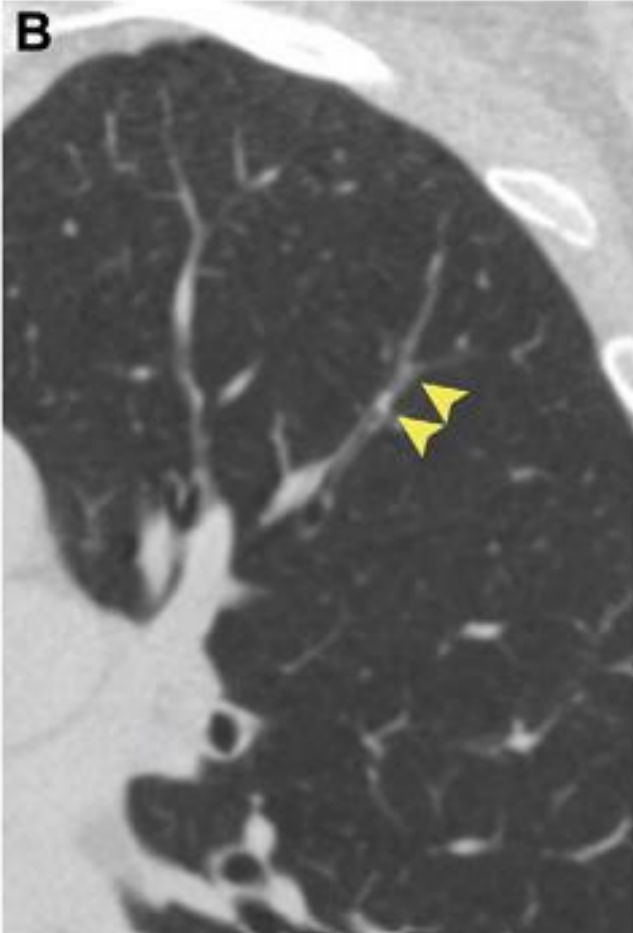
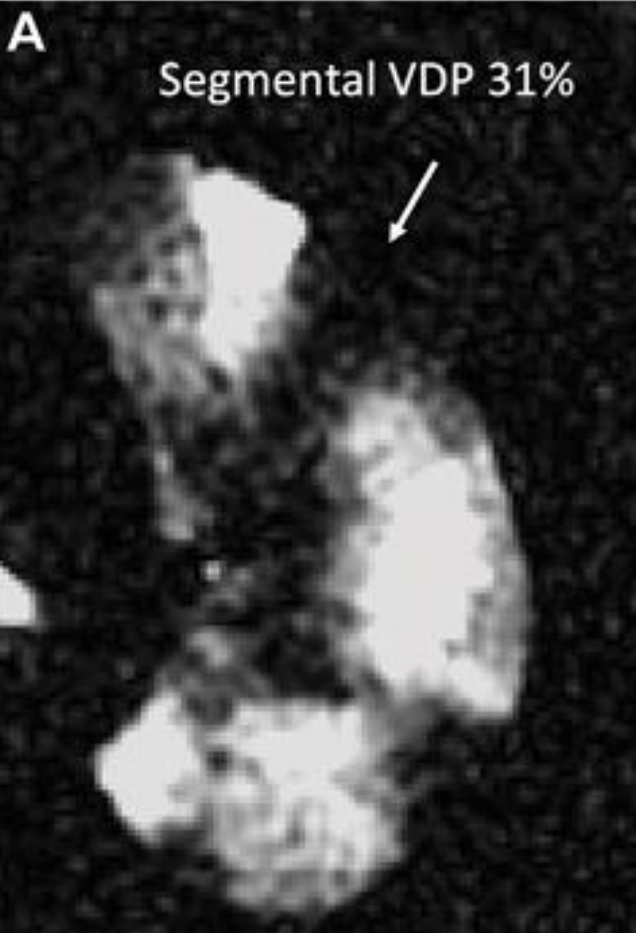
	Patients with severe asthma (n = 48)	Patients with mild-to-moderate asthma (n = 17)	Healthy control subjects (n = 30)	Significance (P value)
Inspiratory				
Lung volume (L)	5.15 (1.5)	5.02 (1.4)	5.49 (1.2)	.4
Mean lung density (HU)	−830.9 (40.8)	−831.5 (42.7)	−837.8 (26.2)	.7
VI −950 (%)	11.2 (5.8)	11.9 (7.6)	10.1 (5.5)	.6
Percentile 15 (HU)	−932.8 (30.4)	−934.3 (28.2)	−930.1 (22.3)	.9
VI −850 (%)	59.1 (15.5)	59.9 (17.2)	61.8 (13.1)	.8
Expiratory				
Lung volume (L)	2.9 (1.0)	2.9 (1.1)	2.8 (0.8)	.9
Mean lung density (HU)	−713.3 (53.2)	−719.5 (63.0)	−695.6 (55.0)	.3
Air-trapping indices				
Expiratory VI −850 (%)	19.7 (11.5)	22.0 (18.0)	16.2 (11.5)	.3
MLD E/I	0.861 (0.05)	0.866 (0.07)	0.830 (0.06)	.04
VI _{−850/−950} E-I (%)	−30.4 (9.7)	−29.1 (18.8)	−36.9 (10.2)	.04
VI _{−850} E-I (%)	−39.1 (11.5)	−37.8 (20.1)	−45.6 (12.0)	.08

Mucus plugs in asthma at CT & Regional defect at ³He MRI

- To assess regional associations between CT mucus plugs scored by individual bronchopulmonary segment and corresponding measurements of segmental ventilation defect percentage (VDP) at hyperpolarized ³He MRI.
- Secondary analysis of participants (n=44) in the Severe Asthma Research Program (SARP) III (NCT01760915) between December 2012 and August 2015 underwent hyperpolarized ³He MRI to determine segmental VDP.

Table 1: Summary of Study Sample Characteristics at Imaging Visit

Characteristic	No Mucus Plug (n = 36)	One or More Mucus Plug(s) (n = 8)	P Value
Severe asthma*	18 (50)	7 (88)	.11
Women*	26 (72)	3 (38)	.10
Mean age and SD (y)	45 ± 16	54 ± 10	.18
Mean BMI and SD (kg/m ²)	29.4 ± 5.7	29.3 ± 6.5	.94
Predicted FEV ₁ (%)*	93.5 (81.1–109.0)	70.7 (67.4–74.3)	<.001
Predicted FEV ₁ /FVC (%)*	97.1 (91.0–100.0)	81.2 (76.7–87.9)	.001
Predicted FVC (%)	97.8 (86.5–105.2)	86.8 (82.5–90.8)	.07
FeNO	16.0 (10.0–28.0)	33.5 (13.5–42.8)	.13
Blood eosinophil count (cells/μL)	204 (108–284)	289 (172–420)	.18
Blood neutrophil count (cells/μL)	3822 (3026–4420)	3390 (3034–3994)	.64
Sputum eosinophils (%) [†]	0.4 (0.0–1.1)	15.0 (1.4–32.2)	.02
Sputum neutrophils (%)	61.7 (48.3–79.4)	38.9 (37.3–47.6)	.052
Plasma IL-5 level (pg/ml) [†]	17.5 (15.7–19.3)	22.3 (21.6–23.0)	<.001
Plasma IL-6 level (pg/ml)	1.2 (0.8–1.8)	1.5 (0.9–1.9)	.53
VDP (%)*	3.1 (1.1–4.4)	11.1 (7.1–18.9)	<.001



Treatment to modify airway remodeling

Targeting treatment to modify airway remodelling

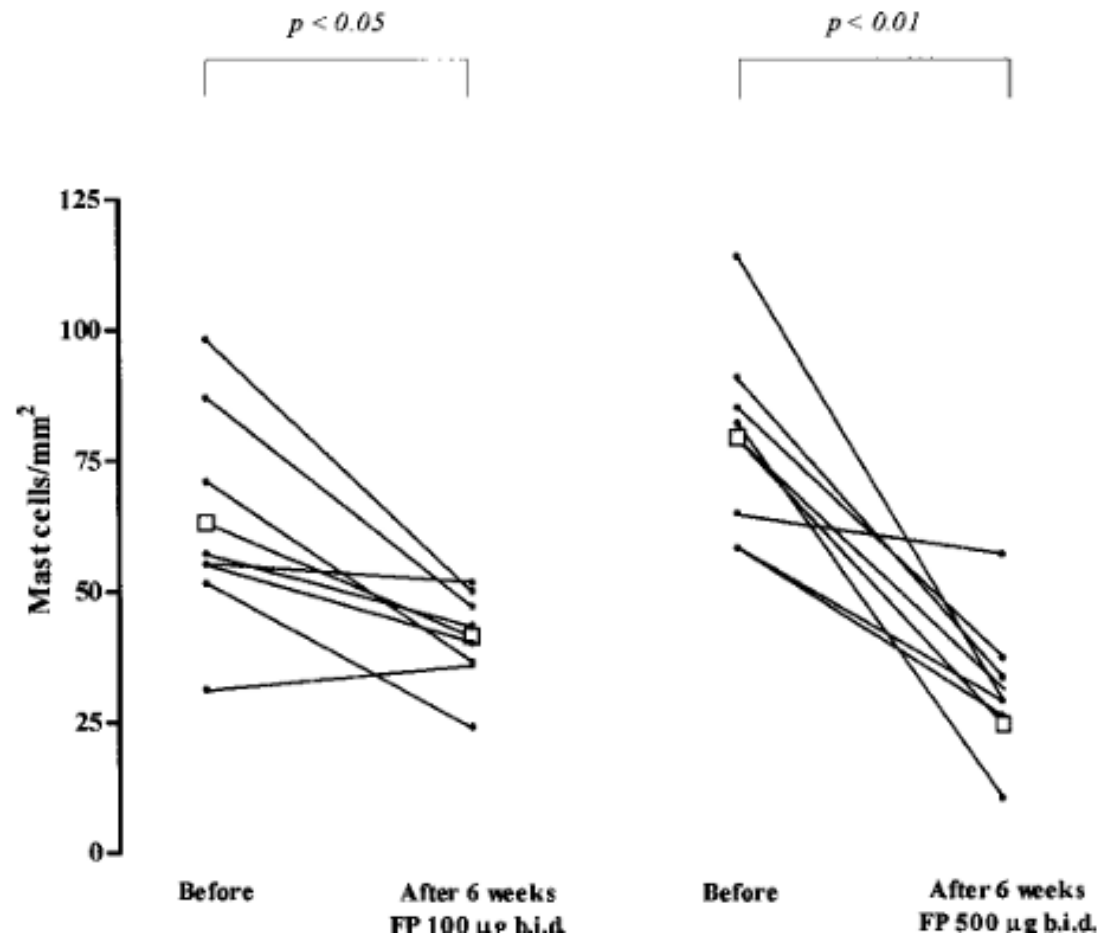
- Various therapies for asthma **target the epithelium either directly or indirectly** and, as well as improving clinical symptoms, may ameliorate features of airway remodelling and lung function decline as measured by FEV1 and other spirometric parameters.
 - **Glucocorticoids**
 - **Biologics targeting T2 inflammation**
 - **Biologics targeting epithelial cytokines**
 - **Bronchial thermoplasty**

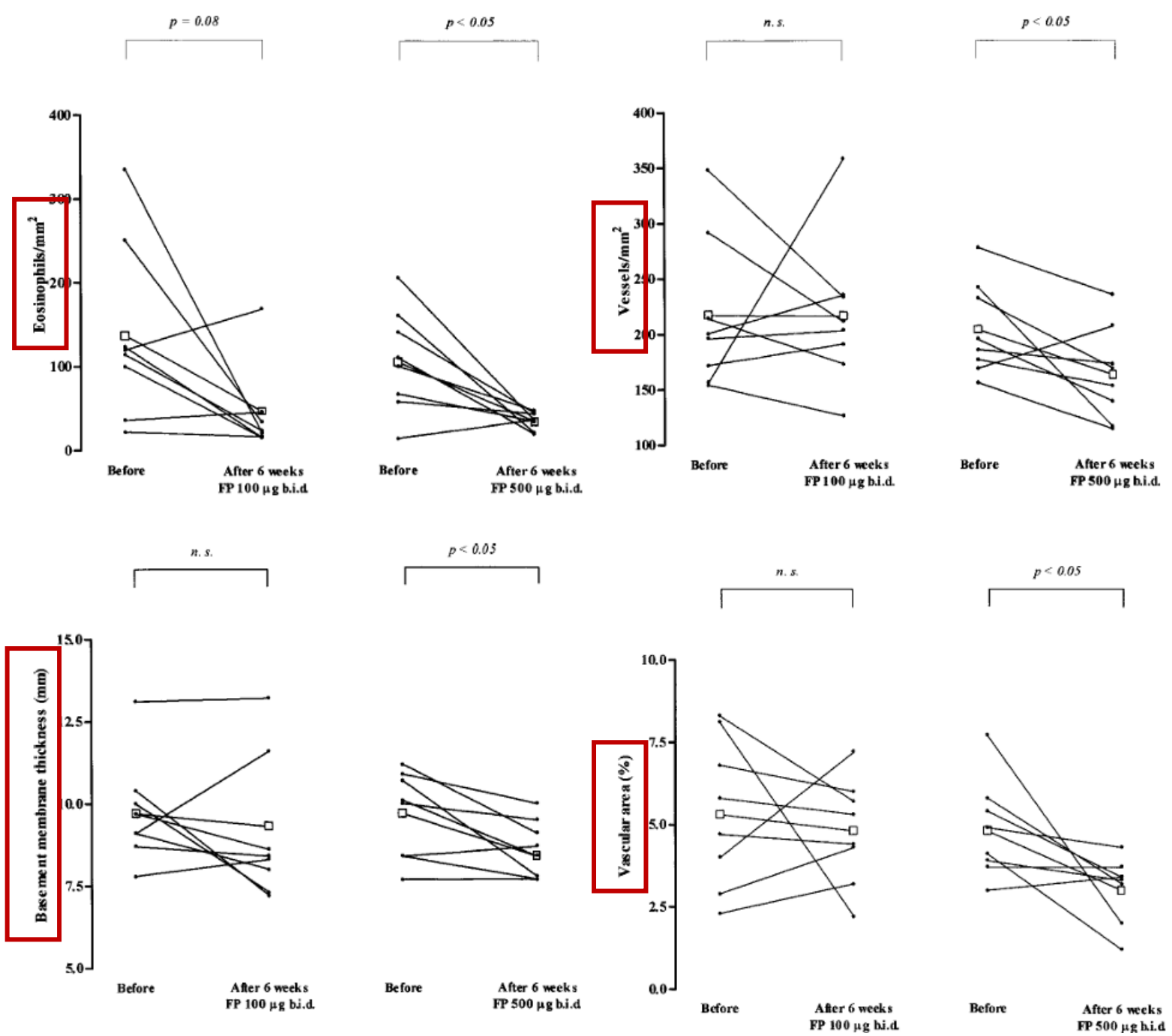
Glucocorticoids as a first-line therapy

- First-line therapy for asthma typically includes inhaled corticosteroids (ICS), targeting glucocorticoid receptors that are expressed almost ubiquitously, including in epithelial cells.
- Glucocorticoids mitigate chronic inflammation, which indirectly contributes to airway remodelling.

Vascular component in airway remodelling & high-dose ICS

- Randomized, double-blind, parallel-group study to assess the effect of 6 weeks treatment with low-dose (100g twice a day) or high-dose(500g twice a day) inhaled fluticasone propionate (FP) on the vascular component of airway remodeling in 30 patients with mild to moderate asthma.





Biologics targeting T2 inflammation

TABLE 1 Effects of biologics for severe asthma on airway remodelling and clinical outcomes [129, 130]

Biologic	Target	GINA eligibility criteria (in addition to having severe asthma)	Biological effects	Effects on airway remodelling	Expected clinical outcomes
Omalizumab	IgE	Severe exacerbations within past year, sensitisation to inhaled allergens, total serum IgE and weight within local dosing range	↓ Circulating total IgE Downregulation of FcεRI receptors on basophils, mast cells and dendritic cells	↓ RBM thickness ↓ Airway wall thickness on CT ↓ Fibronectin deposition Prevents IgE-mediated ECM deposition <i>in vitro</i>	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ Health-related QoL ↑ Symptom control ↓ OCS (possible benefit)
Mepolizumab	IL-5	Severe exacerbations within past year, BEC ≥150 or ≥300 cells·μL ⁻¹ (locally specified)	Blockage of IL-5/IL-5R binding	↓ Airway eosinophils and TGF-β1 ⁺ eosinophils ↓ Tenascin, lumican and procollagen III expression ↓ RBM thickness ↓ Airway wall thickness on CT ↓ ASM mass	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ QoL ↑ Symptom control ↓ OCS
Reslizumab	IL-5	Severe exacerbations within past year, BEC ≥150 or ≥300 cells·μL ⁻¹ (locally specified)	Blockage of IL-5/IL-5R binding	Not reported	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ QoL ↑ Symptom control
Benralizumab	IL-5Rα	Severe exacerbations within past year, BEC ≥150 or ≥300 cells·μL ⁻¹ (locally specified)	↓ Eosinophils and basophils <i>via</i> antibody-dependent cell-mediated cytotoxicity	↓ Airway eosinophils ↓ ASM mass	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ Health-related QoL ↑ Symptom control ↓ OCS
Dupilumab	IL-4Rα	Severe exacerbations within past year, BEC ≥150 and ≤1500 cells·μL ⁻¹ , or F _{ENO} ≥25 ppb, or maintenance OCS	Blockage of IL-4/IL-4Rα binding Blockage of IL-13/IL-4Rα binding	Prevents eosinophil infiltration into lung tissue in a mouse model of asthma	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ Health-related QoL ↑ Symptom control ↓ OCS
Tezepelumab	TSLP	Severe exacerbations within past year	Blockage of TSLP/TSLPR binding	↓ Airway eosinophils ↓ AHR to mannitol ↓ Airway inflammation ↓ TGF-β1 ↑ CT scan-determined lumen area	↑ Lung function (FEV ₁) ↓ Severe exacerbations ↑ Health-related QoL ↑ Symptom control ↓ OCS (possible benefit)

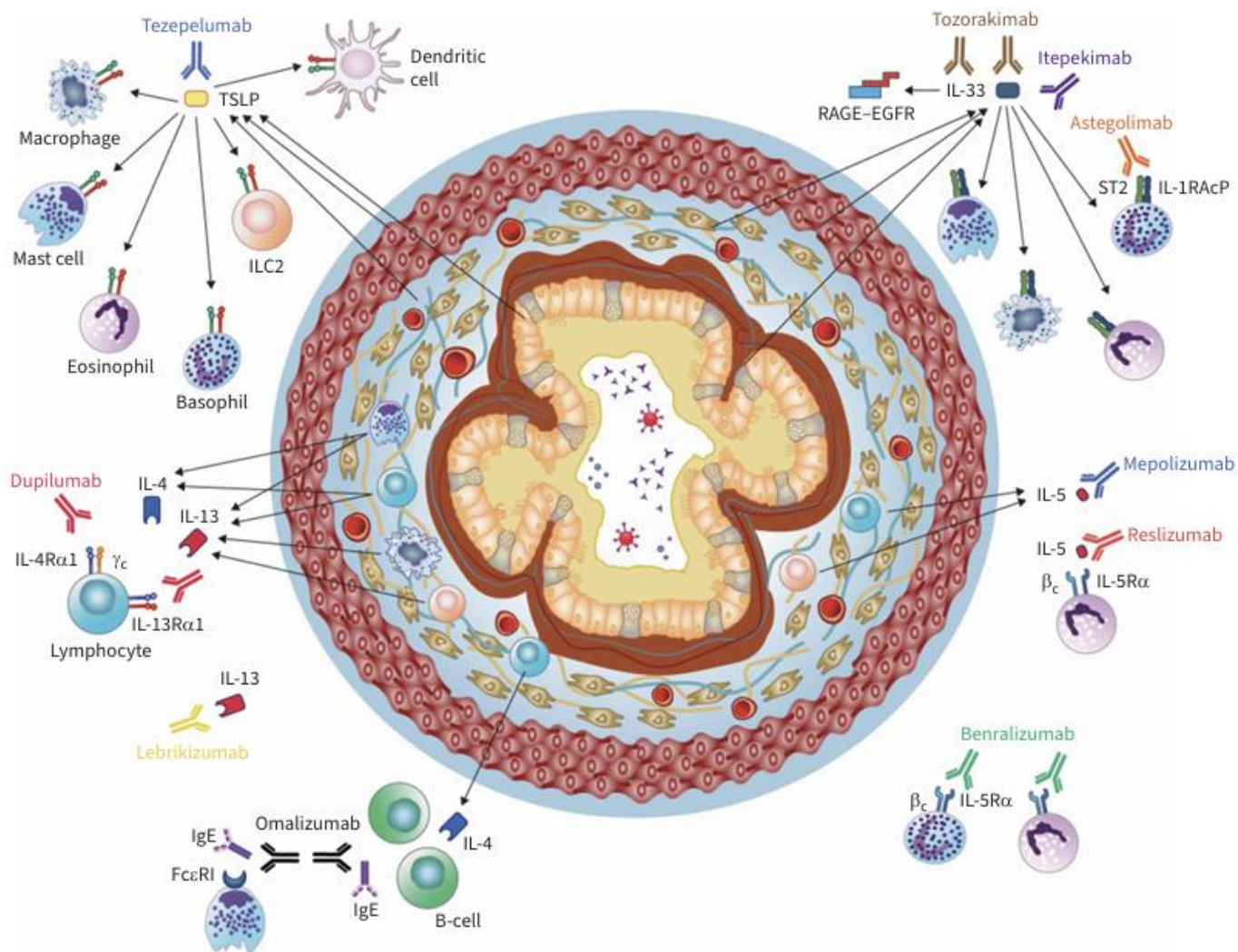
Effect of dupilumab on airway remodelling with uncontrolled asthma_THE VESTIGE STUDY

- Enroll patients aged 18–70 years with uncontrolled, moderate-to-severe asthma, ≥ 300 blood eosinophils/ μL , and FeNO ≥ 25 ppb at screening.
- To assess dupilumab's effect on lung function and structural airway changes using functional respiratory imaging (FRI), a novel technology using high-resolution CT (HRCT) scans.
- This study also assesses key biomarkers of airway inflammation, clinical and patient-reported outcomes (PROs), providing data towards a preliminary understanding of the potential relationships between these parameters.

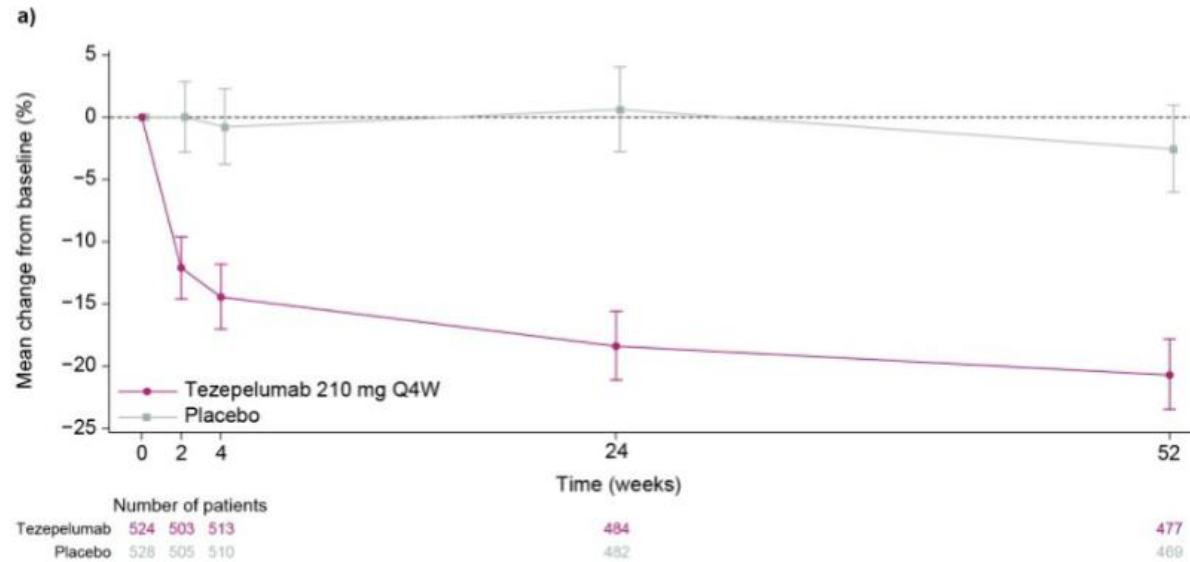
Dupilumab reduces mucus plugging and volume: phase 4 VESTIGE trial

- **Patients (21-70 years) with uncontrolled moderate-to-severe asthma**, elevated type 2 biomarkers (baseline blood eosinophil count ≥ 300 cells/ μ L; FeNO ≥ 25 ppb), pre-BD ppFEV1 $\leq 80\%$, and ≥ 1 exacerbation year prior were **randomized 2:1 to add-on dupilumab 300 mg (N=72) or matched placebo (PBO, N=37) q2w** for 24 weeks.
- **The dupilumab group had reduced mucus scores** (mean difference from baseline: -4.9 [0.8] points vs PBO; $P < 0.001$) and volumes (-0.11 [0.02] mL; $P < 0.001$), were 9.8 times more likely **to achieve FeNO < 25 ppb ($P < 0.001$), and improved in pre-BD ppFEV1 (13.8 [3.1] %, $P < 0.001$).**
- Improvements from baseline to Week 24 in pre-BD FEV1 correlated with lower mucus score in the dupilumab group ($r = -0.61$, $P < 0.0001$).

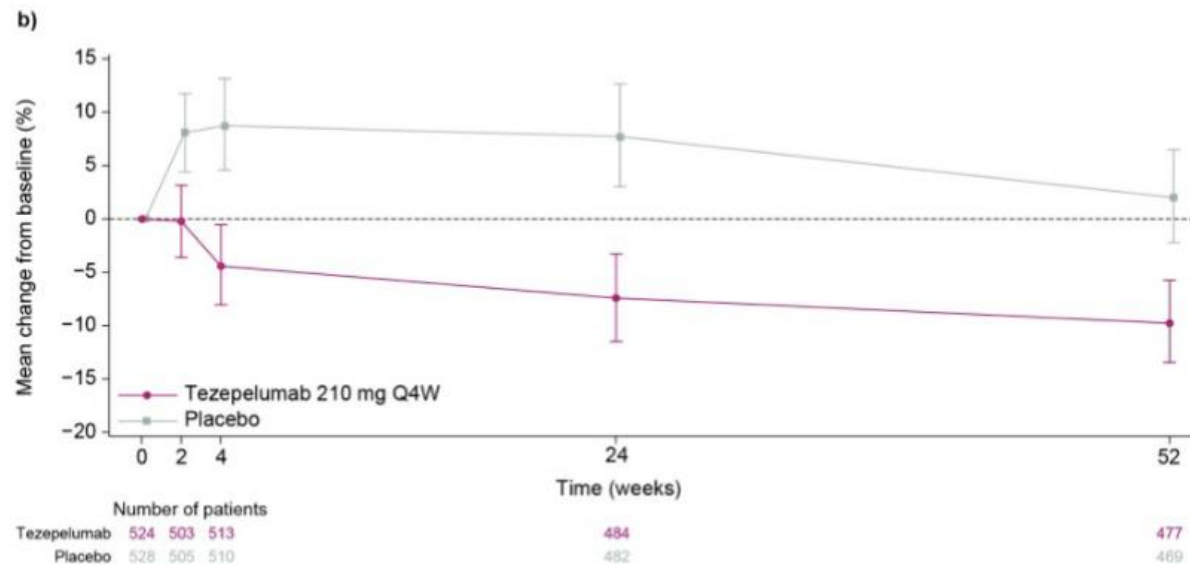
Biologics targeting epithelial cytokines



Tezepelumab Reduces Biomarkers of Airway Remodeling, MMP-10 and MMP-3: from the Phase 3 NAVIGATOR Study



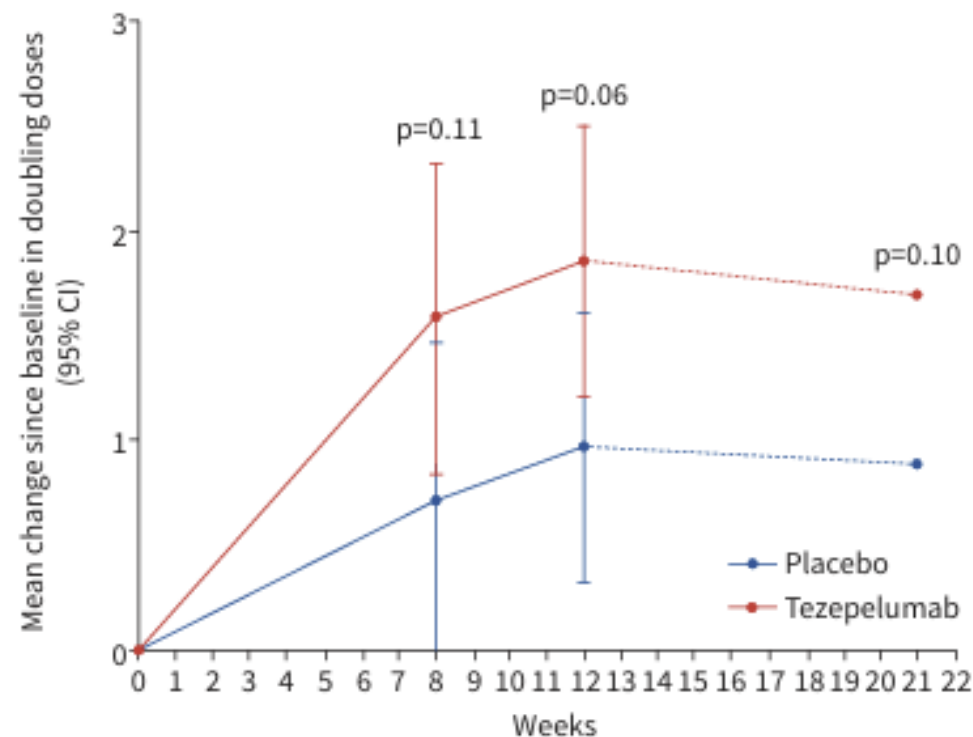
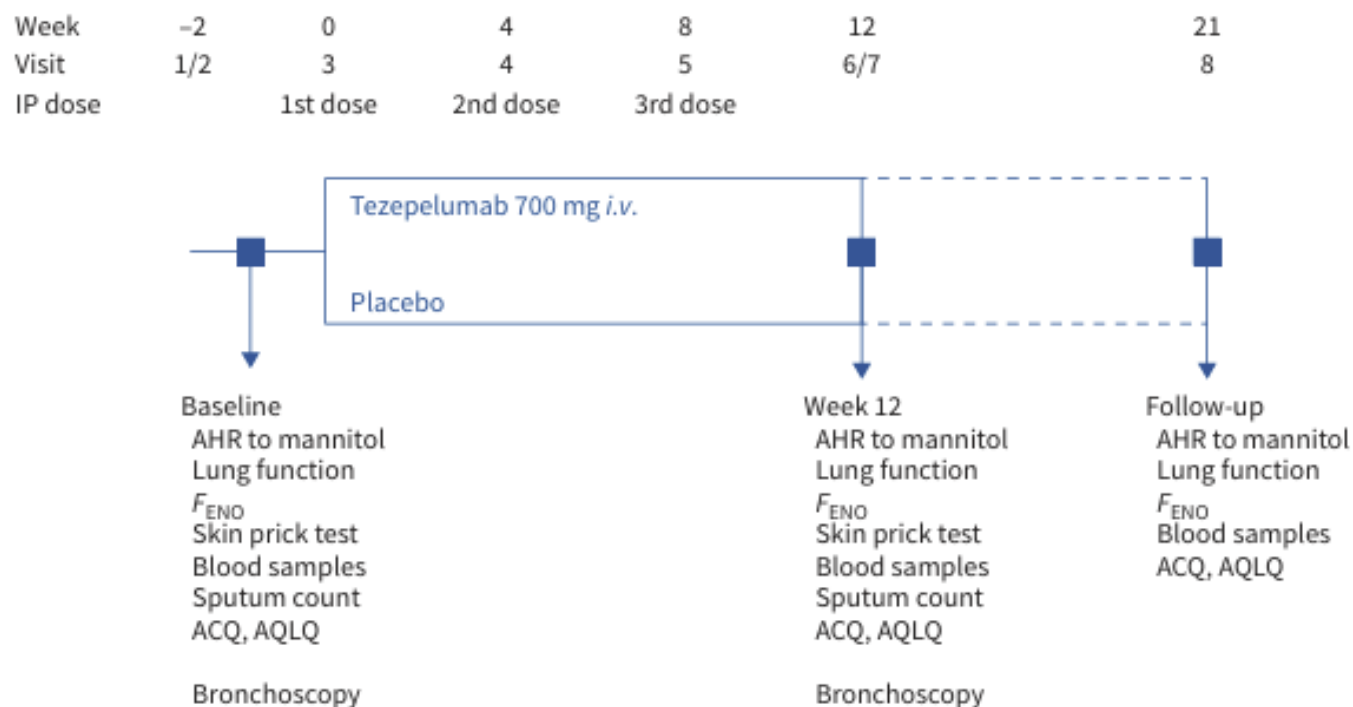
MMP-10



MMP-3

Effect of Tezepelumab on airway hyperresponsiveness in asthma

- Randomised, double-blind, placebo-controlled phase II trial (UPSTREAM) was conducted at a single study centre (University Hospital Bispebjerg) in Copenhagen, Denmark.
- Patients were **randomized (1:1) to a 12-week treatment period** within **tezepelumab 700mg or placebo every 4 weeks** for a total of three doses on top of their regular asthma treatment



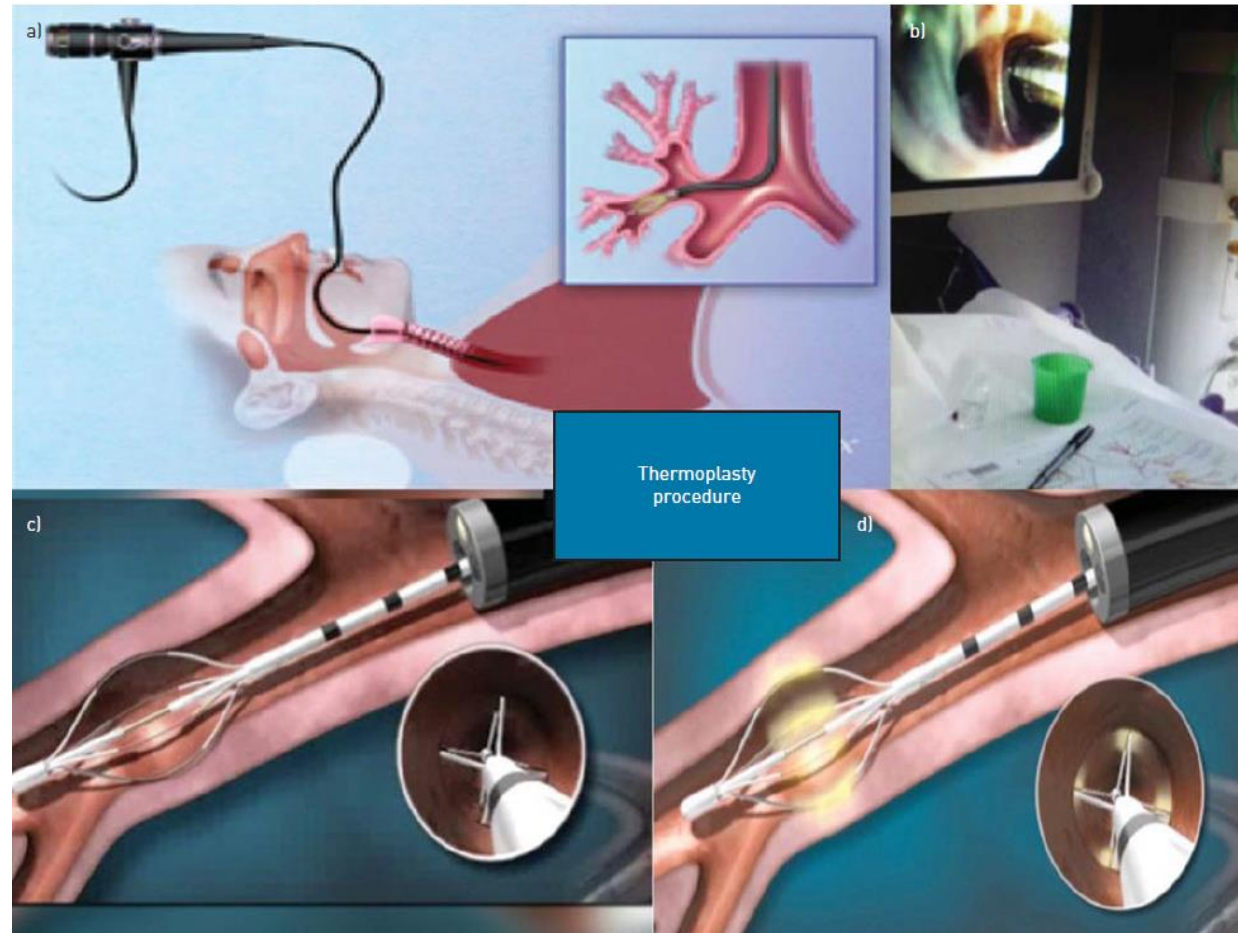
	Overall		Eosinophil high [#]		Eosinophil low [#]	
	Placebo	Tezepelumab	Placebo	Tezepelumab	Placebo	Tezepelumab
Eosinophils	n=19	n=20	n=13	n=10	n=6	n=10
Baseline geometric mean (range)	0.029 (0.0001–4.00)	0.021 (0.0001–0.18)	0.079 (0.0089–4.00)	0.046 (0.0020–0.18)	0.004 (0.0001–0.08)	0.009 (0.0001–0.075)
Week 12 geometric mean (range)	0.035 (0.0009–1.81)	0.007 (0.0009–0.06)	0.039 (0.0009–0.06)	0.009 (0.0009–0.06)	0.027 (0.0045–1.81)	0.005 (0.0009–0.026)
Adjusted ratio between geometric means (95% CI)	1.28 (0.61–2.70)	0.26 (0.13–0.54)	0.67 (0.25–1.75)	0.17 (0.06–0.53)	3.51 (0.76–16.23)	0.52 (0.16–1.69)
p-value for comparison with placebo		0.004		0.07		0.06
Neutrophils	n=18	n=18	n=12	n=10	n=6	n=8
Baseline geometric mean (range)	0.086 (0.015–0.23)	0.054 (0.002–0.80)	0.085 (0.015–0.23)	0.063 (0.002–0.21)	0.088 (0.031–0.23)	0.045 (0.002–0.80)
Week 12 geometric mean (range)	0.100 (0.017–0.59)	0.081 (0.017–0.58)	0.121 (0.041–0.59)	0.097 (0.026–0.33)	0.066 (0.017–0.18)	0.066 (0.017–0.58)
Adjusted ratio between geometric means (95% CI)	1.33 (0.93–1.89)	1.51 (1.06–2.14)	1.44 (0.96–2.16)	1.40 (0.90–2.20)	1.04 (0.47–2.22)	1.96 (0.94–4.06)
p-value for comparison with placebo		0.61		0.94		0.25
MC_{TOT}	n=19	n=20	n=13	n=10	n=6	n=10
Baseline geometric mean (range)	0.326 (0.066–1.34)	0.318 (0.077–0.73)	0.333 (0.066–1.335)	0.342 (0.093–0.690)	0.314 (0.128–0.464)	0.295 (0.077–0.731)
Week 12 geometric mean (range)	0.369 (0.098–2.15)	0.239 (0.058–0.69)	0.484 (0.141–2.146)	0.240 (0.096–0.426)	0.206 (0.098–0.354)	0.239 (0.058–0.685)
Adjusted ratio between geometric means (95% CI)	1.18 (0.82–1.69)	0.75 (0.53–1.06)	1.53 (1.03–2.29)	0.75 (0.47–1.17)	0.62 (0.31–1.24)	0.85 (0.50–1.45)
p-value for comparison with placebo		0.07		0.02		0.46

Potential biologics targeting epithelial cytokines

- Several biologic therapies targeting IL-33 signalling are, or have recently been, in development for asthma.
 - Itepekimab
 - Astegolimab
 - Tozorakimab

Bronchial thermoplasty: new therapeutic option

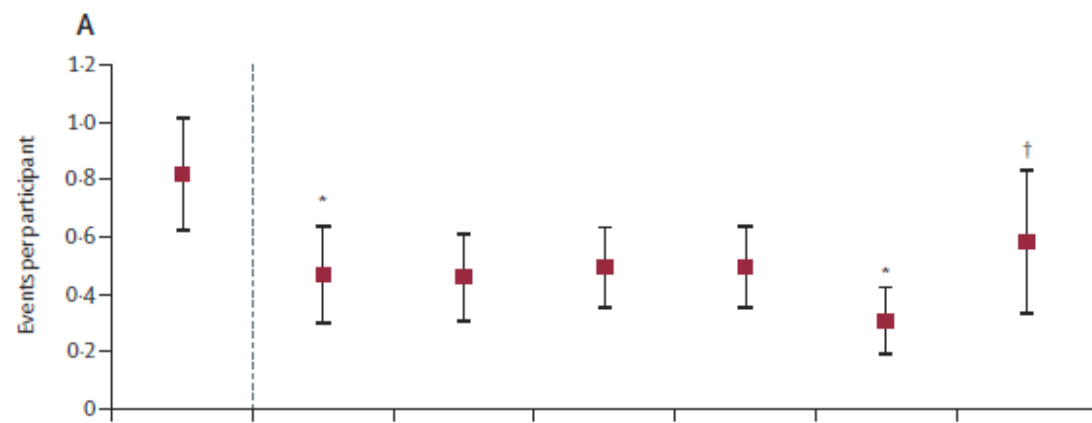
- Bronchial thermoplasty is a nonpharmacological, device-based therapy that delivers controlled thermal energy to the airway wall as part of a series of three bronchoscopic procedures.
- Approved by the US FDA for the treatment of severe persistent asthma in patients aged ≥ 18 years whose asthma is not well controlled with inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs) in 2010



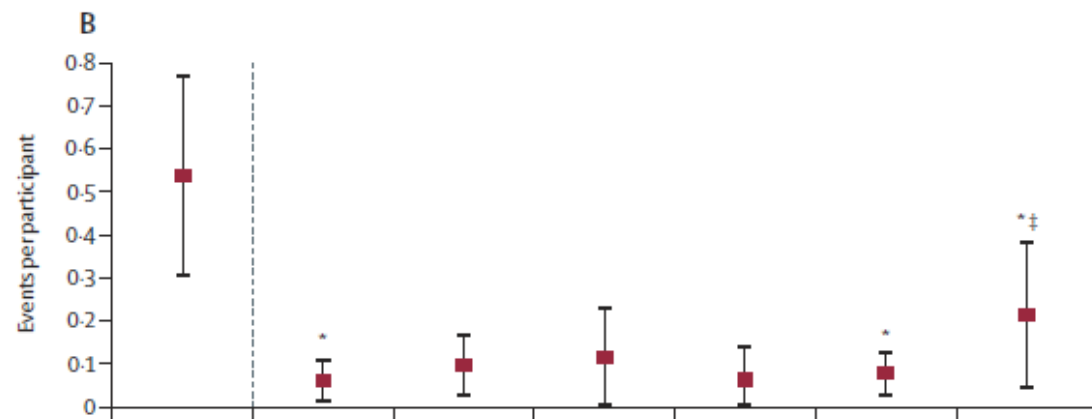
Long term efficacy and safety of bronchial thermoplasty from three RCTs

- BT10+ was an international, multicentre, follow-up study of participants who were previously enrolled in the AIR, RISA, and AIR2 trials and who had 10 or more years of follow-up since bronchial thermoplasty treatment.
- To investigate the efficacy and safety of bronchial thermoplasty **after 10 or more years of follow-up**.

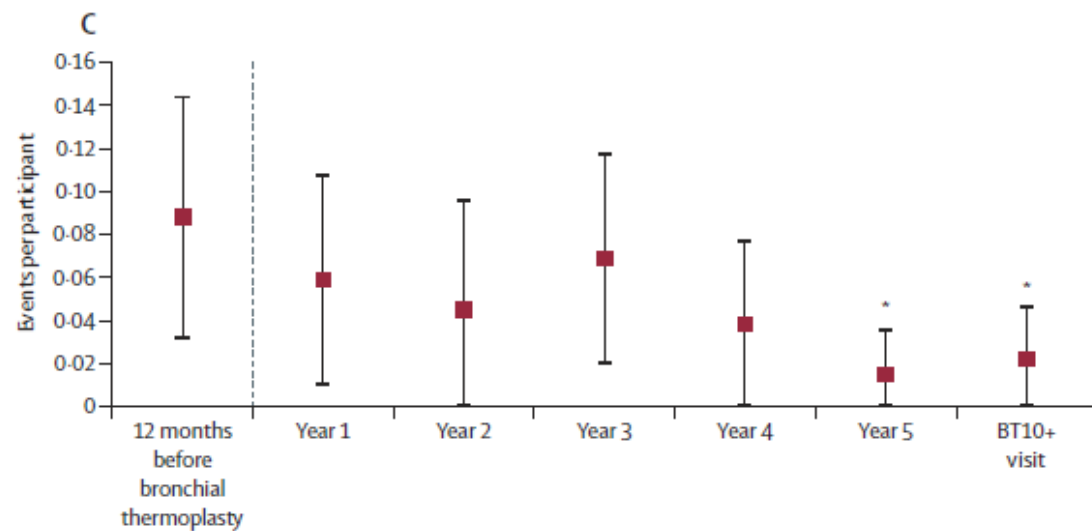
	Control or sham with no post-study bronchial thermoplasty (n=38)	Control or sham with post-study bronchial thermoplasty (n=18)	Bronchial thermoplasty (n=136)
Age (years)	54.4 (11.8)	54.2 (8.9)	53.6 (11.4)
Sex			
Female	19 (50%)	7 (39%)	82 (60%)
Male	19 (50%)	11 (61%)	54 (40%)
Weight (kg)	80.4 (19.1)	96.5 (14.0)	83.7 (19.8)
Height (cm)	167.7 (11.3)	166.6 (8.8)	165.2 (9.1)
Body-mass index (kg/m ²)	28.5 (5.7)	34.9 (5.2)	30.6 (6.5)
Meet current European Respiratory Society and American Thoracic Society Guidelines for Severe Asthma*	26 (68%)	13 (72%)	103 (76%)
FEV ₁			
Pre-bronchodilator, % predicted	74.4 (17.4)	73.4 (17.1)	72.9 (19.4)
Post-bronchodilator, % predicted	80.7 (16.3)	80.1 (15.2)	79.4 (18.5)
Pre-bronchodilator, measured (L)	2.3 (0.8)	2.3 (0.8)	2.2 (0.8)
Post-bronchodilator, measured (L)	2.5 (0.8)	2.5 (0.8)	2.4 (0.7)
Forced vital capacity			
Pre-bronchodilator, % predicted	93.2 (16.4)	87.7 (14.1)	90.2 (15.1)
Post-bronchodilator, % predicted	97.8 (16.3)	93.2 (11.8)	96.5 (14.3)
Pre-bronchodilator, measured (L)	4.0 (1.1)	3.7 (1.0)	3.7 (0.9)
Post-bronchodilator, measured (L)	4.2 (1.1)	3.9 (1.0)	4.0 (0.9)
Residual volume, % predicted	121.2 (41.8)	121.2 (21.2)	120.9 (34.6)
Total lung capacity, % predicted	102.1 (14.7)	101.8 (13.0)	105.1 (14.0)



Severe asthma exacerbation

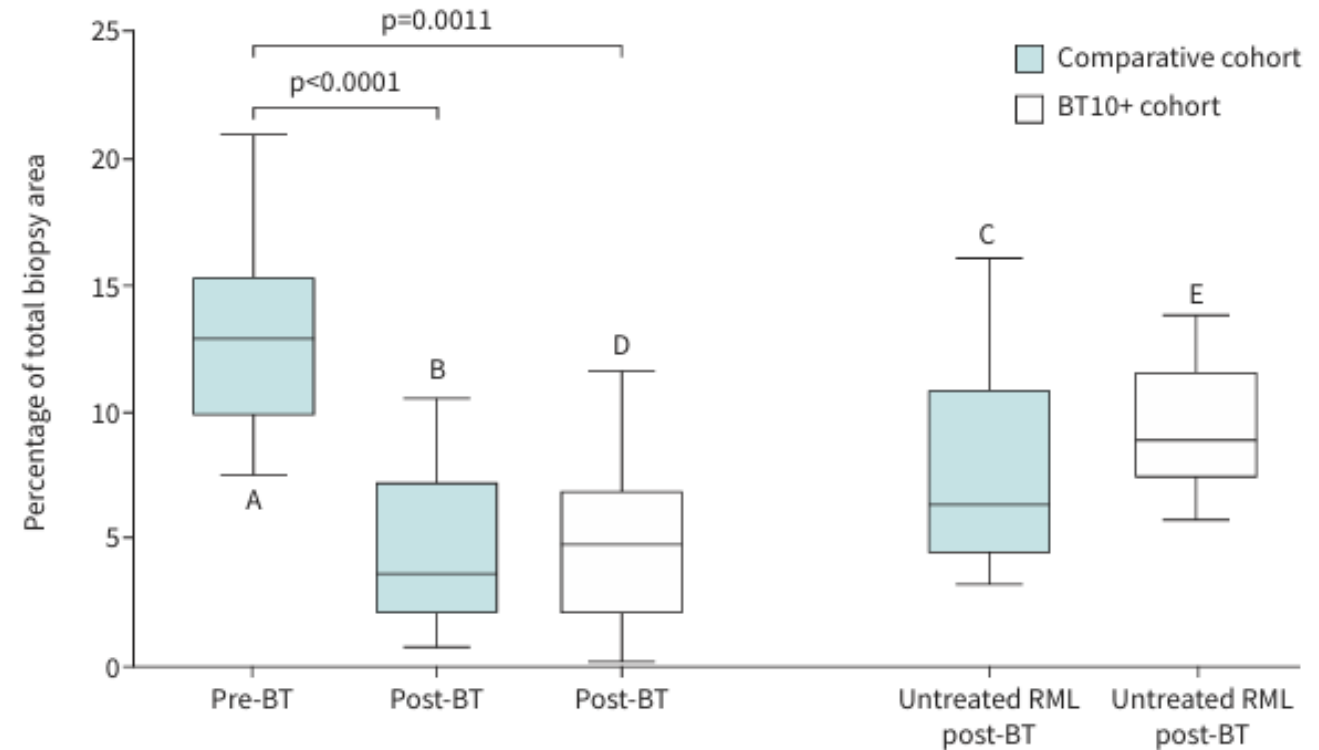
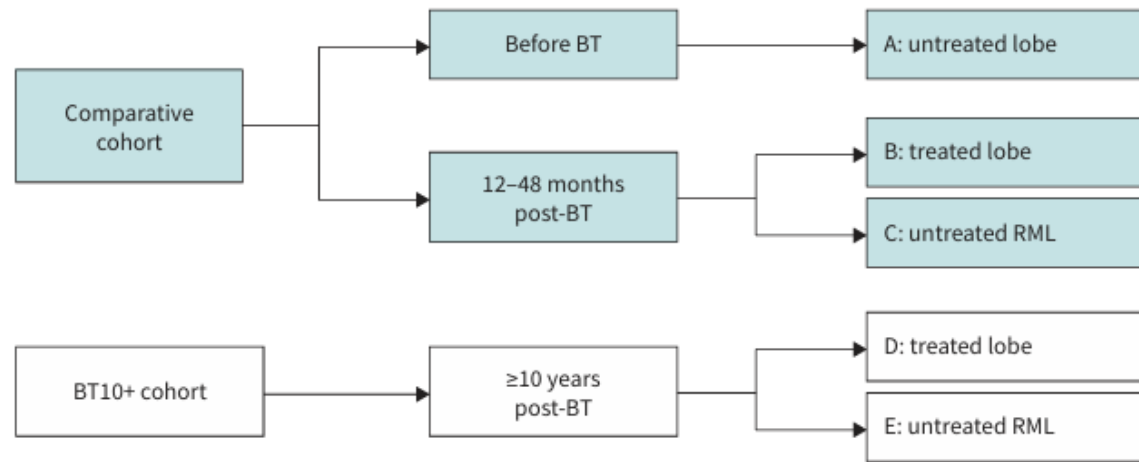


Hospital emergency department visits



Admission to hospital for asthma

Reduction of airway smooth muscle by bronchial thermoplasty



Summary

- Assessment to airway remodelling
 - Remodelling phenotype - structural changes
 - Inflammatory phenotype – airway inflammatory, cytokine
 - Combination of remodeling and inflammatory phenotype
- Treatment to modify airway remodeling – glucocorticoid, biologics, etc.
- Bronchial Thermoplasty – long term effect (+)

경청해 주셔서 감사합니다

