성장을 넘어 성숙으로

Airway Remodeling in Asthma:
Assessment, Treatment, and Prevention

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Concept of airway remodeling in asthma

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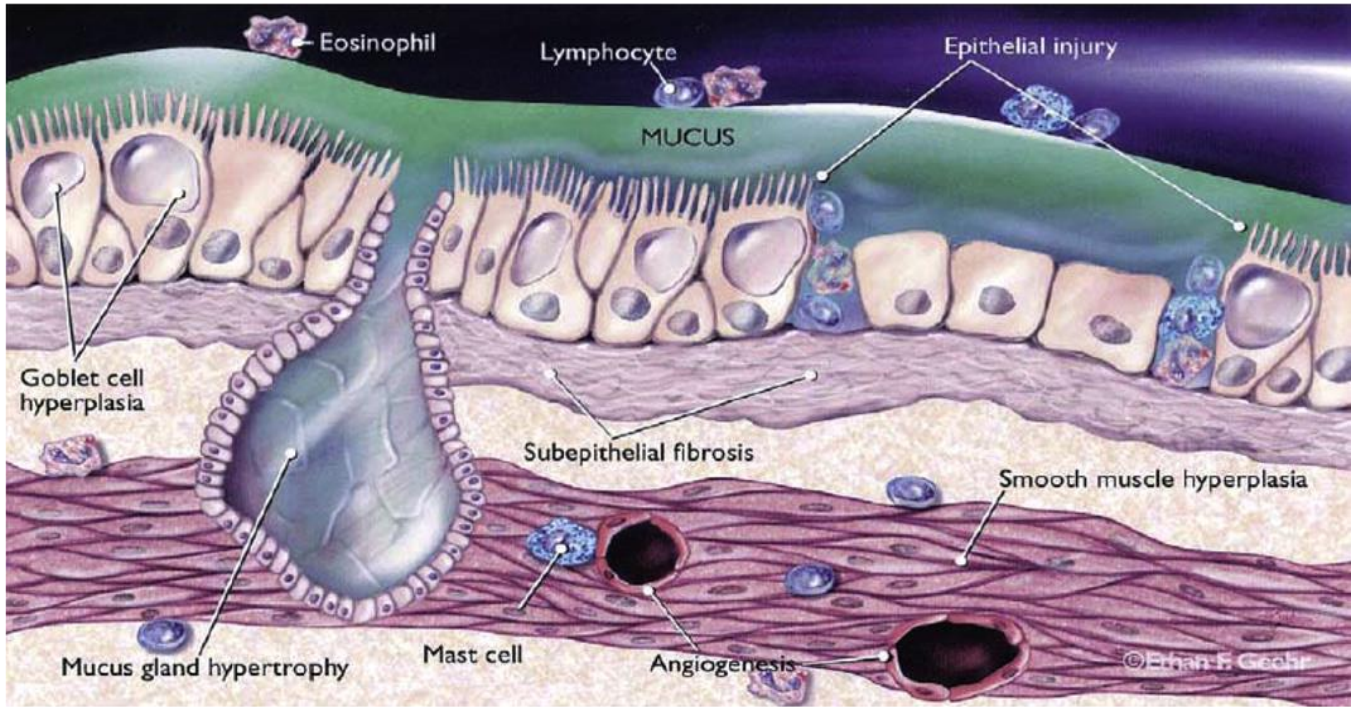
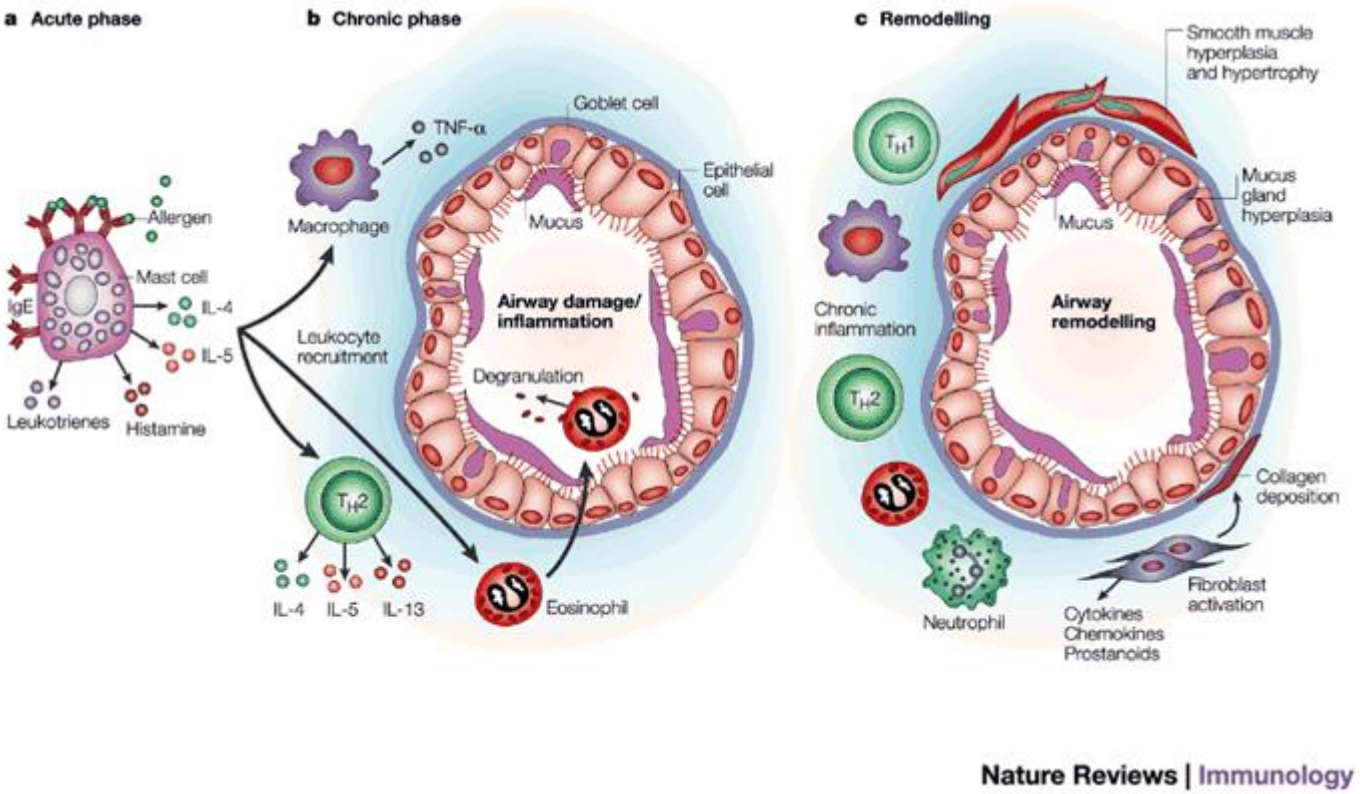
Airway remodeling

Structural changes characterized by increased thickness of the sub-epithelial reticular basement membrane (RBM), increased airway smooth muscle (ASM) mass, angiogenesis and goblet cell hyperplasia which are associated with an irreversible loss in lung function that tracks from childhood to adulthood.



Eur Respir J. 2015 Dec;46(6):1796-804; J Allergy Clin Immunol 2011;128:439-48.
Am J Respir Crit Care Med 2017 Jan; 195(2): e4–e19

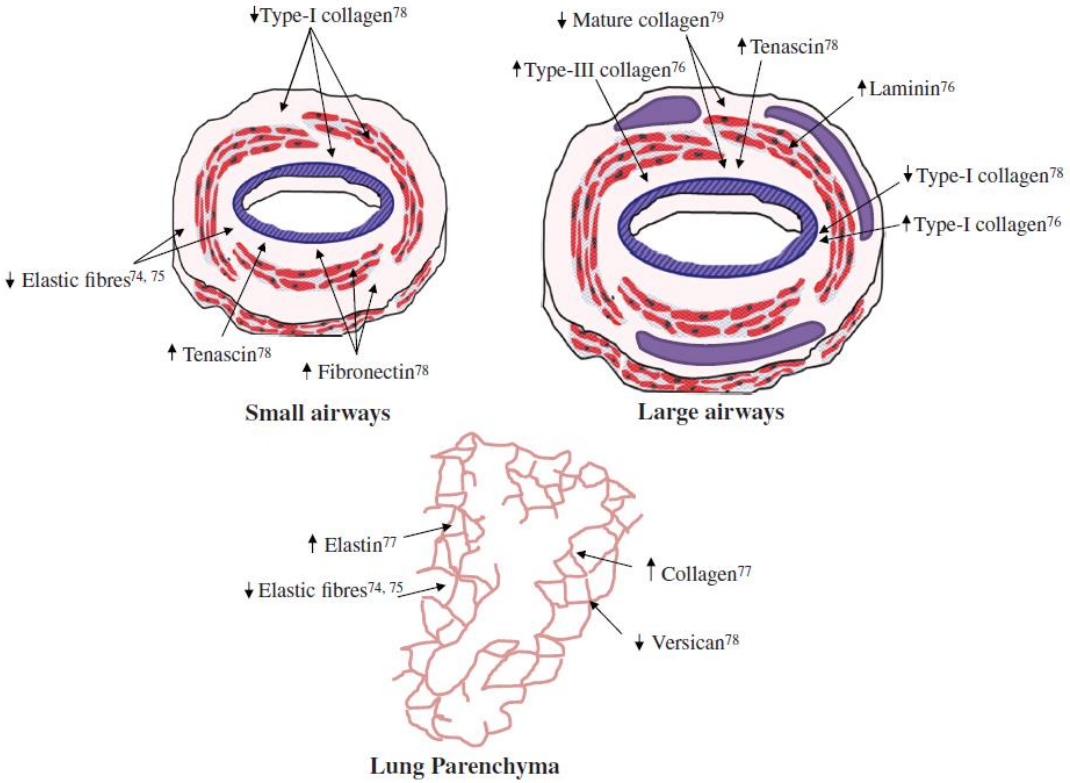
Airway remodeling in asthma



Nature Reviews Immunology volume 2, pages 132–138 (2002)

Airway remodeling in COPD

fixed airflow obstruction appears to be characterized by
a disproportionate increase in the ECM within the smooth muscle layer.



Comparison between asthma and COPD

Table 1. Markers of remodeling in asthma and COPD – large airways

Marker	Asthma	COPD
Epithelial integrity	Damaged, denuded (?)	Preserved, metaplasia
Goblet cells	++	+++ (in chronic bronchitis)
Epithelial basement membrane thickening	+++	(+)
Smooth muscle mass	+++	(+)
Angiogenesis	+++	+
Submucosal glands	+ to +++ (fatal disease)	+++ (bronchitis)
Inflammatory cells	Eosinophils, CD4+, mastcells (in severe asthma: neutrophils, CD8+)	Macrophages, neutrophils, CD8+, CD4+, (subsets of patients: eosinophils)

COPD, chronic obstructive pulmonary disease; (+), +, ++, +++, semiquantitative estimation of, respectively, marker; CD4+, CD4+ T-cells; CD8+, CD8+ T-cells.

Table 2. Markers of remodeling in asthma and COPD – small airways and lung parenchyma

Marker	Asthma	COPD
Goblet cells	?	++
Peribronchiolar fibrosis	+?	+++
Smooth muscle mass	++ (severe asthma)	(+)
Loss of alveolar attachments	0	+++
Emphysema	0	++
Collagen	?	++
Inflammatory cells – small airways	Eosinophils, T-cells, mastcells, (severe disease: neutrophils)	Neutrophils, T-cells, B-cells, macrophages
Inflammatory cells – lung parenchyma	Mastcells, eosinophils, macrophages (severe asthma)	CD4+, macrophages (emphysema)

COPD, chronic obstructive pulmonary disease; 0, not present; ?, unknown or questionable; (+), +, ++, +++, semiquantitative estimation of, respectively, marker; CD4+, CD4+ T-cells; CD8+, CD8+ T-cells.

Two types of airway remodeling

(1) Physiological airway remodeling

: which encompasses structural changes that occur regularly during normal lung development and growth leading to a normal mature airway wall or as an acute and transient response to injury and/or inflammation

: ultimately resulting in restoration of a normal airway structure

Possible beneficial effects
Protection against maximal bronchoconstriction
Prevention of airway collapse from airway wall stiffening

(2) Pathological airway remodeling

: which comprises those structural alterations that occur as a result of either disturbed lung development or as a response to chronic injury and/or inflammation leading to persistently altered airway wall structures and function.

Possible detrimental effects of airway remodelling
Contribution to the decline in lung function
Development of an irreversible component of airway obstruction
Reduction of airway distensibility and of bronchodilator response
Development and persistence of airway hyperresponsiveness
Loss of protective smooth muscle stretch relaxation
Increased contractile response from ASM mass increase and amplifying mechanisms
Loss of lung elastic recoil

Cell Tissue Res (2017) 367:551–569
Curr Opin Pulm Med 2018, 24:56–62

Airway remodeling: primary event vs. secondary event to inflammation

(1) Primary events: parallel with inflammation

: Pohunek et al. (2005) presented one of the first studies to provide evidence for **airway remodeling very early in childhood**

: suggesting that remodeling may be present even before asthma becomes symptomatic.

: relatively little data

: in terms of **prevention**, a lot of work awaits to be done.

(2) Secondary event to inflammation: sequential to inflammation

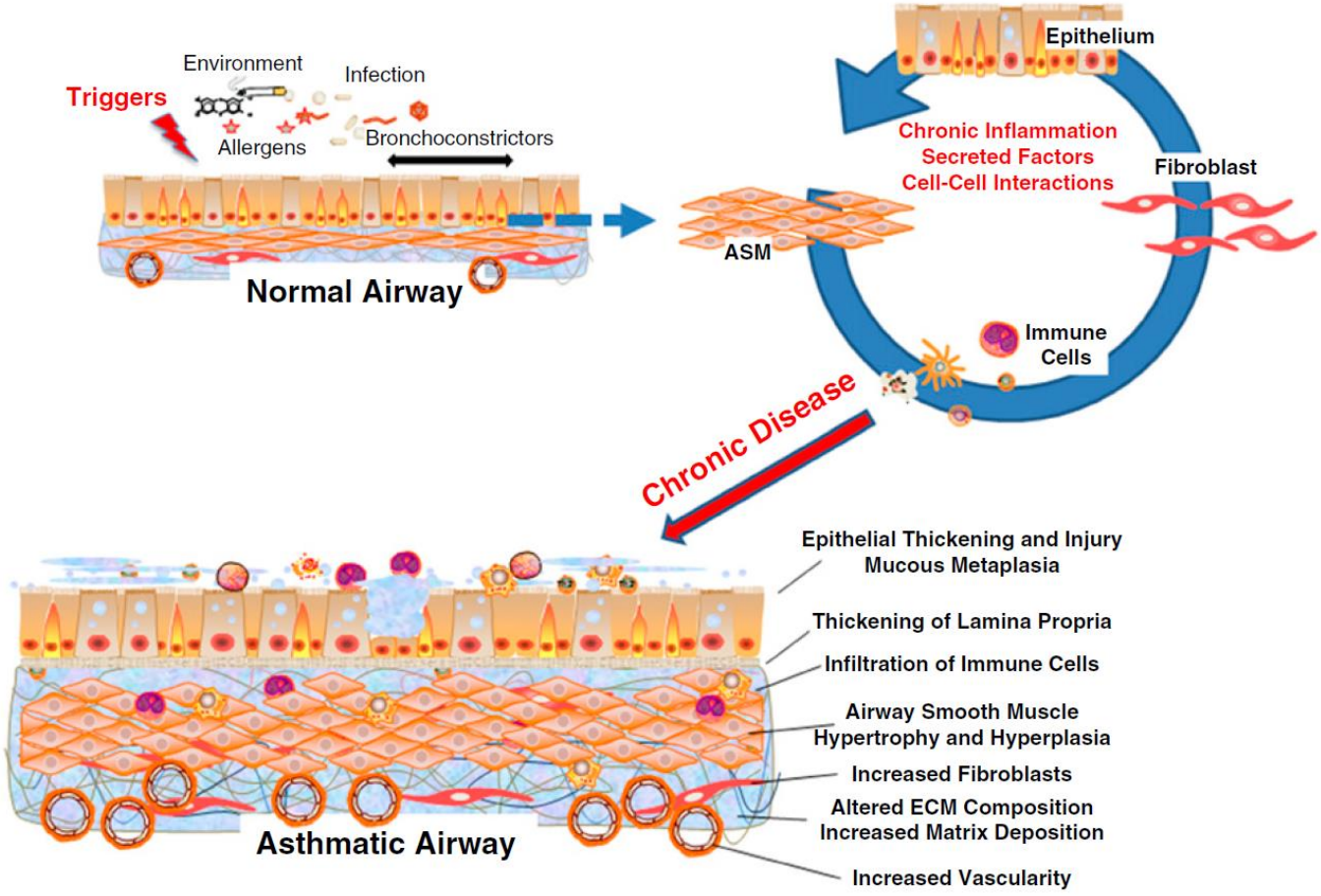
: "Inflammatory theory"

: chronic airway inflammation can be described as the major force driving the processes leading to most aspects of airway remodeling.

: supported by the finding that steroid treatment in asthmatic patients does not only reduce airway inflammation but also has **beneficial effects on airway remodeling**

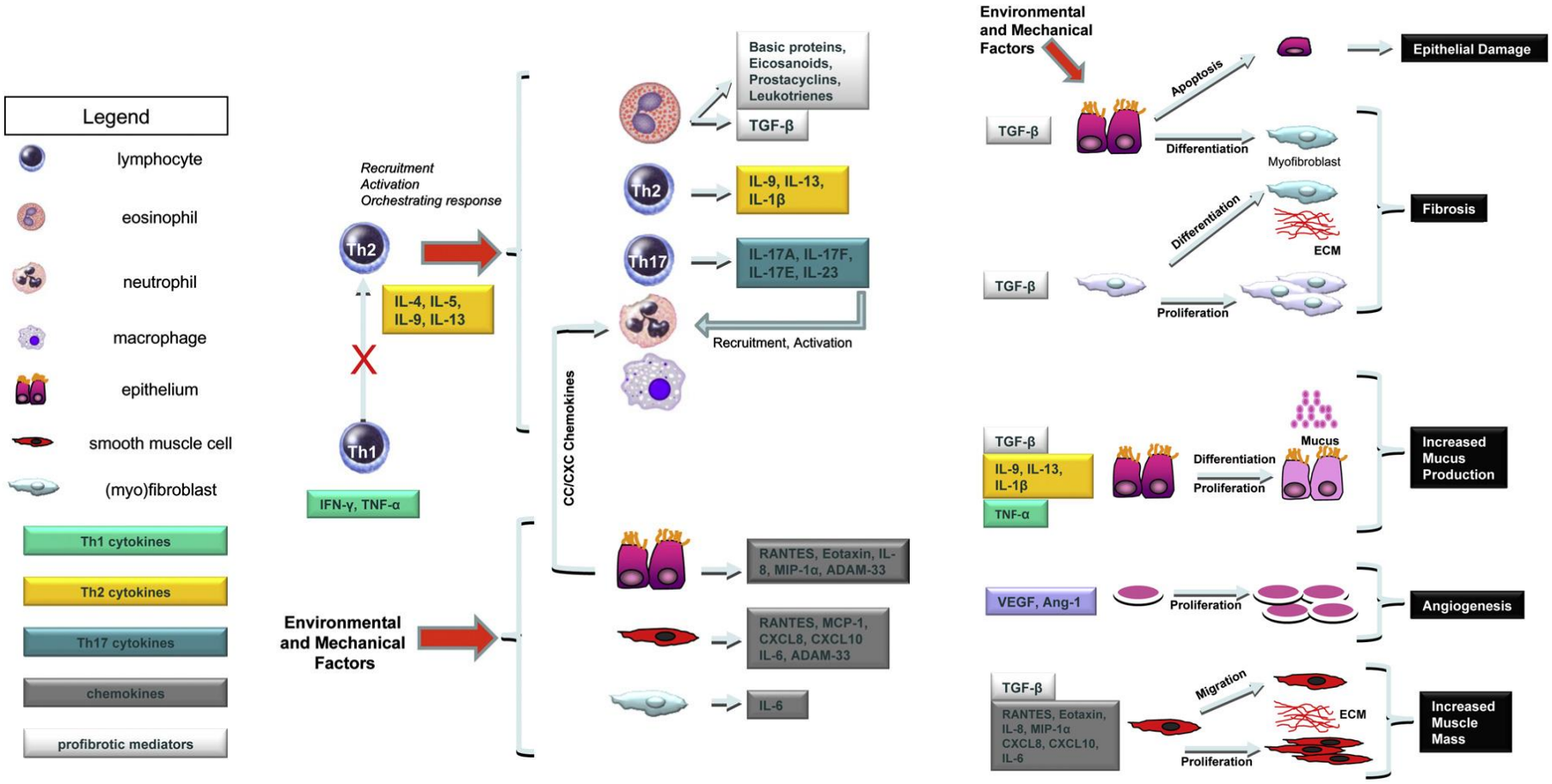
Pohunek et al. 2005; Trigg et al. 1994; Olivieri et al. 1997; Laitinen et al. 1997; Hoshino et al. 1998, 1999, 2001; Sont et al. 1999; Ward et al. 2002; Chetta et al. 2003.

Airway remodeling in asthma



Am J Respir Crit Care Med 2017 Jan; 195(2): e4–e19

Airway remodeling in asthma



J Allergy Clin Immunol 2011;128:451-62.

Relationships between airway inflammation and remodeling: do any exist?

ORIGINAL ARTICLE

Airway Remodeling in Preschool Children with Severe Recurrent Wheeze

Guillaume Lezmi[1,2], Philippe Gosset[3,4,5,6,7], Antoine Deschildre[8], Rola Abou-Taam[1], Bruno Mahut[9], Nicole Beydon[10], and Jacques de Blic[1,2]

[1]AP-HP, Hôpital Necker-Enfants Malades, Service de Pneumologie et d'Allergologie Pédiatriques, Paris, France; [2]Université Paris Descartes, Paris, France; [3]Institut Pasteur de Lille, Centre d'Infection et d'Immunité de Lille, Lille, France; [4]Université Lille Nord de France, Lille, France; [5]Centre National de la Recherche Scientifique, UMR 8204, Lille, France; [6]Institut National de la Santé et de la Recherche Médicale, U1019, Lille, France; [7]Institut Fédératif de la Recherche 142, Lille, France; [8]Unité de Pneumologie-Allergologie Pédiatrique, Clinique de Pédiatrie Jeanne de Flandre, CHRU de Lille, Université Nord de France, Lille, France; [9]Cabinet La Berma, Antony, France; and [10]APHP, Hôpital Armand Trousseau, Service d'Explorations Fonctionnelles Respiratoires, Paris, France

Table 2. Characteristics of the Airway Wall by Age

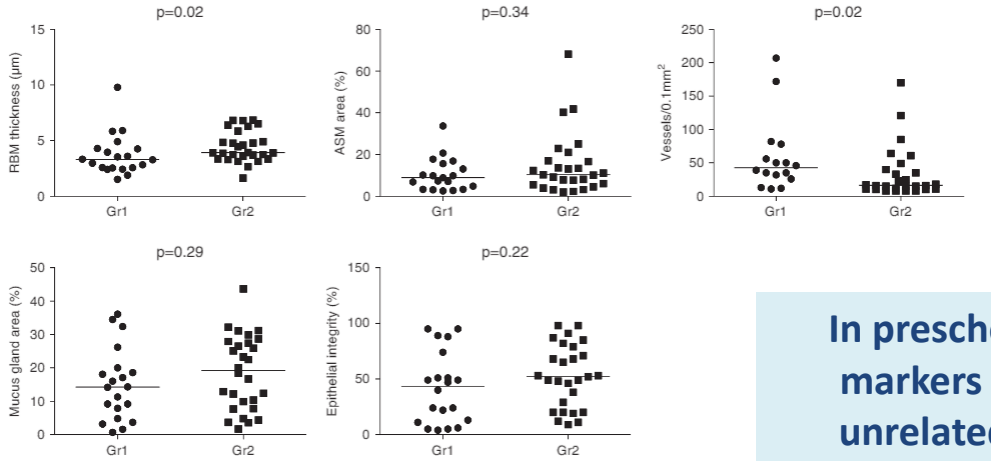
	Group 1	Group 2	Group 3
Age, mo	27.2 (24.5–30.3)	44.5 (41–54.6)	117.7 (102.4–124.3)
Number	20	29	21
RBM thickness, μm	3.3 (2.6–4.3)*†	3.9 (3.5–5.1)†	6.8 (6–8.4)
ASM area, %	8.9 (4.1–14.4)†	10.3 (5.8–16.8)	16.5 (10.5–27.7)
Vessel number, per 0.1 mm^2	42.5 (30.5–61.5)*†	16.5 (11–36.3)	20 (13.30)
Mucus gland area, %	14.3 (7.1–19)	20 (5.8–16.8)†	4.6 (2.4–13)
Epithelial integrity, %	43.5 (12.5–56.8)	52 (24.5–75)	62 (30–85)

Definition of abbreviations: ASM = airway smooth muscle; RBM = reticular basement membrane. Data are expressed as the median (interquartile range). Group 1: preschoolers less than or equal to 36 months. Group 2: preschoolers, 36–59 months. Group 3: schoolchildren.
*$P < 0.05$, versus group 2.
†$P < 0.05$ versus group 3.

Table 3. Bronchoalveolar Lavage Analysis in Preschoolers

	Group 1	Group 2	*P* Value
Number of patients	20	29	
Total cell counts	190 (135–250)	140 (100–205)	0.19
Neutrophils, %	32 (10–53)	10 (4–38)	0.10
Eosinophils, %	0 (0–1)	0 (0–1)	0.81
Lymphocytes, %	5 (1–8)	6 (1–8)	0.48
Macrophages, %	63 (42–82)	78 (61–87)	0.11
Viral infection	0	0	
Positive culture	8	11	0.89

Cell counts are expressed as number × 10^3/ml. Median (interquartile range).



In preschoolers with severe recurrent wheeze, markers of remodeling and inflammation are unrelated, and atopy is associated with ASM.

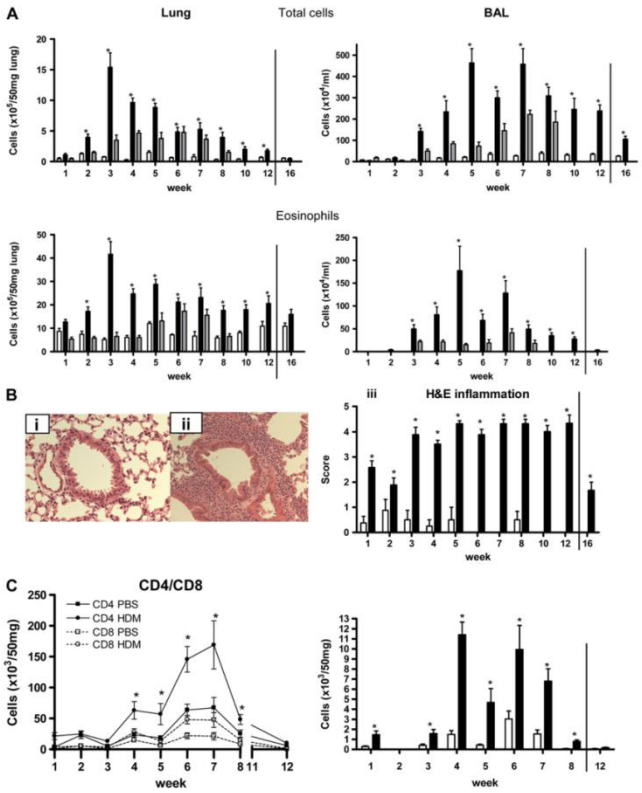
Am J Respir Crit Care Med Vol 192, Iss 2, pp 164–171, Jul 15, 2015

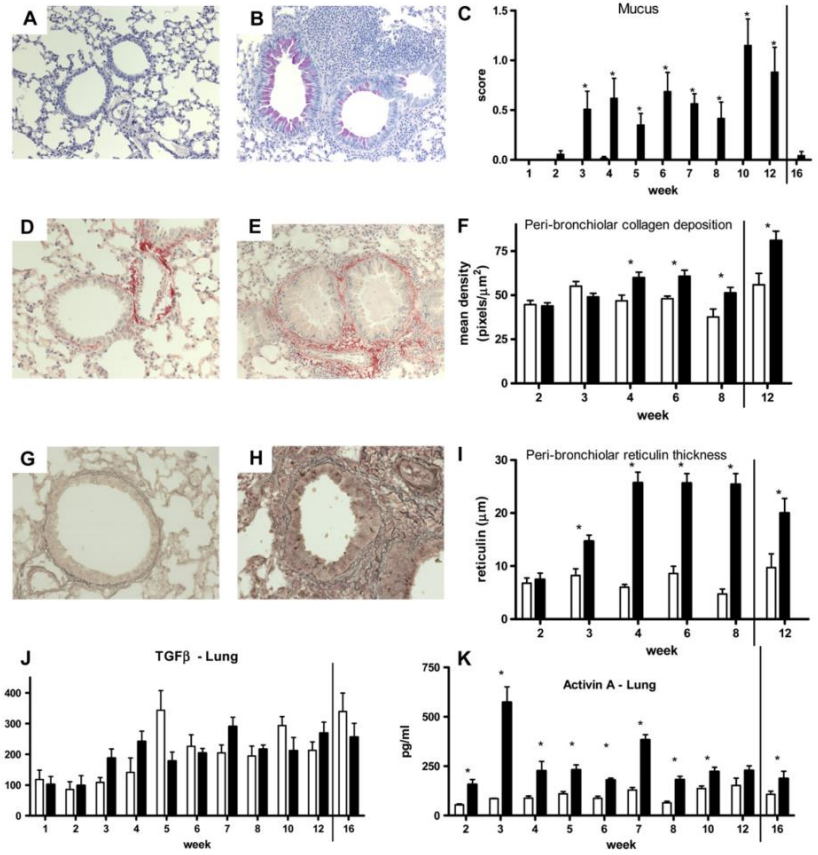
Relationships between airway inflammation and remodeling: do any exist?

Pathophysiological Features of Asthma Develop in Parallel in House Dust Mite–Exposed Neonatal Mice

Sejal Saglani[1,2], Sara A. Mathie[1], Lisa G. Gregory[1], Matthew J. Bell[1], Andrew Bush[2], and Clare M. Lloyd[1]

[1]Leukocyte Biology Section, and [2]Respiratory Paediatrics, National Heart and Lung Institute, Imperial College London, and Medical Research Council and Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom





This is the first description of the temporal relationship between the onset of abnormal lung function, airway inflammation, and remodeling in a neonatal model of AAD, showing their development at a similar time and in parallel.

Am J Respir Cell Mol Biol Vol 41. pp 281–289, 2009

Current challenges facing research and therapeutic advances in airway remodeling

Given the importance of both inflammation and remodeling in asthma pathogenesis, there is a significant disparity in the number of studies that have investigated the contribution of each. Most studies, both clinical and mechanistic, focus on inflammatory parameters alone.


AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Research Statement: Current Challenges Facing Research and Therapeutic Advances in Airway Remodeling

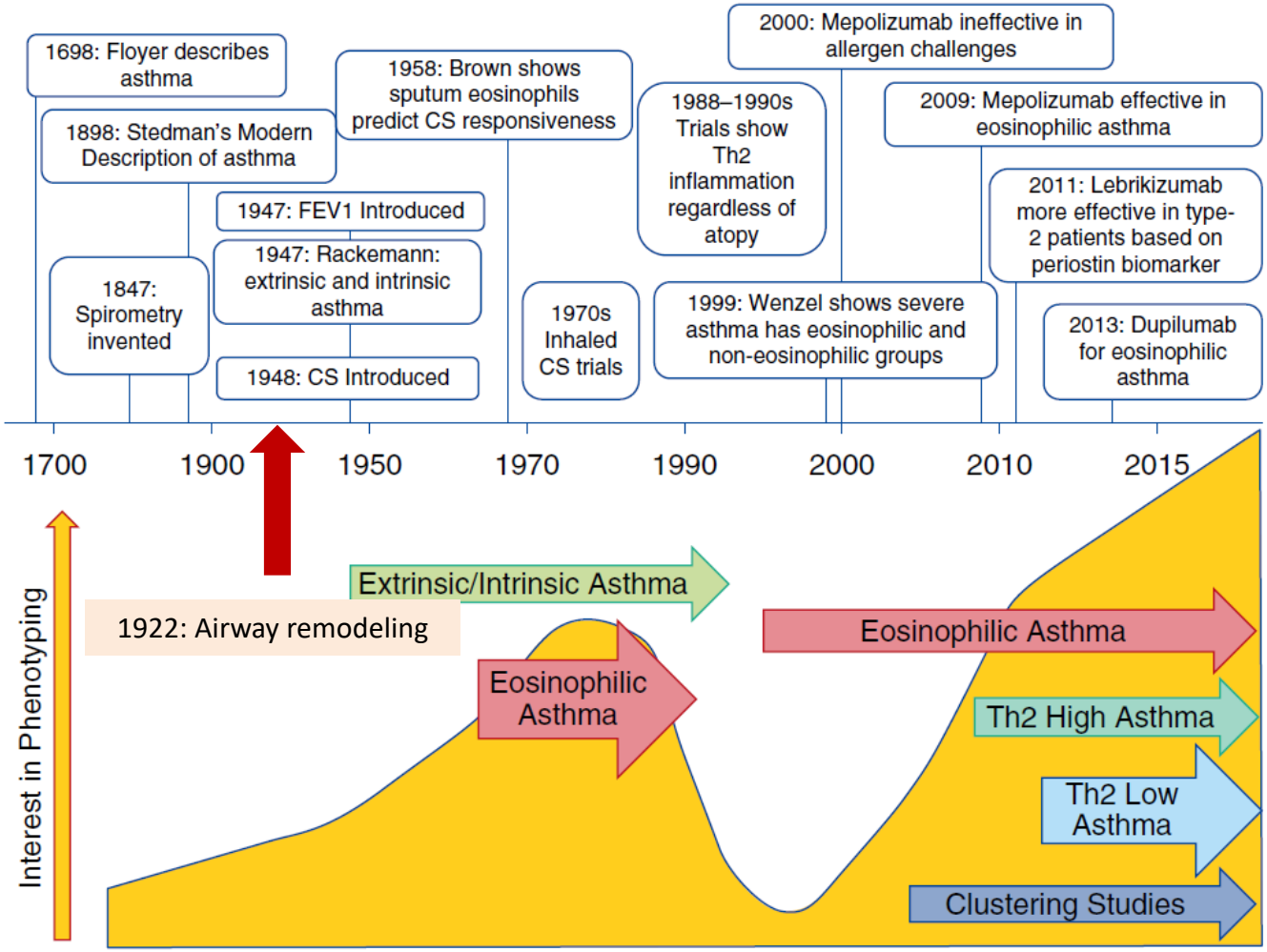
Y. S. Prakash, Andrew J. Halayko, Reinoud Gosens, Reynold A. Panettieri, Jr., Blanca Camoretti-Mercado, and Raymond B. Penn; on behalf of the ATS Assembly on Respiratory Structure and Function

THIS OFFICIAL RESEARCH STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2016

- **Lack of consensus regarding the importance of multiple features of AR**
- **Fundamental methodological limitations:** cost, lack of standardized methodology, relevance of nonhuman model systems, prolonged time frame of AR development in humans, and inherent limitations of tools/techniques
- **Difficulty of proposing "deliverables" for research testing anti-AR drugs**
- **Economic and regulatory issues**

Eur Respir J. 2015 Dec;46(6):1796-804
Am J Respir Crit Care Med 2017 Jan; 195(2): e4–e19

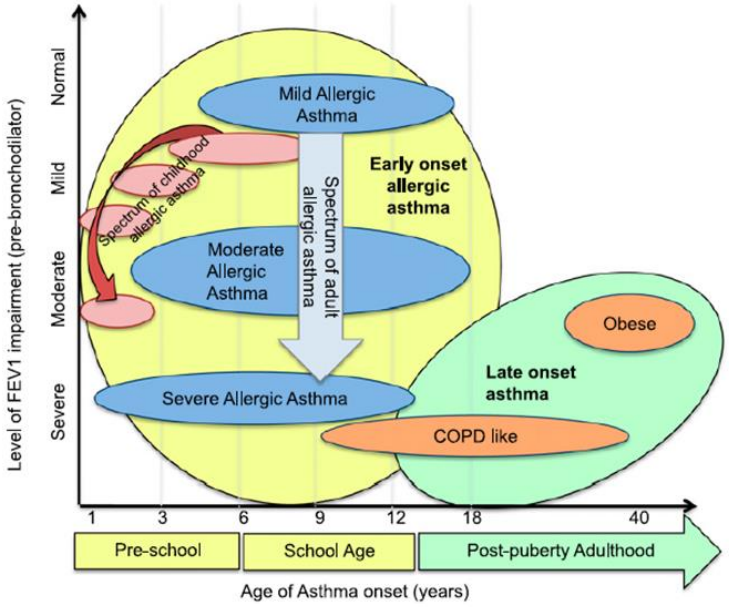
Historical asthma

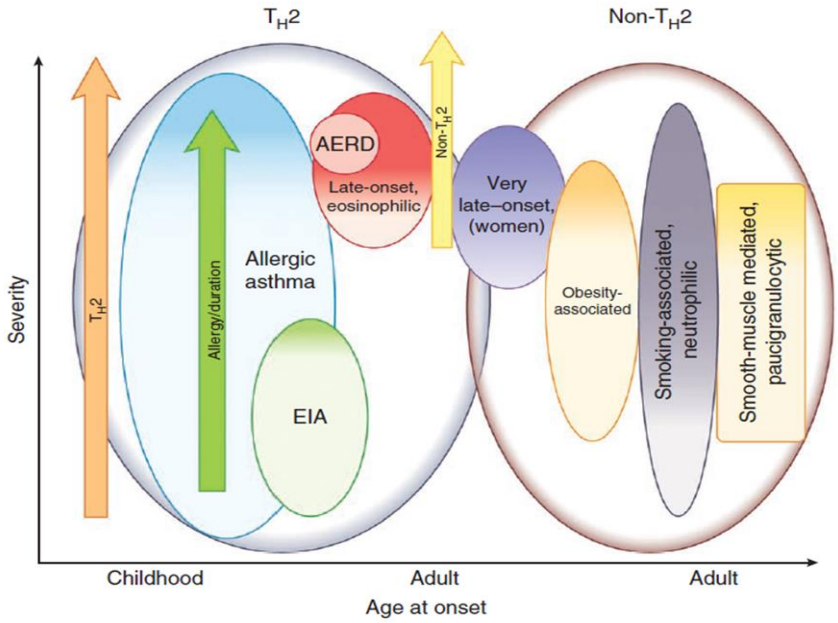


Gauthier M, et al. Am J Respir Crit Care Med. 2015;192(6):660-8.

Evolving concept of asthma

Approaches to identifying phenotypes of asthma

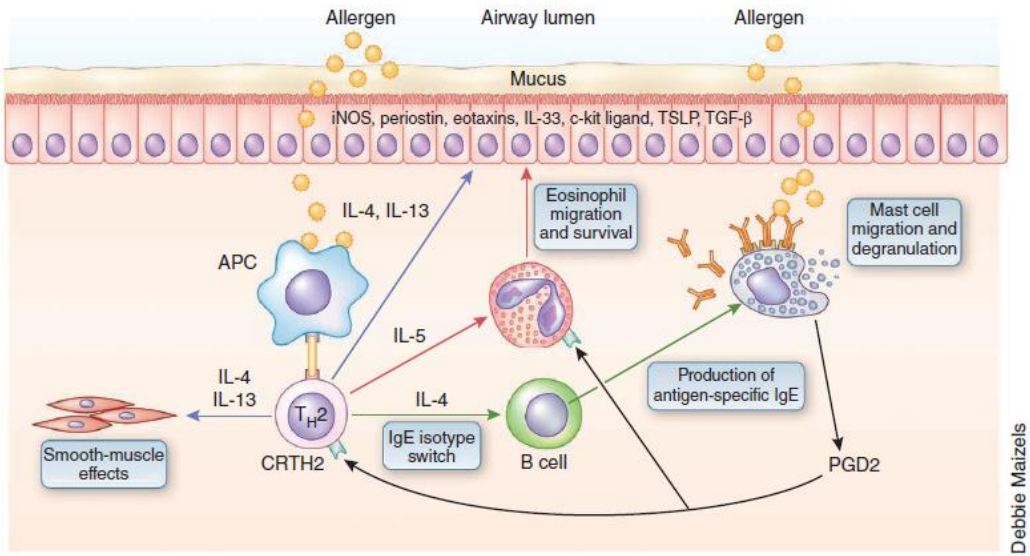


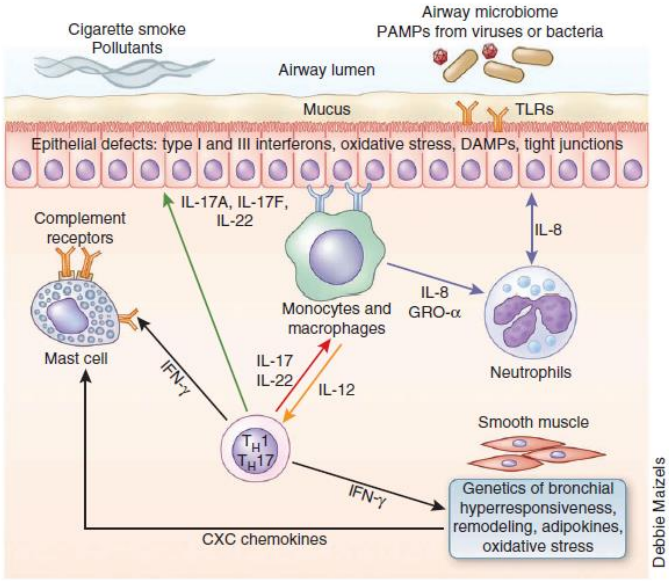


Wenzel S. Nature Medicine 2012;18:716-725
Ann Am Thorac Soc Vol 10, Supplement, pp S118–S124, Dec 2013

Evolving concept of asthma

Eosinophilic and neutrophilic asthmatic inflammation



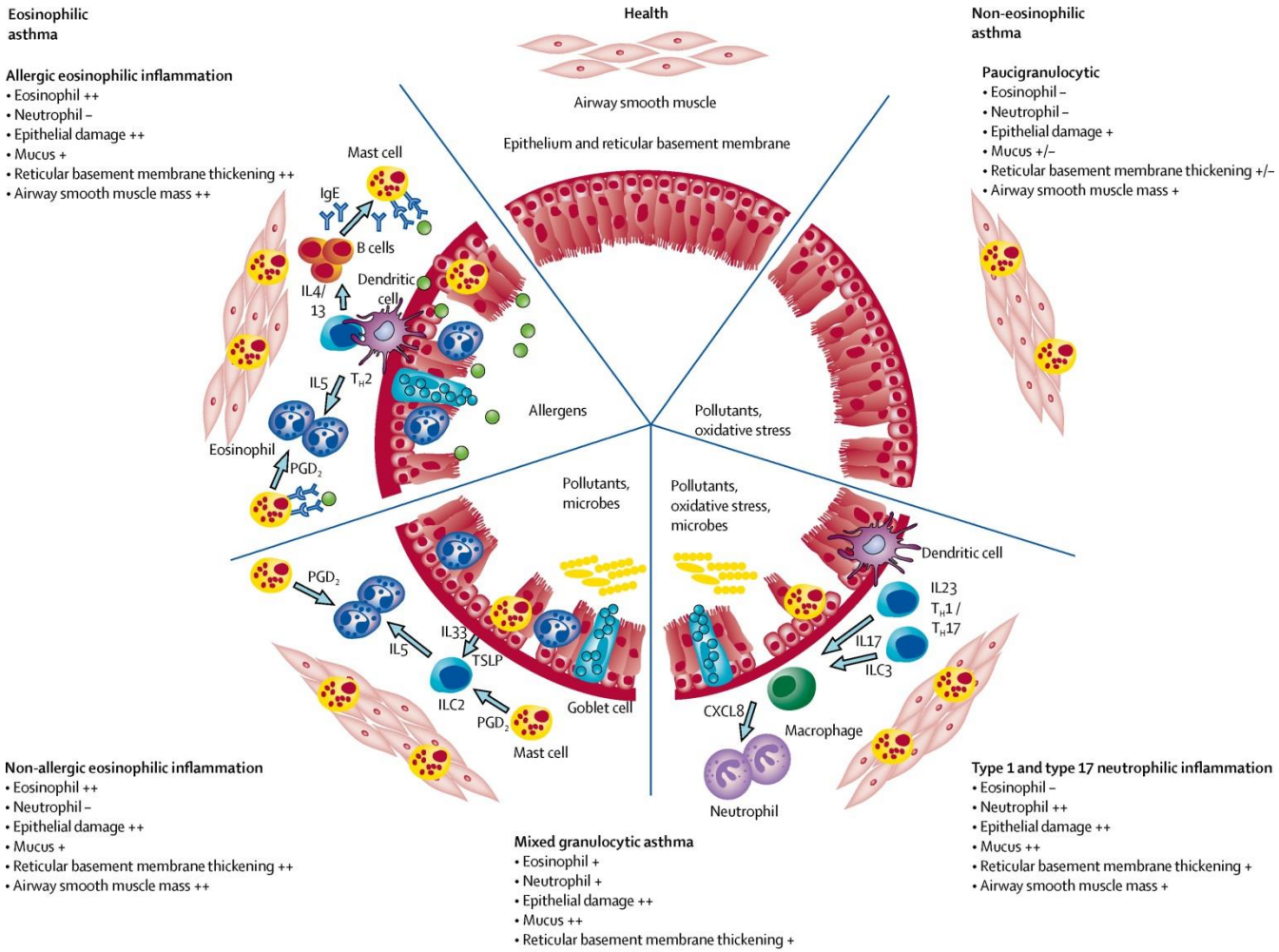


- **Eosinophilia seems to be present in the early-onset/allergic asthma phenotype**
- **Neutrophilic inflammation had not previously been reported in milder asthma**

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

Heterogeneity in asthma

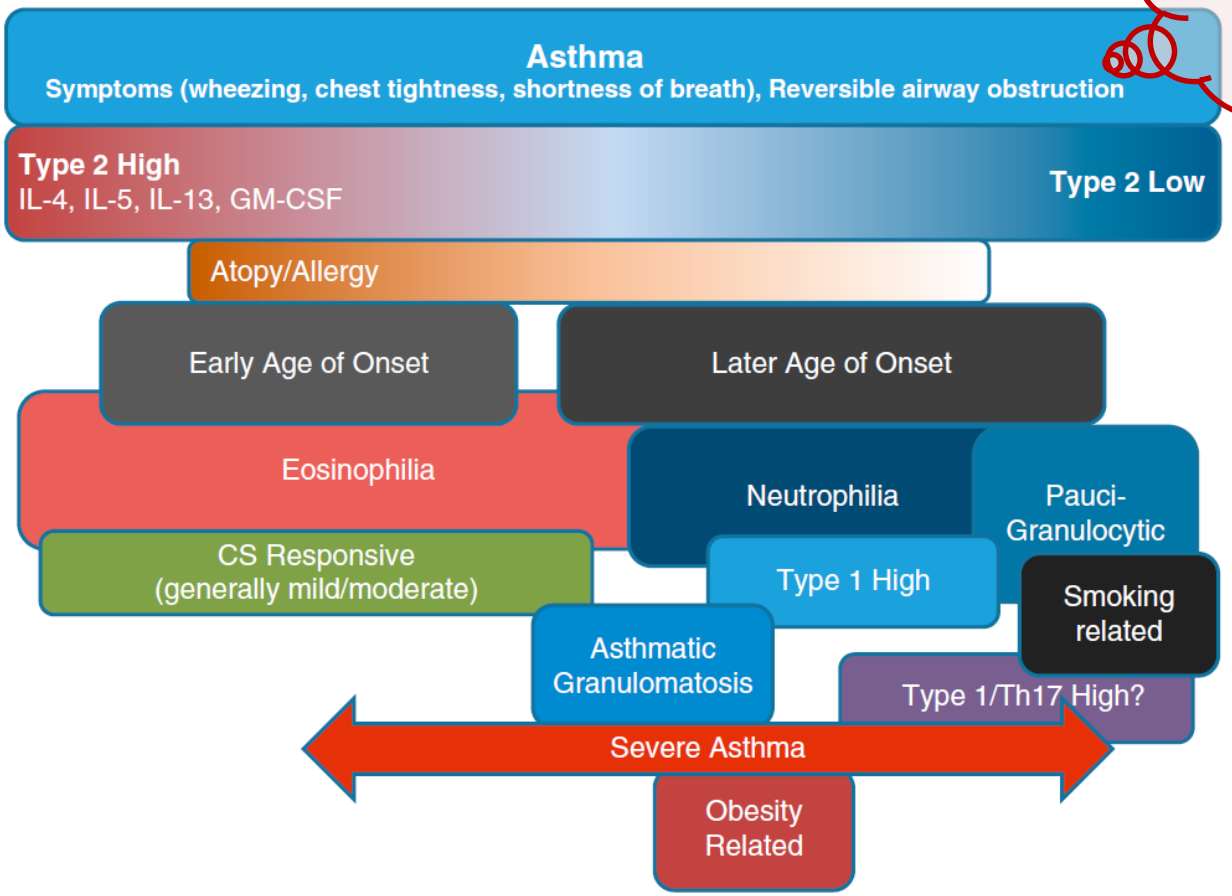


The Lancet 2018 391, 783-800DOI: (10.1016/S0140-6736(17)33311-1)

Evolving concept of asthma

Approaches to identifying phenotypes/endotypes of asthma

Where is the position of **airway remodeling** appropriate?



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

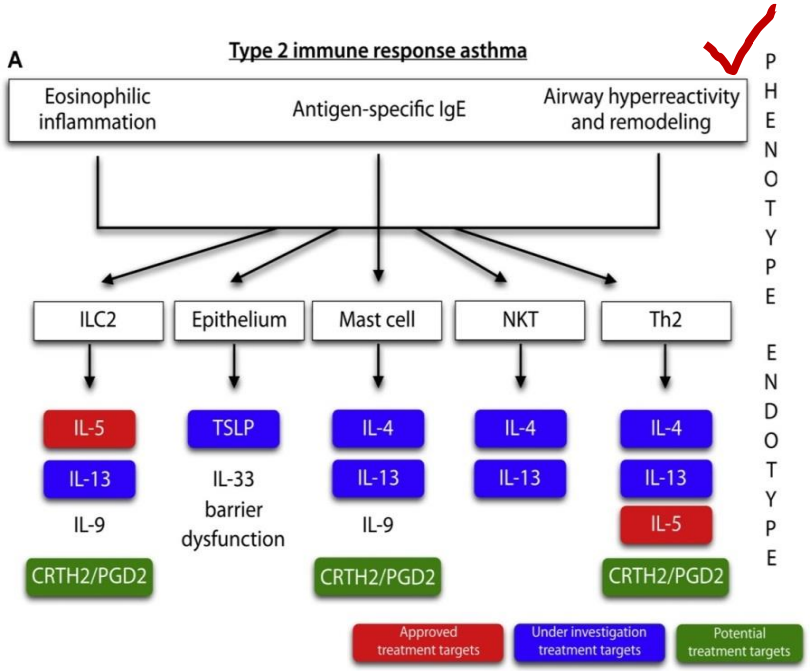
Precision medicine of asthma

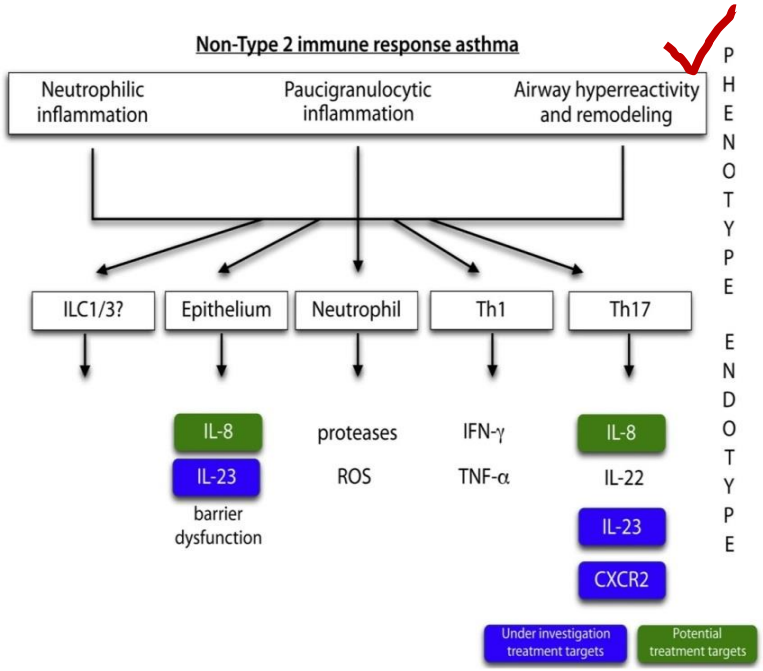
Approaches to identifying phenotypes and endotypes of asthma

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.

Airway remodeling phenotypes/endotypes

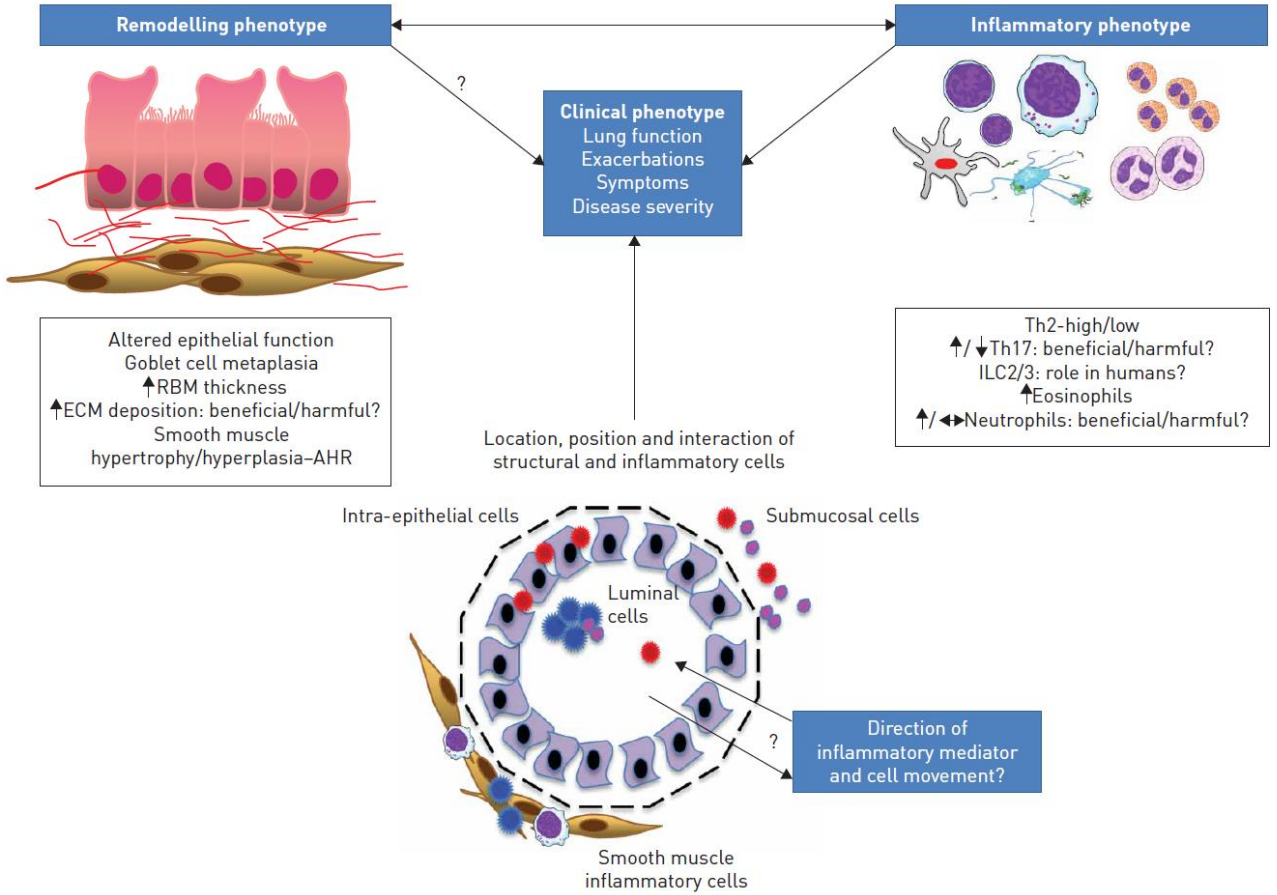


FIGURE 1 Interactions between remodelling, clinical and inflammatory phenotypes determine disease manifestation and the optimal molecular targets for intervention in the individual patient. Remodelling and inflammatory phenotypes may directly influence each other, and the location of inflammatory cells in relation to structural cells is a critical determinant of downstream effects, including mediator release and lung function. However, both remodelling and inflammation may also directly influence clinical manifestation of disease independently of each other. RBM: reticular basement membrane; ECM; extracellular matrix; AHR: airway hyperresponsiveness; Th: T-helper cell; ILC2/3: innate lymphoid cell group 2/3.

Eur Respir J. 2015 Dec;46(6):1796-804

Novel concept of airway remodeling

- **Remodeling phenotypes**
- Unbiased statistical approaches
- Clinical trials incorporating airway biopsies and assessments of airway remodeling as outcome measures.
- The remodeling phenotype of non-eosinophilic, non-inflamed and T-helper type 2 (Th2)-low patients needs to be investigated to allow discovery of effective molecular therapies.

Eur Respir J. 2015 Dec;46(6):1796-804

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2

Asthma severity and airway remodeling

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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.** This group includes the following:

- 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

Limitations of therapy targeted at inflammation

- Currently, the "molecular" approach to asthma management **is based predominantly on inflammatory parameters**.

: it is unlikely that management based on inflammatory phenotype alone is sufficient

- Inflammatory theory: **beneficial effects of steroid** on airway remodeling?

*: **Epithelial damage, vascular remodeling** vs. ECM deposition, ASM hypertrophy/hyperplasia*

- Effects of **bronchodilators** are equal in both types of inflammation (Eos & Non-Eos)

: ASM remodeling is perhaps present in both inflammations

- Adults with **severe steroid-resistant asthma** have increased circulating fibrocytes (progenitors of mesenchymal cells that are less responsive to steroids) compared with patients with milder disease

Eur Respir J. 2015 Dec;46(6):1796-804; Curr Opin Pulm Med 2018, 24:56–62; Am J Respir Crit Care Med 2012; 185: 612–619; J Allergy Clin Immunol 2015; 135: 1186–1195

AHR and Lung function vs. Inflammation

- **Detrimental effects of airway remodeling**
  - Irreversible component of airway obstruction
  - Accelerated decline in pulmonary function
  - Persistence of airway hyper-responsiveness
  - Loss of stretch-induced relaxation of smooth muscle
  - Loss of airway distensibility
  - Increased contractile response
  - Loss of elastic recoil (loss of airway-parenchymal interdependence)

- **A relationship between inflammation and lung function or persistent symptoms is less convincing**
  - Anti-IL-5 targeting agents, Anti-IgE, ICS, Eosinophils
- **Lung function or AHR is more related to remodeling** rather than inflammation

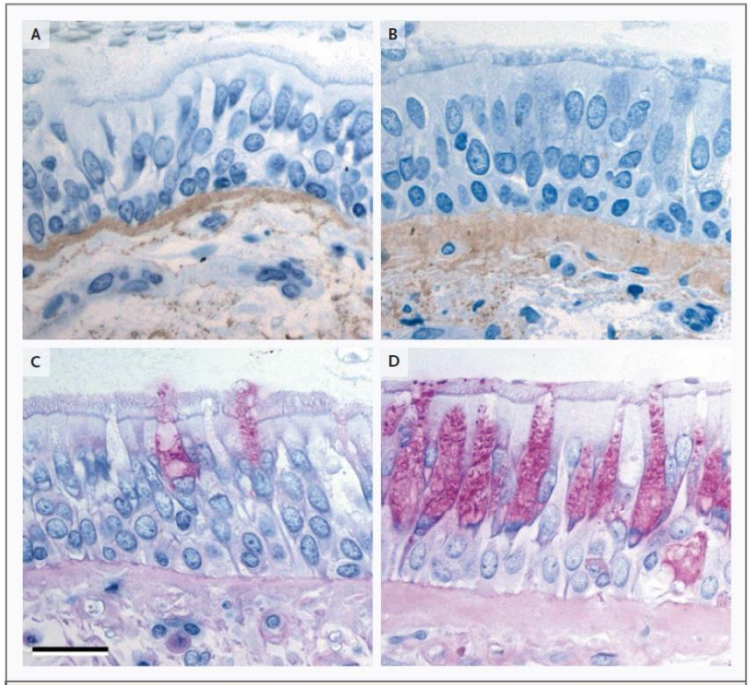
Eur Respir J. 2015 Dec;46(6):1796-804;

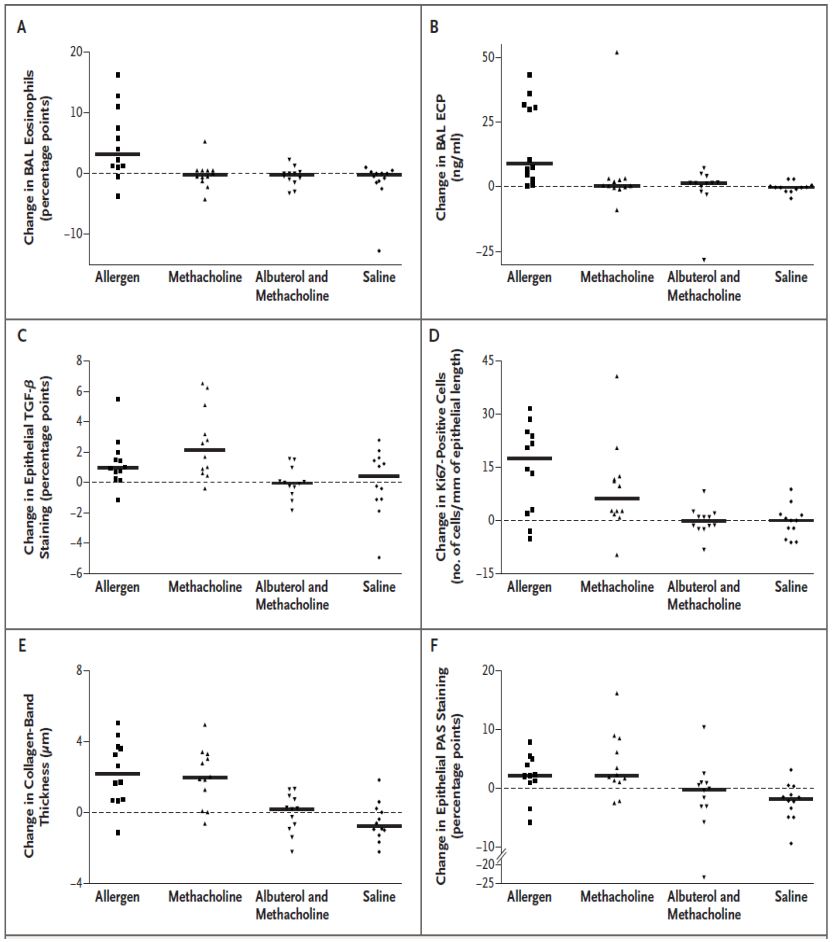
Disconnect between inflammation and remodeling

ORIGINAL ARTICLE

Effect of Bronchoconstriction on Airway Remodeling in Asthma

Christopher L. Grainge, Ph.D., Laurie C.K. Lau, Ph.D., Jonathon A. Ward, B.Sc., Valdeep Dulay, B.Sc., Gemma Lahiff, B.Sc., Susan Wilson, Ph.D., Stephen Holgate, D.M., Donna E. Davies, Ph.D., and Peter H. Howarth, D.M.





Bronchoconstriction without additional inflammation induces airway remodeling in patients with asthma.

N Engl J Med 2011;364:2006-15.

Eosinophilic inflammation vs. Neutrophilic inflammation

- **Neutrophils are pathogenic and are associated with more severe disease. However, this is becoming increasingly less certain.**
  - sputum neutrophilic inflammation is not a marker of disease severity.
- A relationship between neutrophilic inflammation and remodeling **is less apparent** than between eosinophilic inflammation and remodeling.
- Relationship between MMP-9 and neutrophils in asthma has been reported.

Eur Respir J. 2015 Dec;46(6):1796-804; Respir Physiol Neurobiol 2015; 209: 13–16; Lung 2012; 190: 459–462; J Allergy Clin Immunol 2015; 136: 323–333; Allergy 2014; 69: 898–905; Respir Res 2013; 14: 17

Clinical significance of airway remodeling in asthma

- Airway remodeling is a representative pathologic hallmark of asthmatic severity, and these structural changes are speculated to be **one of the factors that make it difficult to treat asthmatic patients** and therefore may be a target for future therapies of severe asthma.

- Prakash et al. reporting the proceedings of a new task force of the American Thoracic Society on Airway Remodeling, stressed the need for **more research in airway remodeling** and for developing, testing, and ultimately improving **drugs that target this phenomenon**.

Severe Asthma, Springer Nature Singapore Pte Ltd. 2018; Am J Respir Crit Care Med 2017 Jan; 195(2): e4–e19; Curr Opin Pulm Med 2018, 24:56–62

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3

Assessment of airway remodeling

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Quantitative approaches to assess airway remodeling

- **Histologic assessment**
  - 2D sectional analyses using light, fluorescence, birefringence, or electron microscopy
  - Quantitative stereological approaches using software program
    - Bronchial biopsy
    - Surgical resection
- **Biomarkers**
  - Sputum, blood, exhaled gas, tissues….
- **Radiologic assessment**
  - HRCT, MRI
  - Quantitative CT
- **Forced oscillation technique**
  - Airway distensibility
- **New bronchoscopic technique**
  - Endobronchial ultrasound (EBUS)
  - EB-optical coherence tomography (EB-OCT)
- **Positron emission tomography (PET)**

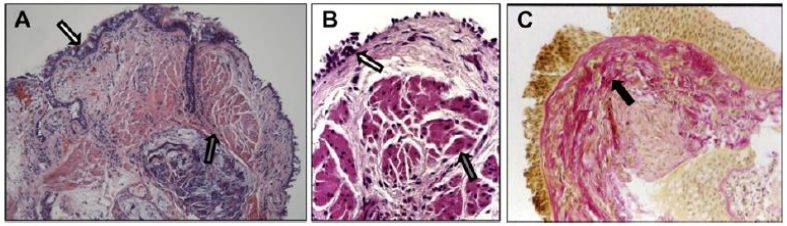
Cell Tissue Res (2017) 367:551–569
Curr Opin Pulm Med 2018, 24:56–62

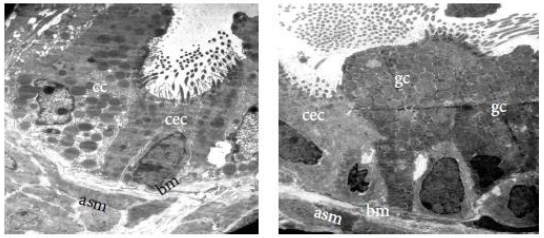
Histologic assessment of airway remodelling

- 2D sectional analyses using light, fluorescence or electron microscopy

: initial approaching methods, general

: limitation for assessment of real airway structures





Normal airway Asthmatic airway

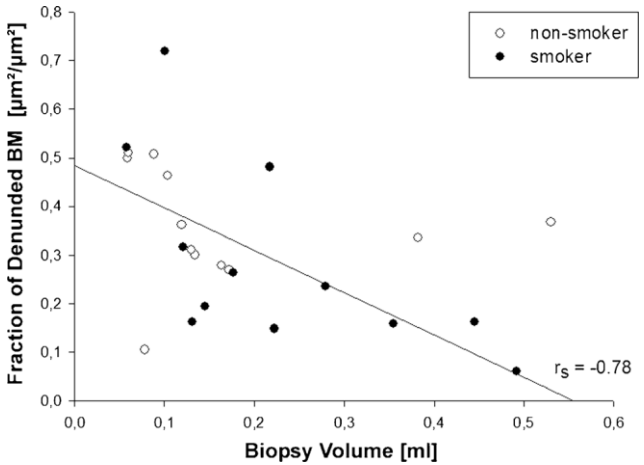
: When two-dimensional (2D) sections are used for quantitative analysis, only incomplete information about the 3D structure are obtained, which bears a high risk of misinterpretations and false conclusions

- Quantitative stereological approaches using software program
  - Bronchial biopsy
  - Surgical resection

Histologic assessment of airway remodelling

- Quantitative **stereological approaches** using software program

  : A few examples could illustrate that using quantitative stereological approaches may challenge some generally accepted views.



The smaller the biopsy, the more mechanical forces may affect the tissues during collection and embedding, which supports the notion that epithelial desquamation is highly prone to artefactual damage.

- RBM thickness as represented in microscopic sections strongly depends on how much the sectioning angle deviates from the ideal situation of a section normal to the RBM surface.

- Although RBM was significantly thicker in asthmatics than in healthy subjects, the measurements made by using design-based stereology were approximately 30% smaller than measurements made with the two classical procedures.

Figure by courtesy of Dr. V.A. Bratu, modified
from Bratu (2008); Fig. 3.4c; Cell Tissue Res (2017) 367:551–569; J Allergy Clin Immunol 112:1243–5; Am J Respir Crit Care Med 181:394–418

Biomarkers

- TIMP/MMP-9 ratio in sputum supernatant
- Blood fibrocytes
- Serum periostin
- FeNO
- Eosinophil in sputum
- Galectin-3
- Others: VEGF, TGF-β

: non-invasive but imperfect markers

Radiologic assessment

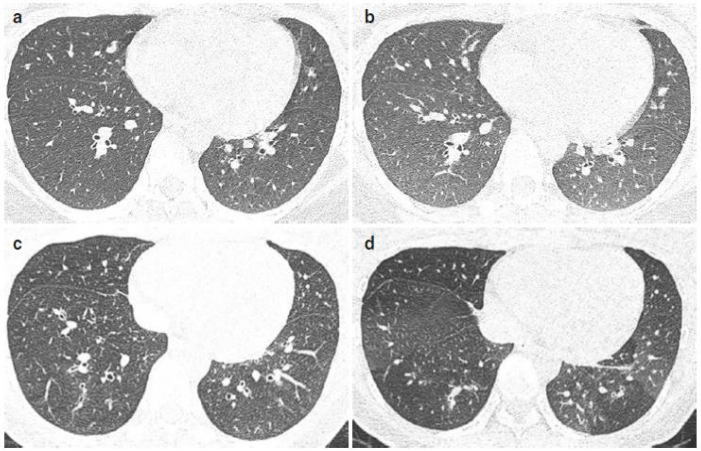
- **HRCT**

: repeatable and accurate tool for noninvasive assessment of proximal airway structural changes in patient with severe asthma.

- **Bronchial wall thickening** (BWT, WA%) – about 60%
- Cylindrical bronchiectasis – about 42%
- Mucoid impaction in the large bronchi
- Thick linear opacity or small centrilobular opacities
- Areas of decreased attenuation (air trapping)

Diagnosis

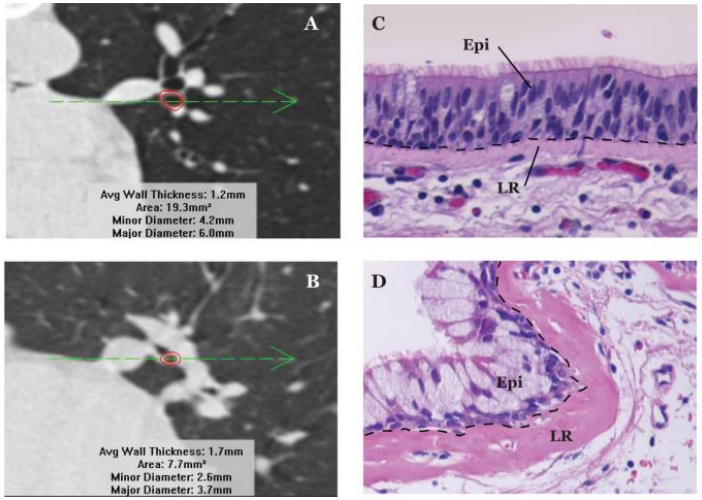
10 years later

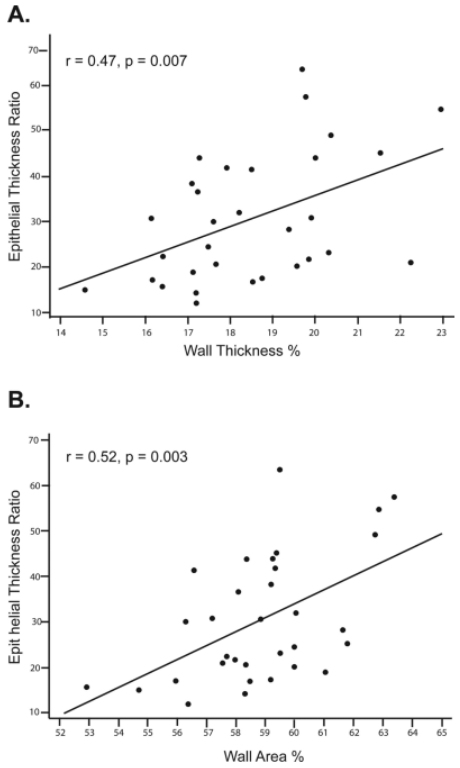


Severe Asthma, Springer Nature Singapore Pte Ltd. 2018; Thorax 2010;65:775-81.

Radiologic assessment

- **Chest CT (HRCT, MDCT)**
- CT of the chest is not indicated in the routine management of asthma.
- WA% and WT percentage (WT%) measured by using CT were increased in patients with severe asthma and correlated with airway epithelial thickness on endobronchial biopsy specimens.





Radiologic assessment

ORIGINAL ARTICLE

Low Attenuation Area Is Associated with Airflow Limitation and Airway Hyperresponsiveness

KA YOUNG LEE, M.D.,[1] SEOUNG JU PARK, M.D.,[1] SO RI KIM, M.D.,[1] KYUNG HOON MIN, M.D.,[1] YEONG HUN CHOE, M.D.,[1] GONG YONG JIN, M.D.,[2] AND YONG CHUL LEE, M.D.[1]*

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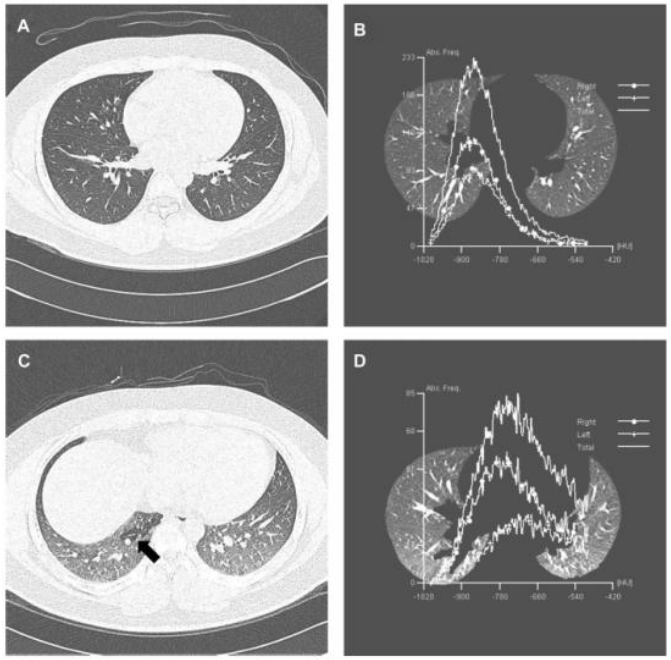
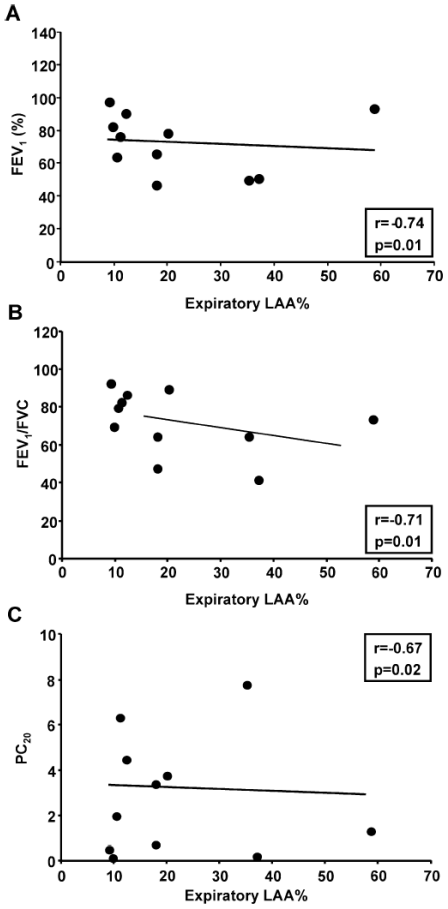




J Ashtma 45:774–779, 2008

Radiologic assessment

- **Chest QCT using specific scanner and image analysis software**

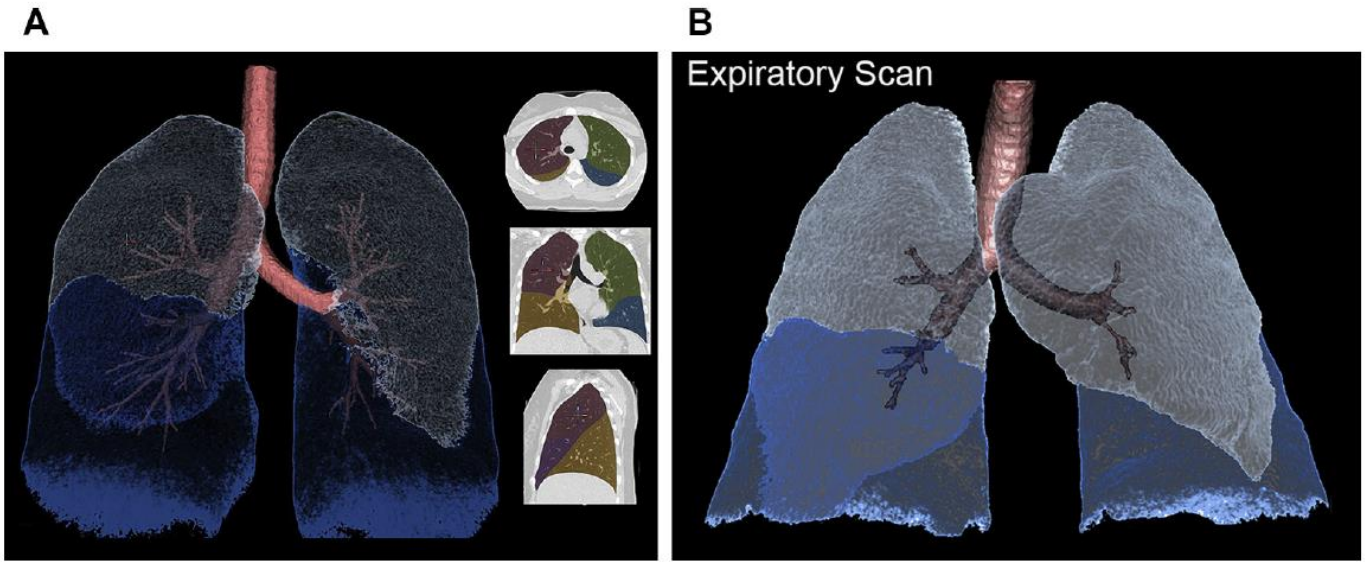


FIG 1. Chest CT for lung density. **A,** Three-dimensional volume rendition of the lung, lobes, and bronchial tree detected from a CT image of the fully inflated (total lung capacity) lung of a healthy subject. **B,** CT scan of the chest showing a similar volume rendition using the expiratory image (in this case functional residual capacity) of a patient with severe asthma. Note the areas of air trapping and pruning of the airways. Image processing was derived by using Apollo software (VIDA Diagnostics, Coralville, Iowa).

J Allergy Clin Immunol 2017;139:1-10.

Radiologic assessment

- **Chest QCT using specific scanner and image analysis software**

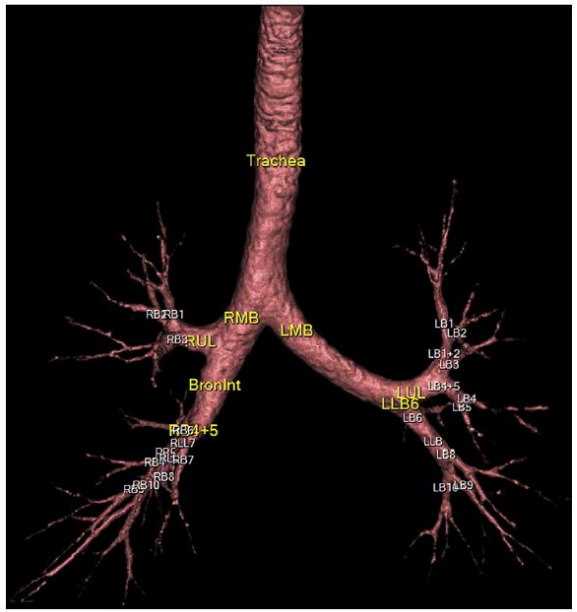


FIG 2. Three-dimensional chest CT scan of the bronchial tree. The figure demonstrates labeling of the bronchial tree out to the segmental bronchi of a patient with severe asthma, enabling each segmental bronchial WT to be measured quantitatively. Image processing was derived by using Apollo software (VIDA Diagnostics, Coralville, Iowa). *BronInt*, Bronchus intermedius; *LLB*, left lower lobe bronchus; *LMB*, left mainstem bronchus; *LUL*, left upper lobe; *RMB*, right mainstem bronchus; *RUL*, right upper lobe.

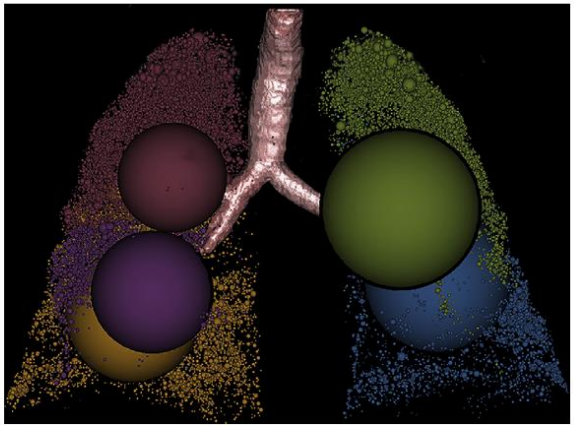
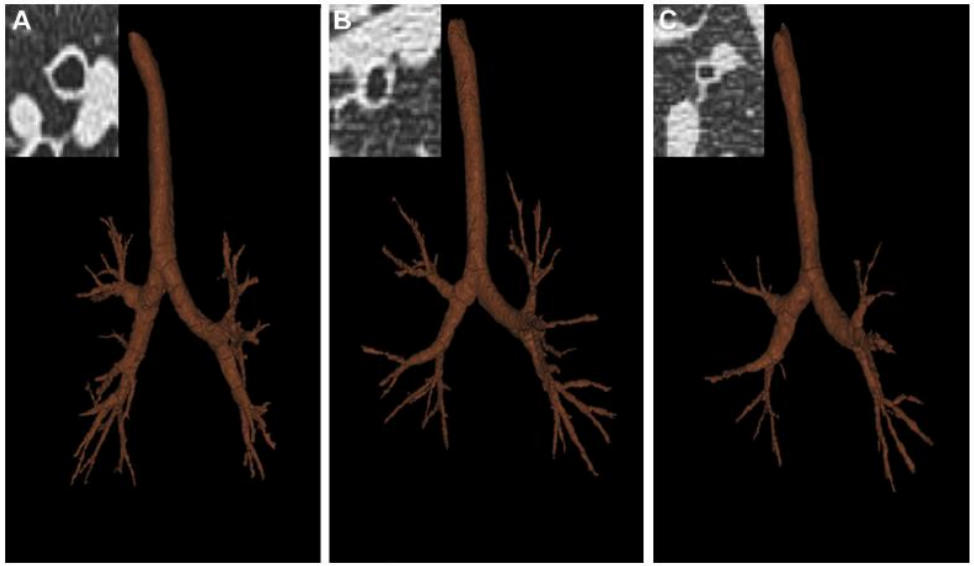


FIG 3. Chest CT scan showing air-trapping distribution. The figure demonstrates the concentration of regions determined to represent air trapping (voxels < −856) on the expiratory CT image of the same patient with severe asthma shown in Fig 1, *B*. Trapped air, which was defined as voxels within the lung field of less than −856 HU, are demonstrated by spheres proportional to the area of air trapping (volume-rendered view). Each lobe is color coded. Image processing was derived by using Apollo software (VIDA Diagnostics, Coralville, Iowa).

pulmonary function biomarkers, which include lung ventilation, quantification of airway microstructures, and gas exchange (Fig 7, *A*).[7,18,41-46] Ventilation defects observed in hyperpolarized gas magnetic resonance images of asthmatic patients (Fig 7, *B*)

Radiologic assessment

- **Chest QCT using specific scanner and image analysis software**



Cluster 1
Severe air trapping, WT, bronchial luminal dilation

Cluster 2
Moderate air trapping

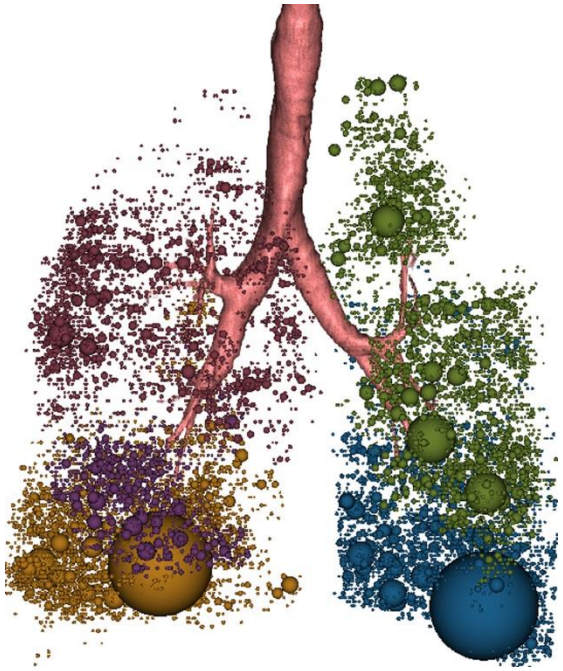
Cluster 3
Severe air trapping, bronchial luminal narrowing

- Airway remodeling with reduced luminal volume and increased percentage WV in asthma
- Not correlated with disease severity
- 3 clusters of asthma patients by index of proximal airway remodeling and air trapping: distinct clinical and radiologic features

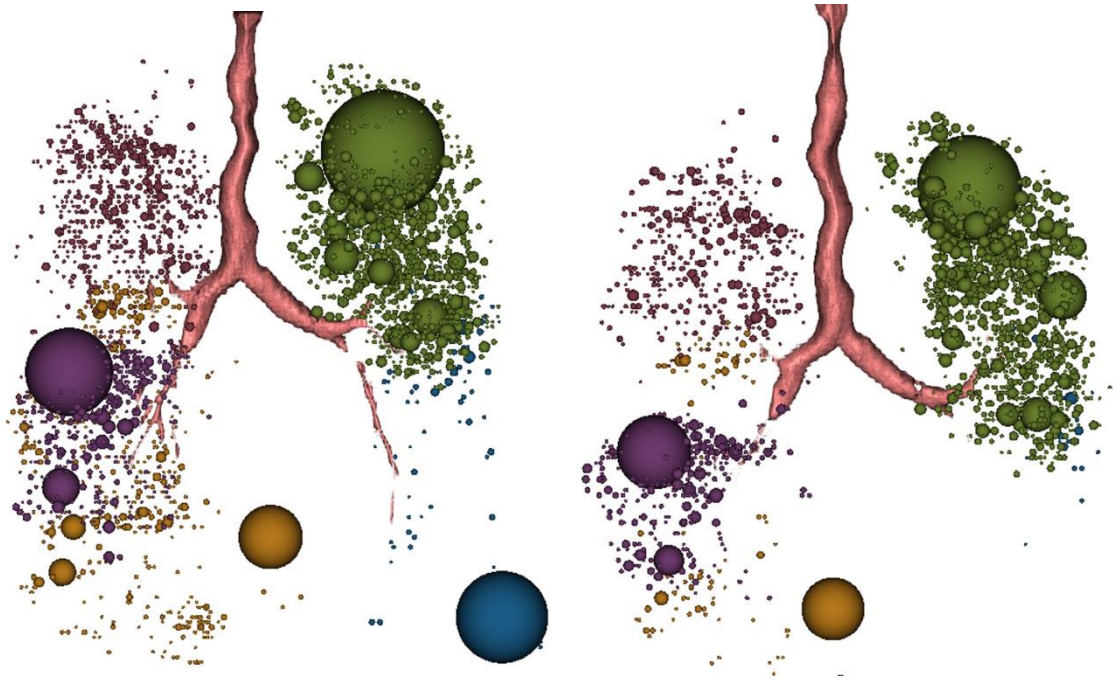
Severe Asthma, Springer Nature Singapore Pte Ltd. 2018; J Allergy Clin Immunol 2014;133:729-38.

Radiologic assessment

- **Chest QCT using specific scanner and image analysis software**



Normal subject



90/F, severe asthma

Severe Asthma, Springer Nature Singapore Pte Ltd. 2018

Radiologic assessment

- **Chest MRI**

- The **ventilation defect percentage**, as measured by using hyperpolarized ^{3}He MRI, has been shown to correlate with the clinical features of asthmatic patients, including medication requirement, airway pathology, severity, symptom score, and atopic markers.

- ^{3}He MRI can be used to measure treatment effects after bronchial thermoplasty.

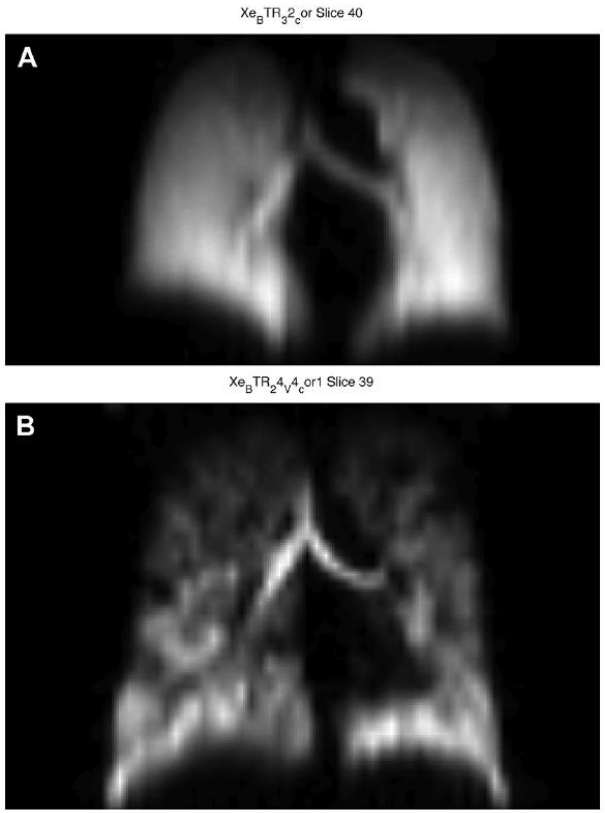


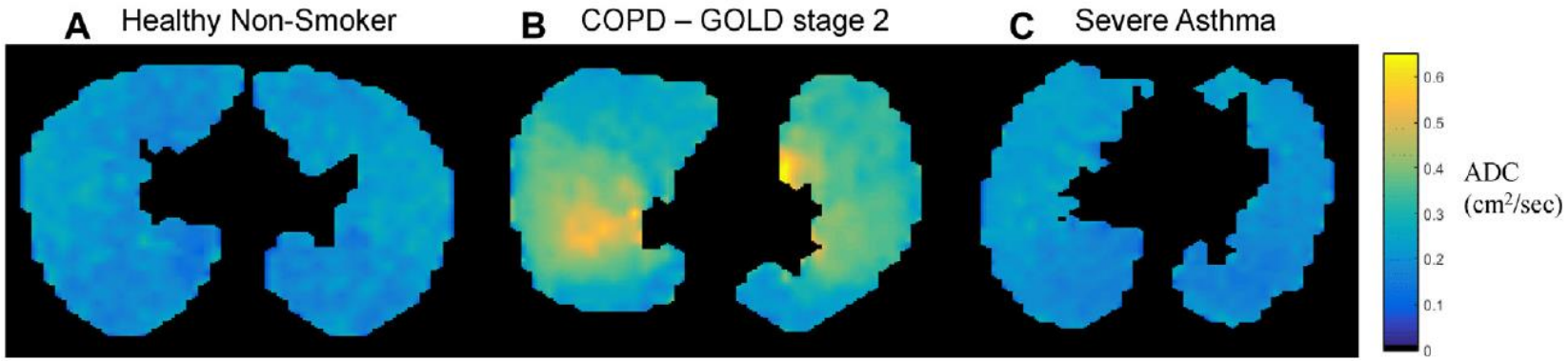
FIG 7. Lung MRI demonstrates ventilation maps based on the distribution of hyperpolarized Xe gas assessed by using magnetic resonance images of a healthy subject **(A)** and an asthmatic patient **(B)**, respectively. Note the patchy regions of poor to no ventilation in patients with severe asthma.

J Allergy Clin Immunol 2017;139:1-10.

Radiologic assessment

- **Chest MRI using apparent diffusion coefficient (ADC)**

- Regions in which the diffusive motion of gas atoms are restricted by normal alveolar walls have lower ADC values, whereas areas of increased alveolar size or alveolar destruction allow for increased diffusion and are characterized by higher ADC values
- Asthmatic patients have been found to have small focal areas of increased ADC values that might represent air trapping.



J Allergy Clin Immunol 2017;139:1-10.

Forced oscillation technique

- Airway distensibility
- Forced oscillation technique (FOT) provides such an index by measuring the change in respiratory system conductance over the corresponding change in lung volume.

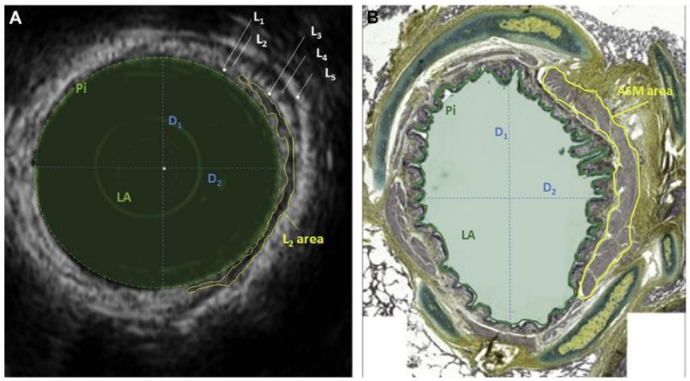
- Mailhot-arouche et al. confirmed the reproducibility of airway distensibility measurements by FOT and suggested a simplified method to increase feasibility.

Front Physiol 2017; 8:223; Curr Opin Pulm Med 2018, 24:56–62

New bronchoscopic technique

- **EBUS (Endobronchial ultrasonography)**

: Radial EBUS can access airways as small as 4 mm in internal diameter, and it can visualize multiple layers of the airway wall



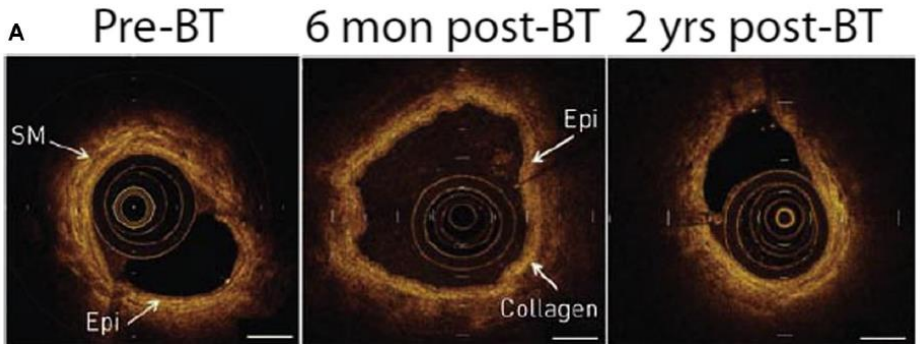
- Like OCT, EBUS offers the ability to monitor serial changes without exposure to ionizing radiation.

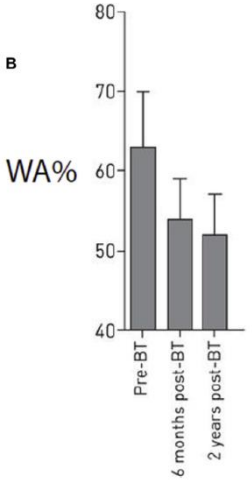
J Allergy Clin Immunol 2017;139:1-10.

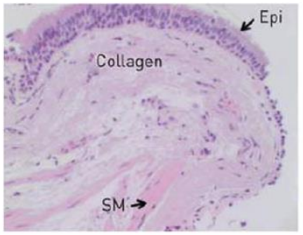
New bronchoscopic technique

- **EB-optical coherence tomography (OCT)**

: a tool that produces a 2-dimensional image of the airway wall by using near-infrared light through a fiberoptic catheter.







- OCT can be used to monitor serial airway changes after a therapeutic intervention, such as bronchial thermoplasty, while avoiding cumulative radiation exposure

J Allergy Clin Immunol 2017;139:1-10.

Positron emission tomography (PET)

- **^{13}NN-PET**

- Measurement of lung ventilation
- Considerable limitation; might not reflect tidal breathing

- **^{18}FDG-PET**

- An imaging biomarker of lung inflammation in asthmatic patients (esp. neutrophilic inflammtion)
- to assess an inflammatory response points to its potential as a tool to better understand asthma pathogenesis, phenotype differences, and responses to anti-inflammatory therapies

J Allergy Clin Immunol 2011; 128:467-78.; Am Rev Respir Dis 1989;139:818-40.; Mol Pharm 2006;3:488-95.

Summary of imaging assessment for airway remodeling

TABLE I. Asthma imaging summary

Modality	Structural assessment	Functional assessment	Clinical utility	Disadvantages
CT	Detailed assessment ● Airway tree ● Vascular tree ● Lung parenchyma	● Regional ventilation ● Parenchymal perfusion	● Noninvasive measure of airway remodeling ● Biomarker to assess response to therapy	● Radiation exposure prohibits serial examinations
MRI	● Lung microstructure using ADC ● Combined with CT for detailed structural evaluation	● High spatial resolution evaluation of regional ventilation ● Gas exchange	● Biomarker to assess response to therapy ● Assessment of ventilation/perfusion ratio	● Less structural detail than CT ● Limited to specialized MRI centers
EBUS	● Access airways as small as 4 mm with visualization of multiple layers of airway wall	● None	● Monitor serial airways changes	● Requires bronchoscopy ● No functional assessment ● Standards not yet established
OCT	● Two-dimensional images of airway wall with spatial resolution of 1-15 μm and penetration of 2-4 mm	● None	● Microscopic view of WT and subepithelial matrix ● Monitor serial airway changes	● Requires bronchoscopy ● Subject to respiratory cycle movement ● Standards not yet established
PET	● Combine with CT for detailed structural evaluation	● Pulmonary inflammation ● Ventilation/perfusion	● Response to anti-inflammatory therapies ● Evaluate inhaled drug delivery	● Limited spatial resolution ● Radiation exposure

J Allergy Clin Immunol 2017;139:1-10.

Current status of assessment of airway remodeling

- Classic histologic assessment is used in the majority of researches and clinical trials.
- Biomarkers are still imperfect.
- Imaging assessment is emerging as a new useful tool for airway remodeling.
- Several imaging modalities are clinically available for use in evaluation of asthmatic patients.
- CT, MRI, and PET are among the modalities that can provide detailed assessment of lung structure and function.
- Measurements from imaging, such as WT, air trapping, and ventilation defects, can serve as biomarkers and be used to assess response to new therapies.

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4

Prevention and treatment for airway remodeling

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Prevention of airway remodelling in asthma

- Still **do not know** how efficiently prevent airway remodeling in asthma
- A large part of airway remodeling seems to happen before the development of symptomatic asthma or early in life Imaging assessment is emerging as a new useful tool for airway remodeling.
- Features of remodeling may vary according to age and type of asthma.
- **Cessation of exposure to environmental sensitizers** can lead to a mild reduction in airway remodeling.
- A prevention or reduction of some airway remodeling features with **corticosteroids**, although these changes are usually modest

Curr Opin Pulm Med 2018, 24:56–62; Clin Exp Allergy 2005; 35:1565–1571; Ann Clin Lab Sci 2004; 34:138–142.

Current therapeutic targets for asthma and their effects on airway remodeling

- **β2-agonists**
  - Limited effect on airway remodeling.
  - Combination therapy with inhaled corticosteroid limits angiogenesis and fibroblast proliferation.
- **ICS (Inhaled corticosteroid):** *limited and controversial data*
  - Mixed anti-proliferative actions on airway smooth muscle cells and human fibroblasts
  - Reduced mucin secretion and limited extracellular matrix deposition
- **CysLTRA (cysteinyl leukotriene receptor antagonist)**
  - Moderate effect on airway smooth muscle mass, goblet cell metaplasia, and sub-epithelial collagen deposition
  - Decreased accumulation of fibroblasts in lungs
- **Muscarinic receptor antagonist**
  - A robust ability in preventing AR in OVA-induced asthma model
- **Bronchial thermoplasty**
  - to improve quality of life for severe asthmatics in the short term

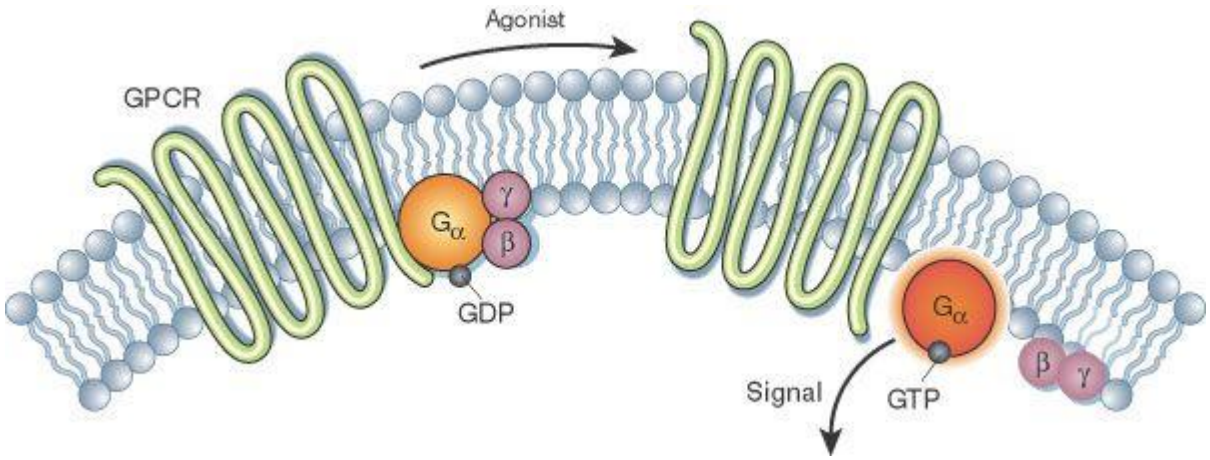
New targets and approaches for airway remodeling

Class of therapeutic drugs	Target	Potential effect on airway remodeling (AR)
G protein–coupled receptor modulators	E-prostanoid receptors	Suppression of airway smooth muscle (ASM) proliferation[72–74].
	Bitter taste receptors (TAS2Rs)	Regulation of ASM proliferation[81,82]. Reversal of allergen-induced AR features, including ASM mass[83]. Alteration of mitochondrial function and induction of autophagy[84].
Biologics	Interleukin-5 (IL-5) cytokine	Reduced subepithelial fibrosis and extracellular matrix (ECM) deposition[85,86].
	Immunoglobulin E	Reduced thickening of reticular lamina[87].
Mitogen-activated protein kinase (MAPK) inhibitors	MEK1 (MAPK kinase)	Regulation of mucus secretion[88,89].
	p38	Reduced ASM mass and goblet cell metaplasia[90].
	c-Jun N-terminal kinases (JNKs)	Reduced mucus secretion and expansion of goblet cells[91,92]. Reduced proliferation of ASM and epithelial cells[93].
	Transforming growth factor-beta-activated kinase 1 (TAK1)	Reduced synthesis of IL-8 in ASM cells and reduced proliferation[94,95].
Receptor tyrosine kinase inhibitors	Epidermal growth factor receptor	Reduced proliferation of ASM and epithelial cells[96–98].
		Regulation of mucus secretion[99–102].
		Reduced ASM thickening and goblet cell metaplasia[103].
	Platelet-derived growth factor receptor	Reduced ASM proliferation[104].
	Stem cell growth factor receptor (c-kit)	Attenuated collagen accumulation in lungs[105].
Non-receptor tyrosine kinase inhibitors	Spleen tyrosine kinase (Syk)	Reduced bronchial edema[106].
	Janus kinase (JAK)	Reduced expression of Gob-5[107].
Other kinase inhibitors	TGF-β receptor type I (T-βRI) kinase	Diminished collagen deposition and reduced proliferation of ASM and epithelial cells in lungs[108].
	Rho-associated protein kinase (ROCK)	Curtailed ECM remodeling process[109].
Phosphodiesterase (PDE) inhibitors	PDEs	Marked reduction in subepithelial fibrosis and epithelial layer thickening[110]. Reduced proliferation of ASM[111].

F1000Research 2018, 7(F1000 Faculty Rev):680

G protein–coupled receptor (GPCR) ligands

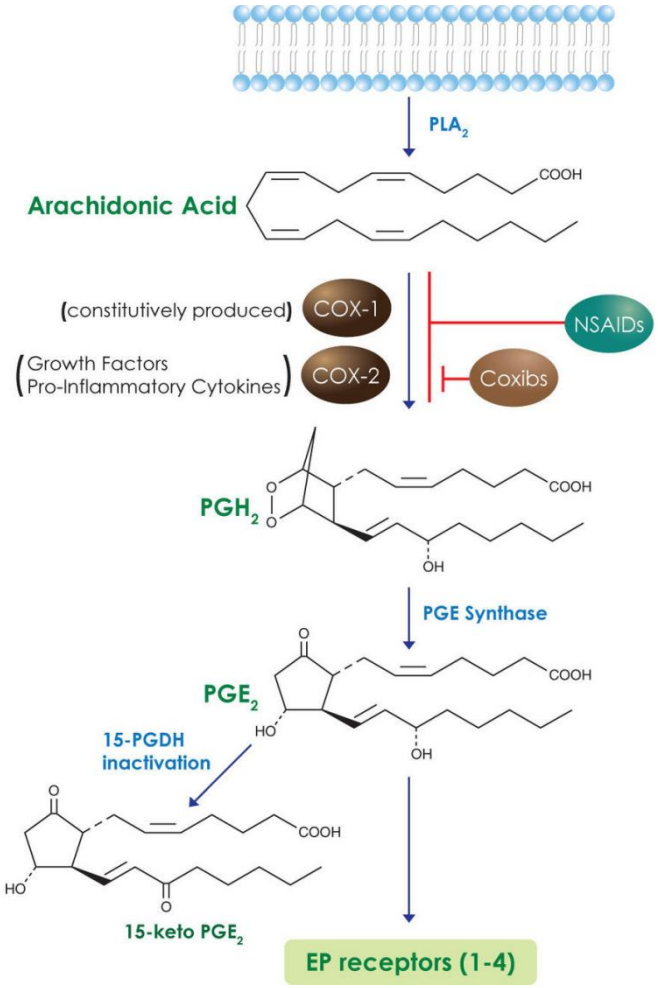
- **β-adrenergic receptor, muscarinic anticholinergic receptor, cysLT receptor are included in GPCR.**

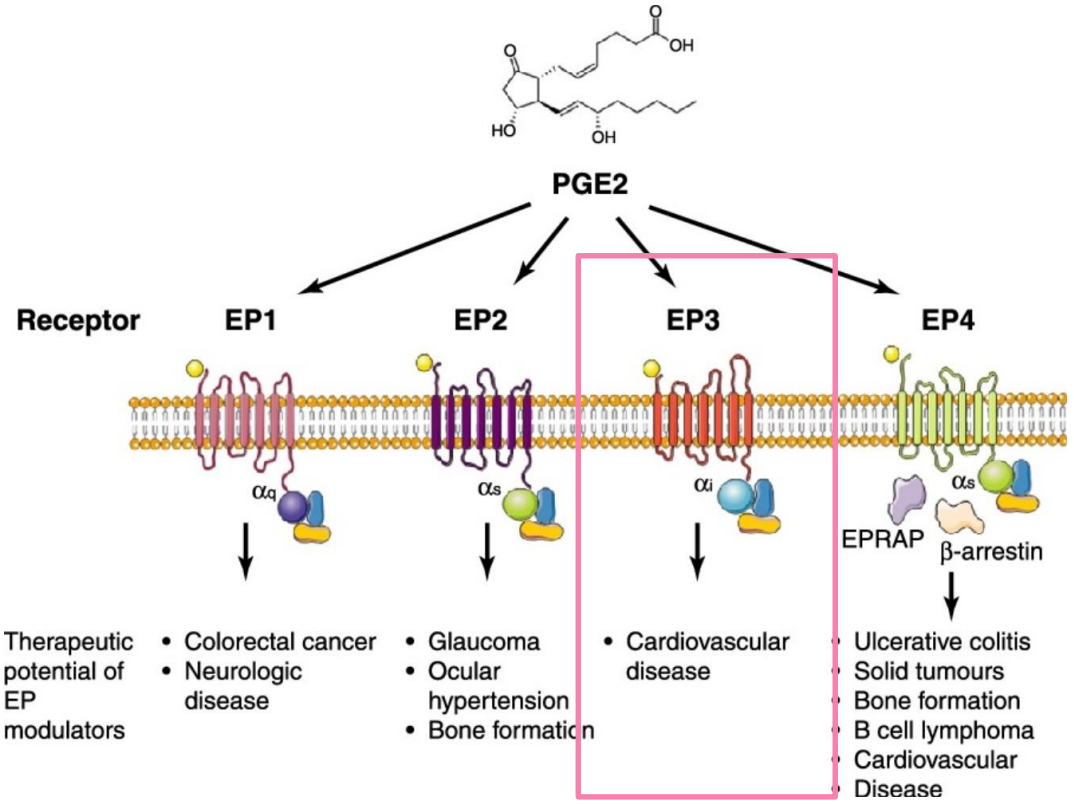


- E-prostanoid receptor agonists
- Bitter taste receptors

G protein–coupled receptor (GPCR) ligands

E-prostanoid receptor agonists





Inhibition for ASM proliferation

F1000Research 2018, 7(F1000 Faculty Rev):680; Discovery Drug Today 2017;22:57-71; Br J Pharmacol. 1998; 125(5): 1102–8.; Mol Pharmacol. 2008; 73(2): 566–74.; FASEB J. 2011; 25(1): 389–97.

G protein–coupled receptor (GPCR) ligands

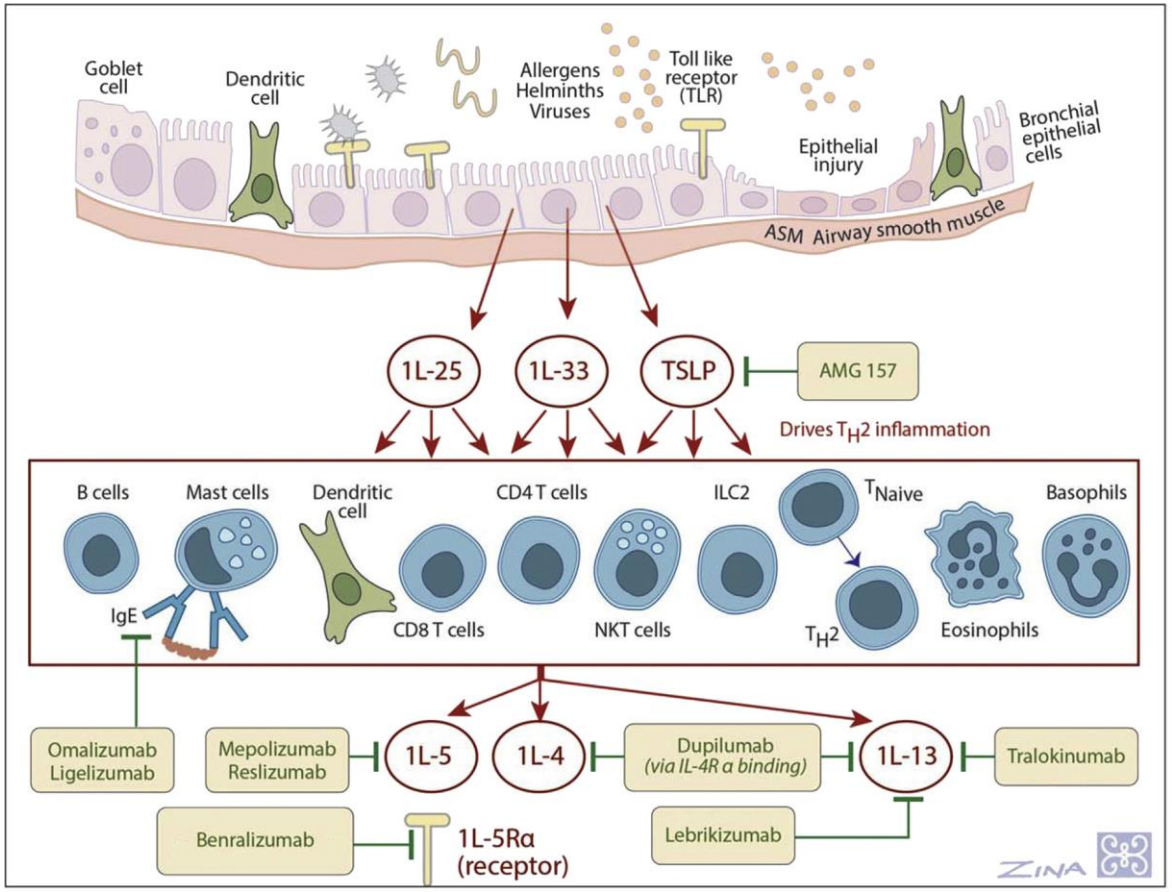
Bitter taste receptors (TAS2R) agonist (Quinine, Chloroquine)

- **Regulation of ASM proliferation by inhibiting**
  - (1) the growth factor–activated protein kinase B (Akt) phosphorylation;
  - (2) transcription factors AP-1, STAT3, E2 factor, and NFAT
  - (3) genes associated with cell cycle progression.

- **Reversal of allergen-induced AR features, including ASM mass.**
- **Alteration of mitochondrial function and induction of autophagy**
- **Modulation of function of ciliated epithelium: increase cilia movement**

F1000Research 2018, 7(F1000 Faculty Rev):680; Sci Rep. 2017; 7: 46166; Science. 2009; 325(5944): 1131–4.

Biologics

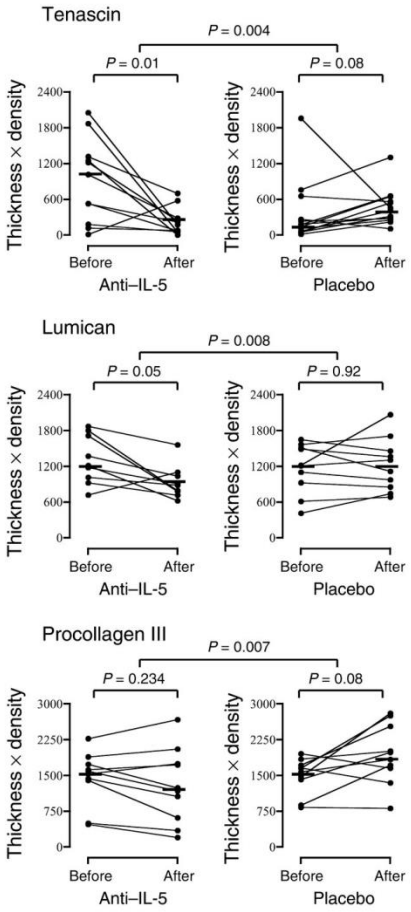


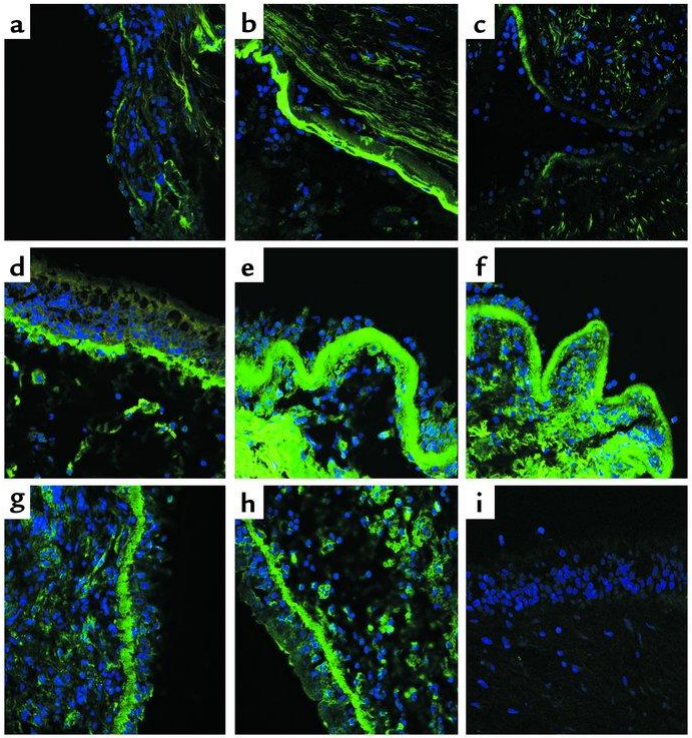
Targeting key cytokines with specific antibodies-biologics, including antibodies targeting interleukin-4 (IL-4), IL-5, and IL-13—can significantly limit recruitment of inflammatory cells to the lungs or blunt their pleiotropic effects in severe asthma.

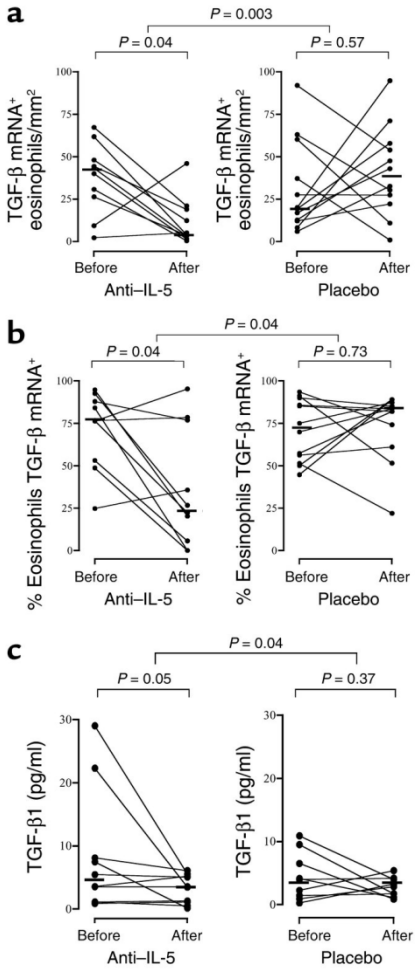
J Allergy Clin Immunol Pract 2017;5:S1-S14;

Biologics: IL-5

- **Anti-IL-5 (Mepolizumab): mild atopic asthmatics**
  - Reduced sub-epithelial fibrosis and extracellular matrix (ECM) deposition



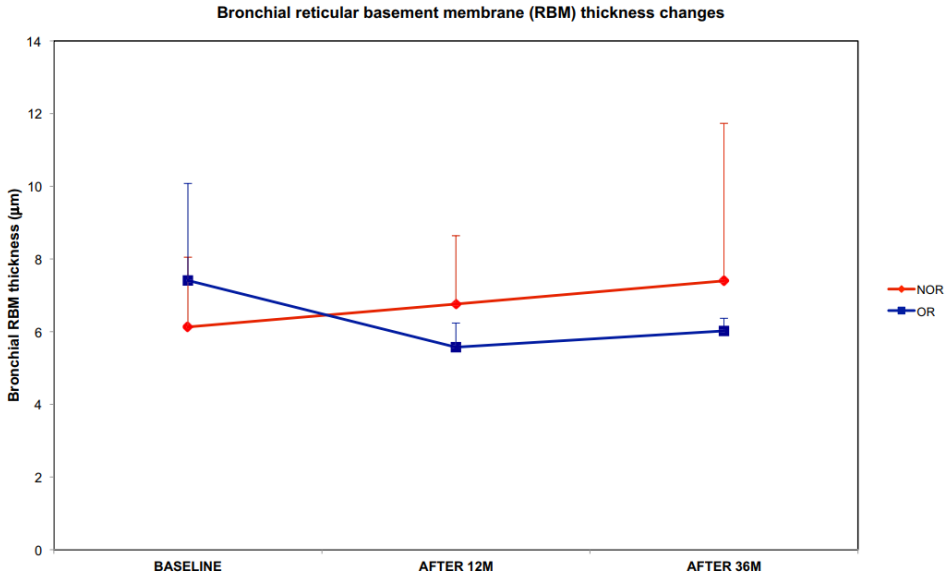


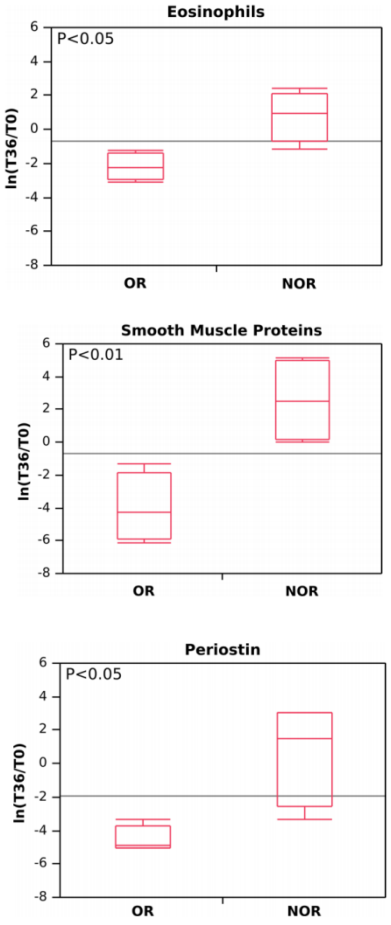


J Clin Invest. 2003; 112(7): 1029–36; Am J Respir Cell Mol Biol. 2000; 23(2): 241–6.

Biologics: IgE

- **Anti-IgE (Omalizumab): severe atopic asthmatics**
  - Reduced the thickening of the reticular lamina





Clin Transl Allergy. 2017; 7: 6.

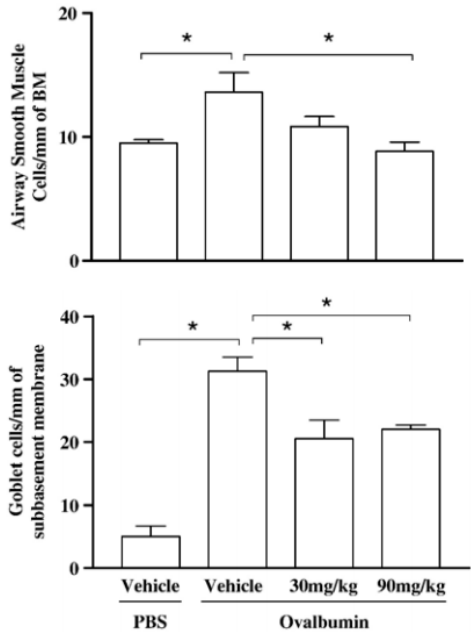
Kinase inhibitors

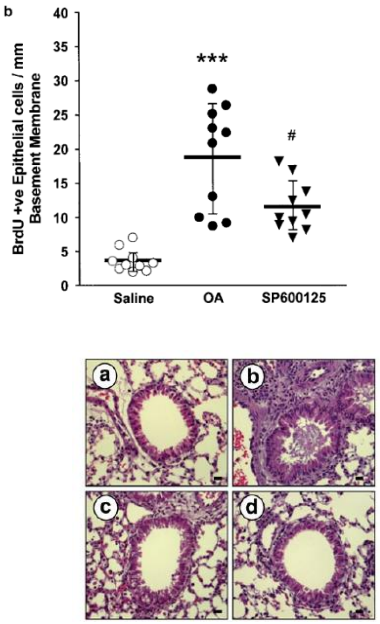
- **Kinases**
  - Protein kinase
    - Serine/threonine kinase
      - PKA, PKG, PKC, CaM kinase, PKB, receptor ser/thre kinase (**MAPK**, **TGF-beta** R)…
    - Tyrosine kinase
      - **Receptor tyrosine kinase**: PDGFR, EGFR, IGF1R, SCFR, VEGFR….
      - Non-receptor tyrosine kinase: JAK..
  - Lipid kinase
    - Phosphatidylinositol kinases: **PI3K**
    - Sphingosine kinases (SK)
  - Carbohydrate kinase

Kinase inhibitors

MAPK & TAK1

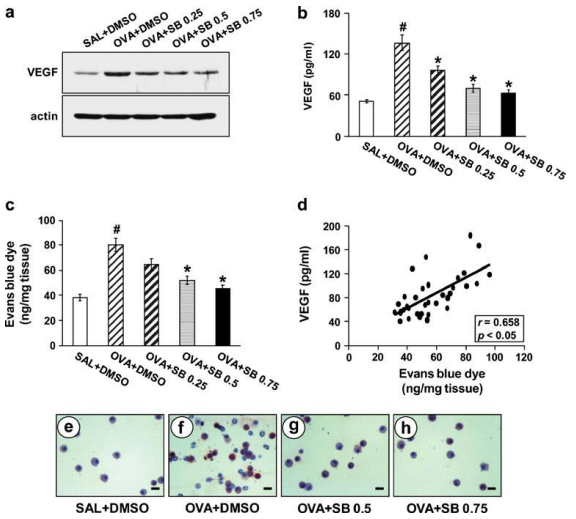
- **To date, no studies in humans have evaluated MAPK inhibitors.**
  - **ERK, p38, JNK, TAK1**
    - Regulation of mucus secretion, ASM mass, goblet cell metaplasia, epithelial cell proliferation, vascular dysfunction, IL-8, VEGF production





Inhibition of p38 MAPK Reduces Expression of Vascular Endothelial Growth Factor in Allergic Airway Disease

So Ri Kim · Kyung Sun Lee · Seoung Ju Park · Myung Shin Jeon · Yong Chul Lee



Eur J Pharmacol. 2006; 544(1–3): 160–7; Eur J Pharmacol. 2005; 506(3): 273–83; Br J Pharmacol. 2003; 140(8): 1373–80; J Clin Immunol. 2012 Jun;32(3):574-86

Kinase inhibitors

RTK

- **EGFR inhibitors**
  - Reduced proliferation of ASM and epithelial cells
  - Regulation of mucus secretion
  - Reduced ASM thickening and goblet cell metaplasia

  : Although these observations are encouraging, some inhibitors of EGFR have failed to produce similar outcomes in clinical studies

- **PDGFR inhibitors**
  - Reduced ASM proliferation

  : Animal and human studies using PDGFR inhibitors that address AR are lacking.

  : Masitinib (c-kit/PDGFR inhibitor) improved outcome of corticosteroid resistant severe asthma

Kinase inhibitors

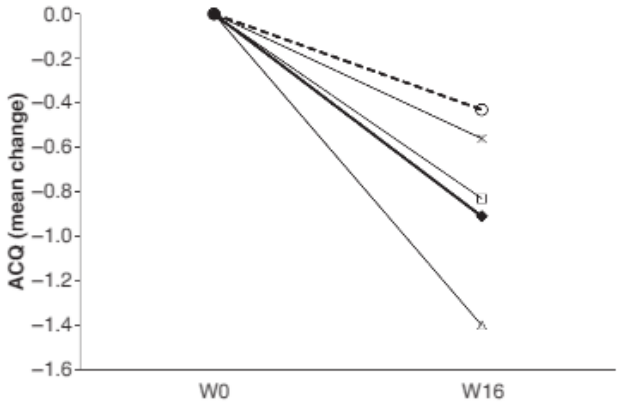
RTK

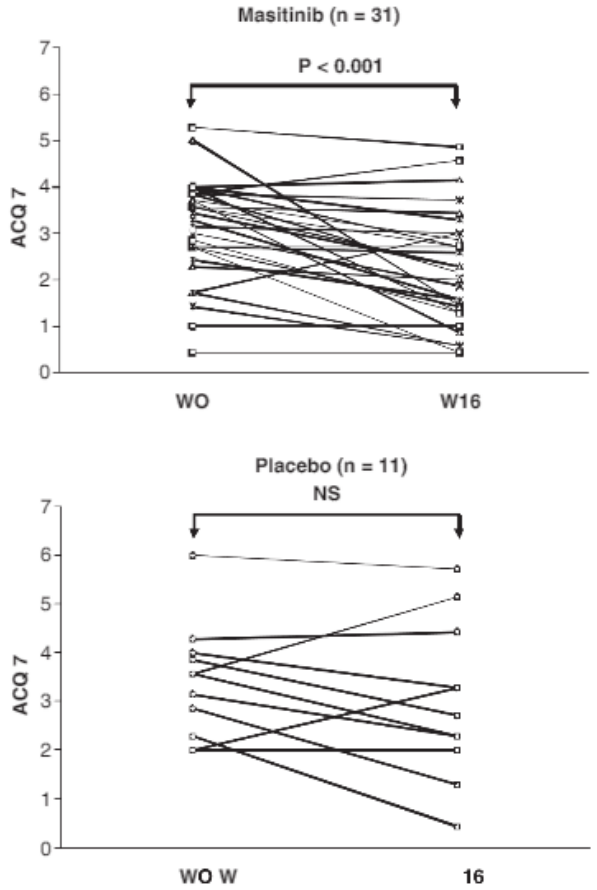
Allergy 2009: 64: 1194–1201

DOI: 10.1111/j.1398-9995.2009.

Original article

Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics





These observations suggest that c-kit and to a lesser extent PDGFR inhibition should be considered as a potential new treatment for severe asthma.

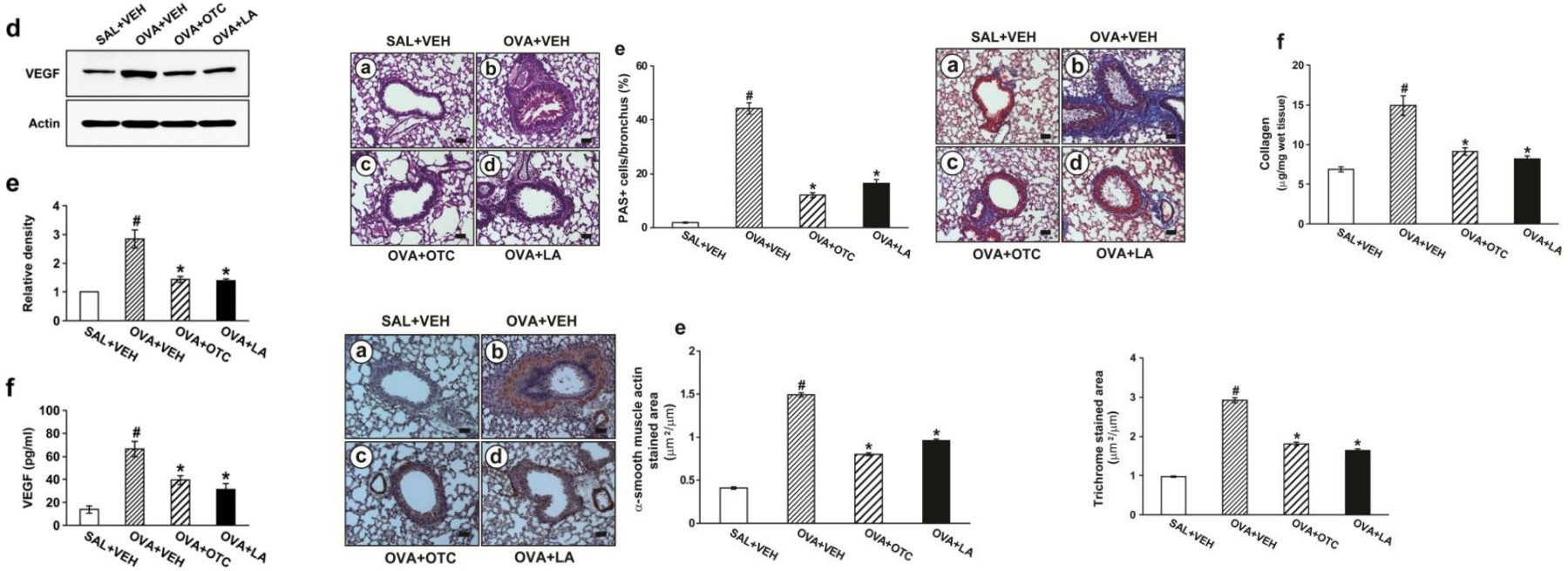
Allergy. 2009; 64(8): 1194–201.

Kinase inhibitors

RTK

- **VEGFR inhibitors**
  - An antagonist of VEGFR-1 and VEGFR-2 (SU5416) has been shown to limit inflammatory responses in animals

  : its impact on AR is unknown and studies in humans are lacking.



Int J Mol Sci. 2012;13(7):7915-37.

Kinase inhibitors

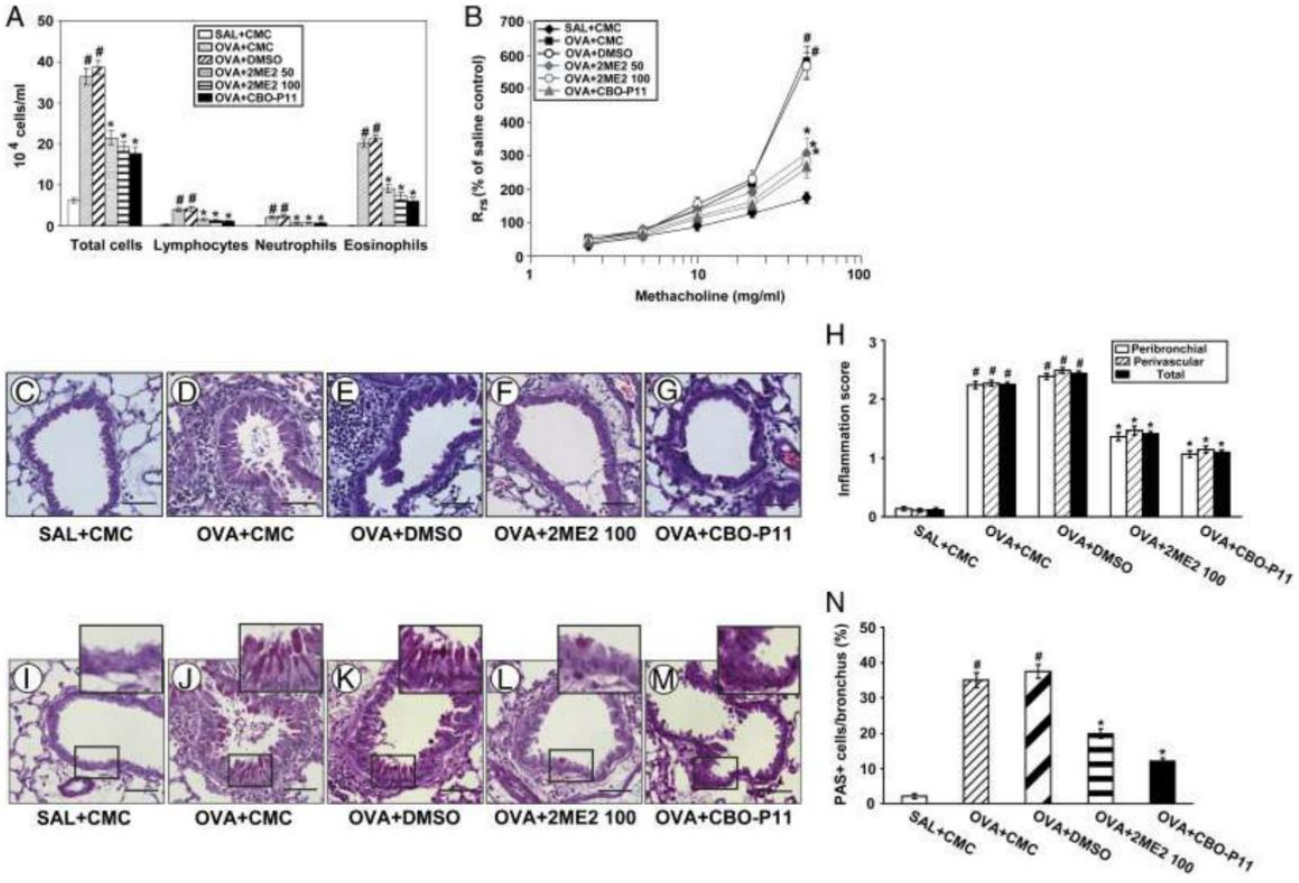
RTK

- **VEGF inhibitors: CBO-P11**

European Journal of Immunology

HIF-1α inhibition ameliorates an allergic airway disease *via* VEGF suppression in bronchial epithelium

So Ri Kim[*1], *Kyung Sun Lee*[*1], *Hee Sun Park*[2], *Seoung Ju Park*[1], *Kyung Hoon Min*[1], *Hee Moon*[1], *Kamal D. Puri*[3] *and Yong Chul Lee*[1]



Eur. J. Immunol. 2010. 40: 2858–2869

Kinase inhibitors

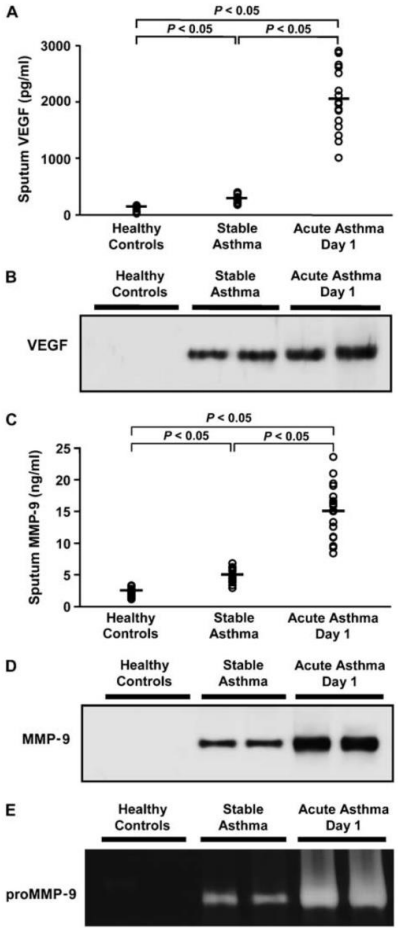
RTK

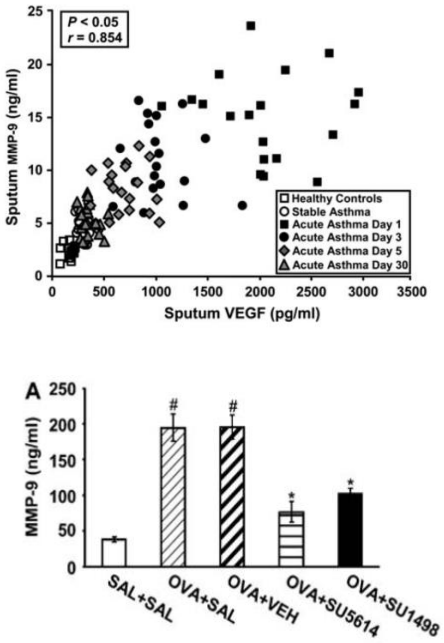
- **VEGFR inhibitors: SU5614, SU1498**

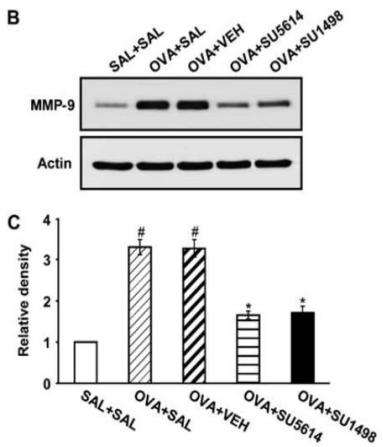
Vascular Endothelial Growth Factor Modulates Matrix Metalloproteinase-9 Expression in Asthma

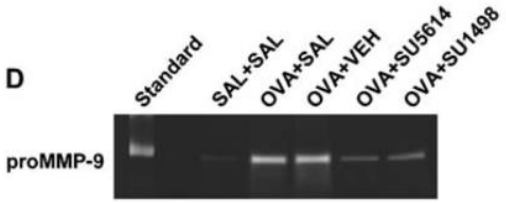
Kyung Sun Lee*, Kyung Hoon Min*, So Ri Kim, Seoung Ju Park, Hee Sun Park, Gong Yong Jin, and Yong Chul Lee

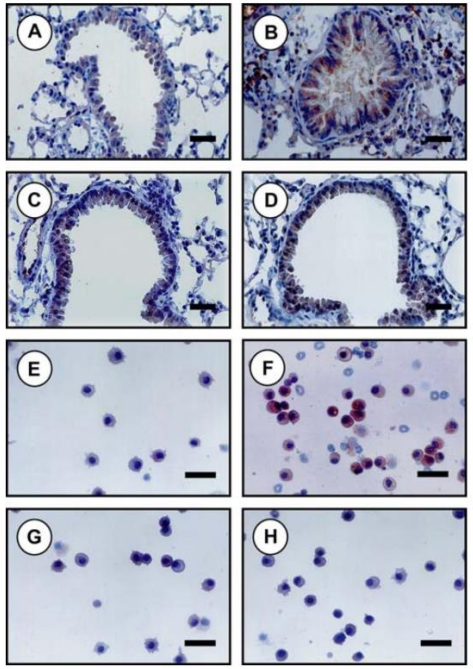
Department of Internal Medicine, Department of Radiology, Airway Remodeling Laboratory, and Research Center for Allergic Immune Diseases, Chonbuk National University Medical School, Jeonju, Republic of Korea









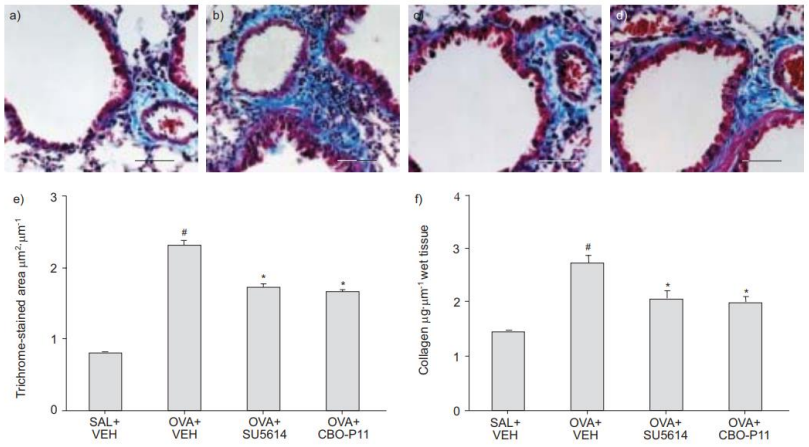


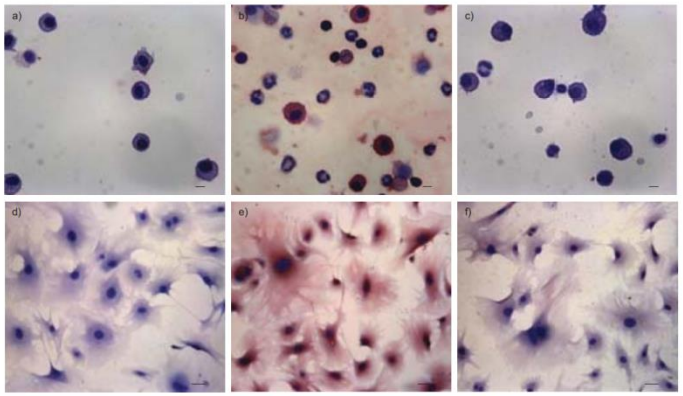
Am J Respir Crit Care Med Vol 174. pp 161–170, 2006

Kinase inhibitors

RTK

- **VEGFR inhibitors: SU5614, CBO-P11**

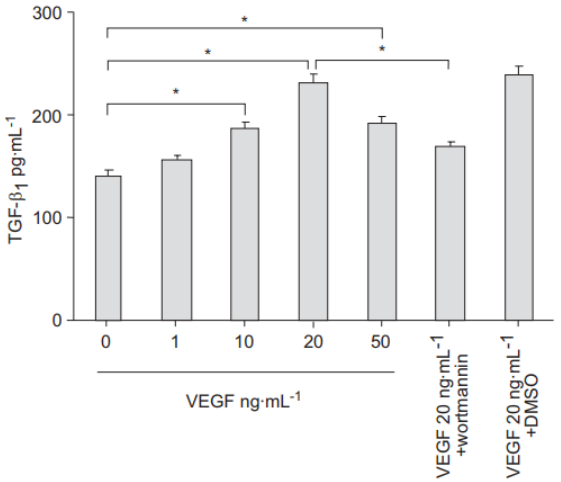




Eur Respir J 2008; 31: 523-531
DOI: 10.1183/09031936.00125007

Inhibition of VEGF blocks TGF-β_1 production through a PI3K/Akt signalling pathway

K.S. Lee*,+, S.J. Park*,+, S.R. Kim*,+, K.H. Min*, K.Y. Lee*, Y.H. Choe*, S.H. Hong*, Y.R. Lee#, J.S. Kim#, S.J. Hong* and Y.C. Lee*



Kinase inhibitors

RTK

- **VEGF inhibitors: Bevacizumab**
  - Anti-VEGF caused significant reduction in epithelial, subepithelial muscle, and basement membrane thickness
  - Goblet and mast cell numbers were significantly lower
  - Effects of dexamethasone on epithelial and basement membrane thickness is comparable to Bevacizumab

: suggesting as a steroid-sparing agent for AR

Ann Allergy Asthma Immunol. 2013 Mar;110(3):150-5.

Kinase inhibitors

multiple RTK

- **PDGFR/VEGFR/FGFR inhibitor: Nintedanib**
  - Suppression of goblet cell hyperplasia, total lung collagen level, and airway smooth muscle area (OVA-chronic animal model)
  - Reduction of collagen contents (OVA, HDM, Cockroach allergen induced severe chronic model)

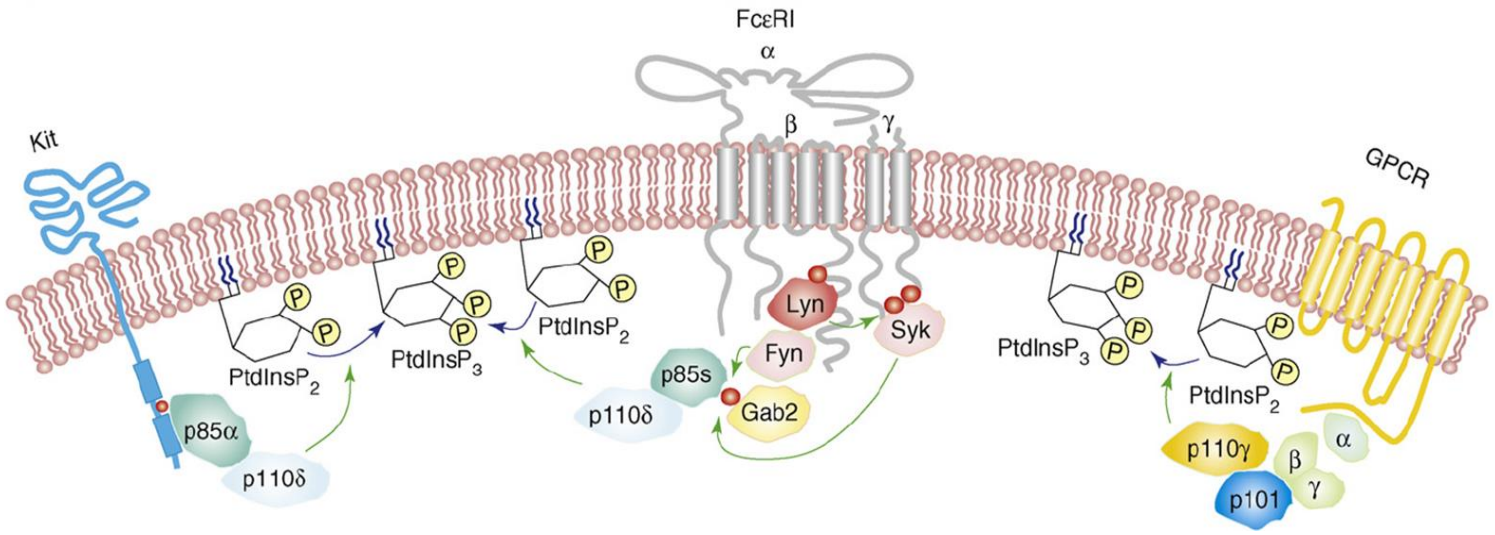
: it is expected to apply to humans

Exp Lung Res. 2017; 43(4–5): 187–96.; Am J Respir Crit Care Med 2018:197;A1062

Kinase inhibitors

PI3K

- A family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking
- An intracellular signaling pathway important in regulating the cell cycle.
- **Extensive investigation in asthma and COPD**

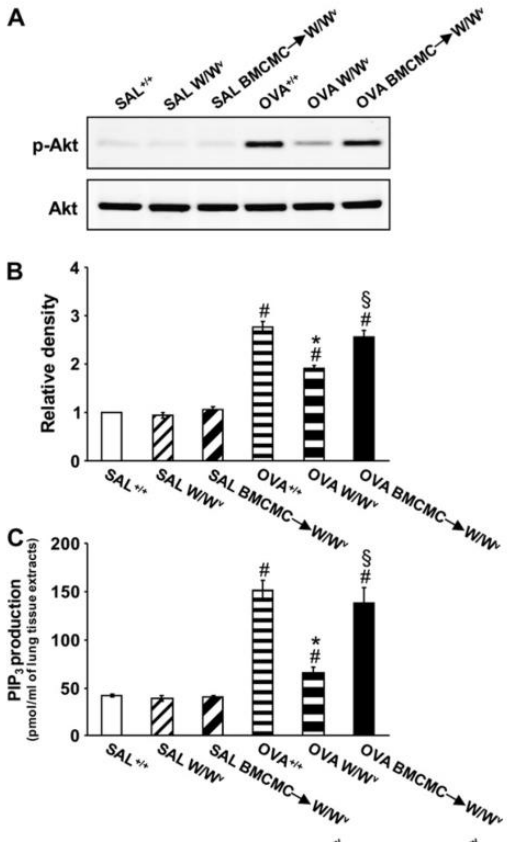


Trends in Immunology 2008;29:493-501

Kinase inhibitors

PI3K

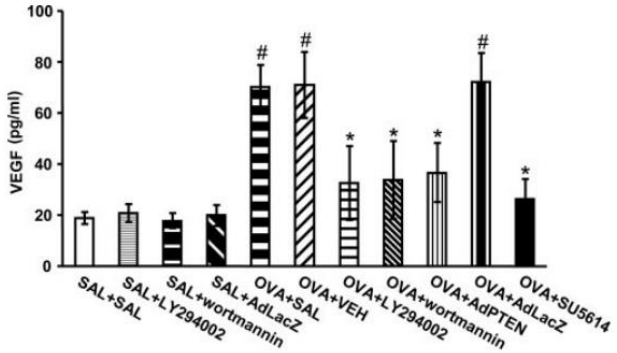
- **PI3K-VEGF**

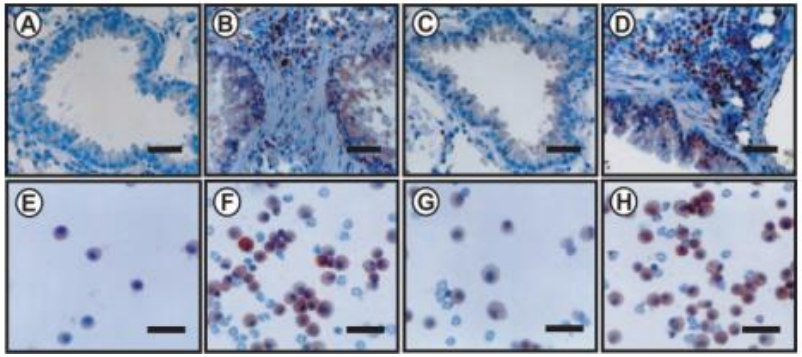


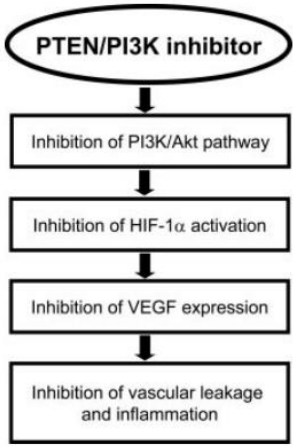
Mast Cells Can Mediate Vascular Permeability through Regulation of the PI3K–HIF-1α–VEGF Axis

Kyung Sun Lee[1]*, So Ri Kim[1]*, Seoung Ju Park[1], Kyung Hoon Min[1], Ka Young Lee[1], Yeong Hun Choe[1], Seung Yong Park[1], Ok Hee Chai[2], Xin Zhang[2], Chang Ho Song[2], and Yong Chul Lee[1]

[1]Department of Internal Medicine and Airway Remodeling Laboratory and [2]Department of Anatomy, Chonbuk National University Medical School, Jeonju, South Korea





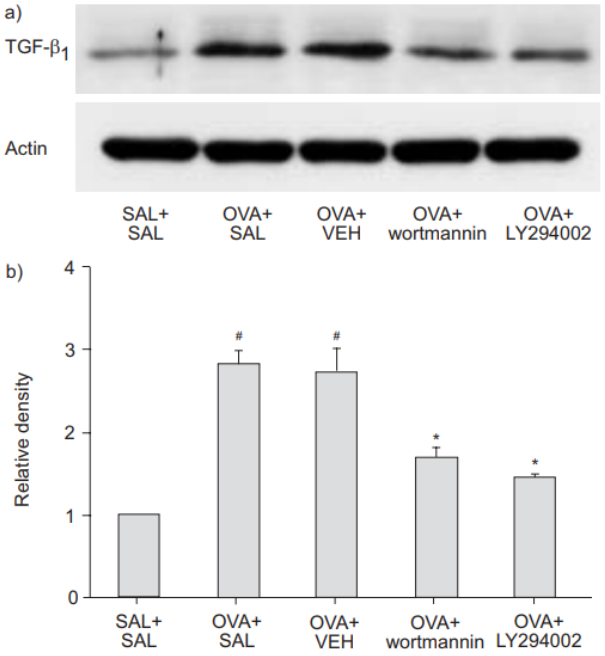


Am J Respir Crit Care Med. 2008 Oct 15;178(8):787-97; Mol Pharmacol. 2006 Jun;69(6):1829-39.

Kinase inhibitors

PI3K

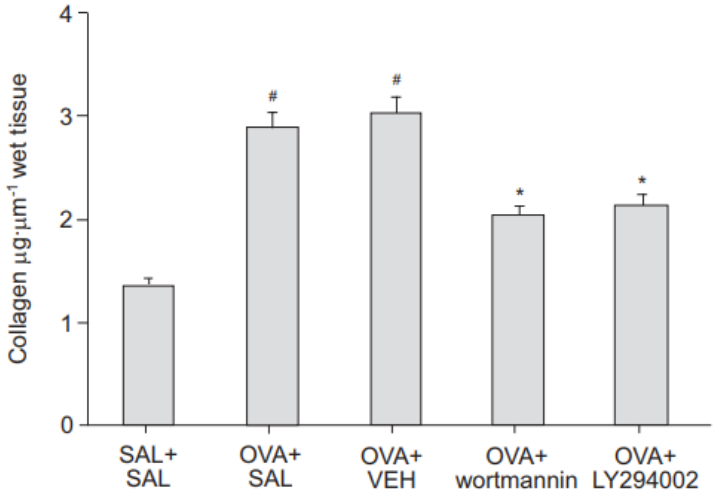
- **PI3K-TGF-β1**



Eur Respir J 2008; 31: 523–531
DOI: 10.1183/09031936.00125007

Inhibition of VEGF blocks TGF-β_1 production through a PI3K/Akt signalling pathway

K.S. Lee*,+, S.J. Park*,+, S.R. Kim*,+, K.H. Min*, K.Y. Lee*, Y.H. Choe*, S.H. Hong*, Y.R. Lee#, J.S. Kim#, S.J. Hong¶ and Y.C. Lee*

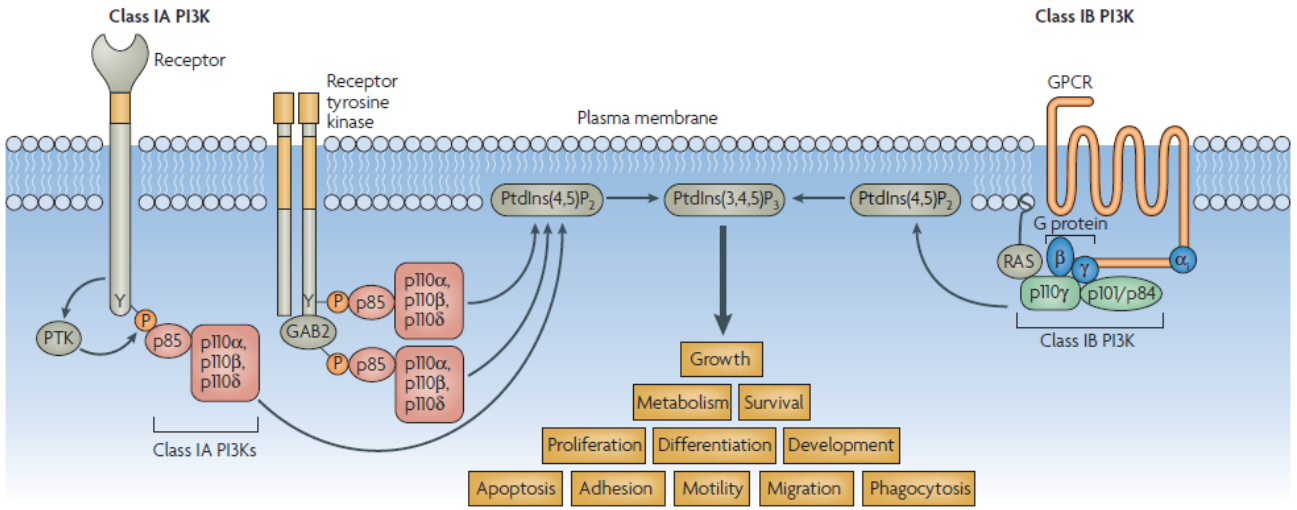


Lancet 2018; 391: 1076–84

Kinase inhibitors

PI3K-δ

- Class IA isoforms, PI3Kα/β/δ, interact with tyrosine kinases such as growth factor receptor tyrosine kinases
- Class IB member PI3Kγ interacts with G-protein-coupled receptors



- Nebulized doses of a novel phosphoinositide 3-kinase δ inhibitor (PI3Kδ), GSK2269557 (Nemiralisib) is under clinical trials

Eur Respir J. 2013; 42: 729; Nat. Rev. Immunology 2007:7;191-201

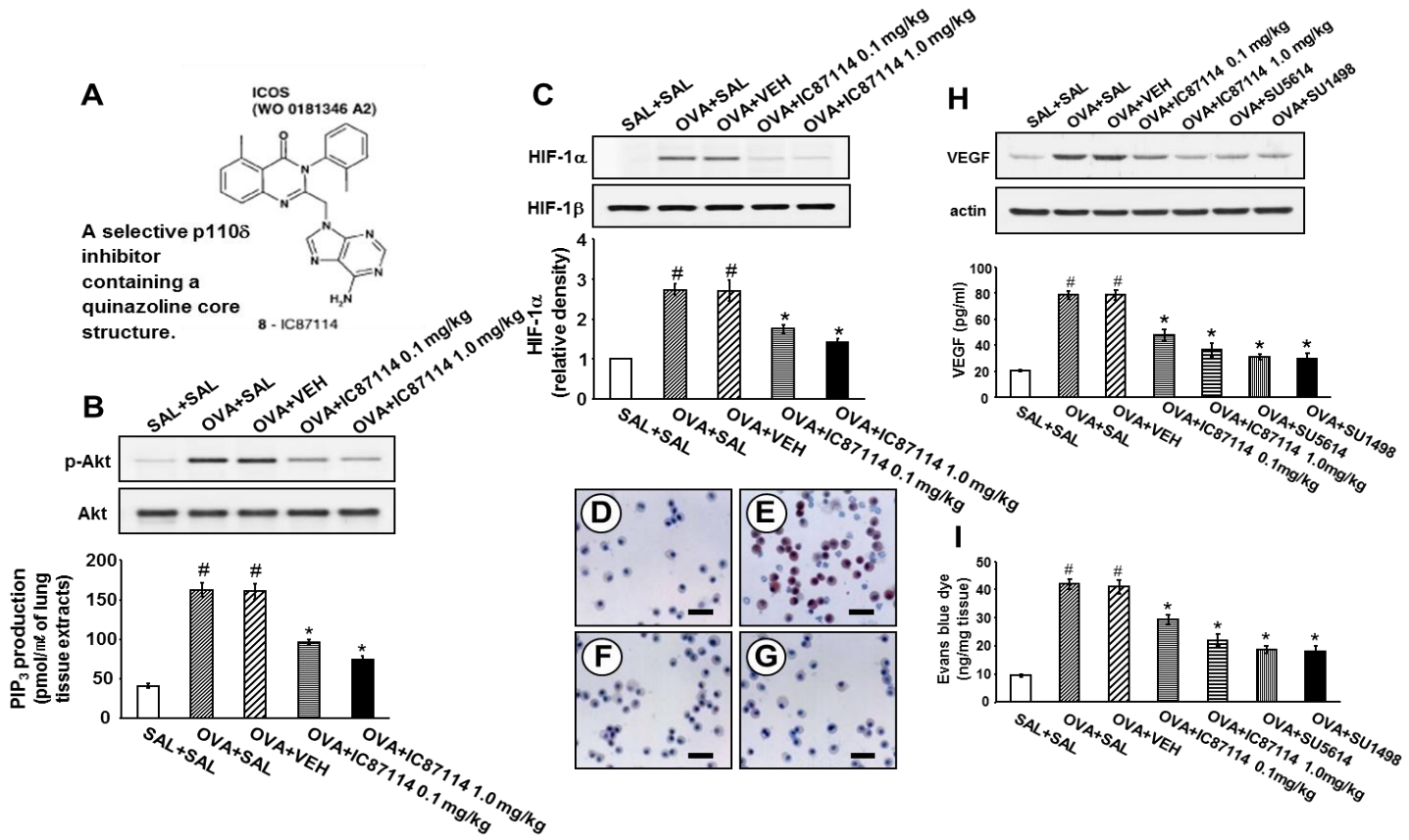
Kinase inhibitors

PI3K-δ

- **PI3K-δ-VEGF**

Phosphoinositide 3-kinase-δ inhibitor reduces vascular permeability in a murine model of asthma

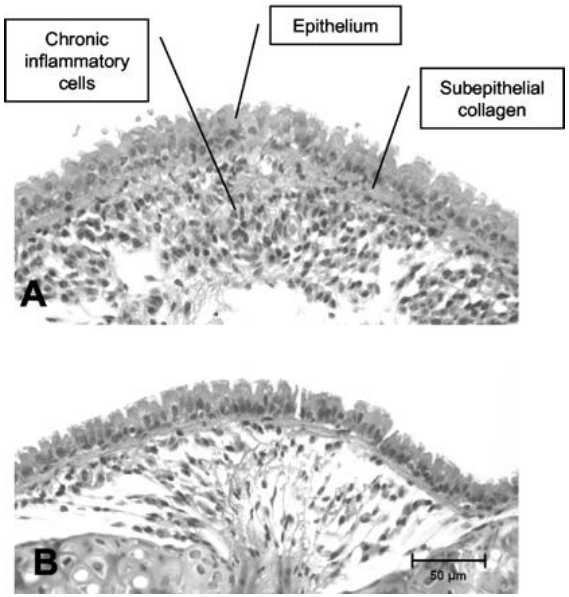
Kyung Sun Lee, PhD,[a,b,c] Seoung Ju Park, MD,[a,b,c] So Ri Kim, MD,[a,b,c] Kyung Hoon Min, MD,[a,b,c] Sun Mi Jin, BS,[b,c] Kamal D. Puri, PhD,[d] and Yong Chul Lee, MD, PhD[a,b,c] *Jeonju, South Korea, and Bothell, Wash*

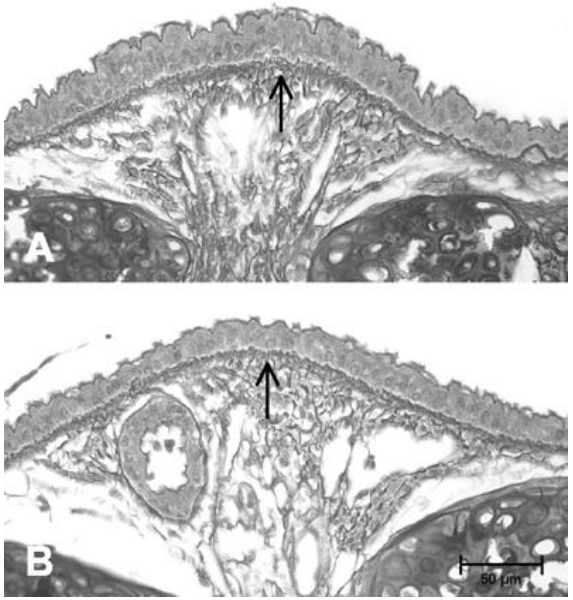


Small molecules

PDE inhibitors

- Marked reduction in subepithelial fibrosis and epithelial layer thickening (PDE4 inhibitor, roflumilast)
- Reduced proliferation of ASM (PDE3 inhibitor/ PDE8 inhibitor)

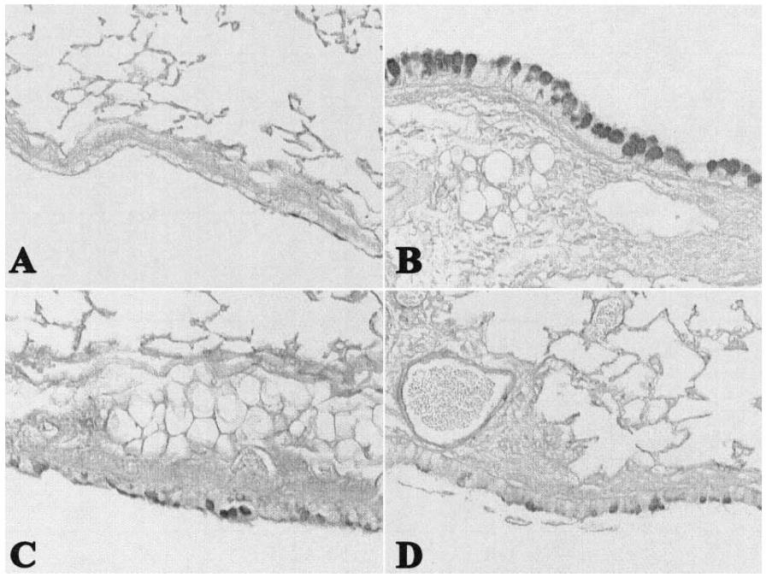


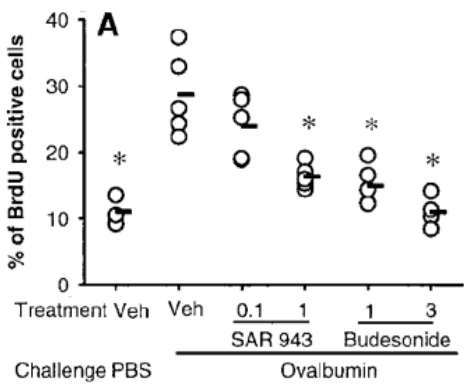


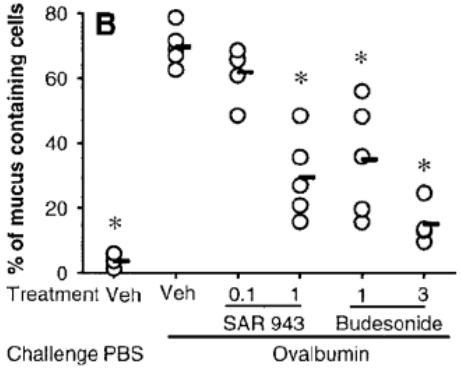
J Pharmacol Exp Ther. 2003 Oct;307(1):349-55; Am J Physiol. 1999 Mar;276(3 Pt 1):L412-9.; Am J Respir Cell Mol Biol. 2018 Apr;58(4):530-541

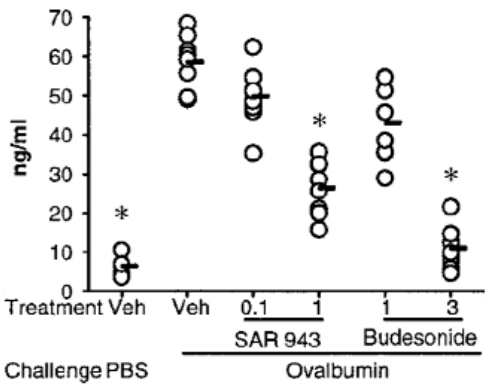
Small molecules

Rapamycin derivative (mTOR)









Am J Respir Crit Care Med Vol 167. pp 193–198, 2003

Future directions: Management for AR

- A growing arsenal of **small-molecule inhibitors and biologics** in conjunction with non-pharmacological interventions such as **bronchial thermoplasty** has shown promise in addressing this unmet clinical need.
- As our understanding of mechanisms underlying AR improves, so will the drug development approaches as well as the phenotyping capabilities that accurately assess AR in humans.
- These advances will undoubtedly fulfill our need for **more refined, efficacious, and safer drugs that enable us to finally control the entire spectrum of asthma pathology.**

Take home message

- **Inflammation and remodeling** are critical components of the pathophysiology of asthma.
- To date mechanistic studies and drug discovery **have focused on inflammatory targets**.
- Although these novel therapeutics (predominantly monoclonal antibodies to IgE and Th2 cytokines IL-5 and IL-13) have achieved improvements in disease control, they are only applicable to **a subgroup of patients** and do not result in disease modification.
- To make a step-change in asthma therapy,
  - the focus of research now needs to be on investigating mechanisms underlying **Th2-low phenotypes and airway remodeling**
  - the approaches used will have **to reflect disease heterogeneity**, and include complex experimental approaches with in vitro, in vivo, animal and human studies.

THANK YOU

감사합니다