Asthma: New developments, new treatments

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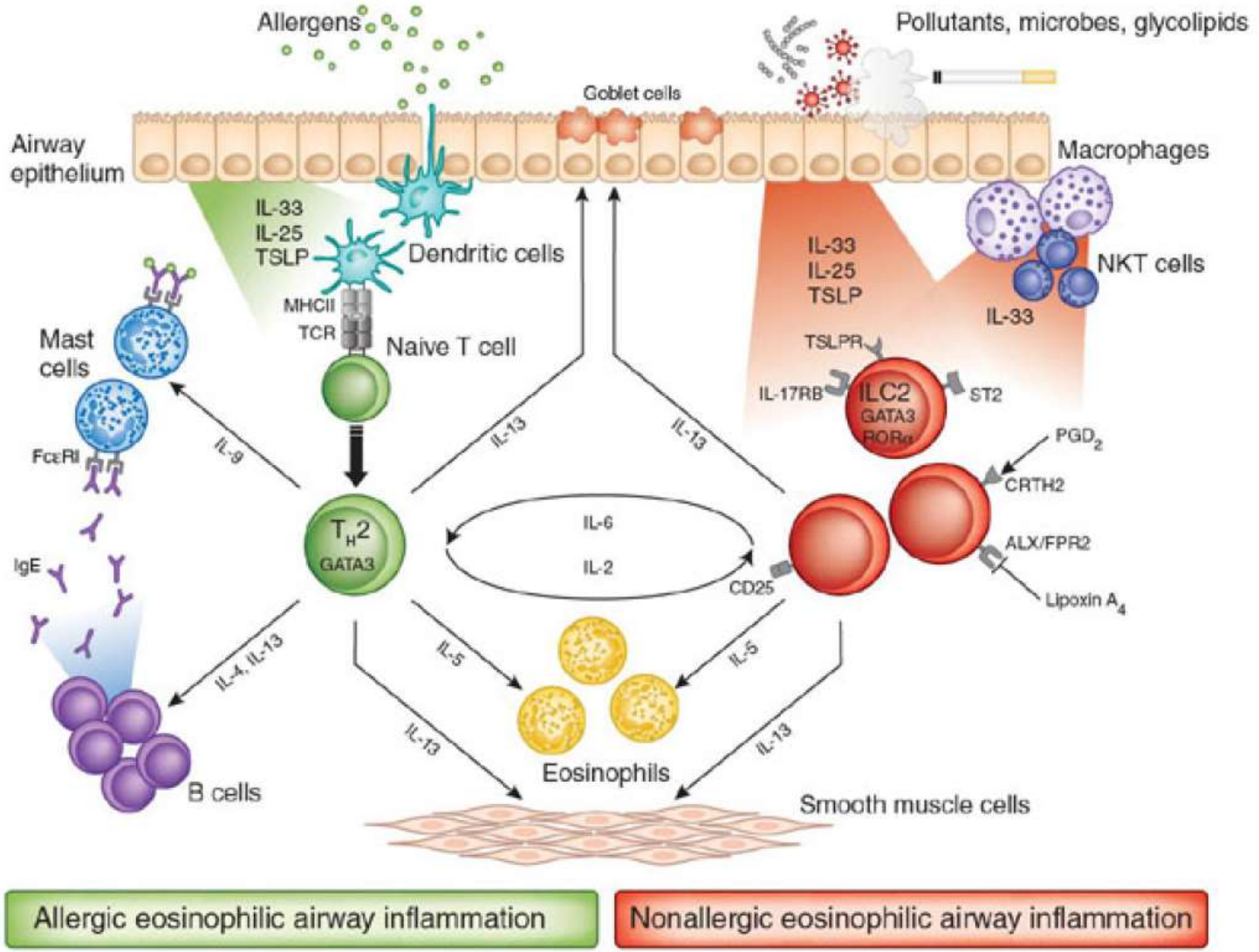
Endotypes, Phenotypes, Genotypes

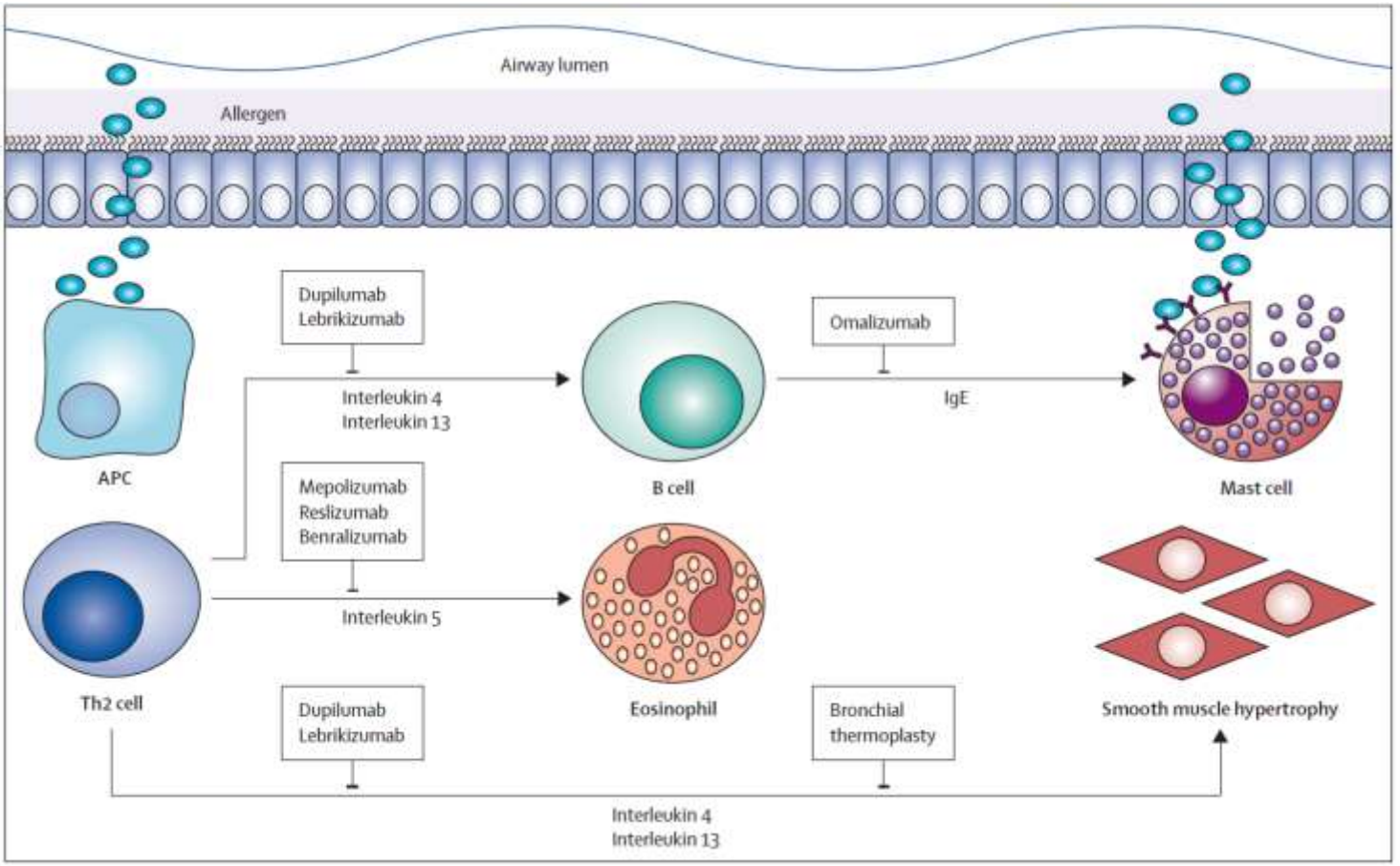
- Endotype= a “subtype of disease defined functionally and pathologically by a molecular mechanism or by treatment response”
- refer to specific groups of people (rather than their characteristics) and demand that these groups share some common underlying biology.
- value of identifying endotypes - point to specific therapeutic approaches.
- several challenges
- development of effective and specific therapeutic blockers for the pathways of interest
- developing non-invasive biomarkers that identify people who comprise the endotype.

Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008; 372:1107–1119.

Pathways: eosinophilic inflammation



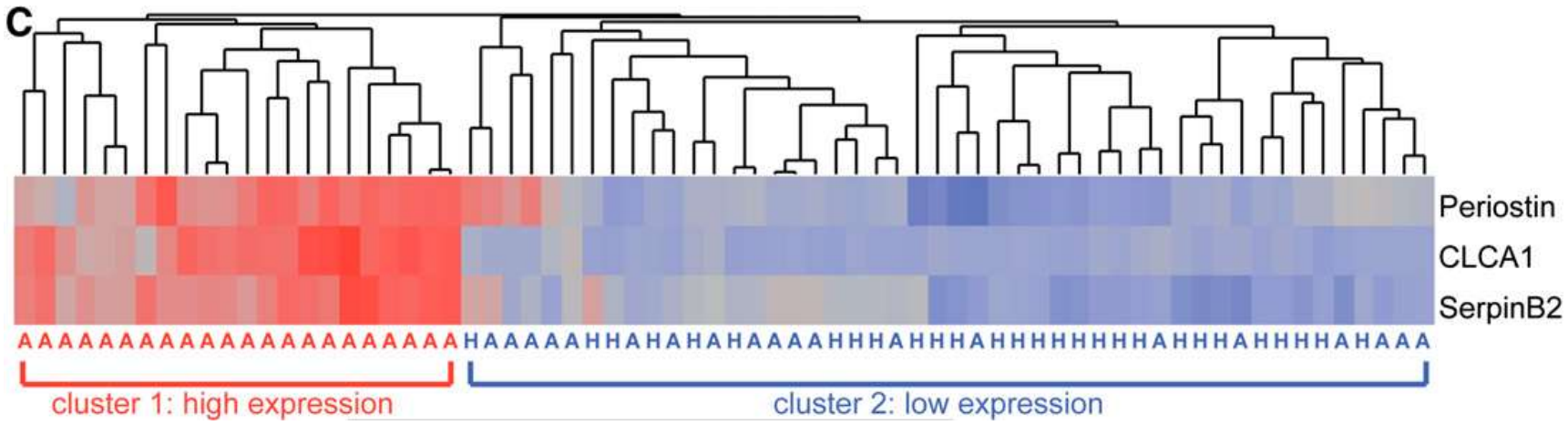
New Agents

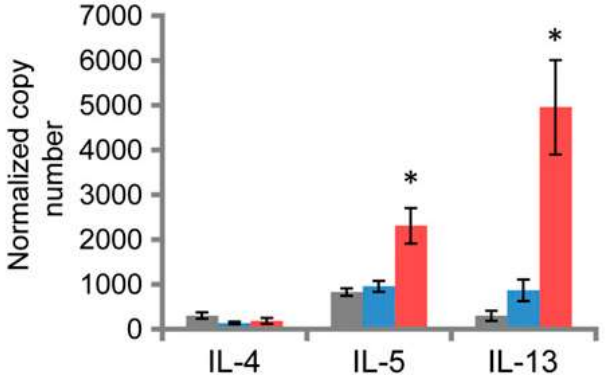

Airway lumen
Allergen
APC
Dupilumab
Lebrikizumab
Interleukin 4
Interleukin 13
B cell
Omalizumab
IgE
Mast cell
Mepolizumab
Reslizumab
Benralizumab
Interleukin 5
Th2 cell
Eosinophil
Smooth muscle hypertrophy
Dupilumab
Lebrikizumab
Bronchial thermoplasty
Interleukin 4
Interleukin 13

Type 2 Inflammation

- **Mediated by 1L-2, 1L-4, 1L-13**
- **Type 2-high & type -2 -low**

  identified by gene expression levels





	Spearman ρ	p-value
IL-13 vs. IL-5	***0.58***	***<10⁻⁴***
IL-13 vs. IL-4	0.13	0.38
IL-4 vs. IL-5	0.14	0.36

Type 2 Inflammation

- Mediated by 1L-2, 1L-4, 1L-13
- Type 2-high & type -2 -low

  identified by gene expression levels
- Substantial difference in eosinosophil counts in airway & blood, serum 1gE and IL-3, -13 expression
- Type 2-high – best response to ICS

Severe asthma variant

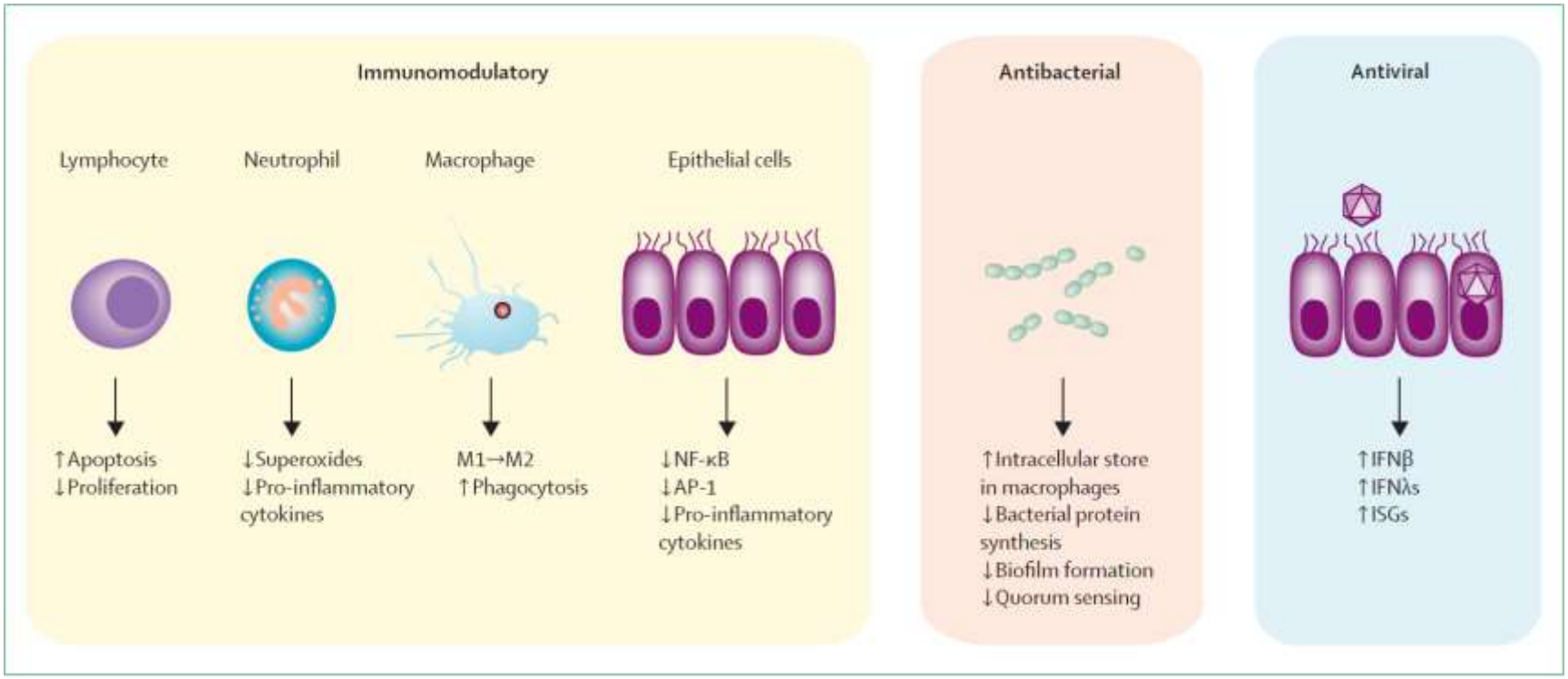
- Non-eosinophilic / paucigranulocytic
- Not well defined
- No specific treatment
- Continue with ICS /LABA

SEVERE ALLERGIC ASTHMA

- High serum lgE
- High eosinophil
- High FeNO

ASTHMA -↓STEROID SENSITIVITY

- May have ↑ sputum neutrophils
- Specific endotypes – not established
- Macrolides studied
- No strong evidence as a targeted treatment



Brusselle G G, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre r d-b p-c trial. Thorax 2013; 68: 322–29.
Wong EH, et al. The role of macrolides in asthma. Lancet Respir Med 2014; 2: 657–70.

SEVERE ASTHMA SUB-TYPE

- Sub-type –persistently raised sputum eosinophils
- Bronchial epithelium release eosinophil chemotactic factors e.g. eotaxin 3
- IL-13 induces selective production of eotoxin 3- assoc with severity and sputum eosinophils
- ? Biomarker for CS insensitive asthma

Larose M, et al. Correlation between CCL26 production by human bronchial epithelial cells and airway eosinophils: involvement in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2015; 136: 904–13.

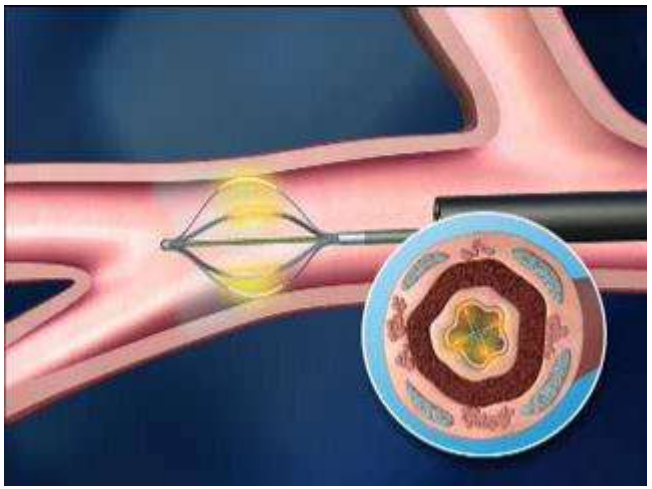
ASTHMA WITH AIRWAY REMODELLING

- Increased airway-wall thickness
- Multidetector CT –can measure above & quantify
- Severe asthma assoc with ↑ wall thickness cf mild to moderate cases
- Wall area & thickness inversely correlated to FEV1 & positively assoc with BDR
- Biological / thermoplasty could provide opportunity
- IL5 –positive effect

Aysola RS et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. Chest 2008; 134: 1183–91.
Haldar P, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N E J M 2009; 360: 973–84.

BRONCHIAL THERMOPLASTY 1

- Alair BT system
- Thermal energy -3 sessions , 3 weeks apart
- AIR, RISA, AIR-2
- 5 yr –sustained reduction in exacerb & health
- NB- exclusion criteria :FEV1 < 50 %; ≥3 exacerbations



BRONCHIAL THERMOPLASTY 2

- Works in part by ↓smooth muscle mass
- ≥60% decrease within few weeks
- + effects on adjacent /untreated airways
- ↓sub-epithelial fibrosis
- ↓BAL TGF-β, chemokine ligand 5 & eosinophils
- nerve cell receptors

Denner D et al. Airway inflammation after bronchial thermoplasty for severe asthma. *Ann Am Thorac Soc* 2015; 12: 1302–09.
Chakir J et al. Eff ects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. *Ann Am Thorac Soc* 2015; 12: 1612–18.
Pretolani M et al. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *AJRCCM* 2014; 190: 1452–54.
Bergqvist A et al. Selective structural changes following bronchial thermoplasty. *Am J Respir Crit Care Med* 2015; 191: A4171.

Bronchial Thermoplasty PREDICTORS

- Shorter duration
- Freq exacerbations
- Less air trapping MDCT

Sarikonda K et al. Predictors of bronchial thermoplasty response in patients with severe refractory asthma. *AJRCCM* 2014; **189:** A2429.

ANTI-IgE

- Omaluzimab: lgGIk humanised monoclonal Ab
- 4/12 therapeutic trial: QOL , exac freb & HCU
- Post –hoc analysis – beneficial in type 2 asthma ; blood eosinophil & FeNO –better biomarkers of response than IgE

Hanania NA et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013 Apr 15;187(8):804-11.

Anti –interleukin 5 (i)

- IL-5-activation & recruitment of eosinophils
- Mepoluzimab – eosinophils >150/ul
- DREAM ↓ exacerbations
- SIRIUS ↓ Oral Corticosteroids
- MENSA ↑ Asthma control
- less consistent effects on FEV1,
- (Dose 100ug sc)

Abhaya Trivedi, Ian D Pavord, Mario Castro. Bronchial thermoplasty and biological therapy as targeted treatments for severe uncontrolled asthma. Lancet Respir Med 2016; 4: 585–92.

Anti –IL5 (ii)

- Reslizumab – IgG 4k humanized MAb
- Prevent binding of Il-5 to eosinophils
- dose 3mg /kg iv monthly
- ↓exacerbations (50-60%)
- ↑PFT (200 ml)

Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, d-b, r p-c, phase 3 trials. Lancet Respir Med 2015; 3: 355–66.

Anti IL-5 (iii)

- Benraluzimab Ig G Ik mAB targets Il-5 Rα
- Depletes eosinophils through ab mediated cell mediated cytotoxicity
- Rx > 300 eosinophils /ul
- effects ↓exacerbation (40-60%)
- Dose 20 &100 mg sc monthly

Laviolette M, Gossage D, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 2013; 132: 1086–96.

Anti IL -13

- Induces production of periostin
- Lebrikizumab –lg G4 mAb targets Il-13
- Improves FEV1
- Greater improvement with high periostin
- FeNO ↑ -induction of nitric oxiode synthese by IL-13
- FeNO strongly assoc response to lebrikizumab

Hanania N, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. Thorax 2015; 70: 748–56.

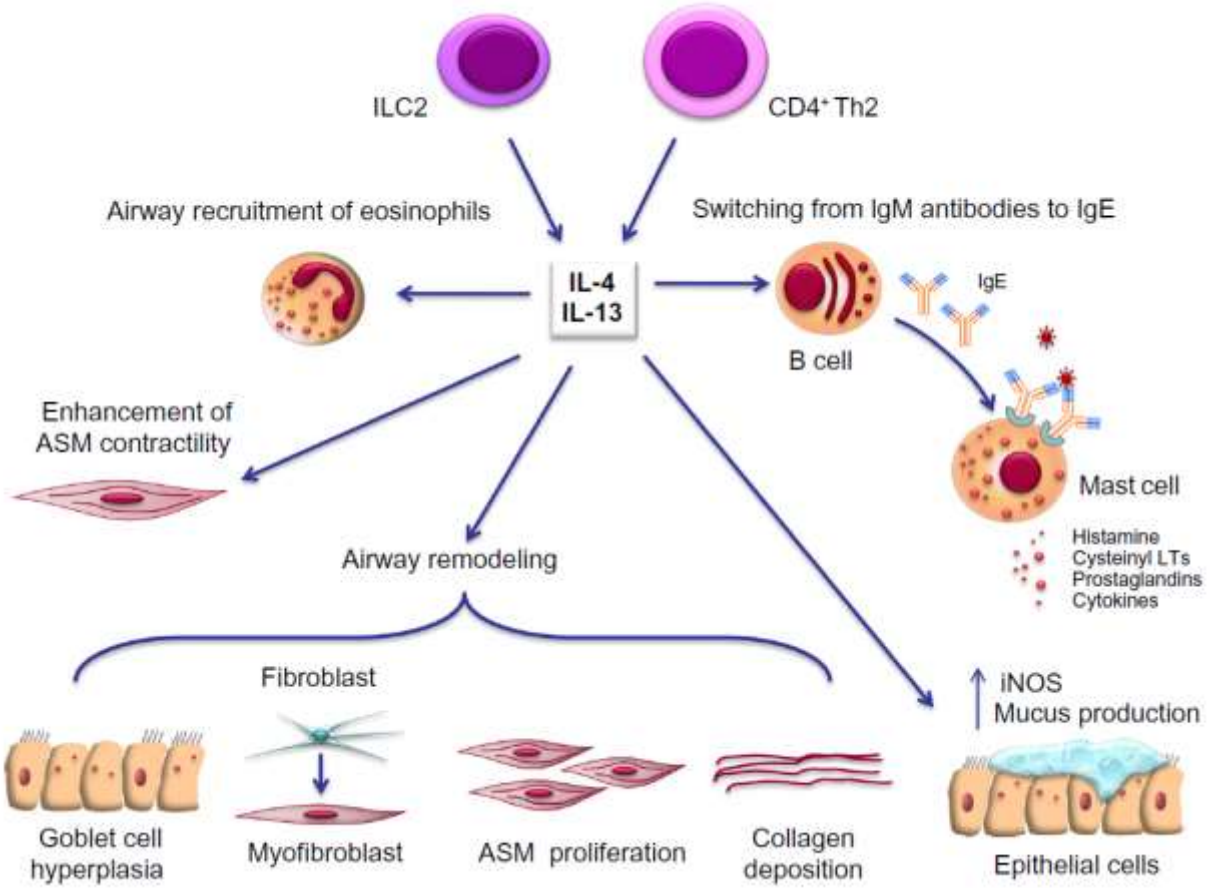
Lebrikizumab

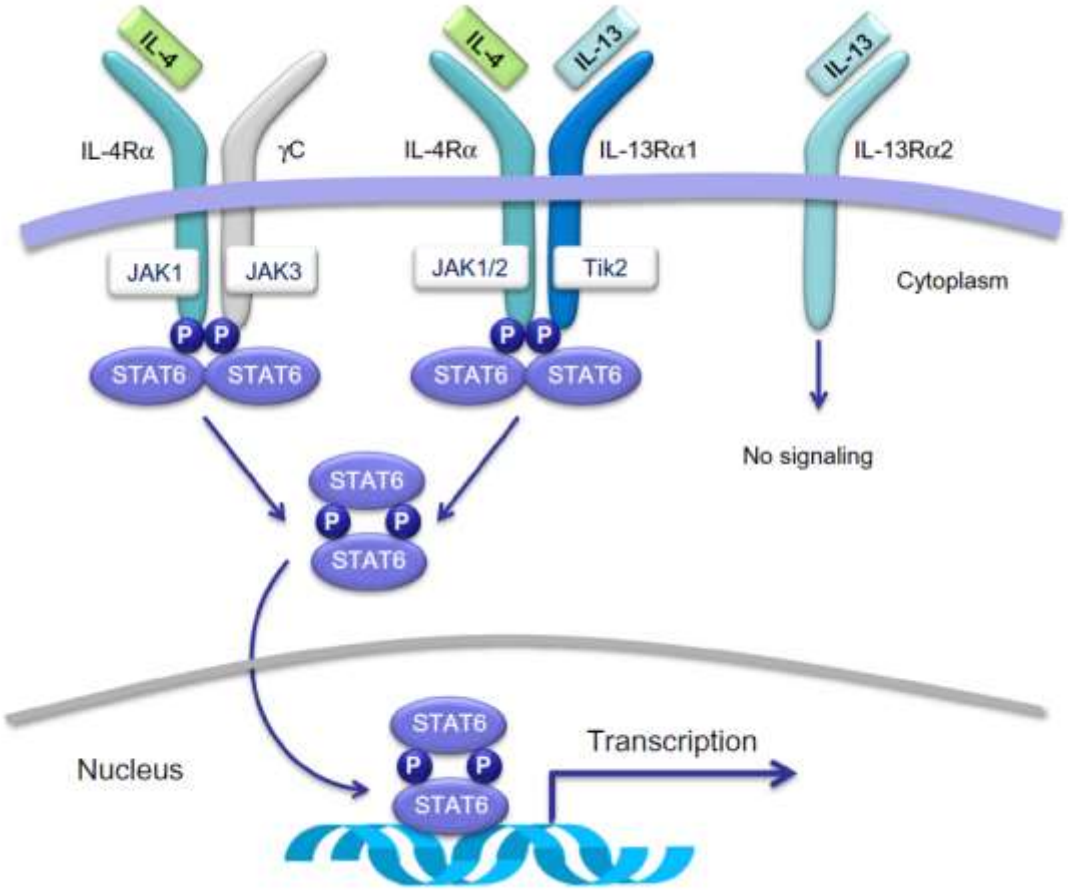
- After phase II
- 2 phase III: Lavolta 1 & Lavolta II
- First met primary endpoint but Lavolta II did not
- Premature termination of development

- Other anti-IL-13 agents
- Tralokinumab
- Anrukinzumab
- GSK679586

IL-4 & IL-13

Pleiotropic effects of IL-4 and IL-13 in asthma pathobiology




IL-4
IL-4
IL-13
IL-13
IL-4Rα
γC
IL-4Rα
IL-13Rα1
IL-13Rα2
JAK1
JAK3
JAK1/2
Tik2
Cytoplasm
P
P
P
P
STAT6
STAT6
STAT6
STAT6
No signaling
STAT6
P
P
STAT6
STAT6
P
P
STAT6
Transcription
Nucleus

IL-4 & IL-13

- IL-4 activates the type I receptor that controls Th2 differentiation
- Type II receptor activated by IL-13 &IL-14
- Dupilumab targets α subunit of IL-4 –inhibits both cytokines
- Improved lung function, reduced exacerbation rate & QOL irrespective of eosinophil count.

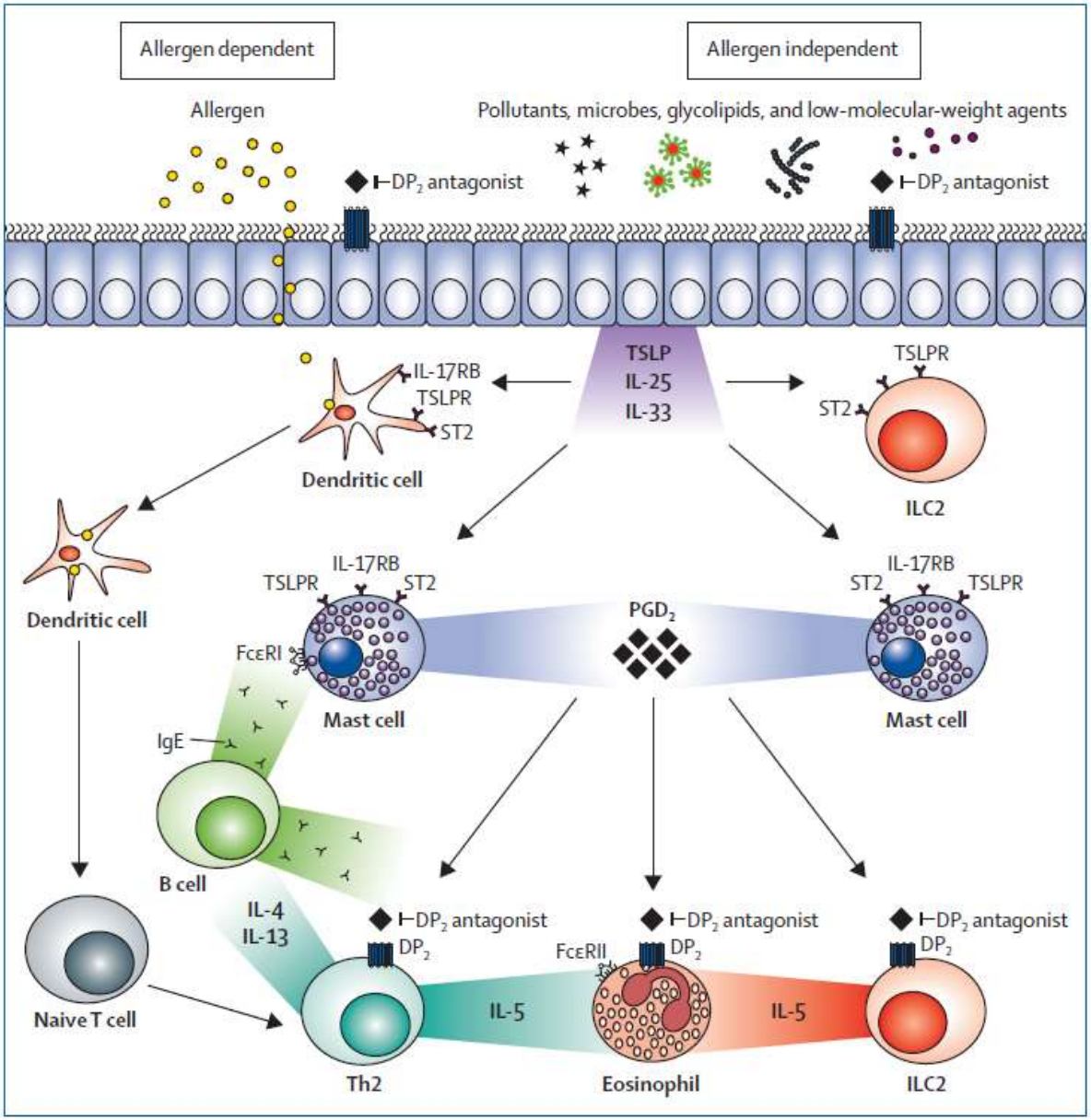
Wenzel S, et al.
Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose ICS+LABA: a r d-b p-c pivotal phase 2b dose-ranging trial. Lancet. 2016 Jul 2;388(10039):31-44.

Breaking News: Game-changer

The Telegraph

FEVIPIPRANT

Breaking News: Game-changer



Fevipiprant

- prostaglandin D2 acts on the PGD2 receptor 2 (DP2 receptor = CRTH2- chemoattractant receptor-homologous molecule expressed on T-helper-2 cells (CRTH2).
- The DP2 receptor
- mediates migration of T-helper-2 cells, delays their apoptosis, stimulates production of IL-4, -5, and interleukin-13.
- affects the migration of and cytokine release from type 2 innate lymphoid cells;
- expressed by eosinophils, mediates chemotaxis & degranulation.
- Number of DP2-positive cells in bronchial submucosa increases with asthma severity
- DP2 receptor is a promising new drug target.
- Fevipiprant (QAW039),oral, antagonist of DP2 receptor (NOT DP1-involved in general homeostasis)

Fevipiprant

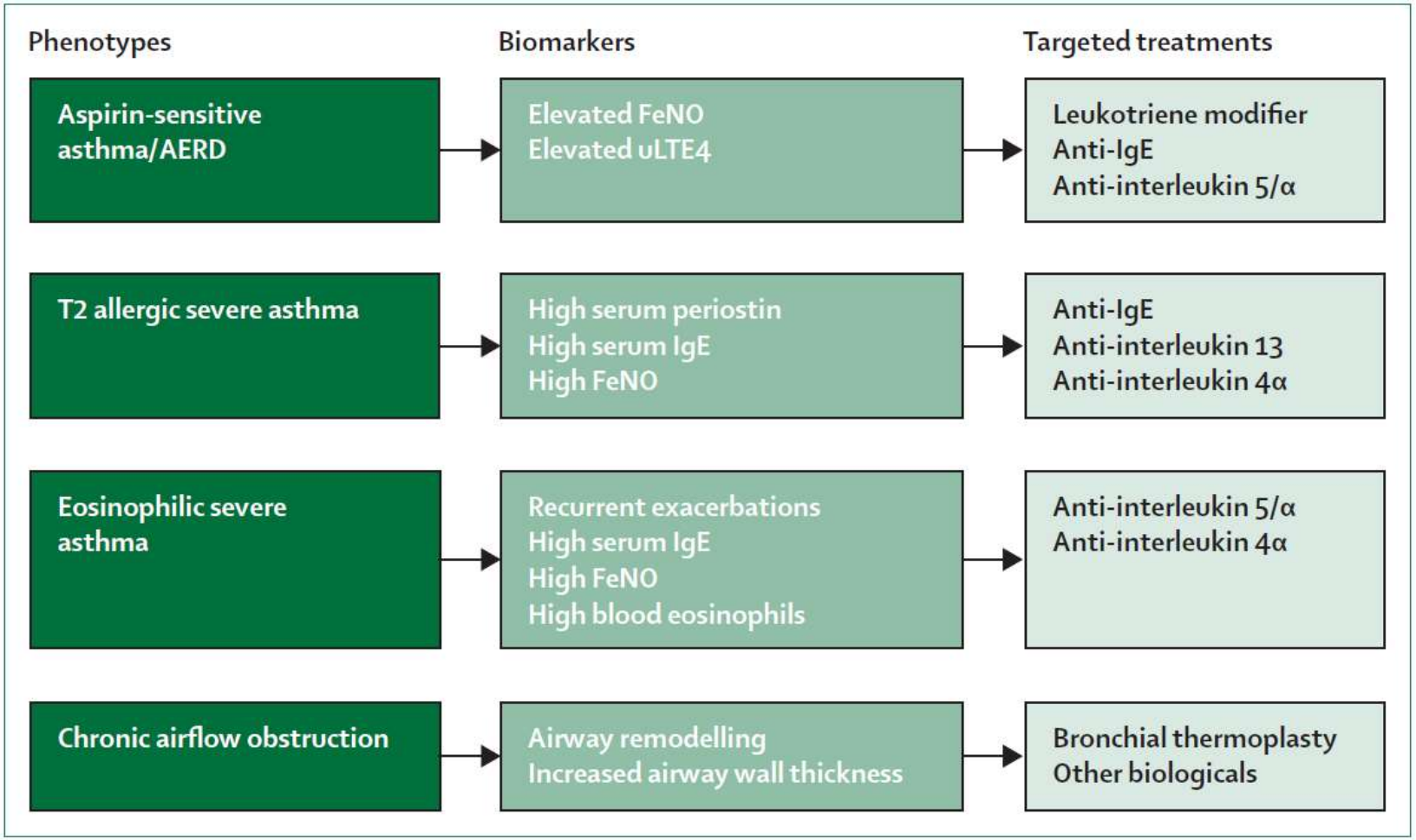
- reduced eosinophilic airway inflammation
- well tolerated in patients with persistent moderate-to-severe asthma and raised sputum eosinophil counts despite ICS.
- Long-term clinical studies underway

Gonem et al, Lancet Respir Med 2016 Published Online August 5, 2016

FUTURE TARGETED TREATMENTS

- IL-33
- Thymic stromal lymphopoeitin (TSLP-an IL-7 like cytokine)
- IL-25

Conclusion: Targeted Treatment



Abhaya Trivedi, Ian D Pavord, Mario Castro. Bronchial thermoplasty and biological therapy as targeted treatments for severe uncontrolled asthma. Lancet Respir Med 2016; 4: 585–92.