Severe asthma
;Endotype-based therapeutic approach

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MedEd Quiz

10th Sep. 2017 NEJM

Which one of the following statements about severe asthma is true?

A. Health care costs per patient are higher than those for type 2 diabetes.

B. Most recently approved biologic interventions target non–type 2 inflammation.

C. Twenty-five percent of adults with asthma have severe asthma.

D. In approximately 20% of patients thought to have severe asthma, the disease is reclassified after steps to confirm the diagnosis are applied.

Words related to severe asthma in 2016-2017

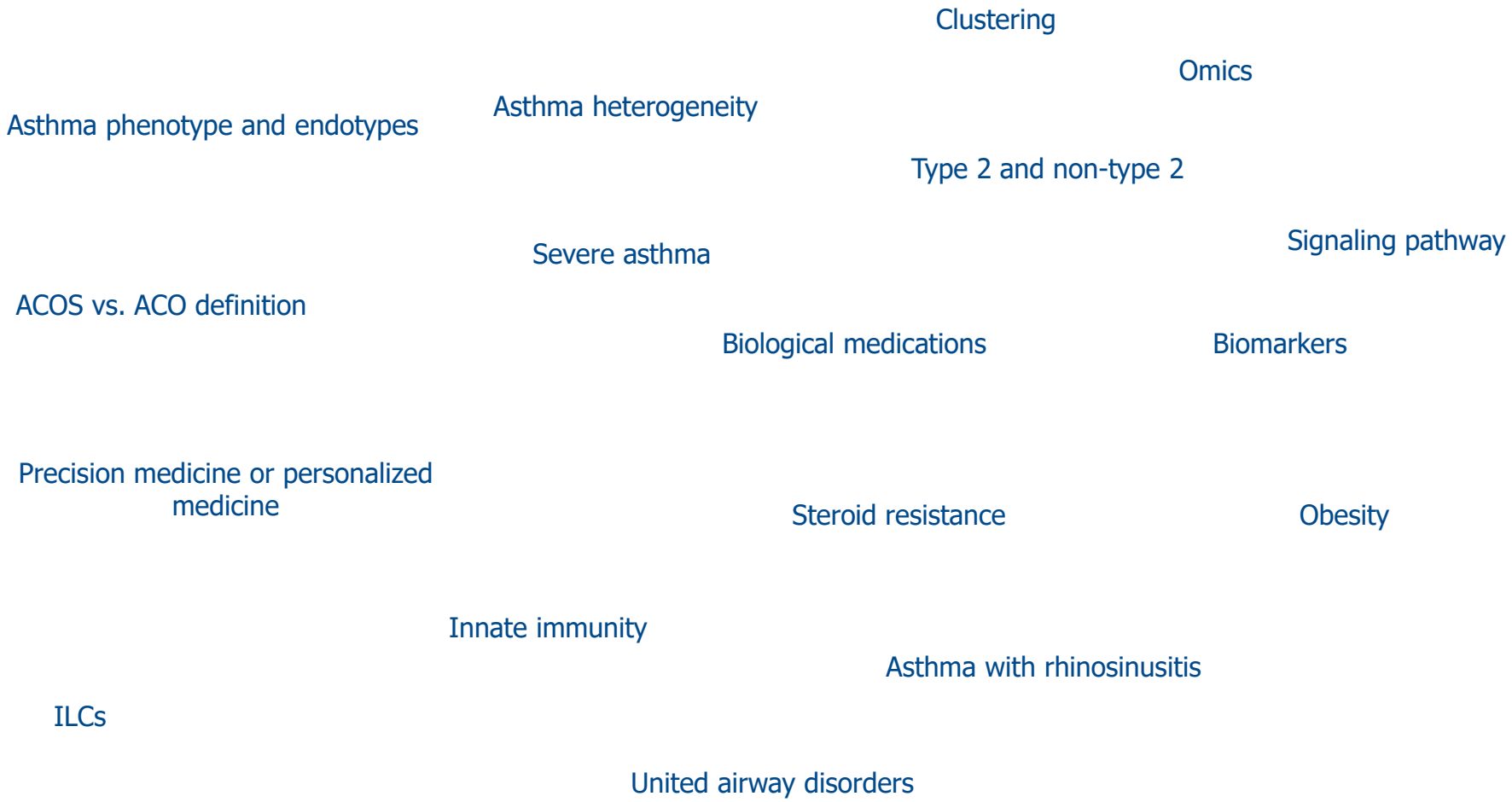
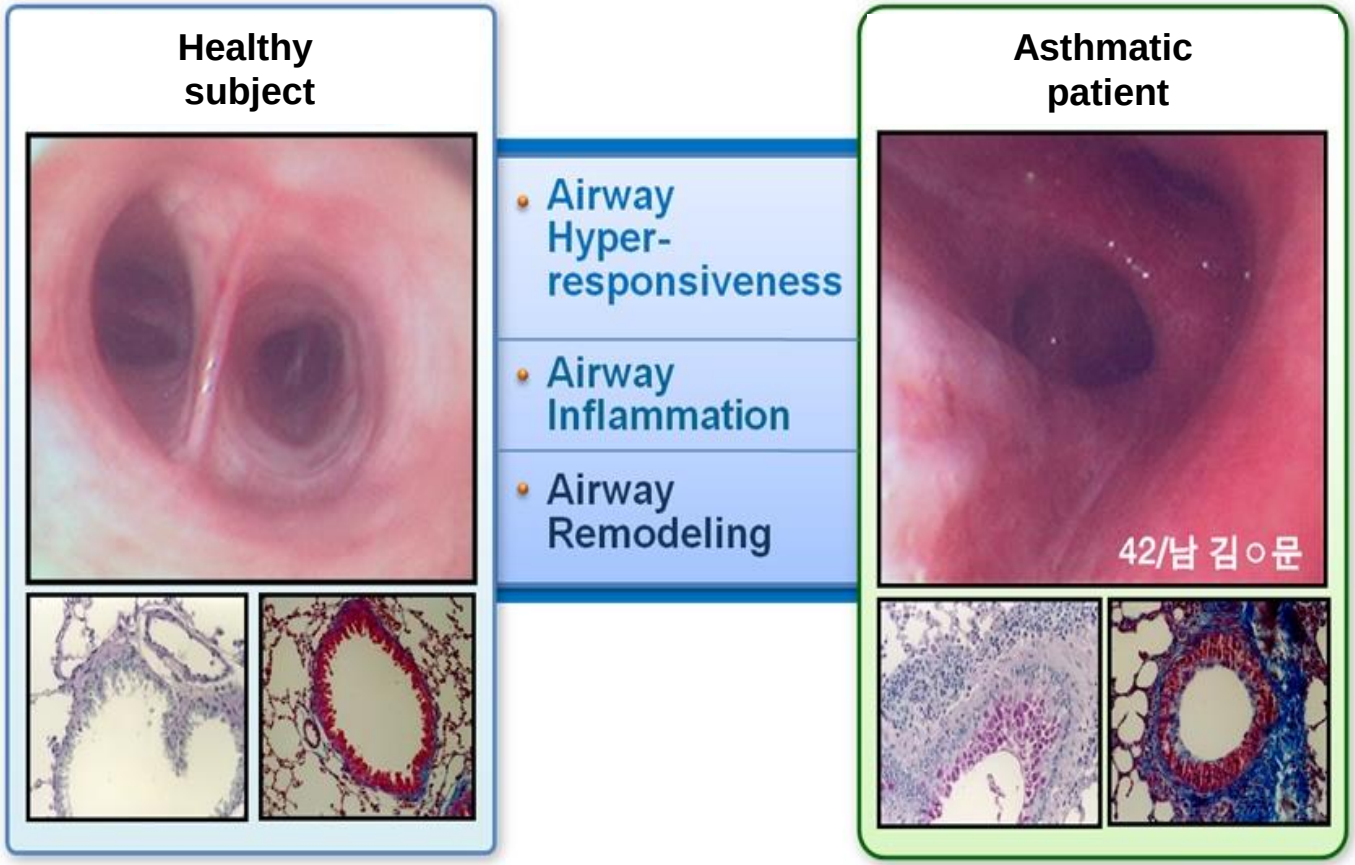


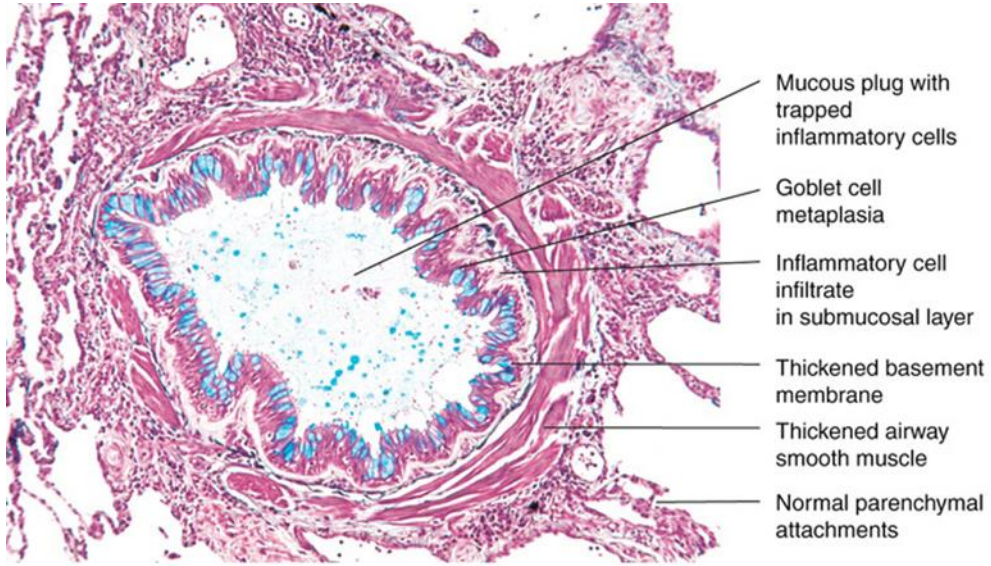
Table of content

Changing concept of asthma

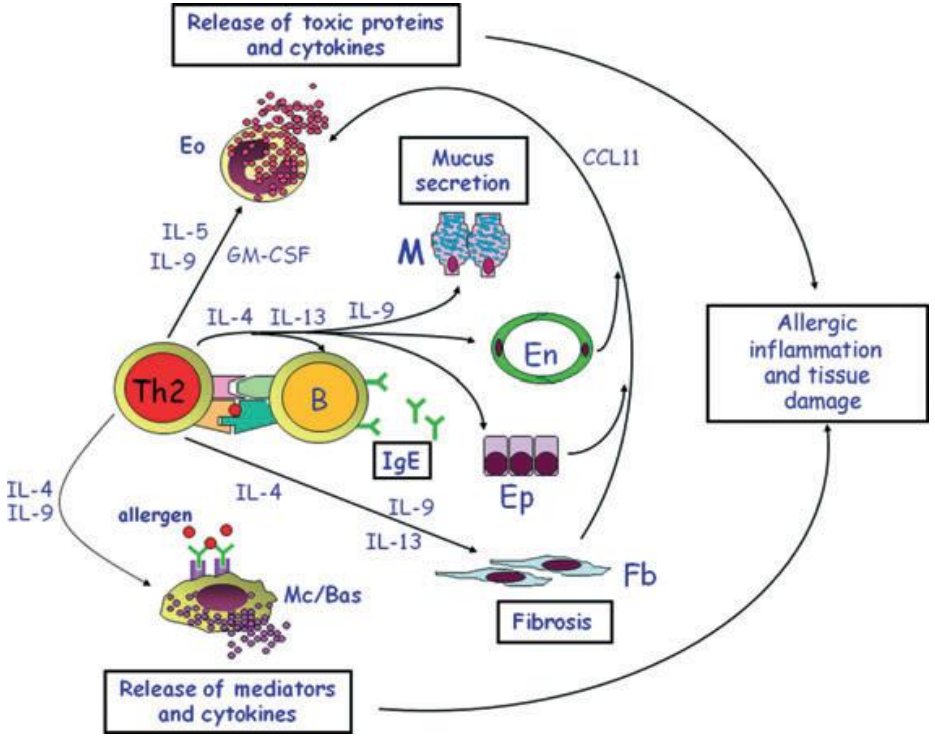
Classic concept of asthma



Changing concept of asthma
Th1/Th2 paradigm



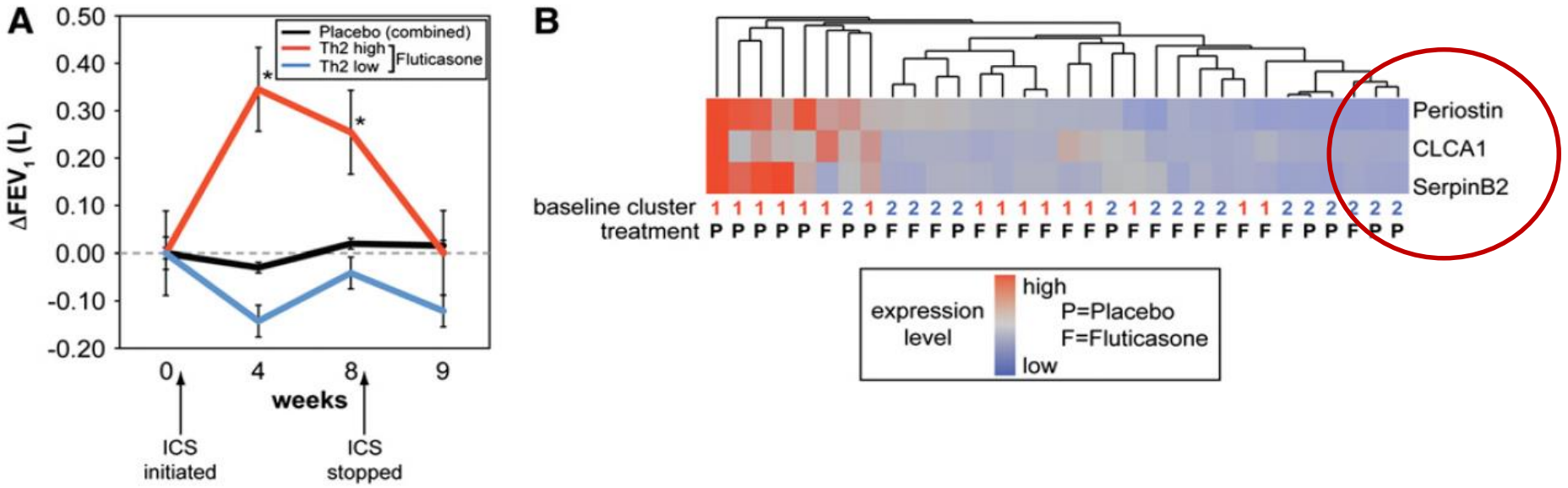
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



Cosmi L et el. Allergy 2011;66(8):989-98
Mosmann TR et al., Immunol 1986;136(7):2348-57.
Barnes PJ. J Clin Invest 2008;118(11):3546-56.

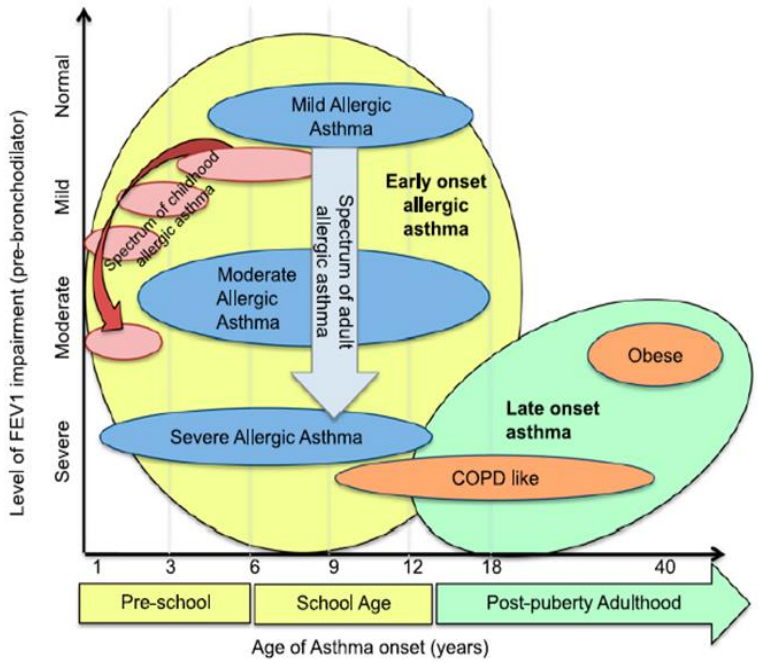
Changing concept of asthma
Th2-high asthma vs Th2-low asthma

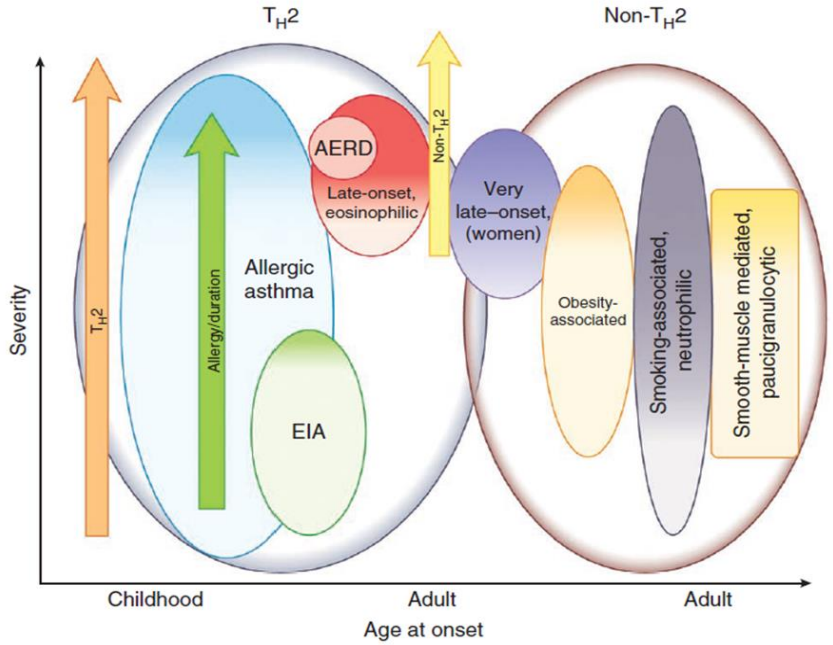
- Th2-high asthma vs Th2-low asthma
  - Those in **the type 2–high cluster were more atopic, had higher tissue eosinophil counts, and had more bronchial hyperresponsiveness**
  - Type 2 signature genes found in human bronchial epithelial cells
    : up-regulated by *IL-13 stimulation*



Woodruff PG et al. Am J Respir Crit Care Med 2009;180:388–395

Changing concept of asthma
Various phenotypes of asthma (recent)





Wenzel S. Nature Medicine 2012;18:716-725
Ann Am Thorac Soc Vol 10, Supplement, pp S118–S124, Dec 2013

Concept of severe asthma

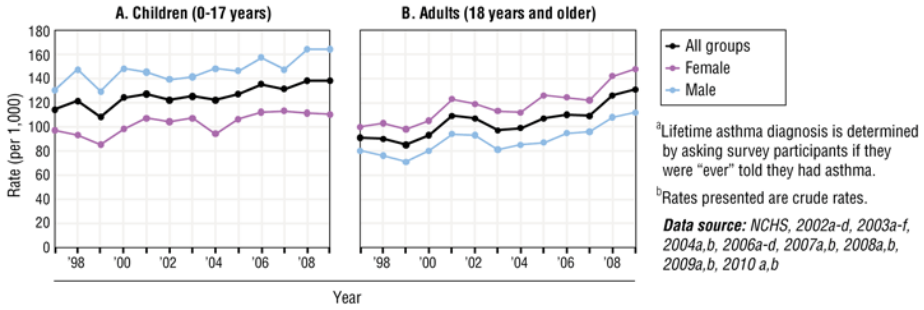
What is a severe asthma?

- **UNIFORM DEFINITION OF SEVERE ASTHMA**
  - Severe asthma is defined by the **level of current clinical control** and **risks**
  - as *"Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)."*

  – Using this definition, both interventional studies and surveys suggest that **at least 5–10%** of the asthma population has **"severe" asthma**.

  – An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease. It is estimated that the number of people with asthma will grow by more than 100 million by 2025.

Exhibit 5-29. Estimated lifetime asthma diagnosis prevalence in children and adults in the U.S., 1997-2009[a,b]



[a]Lifetime asthma diagnosis is determined by asking survey participants if they were "ever" told they had asthma.

[b]Rates presented are crude rates.

Data source: *NCHS, 2002a-d, 2003a-f, 2004a,b, 2006a-d, 2007a,b, 2008a,b, 2009a,b, 2010 a,b*

Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma
J Allergy Clin Immunol 2010;126:926-38

Concept of severe asthma

What is a severe asthma? : steroid resistance

- Severe asthma includes 3 groups, each carrying different public health messages and challenges:

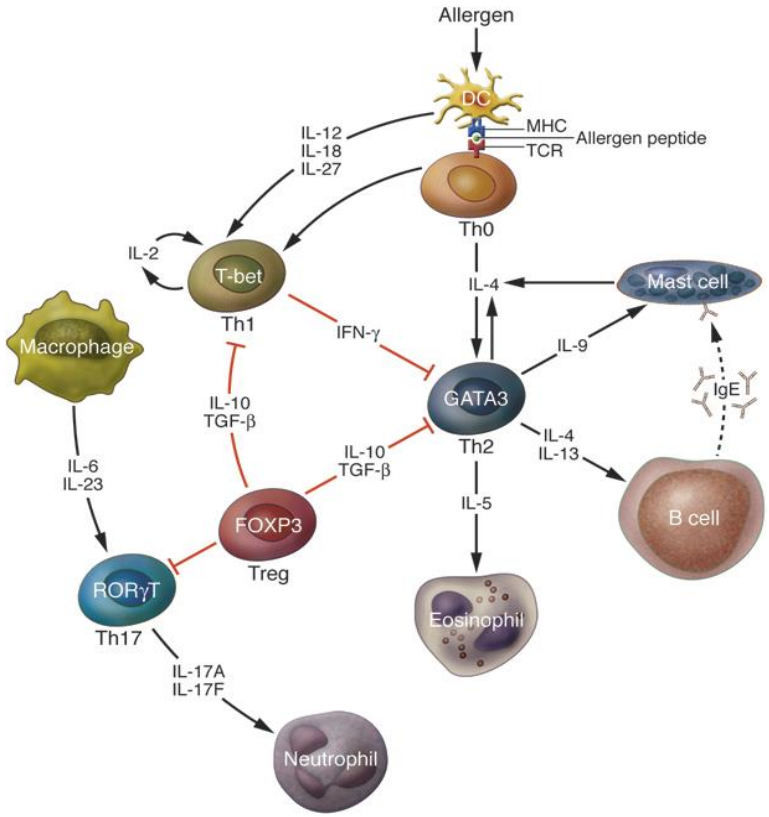
1. Untreated severe asthma.
2. Difficult-to-treat severe asthma.
3. **Treatment-resistant severe asthma.**
   - Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma.

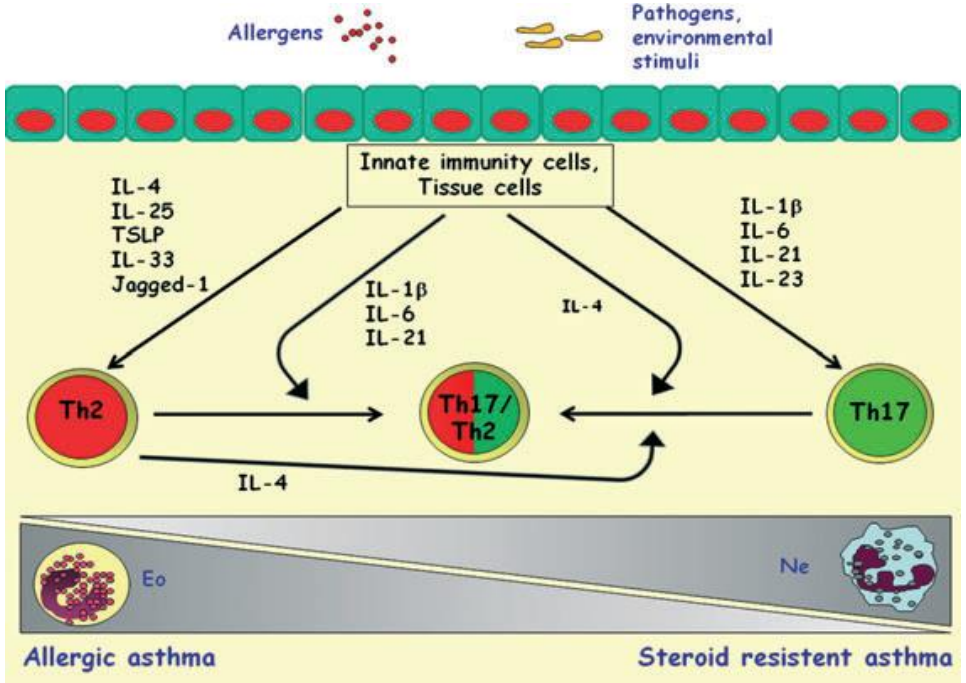
   - Asthma for which control can be maintained only with the highest level of recommended treatment.

Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma
J Allergy Clin Immunol 2010;126:926-38

Changing concept of asthma

Allergic and non-allergic asthmatic inflammation (Th2 and Non-Th2 ; Th1 or Th17)



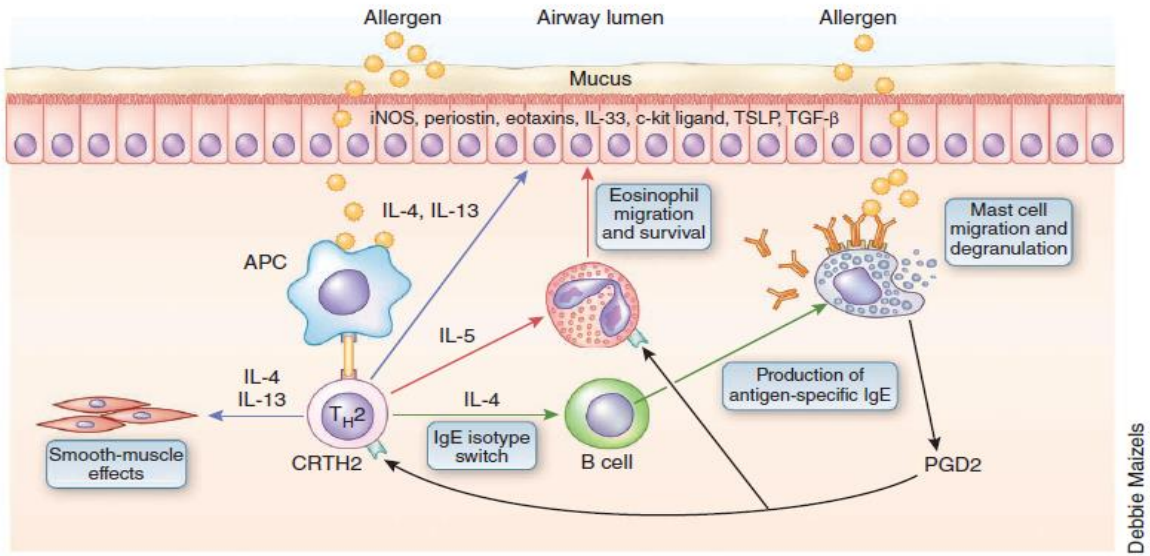


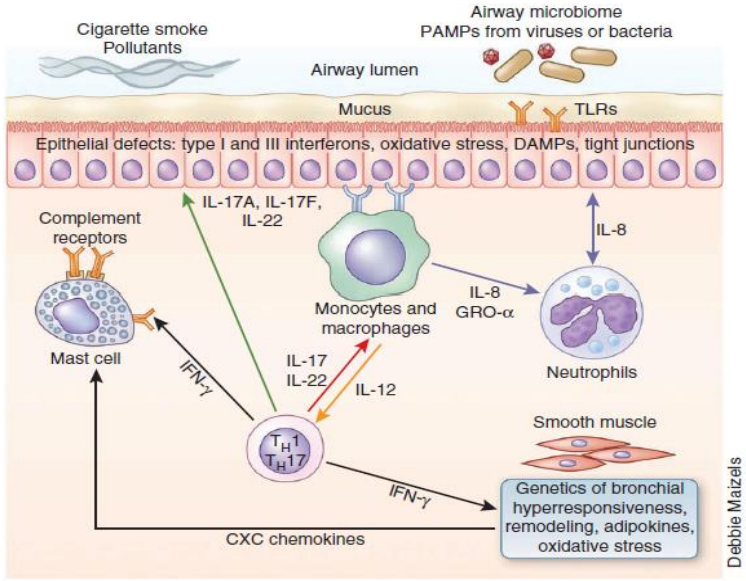
- Non-Th2 asthma has been accepted as neutrophilic dominant airway inflammation with showing steroid-resistance
- Th1 activation such as IFN-γ could enhance mast-cell responses; interestingly, CXC chemokines, induced by IFN-γ, are known mast-cell chemo-attractants to smooth muscle

Cosmi L et el. Allergy 2011;66(8):989-98
Barnes PJ. J Clin Invest 2008;118(11):3546-56

Changing concept of asthma

Allergic and non-allergic asthmatic inflammation (eosinophilic and neutrophilic)





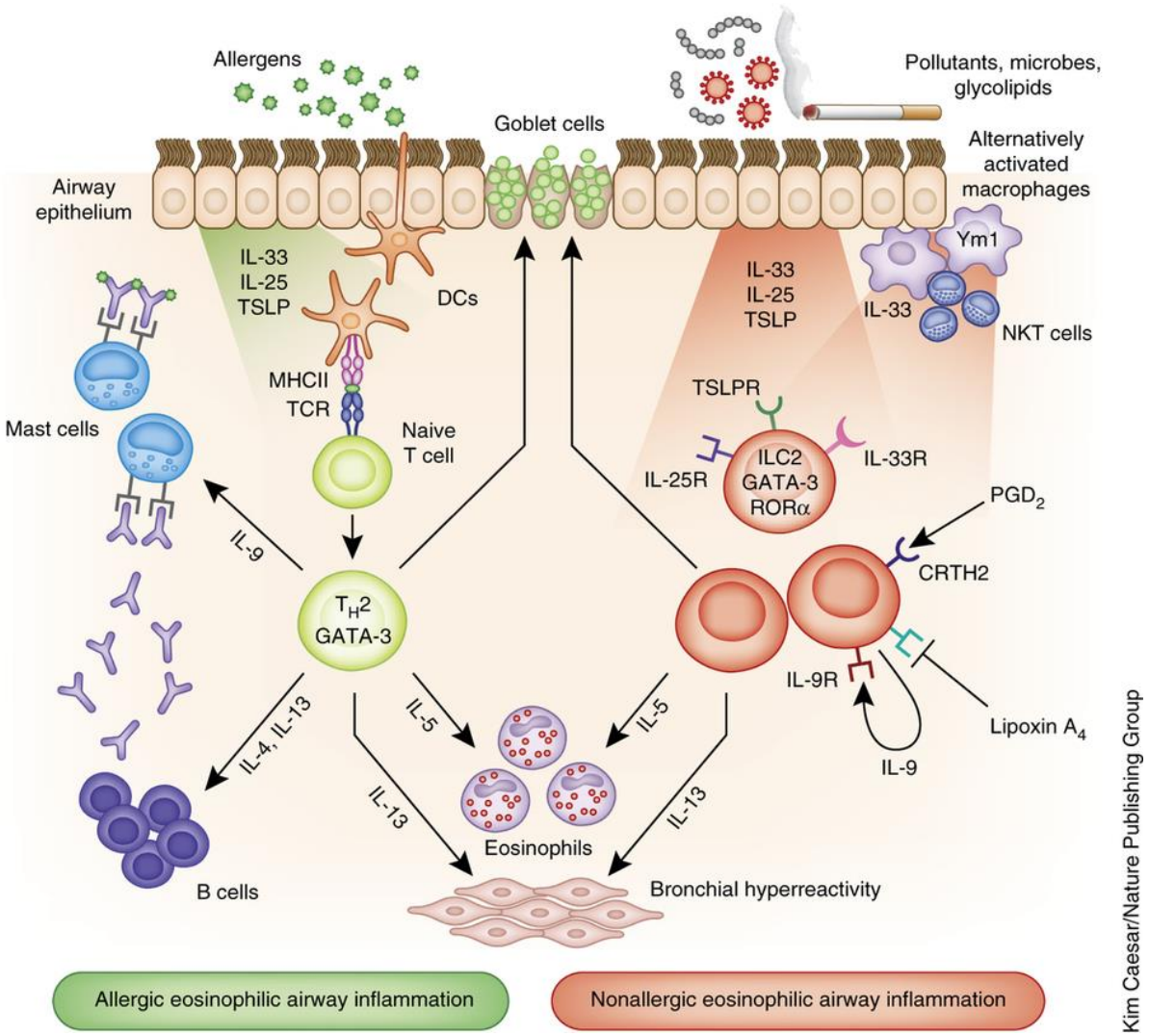
- **Eosinophilia seems to be present in the early-onset/allergic asthma phenotype**
- **Neutrophilic inflammation had not previously been reported in milder asthma**

Wenzel S. Nature Medicine 2012;18:716-725
Wenzel, S et al. Am. J. Respir. Crit. Care Med. 1997;156, 737-743

Changing concept of asthma

Allergic and non-allergic eosinophilic asthmatic inflammation (Non allergic type 2 inflammation)

Contribution of ILCs to asthmatic inflammation



Lambrecht BN & Hammad H. Nat Immunol. 2015 ;16(1):45-56
Brusselle G, et al. Nat Med 2013 ;19, 977-979

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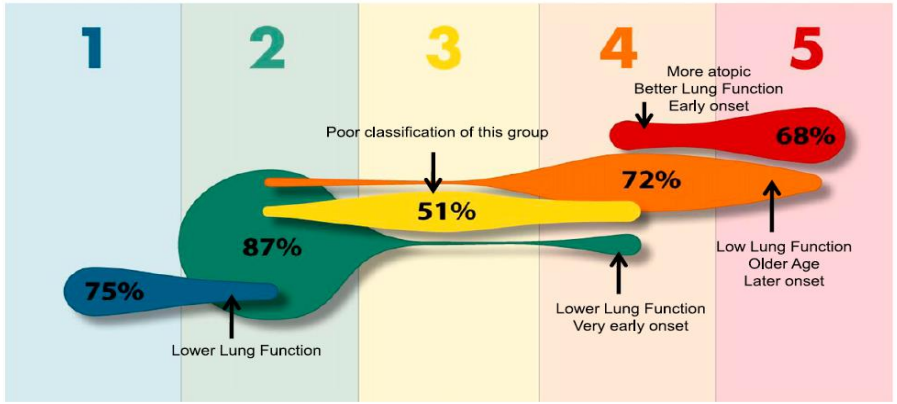
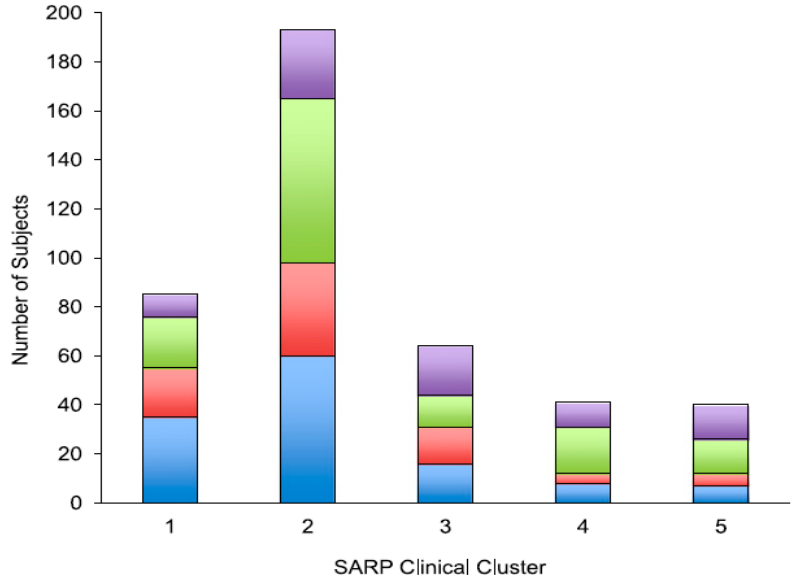
Changing concept of asthma

Approaches to identifying phenotypes of severe asthma



Orange: severe atopic asthma



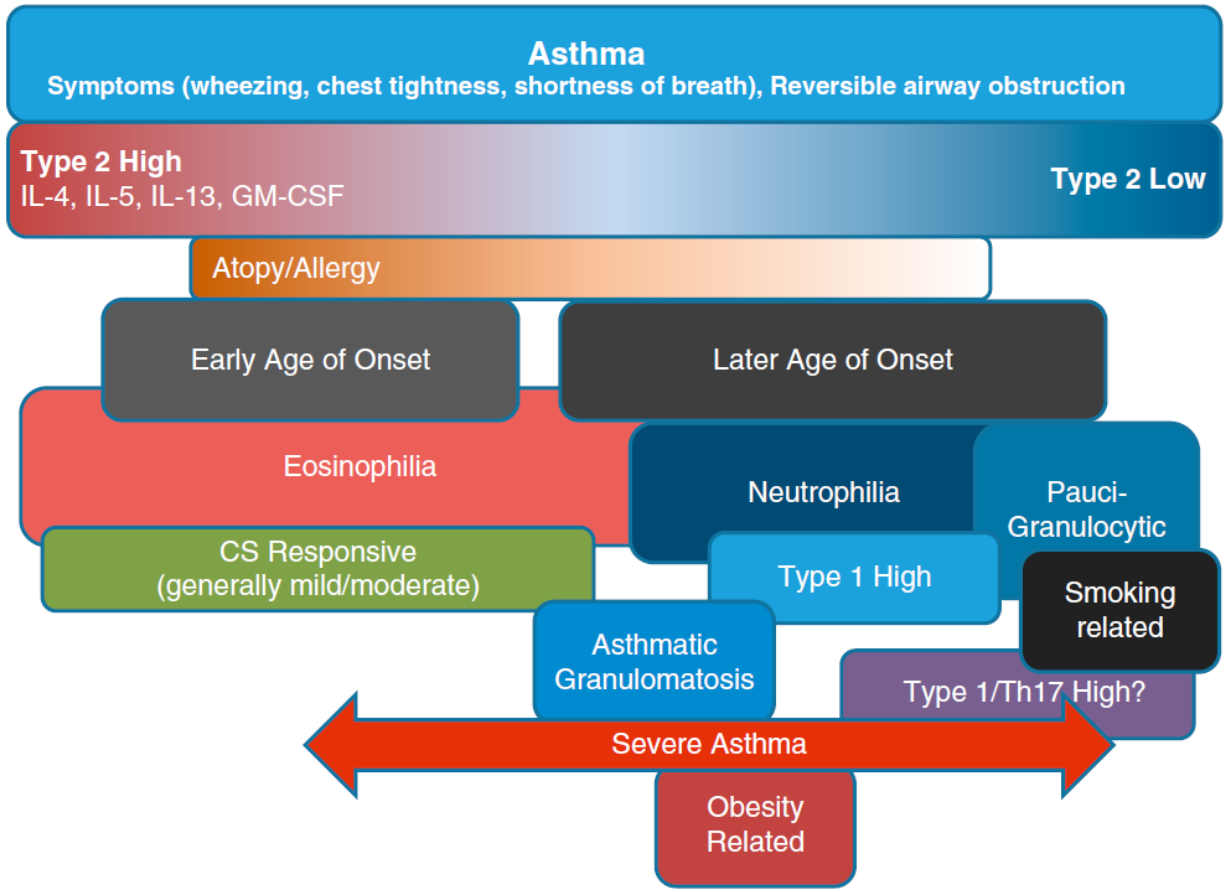
Blue, paucigranulocytic; red, eosinophil predominant; green, neutrophil predominant; purple, mixed granulocytic.

- Eosinophilia can be present in the early-onset/allergic asthma phenotype but is not always associated with IgE-mediated allergy
- phenotypic approaches have identified a severe, adult-onset, highly eosinophilic asthma phenotype often present despite high ICS doses and often requiring systemic corticosteroids.
- is associated with sinus disease, nasal polyps, higher urinary leukotrienes, and more aspirin-sensitive disease

Ann Am Thorac Soc Vol 10, Supplement, pp S118 - S124, Dec 2013

Changing concept of asthma

Approaches to identifying phenotypes of asthma



Gauthier M, et al. Am J Respir Crit Care Med. 2015;192(6):660-8.

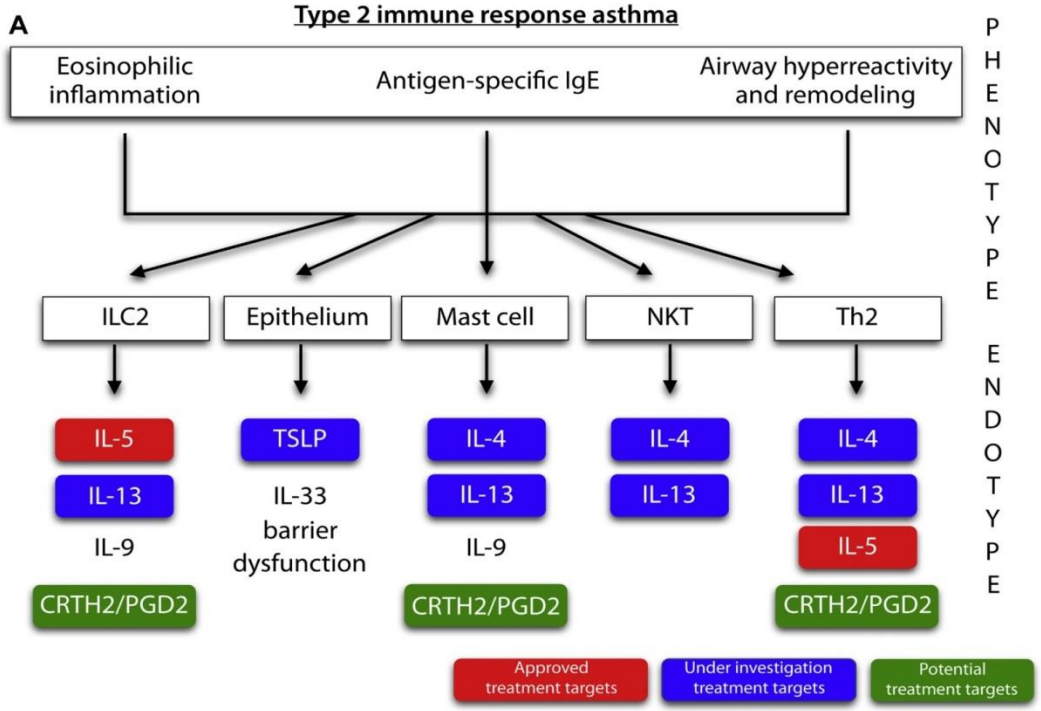
Precision medicine of asthma

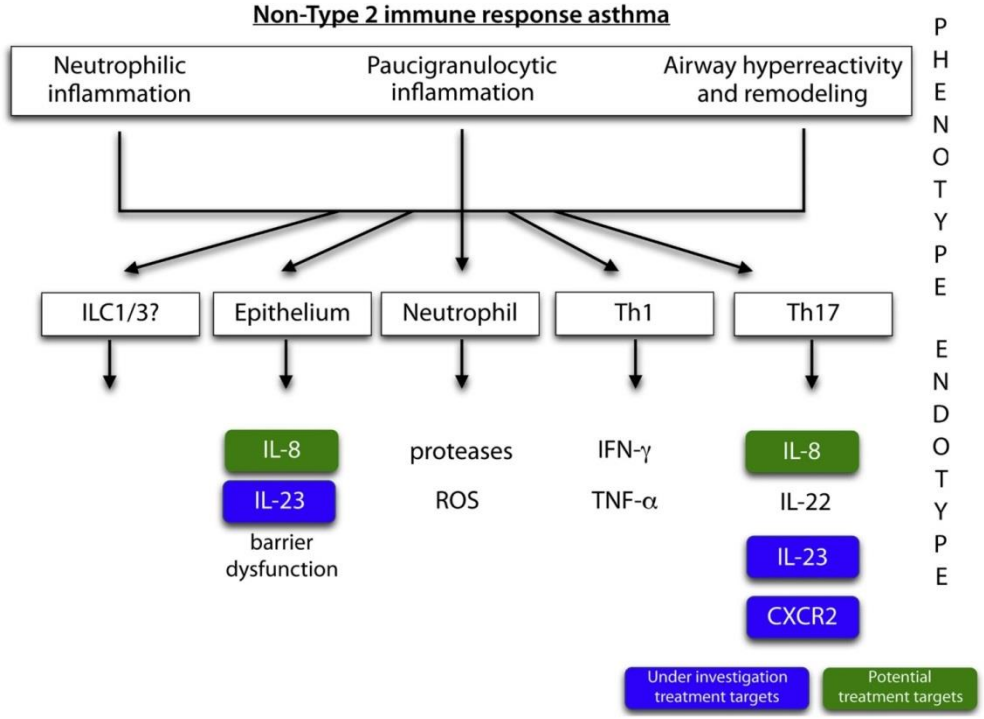
Approaches to identifying phenotypes and endotypes of asthma

PRACTALL consensus report

Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

Antonella Muraro, MD,[a] Robert F. Lemanske, Jr, MD,[b] Peter W. Hellings, MD,[c] Cezmi A. Akdis, MD,[d] Thomas Bieber, MD,[e] Thomas B. Casale, MD,[f] Marek Jutel, MD,[g] Peck Y. Ong, MD,[h] Lars K. Poulsen, PhD,[i] Peter Schmid-Grendelmeier, MD,[j] Hans-Uwe Simon, MD,[k] Sven F. Seys, PhD,[l] and Ioana Agache, MD[m] *Padua, Italy, Madison, Wis, Leuven, Belgium, Davos and Bern, Switzerland, Bonn, Germany, Tampa, Fla, Wroclaw, Poland, Los Angeles, Calif, Copenhagen, Denmark, and Brasov, Romania*

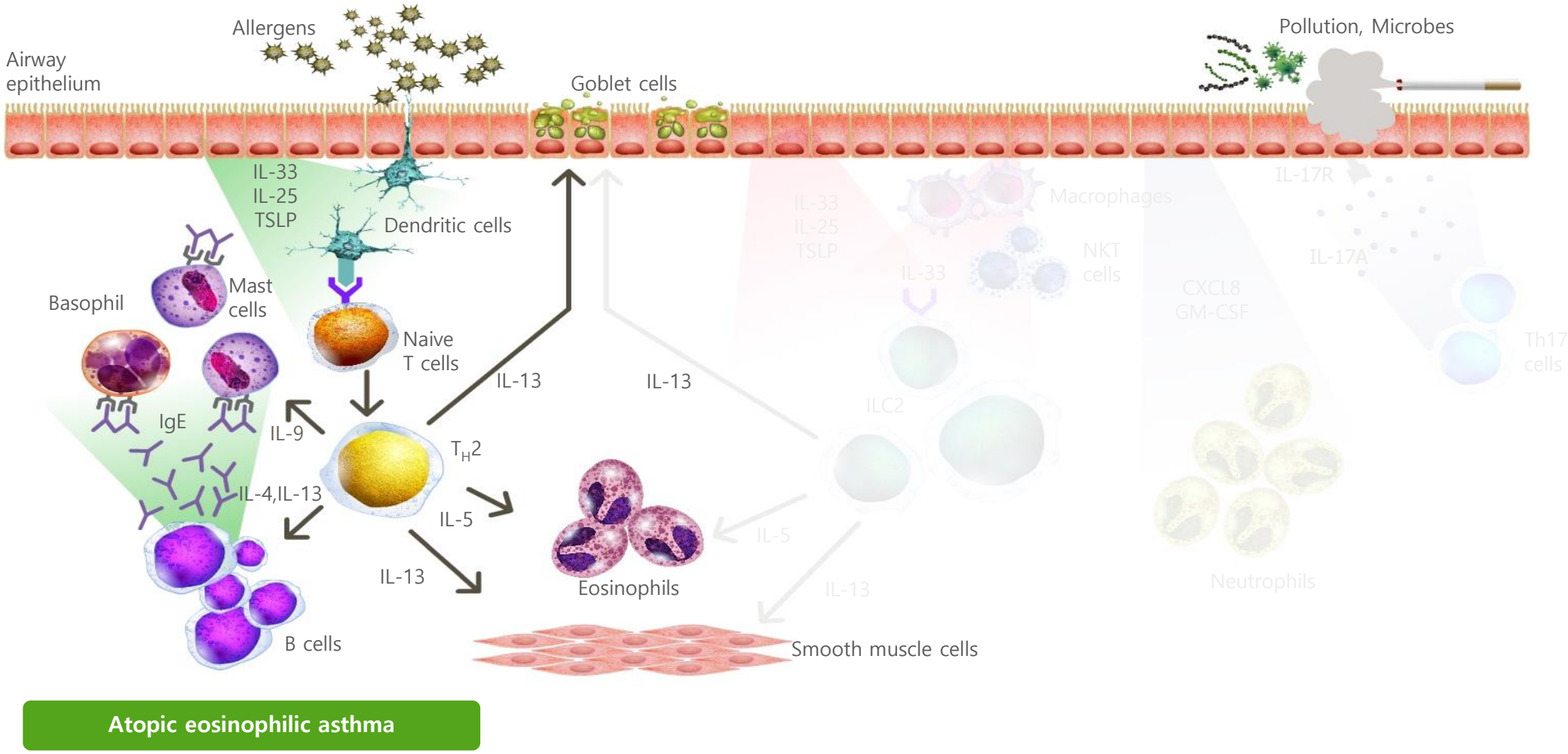




Journal of Allergy and Clinical Immunology 2016;137:1347-1358.

Evolving concept of asthma

Pathophysiology of different asthma phenotypes



Atopic eosinophilic asthma

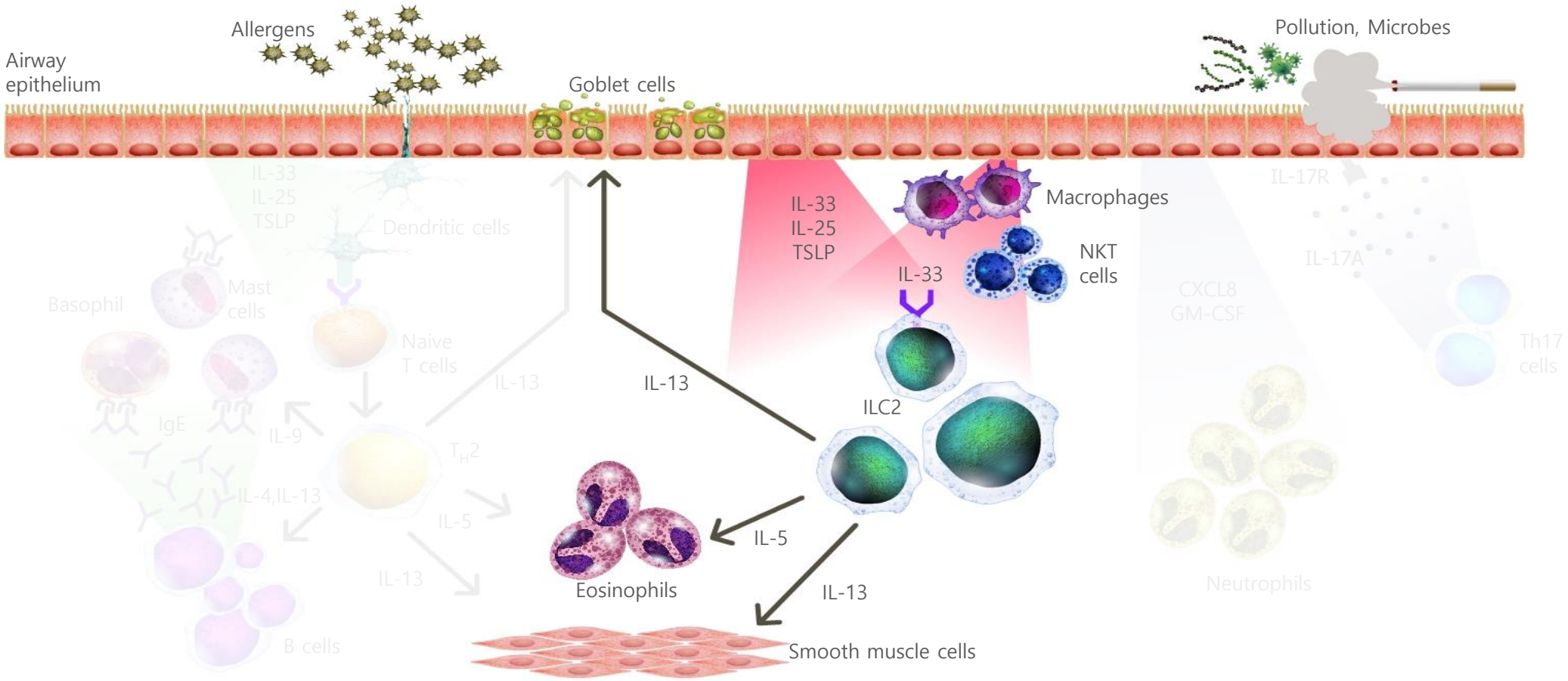
Adapted from Brusselle *et al.* 2014

Brusselle G, *et al. Ann Am Thorac Soc.* 2014:11;S322-S328.

Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor

Evolving concept of asthma

Pathophysiology of different asthma phenotypes



Non-atopic eosinophilic asthma

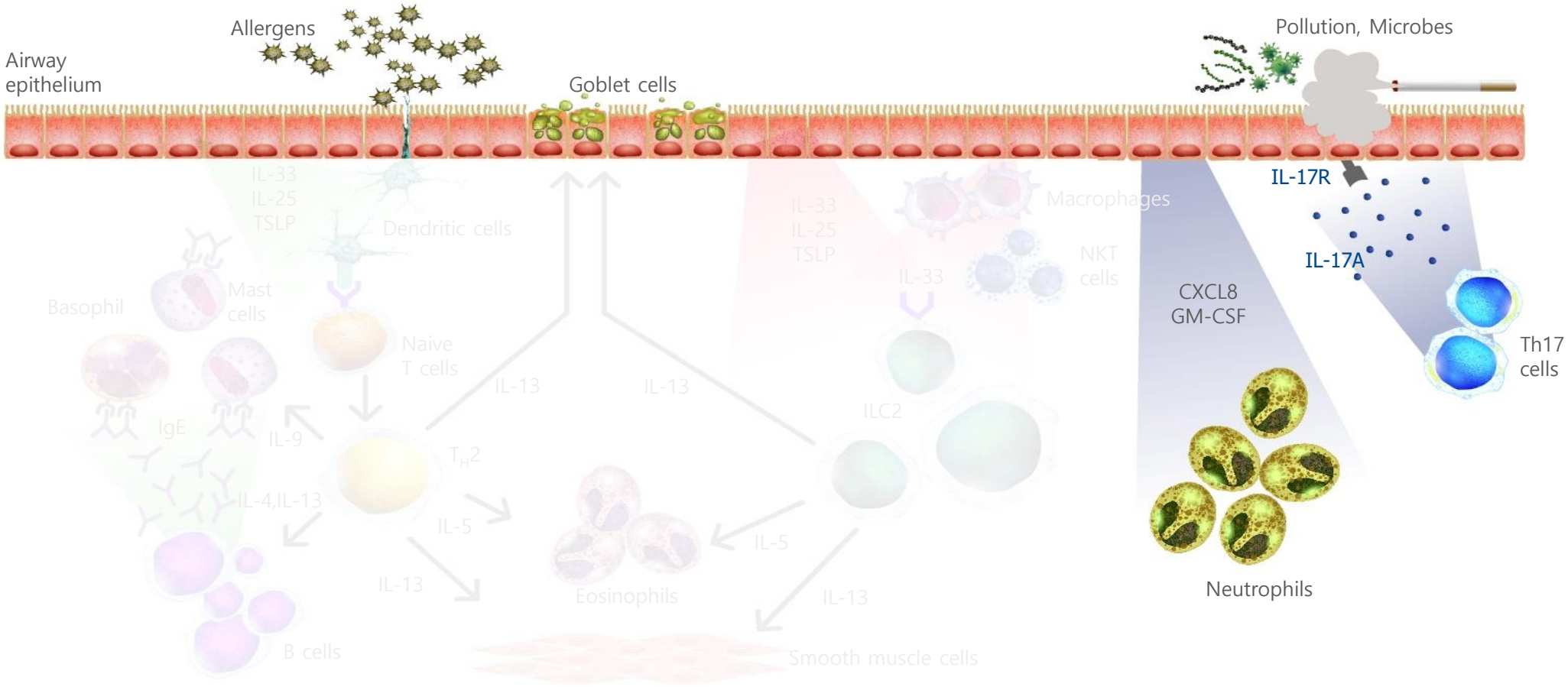
Adapted from Brusselle *et al.* 2014

Brusselle G, *et al. Ann Am Thorac Soc.* 2014:11;S322-S328.

Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor

Evolving concept of asthma

Pathophysiology of different asthma phenotypes



Neutrophilic asthma

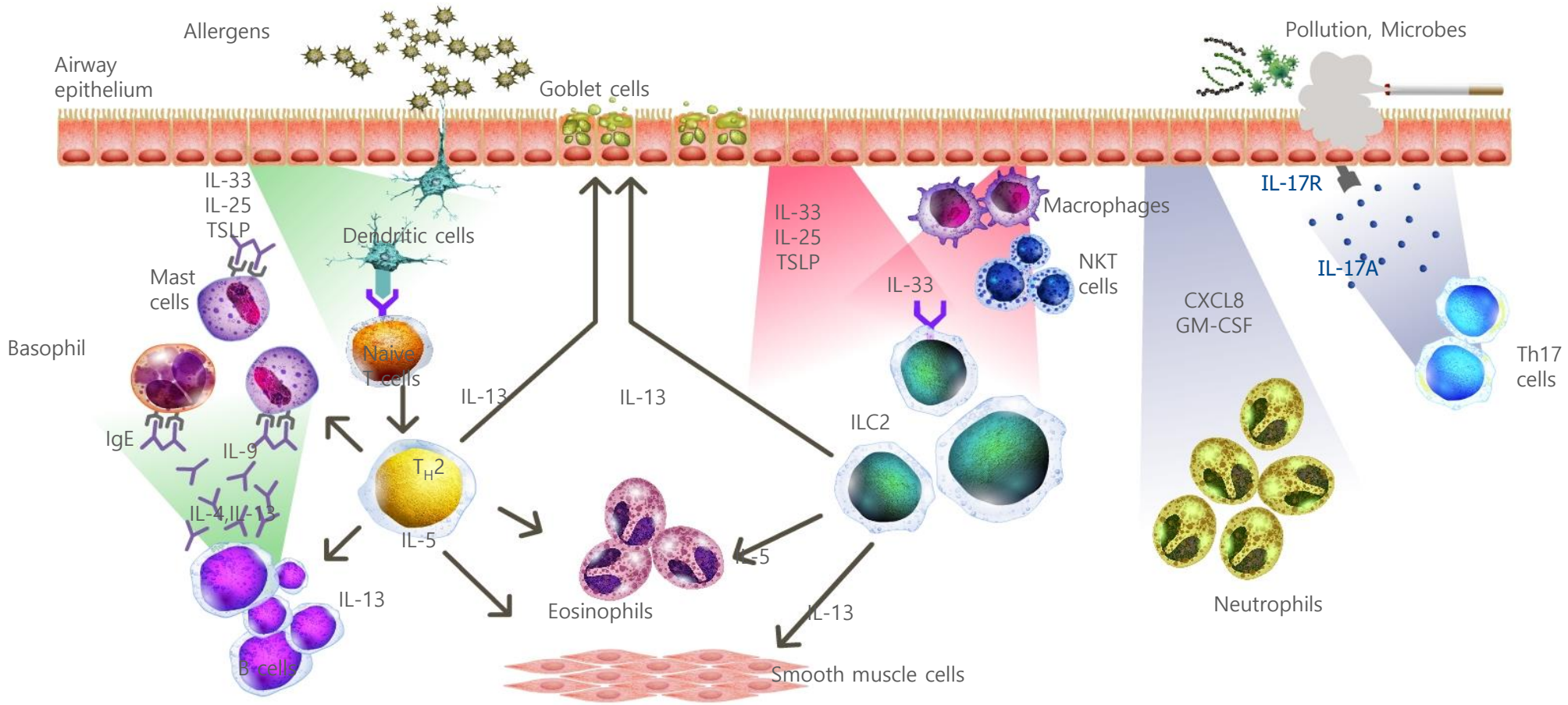
Adapted from Brusselle *et al.* 2014

Brusselle G, *et al. Ann Am Thorac Soc.* 2014:11;S322-S328.

Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor

Cytokine-targeted therapy

Endotype-based approach



Adapted from Brusselle *et al.* 2014

Brusselle G, *et al. Ann Am Thorac Soc.* 2014:11;S322-S328.

Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
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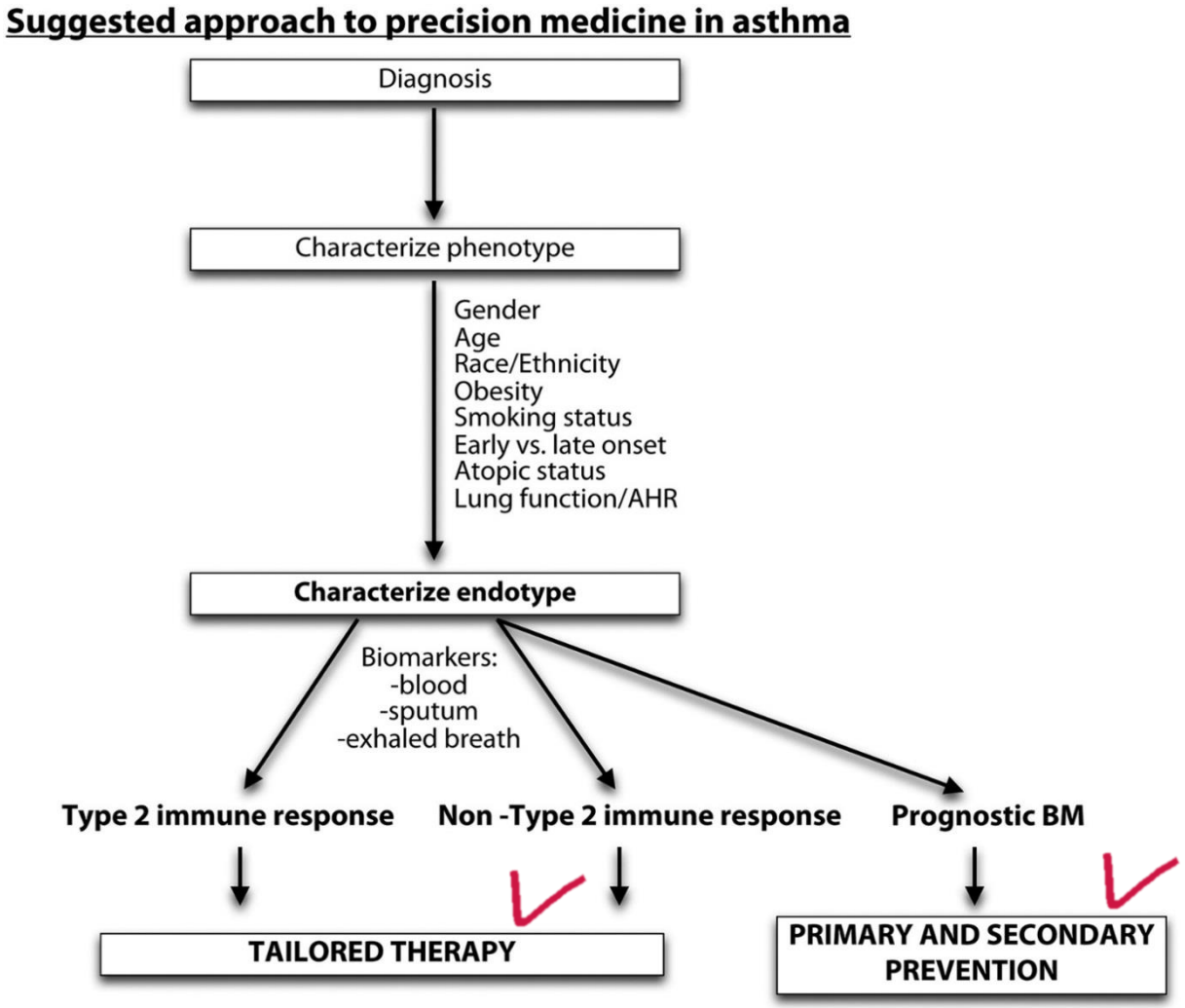
Approach to precision medicine for asthma



Journal of Allergy and Clinical Immunology 2016;137:1347-1358.

Asthma phenotypes to endotypes: vise versa?
U-BIOPRED

T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED

Chih-Hsi Scott Kuo[1,2,3], Stelios Pavlidis[4], Matthew Loza[4], Fred Baribaud[4], Anthony Rowe[4], Ioannis Pandis[3], Ana Sousa[5], Julie Corfield[6,7], Ratko Djukanovic[8], Rene Lutter[9], Peter J. Sterk[9], Charles Auffray[8,10], Yike Guo[3], Ian M. Adcock[1,2,11] and Kian Fan Chung[1,2,11] on behalf of the U-BIOPRED Study Group[12]

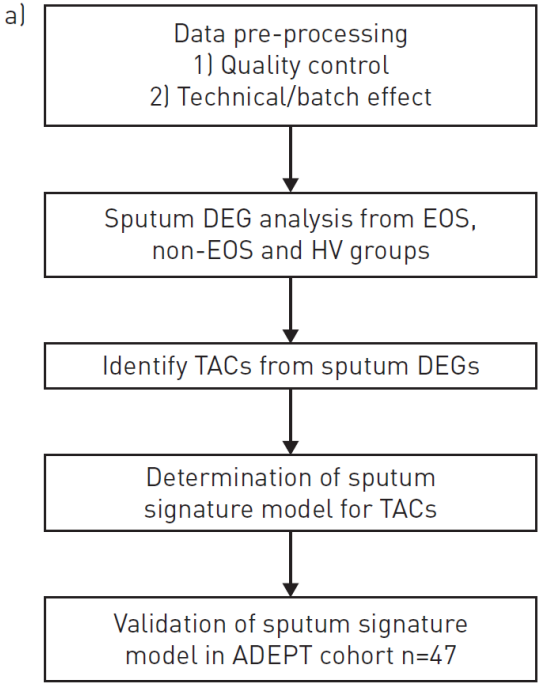
Affiliations: [1]Airways Disease, National Heart and Lung Institute, Imperial College London, London, UK. [2]Biomedical Research Unit, Royal Brompton and Harefield NHS Trust, London, UK. [3]Dept of Computing and Data Science Institute, Imperial College London, London, UK. [4]Janssen R&D, High Wycombe, UK. [5]Respiratory Therapeutic Unit, GSK, Stockley Park, UK. [6]AstraZeneca R&D, Mölndal, Sweden. [7]Areteva R&D, Nottingham, UK. [8]Faculty of Medicine, Southampton University, Southampton, UK. [9]Faculty of Medicine, University of Amsterdam, Amsterdam, The Netherlands. [10]European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL, Université de Lyon, Lyon, France. [11]These authors contributed equally to this work. [12]A full list of the U-BIOPRED Consortium project team member and their affiliations can be found in the Acknowledgements section.

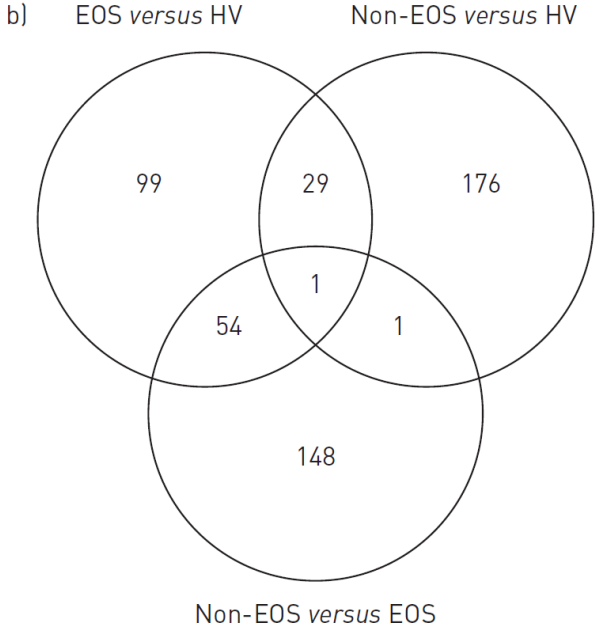
Correspondence: K.F. Chung, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London SW3 6LY, UK. E-mail: f.chung@imperial.ac.uk

@ERSpublications
Clustering of transcriptomic genes from sputum cells defined one Th2- and two non-Th2-associated phenotypes http://ow.ly/UEkA3069ZYL

Cite this article as: Kuo C-HS, Pavlidis S, Loza M, *et al*. T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED. *Eur Respir J* 2017; 49: 1602135 [https://doi.org/10.1183/13993003.02135-2016].

Clustering using clinical features alone has not yielded information on the underlying biology as similar inflammatory cell profiles have been seen between these clinical clusters





Eur Respir J 2017;49:1602135.

Asthma phenotypes to endotypes: vise versa?

U-BIOPRED

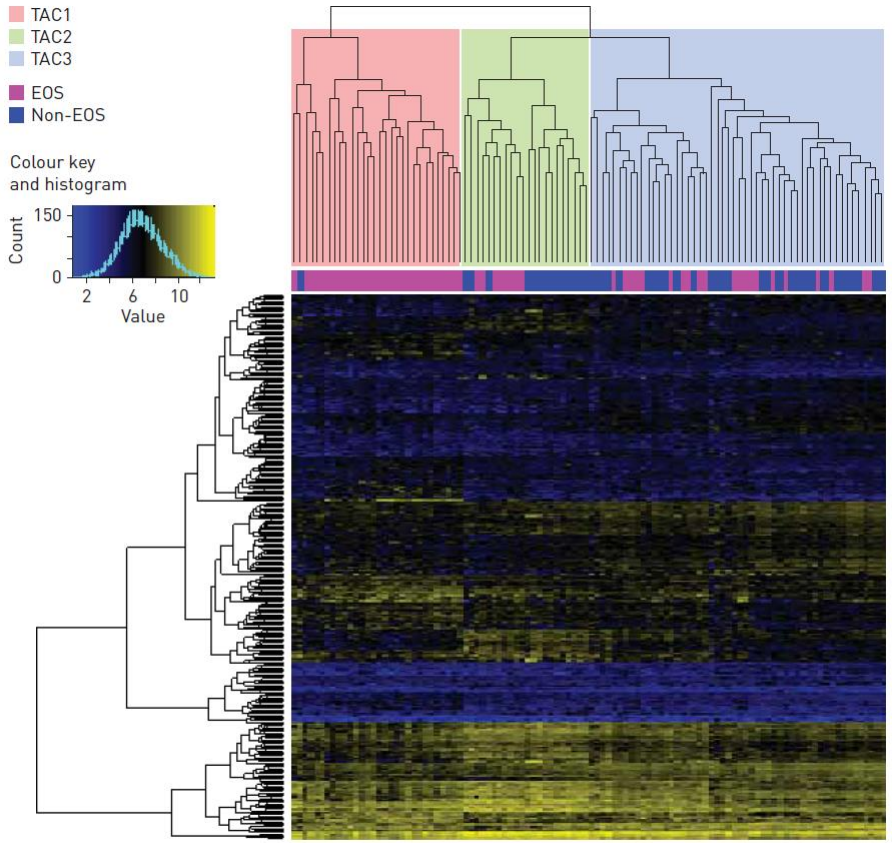


FIGURE 3 Heatmap of hierarchical clustering on 104 asthmatic subjects (columns) with 508 transcriptomic features (rows). Clustering results in three transcriptome-associated clusters: TAC1, TAC2 and TAC3. The sputum granulocyte status for each participant is mapped underneath the column dendrogram. EOS: eosinophilic.

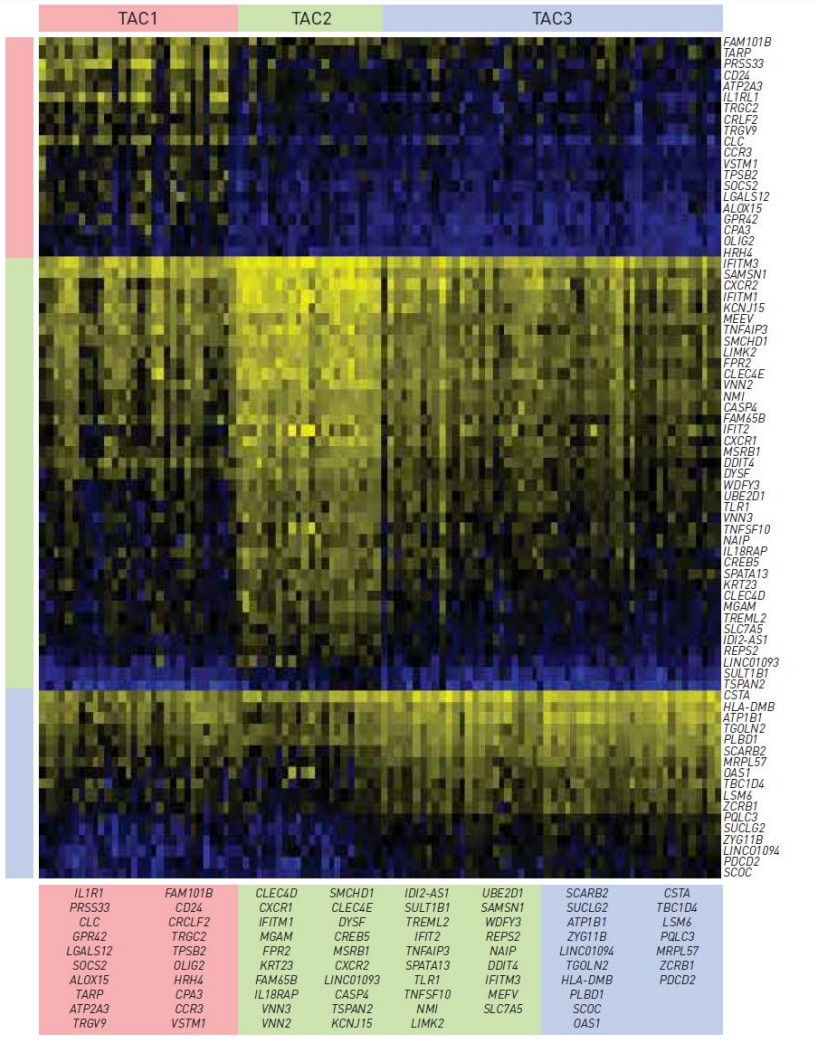


FIGURE 4 Heat map showing the signature of genes that best discriminate each transcriptome-associated cluster (TAC) derived using the shrunken centroid method. Columns represents 104 asthmatic subjects and rows represent 76 genes. The signatures of genes in the corresponding colours of each TAC (TAC1: 20 genes; TAC2: 39 genes; TAC3: 17 genes) are shown.

Eur Respir J 2017;49:1602135.

Asthma phenotypes to endotypes: vise versa?
U-BIOPRED

- The **transcriptome** is the set of all RNA molecules in one cell or a population of cells. It is sometimes used to refer to all RNAs, or just mRNA, depending on the particular experiment.
- It differs from the exome in that it includes only those RNA molecules found in a specified cell population, and usually includes the amount or concentration of each RNA molecule in addition to the molecular identities.

TAC 1: Multiple **cytokine receptors and signalling** (IL1RL1, SOCS2, CCR3, CRLF2), enzymes found in **macrophages, mast cells and eosinophils** (PRSS33, CLC, ALOX15, TPSB2, CPA3), and a cell adhesion molecule on granulocytes and B-cells involved in the damaged-induced **adaptive immune response** (CD24) → **Type 2: interleukin (IL)-13/Th2-high predominantly EOS cluster**

TAC 2: the **IFN and TNF super-families** (IFIT2, TNFSF10, IFIH1, TNFAIP3, IFITM1, IL18RAP), leukocyte surface receptors mediating innate immunity (FPR2, TREML2, TLR1), **neutrophil** chemotaxis and migration (CXCR1, CXCR2, VNN2, VNN3), **inflammasomes** (CASP4, MEFV, NAIP), and **pattern recognition** (CLEC4D, CLEC4E)

TAC 3: glucose and succinate metabolism (SUCLG2, TBC1D4), ubiquitination (ZYG11B), **mitochondrial function** (MRPL57, PDCD2), energy consumption (ATP1B1), and **endo/lysosomal function** and transport (SCARB2, TGOLN2, SCOC)

→ **Non-Type 2**

TAC 2- interferon (IFN)/tumour necrosis factor (TNF)-α/inflammasome-associated

TAC 3- metabolic and mitochondrial pathways

Eur Respir J 2017;49:1602135.

Asthma phenotypes to endotypes: vise versa?

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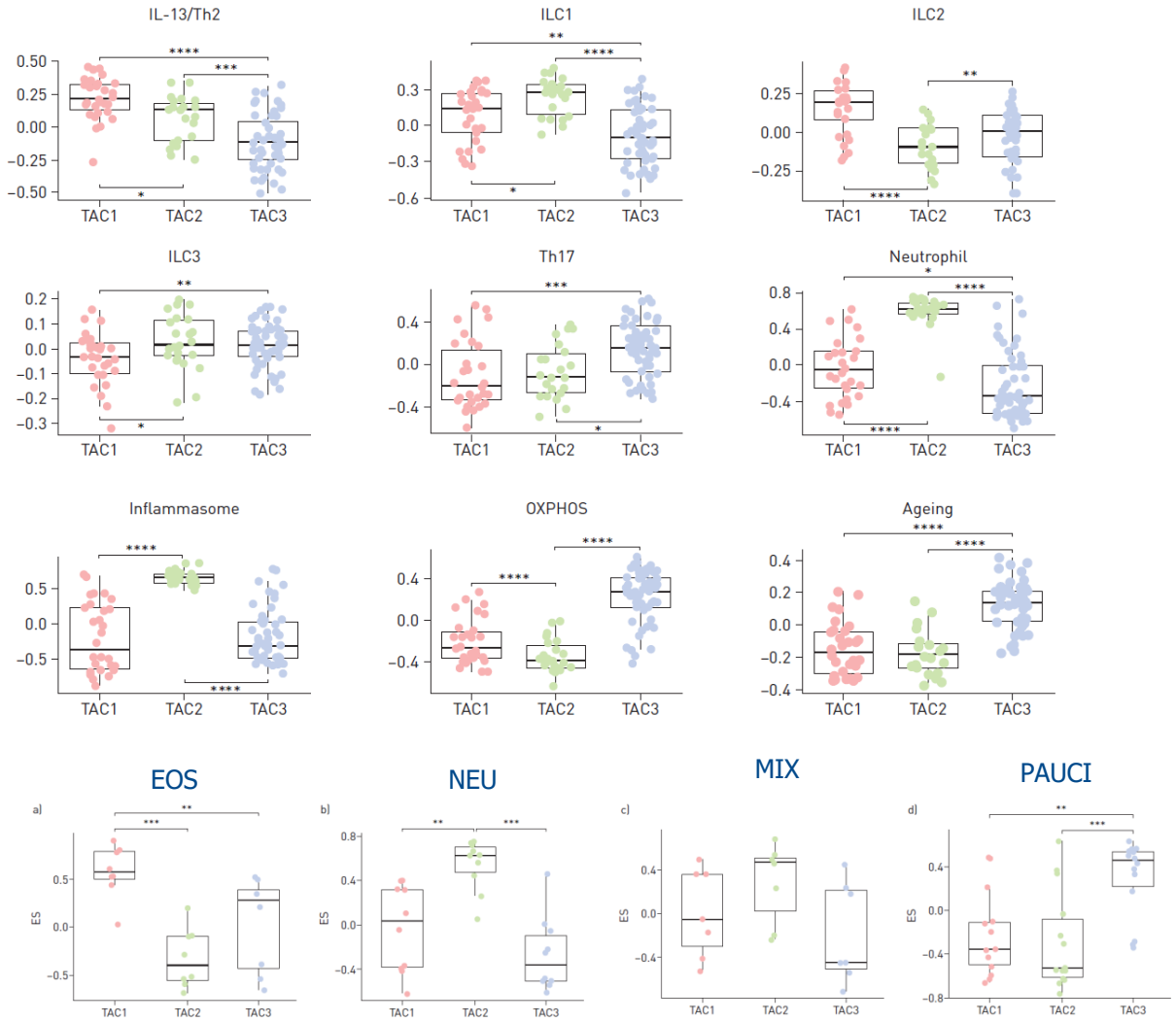
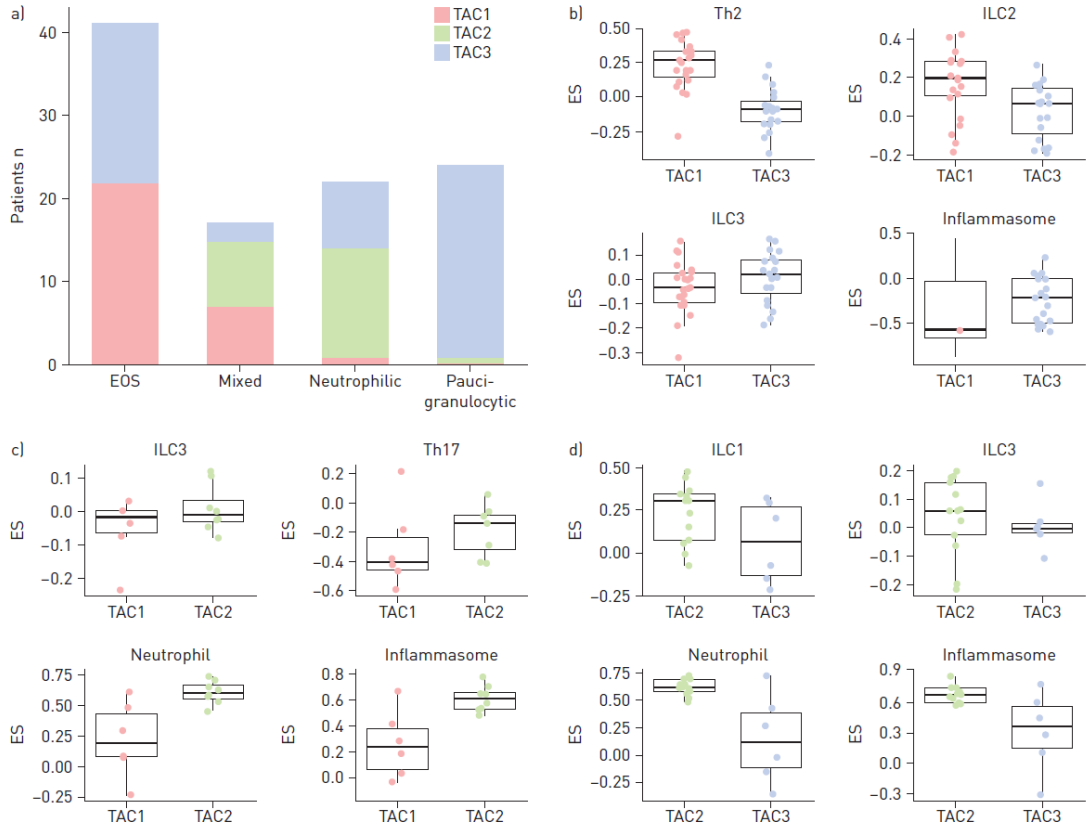




Eur Respir J 2017;49:1602135.

Asthma endotypes to pheynotypes

- TAC 1 contains a greater enrichment for IL-13/Th2 and ILC2 signatures, and is associated with blood and sputum eosinophilia, reflecting severe asthma characterised by mast cell and eosinophil activation and upregulation of receptors for TSLP, IL-33, IL-3 and CCL11 (CCR3).

: **relatively typical Type 2 severe asthma**

- TAC2 is **inflammasome**-dominant with IFN and TNF superfamily upregulation and high expression of DAMPs (damage-associated molecular patterns), and is associated predominantly with **neutrophilic inflammation** and **highest CRP** levels and with chronic airflow obstruction of a lesser severity than that found in TAC1.

: **neutrophilic non-Type 2 severe asthma**

- TAC3 highlighted metabolic, ubiquitination enzymes and mitochondrial energy metabolic genes, with the highest expression scores for **mitochondrial oxidative stress** (OXPHOS) and **ageing** gene signatures associated with **paucigranulocytic** and mild **EOS** inflammation. TAC3 is characterized by the lowest oral corticosteroid use, mild airflow obstruction and less frequent exacerbations than TAC1.

: Eosinophilic or pauci-granulcytic non-type 2 severe asthma

- TAC1: Th2 and ILC2 signature vs. TAC3: inflammsome signature
- In addition to overlapping sputum eosinophilia, biomarkers such as exhaled nitric oxide (eNO) and periostin were no different in the three TACs

Eur Respir J 2017;49:1602135.

Comments

- The novel molecular phenotyping based on sputum cells yielded three distinct clinical clusters.
- In TAC 3, how mitochondrial oxidative stress and ageing signatures drive asthma with little evidence of inflammation (paucigranulocytic inflammation and low serum CRP) is unclear. Further research examining the role of other cell types (e.g. macrophages and epithelial cells) may help determine these mechanisms.
- Understanding of the differences between ILC2 vs. inflammsome signatures in the pathogenesis of severe eosinophilc asthma is needed.
- A fresh framework on which to phenotype asthma and a more precise targeting of specific treatments.

NLRP3 inflammasome in severe neutrophilic asthma

OVA-LPS induced asthma (TAC 2)

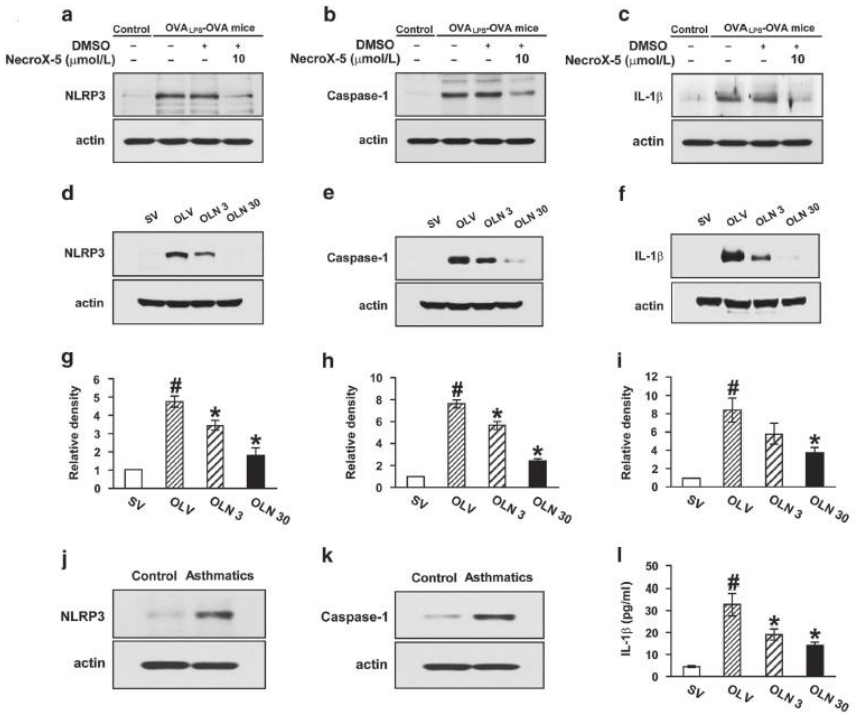
OPEN

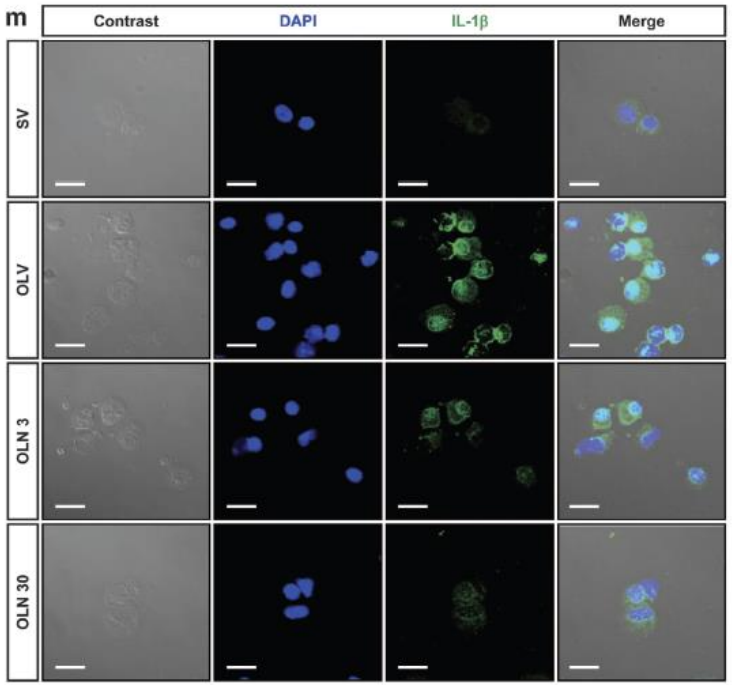
Citation: Cell Death and Disease (2014) 5, e1498; doi:10.1038/cddis.2014.460

www.nature.com/cddis

NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation

SR Kim[1,4], DI Kim[1,4], SH Kim[2], H Lee[1], KS Lee[1], SH Cho[3] and YC Lee[*,1]





Kim SR. et al Cell Death and Disease (2014) 5, e1498

Role of mROS in neutrophilic severe asthma

OVA-LPS induced asthma (TAC 2)

OPEN

Citation: Cell Death and Disease (2014) 5, e●; doi:10.1038/cddis.2014.
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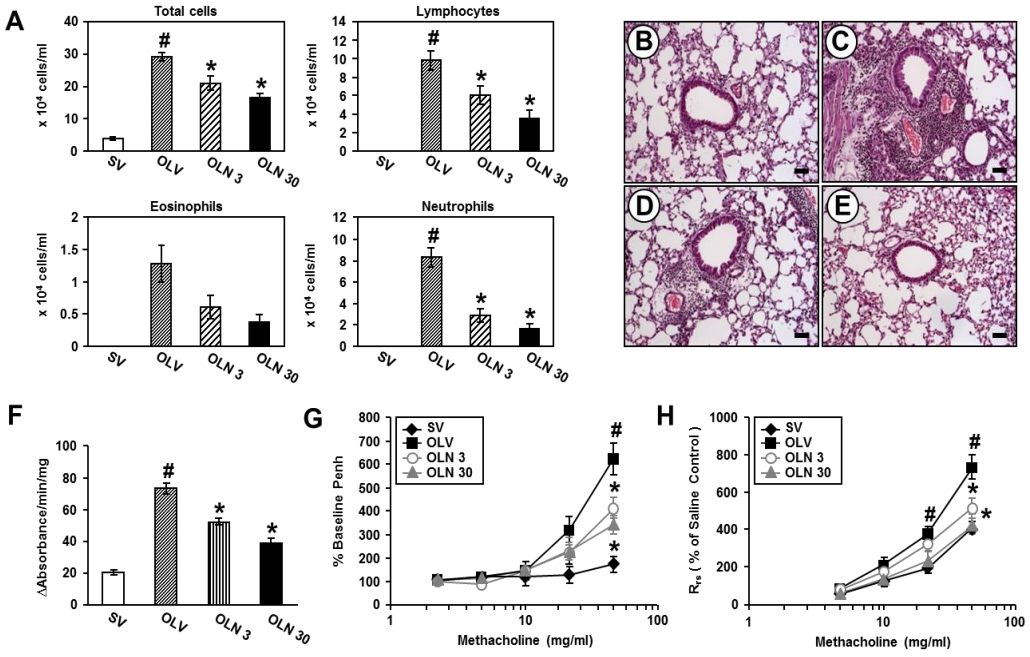
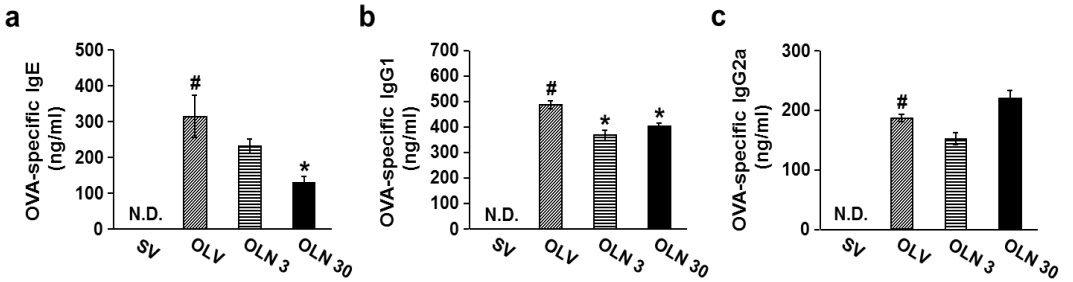
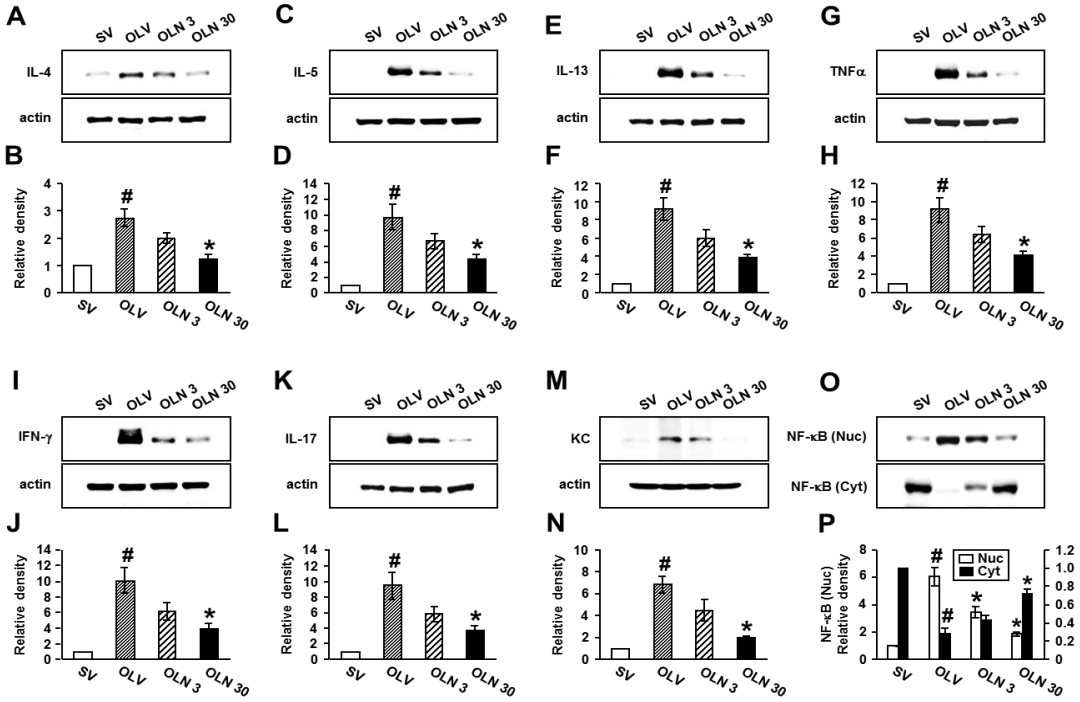
www.nature.com/cddis

NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation

SR Kim[1,4], DI Kim[1,4], SH Kim[2], H Lee[1], KS Lee[1], SH Cho[3] and YC Lee[*,1]



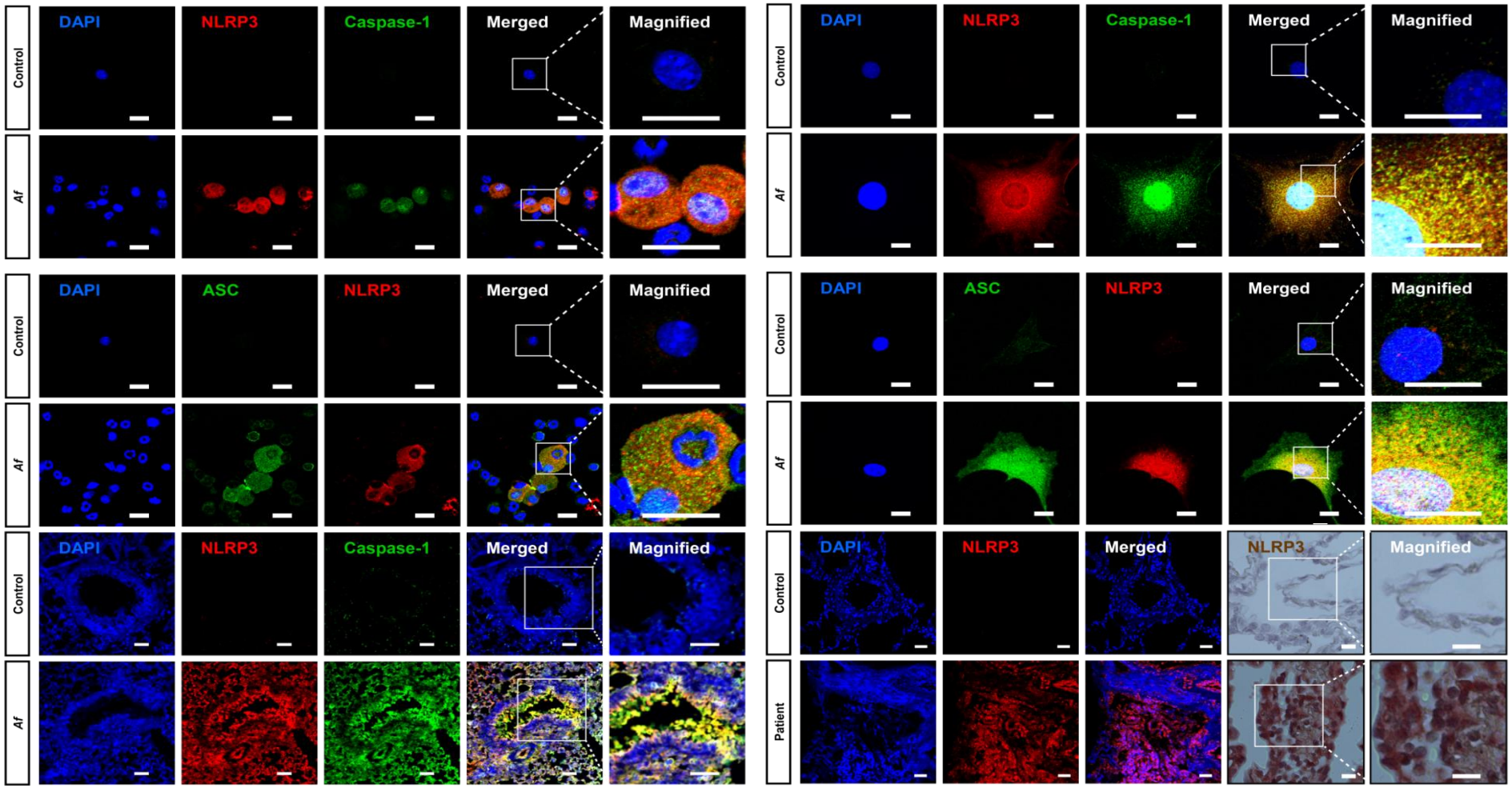




Kim SR et al, Cell Death and Disease 2014:5 e1498

NLRP3 inflammasome in severe eosinophilic asthma

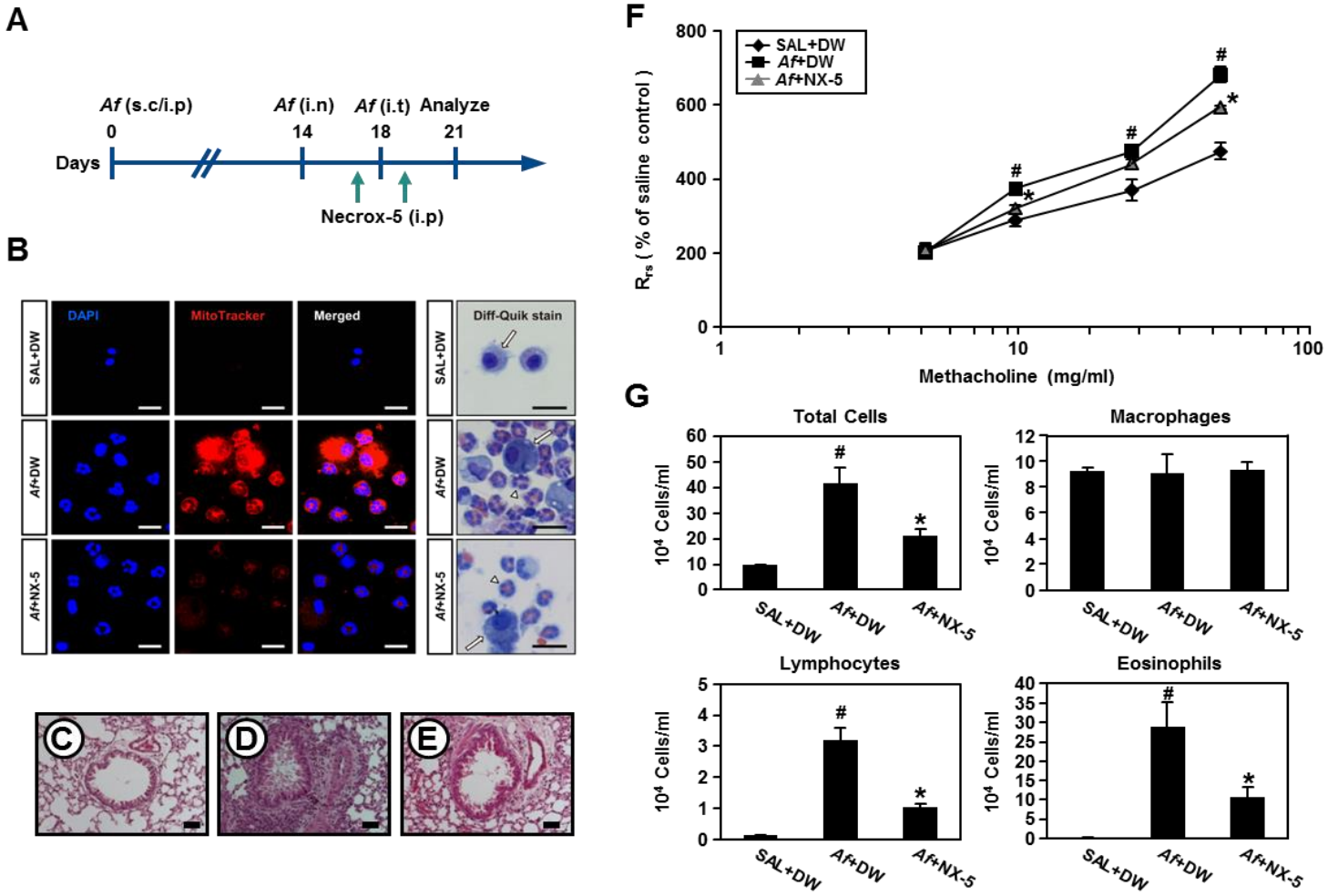
Af-induced asthma (TAC 3)



Unpublished data
In process

Role of mitochondrial ROS in eosinophilic severe asthma

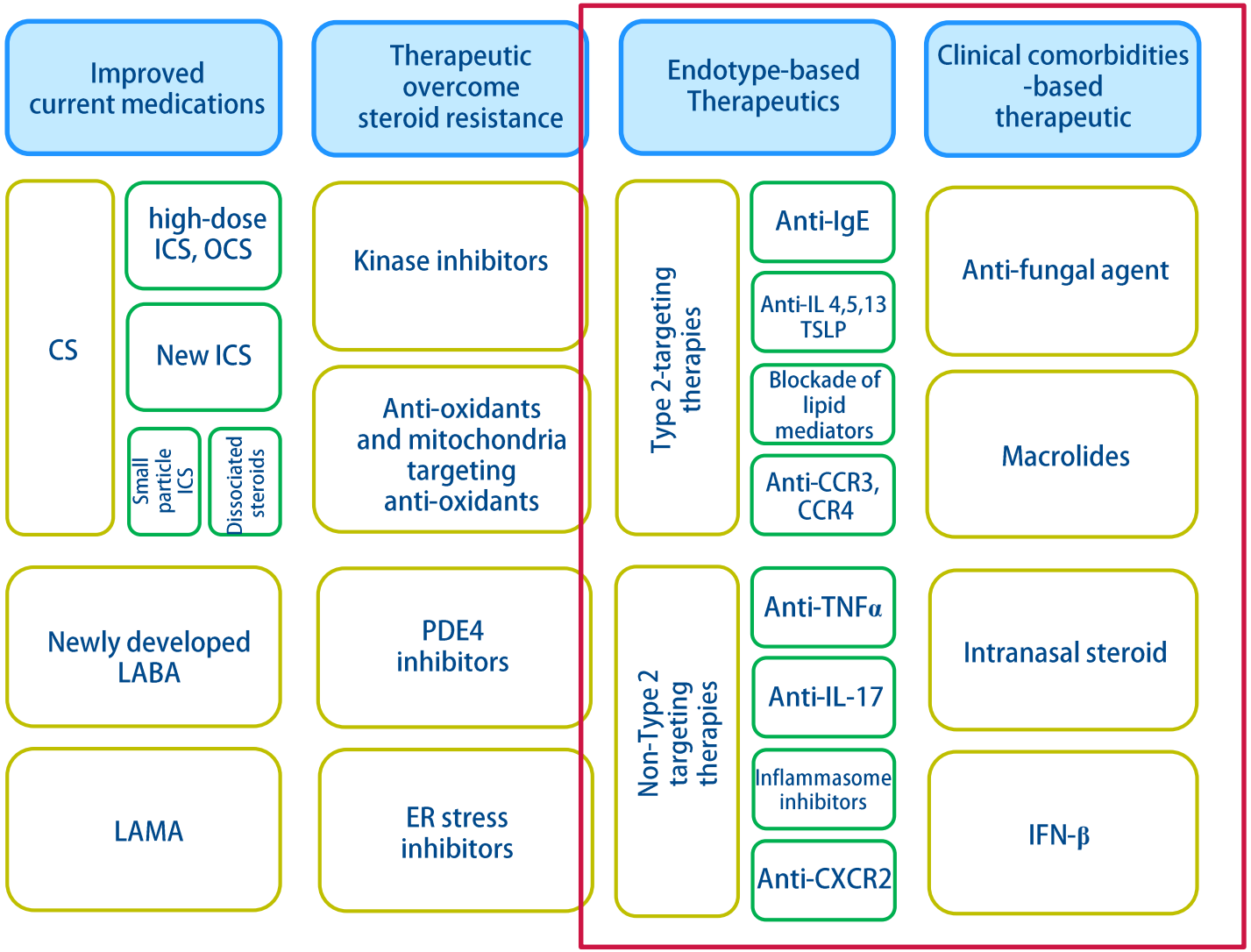
Af-induced asthma (TAC 3)



Unpublished data
In process

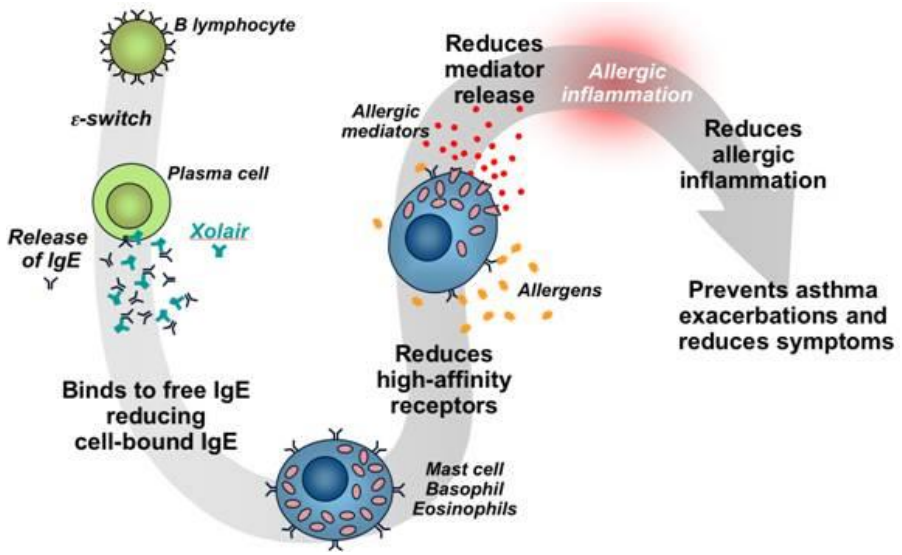
Table of content

Pharmacologic therapeutic approaches for severe asthma



Type 2 related inflammation targeting therapies
Anti-IgE Approach

- Anti-IgE monoclonal antibody
  - Omalizumab (Xolair, AstraZeneca, London)
  - QGE031 (**ligelizumab;** Novartis, Basel, Switzerland)
  - Quilizumab (Genentech, San Francisco, CA, USA); inhaled form



Target	Biologic therapies used	Type of study	Major outcome
IgE	Anti-IgE mAb (rhuMAb-E25, omalizumab)	Allergen challenge: mild-to-moderate allergic asthma	↓ Early and late asthmatic response, ↓ serum free IgE
		Chronic moderate-to-severe allergic asthma	↓ Asthma exacerbations, ↓ serum free IgE
		Chronic severe allergic asthma	↓ Asthma exacerbations greater when subanalyzed by type 2–high phenotypes (↑ FENO levels, blood eosinophil counts, or serum periostin levels)

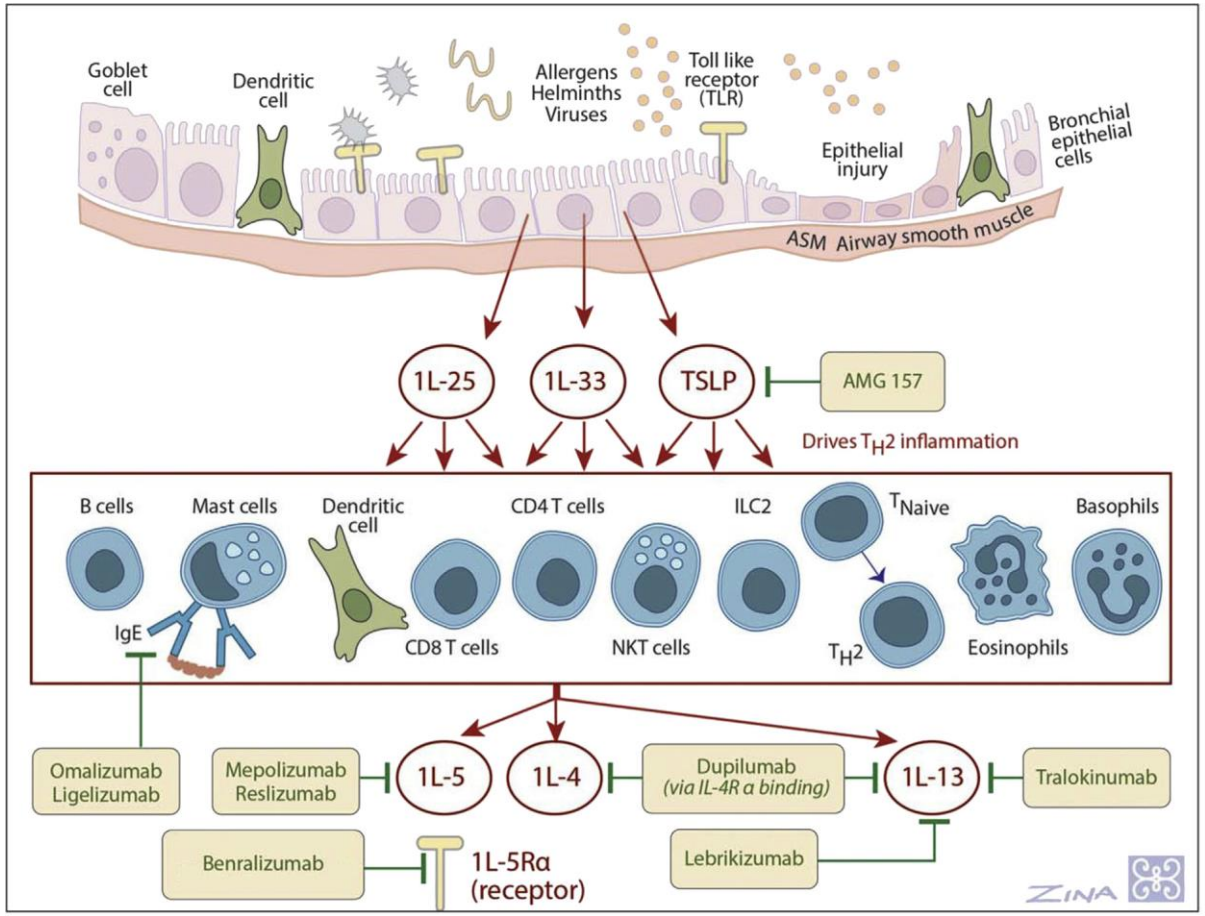
Gauthier M, et al. Am J Respir Crit Care Med. 2015;192(6):660-8.; Chung KF, et al. Eur Respir J 2014; 43: 343-73.; Boulet LP, et al. Am J Respir Crit Care Med 1997;155:1835-40.; Fahy JV et al. Am J Respir Crit Care Med 1997;155:1828-34.; van Rensen EL, et al. Allergy 2009;64:72-80.; Corren J, et al. J Allergy Clin Immunol 2011;127:398-405. Milgrom H, et al. N Engl J Med 1999;341:1966-73. Milgrom H, et al. Pediatrics 2001;108:E36. Busse W, et al. J Allergy Clin Immunol 2001;108:184-90. Soler M, et al. Eur Respir J 2001;18:254-61. Holgate ST, et al. Clin Exp Allergy 2004;34:632-8. Humbert M, et al. Allergy 2005;60:309-16. Hanania NA, et al. Ann Intern Med 2011;154:573-82. Busse WW, et al. N Engl J Med 2011;364:1005-15. Lanier B, et al. J Allergy Clin Immunol 2009;124:1210-6. Hanania NA, et al. Am J Respir Crit Care Med 2013;187:804-11. Vignola AM, et al. Allergy 2004;59:709-17.

Type 2 related inflammation targeting therapies
Anti-IgE Approach

- **Omalizumab**
  - is not US Food and Drug Administration (FDA) approved for use in children younger than 6 years (2016)
  - use of omalizumab has been limited by its expense, multiple injections and injection-site reactions, a black box warning on anaphylaxis, and new warnings on cardiovascular risk.
  - Little information on biomarkers
  - Numerous clinical trials have demonstrated the clinical efficacy of omalizumab in reducing maintenance doses of oral corticosteroids and ICSs and in reducing exacerbations in patients including children with severe asthma
- **Ligelizumab**
  - A humanized anti-IgE antibody with a 50-fold higher affinity for IgE than omalizumab
  - good pharmacologic effects including reduction of concentration of IgE in allergic patients with well-controlled asthma

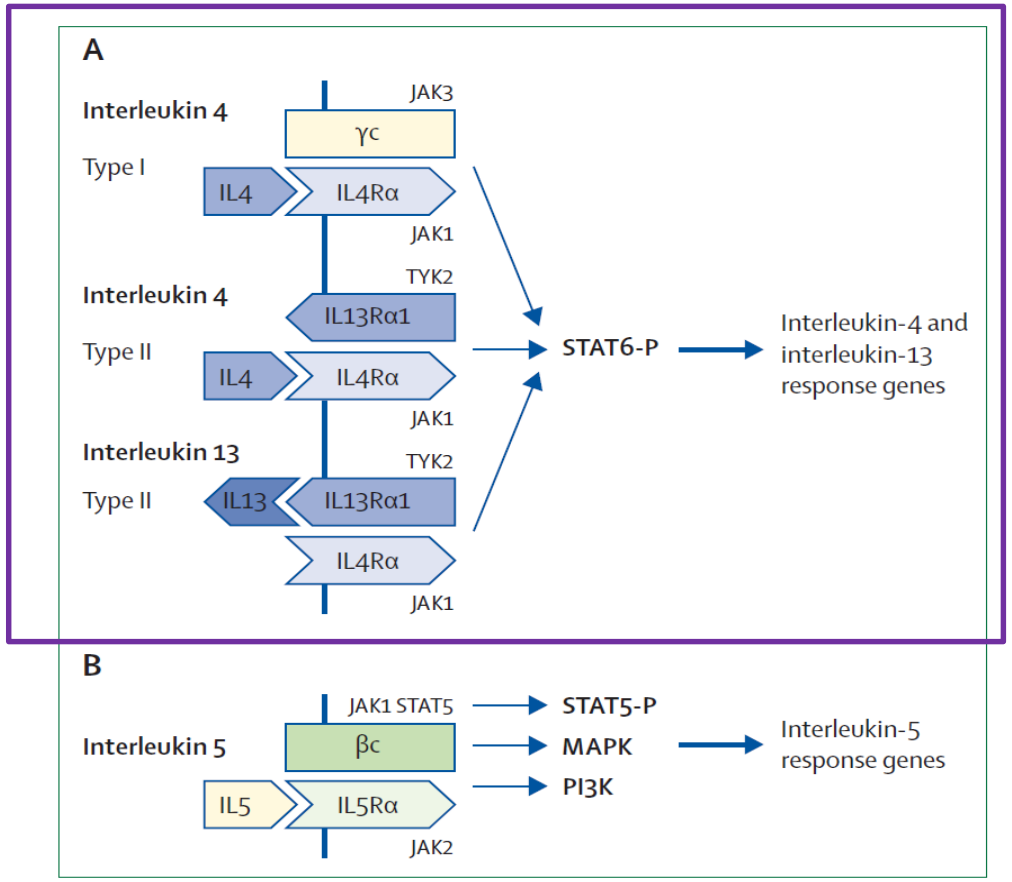
Chipps BE, et al. J Allergy Clin Immunol. 2017;139(5):1431–44.
Hanania NA, et al. Ann Intern Med. 2011;154(9):573–82.
Arm JP, et al. Clin Exp Allergy. 2014;44(11):1371–85.

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-4/IL-13, IL-5, and TSLP



J Allergy Clin Immunol Pract 2017;5:S1-S14

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-4/IL-13



Both IL-4 and IL-13 bind to the heterodimeric combination of the α1 chain of the IL-13 receptor (IL-13Rα1) and the α chain of the IL-4 receptor IL-4Rα1), which leads to the signaling of both IL-4 and IL-13.

- Anti-IL-4Rα antibody
  - Pitrakinra (SC, inhalaiton; investigation: Aerovance, Berkeley, CA, USA)
  - AMG 317 (Amgen, Thousand Oaks, CA, USA)
  - Dupilumab (Rebeneron, Tarrytown, NY, USA)
- Anti-IL-4 antibody
  - Currently no development in asthma
- Anti-IL-13 antibody
  - Lebrikizumab (Genentech, San Francisco, CA, USA)
  - Tralokinumab (MedImmune, Cambridge, UK)
  - GSK679586 (GlaxoSmithKline, Greater London, UK)
  - Anrukinzumab (IMA-638; Pfizer (former Wyeth), New York, NY, USA)

Chung KF. Lancet 2015; 386: 1086–96

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-4/IL-13

Target	Biologic therapies used	Type of study	Major outcome
IL-4 and IL-13	Mutant IL-4 (pitrakinra); IL-13 antibody (IMA-638)	Allergen challenge: mild allergic asthma	↓ Late asthmatic response
	IL-4Rα mAb (AMG 317); mutant IL-4 (pitrakinra)	Chronic moderate-to-severe asthma	No effect on prespecified clinical asthma outcomes in "all comers," + SNPs of IL-4Rα gene associated with clinical response (pitrakinra)
	IL-13 mAb (lebrikizumab, tralokinumab)	Chronic moderate-to-severe asthma	↑ FEV_1; greatest clinical benefit when subanalyzed by type 2–high phenotypes (↑ periostin and sputum IL-13^+)
	IL-13 mAb (GSK679586)	Very severe asthma	No effect on prespecified clinical asthma outcomes
	IL-4Rα mAb (dupilumab)	Chronic moderate-to-severe asthma with type 2–high phenotype (blood eosinophils ≥300 cells/μL or sputum eosinophils ≥3%)	↓ Asthma exacerbations, ↓ FENO, ↓ β-agonist use, ↑ FEV_1

- Effects observed in type 2 phenotype-patients not in all asthmatics
  - Dupilumab : high eosinophils, add-on therapy irrespecitve of blooed eosinophils
  - Lebrikizumab and tralokinumab: high serum periostin or sputum IL-13

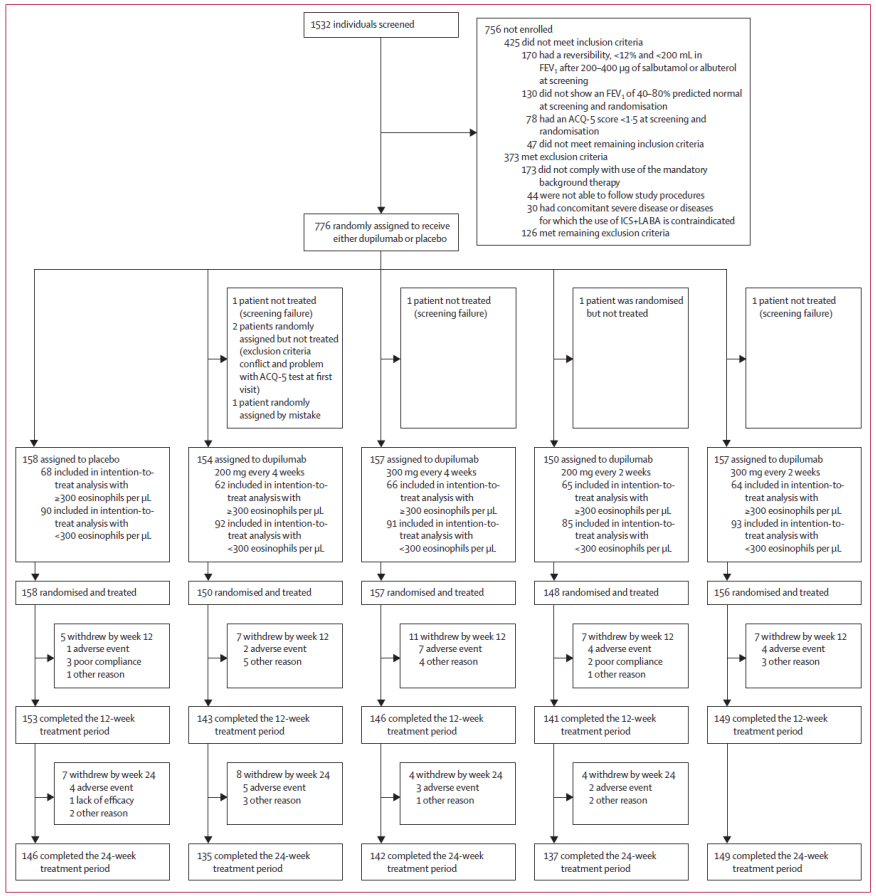
Wenzel S, et al. Lancet 2007;370:1422-31.; Gauvreau GM, et al. Am J Respir Crit Care Med 2011;183:1007-14.; Slager RE, et al. J Allergy Clin Immunol 2012;130:516-22.e4.; Piper E, et al. Eur Respir J 2013;41:330-8.; Corren J, et al. Am J Respir Crit Care Med 2010;181:788-96.; DeBoever EH, et al. J Allergy Clin Immunol 2014;133:989-96.; Wenzel S, et al. N Engl J Med 2013;368:2455-66.

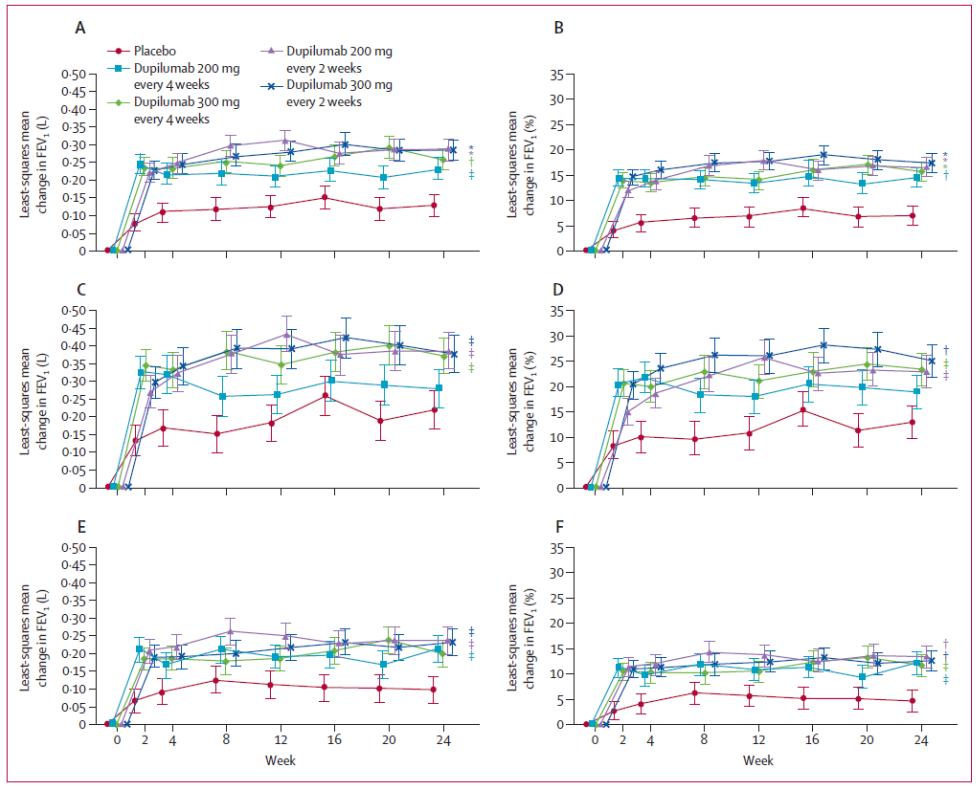
Type 2 related inflammation targeting therapies

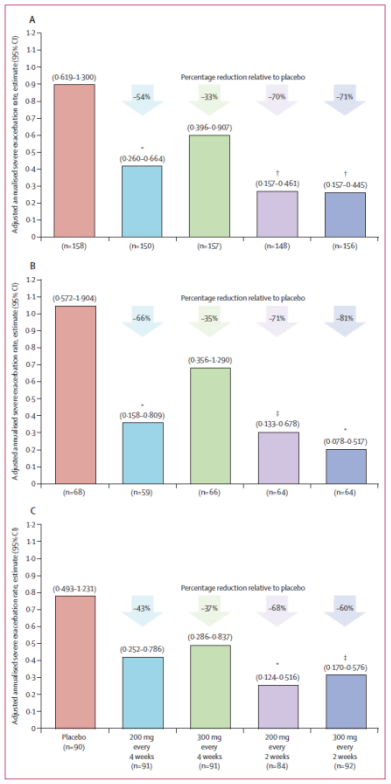
Inhibition of cytokines: Targeting IL-4/IL-13-Dupilumab

Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

Sally Wenzel, Mario Castro, Jonathan Corren, Jorge Maspero, Lin Wang, Bingzhi Zhang, Gianluca Pirozzi, E Rand Sutherland, Robert R Evans, Vijay N Joish, Laurent Eckert, Neil M H Graham, Neil Stahl, George D Yancopoulos, Mariana Louis-Tisserand, Ariel Teper







- Dupilumab added to medium to-high-dose inhaled corticosteroids plus long-acting β2-agonist therapy in adults with uncontrolled persistent asthma **irrespective of baseline eosinophil count** significantly improved lung function, reduced the rate of severe exacerbations, and decreased FeNO in all dupilumab treated groups compared with placebo-treated patients.

Lancet 2016:388:31-44

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-4/IL-13-Dupilumab

- Dupilumab treatment showed significant improvements in both **lung function** and annualised exacerbation rates across a broad range of patients with asthma.
- Dupilumab is unique among biologics as it might also ameliorate comorbid conditions that frequently exist in this population such as nasal polyps and, especially, atopic dermatitis.
- It is difficult to directly compare the results with anti IL-5 therapy since the population in this trial may have been somewhat less severe than those included in the IL-5 registration trials.
- Further investigation of predictive biomarkers is necessary.
- In 2017, the use of dupilumab for patients with atopic dermatitis is approved by US FDA, and based on favorable results from several clinical studies, the approval for severe asthma is also expected in the near future.

Lancet 2016:388:31-44

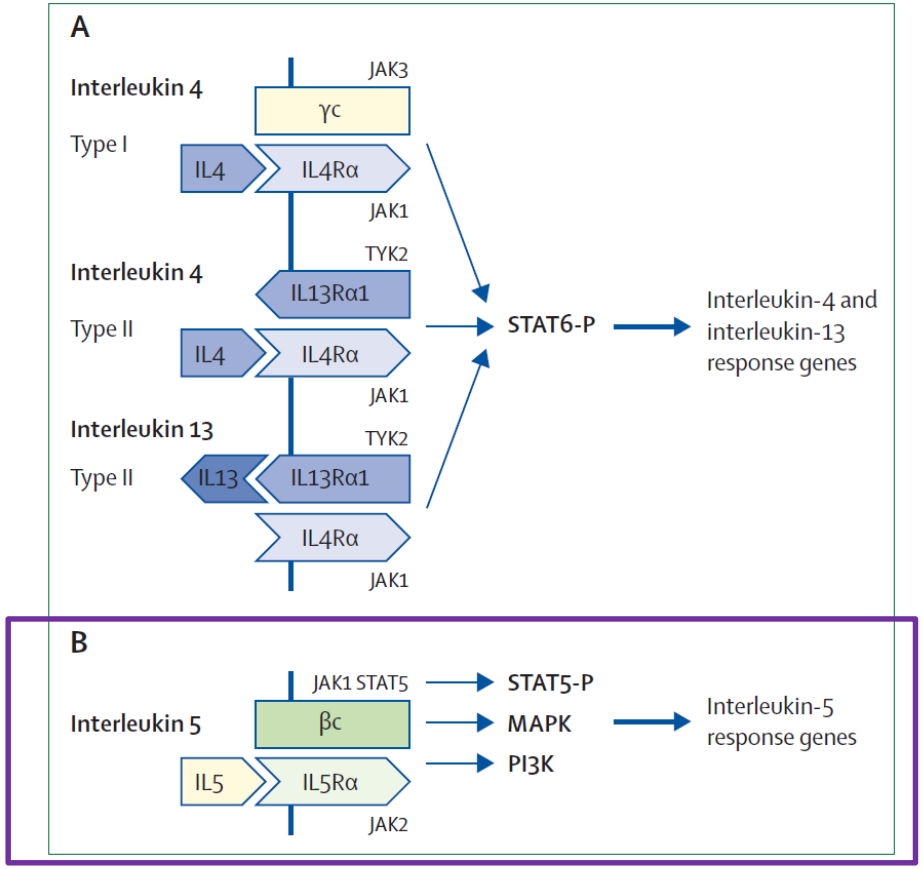
Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-13-Lebrikizumab, tralokinumab

- A recent report regarding replicate phase III clinical trials (NCT01867125, NCT01868061) has also revealed that lebrikizumab did not consistently show significant reduction in asthma exacerbations in biomarker high patients (LAVOLTA I and LAVOLTA II).

- In cases of tralokinumab and GSK679586, they showed no significant efficacy on asthma outcomes such as asthma control, pulmonary function, or exacerbations.

Eur Respir J. 2013;41(2):330–8; J Allergy Clin Immunol. 2014;133(4):989–96; Lancet Respir Med. 2016;4(10):781–96 ; Lancet Respir Med. 2015;3(9):692–701

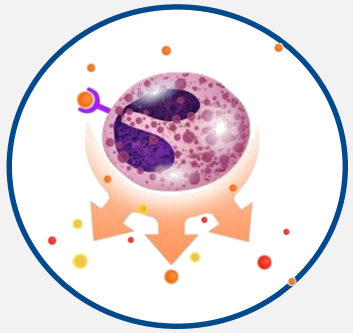
Asthma pathogenesis
Biologic therapy of severe asthma



IL-5[1]

Major cytokine responsible for eosinophil:

- ✓ Recruitment
- ✓ Maturation
- ✓ Activation
- ✓ Survival

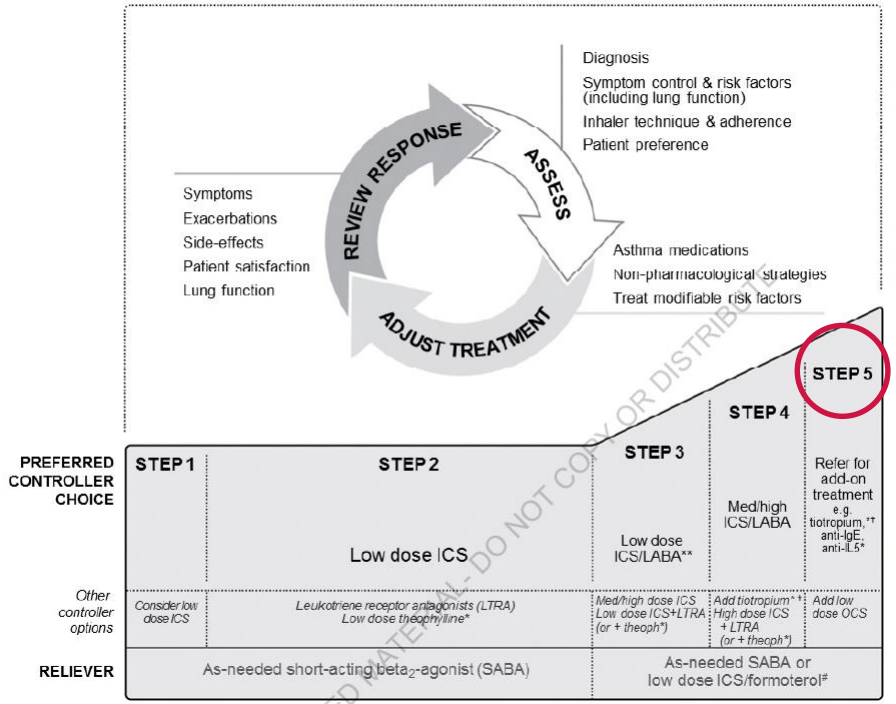


- **Anti-IL-5 antibody**
  - **Mepolizumab** (GlaxoSmithKline, Greater London, UK)
  - **Reslizumab** (Teva, Philadelphia, PA, USA)
- **Anti-IL-5Rα antibody**
  - **Benralizumab** (MedImmune, Gaithersburg, MD, UK)

Chung KF. Lancet 2015; 386: 1086–96

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-5-mepolizumab and resulizumab

- The IL-5 neutralizing antibodies, **mepolizumab and reslizumab**, have started to be prescribed by physicians and recommended as a therapeutic option by international guidelines for patient with severe asthma showing high blood/sputum eosinophil counts worldwide.



- Add-on anti-IL-5 treatment (sc mepolizumab, iv resulizumab): for patients aged ≥ 12 years with severe eosinophilic asthma that is uncontrolled on step 4 treatment.

Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (updated 2017). 2017.

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-5-Benralizumab

Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study

Mario Castro, Sally E Wenzel, Eugene R Bleecker, Emilio Pizzichini, Piotr Kuna, William W Busse, David L Gossage, Christine K Ward, Yanping Wu, Bing Wang, Deepak B Khatry, René van der Merwe, Roland Kolbeck, Nestor A Molfino, Donald G Raible

- Benralizumab at 20 mg and 100 mg doses seemed to reduce asthma exacerbations in adults with uncontrolled eosinophilic asthma and baseline blood eosinophils of at least 300 cells per µL.

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

*Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators**

- These results confirm the efficacy and safety of benralizumab for patients with severe asthma and elevated eosinophils, which are uncontrolled by high-dosage ICS plus LABA, and provide support for benralizumab to be an additional option to treat this disease in this patient population.

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

- Benralizumab significantly reduced annual exacerbation rates and was generally well tolerated for patients with severe, uncontrolled asthma with **blood eosinophils 300 cells per µL or** greater. Our data further refine the patient population likely to receive the greatest benefit from benralizumab treatment.

Lancet Respir Med 2014; 2: 879-90.; Lancet 2016; 388: 2115–27; Lancet 2016; 388: 2128–41

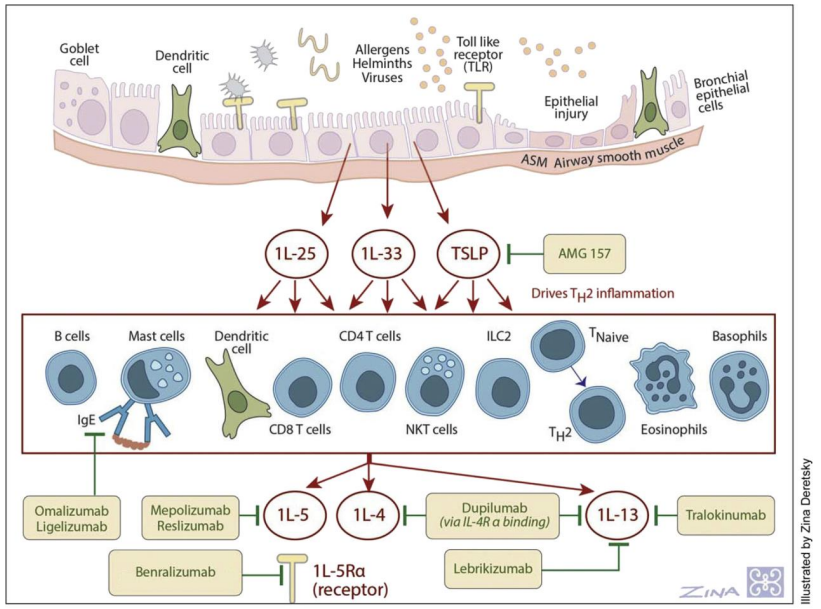
Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting IL-5

- Unlike mepolizumab and resulizumab, **benralizumab** showed some pharmacologic effects on asthmatic features in non-eosinophilic asthma which can be explained by the expression of IL-5Rα on other cells such as basophils and mast cells.
- Lung function: resulizumab and benralizumab > mepolizumab
- Benralizumab can induce the apoptosis of eosinophils.

J Allergy Clin Immunol. 2013;132(5):1086–96.e5; Lancet Respir Med. 2015;3(5):355–66; Lancet Respir Med. 2014;2(11):879–90.

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting TSLP

- An IL-7-related cytokine secreted by airway epithelial cells
- Innate "alarmin" capable of regulating type 2 responses
- **Tezepelumab (AMG157, MEDI9929)** is a human anti-TSLP mAb that binds human TSLP preventing receptor interaction
  - Under clinical trials (Phase 2): severe asthma, add-on therapy, and cellular phenotypes



J Immunol. 2008;181(4):2790–8; J Allergy Clin Immunol Pract 2017;5:S1-S14;

Type 2 related inflammation targeting therapies
Inhibition of cytokines: Targeting TSLP

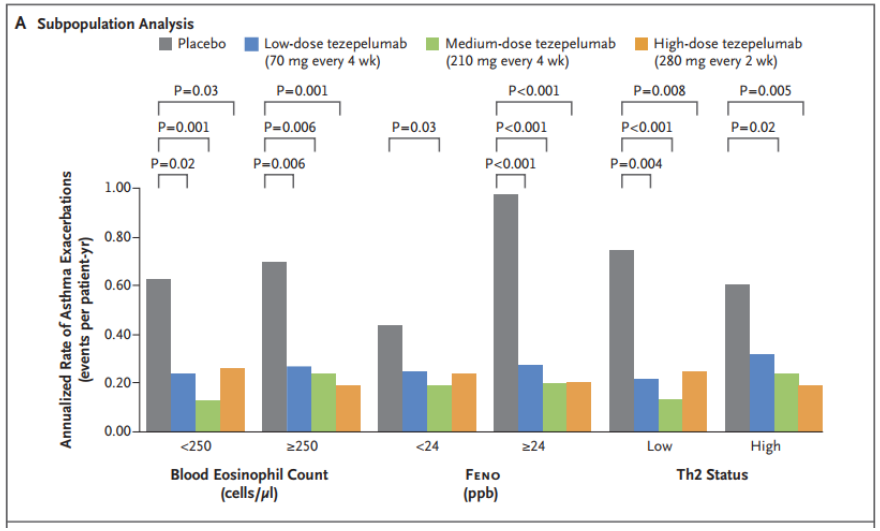
ORIGINAL ARTICLE

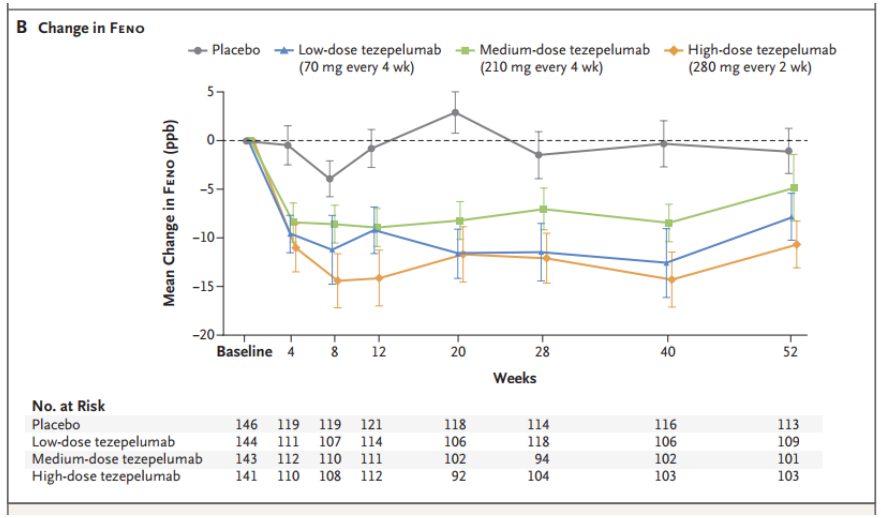
Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

ABSTRACT

- Among patients treated with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids, those who received tezepelumab had lower rates of clinically significant asthma exacerbations than those who received placebo, **independent of baseline blood eosinophil counts**.

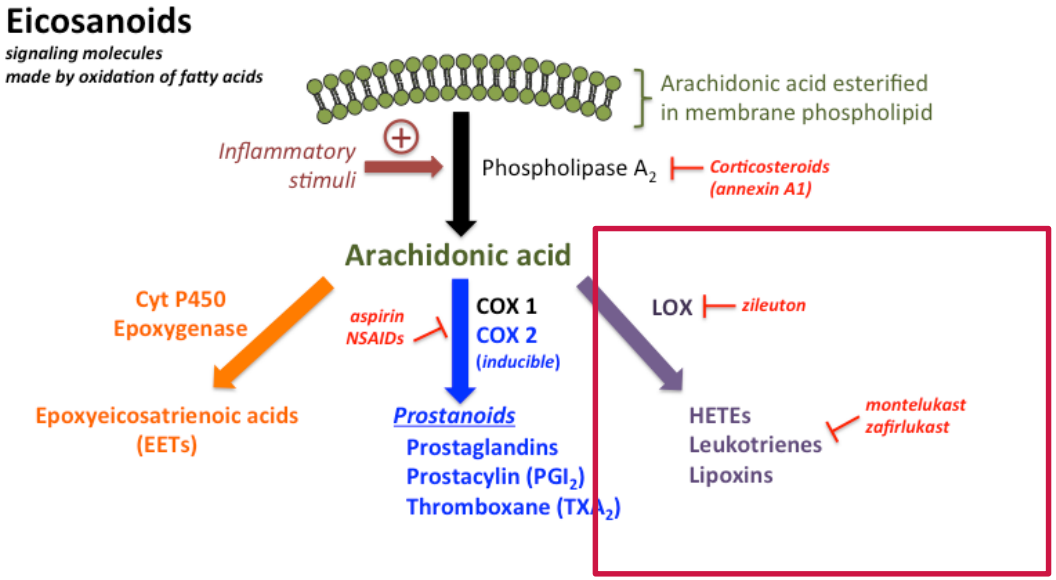


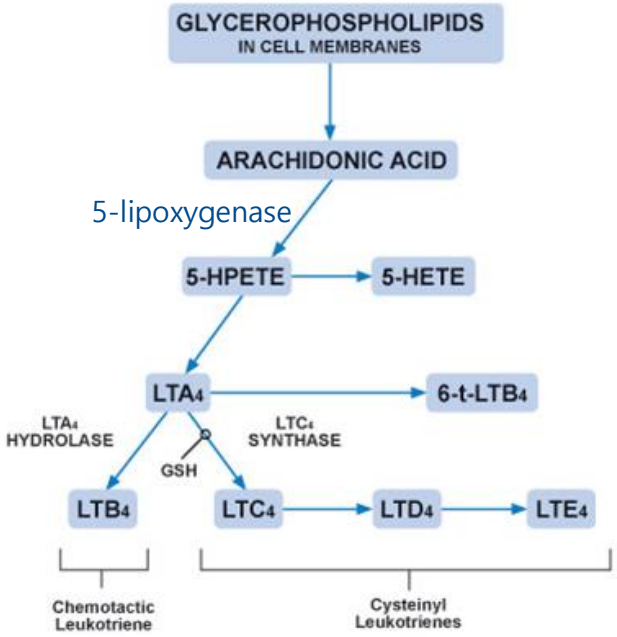


N Engl J Med 2017;377:936-46

Type 2 related inflammation targeting therapies
Blockade of Lipid Mediators: CysLTs

- **A cysteinyl leukotriene-receptor antagonist (LTRAs)**
  - An only antagonist against lipid mediators currently used in asthma therapy
  - Montelukast and zafirlukast, are much less effective than ICSs and have little place as add-on therapy in patients with severe asthma





N Engl J Med 2007; 357:1841-1854

Type 2 related inflammation targeting therapies
Blockade of Lipid Mediators: LTB4 and BLTs, 5-LO inhibitors

- **LTB4: under investigation (mixed or non-type 2)**
  - a potent chemoattractant for neutrophils, mast cells, and T cells, and its expression levels are increased in patients with severe asthma
  - Two receptors: BLT1-high affinity and BLT2-low affinity

- **5-LO inhibitors:** zileuton-withdrawn: new molecules with under investigation

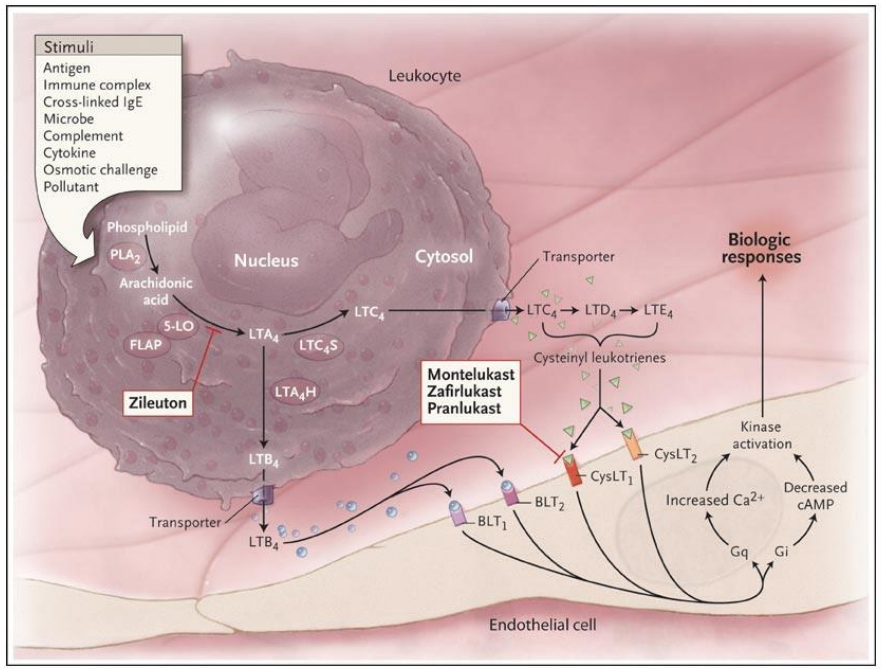


Table 1. **Leukotriene Synthesis and Receptor Expression in Leukocyte Subgroups.***

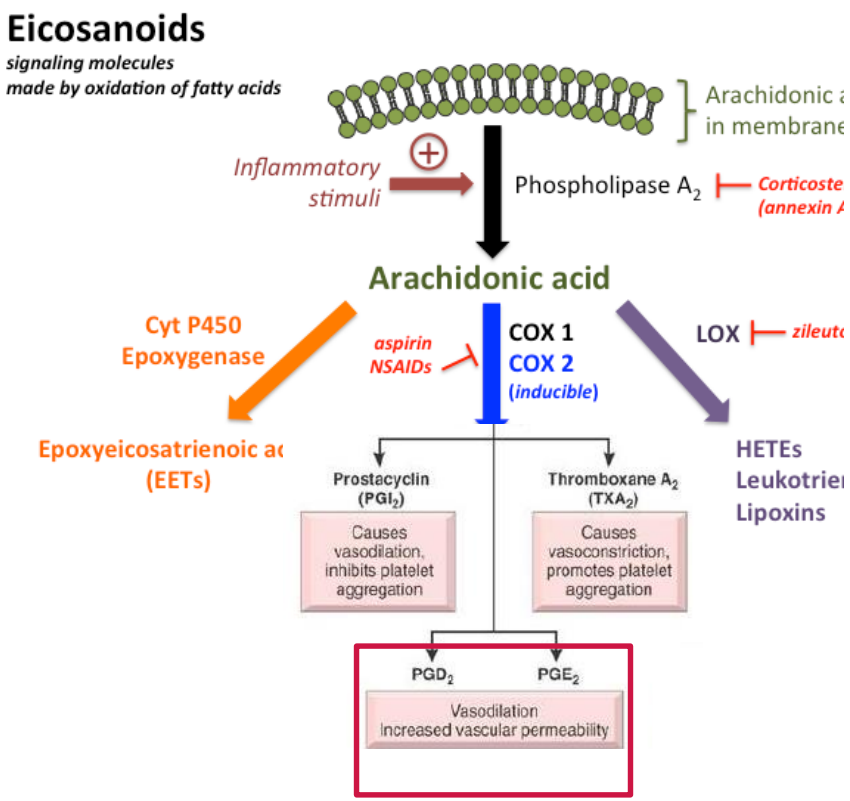
Type of Cell	Relative Synthetic Capacity		Receptor Expression			
	LTB_4	Cysteinyl Leukotrienes	BLT_1	BLT_2	$CysLT_1$	$CysLT_2$
Neutrophil	+++	–	+	+	±	±
Macrophage or monocyte	++	++	+	+	+	+
Eosinophil	–	+++	+	+	+	+
Basophil	–	+++	+	–	+	+
Mast cell	+	+++	+	+	+	+
B lymphocyte	–	–	ND	+	+	ND
CD4 T lymphocyte	–	–	+	+	+	ND
CD8 T lymphocyte	–	–	+	+	ND	ND
Dendritic cell	++	+	+	+	+	ND
Hematopoietic progenitor cell	–	–	ND	+	+	ND

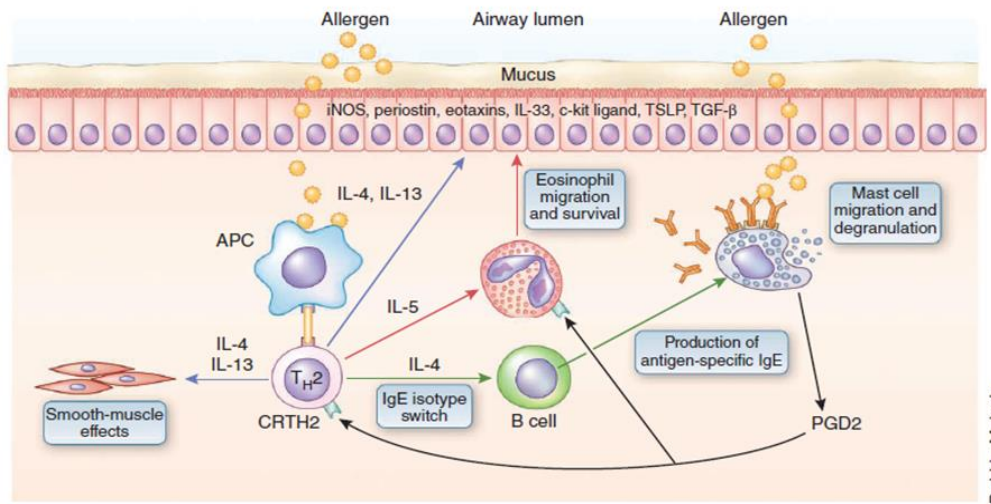
* Relative synthetic capacity is expressed by the number of plus (+) signs; a minus sign (–) denotes no or negligible synthetic capacity. Receptor expression is classified as positive (+), negative (–), minimal (±), or not determined (ND). With respect to cells for which discrepancies exist in reports on leukotriene synthesis or receptor expression, the table lists the best available information taken from primary cells, particularly those that are human in origin.

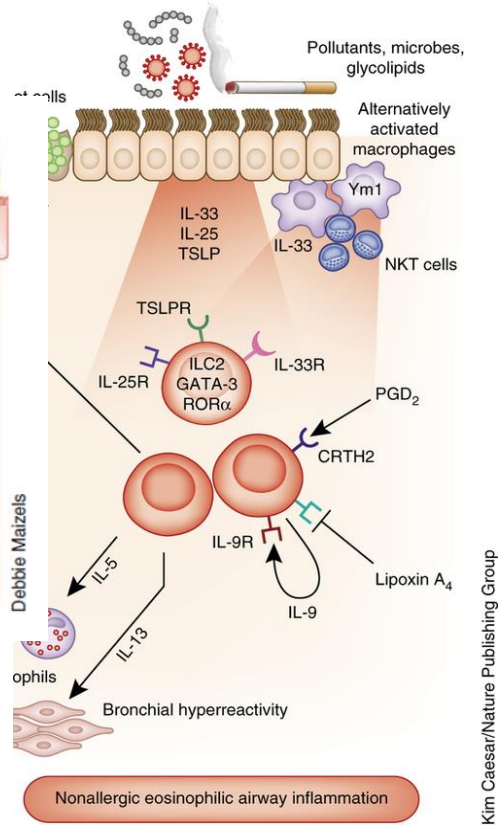
N Engl J Med 2007; 357:1841-1854

Type 2 related inflammation targeting therapies
Blockade of Lipid Mediators: PGD2/CRTH2

- **PGD2 and GRTH2 inhibition**
  - More expression in the patients with severe asthma
  - CRTH2 antagonists: AMG-853, OC000459, MK-7246, BI671800, and fevipiprant (QAW039)



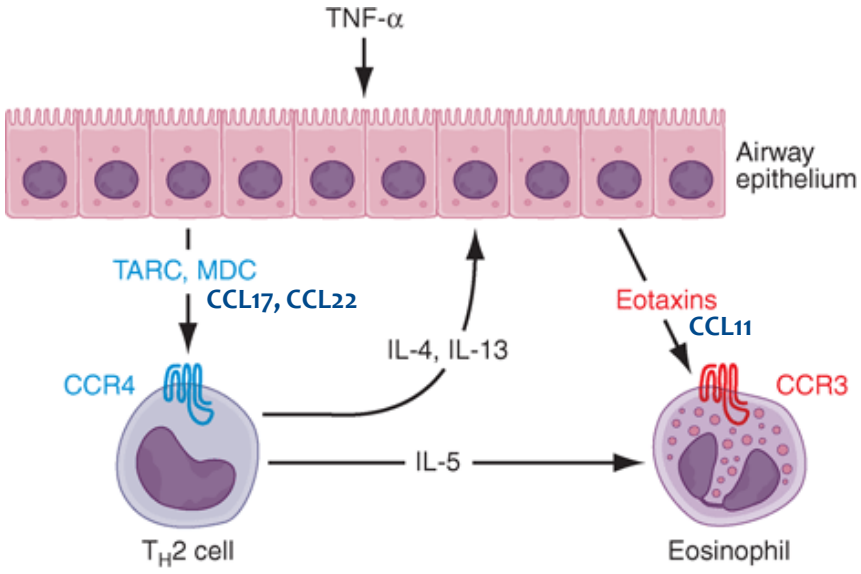




Nat Immunol. 2015 ;16(1):45-56; Nat Med 2013 ;19, 977-979; Nature Medicine 2012;18:716-725

Type 2 related inflammation targeting therapies

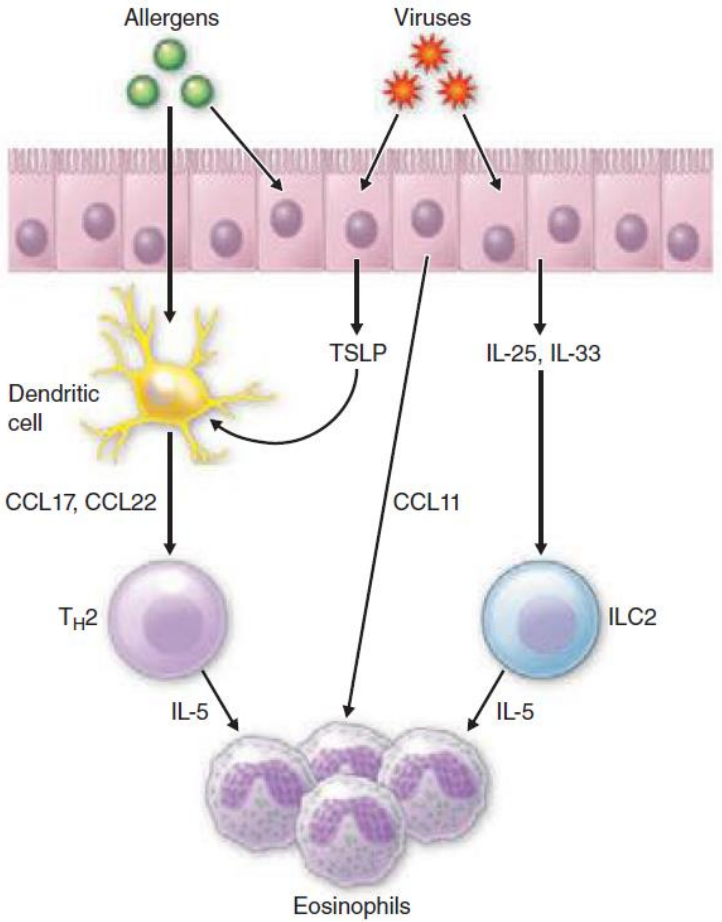
Chemokine receptor antagonists: CCR3 and CCR4



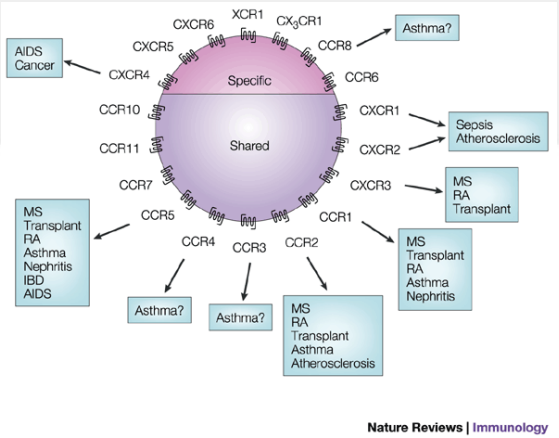
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

TARC: thymus and activation regulated chemokine
MDC: macrophage-derived chemokine
TSLP: thymus stimulated lymphopoeitin

[Harrison's Principles of Internal medicine 18th edition]



[Harrison's Principles of Internal medicine 19th edition]

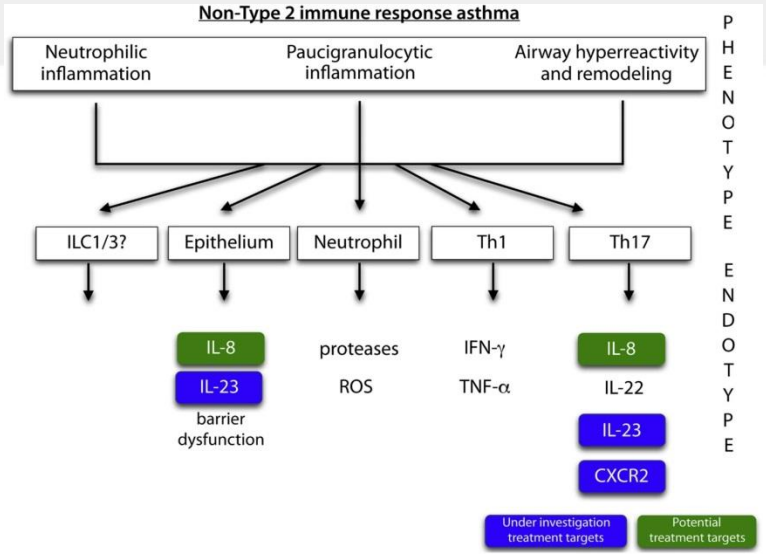


Nature Reviews | Immunology

- **CCR3 and CCR4 inhibition**
  - Anti-CCR3 inhaled oligonucleotides
  - Anti-CCR4 Ab: mogamulizumab and small chemicals: GSK2239633

Rothenberg ME. Cell 165, April 21, 2016

Non-Type 2 related inflammation targeting therapies
Anti-TNF-α



- **Etanercept, infliximab, golimumab**
  - Current evidence suggests that the risk of anti-TNF-α therapies such as infections outweighs benefit in severe asthma.

ORIGINAL ARTICLE

Evidence of a Role of Tumor Necrosis Factor α in Refractory Asthma

Mike A. Berry, M.R.C.P., Beverley Hargadon, R.G.N., Maria Shelley, R.G.N., B.A., Debbie Parker, B.Sc., Dominick E. Shaw, M.R.C.P., Ruth H. Green, M.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Christopher E. Brightling, Ph.D., M.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

ABSTRACT

BACKGROUND

The development of tumor necrosis factor α (TNF-α) antagonists has made it feasible to investigate the role of this cytokine in refractory asthma.

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A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-α Blockade in Severe Persistent Asthma

Sally E. Wenzel[1*], Peter J. Barnes[2], Eugene R. Bleecker[3], Jean Bousquet[4], William Busse[5], Sven-Erik Dahlén[6], Stephen T. Holgate[7], Deborah A. Meyers[3], Klaus F. Rabe[8], Adam Antczak[9‡], James Baker[10], Ildiko Horvath[11], Zsuzsanna Mark[12], David Bernstein[13§], Edward Kerwin[14], Rozsa Schlenker-Herceg[15], Kim Hung Lo[15], Rosemary Watt[15], Elliot S. Barnathan[15], and Pascal Chanez[16‖], on behalf of the T03 Asthma Investigators[†]

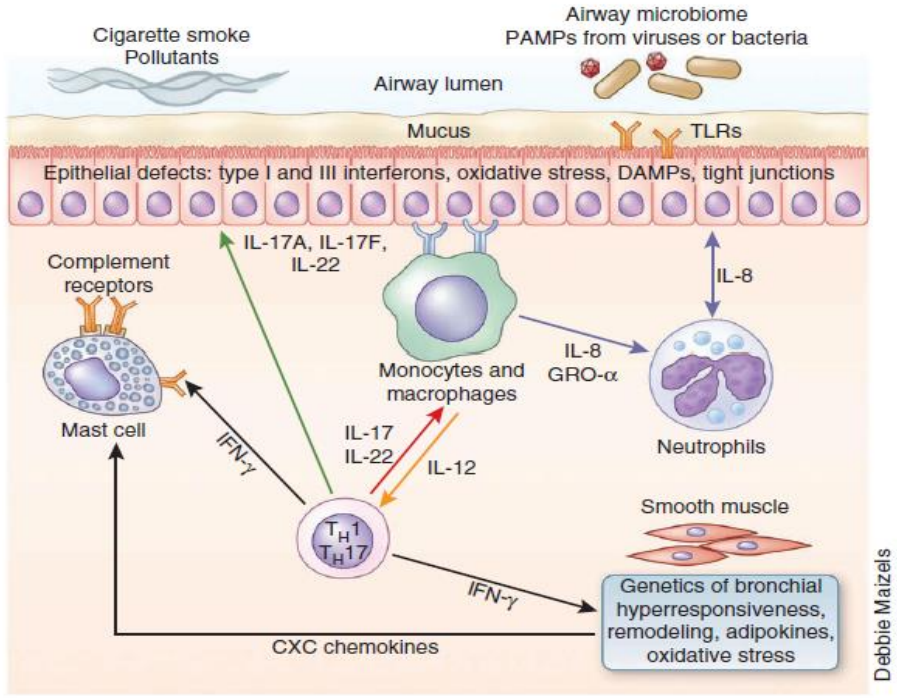
Non-Type 2 related inflammation targeting therapies
Anti-IL-17

Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma

William W. Busse[1], Stephen Holgate[2], Edward Kerwin[3], Yun Chon[4], JingYuan Feng[4], Joseph Lin[4], and Shao-Lee Lin[4]

[1]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [2]University of Southampton, Southampton, United Kingdom; [3]Clinical Research Institute of Southern Oregon, PC, Medford, Oregon; and [4]Amgen Inc., Thousand Oaks, California

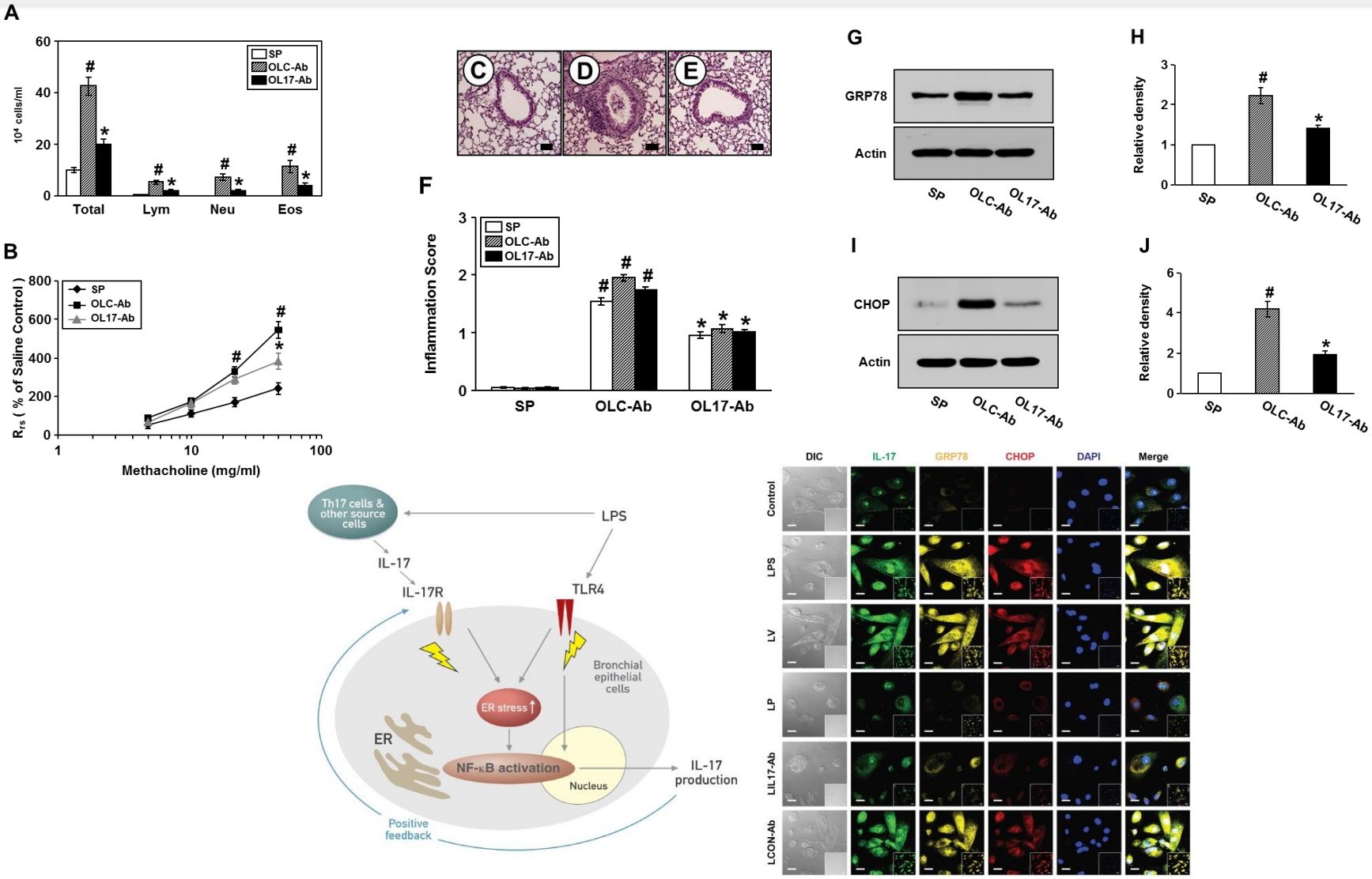
- **Brodalumab** had no effect on asthma control scores, symptom-free days, and FEV1 in non-phenotyped patients with inadequately controlled moderate-to-severe asthma who were receiving inhaled corticosteroid therapy.
- A follow-up phase IIb study focusing on this phenotype had been performed, but it was stopped because of a lack of reported efficacy in an interim analysis.
- A study using **secukinumab** (AIN457) also has been terminated with no significant beneficial effects on patient group.
- Needs for more selective populations of severe asthma and novel biomarkers



Am J Respir Crit Care Med. 2013;188(11):1294–302

Non-Type 2 related inflammation targeting therapies

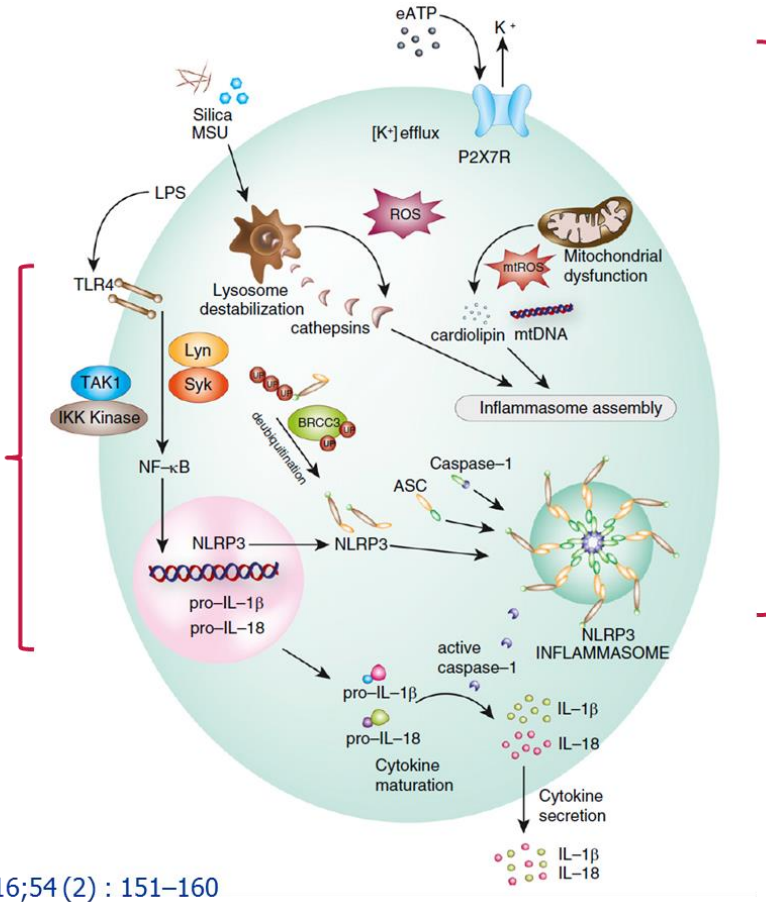
Anti-IL-17; other cellular target or more specific phenotype-patient



Lee YC & Kim SR et al. Unpublished data; Kim SR et al. Theranostics 2015; 5(12): 1343-1362

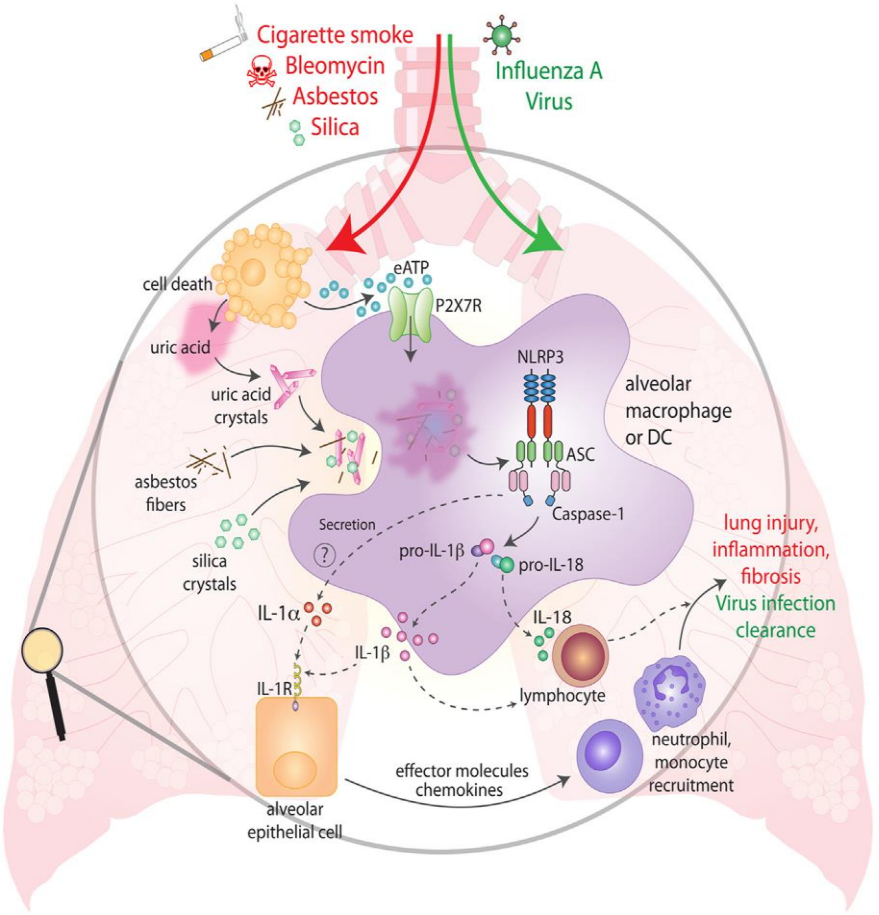
Non-Type 2 related inflammation targeting therapies
Inflammasome inhibitor

First step (priming)
: the sequential ligand dependent activation of TLRs (e.g., TLR4) or related receptors that, in turn, stimulates NF-kB–dependent transcription of NLRP3, leading to NLRP3 protein synthesis.



Second step (assembly)
: a second activation signal generated by ion flux, phagosomal destabilization, mitochondrial reactive oxygen species (mtROS) or mitochondrial DAMPs results in NLRP3–inflammasome assembly

Am J Respir Cell Mol Biol 2016;54 (2) : 151–160

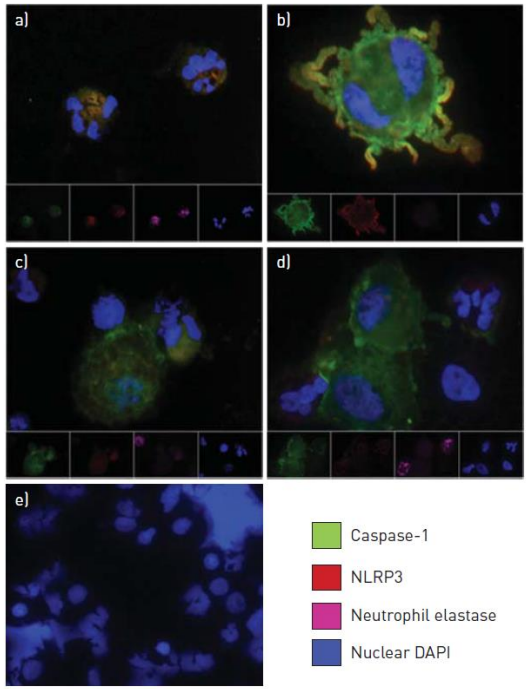


Am J Pathol 2014;184 : 42-54

Non-Type 2 related inflammation targeting therapies
Inflammasome inhibitor

Elevated expression of the NLRP3 inflammasome in neutrophilic asthma

Jodie L. Simpson[1,6], Simon Phipps[2,3,6], Katherine J. Baines[1], Kevin M. Oreo[4], Lakshitha Gunawardhana[1] and Peter G. Gibson[1,4,5]



Neutrophilic asthma

Eosinophilc or paucigranulocytic asthma

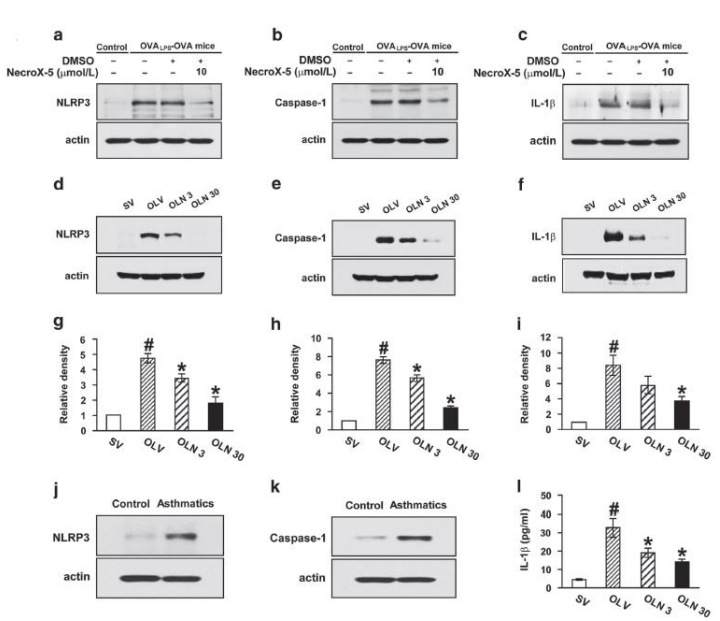
OPEN

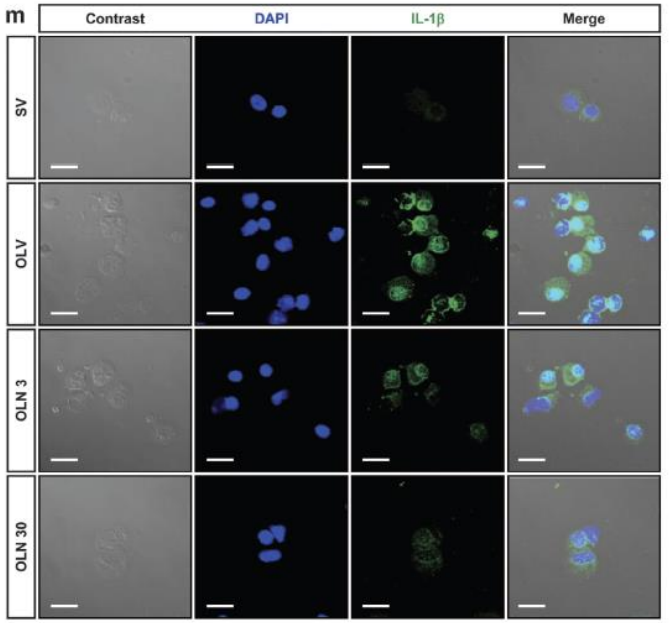
Citation: Cell Death and Disease (2014) 5, e1498; doi:10.1038/cddis.2014.460

www.nature.com/cddis

NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation

SR Kim[1,4], DI Kim[1,4], SH Kim[2], H Lee[1], KS Lee[1], SH Cho[3] and YC Lee[*,1]



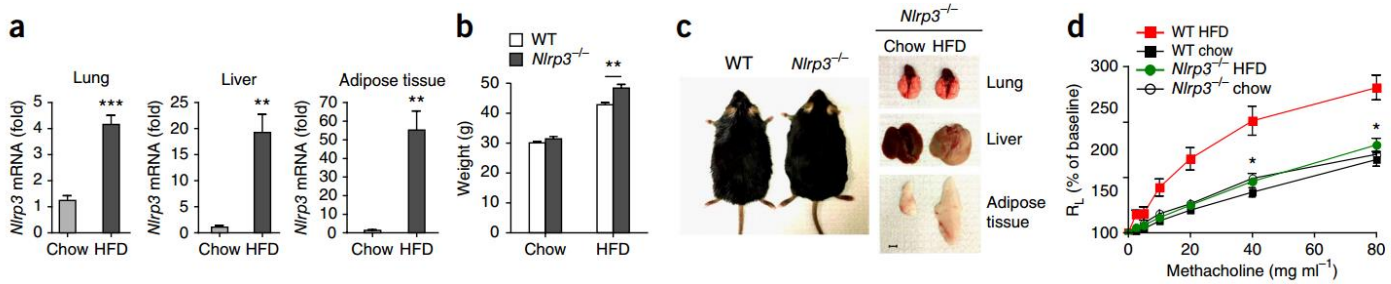


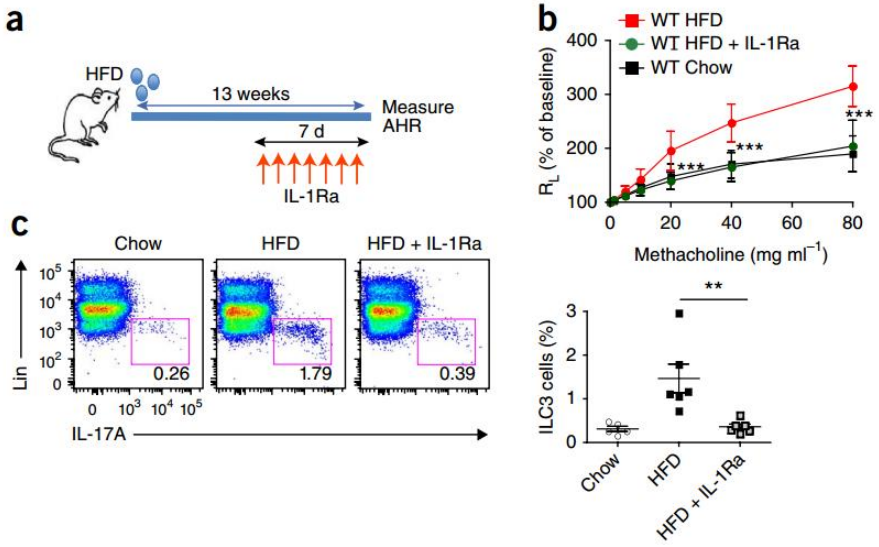
Eur Respir J 2014; 43: 1067–1076; Cell Death and Disease 2014:5 e1498

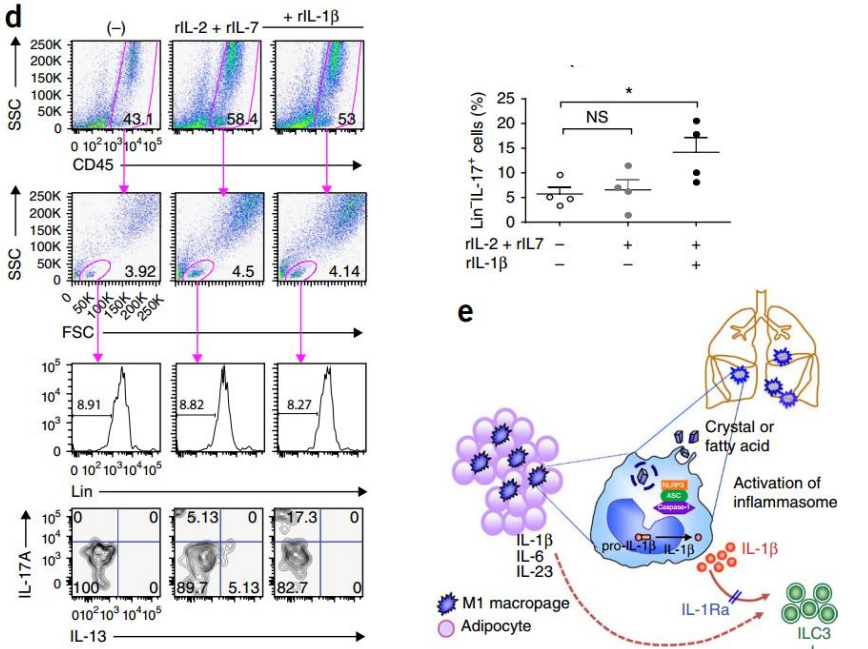
Non-Type 2 related inflammation targeting therapies
Inflammasome inhibitor

Interleukin-17–producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity

Hye Young Kim[1], Hyun Jun Lee[1], Ya-Jen Chang[1], Muriel Pichavant[1], Stephanie A Shore[2], Katherine A Fitzgerald[3], Yoichiro Iwakura[4], Elliot Israel[5], Kenneth Bolger[6], John Faul[6], Rosemarie H DeKruyff[1] & Dale T Umetsu[1]







Blockade of IL-1b with an IL-1b receptor antagonist abolished obesity-induced AHR and reduced the number of ILC3 cells. suggesting that obesity-associated asthma is facilitated by inflammation mediated by NLRP3, IL-1b and ILC3 cells.

Nat Med, 2014; 20: 54–61

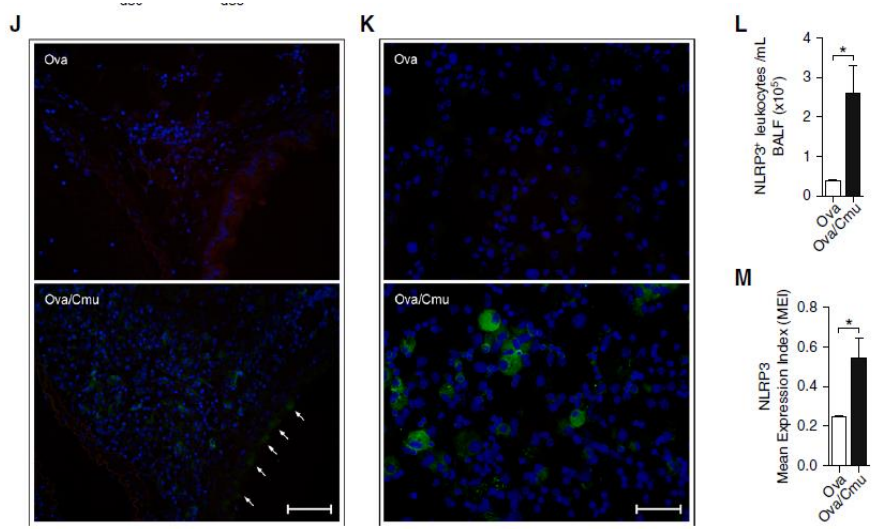
Non-Type 2 related inflammation targeting therapies
Inflammasome inhibitor

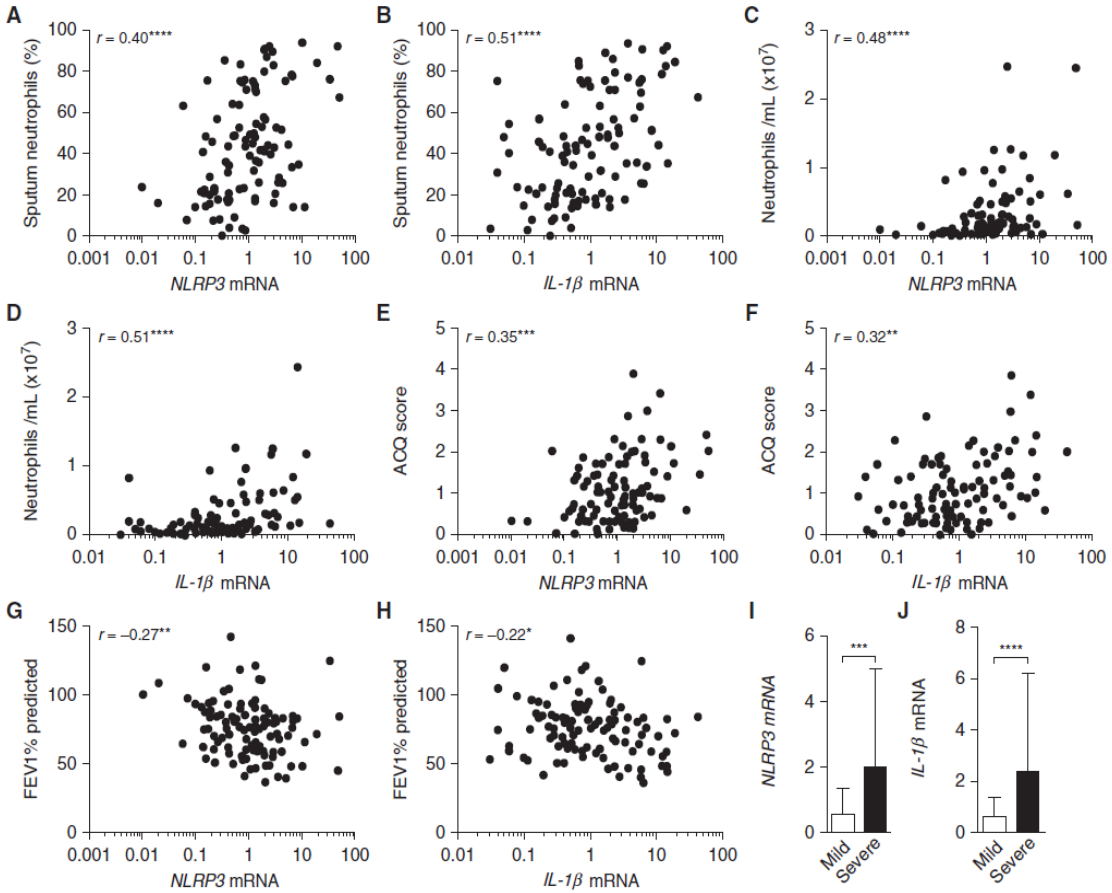
ORIGINAL ARTICLE

Role for NLRP3 Inflammasome–mediated, IL-1β–Dependent Responses in Severe, Steroid-Resistant Asthma

Richard Y. Kim[1*], James W. Pinkerton[1*], Ama T. Essilfie[1], Avril A. B. Robertson[2], Katherine J. Baines[1], Alexandra C. Brown[1], Jemma R. Mayall[1], M. Khadem Ali[1], Malcolm R. Starkey[1], Nicole G. Hansbro[1], Jeremy A. Hirota[3], Lisa G. Wood[1], Jodie L. Simpson[1], Darryl A. Knight[1], Peter A. Wark[1], Peter G. Gibson[1], Luke A. J. O'Neill[4], Matthew A. Cooper[2], Jay C. Horvat[1*], and Philip M. Hansbro[1*]

[1]Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, Newcastle, New South Wales, Australia; [2]Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia; [3]James Hogg Research Centre, University of British Columbia, Vancouver, British Columbia, Canada; and [4]School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland

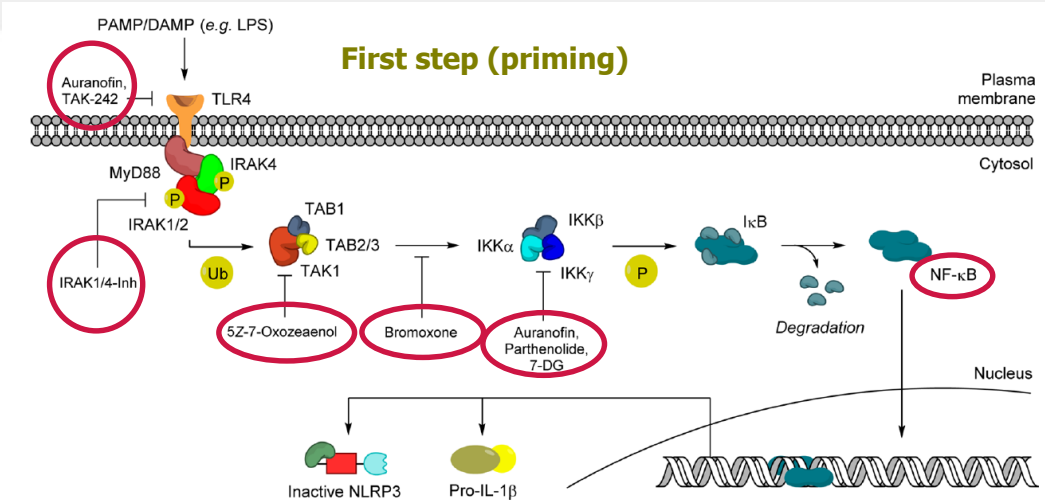


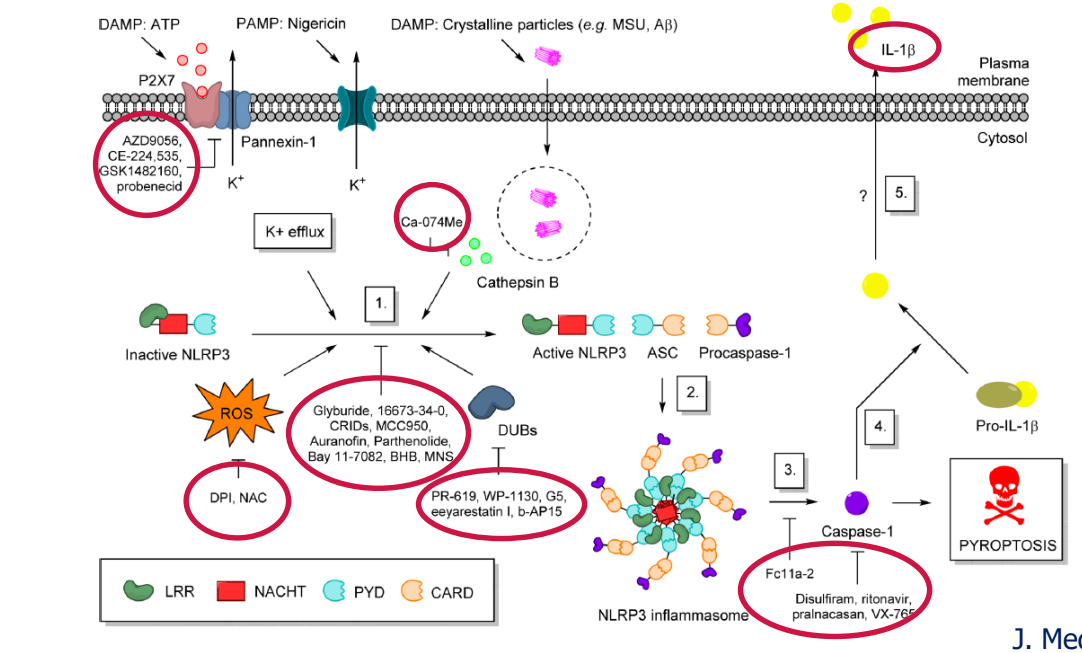


Am J Respir Crit Care Med Vol 196, Iss 3, pp 283–297, Aug 1, 2017

Non-Type 2 related inflammation targeting therapies

Inflammasome inhibitors





Compound	IC_{50} (μM, IL-1β release)	Target(s)	Mechanism of action
1	12 ± 5	NLRP3 (indirectly)	Prevents ASC oligomerisation, independent of K_{ATP} channels
3	-	NLRP3 (indirectly), ASC?	Prevents ASC oligomerisation
4	0.21 ± 0.06	NLRP3 (indirectly)	*n/a*, reversible inhibitor
5	0.26 ± 0.05	NLRP3 (indirectly)	*n/a*, reversible inhibitor
6	0.35	GSTO 1-1	Cysteine modification, blocks NLRP3 activation
7	0.25	GSTO 1-1	Cysteine modification, blocks NLRP3 activation
8	0.0075	NLRP3	Prevents ASC oligomerisation
9	-	NLRP1b, NLRP3, TLR4, IKK, TrxR,	Cysteine modification, blocks NLRP3 priming
12	2.59	NLRP1, NLRP3, caspase-1, IKK, NF-κB	Cysteine modification, inhibits NLRP3 ATPase activity
13	-	NLRP3, IKK, E2/3 enzymes, PTPs	Cysteine modification, inhibits NLRP3 ATPase activity
14	-	NLRP3 (indirectly)	Prevents K^+ efflux, independent of its known targets
15	-	NLRP3 (indirectly)	Prevents autocleavage of procaspase-1
16	~2	NLRP3	Cysteine modification? Inhibits NLRP3 ATPase activity

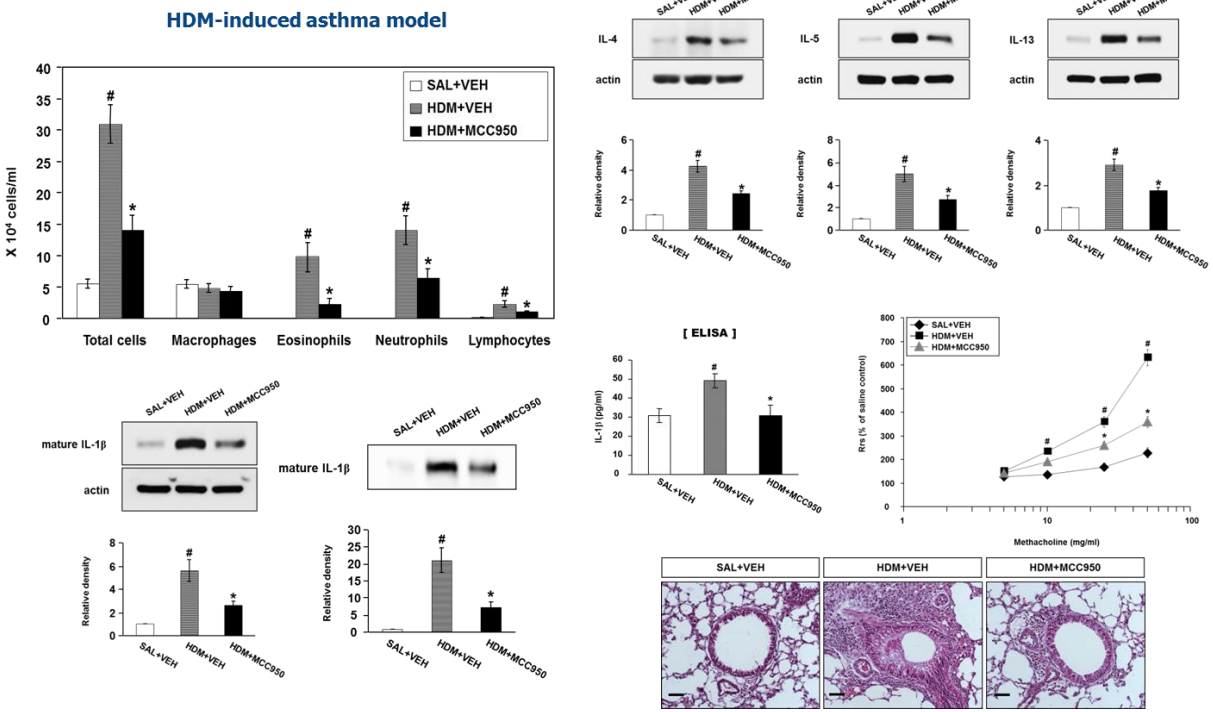
MCC950

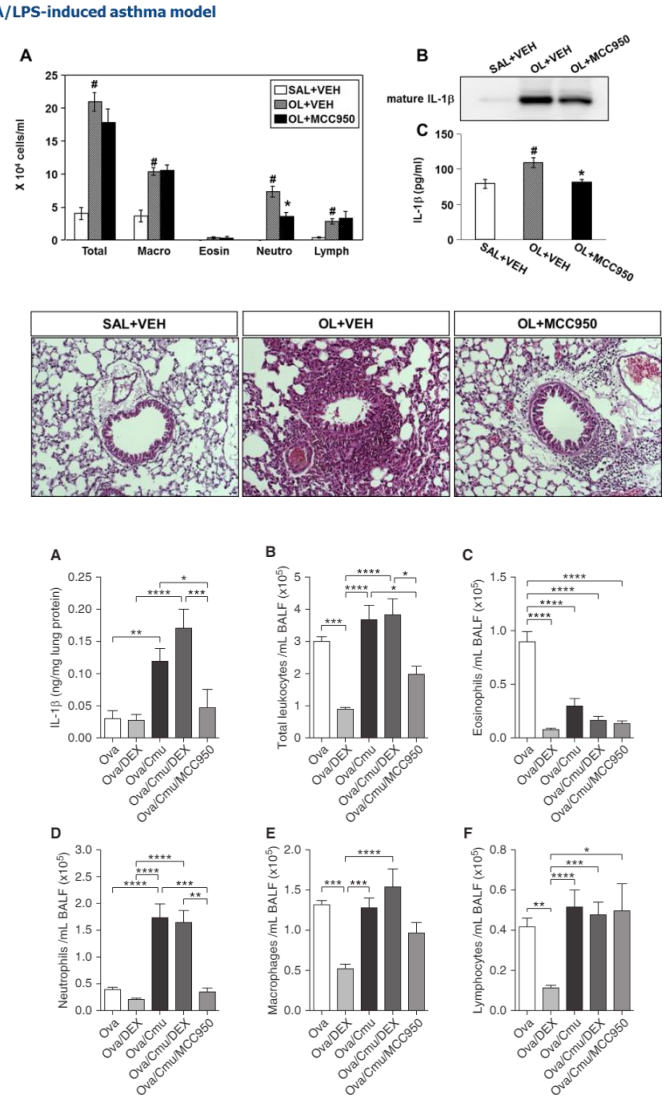
19	0.42	Caspase-1	Blocks pro-IL-1β cleavage
20	0.67 ± 0.55	Caspase-1	Blocks pro-IL-1β cleavage
23	0.0057	TLR4	Cysteine modification, blocks NLRP3 priming
24	~0.17	Upstream of IKK	Cysteine modification? Blocks NLRP3 priming
25	-	TAK1	Cysteine modification, blocks NLRP3 priming
30	-	PKR	Cysteine modification?, prevents PKR-IKK and PKR-ASC interactions
31-35	-	DUBs	Cysteine modification, blocks NLRP3 activation
36-39	-	P2X7R	Prevents K^+ efflux, blocks NLRP3 activation
40	-	Panx1?	Blocks NLRP1-3 activation
2, 41-47	-	Various ion channels, Ca^{2+}	Prevents cytosolic fluxes, blocks NLRP3 activation
48-49	-	NOX, ROS	Blocks NLRP3 priming
50	-	Cathepsin B	Blocks lysosomal destabilisation-induced NLRP3 inflammasome activation?
51, 53	-	Syk	Blocks ROS synthesis, prevents ASC oligomerisation
54	-	IRAK1/4	Blocks NLRP3 priming, prevents ASC oligomerisation

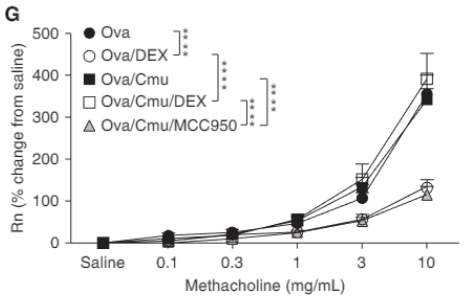
J. Med. Chem. 2016, 59, 1691−1710

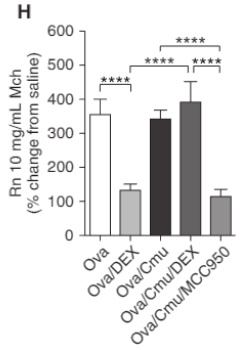
Non-Type 2 related inflammation targeting therapies

Inflammasome inhibitor: pre-clinical data







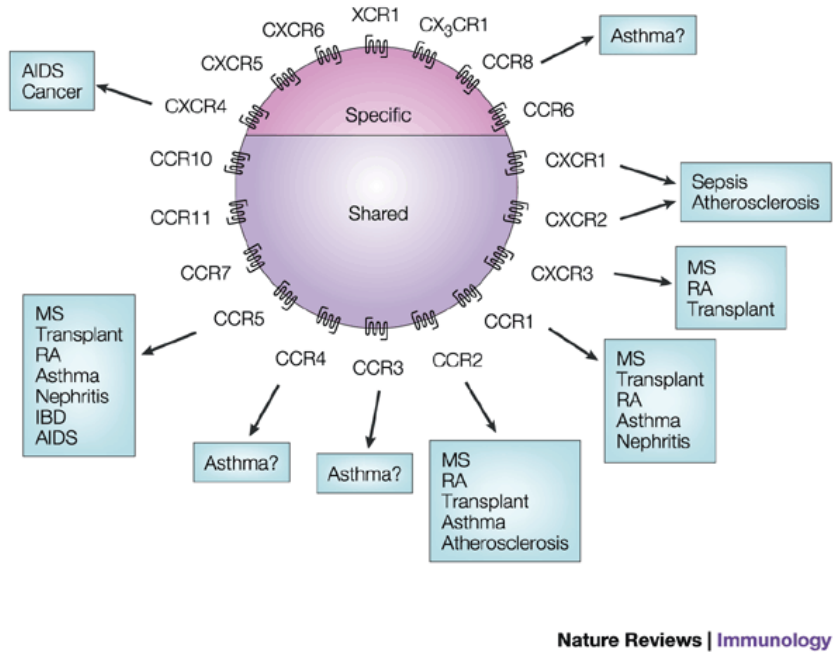


Unpublished data; Am J Respir Crit Care Med Vol 196, Iss 3, pp 283–297, Aug 1, 2017

Non-Type 2 related inflammation targeting therapies
Chemokine receptor antagonist: CXCR2

- **CXCL8** is a chemokine involved in the chemo-attraction and activation of neutrophils through **the CXCR2** receptor.

- **SCH-527123**
  - Oral CXCR1/CXCR2 antagonist
  - reduced sputum neutrophilia in adults with severe asthma
- **Reparixin, AZD-8309, SB-656933, GSK1325756, and AZD5069**
  - Under development
  - Entered to clinical trials, esp infectious airway inflammation



Eur Respir J. 2010;35(3):564–70; Clin Exp Allergy. 2012;42(7):097–1103; Nat Rev Immunol. 2016;16(6):378–91

Clinical comorbidities-based therapeutic modalities
Severe asthma with fungal sensitization (SAFS)

- The criteria for defining SAFS are
  - Severe asthma (British Thoracic Society step 4 or worse)
  - Exclusion of ABPA (total IgE <1000 IU/mL)
  - Evidence of sensitization to one or more fungi, by skin prick test or RAST test
- Treatment of SAFS initially should be similar to that of severe asthma, including the use of omalizumab.
  - The potential role of itraconazole as a specific therapy in SAFS requires more evidence before it can be incorporated in routine practice

- **Aspergillus fumigatus**, Alternaria alternata, Cladosporium herbarum, Penicillium chrysogenum,Candida albicans, Trichophyton mentagrophytes, or Botrytis cinerea

Lee YC & Kim SR et al, Thorax. 2016 Jan;71(1):52-63
Clinical and Translational Allergy 2014, 4:14

Clinical comorbidities-based therapeutic modalities
Antifungal agents: ABPA & SAFS

- Two closely related subgroups of patients with severe allergic asthma

- **Azoles: itraconazol/ as an add-on therapy**
  - ABPA in asthma patients; recommended
  - SAFS: improvement of asthma symptom score and lung function and reduction of serum IgE levels

- **Polyene: Amphotericin B, liposomal amphotericin**
  - Nebulized or inhaled formulation
  - ABPA: two reports
  - SAFS: no clinical report

Respir Med. 2004;98(10):915–23; Cochrane Database Syst Rev. 2004;3:CD001108; Am J Respir Crit Care Med. 2009;179(1):11–8;
Pediatrics. 2010;126(4):e982–5.; Pediatrics. 2010;125(5):e1255–8; Pediatr Pulmonol. 2010;45(11):1145–8

Clinical comorbidities-based therapeutic modalities
Macrolides: infections and bronchiectasis

- Some of severe asthma are chronically infected with atypical bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*
  - Long term macrolides: Controversial

- Severe asthma with structural disorders esp., bronchiectasis
  - Low-dose macrolides: reduce neutrophilic inflammation in the airways
  - the treatment with low-dose azithromycin resulted in the significant reduction of exacerbation rate but not infection rate

JAMA. 2013;309(12):1251–9; Thorax. 2013;68(4):322–9

Clinical comorbidities-based therapeutic modalities
Intranasal corticosteroids: allergic rhinitis

- Controversial: as add-on therapy on asthma outcome of severe asthma patients
  - Effective in case of the patients without any corticosteroid therapy
  - Intranasal inhalation to lung

- The selection of adequate inhaled technique or the dual inhaled therapy: prospective study

Allergy. 2013;68(5):569–79

Clinical comorbidities-based therapeutic modalities
IFN-β: Viral Infection-Associated Asthma Exacerbation

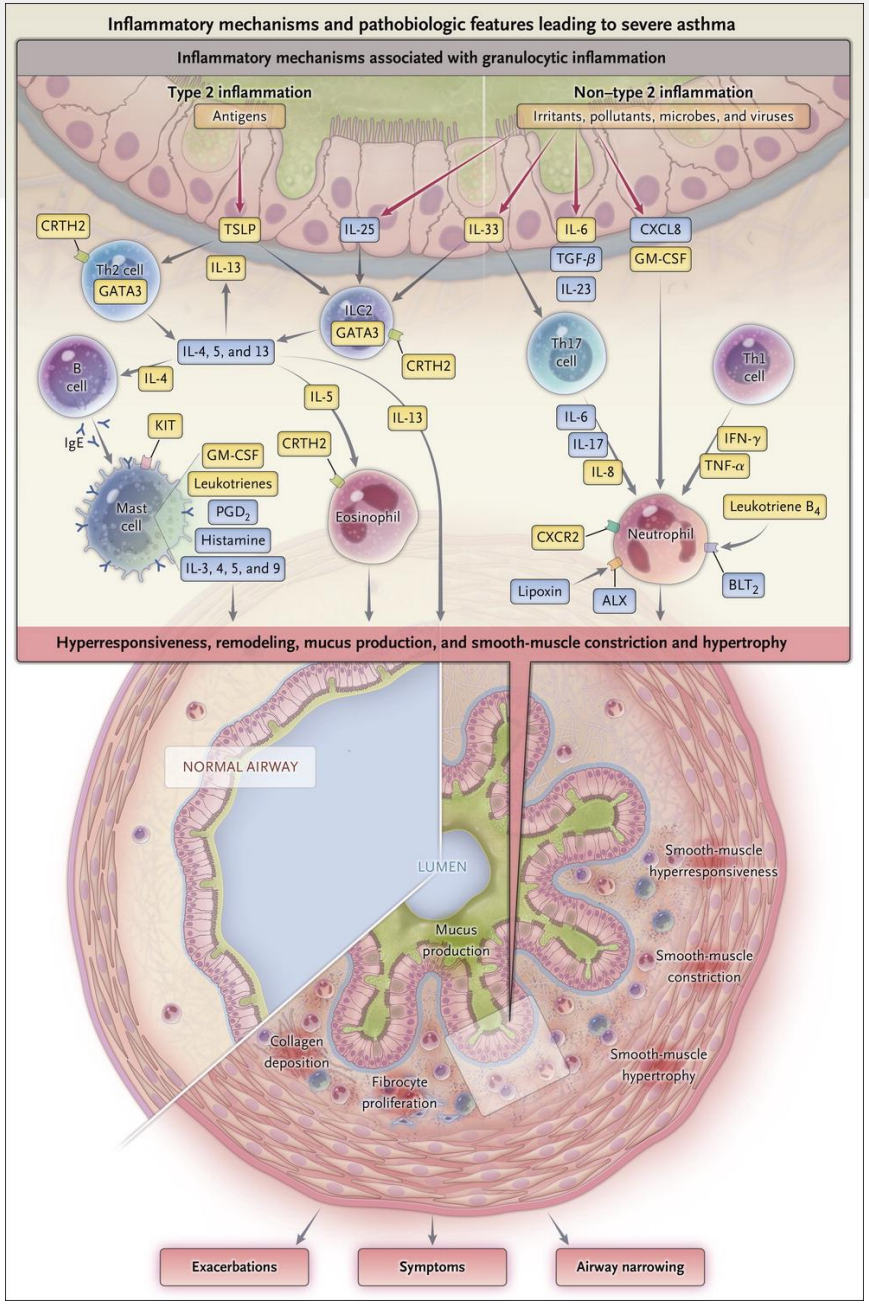
- Most asthma exacerbations are triggered by viral infections (up to 80%): **rhinovirus**, respiratory syncytial virus, influenza…
  - an impaired interferon (IFN) response to infection?
  - asthmatic bronchial epithelium failed to mount an effective innate immune response involving IFN-β
- **SNG001:** Selective patients; moderate to severe patient of asthma
  - a beneficial clinical effect of treatment presented as reduction in ACQ-6 score in patients treated with IFN-β
  - Phase II clinical trial on more severe asthma has been recently completed.

N Engl J Med. 2013;368(15):1398–407; J Exp Med. 2005;201(6):937–47; Am J Respir Crit Care Med. 2014;190(2):145–54.

Table of content

Take home messages (1)

Improved current medications		Therapeutic overcome steroid resistance	Endotype-based Therapeutics		Clinical comorbidities -based therapeutic
CS	high-dose ICS, OCS	Kinase inhibitors	Type 2-targeting therapies	Anti-IgE	Anti-fungal agent
	New ICS			Anti-IL4,5,13 TSLP	
	Small particle ICS / Dissociated steroids	Anti-oxidants and mitochondria targeting anti-oxidants		Blockade of lipid mediators	Macrolides
				Anti-CCR3, CCR4	
Newly developed LABA		PDE4 inhibitors	Non-Type 2 targeting therapies	Anti-TNFα	Intranasal steroid
				Anti-IL-17	
LAMA		ER stress inhibitors		Inflammasome inhibitors	IFN-β
				Anti-CXCR2	



Take home messages (2)

- As the term "asthma" changes to the general medical term like cancer and anemia, the endotyping and phenotyping studies are more required for the application of precision medicine.
- **Molecular endotypes** provide many information on the novel mechanisms of asthma, especially severe asthma.
- Endotype-based therapeutic approach is useful to apply precision medicine to severe asthma patients.
- More valid biomarkers are essential for the selection of the therapeutic candidates for the specific treatment.
- More subdivided populations should be defined in the patients showing the same clinical cluster or similar cellular inflammatory profiles for the precision curative and preventive medicine.

Discussion and Closing

Thank you for your attention