The use of biological medications in asthma
: IL-5 pathway and anti-IL-5

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Definition

- **Biological Medication?**
  - **A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines.**
  - **Also called biologic agent and biological agent.**

- **Biomarkers?**
  - **Characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.**

Historical asthma

Asthma

was used by the ancient doctors

- Hippocrates, Galen, Aretaeus, Celsus…..

"Various forms of dyspnea"

- In 4th-5th century, a better description of Asthma was released…

" Asthma occurs oftener in men than in women, in middle age than in children or old men, and in the delicate rather than in the strong. More in winter than in summer and more at night than by day. In some it begins after disease, whereas in others it begins without obvious cause. . . . The patient has a feeling of suffocation, heaviness and burning heat in the chest, and a feeling of spasm in the bowels. It begins with violent suffering, wheezing and hissing in the chest, and the voice is weak, the neck and face stretched and red, the expression anxious . . . there are tears . . . And the pulse is weak. Asthma is distinct from other diseases, where there is difficult breathing, as well as from pneumonia, orthopnoea . . . etc."

Mutius E, et al. NEJM 2012;366:727-34.

Historical asthma

Asthma

was considered as an idiosyncrasy, for a long time

one of anaphylaxis or allergy

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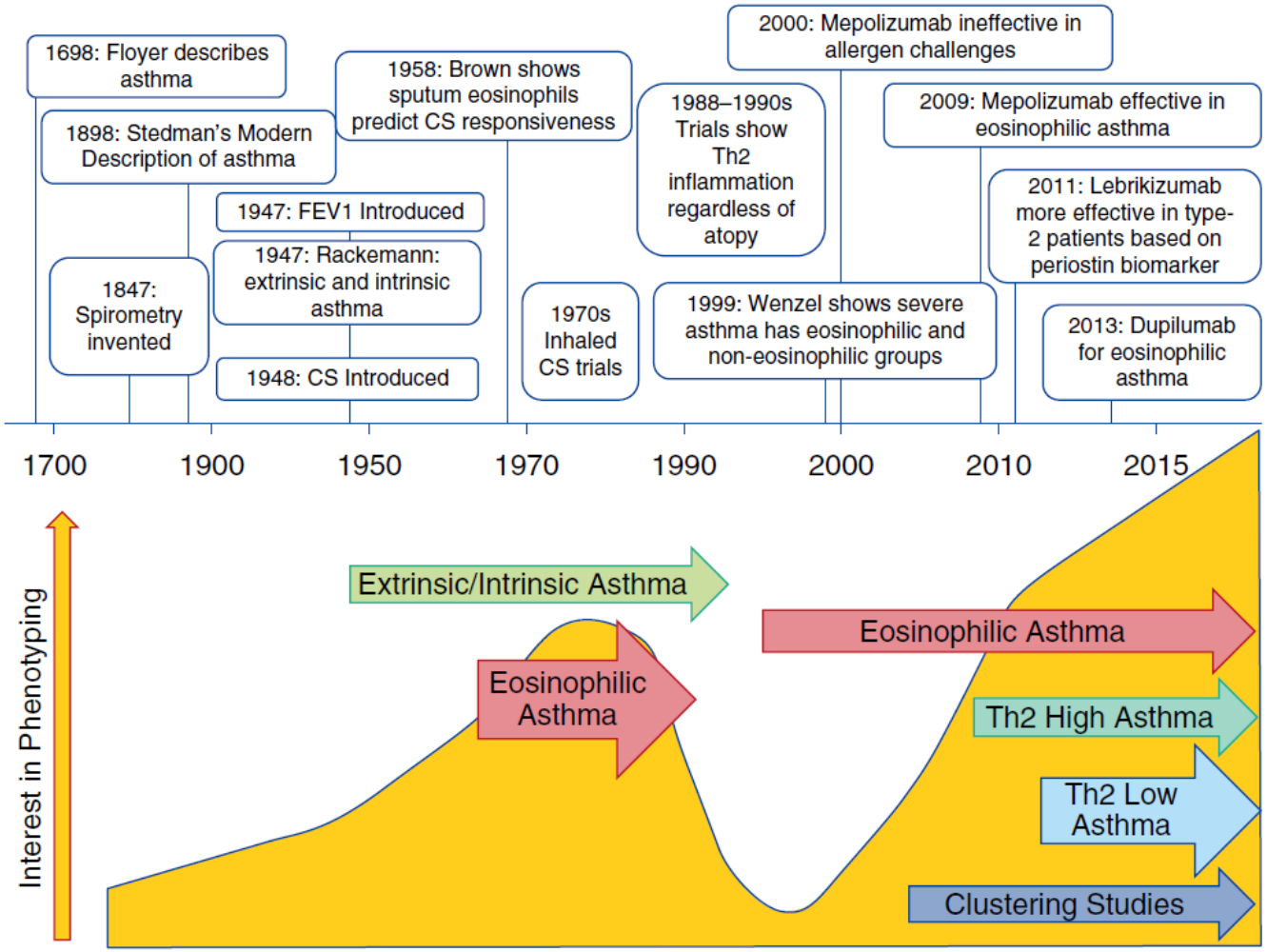
No medical literature to speak of until 17th century..
Many papers on asthma were written in the 17th -18th century.

Mutius E, et al. NEJM 2012;366:727-34.

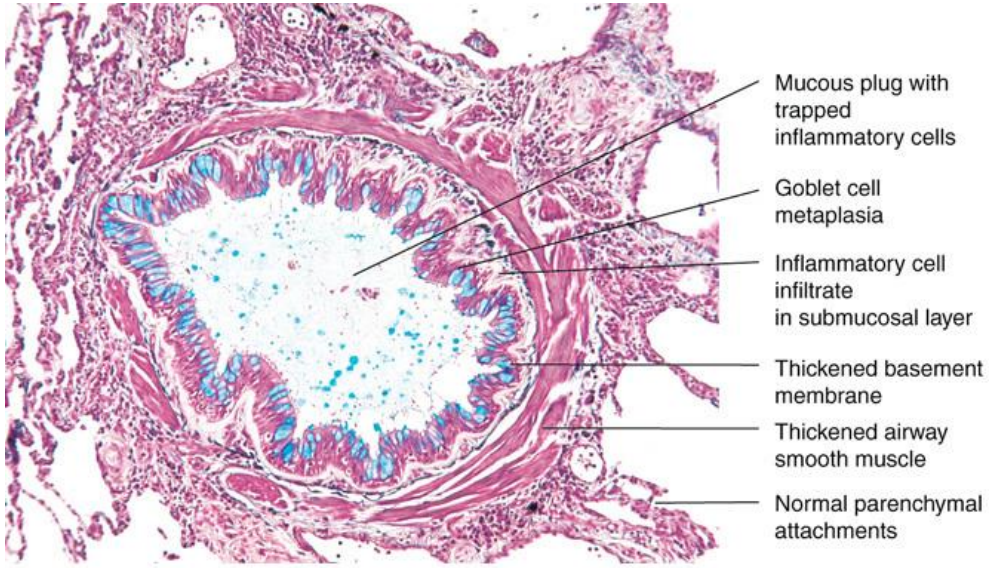
Historical asthma



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

Evolving concept of asthma

eosinophil



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

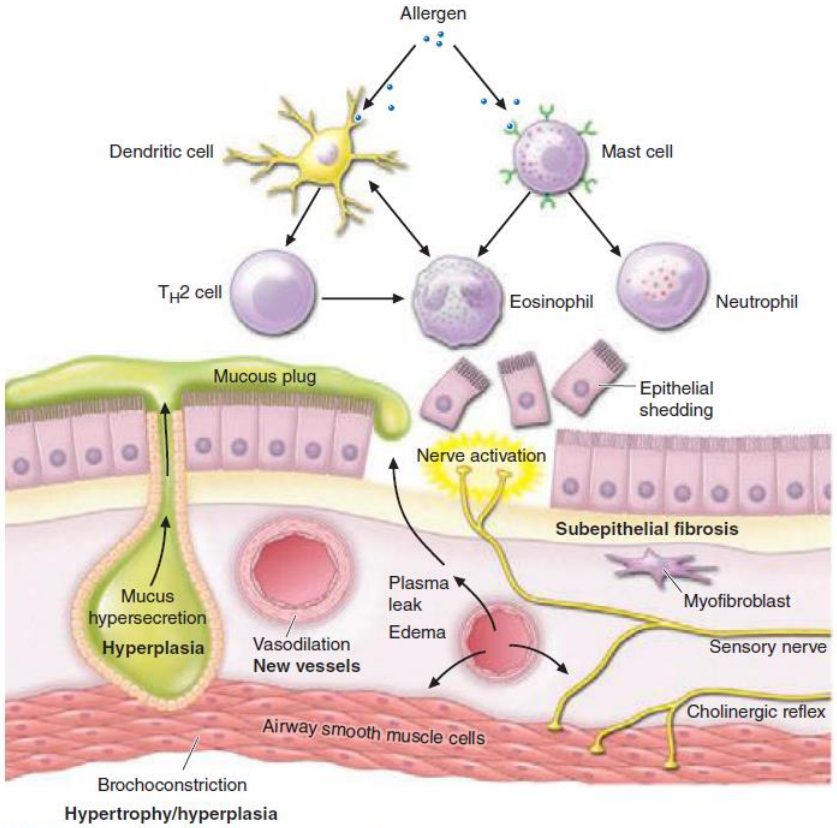
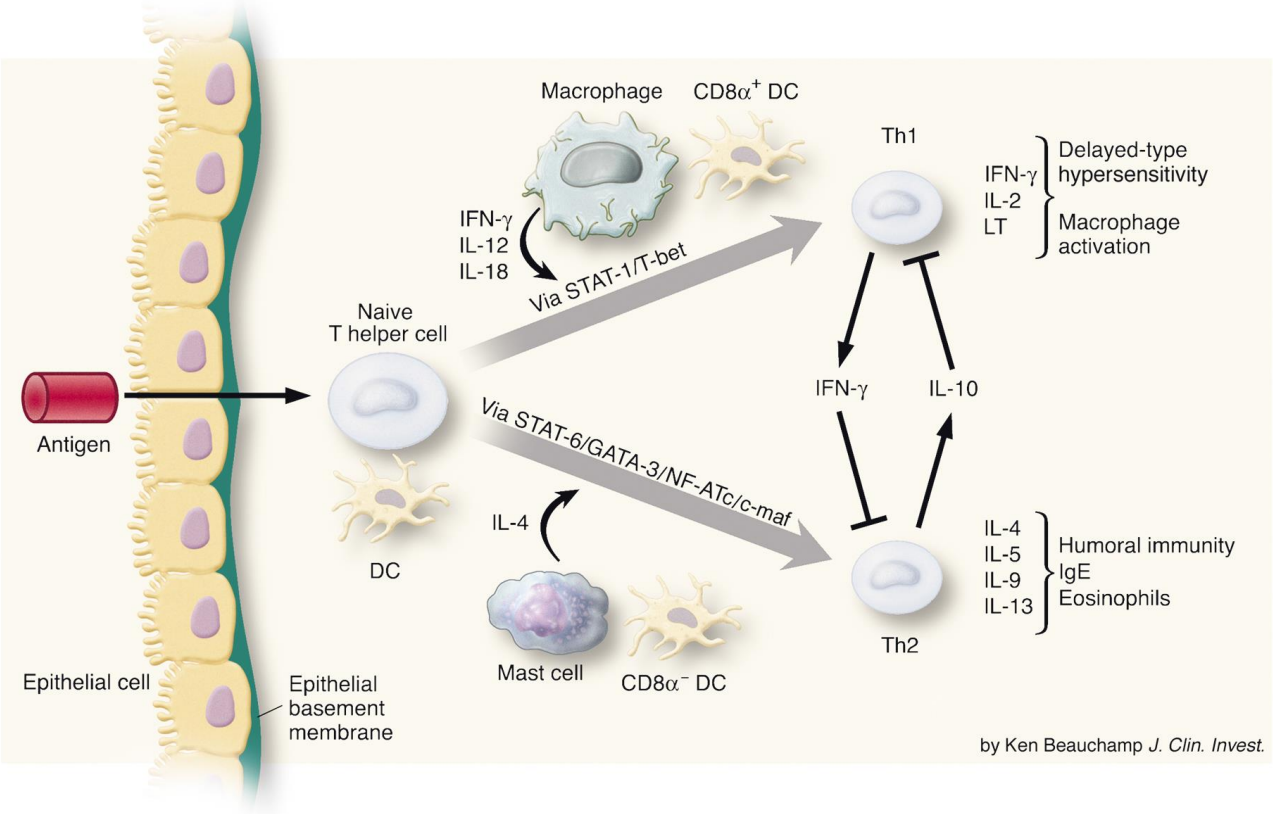


FIGURE 309-3 **The pathophysiology of asthma is complex** with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

- **The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells.**
- **Many inflammatory cells are known to be involved in asthma with no key cell that is predominant.**

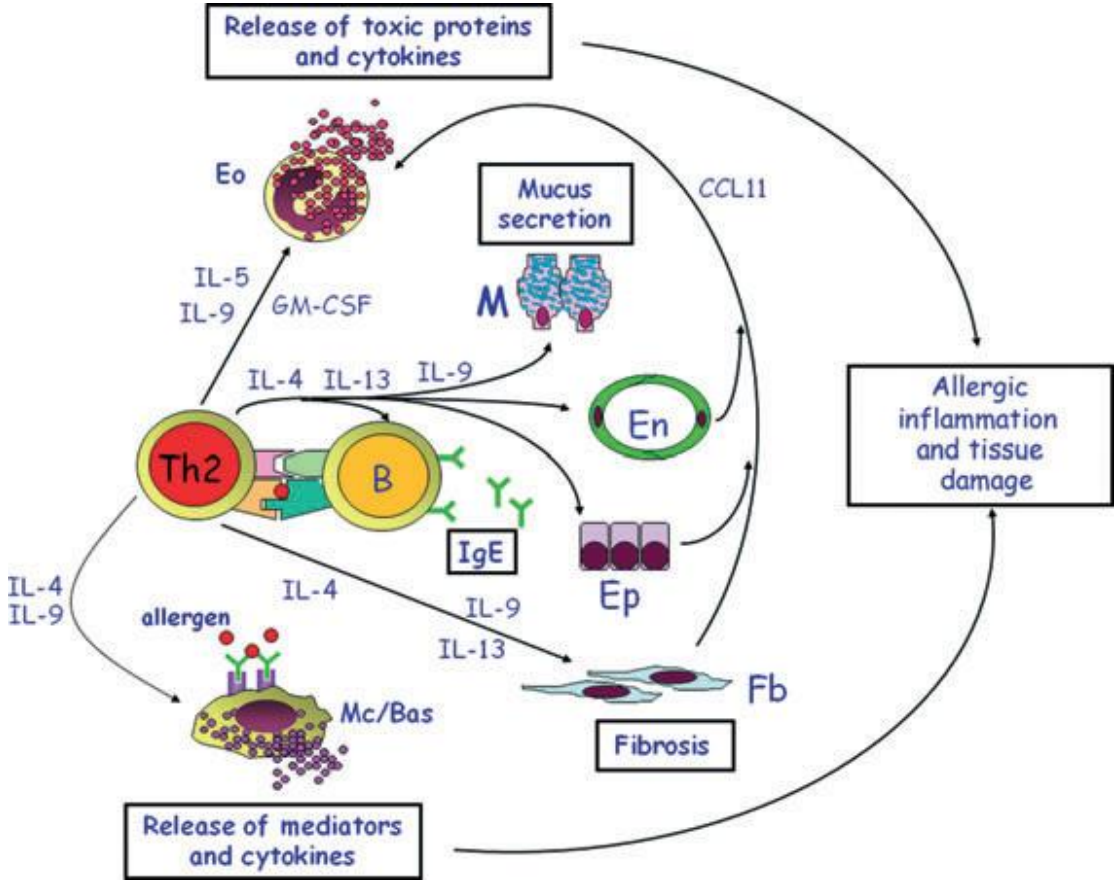
Evolving concept of asthma

Th1/Th2 paradigm



Evolving concept of asthma

Th1/Th2 paradigm

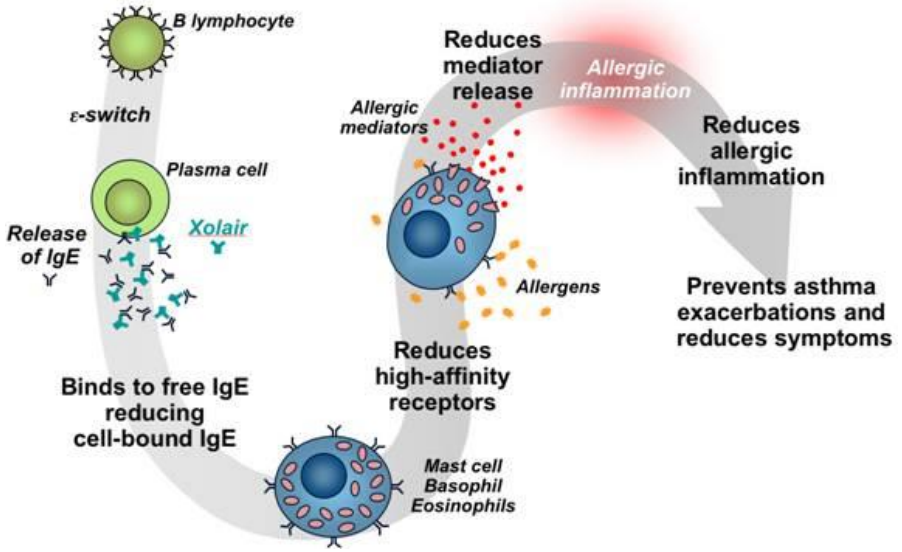


Cosmi L et el. Allergy 2011;66(8):989-98
Mosmann TR et al., Immunol 1986;136(7):2348–57.
Barnes PJ. J Clin Invest 2008;118(11):3546–56.

Th2-targeted therapy

IgE-targeted therapy

- 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.

Th2-targeted therapy

IgE-targeted therapy

- **Omalizumab**
  - is not US Food and Drug Administration (FDA) approved for use in children younger than 12 years
  - 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
  - Allergic rhinitis: positive data
    - Not Approved due to high cost and side effect profile
  - Food allergy, atopic dermatitis: small studies
  - Urticaria
    - For chronic idiopathic urticaria, the FDA approved a dose of 150 or 300 mg administered subcutaneously every 4 weeks for patients 12 years or older; this is not dependent on serum IgE level or body weight, and length of treatment has not been defined.

Fajt ML et el. J Allergy Clin Immunol 2015;135:299-310.

Th2-targeted therapy

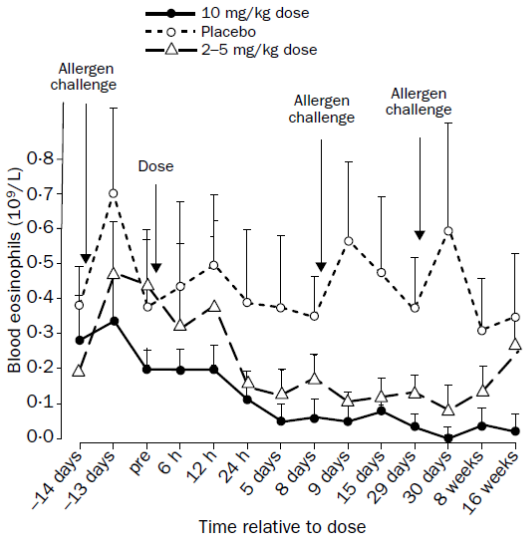
- **Th2 cytokine-targeted therapy: IL-5 (Mepolizumab, GSK, UK)**
  - **Identification of Th1 and Th2 immunity in the early 1990s and widespread efficacy of inhaled corticosteroids (ICSs) led to the hypothesis that asthma/allergies were primarily driven by Th2 immunity involving the cytokines IL-4, IL-5, and IL-13.**
  - **Despite this, pathobiologic studies suggested differences in inflammatory/immune processes across asthmatic patients, and early studies of Th2-targeted therapies were not efficacious.**

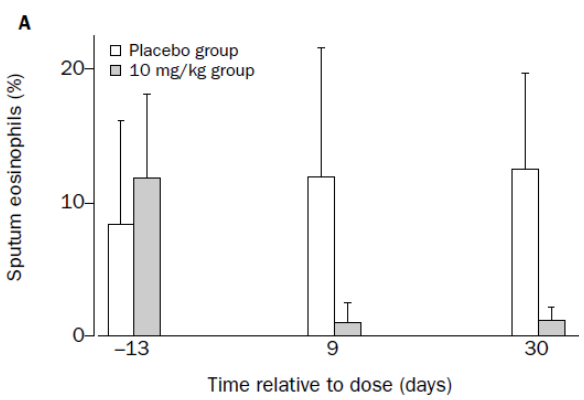
Leckie MJ et al. Lancet 2000; 356: 2144-48.
Kips JC, et al. Am J Respir Crit Care Med 2003;167:1655-9.
Flood-Page P, et al. Am J Respir Crit Care Med 2007;176:1062-71.

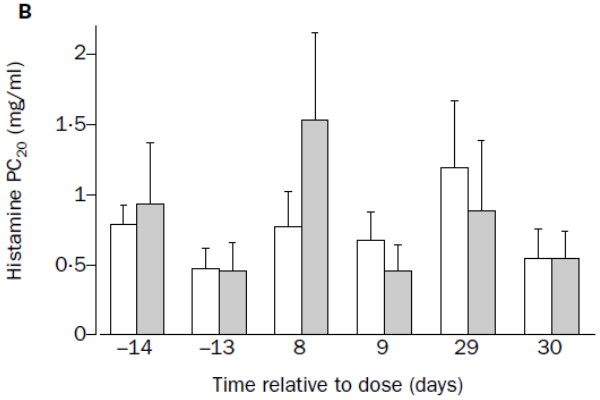
Early reports

Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response

Margaret J Leckie, Anneke ten Brinke, Jamey Khan, Zuzana Diamant, Brian J O'Connor, Christine M Walls, Ashwini K Mathur, Hugh C Cowley, K Fan Chung, Ratko Djukanovic, Trevor T Hansel, Stephen T Holgate, Peter J Sterk, Peter J Barnes







This study might suggest eosinophils (and IL-5) are not as critical to traditional allergic asthma phenotypes and their allergic reactions.

Leckie MJ et al. Lancet 2000; 356: 2144-48

Evolving concept of asthma

Th2 inflammation to type 2 inflammation

- Th2-high asthma vs Th2-low asthma

T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma

Prescott G. Woodruff[1,2], Barmak Modrek[3], David F. Choy[4], Guiquan Jia[4], Alexander R. Abbas[3], Almut Ellwanger[1], Joseph R. Arron[4]*, Laura L. Koth[1,5], and John V. Fahy[1,2]*

[1]Division of Pulmonary and Critical Care Medicine and [2]Cardiovascular Research Institute, Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California; [3]Department of Bioinformatics and [4]ITGR Biomarker Group, Genentech, Inc., South San Francisco, California; and [5]Lung Biology Center, Department of Medicine, Cardiovascular Research Institute, University of San Francisco, San Francisco, California

Rationale: T-helper type 2 (Th2) inflammation, mediated by IL-4, IL-5, and IL-13, is considered the central molecular mechanism underlying asthma, and Th2 cytokines are emerging therapeutic targets. However, clinical studies increasingly suggest that asthma is heterogeneous.

Objectives: To determine whether this clinical heterogeneity reflects heterogeneity in underlying molecular mechanisms related to Th2 inflammation.

Methods: Using microarray and polymerase chain reaction analyses of airway epithelial brushings from 42 patients with mild-to-moderate asthma and 28 healthy control subjects, we classified subjects with asthma based on high or low expression of IL-13–inducible genes. We then validated this classification and investigated its clinical implications through analyses of cytokine expression in bronchial biopsies, markers of inflammation and remodeling, responsiveness to inhaled corticosteroids, and reproducibility on repeat examination.

Measurements and Main Results: Gene expression analyses identified two evenly sized and distinct subgroups, "Th2-high" and "Th2-low" asthma (the latter indistinguishable from control subjects). These subgroups differed significantly in expression of IL-5 and IL-13 in bronchial biopsies and in airway hyperresponsiveness, serum IgE, blood and airway eosinophilia, subepithelial fibrosis, and airway mucin gene expression (all $P < 0.03$). The lung function improvements expected with inhaled corticosteroids were restricted to Th2-high asthma, and Th2 markers were reproducible on repeat evaluation.

Conclusions: Asthma can be divided into at least two distinct molecular phenotypes defined by degree of Th2 inflammation. Th2 cytokines are likely to be a relevant therapeutic target in only a subset of patients with asthma. Furthermore, current models do not adequately explain non–Th2-driven asthma, which represents a significant proportion of patients and responds poorly to current therapies.

AT A GLANCE COMMENTARY

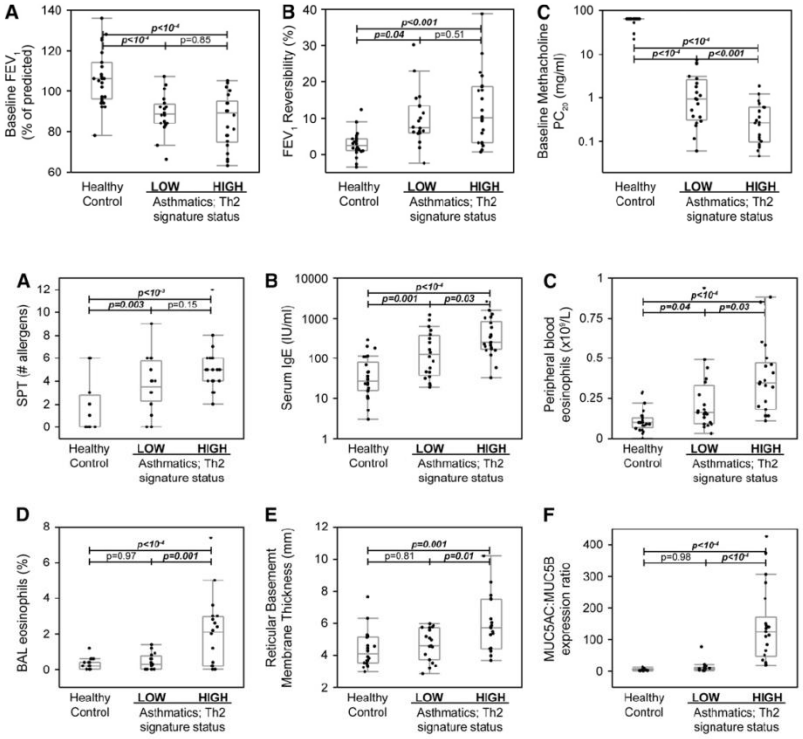
Scientific Knowledge on the Subject

Clinical studies increasingly suggest that asthma is heterogeneous, but the molecular basis for this heterogeneity is uncertain.

What This Study Adds to the Field

This study suggests that asthma can be divided into at least two distinct molecular phenotypes defined by degree of Th2 inflammation. Therapies targeting Th2 cytokines may be effective in only a subset of patients with asthma. Non–Th2-driven asthma represents a significant proportion of patients and responds poorly to current therapies.

responses and mediated by cytokines including IL-4, IL-5, and IL-13. IL-13 is produced by activated T cells, basophils, eosinophils, and mast cells and is thought to be a central mediator of inflammation in asthma based on animal models (1, 2) and on findings of elevated levels of IL-13 in the airways of patients with asthma (3). Consequently, much of the ongoing basic research in asthma is directed at understanding how Th2 cytokines cause asthma-like pathology and physiology (4), and inhibitors of Th2 cytokines are under development as novel asthma therapies (5). However, there is increasing evidence that a significant proportion of human asthma may be driven by alternative forms of inflammation. In particular, studies of the cellular components of airway inflammation in asthma provide evidence for distinct eosinophilic and noneosinophilic pheno-



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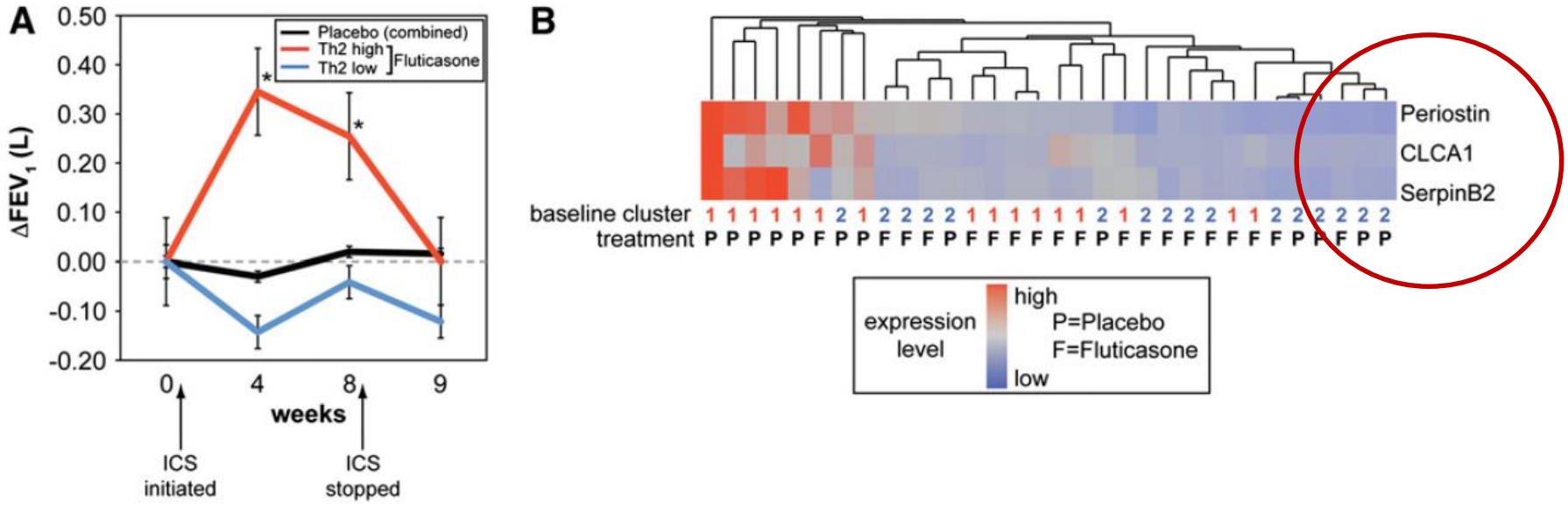
Woodruff PG et al. Am J Respir Crit Care Med 2009;180:388–395

Evolving concept of asthma

Th2 inflammation to type 2 inflammation

- **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

Evolving concept of asthma

Bio markers in type 2 molecular phenotypes

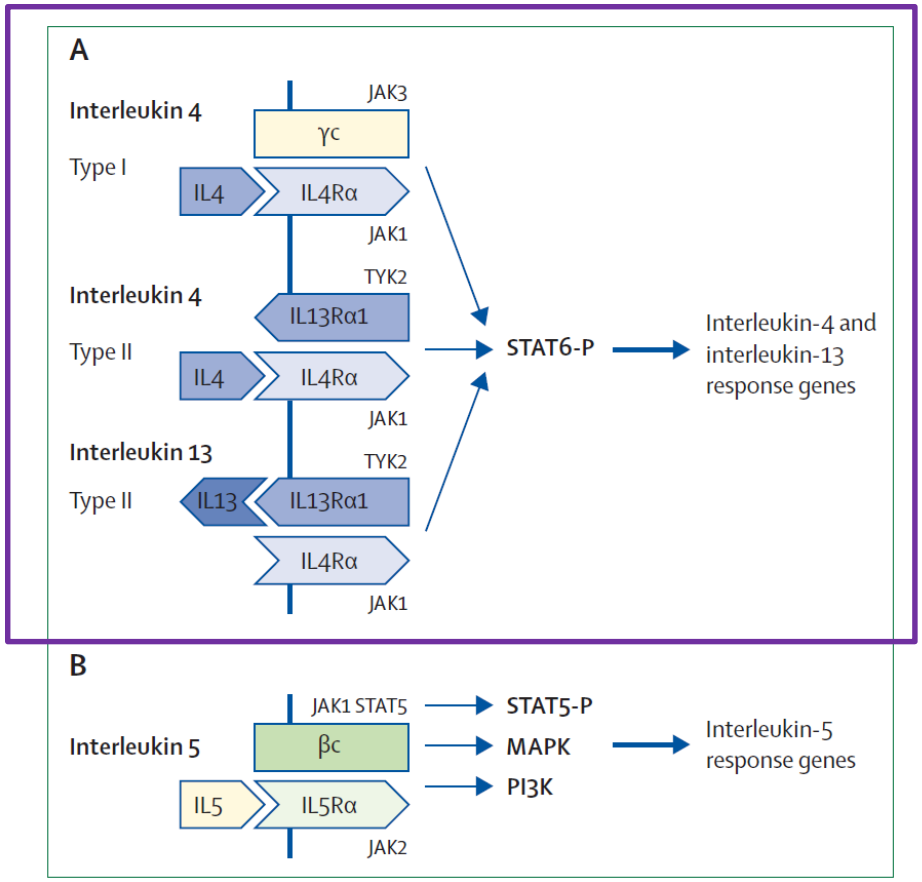
- **Type 2 biomarkers identified to date**
  - **periostin**
  - **fraction of exhaled nitric oxide (FENO)**
  - **sputum/blood eosinophils**

  - ***Several type 2-related biomarkers have emerged, although their specific utility across type 2 therapies remains to be determined.***

Fajt ML et el. J Allergy Clin Immunol 2015;135:299-310.

Type 2/Th2-targeted therapy

Targeting the canonical type 2 cytokines IL-4 and 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/Th2-targeted therapy

Targeting the canonical type 2 cytokines IL-4 and IL-13

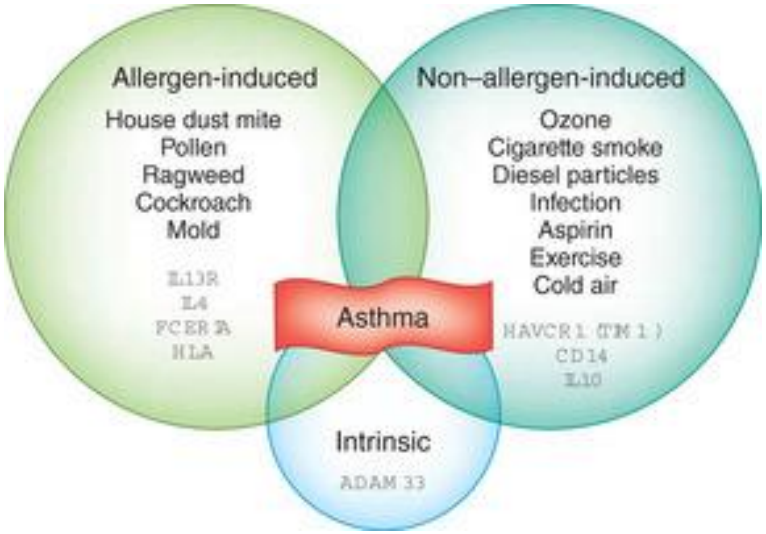
Target	Biologic therapies used	Type of study	Major outcome
IL-4 and IL-13	Mutant IL-4 (pitrakinra); IL-13 antibody (IMA-638)	Allergen challenge: mild allergic asthma	↓ Late asthmatic response
	IL-4Rα mAb (AMG 317); mutant IL-4 (pitrakinra)	Chronic moderate-to-severe asthma	No effect on prespecified clinical 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
  - Lebrikizumab and tralokinumab: high serum periostin or sputum IL-13
- **Allergic diseases : atopic dermatitis**

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.

Evolving concept of asthma

Approaches to identifying phenotypes of asthma

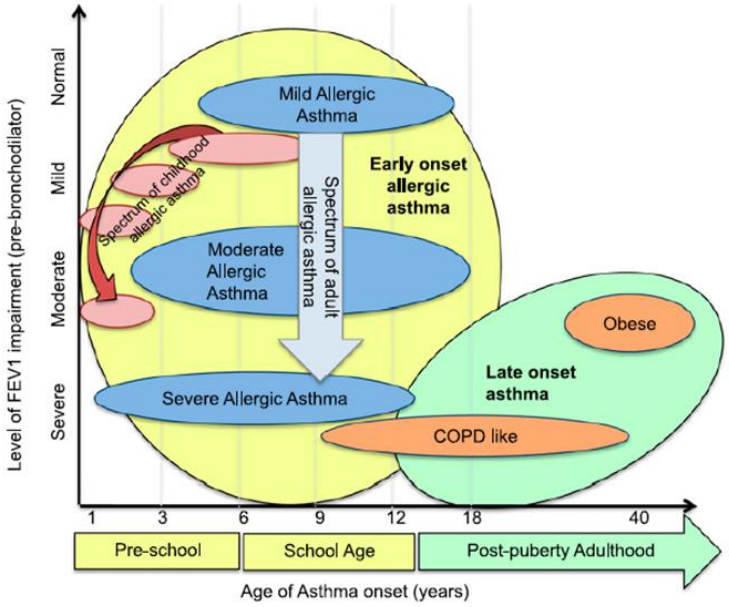


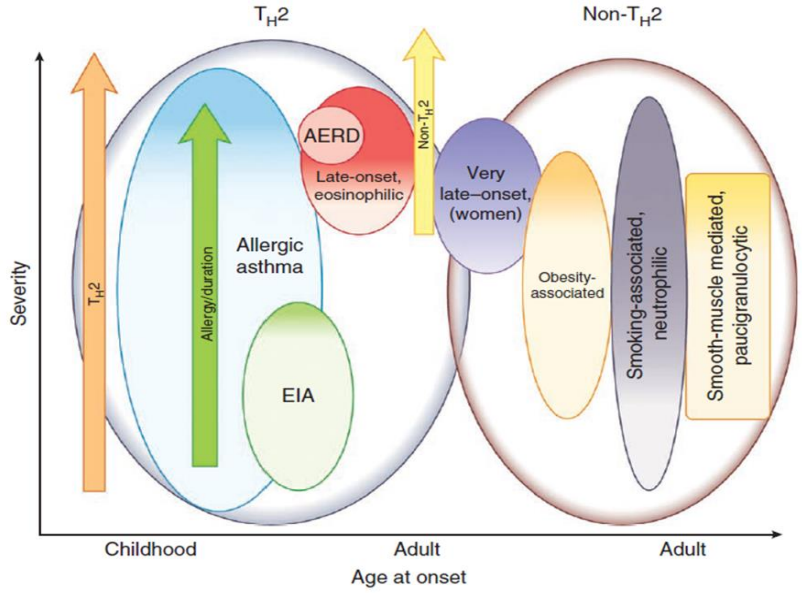
- **Asthma phenotyping began decades ago with the concepts of extrinsic (allergic) and intrinsic (non-allergic) asthma.**
- **Extrinsic asthma**
  - **developed the disease early in life,**
  - **atopic (they made IgE specific to identifiable allergens)**
  - **identifiable allergic triggers**
- **Intrinsic asthma**
  - **later in life (after 40 years of age),**
  - **associated with aspirin-exacerbated respiratory disease (AERD) but not with allergic sensitization**
- **Not correlated with Th2 cytokines and responses to corticosteroids leading that the distinctions between extrinsic and intrinsic asthma fell out of favor**

Wenzel S. Nature Medicine 2012;18:716-725

Evolving concept of asthma

Approaches to identifying phenotypes of asthma



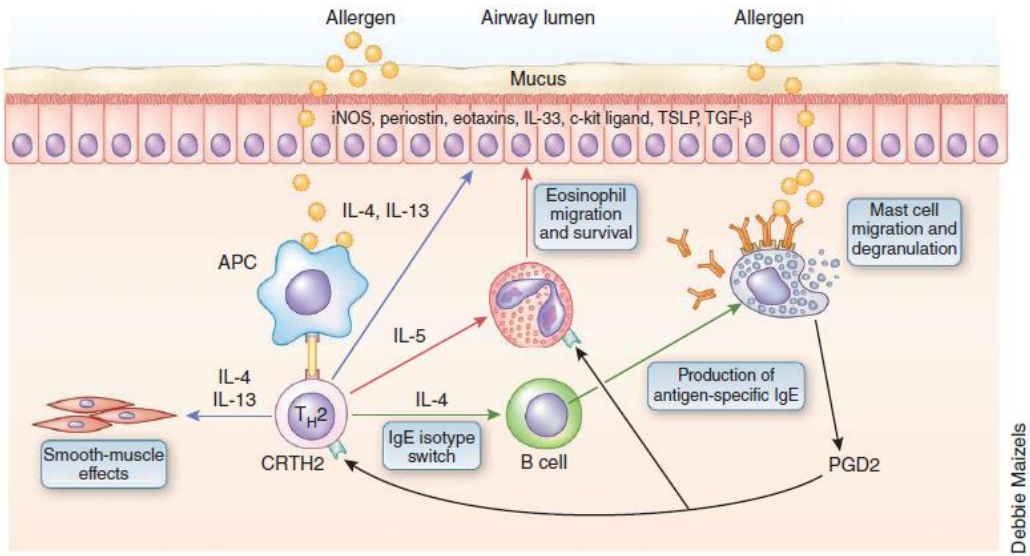


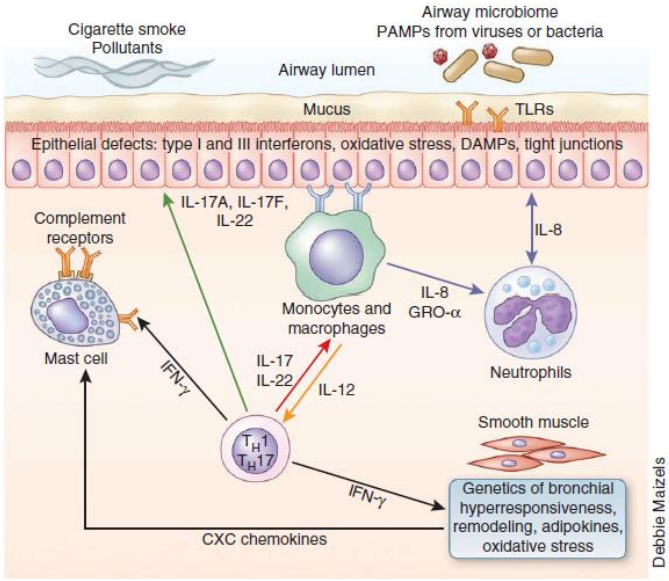
Wenzel S. Nature Medicine 2012;18:716-725

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

Evolving concept of asthma

Allergic and non-allergic asthmatic inflammation



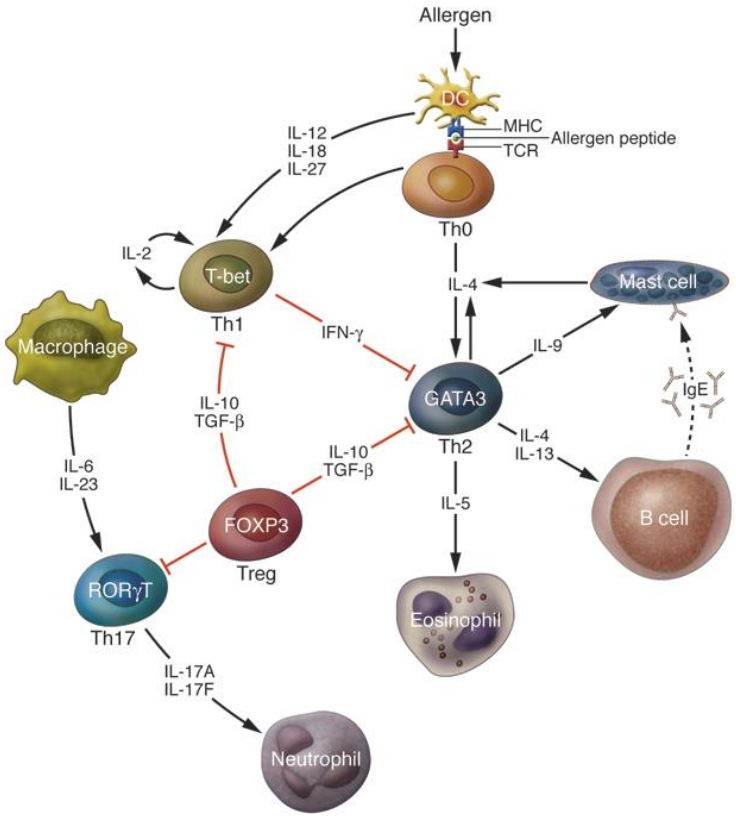


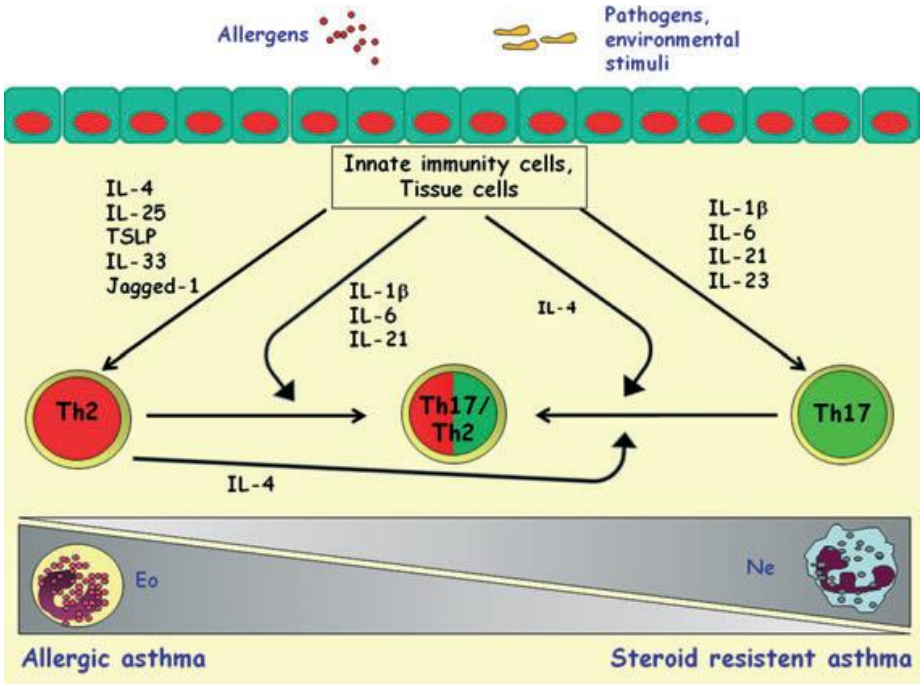
- Eosinophilia seems to be present in the early-onset/allergic asthma phenotype
- Neutrophilic inflammation had not previously been reported in milder asthma

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

Evolving concept of asthma

Allergic and non-allergic asthmatic inflammation



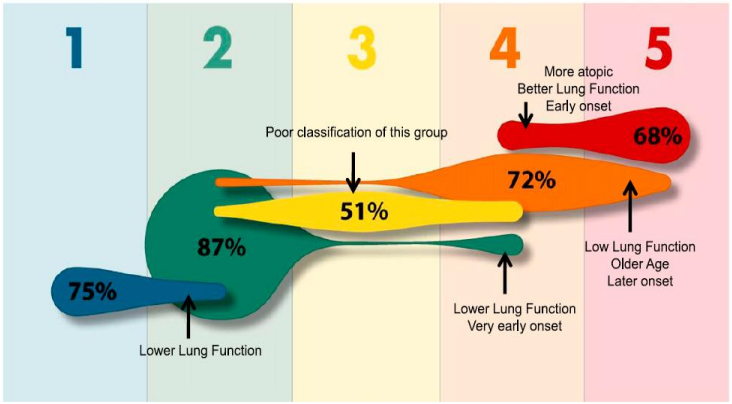


- Non-Th2 asthma has been accepted as neutrophilic dominant airway inflammation with showing steroid-resistance
- Th1 activation such as IFN-γ could enhance mast-cell responses; interestingly, CXC chemokines, induced by IFN-γ, are known mast-cell chemo-attractants to smooth muscle

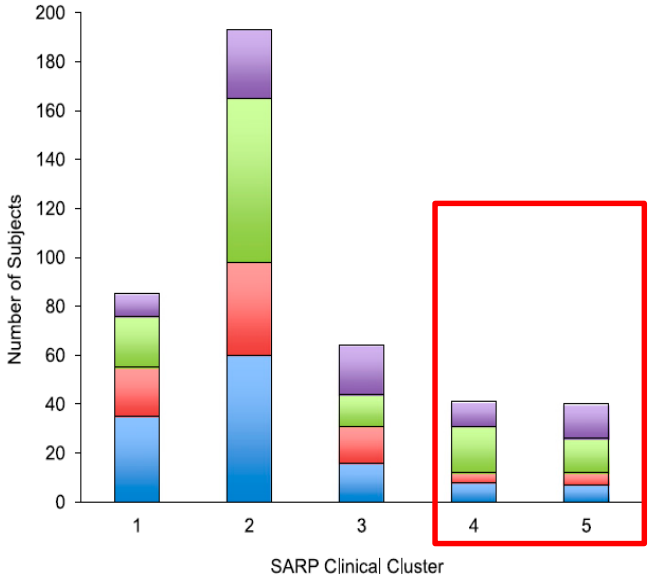
Cosmi L et el. Allergy 2011;66(8):989-98
Barnes PJ. J Clin Invest 2008;118(11):3546-56

Evolving concept of asthma

Approaches to identifying phenotypes of severe asthma



Orange: severe atopic asthma



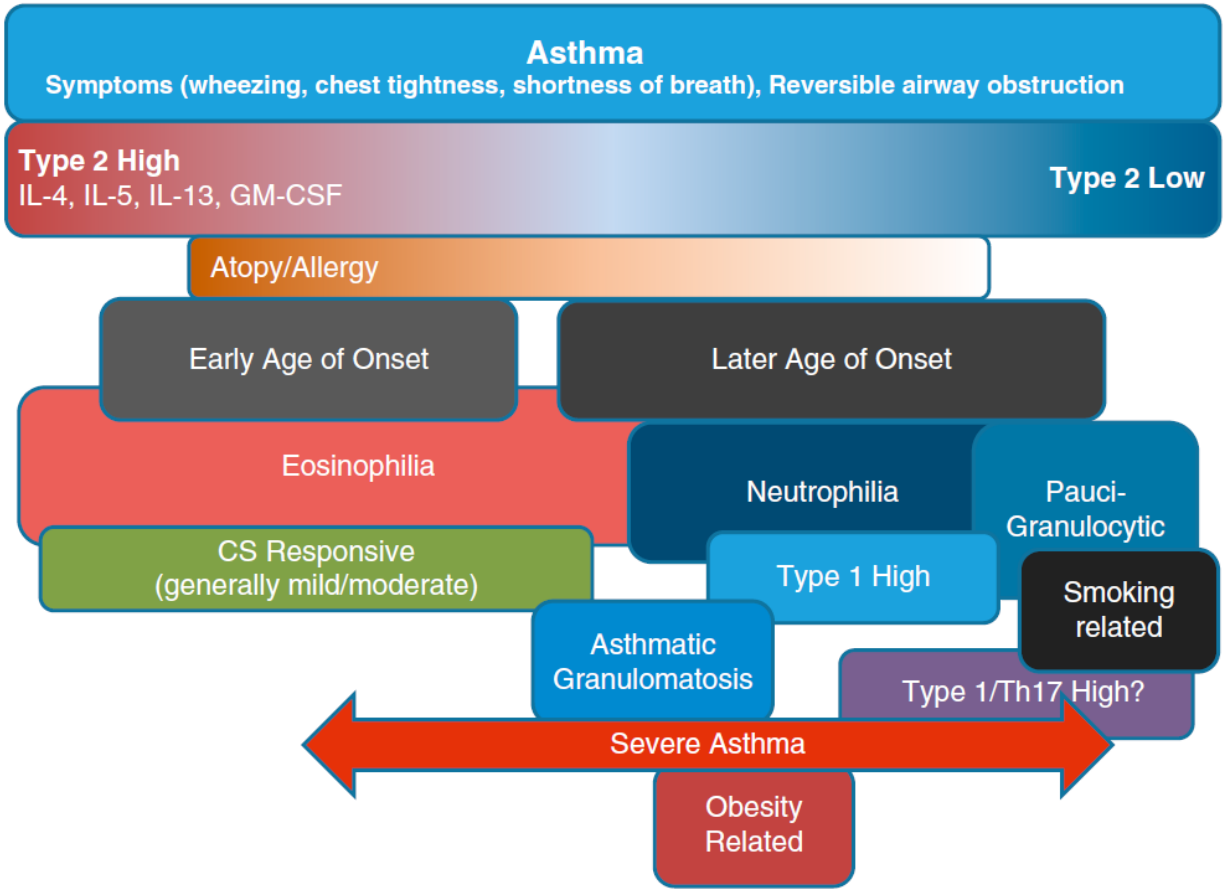
Blue, paucigranulocytic; red, eosinophil predominant; green, neutrophil predominant; purple, mixed granulocytic.

- 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

Evolving concept of asthma

Approaches to identifying phenotypes of asthma



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

Evolving concept of asthma

Risk factors: Asthma and severe asthma

Risk factors for asthma include[1]:

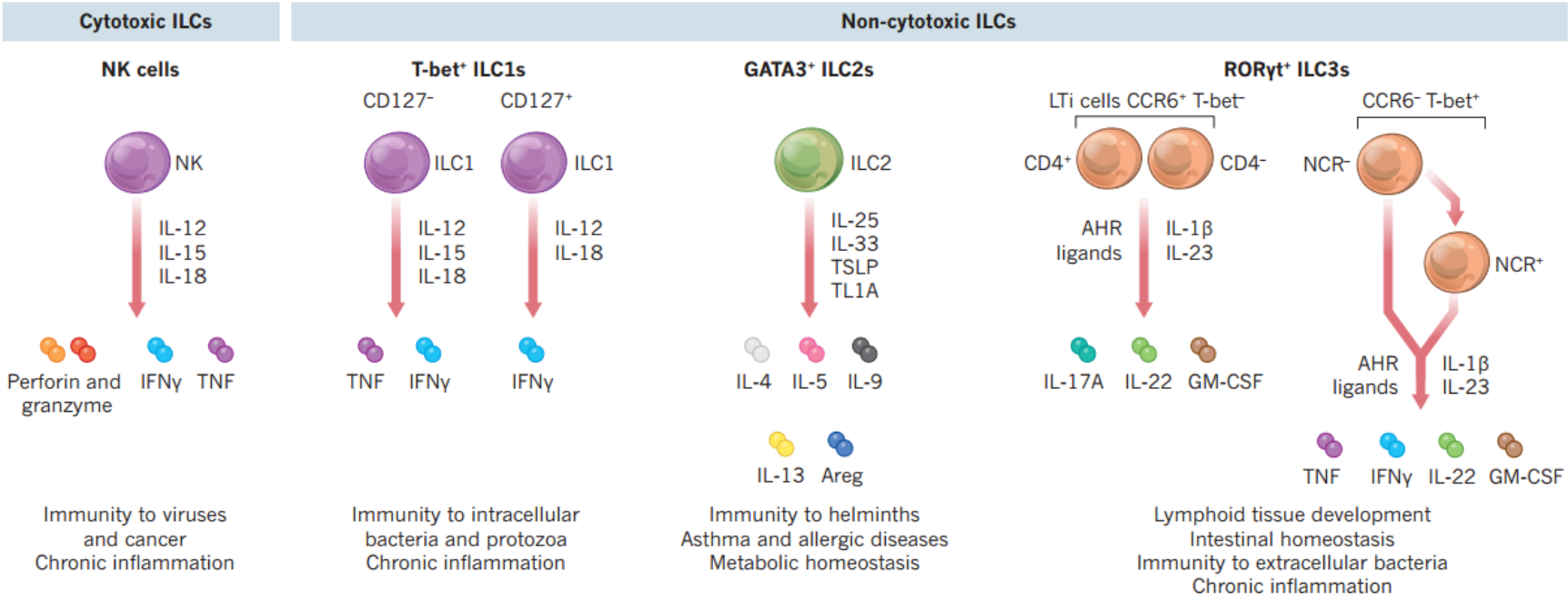
- Atopy
- AHR
- Gender (female sex in adult-onset asthma and male sex in childhood asthma)[2]
- Ethnicity (susceptibility linked to ethnic-specific genetic variations)
- Economic disadvantages[3]
- Indoor/outdoor allergens
- Pollution (eg PM2.5)
- **Obesity**
- **Occupational exposure**
- **Tobacco smoking**
- **Respiratory infections/Rhinitis**

Also associated with severe asthma.

1. Barnes P. Asthma. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, N Y: McGraw-Hill.
2. GINA. http://www.ginasthma.org/documents/4. Accessed September 2015. 3. Chung KF, *et al. Eur Respir J.* 2014;43: 343-373.

Evolving concept of asthma

Innate lymphoid cell family

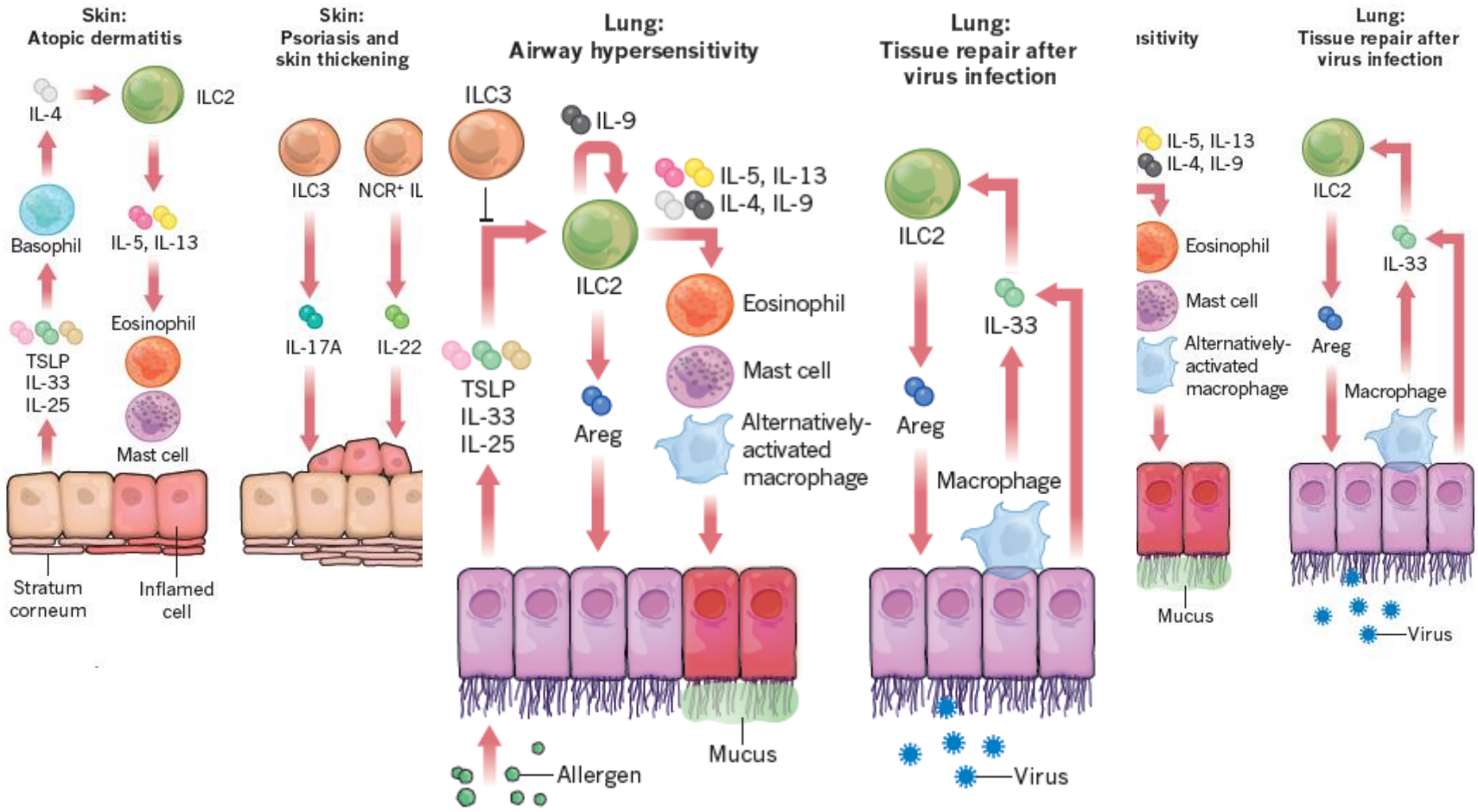


- A distinct arm of the innate immune system that are regulated by multiple endogenous mammalian cell-derived factors
- A classic lymphoid cell morphology, but lack the expression of cell-surface molecules that identify other immune cell types
- ILCs lack expression of somatically rearranged antigen receptors and so do not exhibit any degree of antigen specificity

Artis D & Spits H. Nature. 2015 Jan 15;517(7534):293-301.

Evolving concept of asthma

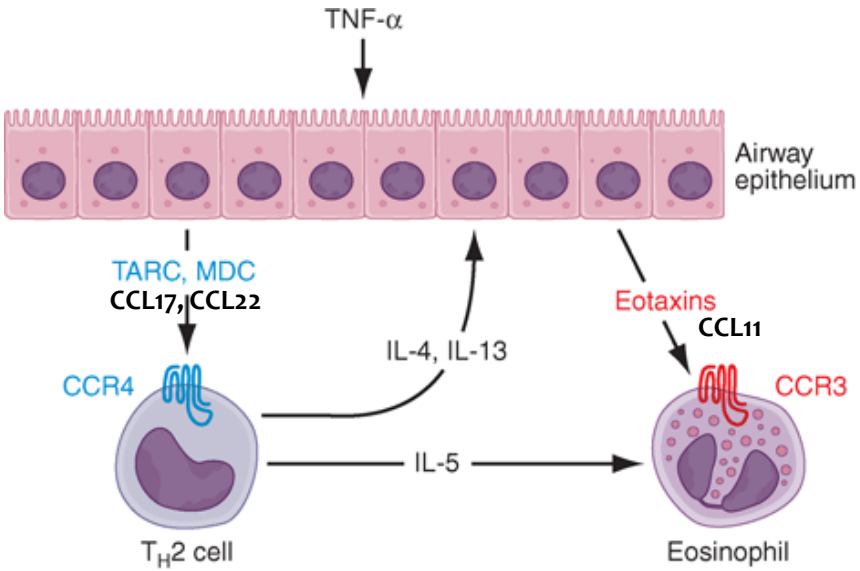
Innate lymphoid cell family



Artis D & Spits H. Nature. 2015 Jan 15;517(7534):293-301.

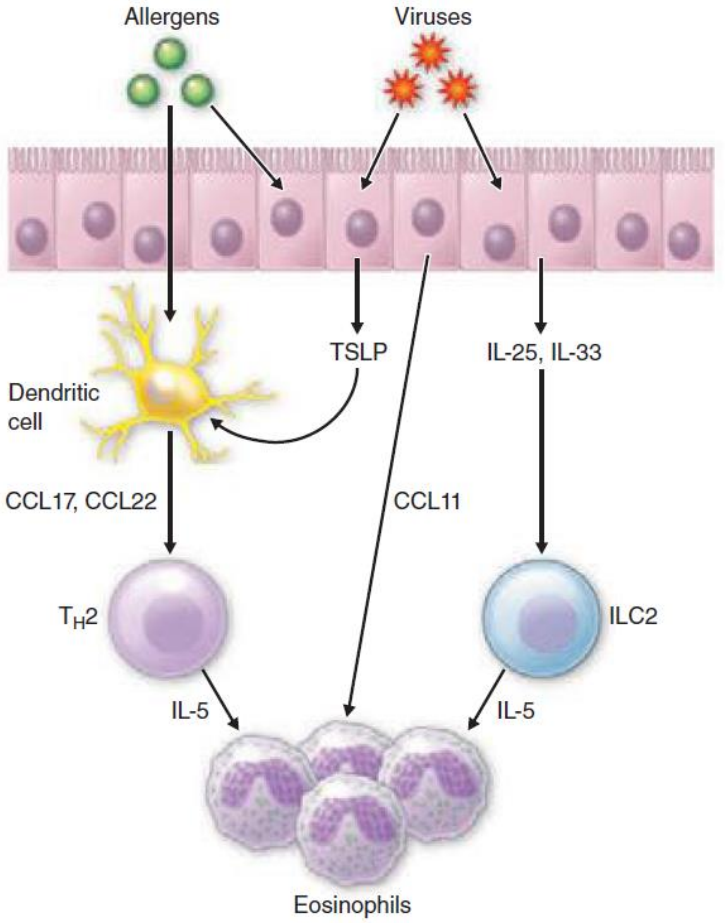
Evolving concept of asthma

Allergic and non-allergic eosinophilic asthmatic inflammation



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

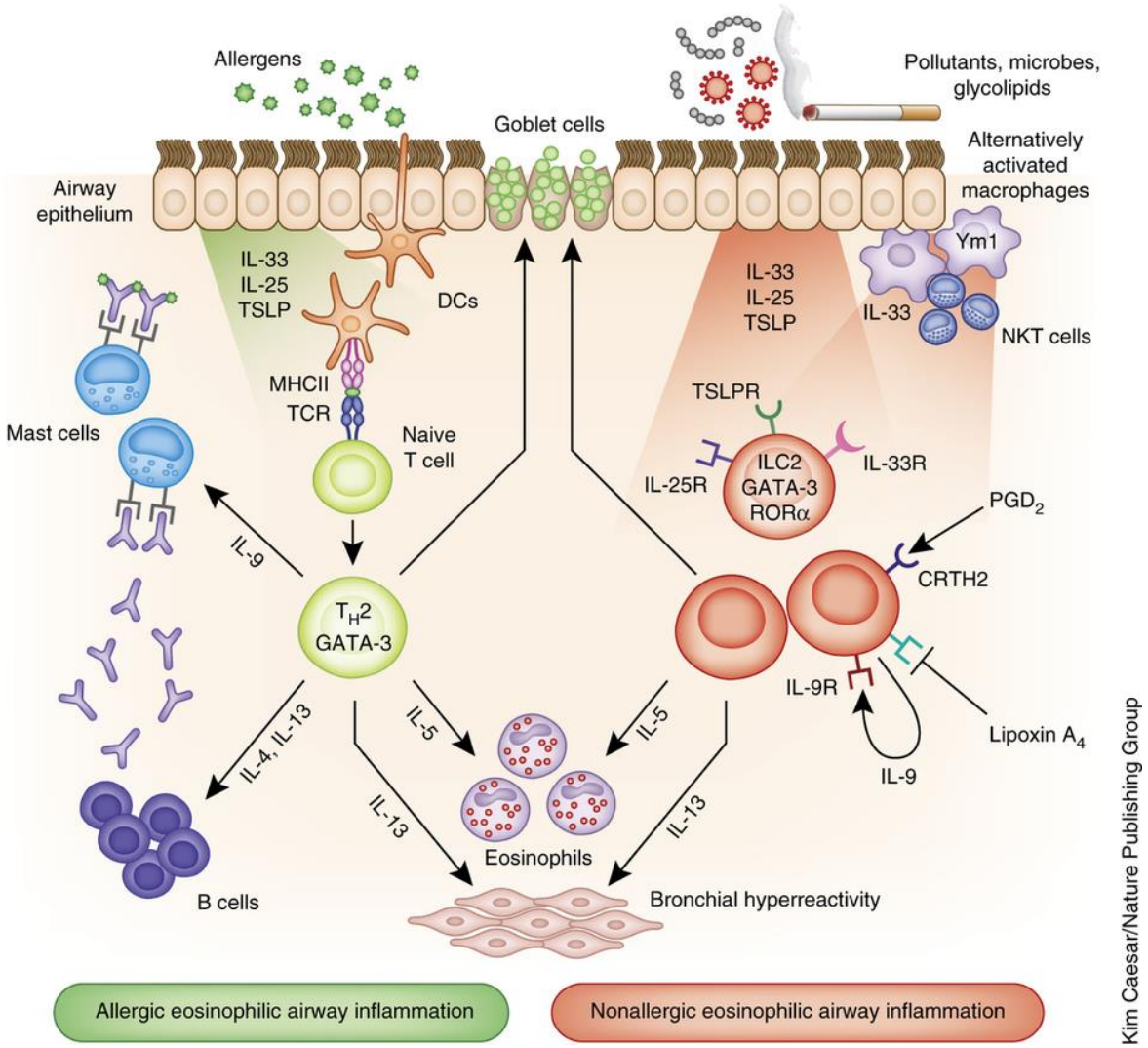
[Harrison's Principles of Internal medicine 18th edition]



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

Evolving concept of asthma

Allergic and non-allergic eosinophilic asthmatic inflammation

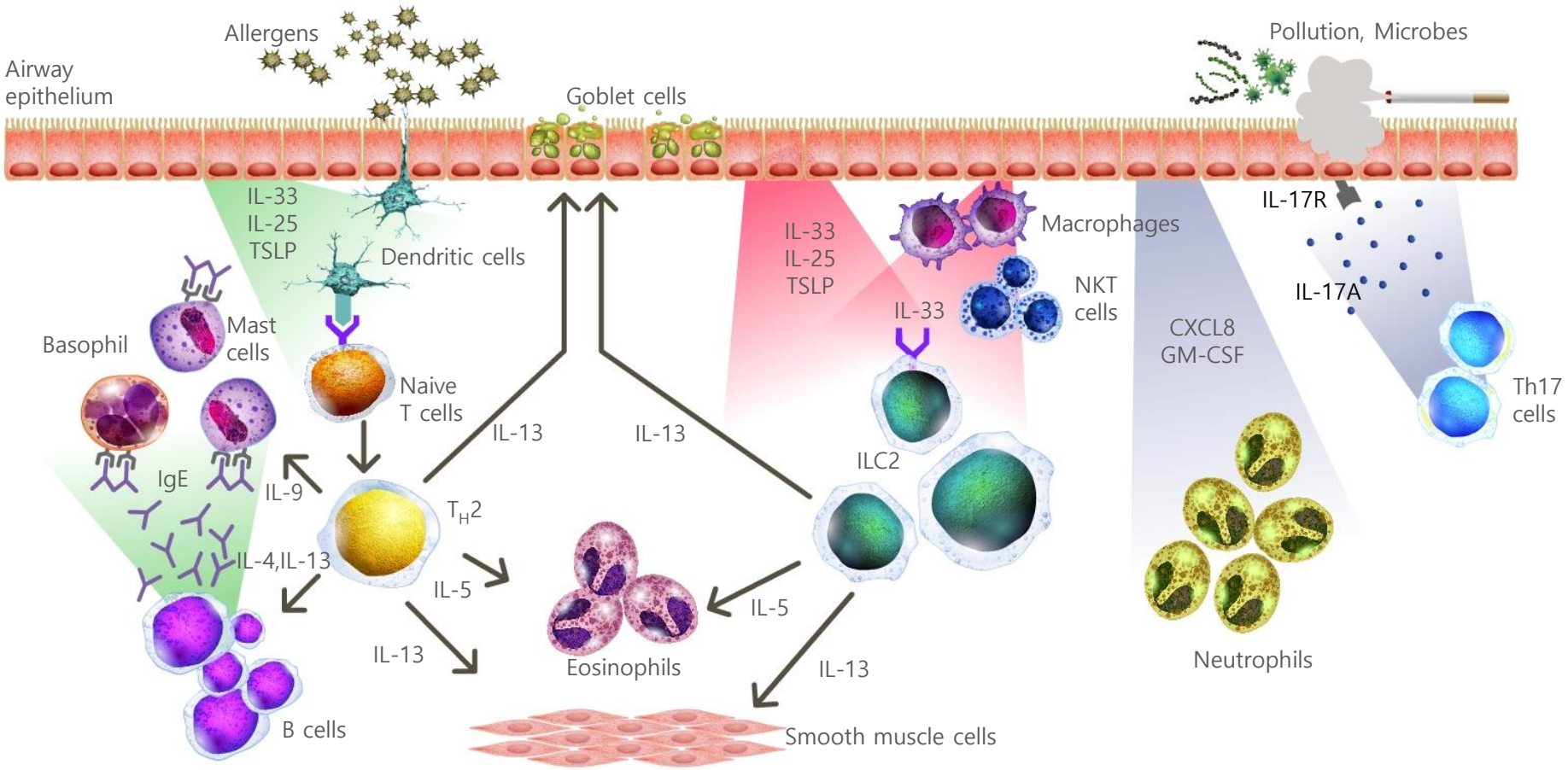


Kim Caesar/Nature Publishing Group

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

Evolving concept of asthma

Pathophysiology of different asthma phenotypes



Atopic eosinophilic asthma | **Non-atopic eosinophilic asthma** | **Neutrophilic asthma**

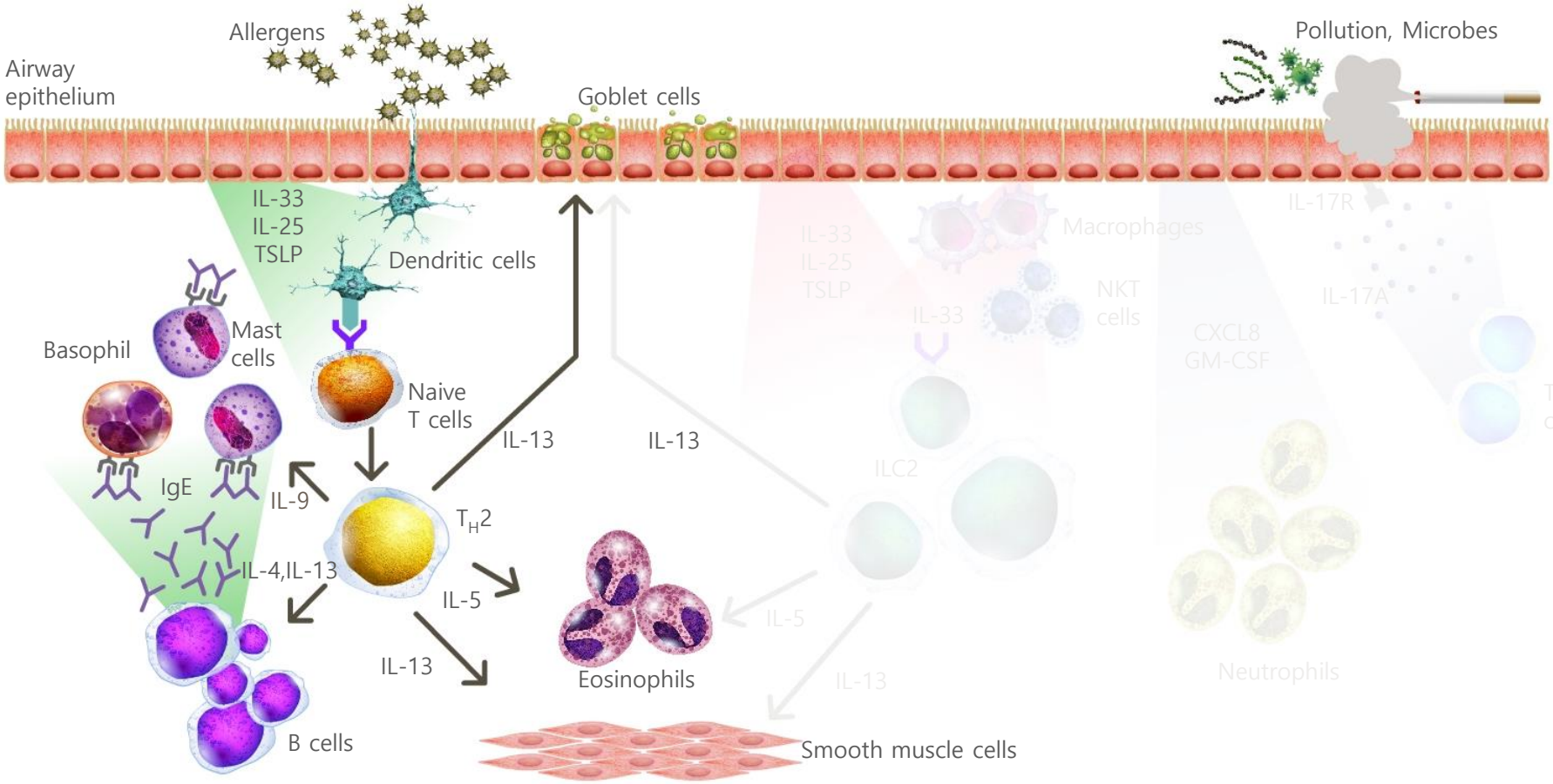
Adapted from Brusselle *et al.* 2014

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

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.

호흡기전문질환센터
Specialized Care Center for Respiratory and Allergic Diseases

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

Evolving concept of asthma

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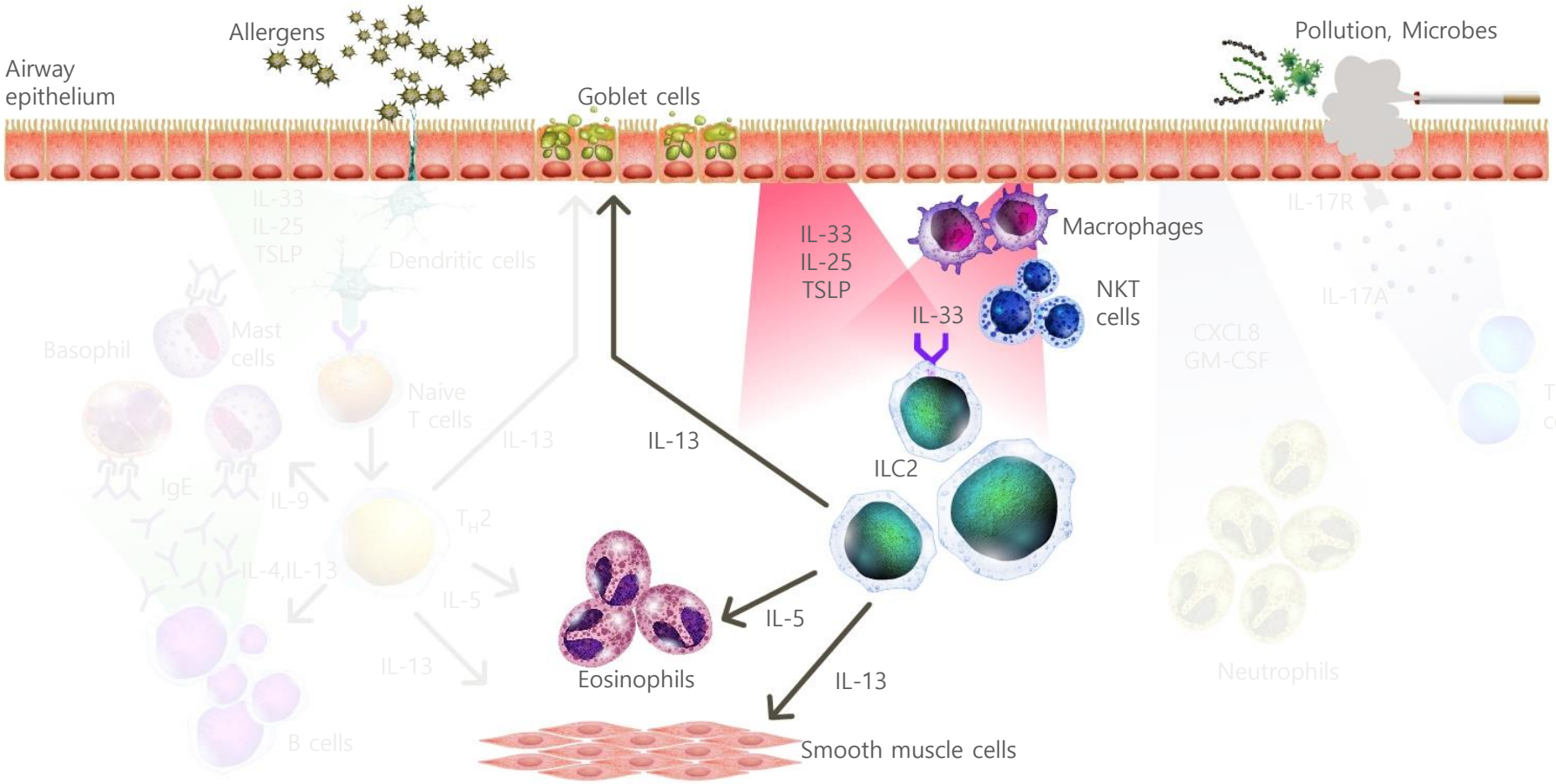

Non-atopic eosinophilic asthma

Adapted from Brusselle *et al.* 2014

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

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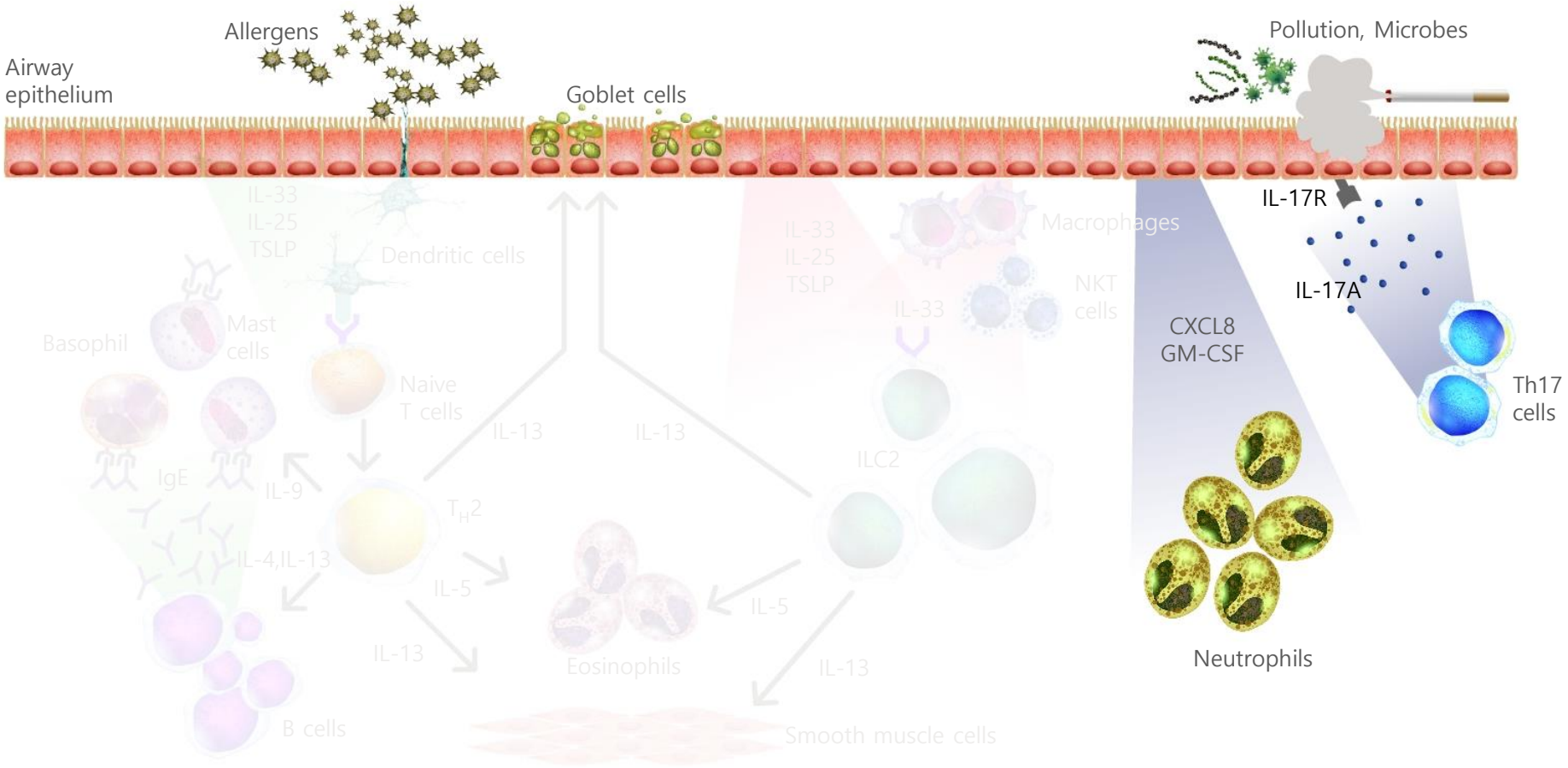
Evolving concept of asthma

Pathophysiology of different asthma phenotypes



Neutrophilic asthma

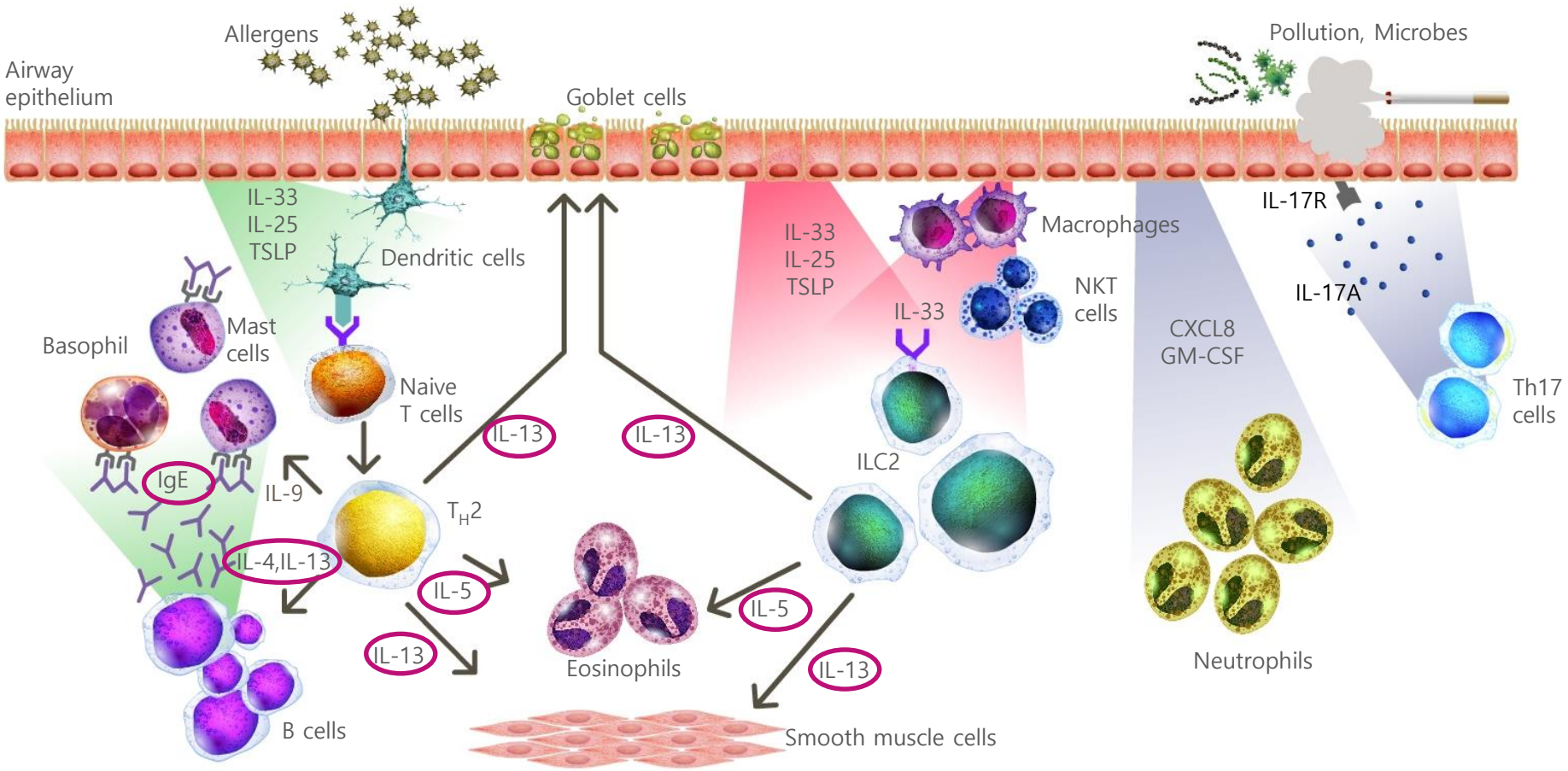
Adapted from Brusselle *et al.* 2014

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

Revaluing the therapy targeting pro-eosinophilic type 2 cytokine IL-5



Atopic eosinophilic asthma | **Non-atopic eosinophilic asthma** | **Neutrophilic asthma**

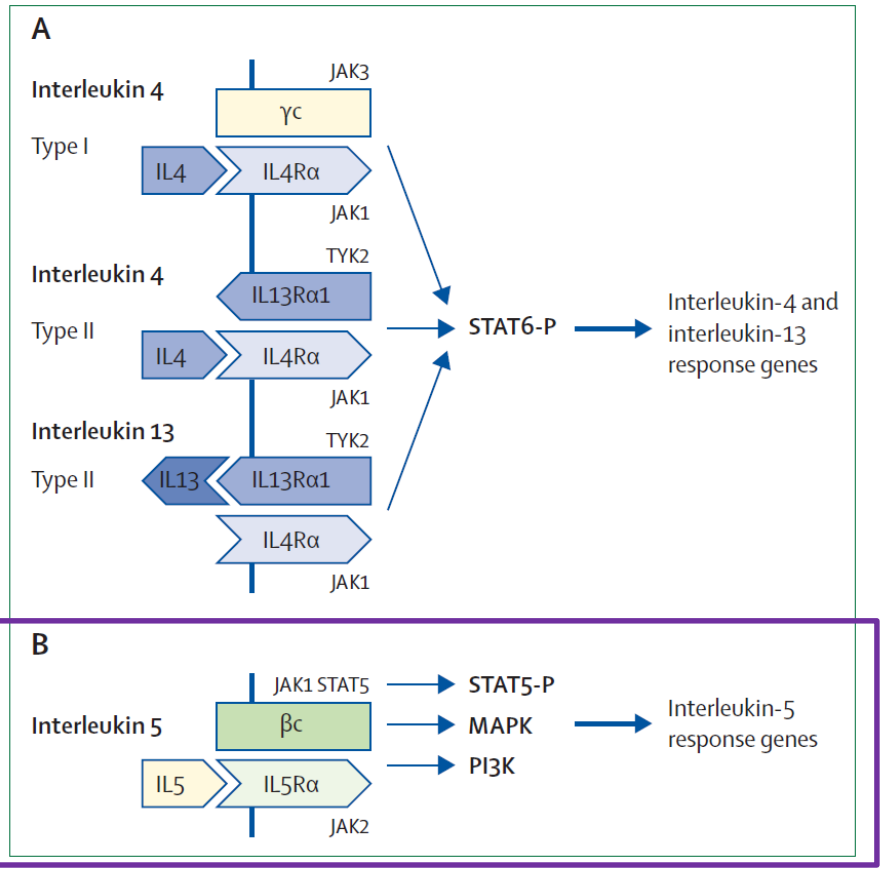
Adapted from Brusselle *et al.* 2014

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

Type 2/Th2-targeted therapy

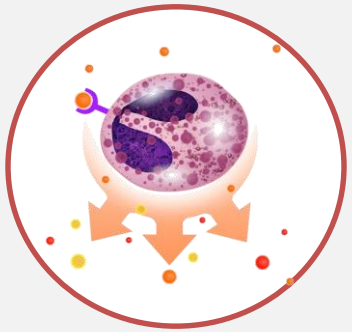
Targeting the pro-eosinophilic type 2 cytokine IL-5



IL-5[1]

Major cytokine responsible for eosinophil:

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

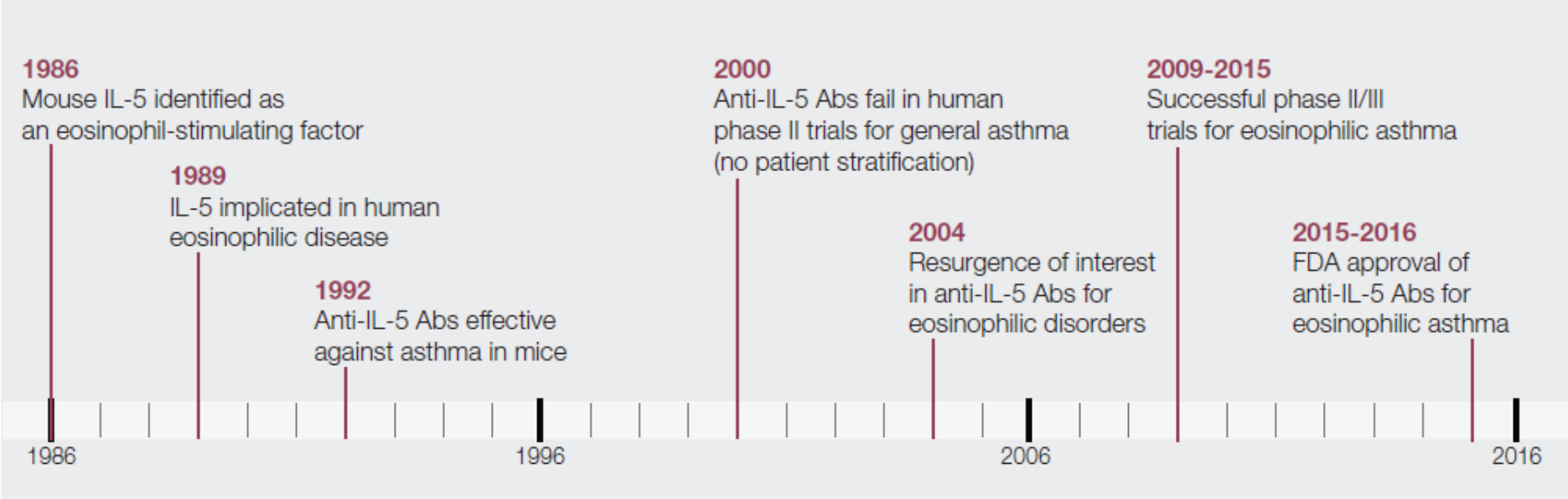


- **Anti-IL-5 antibody**
  - **Mepolizumab** (GlaxoSmithKline, Greater London, UK)
  - **Reslizumab** (Teva, Philadelphia, PA, USA)
- **Anti-IL-5Rα antibody**
  - **Benralizumab** (MedImmune, Gaithersburg, MD, UK)

Chung KF. Lancet 2015; 386: 1086–96

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5



References for further reading are available with this article online: www.cell.com/cell/fulltext/S0092-8674(16)30411-1

Rothenberg ME. Cell 165, April 21, 2016

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

- **Studies in patients with non-phenotyped asthma**
- **Two subsequent studies with 3 intravenous doses of anti–IL-5 antibody in patients**

  : Negative results
  - with mild (no ICSs) atopic asthma
  - moderate persistent asthma (with ICSs)

- **Anti-IL-5, was not effective in non-selected asthmatic patients**

Leckie MJ et al. Lancet 2000; 356: 2144-48
Flood-Page P, et al. Am J Respir Crit Care Med 2003;167:199-204.
Flood-Page P, et al. Am J Respir Crit Care Med 2007;176:1062-71.

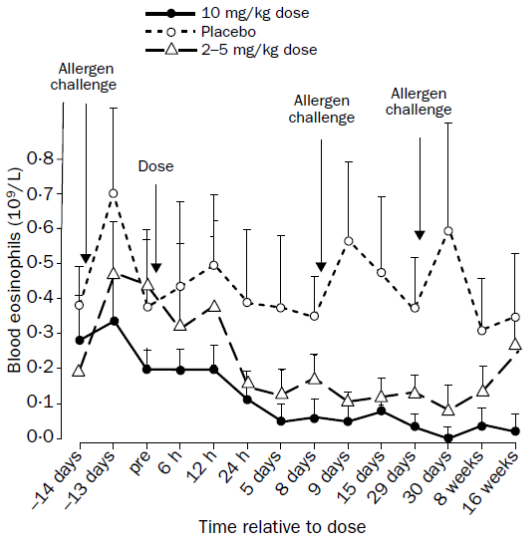
Mepolizumab (SB 240563)

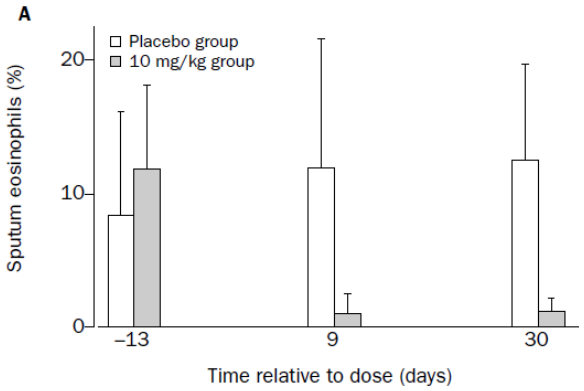
A double-blind, randomised, placebo controlled, single dose, parallel group study in three centres.

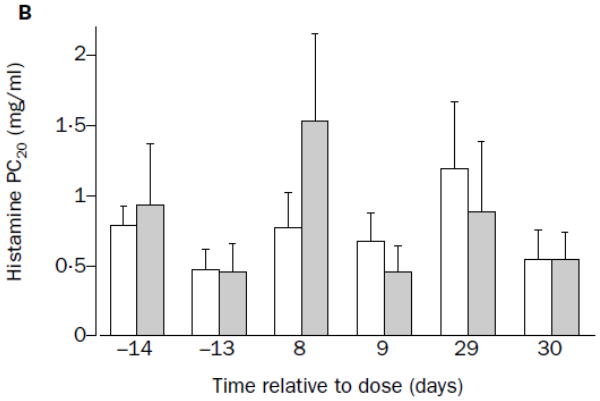
Early reports

Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response

Margaret J Leckie, Anneke ten Brinke, Jamey Khan, Zuzana Diamant, Brian J O'Connor, Christine M Walls, Ashwini K Mathur, Hugh C Cowley, K Fan Chung, Ratko Djukanovic, Trevor T Hansel, Stephen T Holgate, Peter J Sterk, Peter J Barnes







This study might suggest eosinophils (and IL-5) are not as critical to traditional allergic asthma phenotypes and their allergic reactions.

Leckie MJ et al. Lancet 2000; 356: 2144-48

Eosinophil's Role Remains Uncertain as Anti–Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway

Patrick T. Flood-Page,* Andrew N. Menzies-Gow,* A. Barry Kay, and Douglas S. R

Department of Allergy and Clinical Immunology, National Heart and Lung Institute, Faculty of Medicine, Ir

Mepolizumab (SB 240563)

Twenty-four patients with mild asthma received three intravenous doses of either 750 mg of mepolizumab or placebo in a randomized, double-blind, parallel-group fashion over 20 weeks.

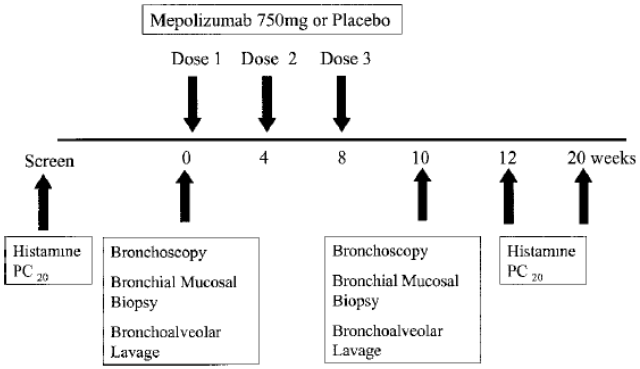
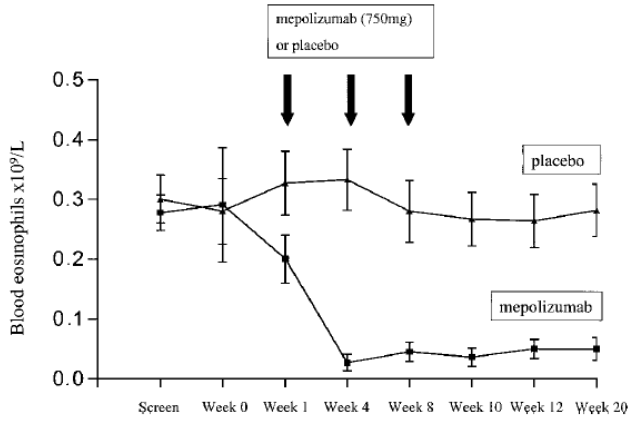
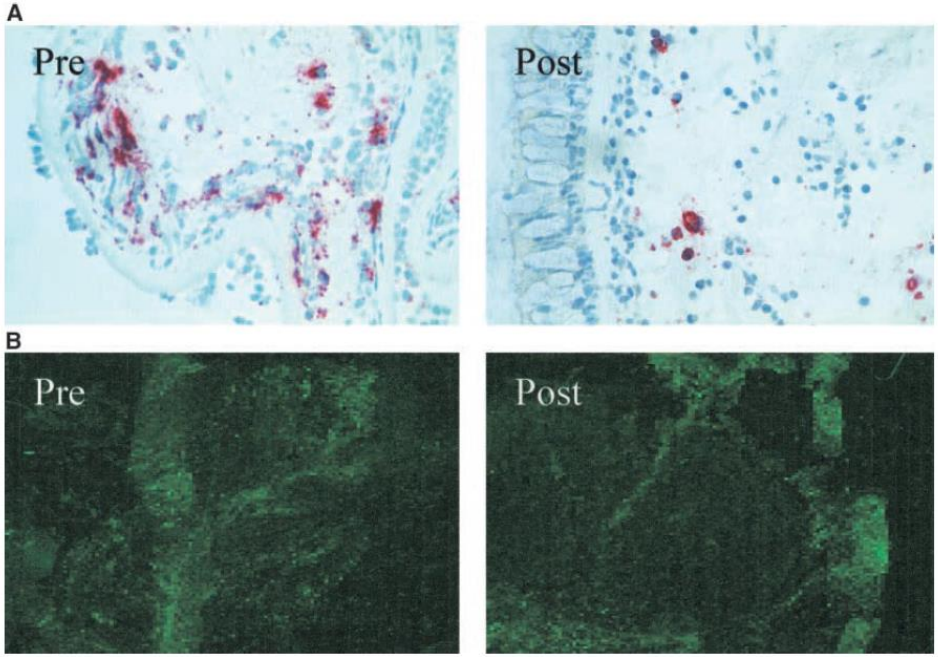


Figure 1. Study design.



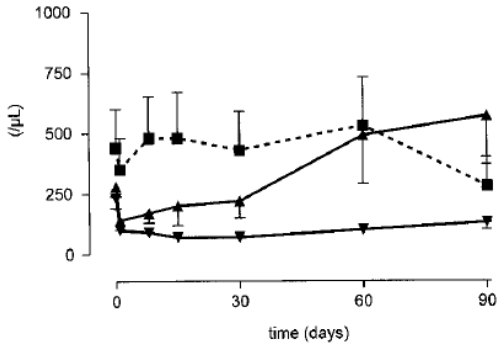


Flood-Page P, et al. Am J Respir Crit Care Med 2003;167:199-204.

Effect of SCH55700, a Humanized Anti-Human Interleukin-5 Antibody, in Severe Persistent Asthma

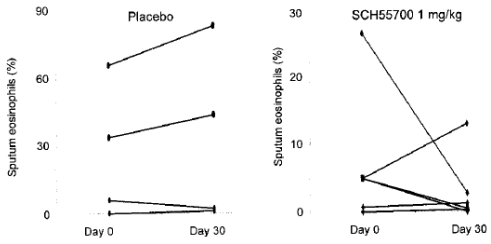
A Pilot Study

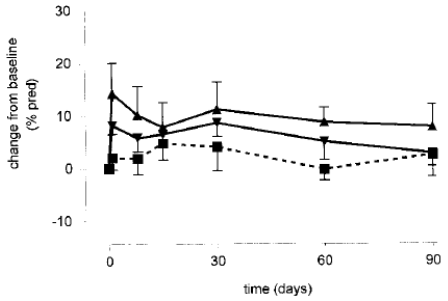
Johan C. Kips, Brian J. O'Connor, Stephen J. Langley, Ashley Woodcock, Huib A. M. Kerstjens, Dirkje S. Postma, Mel Danzig, Francis Cuss, and Romain A. Pauwels



Reslizumab (SCH55700)

A double –blind, randomized, multicenter trial ,
a rising single dose of SCH55700 or placebo was administered IV to persistent severe asthma



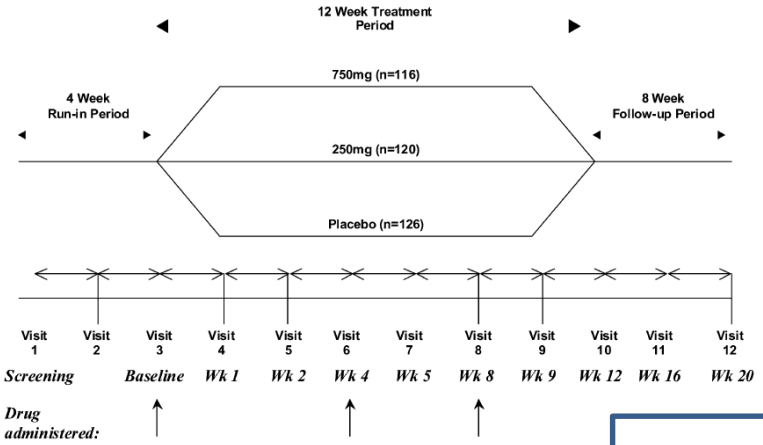


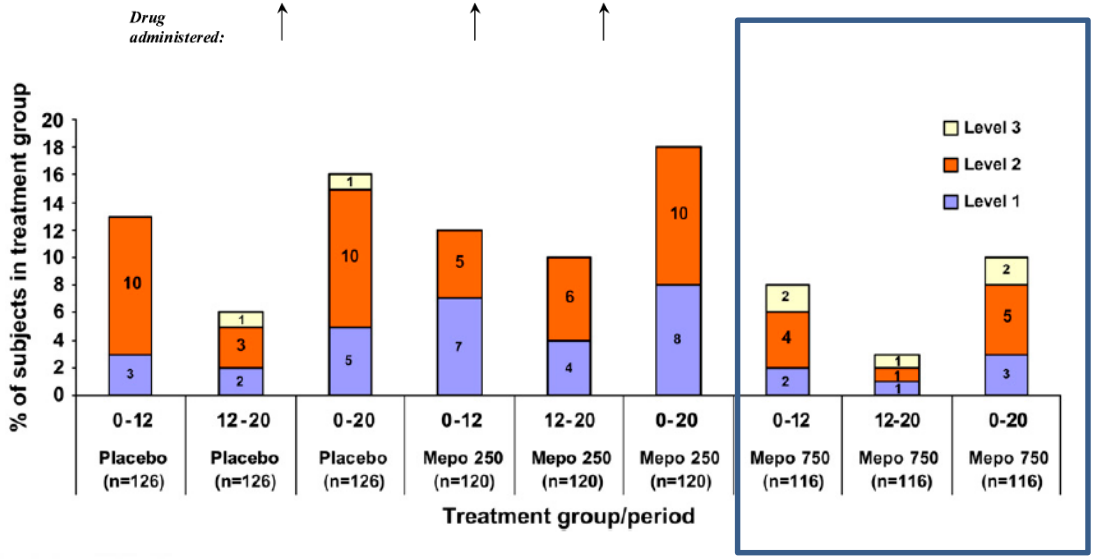
Kips JC, et al. Am J Respir Crit Care Med 2003;167:1655-1659.

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page[1], Cheri Swenson[2], Isidore Faiferman[3], John Matthew
Douglas Robinson[4], Sally Wenzel[5], William Busse[2], Trevor T. Hansel[4], a
International Mepolizumab Study Group*

Mepolizumab (SB 240563)
a randomized, placebo-controlled trial administering mepolizumab monthly for 3 months to patients with moderately severe asthma and with persistent symptoms despite inhaled corticosteroid treatment.



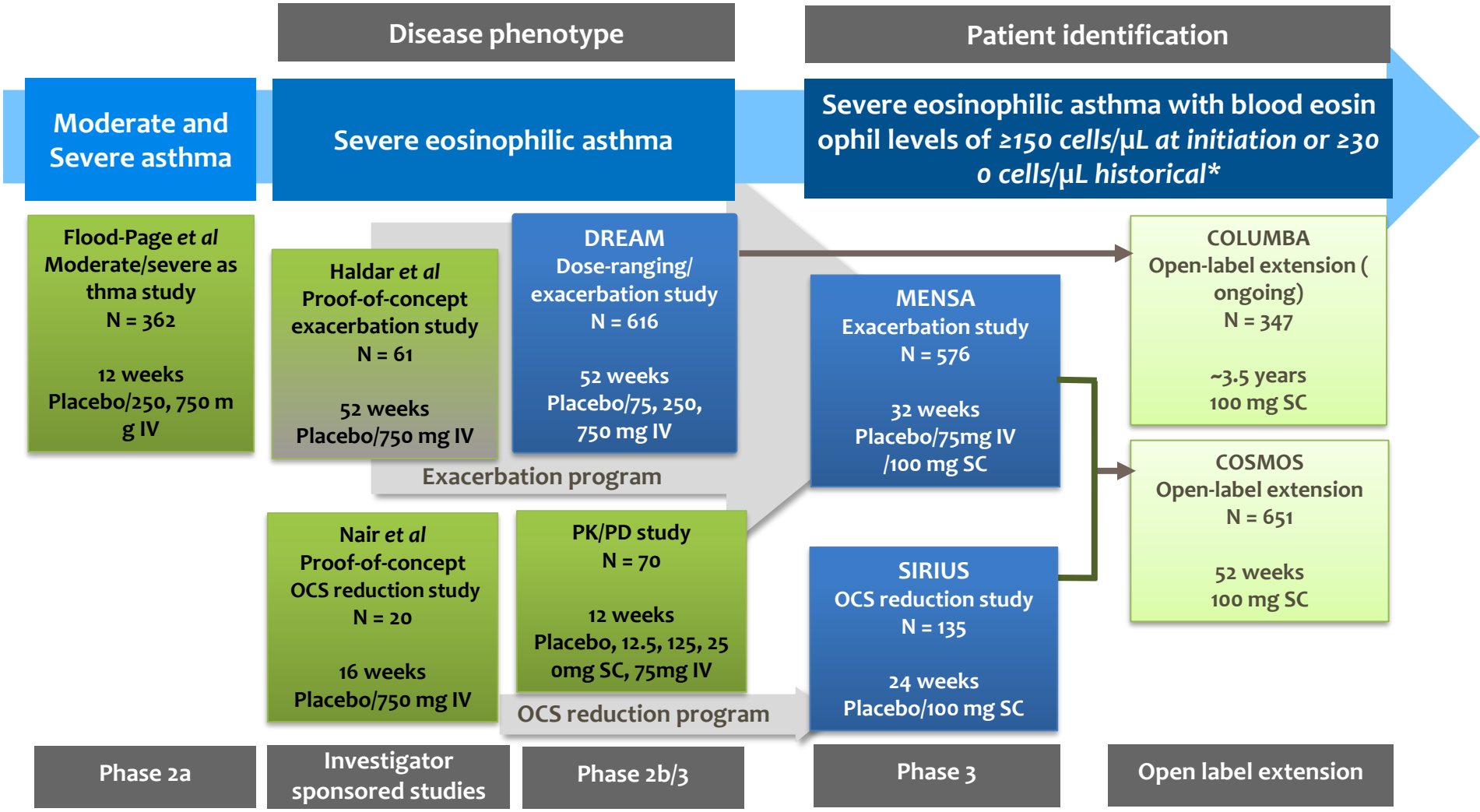


Overall the study showed disappointing clinical results, but informed on the development of future studies which focused on a more severe patient population with eosinophilic inflammation.

Flood-Page P, et al. Am J Respir Crit Care Med 2007;176:1062-71.

Clinical Development Programme for Mepolizumab

- **Key Clinical Efficacy/Safety Studies and Identification of Right Patients**



* A blood eosinophil count of ≥150 cells/µL at treatment initiation or ≥300 cells/µL in the previous 12 months

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

- Studies in patients with non-phenotyped asthma
- Two subsequent studies with 3 intravenous doses of anti–IL-5 (mepolizumab) in patients

  : Negative results
  - with mild (no ICSs) atopic asthma
  - moderate persistent asthma (with ICSs)

- Anti-IL-5, was not effective in non-selected asthmatic patients

Leckie MJ et al. Lancet 2000; 356: 2144-48
Flood-Page P, et al. Am J Respir Crit Care Med 2003;167:199-204.
Flood-Page P, et al. Am J Respir Crit Care Med 2007;176:1062-71.

- **Studies targeting patients with eosinophilic asthma**
  - **Sputum eosinophilia of greater than 3%**
  - **Moderate-to severe asthma or oral corticosteroid -dependent asthma**
  - **Mepolizumab: positive data**

Haldar P, et al. N Engl J Med 2009;360:973-84
Nair P, et al. N Engl J Med 2009;360:985-93
Pavord ID, et al. Lancet 2012;380:651-9
Ortega HG, et al. N Engl J Med 2014;371:1198-207
Bel EH, et al. N Engl J Med 2014;371:1189-97

Type 2/Th2-targeted therapy

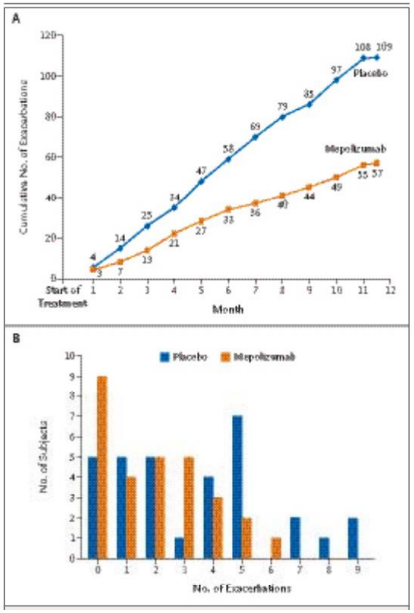
Targeting the pro-eosinophilic type 2 cytokine IL-5

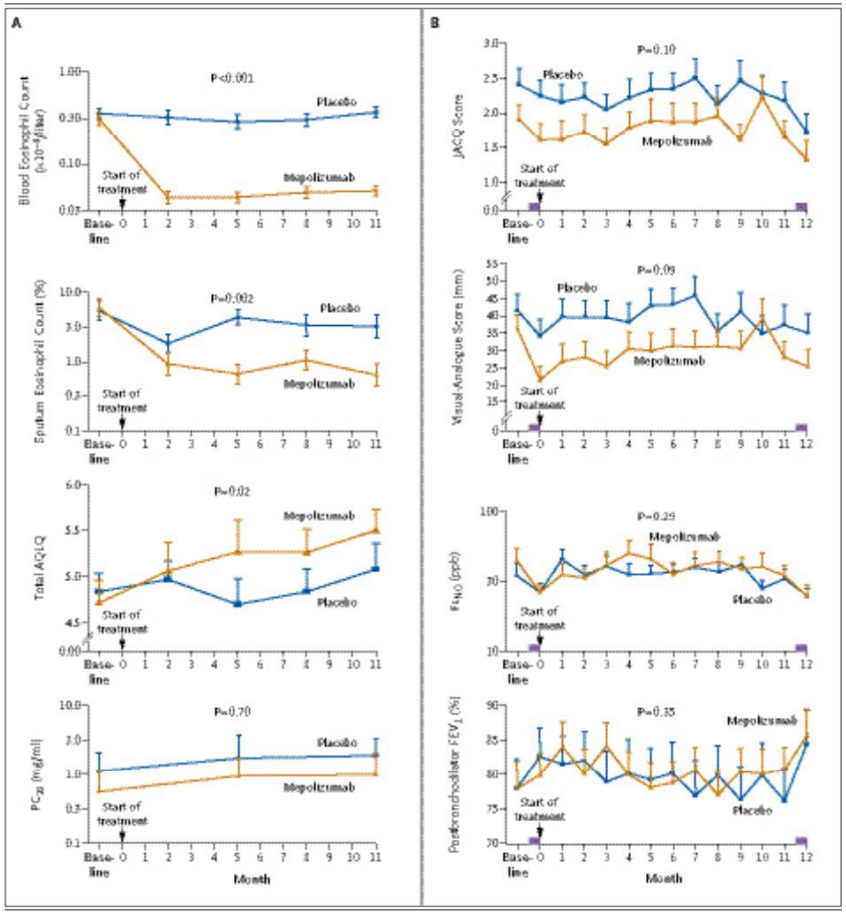
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P., Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc., Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.





Reduction in exacerbation rate and improvement in AQLQ.
No effect on FEV1 or bronchial hyper-responsiveness

Haldar P, et al. N Engl J Med 2009;360:973-84

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,
Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D.,
Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D.,
Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

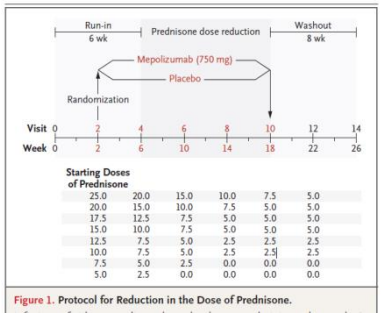


Figure 1. Protocol for Reduction in the Dose of Prednisone.

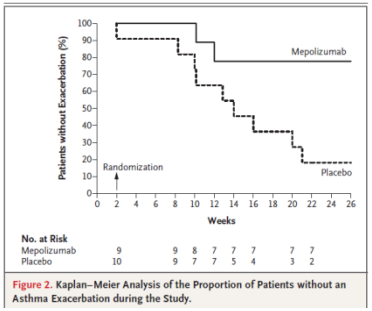
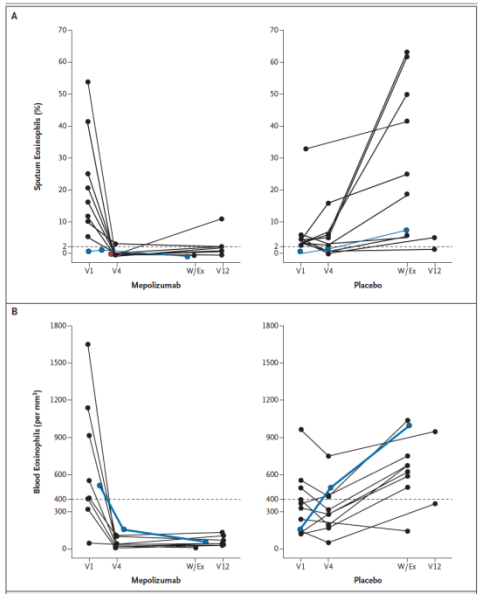


Figure 2. Kaplan–Meier Analysis of the Proportion of Patients without an Asthma Exacerbation during the Study.



Reduction in exacerbations and in prednisolone dose with improved asthma control and FEV1

Table 2. Primary Outcomes.*

Variable	Mepolizumab				Placebo					
	Visit 1 (Baseline)	Visit 4 (4 Wk after First Dose)	Visit 12 (4 Wk after Last Dose)	Visit 14 (8 Wk after Last Dose)	Visit 1 (Baseline)	Visit 4 (4 Wk after First Dose)	Visit 12 (4 Wk after Last Dose)	Visit 14 (8 Wk after Last Dose)	Exacerbation	4 Wk after Exacerbation
No. of patients	9	9	7	7	11	10	2	2	9	9
Sputum eosinophils (%)										
Median	16.6	0†	1.3†	0.3†	4.0	3.0	3.2	5.0	25.3	4.0
Range	1.6–54.3	0–4.0	0–11.3	0–4.6	0–35.3	0–16.3	1.3–5.0	1.0–9.0	5.0–63.7	1.3–52.5
Blood eosinophils (per mm³)	664.4±492.5	49.5±37.5†	64.5±37.9†	76.3±39.4†	352.1±253.7	295.8±207.4	657.0±413.2	1224.0±1383.0	655.5±254.8	622.4±498.4
FEV_1 after bronchodilation										
Value (liters)	2.0±0.9	2.1±1.0	2.4±1.1‡	2.3±0.9	2.2±0.9	2.3±0.9	2.3±0.4	2.3±0.4	2.0±1.0	2.2±0.8
% of predicted value	66.6±18.3	69.7±17.7	71.9±17.3‡	70.3±13.2	74.3±17.8	75.6±17.0	78.4±20.9	78.1±19.2	60.9±20.7	74.4±14.4
Juniper Asthma Control Questionnaire§	1.9±0.8	1.3±0.9†	1.2±0.8†	1.3±0.9†	1.8±0.9	1.6±0.9	1.2±0.5	1.2±0.3	2.0±1.0	1.6±1.4
Cough score¶	6.0±0.8	5.2±0.8†	5.3±1.0†	5.5±1.0	6.3±1.0	5.2±1.2	NA	NA	5.8±1.1	6.2±1.0
Symptoms score‖	29.4±2.9	28.7±4.9	31.6±2.3	30.1±4.0	29.8±5.1	30.8±2.9	33.2±1.6	32.5±3.5	27.2±4.2	29.4±7.3

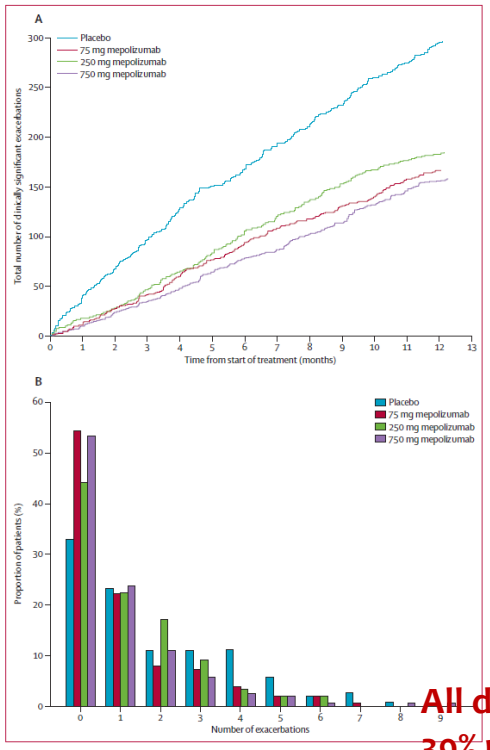
Nair P, et al. N Engl J Med 2009;360:985-93

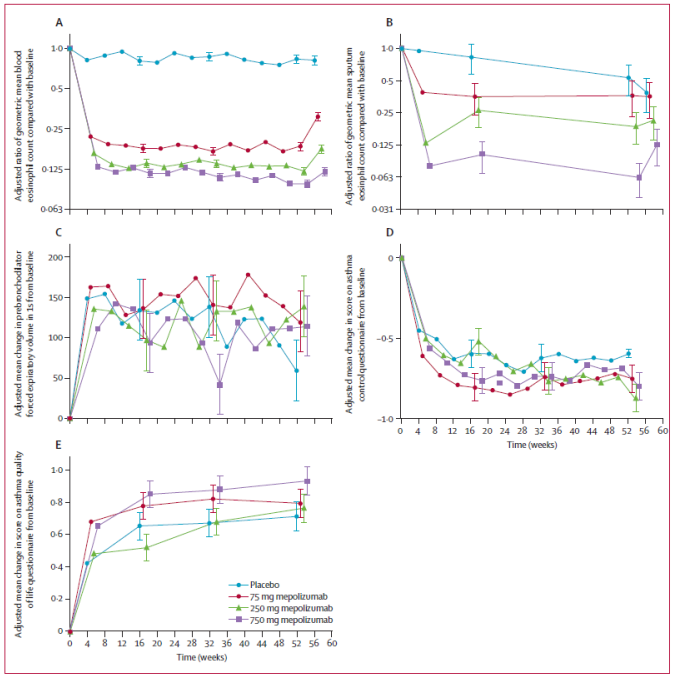
Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

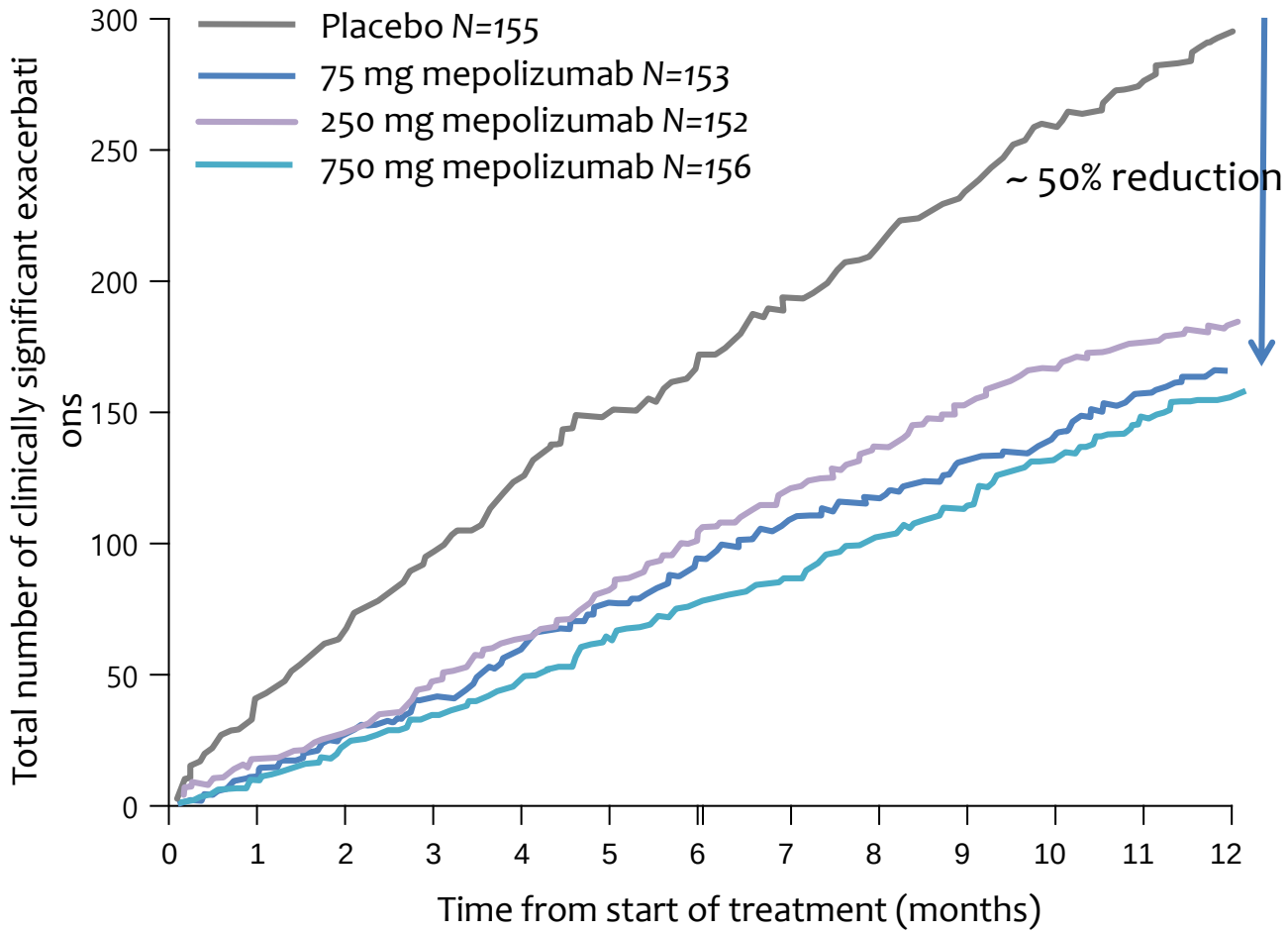




All doses of mepolizumab reduced exacerbations: 48% reduction with 75 mg; 39% reduction with 250 mg; 52% reduction with 750 mg.
No effect on ACQ, AQLQ, or FEV1

Pavord ID, et al. Lancet 2012;380:651-9

Reduction in the cumulative number of exacerbations over time



Rate of clinically significant exacerbations/yr

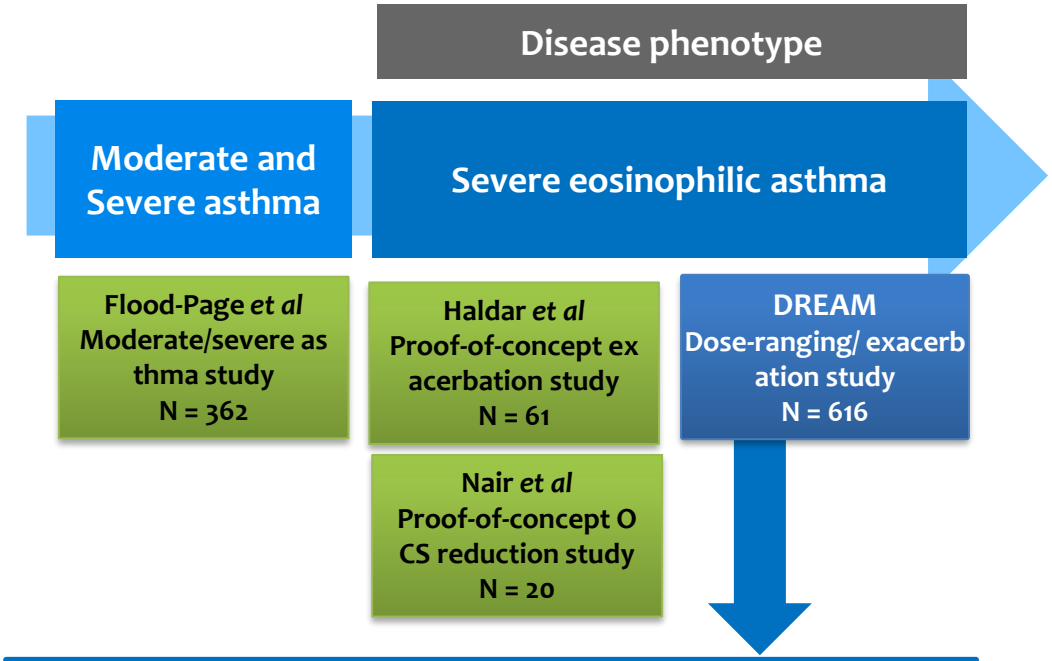
- Placebo: 2.40
- 250mg: 1.46 (39% reduction, p<0.001)
- 75 mg: 1.24 (48% reduction, p<0.001)
- 750 mg: 1.15 (52% reduction, p<0.001)

Pavord et *al.Lancet* 2012; 380(9842):651-659

Mepolizumab 75mg, 250mg and 750mg IV are not licensed doses/routes of administration

Identifying Responders to Mepolizumab

- **Blood eosinophil count as a predictor of response to mepolizumab**



DREAM: Subjects with markers of eosinophilic airway inflammation in the previous 12 months[1]:

- Blood Eos ≥ 300 cells/μl, or
- Sputum Eos ≥ 3%, or
- FeNO ≥50ppb, or
- Prompt deterioration of asthma control following a ≤25 % reduction in regular maintenance dose of ICS or OCS

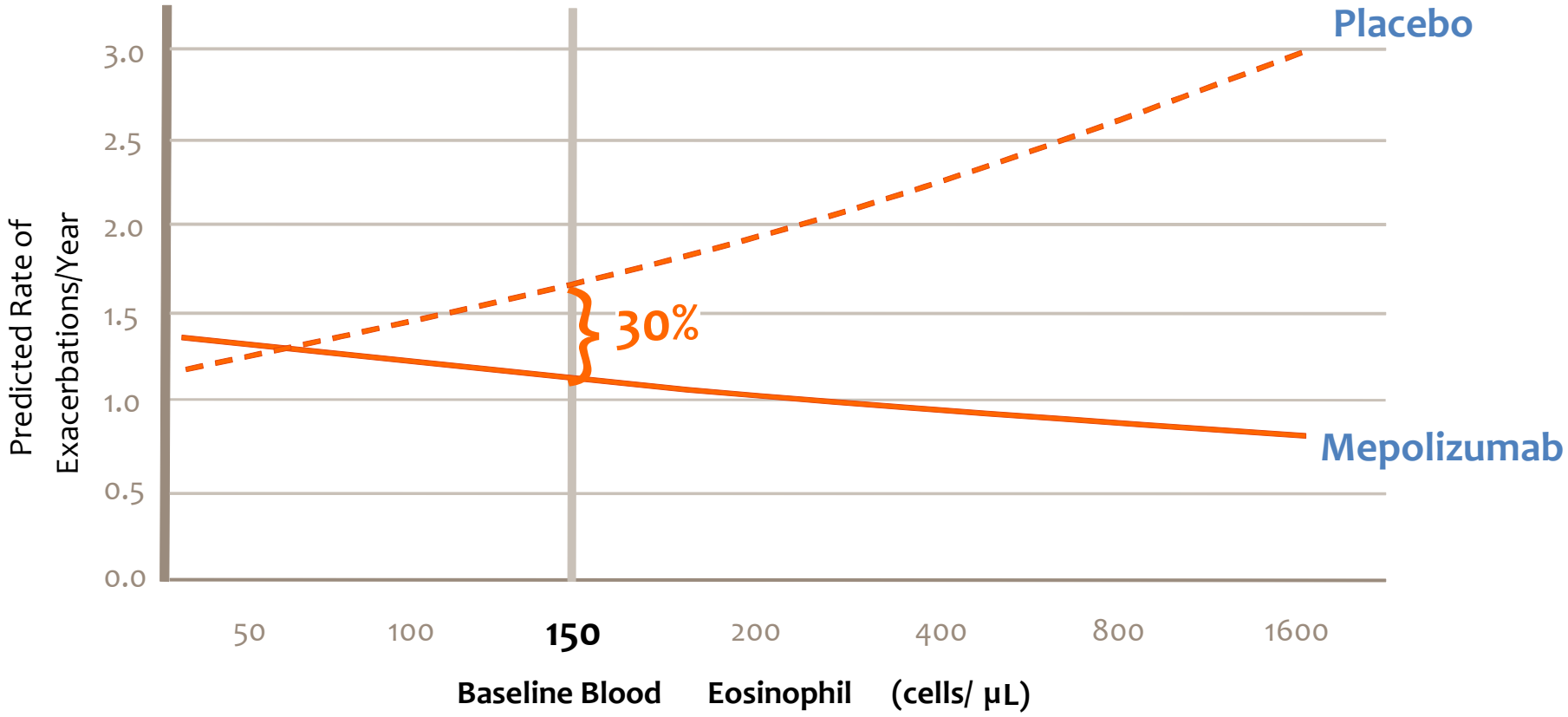
Modeling of covariates in DREAM

- **Blood eosinophil** thresholds were found to be the specific **responder biomarker** to identify target population likely to respond to mepolizumab treatment[1]
- Sputum eosinophils did not predict treatment response to mepolizumab[1]

Katz LE, et al. An Am Thorac Soc. 2014;11:531-536.

DREAM Modeling Analysis

30% reduction in exacerbation was considered **clinically meaningful**
- achieved at a baseline **blood eosinophil count of 150 cells/μL**



Yancey SW, et al. Presented at AAAAI 2016. Manuscript accepted

Summary of the DREAM study

Efficacy

- Mepolizumab reduced the frequency of clinically significant exacerbations in subjects with eosinophilic inflammation and a history of frequent exacerbations in all treatment groups ($P < .001$)
- The rate of exacerbations requiring hospitalisation and/or ED visit was lower for subjects in the mepolizumab groups compared with placebo

Safety

- Mepolizumab was generally well tolearated.
- The most frequently reported AE was headache.

Key learning

- Subgroup analysis led to the identification of blood eosinophils as a biomarker to predict response to mepolizumab. The clinical utility of the identified eosinophil thresholds were evaluated in further studies of mepolizumab.

1. Pavord ID, et al. *Lancet*. 2012;380:651-659. 2. Katz LE, et al. *An Am Thorac Soc*. 2014;11:531-536.

Mepolizumab 75mg, 250mg and 750mg IV are not licensed doses/routes of administration

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

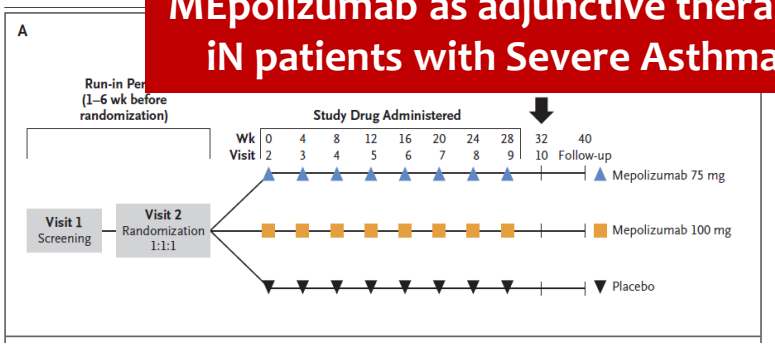
MENSA study
MEpolizumab as adjunctive therapy iN patients with Severe Asthma

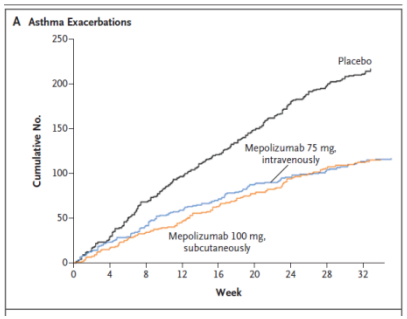
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*





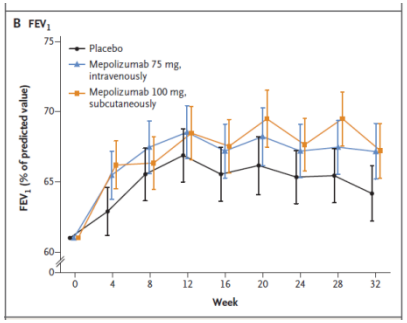


Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.74	0.93	47 (28 to 60)†	<0.001	0.83	53 (36 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (−41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (−66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	−0.50±0.07	−0.92±0.07	−0.42 (−0.61 to −0.23)	<0.001	−0.94±0.07	−0.44 (−0.63 to −0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	−9.0±1.2	−15.4±1.2	−6.4 (−9.7 to −3.2)	<0.001	−16.0±1.1	−7.0 (−10.2 to −3.8)	<0.001

* Plus–minus values are means ±SE.
† The between-group difference in this category is the percent reduction as compared with the placebo group.

Rate of exacerbation reduced by 47% with IV mepolizumab and by 53% with SC mepolizumab. Baseline FEV1 increased by a mean of 100 mL with IV mepolizumab, and 98 mL with SC mepolizumab. ACQ-5 improved by 0.42 and 0.44 points, respectively

호흡기전문질환센터
Specialized Care Center for Respiratory and Allergic Diseases

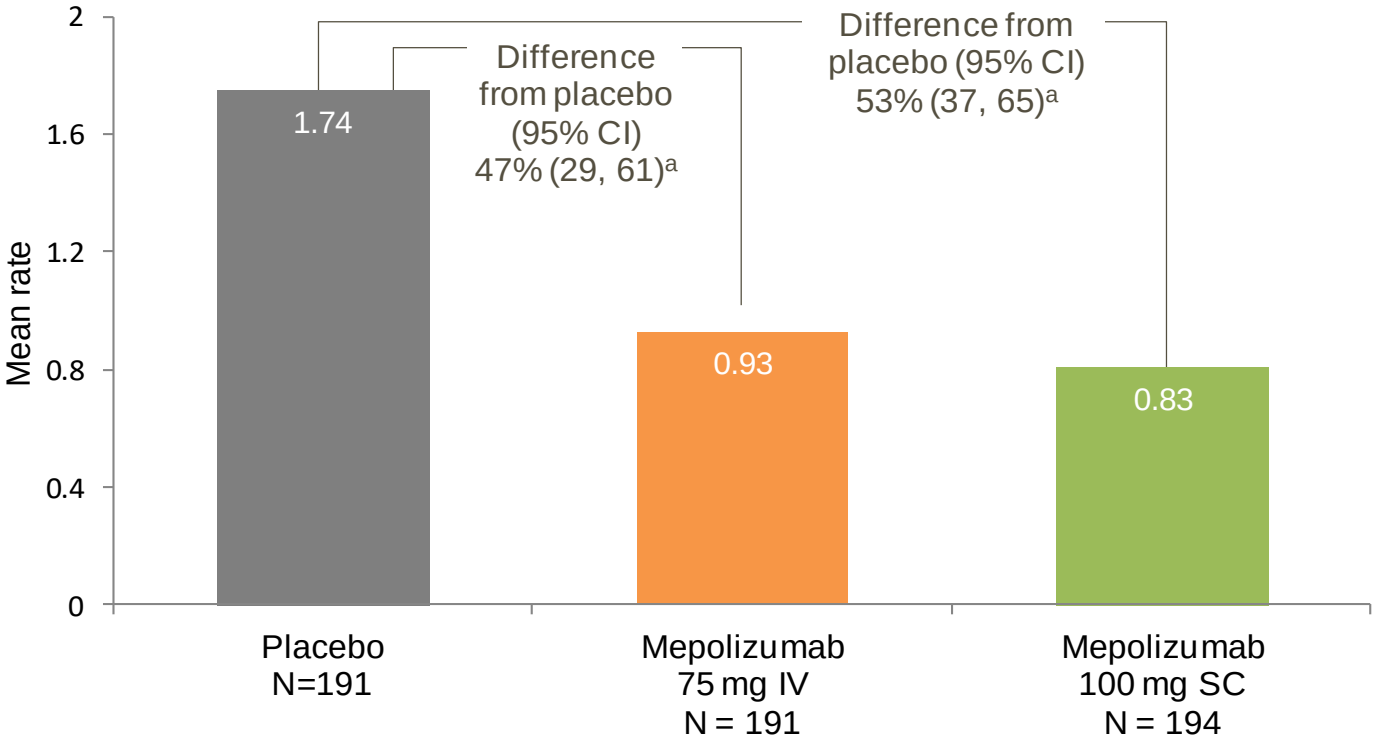
Ortega HG, et al. N Engl J Med 2014;371:1198-207

Key Inclusion Criteria (MENSA)

Background Medication	Exacerbation History	Eosinophilic inflammation
Documented requirement for regular treatment with **high-dose inhaled corticosteroids** and ≥3 months of treatment with **additional controller therapy** with or without maintenance OCS	History of **≥2 exacerbations** requiring treatment with systemic steroids in previous 12 months *Subjects on maintenance OCS required two-fold or greater increase*	**≥150 cells/μL** in peripheral blood **at Visit 1** OR **≥300 cells/μL** in peripheral blood during the **12 months prior to Visit 1**

Nair P, *et al. N Engl J Med.* 2014;371(13):1198-1207.

Significant Reduction in Clinically Significant Exacerbations – Primary Endpoint



Frequency of clinically significant exacerbations significantly lower at week 32 in all treatment groups as compared with placebo (*P* < .001)

[a]The between-group difference in this category is the percent reduction as compared with the placebo group.

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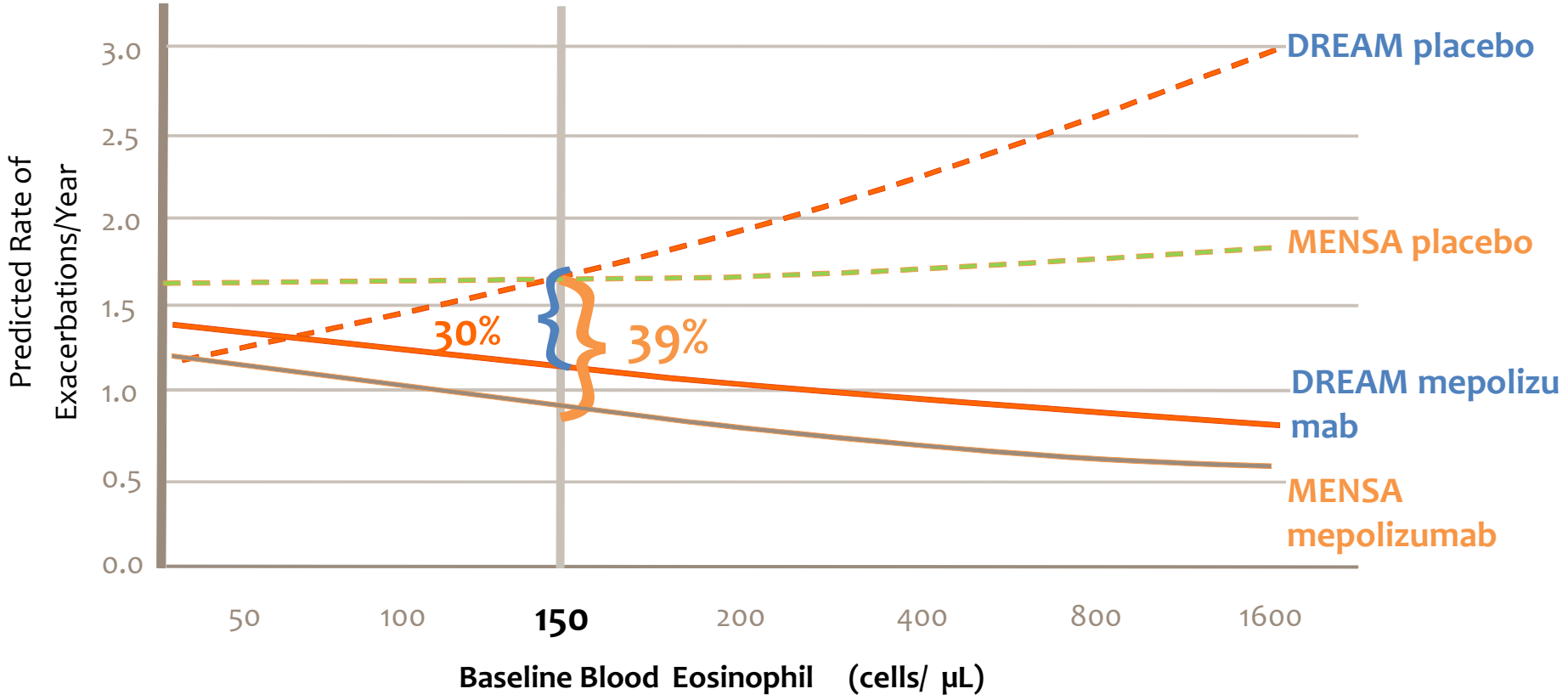
Specialized Care Center for Respiratory and Allergic Diseases

Ortega HG, *et al*. *N Engl J Med*. 2014; 371: 1198-1207.

Mepolizumab 75mg IV is not licensed doses/routes of administration

DREAM and MENSA Modelling Analysis

Meaningful reduction in exacerbation was achieved at a baseline **blood eosinophil count of 150 cells/µL** in MENSA analysis



Yancey SW, et al. Presented at AAAAI 2016. Manuscript accepted

Summary of the MENSA Study

Efficacy

- Mepolizumab produced a 53% (SC) and 47% (IV) reduction (both *P* < .001) in the rate of clinically significant exacerbations compared with placebo [1,2]
- Treatment with mepolizumab improved quality of life [1]

Safety

- Mepolizumab is well tolerated when administered IV or SC[1]
- Most frequently reported AEs were nasopharyngitis and headache[1]

Key learning

- The MENSA study confirmed the efficacy of mepolizumab with **similar results of both IV and SC administrations in patients** with severe eosinophilic asthma identified based on blood eosinophil counts as follows:
  - ≥150 cells/μL at the Screening visit, or
  - ≥ 300 cells/μL within 12 months prior to the Screening visit

1. Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207.
2. Pavord ID, et al. *Lancet*. 2012;380:651-659.

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine I

SIRUS study
Steroid Reduction with MepolizUmab Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

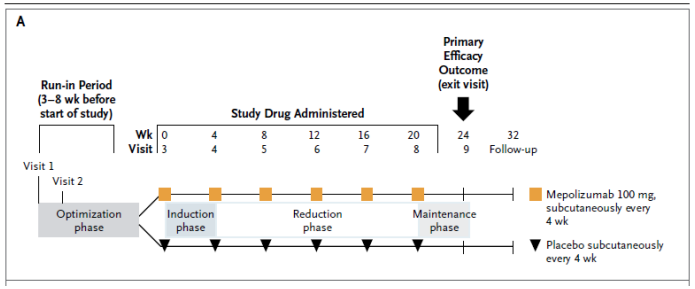
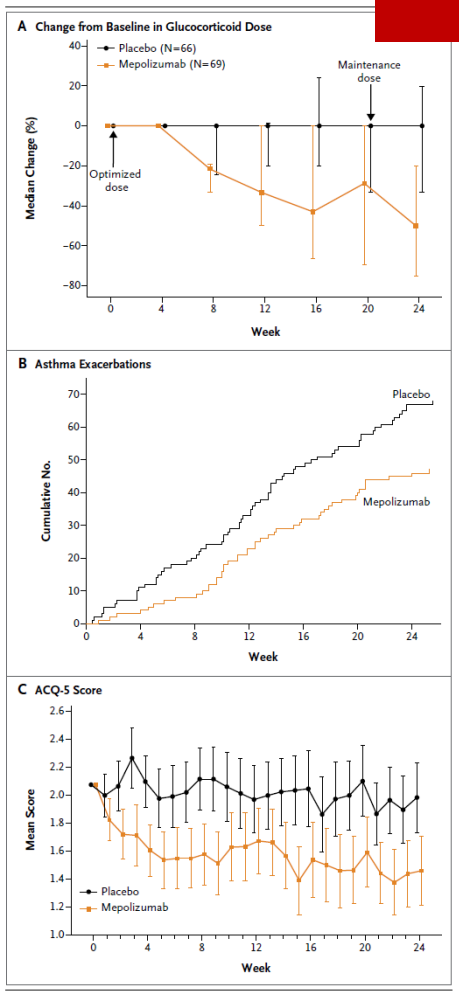


Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (−20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007



Primary endpoint is decrease in dose of OCS.

Reduced exacerbation rates by 32%.

ACQ-5 improved by 0.52 points.

Trend towards greater changes from baseline of FEV1 in mepolizumab group

Bel EH, et al. N Engl J Med 2014;371:1189-97

호흡기
Specialized Care Center for Respiratory and Allergic Diseases

Key Inclusion Criteria

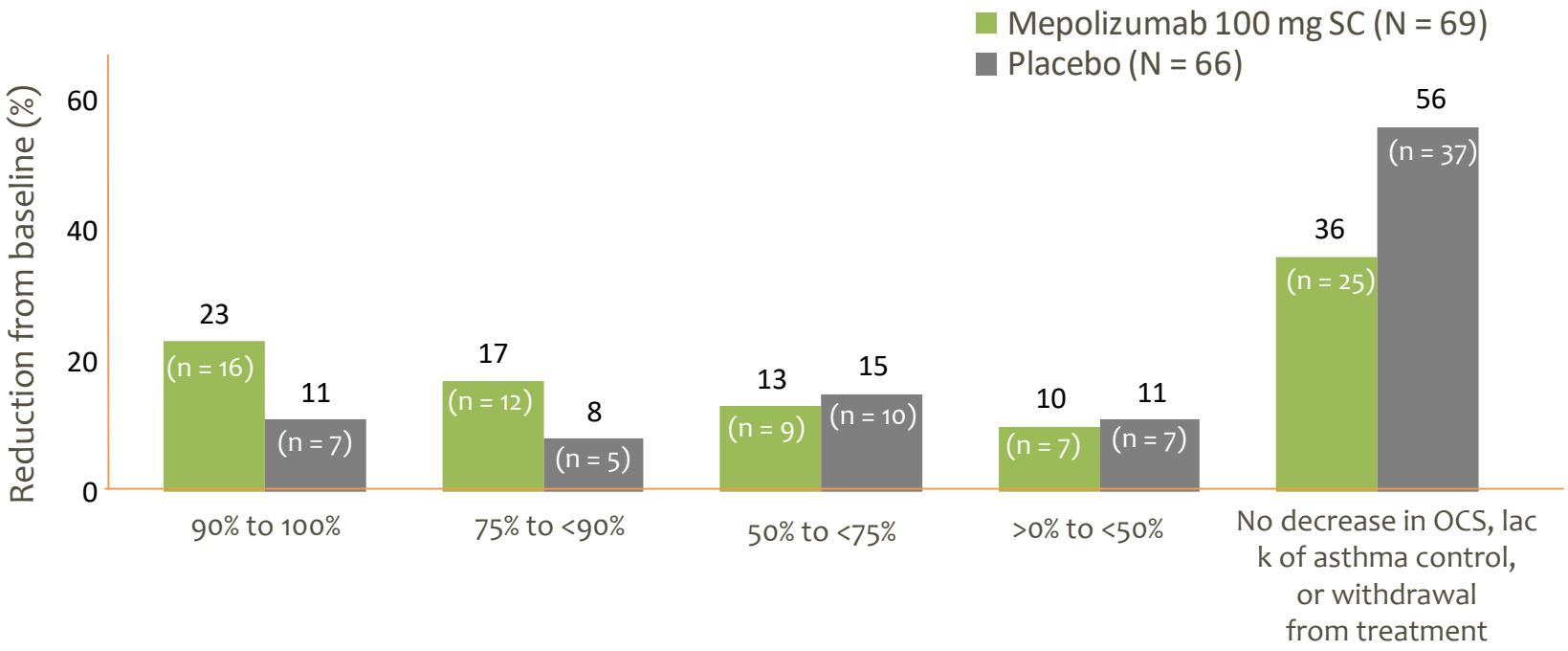
Background Medication	OCS Dependency	Eosinophilic inflammation
Documented requirement for regular treatment with **high-dose inhaled corticosteroids** and ≥3 months of treatment with **additional controller therapy**	Use of **maintenance systemic corticosteroids** for minimum last 6 months (5 to 35 mg/day prednisolone or equivalent at Visit 1) *No requirement for history of frequent exacerbations*	**≥150 cells/μL** in peripheral blood **at Visit 1** OR **≥300 cells/μL** in peripheral blood during the **12 months prior to Visit 1**

Ortega et al. *N Engl J Med*. 2014;371(13):1198-1207.

Significant reduction in OCS dose vs. placebo

- Primary endpoint

Analysis of OCS % reduction from baseline during Weeks 20-24 by reduction categories



Odds of subjects receiving mepolizumab in achieving categorical reduction in OCS were 2.39 times greater than placebo (*P* = .008)

Note: Analysed using a proportional odds model (multinomial [ordered] logistic generalised linear model), with terms for treatment group, reg ion, duration of OCS use at baseline (<5 yrs vs ≥5 yrs), and baseline OCS dose (optimised dose).

Bel EH, et al. *N Engl J Med.* 2014;371:1189-1197

Summary of the SIRIUS study

Efficacy

- Mepolizumab in addition to the standard of care reduced the maintenance dose of OCS compared with placebo (*P* = .008)
- Mepolizumab provided statistically significant improvements in most of the secondary endpoints of OCS reduction compared with placebo except for end point of total reduction in daily OCS dose
  - Although not significant, this end point still favoured mepolizumab

Safety

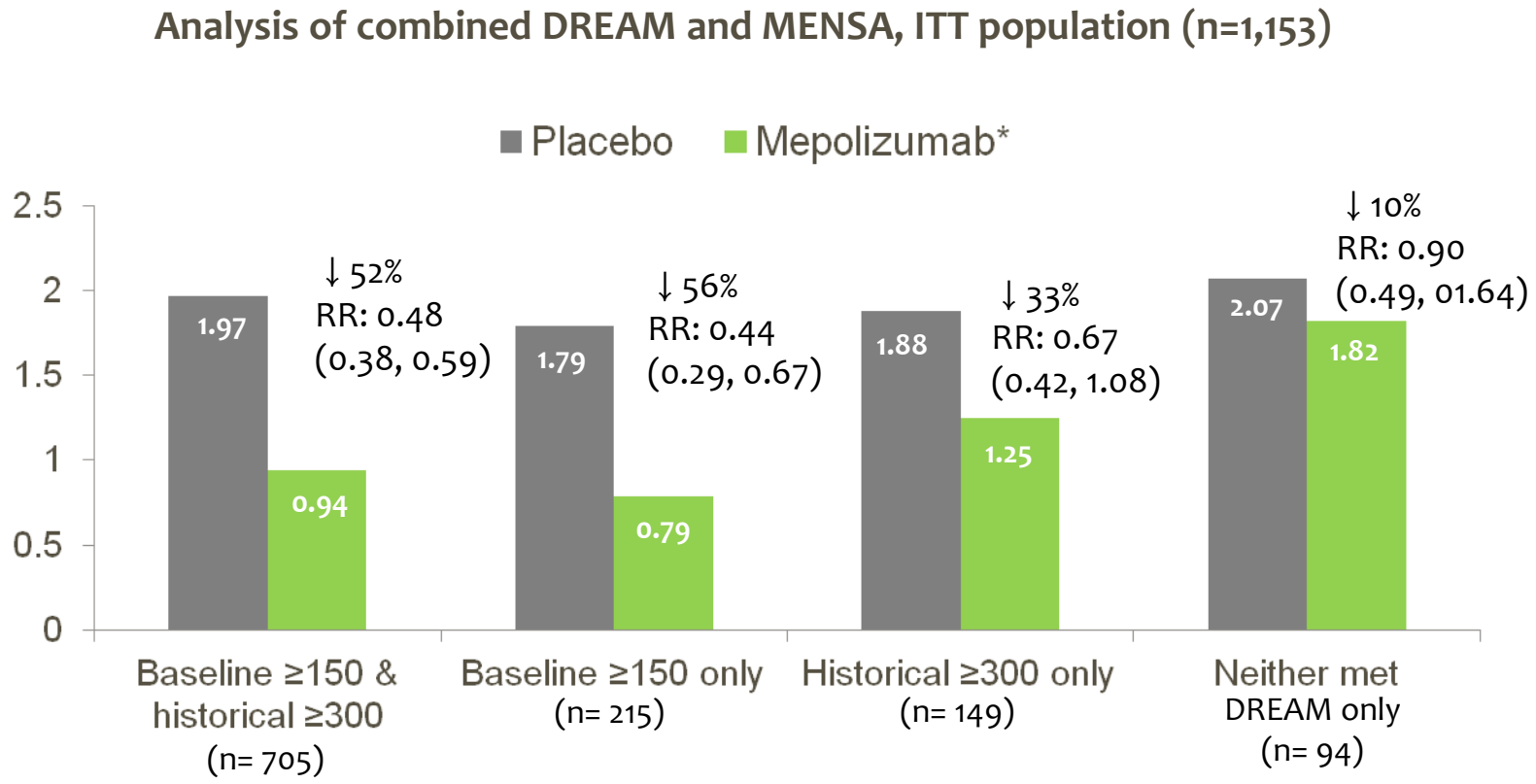
- Incidence of AEs was comparable between the treatment groups

Key learning

- The SIRIUS study confirmed the efficacy of mepolizumab in severe asthma patients on OCS maintenance treatment and identified based on blood eosinophil counts as follows:
  - ≥150 cells/μL at the Screening visit, or
  - ≥300 cells/μL within 12 months prior to the Screening visit

Bel EH, et al. N Engl J Med. 2014;371:1189-1197

Rate ratio for exacerbation reduction by eosinophil criteria



Meaningful reductions in exacerbation frequency of ≥30% were observed in patients with baseline e osinophil levels of ≥150 cells/µL at initiation or ≥300 cells/µL historical*

*All mepolizumab doses combined for the analysis; †7 patients had missing baseline eosinophils in MENSA and are excluded fro m the analysis. RR, Rate Ratio; 95% Confidence Intervals in brackets.

* A blood eosinophil count ≥150 cells/µL at treatment initiation or ≥300 cells/µL in the 12 months

Type 2/Th2-targeted therapy

2nd FDA approved biomedical drug for asthma

MediaPress releasesGSK's Nucala® (mepolizumab) receives.....

GSK's Nucala® (mepolizumab) receives approval from US FDA

04 November 2015

Issued: London UK – LSE Announcement

- **First anti-IL5 treatment for adults and adolescents with severe asthma with an eosinophilic phenotype**

GlaxoSmithKline plc (LSE/NYSE: GSK) today received approval from the US Food and Drug Administration (FDA) for its Biologics License Application (BLA) for Nucala® (mepolizumab) as an add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Nucala is not approved for the treatment of other eosinophilic conditions or relief of acute bronchospasm or status asthmaticus.

Nucala is the first and only approved biologic therapy that targets interleukin-5 (IL-5), which plays an important role in regulating the function of eosinophils, an inflammatory cell known to be important in asthma. It is administered as a 100mg fixed dose subcutaneous injection every four weeks. Patients will receive Nucala in addition to their normal medications for severe asthma, which include high-dose inhaled corticosteroids plus at least one additional asthma control medicine, and may include oral corticosteroids.–

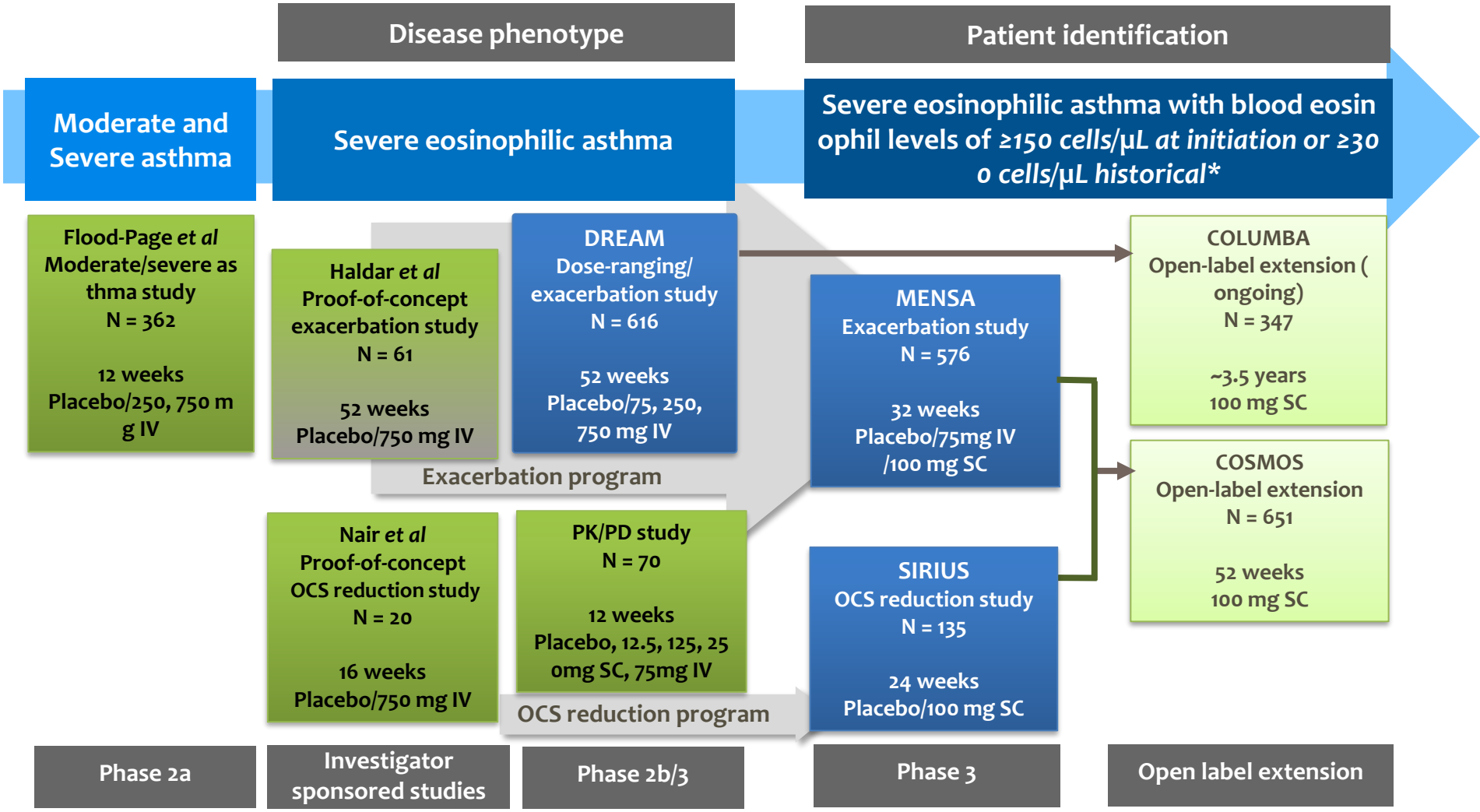
This is the first marketing authorisation granted for mepolizumab anywhere in the world

Eric Dube, Senior Vice President & Head, GSK Global Respiratory Franchise, said: "Following today's approval, GSK can now offer, as part of our overall respiratory portfolio, a first-in-class biologic treatment for severe asthma patients whose condition is driven by eosinophilic inflammation. Our research has allowed us to better understand the specific role eosinophils play in severe asthma. We are proud of our contribution to this emerging area of science that has led to the approval of the first anti-IL5 treatment. We aim to offer this medicine to patients as soon as possible."

100 mg SC every 4 weeks
> 12 years old

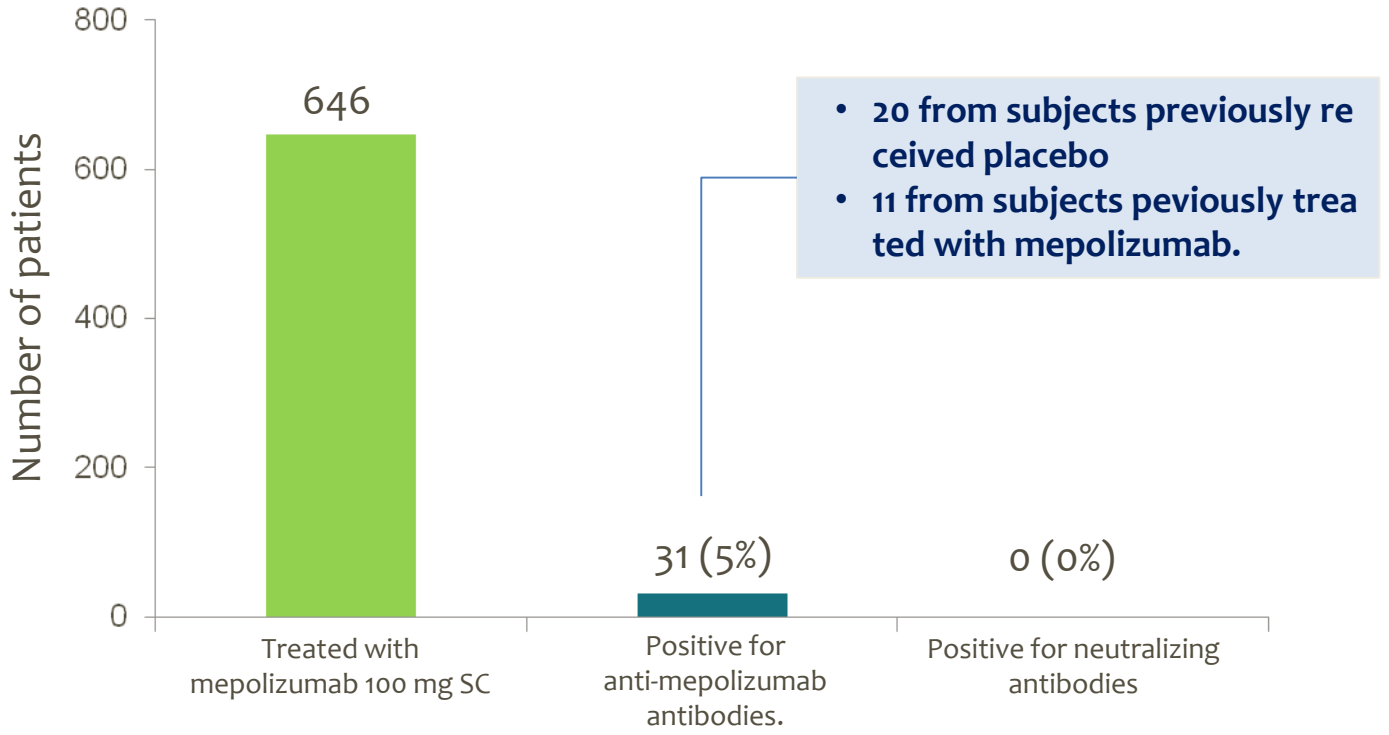
Clinical Development Programme for Mepolizumab

- **Key Clinical Efficacy/Safety Studies and Identification of Right Patients**



* A blood eosinophil count of ≥150 cells/µL at treatment initiation or ≥300 cells/µL in the previous 12 months

Immunogenicity results

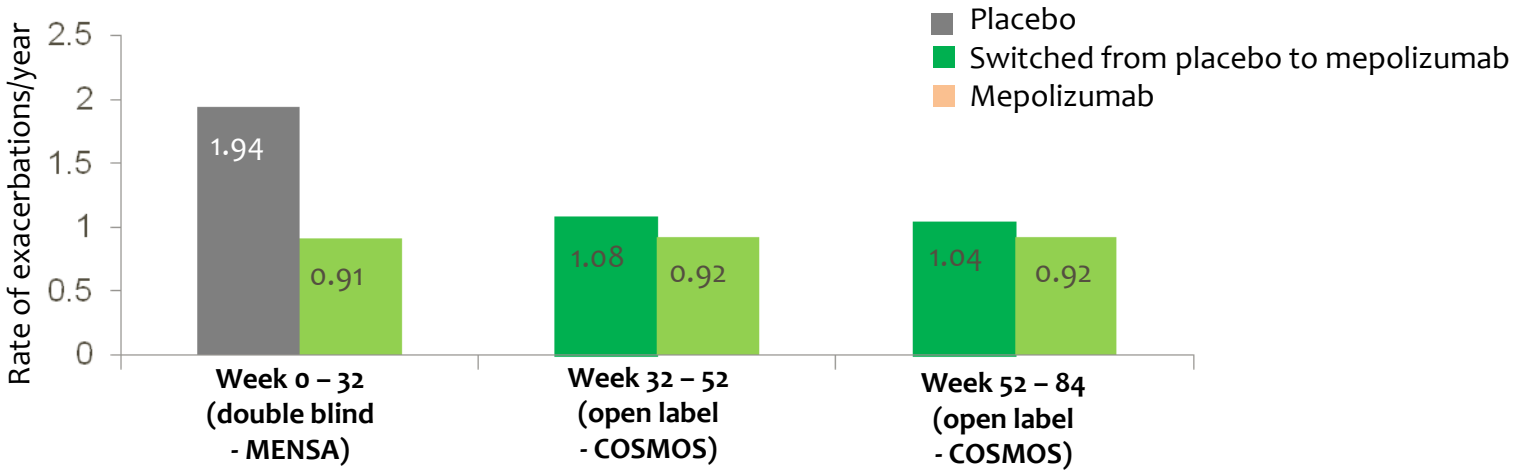


The majority of ADA-positive subjects developed ADA within 16 weeks of first dose and positivity decreased over time

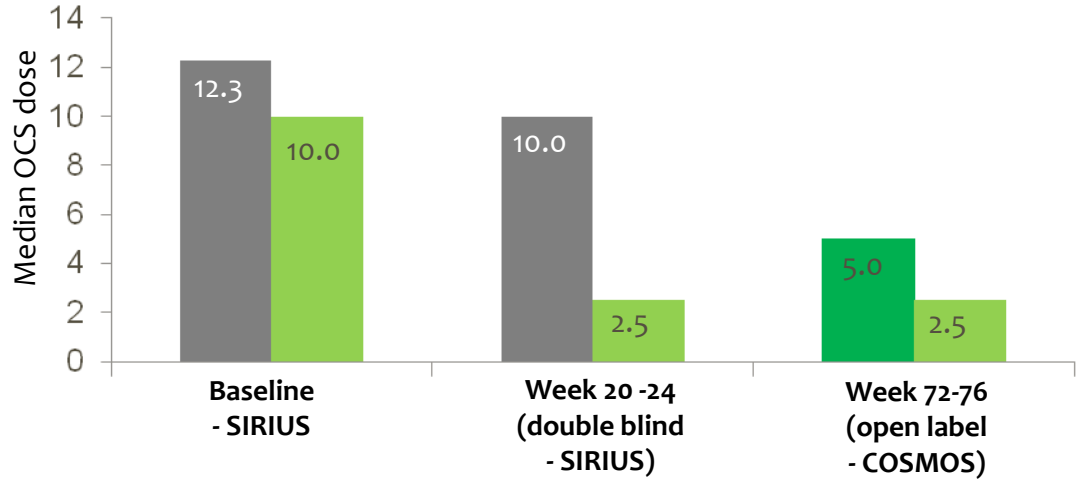
GSK Data on File – COSMOS CSR Data.

Durability of Response with continuous Mepolizumab

Exacerbation rates (MENSA participants only), n= 470



OCS dose during each reporting period (SIRIUS participants only), n=115



GSK Data on File – COSMOS CSR Data.

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

- **Reslizumab**
- One studied in patients with poorly controlled asthma taking high-dose ICSs and additional controllers with persistent sputum eosinophils (>3% on 2 occasions): **Marginal positive data**

- Two duplicate studies with patients inadequately controlled on ICS with a blood eosinophil count of >400 cells per µL with one or more exacerbations in the previous year: **Positive data**
  - **Significantly reduced exacerbations and improvement in FEV1, AQLQ scores, and ACQ-7 scores**
  - **Continued clinical trials and investigation**

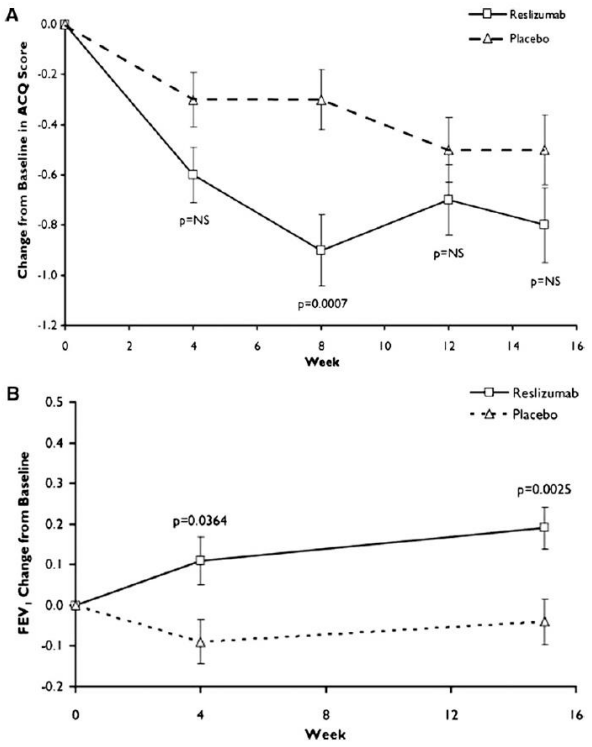
Castro M, et al, Am J Respir Crit Care Med 2011; 184: 1125–32.
Castro M, et al. Lancet Respir Med 2015; 3: 355–66.

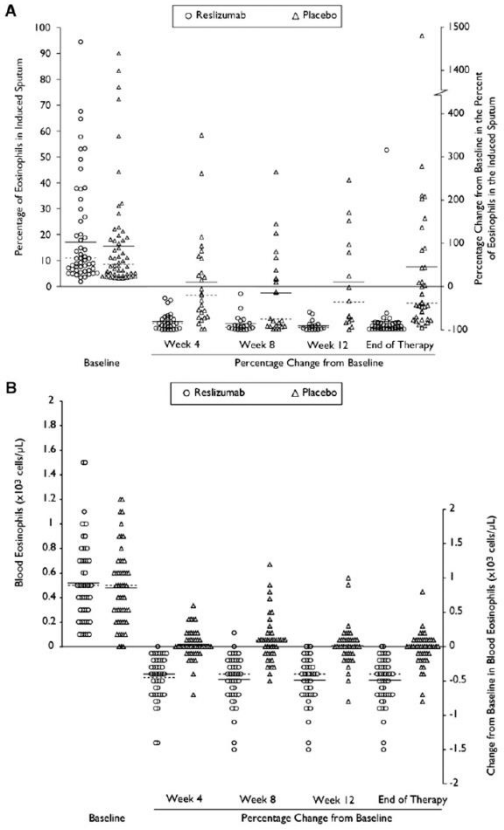
Reslizumab for Poorly Controlled, Eosinophilic Asthma

A Randomized, Placebo-controlled Study

Mario Castro[1], Sameer Mathur[2], Frederick Hargreave[3†], Louis-Philippe Boulet[4], Fang Xie[5], James Young[6], H. Jeffrey Wilkins[5], Timothy Henkel[5], and Parameswaran Nair[3]; for the Res-5-0010 Study Group

Selective patients: sputum eosinophils (>3% on 2 occasions)

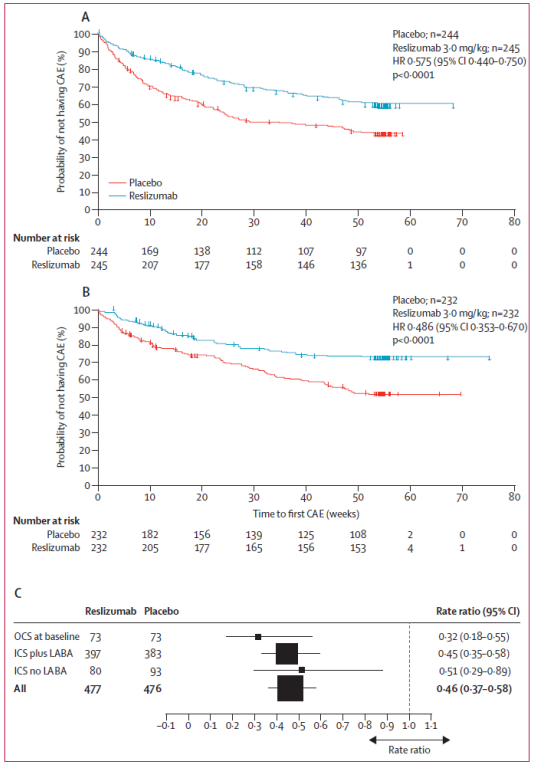


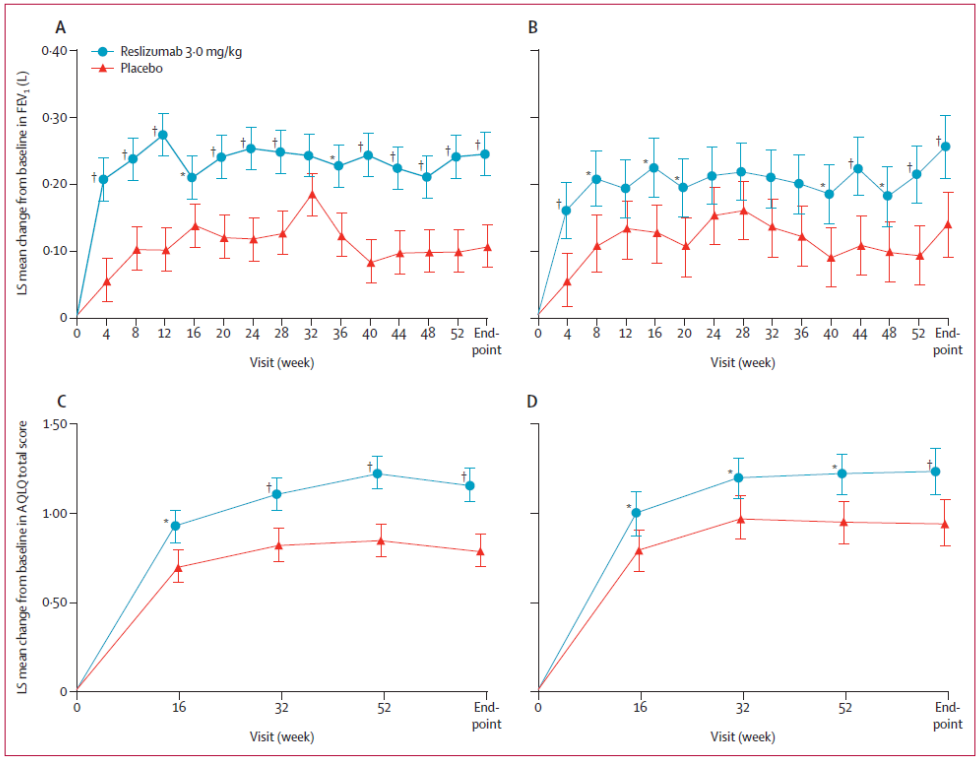


Castro M, et al, Am J Respir Crit Care Med 2011; 184: 1125–32.

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O'Brien, Stephanie Korn





Castro M, et al. Lancet Respir Med 2015; 3: 355–66.

Type 2/Th2-targeted therapy

3rd FDA approved biomedical drug for asthma

Teva Announces FDA Approval of CINQAIR® (reslizumab) Injection

New Biologic for Add-On Maintenance Treatment in Adults with Severe Asthma and an Eosinophilic Phenotype

JERUSALEM--(BUSINESS WIRE)--Mar. 23, 2016-- Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) today announced that the U.S. Food and Drug Administration (FDA) has approved CINQAIR® (reslizumab) Injection, an interleukin 5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.

CINQAIR® is administered by intravenous (IV) infusion at a weight-based dose of 3 mg/kg once every four weeks. The treatment is expected to become commerci patients, by prescription, during the second quarter of 2016.

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

- **Benralizumab (A humanized mAb targeting IL-5Rα)**
- **One studied in patients on high-dose ICS, with 2-6 exacerbations per year, raised blood eosinophil count, blood eosinophil index and FENO >50 ppb: Positive data**
  - **Exacerbation, FEV1, ACQ-6 score in eosinophilic asthma**
  - **Three doses of benralizumab tested: 2 mg, 20 mg, and 100 mg doses in patients with eosinophilic**

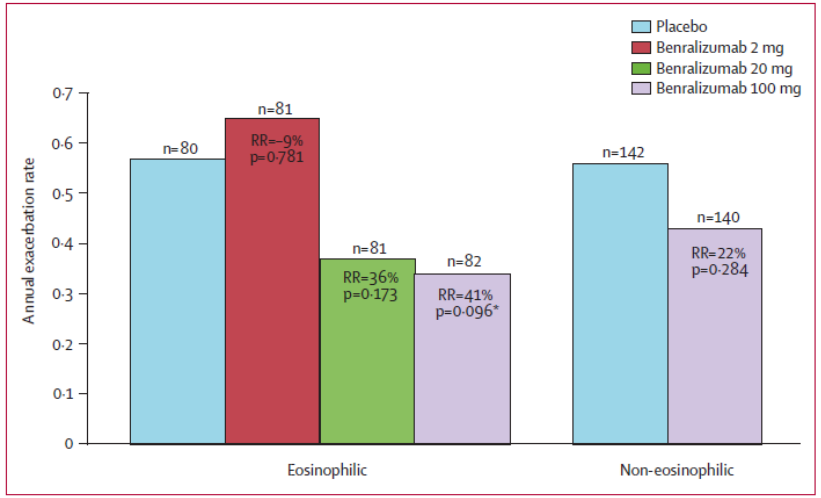
  asthma, and only 100 mg dose in patients with noneosinophilic asthma
- **The other study with patients presenting with acute exacerbation of asthma in ER.: Positive data**
  - **Reduced subsequent exacerbation rate by 49% including hospitalization by 60%.**
  - **Single infusion of benralizumab.**

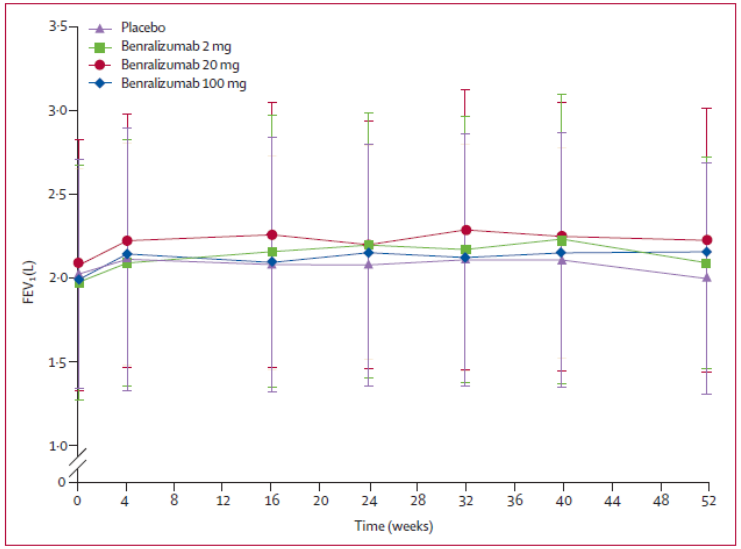
Castro M, et al. Lancet Respir Med 2014; 2: 879-90.
Nowak RM, et al. Am J Emerg Med 2015; 33: 14-20.

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

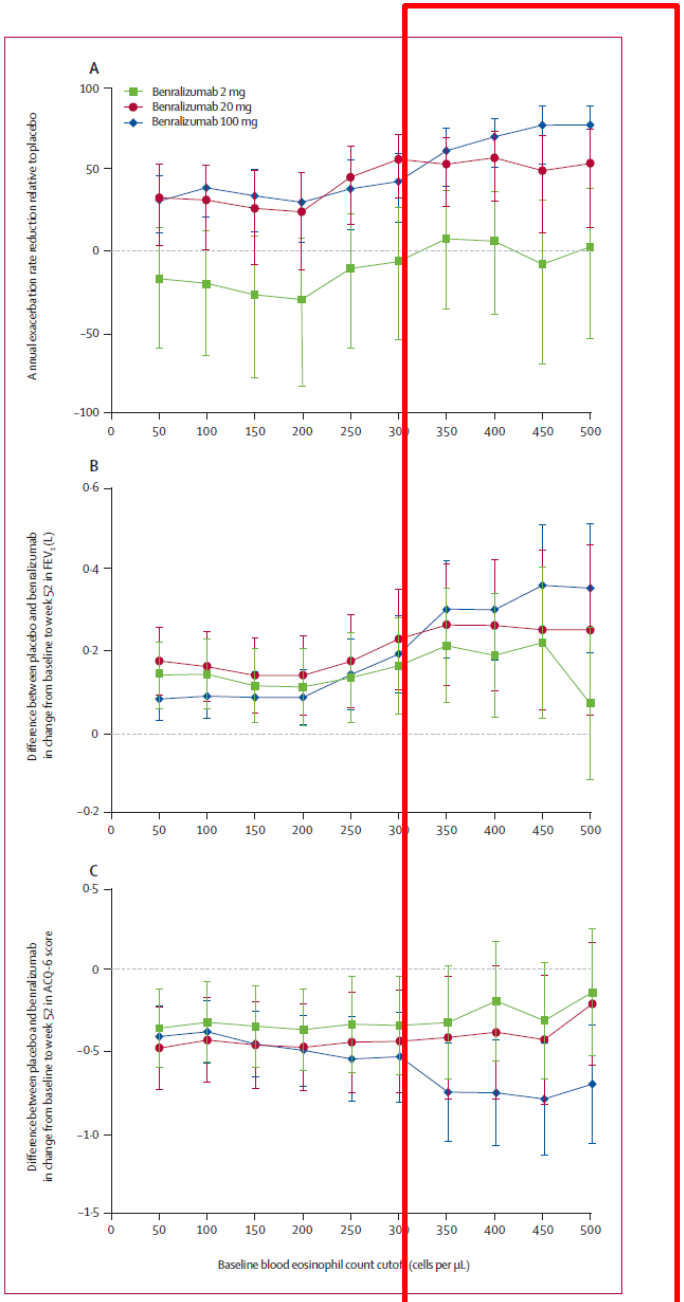
Mario Castro, Sally E Wenzel, Eugene R Bleecker, Emilio Pizzichini, Piotr Kuna, William W Busse, David L Gossage, Christine K Ward, Yanping Wu, Bing Wang, Deepak B Khatry, René van der Merwe, Roland Kolbeck, Nestor A Molfino, Donald G Raible

Selective patients: sputum eosinophils (≥2%) or FeNo ≥ 50 ppb



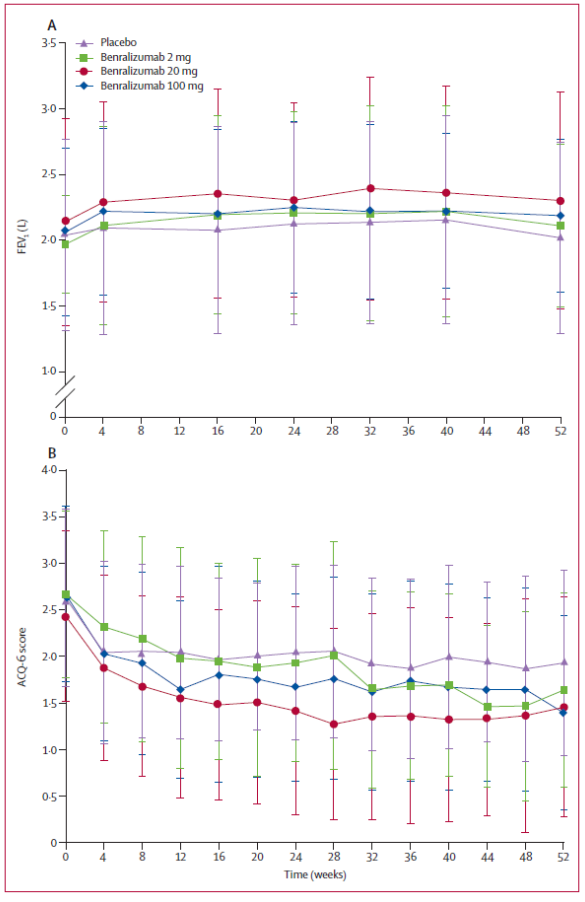


Castro M, et al. Lancet Respir Med 2014; 2: 879-90.



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



Castro M, et al. Lancet Respir Med 2014; 2: 879-90.

AstraZeneca's benralizumab succeeds in severe asthma

9th October 2014

by

Kevin Grogan

AstraZeneca has been boosted by positive mid-stage data on benralizumab for severe, uncontrolled asthma.

The Phase IIb study, data from which has been published in *The Lancet Respiratory Medicine*, evaluated adult patients with severe eosinophilic asthma that remained uncontrolled despite the use of inhaled corticosteroids and long-acting beta agonists for at least one year, and who had experienced at least two exacerbations in the past year. The trial met its primary endpoint, with patients on benralizumab experiencing a statistically significant reduction in their asthma exacerbation rate versus placebo over a year.

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5
Severe asthma with fungal sensitization (SAFS)

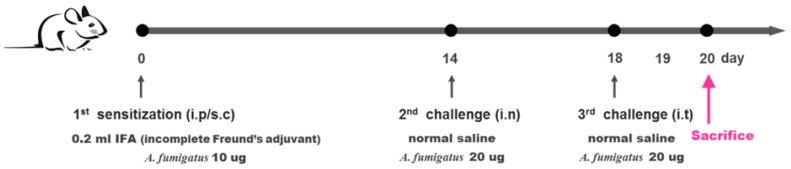
- **The criteria for defining SAFS are**
  - Severe asthma (British Thoracic Society step 4 or worse)
  - Exclusion of ABPA (total IgE <1000 IU/mL)
  - Evidence of sensitization to one or more fungi, by skin prick test or RAST test

- **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**

ORIGINAL ARTICLE

Phosphoinositide 3-kinase-δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

Kyung Sun Lee,[1] Jae Seok Jeong,[2] So Ri Kim,[1,3] Seong Ho Cho,[4] Narasaiah Kolliputi,[4] Yun Hee Ko,[1,3] Kyung Bae Lee,[1,3] Suk Chul Park,[1,3] Hae Jin Park,[1,3] Yong Chul Lee[1,3]



Lee YC et al, Thorax. 2016 Jan;71(1):52-63

Type 2/Th2-targeted therapy

Targeting the pro-eosinophilic type 2 cytokine IL-5

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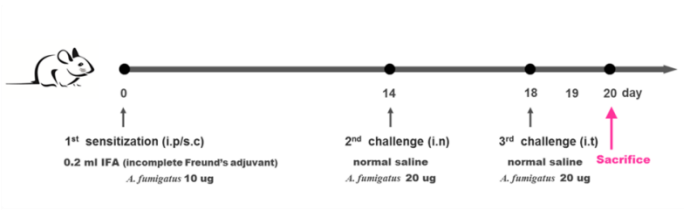

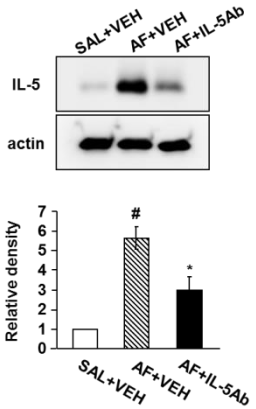

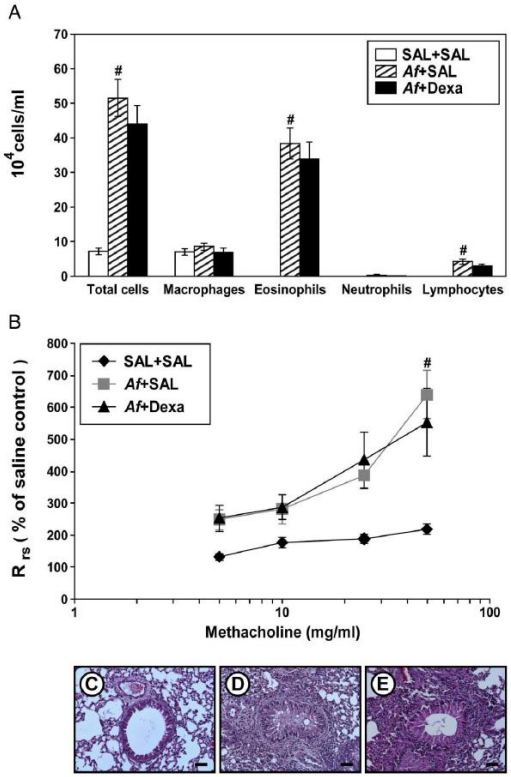

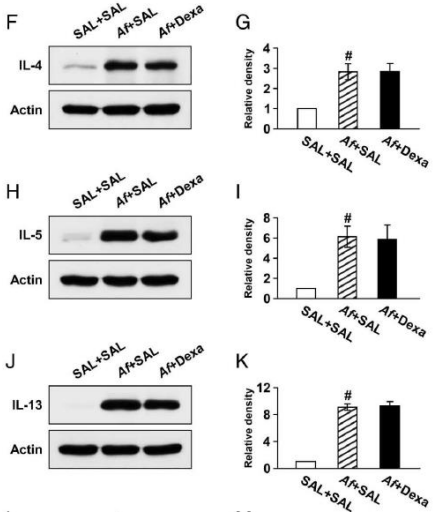

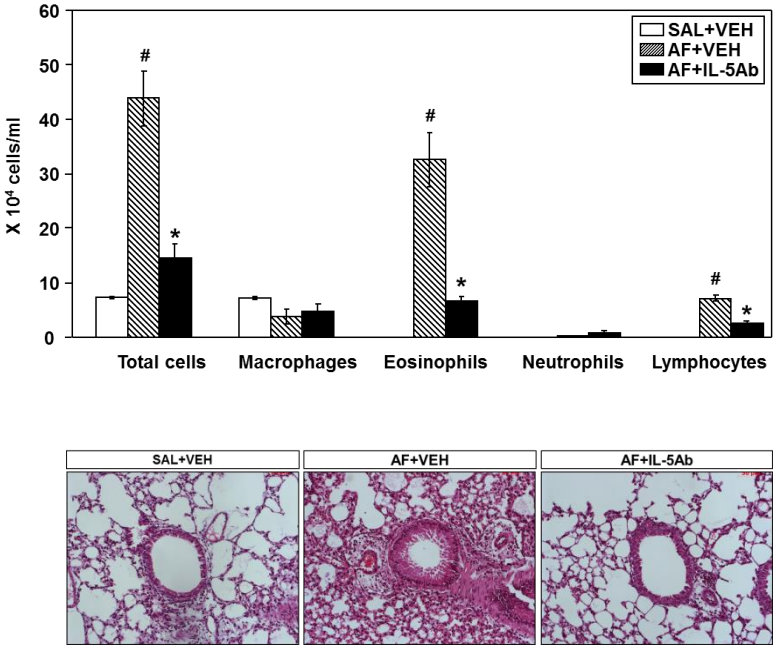

Lee YC et al, Thorax. 2016 Jan;71(1):52-63

Unpublished data

Anti-IL-5 therapy for other lung diseases beyond asthma

- Hypereosinophilic syndrome (HES)
- Eosinophilic Granulomatosis and Polyangitis (EGPA)
- Chronic eosinophilic pneumonia (CEP)
- Chronic bronchitis (in COPD)
- Nasal polyposis, atopic deramtitis

World Allergy Organ J. 2014; 7(1): 32.

Summary

- Asthma has been defined traditionally by using nonspecific clinical and physiologic variables that encompass multiple different phenotypes and treated with nonspecific anti-inflammatory therapies.
- Recent molecular and genetic studies have identified clinical and inflammatory phenotypes that associate with specific biomarkers.
- Biomarkers for type 2 (TH2) inflammation, including FENO levels and blood/sputum eosinophilia and serum periostin levels, have helped identify a type 2 molecular phenotype of asthma.
- Treatment of type 2–high patients with biologic agents targeting IgE and the canonical type 2 cytokines IL-4, IL-5, and IL-13 are emerging as efficacious asthma therapies.
- Biologics targeting IL-5 pathway achieved FDA approval firstly among several agents and they have shown pharmacologic effects of reduction of exacerbation/hospitalization, improvement of FEV1 and quality of life, and OCS sparing as well as relative pharmacologic safety.

Future direction

- **Biomarkers to identify a type 2–low asthma phenotype and potentially to guide therapy are unknown.**
- **Although these targeted biologic agents are efficacious in treating some phenotypes of asthma and allergic disease, some patients might respond better to one biologic agent than another or not at all.**
- **The reasons for these differential responses are unknown.**

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Many thanks to your attention