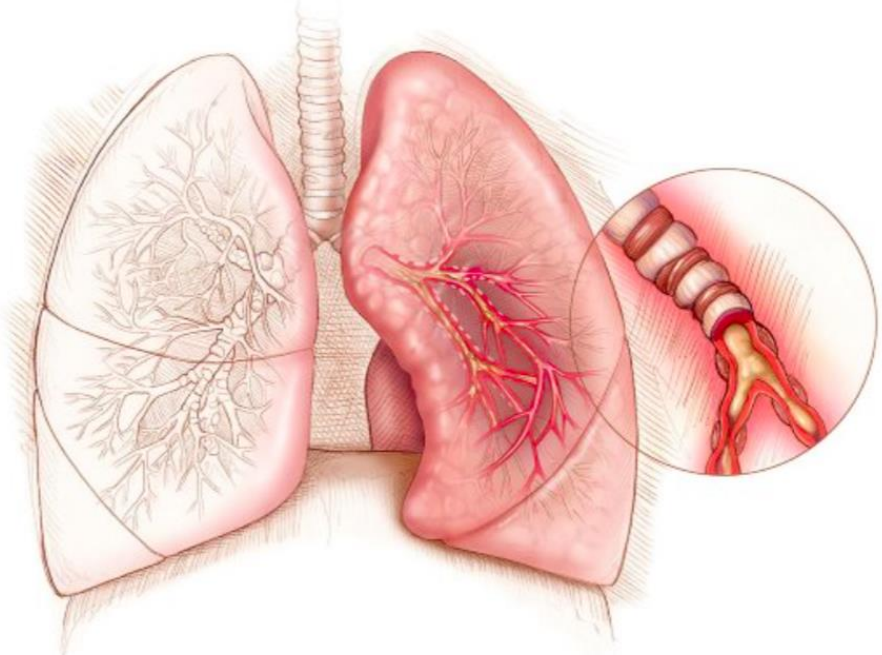
台大醫院 雲林分院

2019台灣胸腔暨重症加護醫學會

2019 Taiwan Society of Pulmonary and Critical Care Medicine

From Immune Pathway to Clinical Practice: The Role of Anti-IgE in Disease-Modifying Effect of asthma

?



台大醫院雲林分院
胸腔內科
陳彥甫 醫師

Outlines

- **Airway remodeling in asthma**
- **The role of IgE in airway remodeling of asthma**
  - Classical and Cytokinergic IgE
  - IgE plays an important role in severe asthma
  - Effects of IgE on airway smooth muscle cells
- **Evidences of anti-IgE reverse Airway remodeling of asthma**
  - The relationship between omalizumab and related inflammatory mediators
  - The efficacy of omalizumab in reducing blood eosinophils
  - Structure change after omalizumab treatment
  - Lung function improvement after omalizumab treatment

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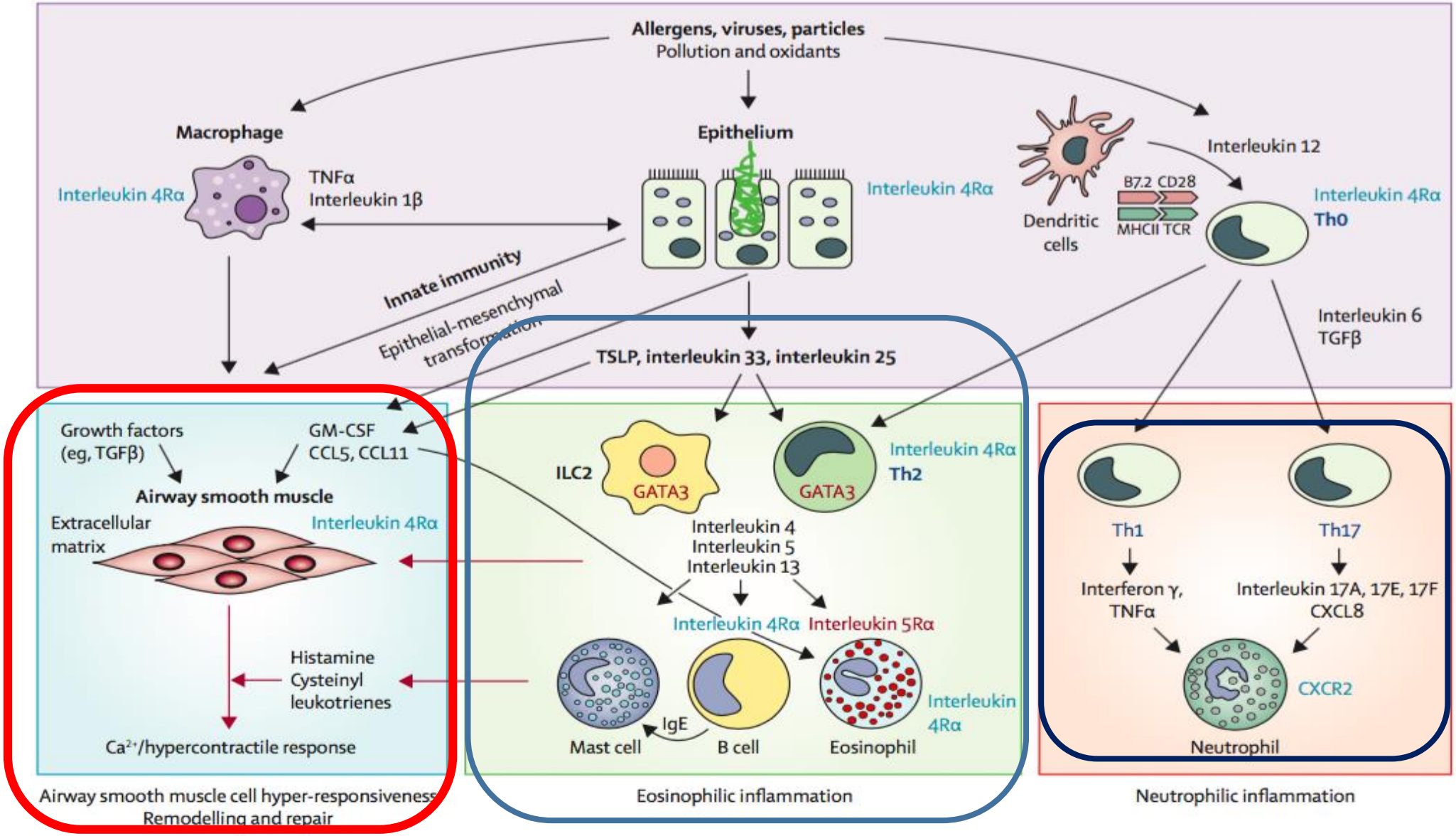
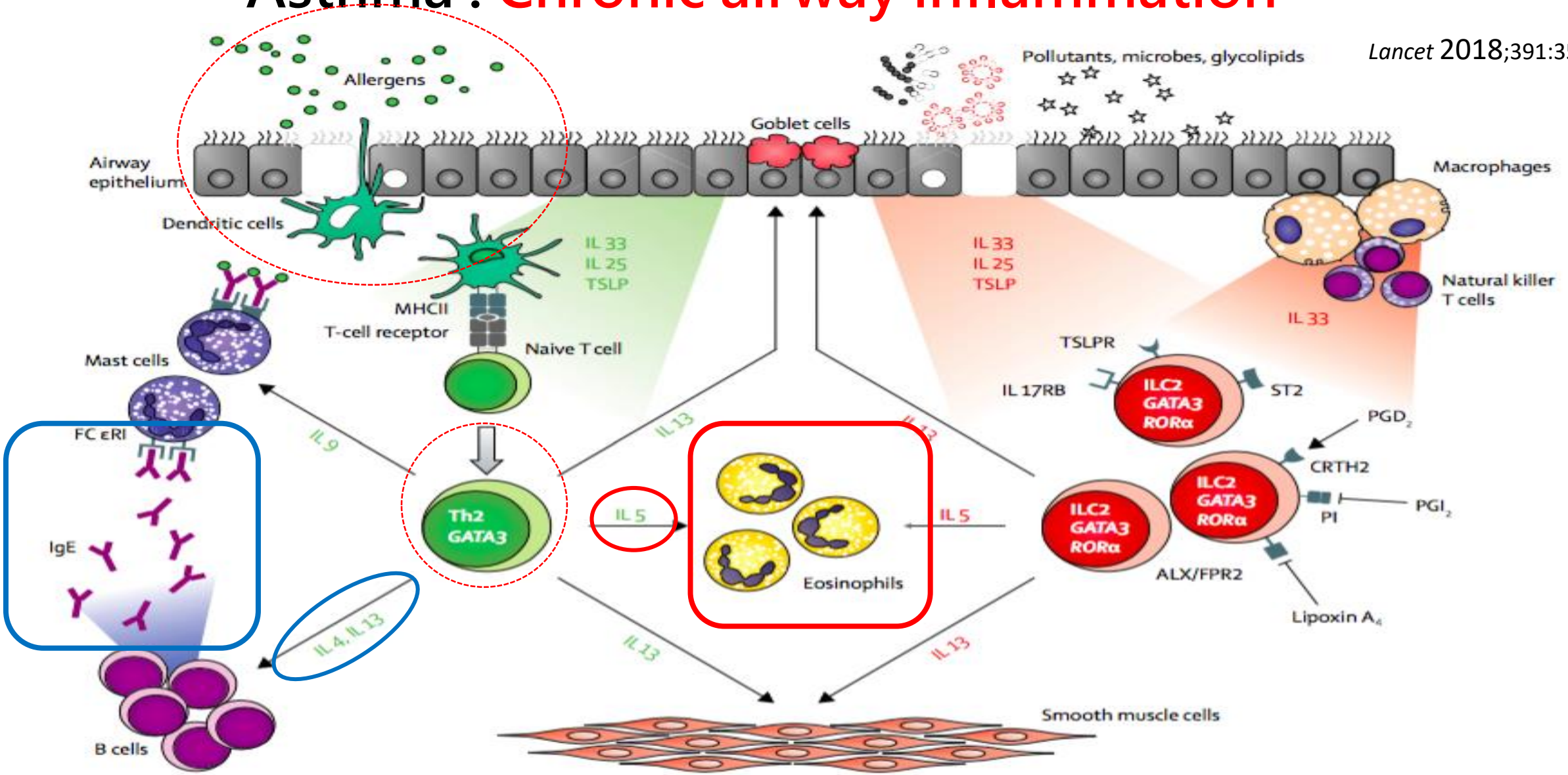
Pathophysiological mechanisms underlying asthma



Lancet 2015;386:1086

Asthma : Chronic airway inflammation

Lancet 2018;391:350



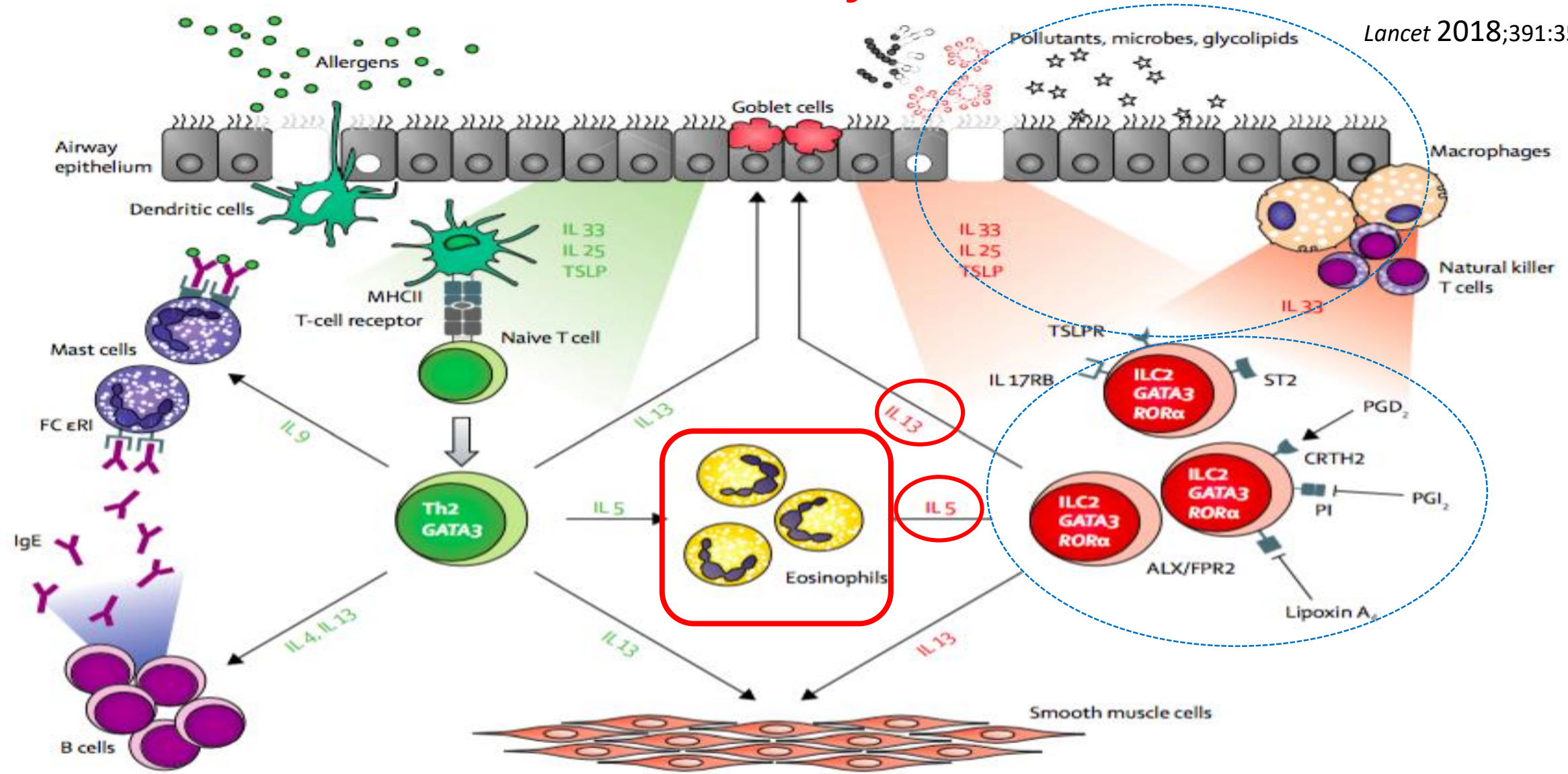
Allergic(atopic) eosinophilic asthma

Inhaled corticosteroid resistant

Late-onset non-allergic eosinophilic airway inflammation
Intrinsic asthma

Asthma: Chronic airway inflammation

Lancet 2018;391:350



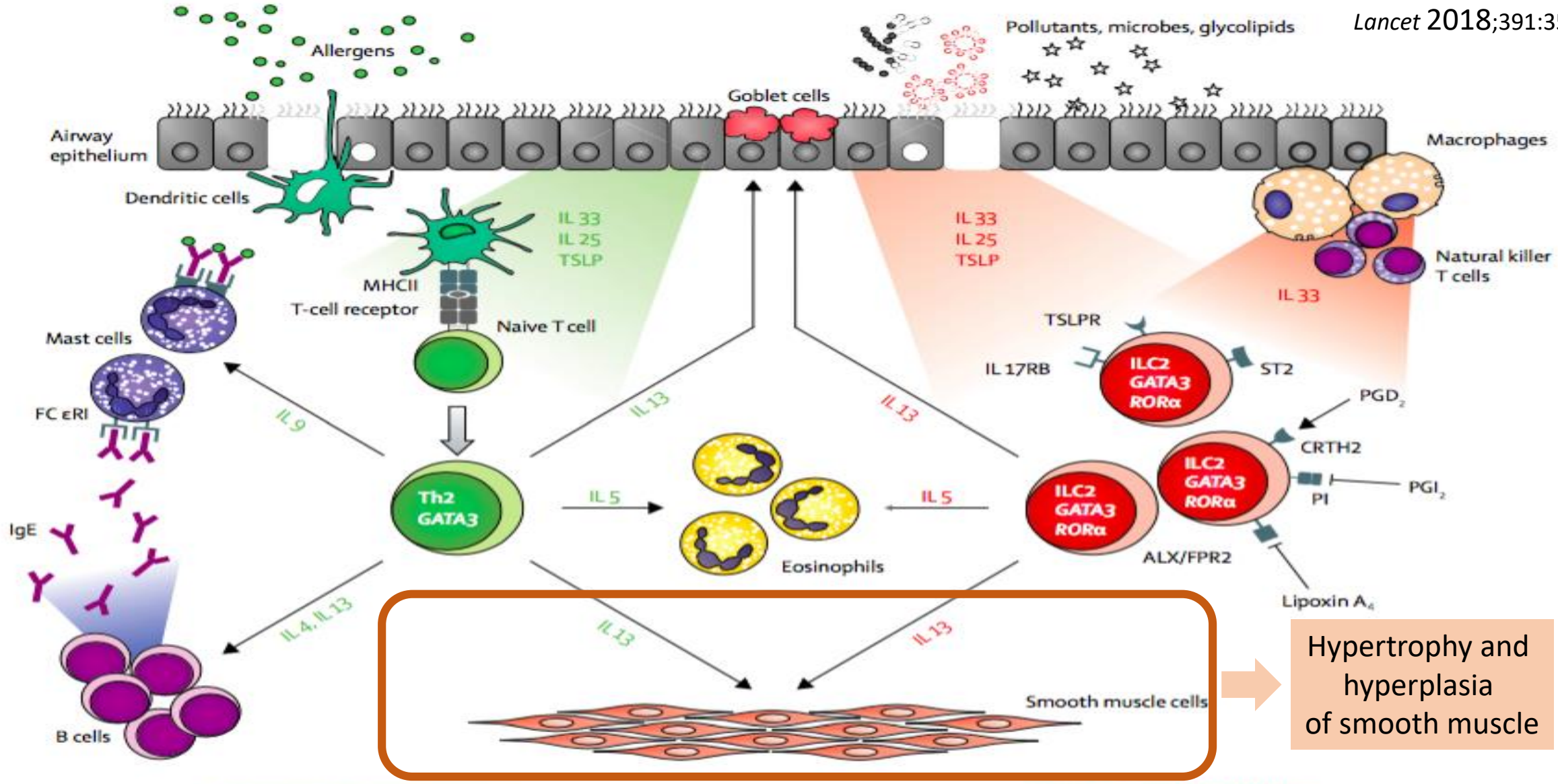
Inhaled corticosteroid sensitive

Early-onset allergic eosinophilic airway inflammation
Extrinsic asthma

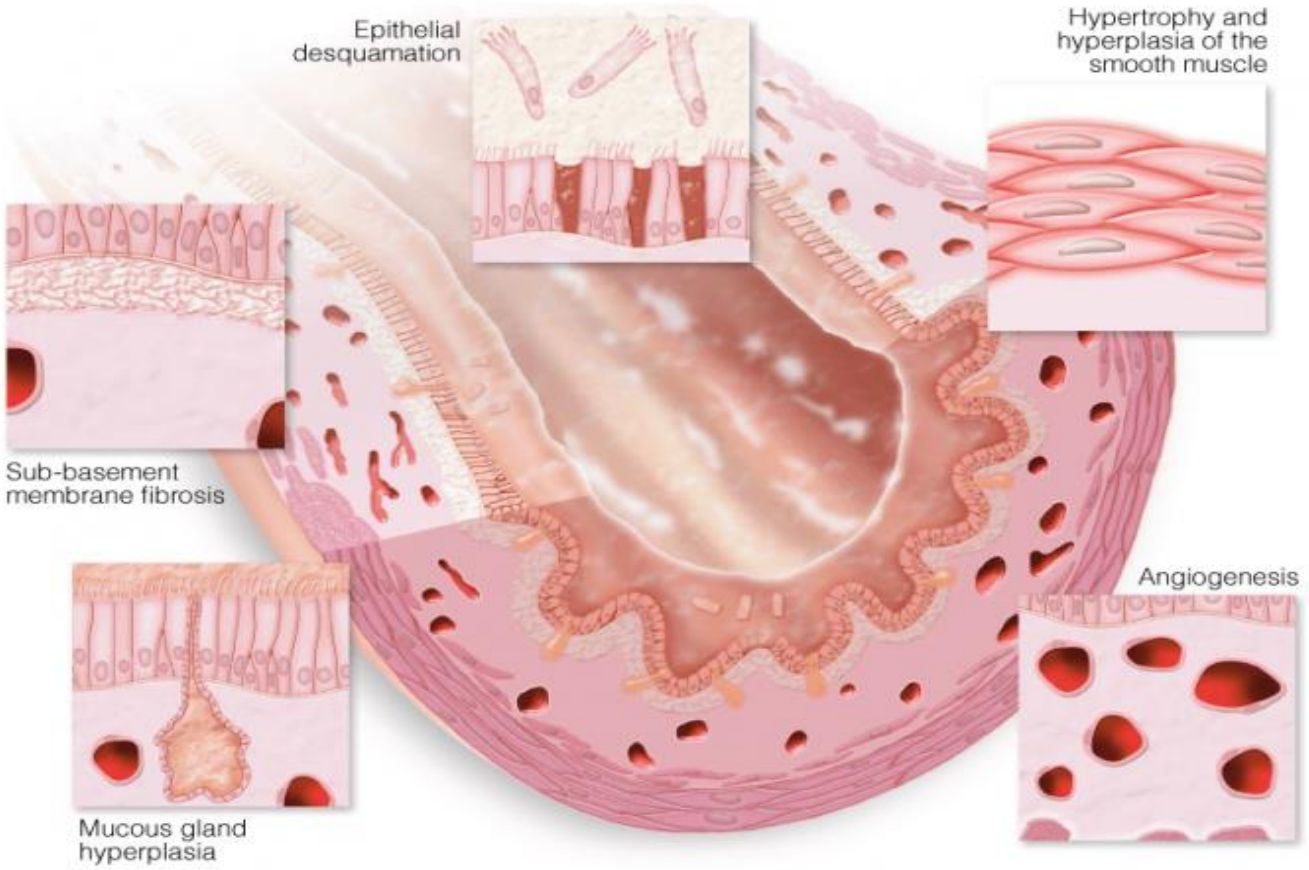
Non-Allergic(atopic) eosinophilic asthma

Asthma : Airway remodeling (Smooth muscle cells)

Lancet 2018;391:350



Airway remodeling in asthma



- First described in 1922 by Hubert and Koessler in cases of fatal asthma
- Documented in all degrees of asthma severity
- In both large and small airways wall.

C Bergeron et al. Can Respir J 2010;17(4): e85-e94.
Redington AE, Howarth PH. Thorax 1997;52:310-2
Huber HL, Koessler KK. Arch Intern Med 1922;30:689–760

Airway remodeling: **structural changes** that occur in the airway wall in asthma!

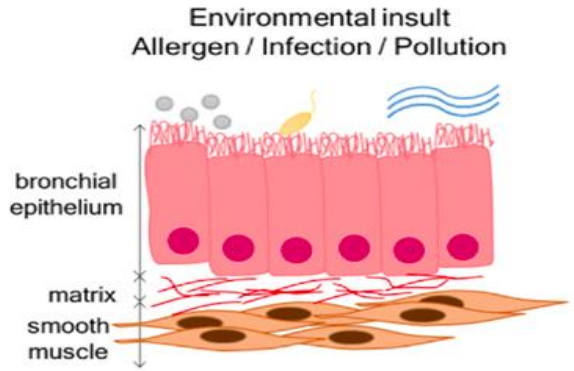
- Thickening of the lamina reticularis
- Structural changes : epithelium, submucosa, **smooth muscle**, and vasculature of the airway

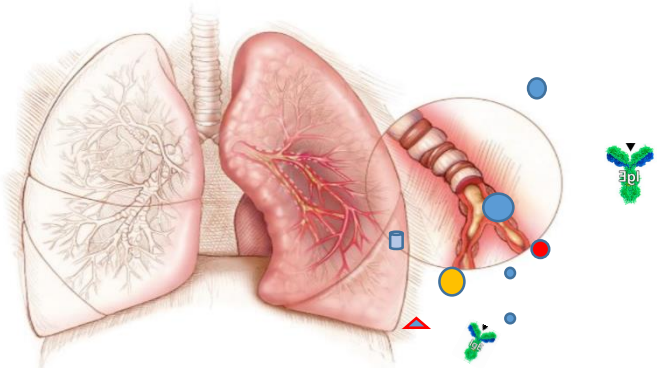
Rabe et al. Allergy 66 (2011) 1142–1151

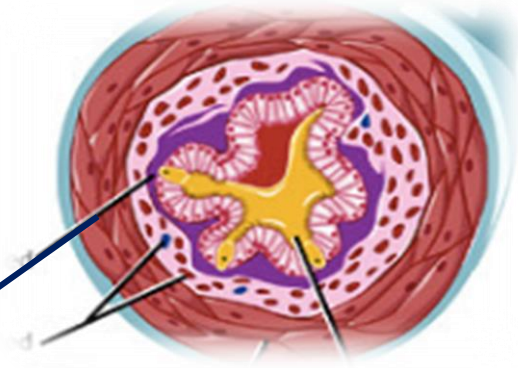
Airway remodeling, cause ?

- Repetitive injury to the airway wall arising from cycles of inflammation and repair.

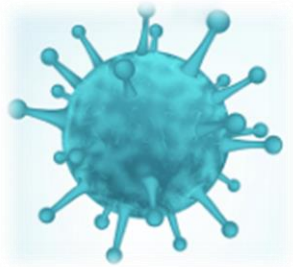
Beckett, Howarth Thorax 2003;58:163–174







- May occur in response to chronic inflammation



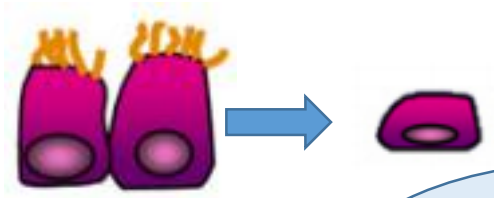
Lloyd CM, Gonzalo JA, Coyle AJ, Gutierrez-Ramos JC. Adv Immunol2001; 77: 263–295.
Kumar RK, Foster PS. Am J Respir Cell Mol Biol 2002;27: 267–272.
Lloyd CM, Robinson DS, McMillan SJ. Drug Discov Today: Disease Models2004; 1: 425–430.

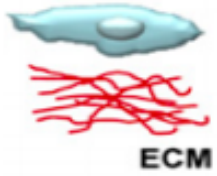
- Immune-mediated events such as viral infection

Eur Respir J 2007; 29: 1020–1032

Rabe et al. Allergy 66 (2011) 1142–1151

Main characteristics of airway remodeling





Epithelial Alteration

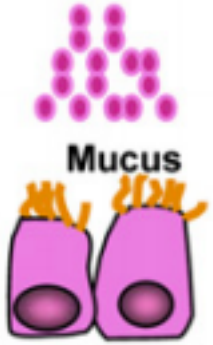
Subepithelial Fibrosis

Increased smooth Muscle Mass

Inflammation

Airway Remodeling

Goblet & Mucous Glands Hyperplasia

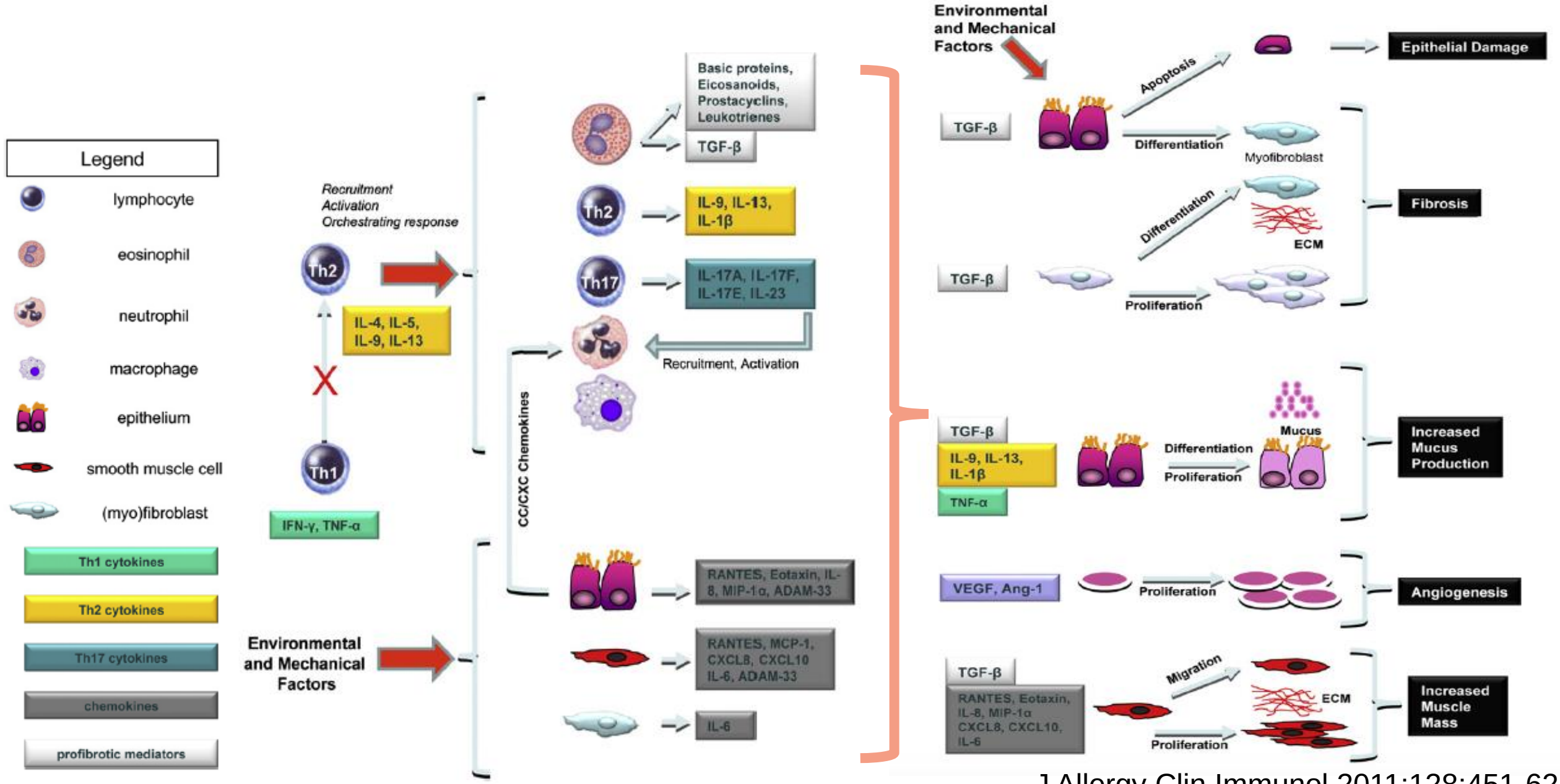


Loss of Cartilage integrity

Angiogenesis

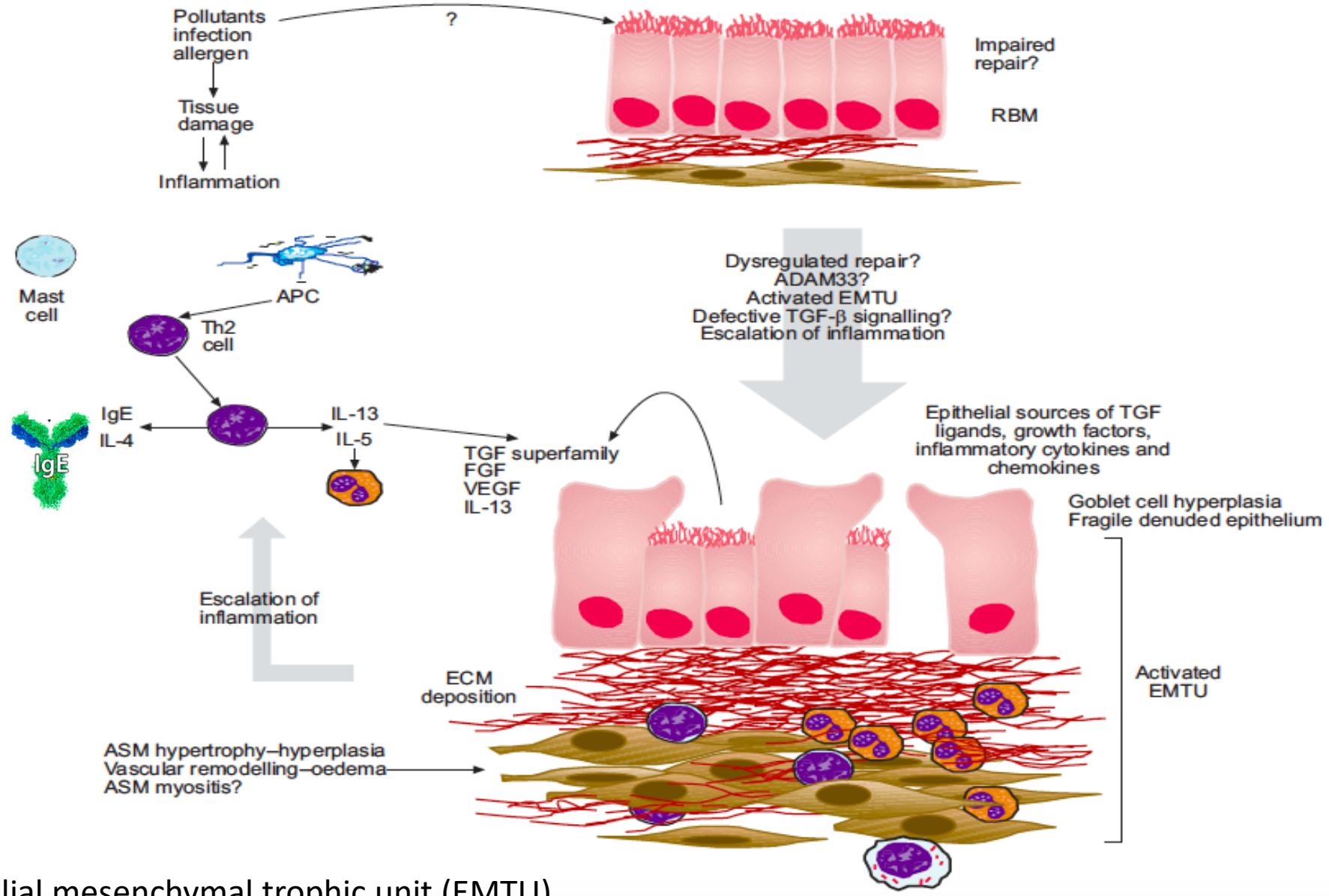
Modified from Proc Am Thorac Soc Vol 6. pp 301–305, 2009

Mechanisms of airway remodeling in asthmatic patients



J Allergy Clin Immunol 2011;128:451-62

Pathogenesis of **airway remodeling** in allergen-induced asthma



activated epithelial mesenchymal trophic unit (EMTU)

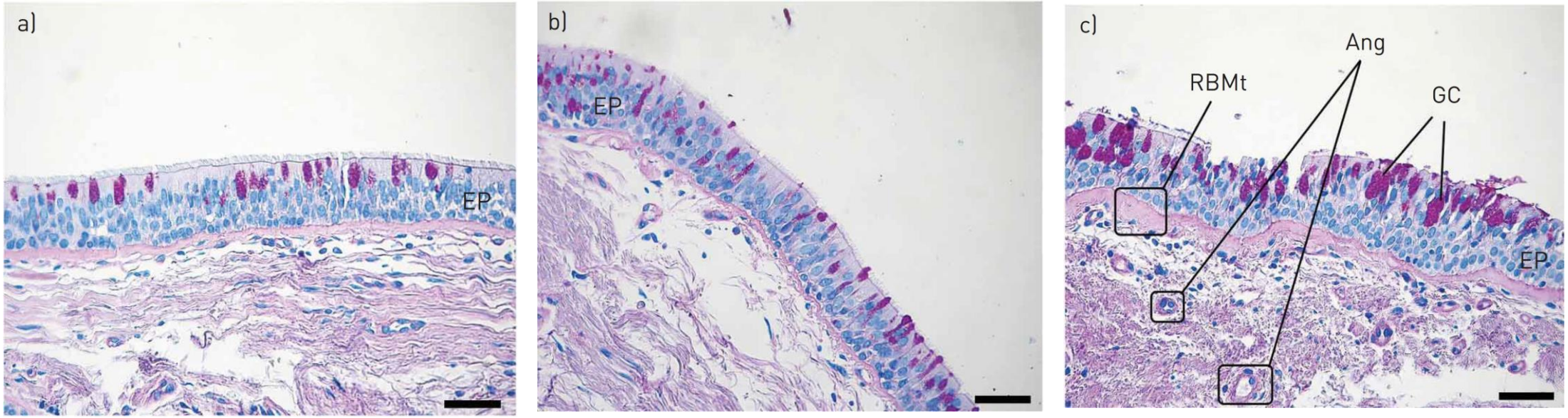
Eur Respir J 2007; 29: 1020–1032

Microscopic features of endobronchial biopsies from asthma patients

Health control

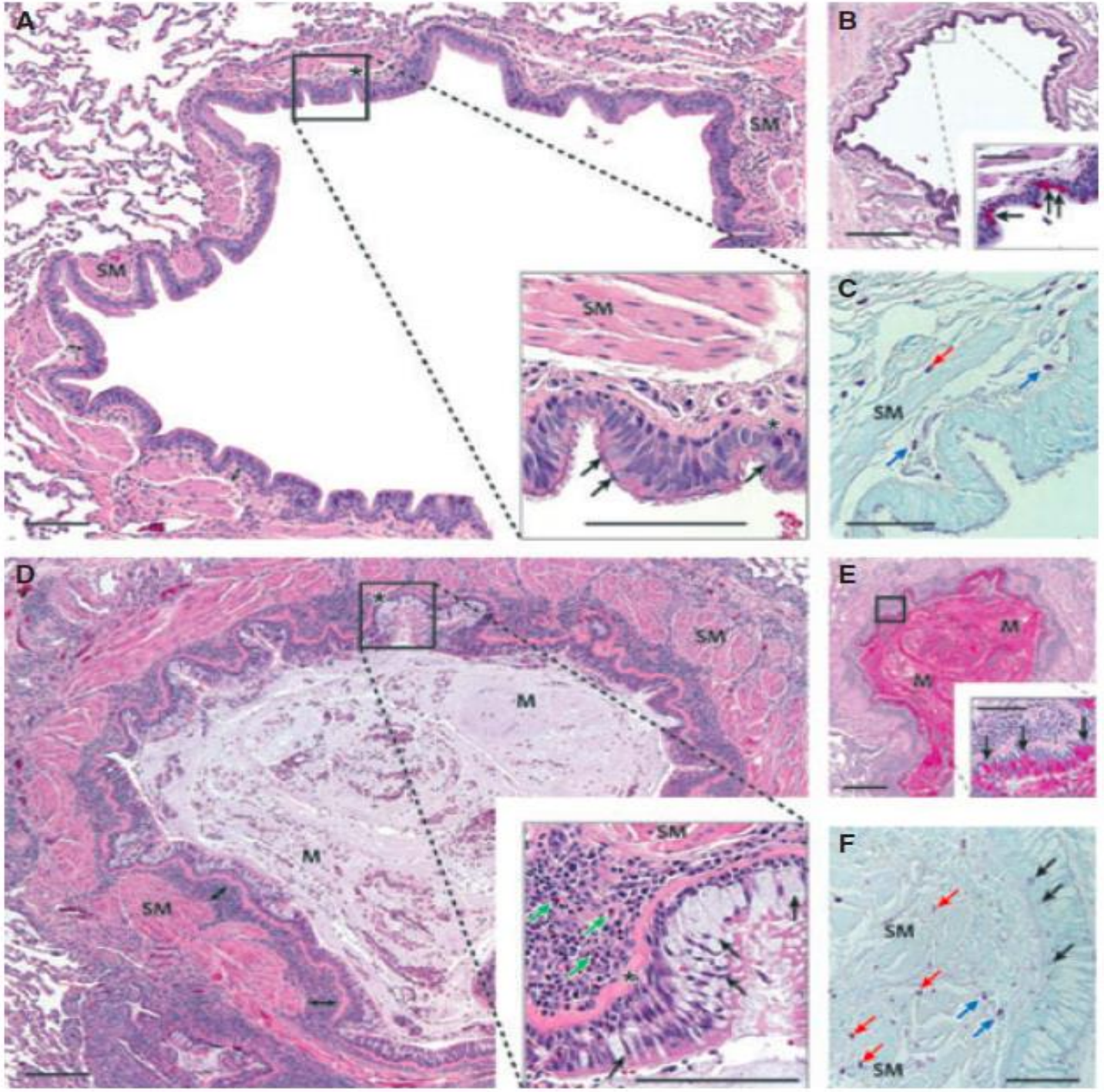
Mild asthmatics

Severe asthmatics



GC : goblet cell; EP: epithelium; **RBMt**: reticular basement membrane; Ang: angiogenesis. Scale bars=50 μm.

Eur Respir Rev 2015; 24: 594–601



Tissue sections from
non-asthmatic airway

- **Increased goblet cells** (black arrows)
- **Thickening of basement membrane** and **lamina reticularis** (asterisks)
- **Increased mast cells** (blue arrows, red arrow in C/F),
- **Eosinophils** (green arrows in inset D)
- **Mucus (M)** fills the airway lumen
- **Bronchial smooth muscle** increased

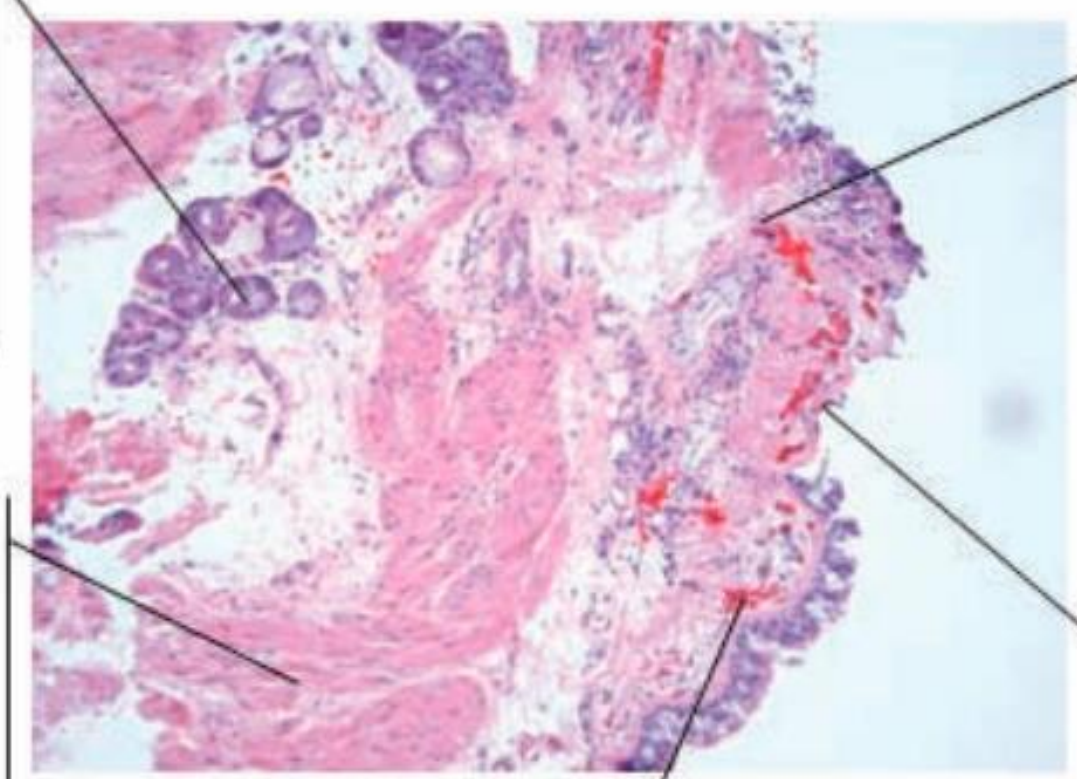
Tissue sections from severe
asthmatic airways

Rabe et al. Allergy 66 (2011) 1142–1151

Clinical consequences of airway remodeling

Goblet and mucous gland hyperplasia

Subepithelial fibrosis



Increased smooth muscle mass

Epithelial alternation

Angiogenesis

Can Respir J 2010;17(4): e85-e94. Can Respir J 2010;17(4): e85-e94.

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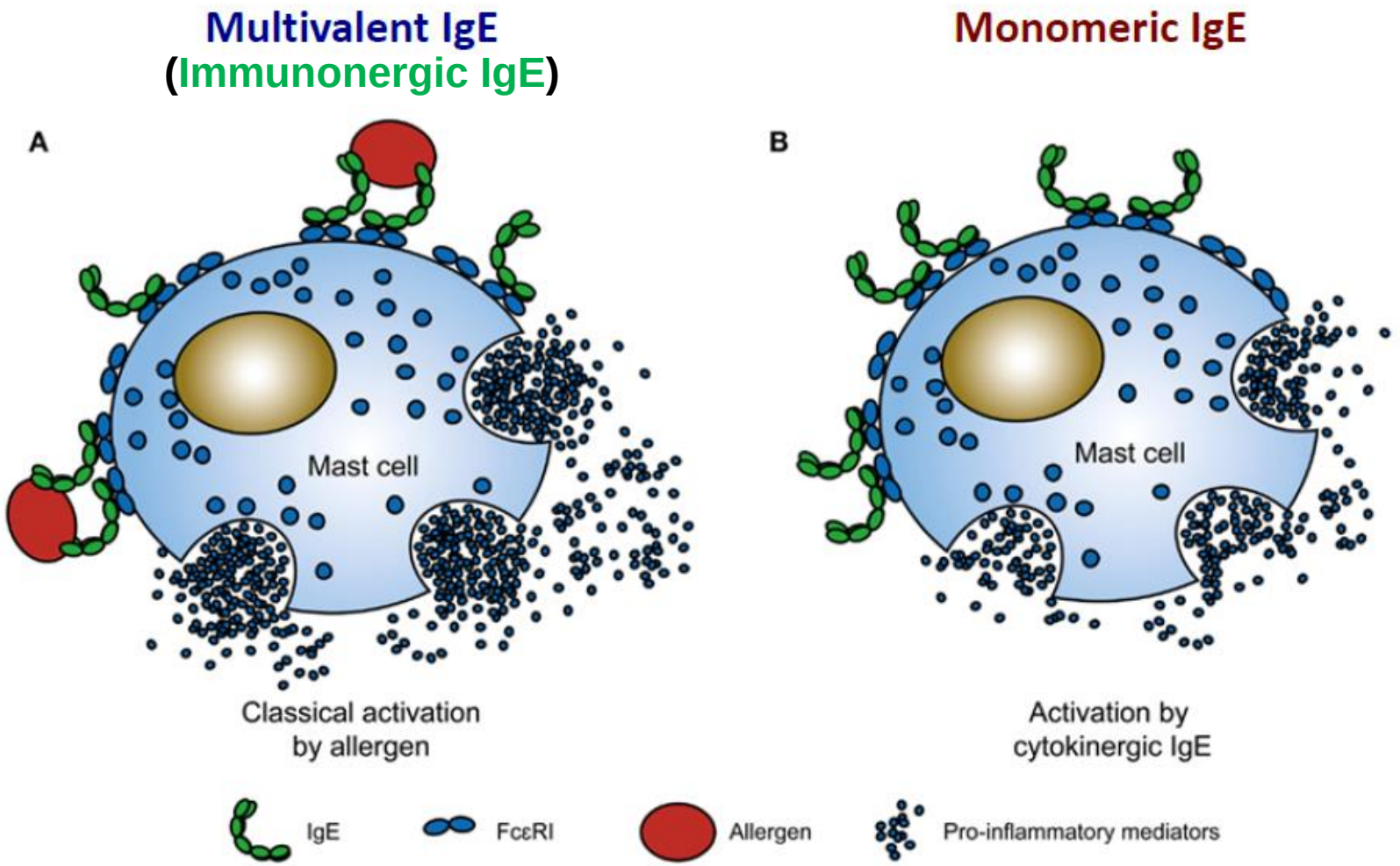
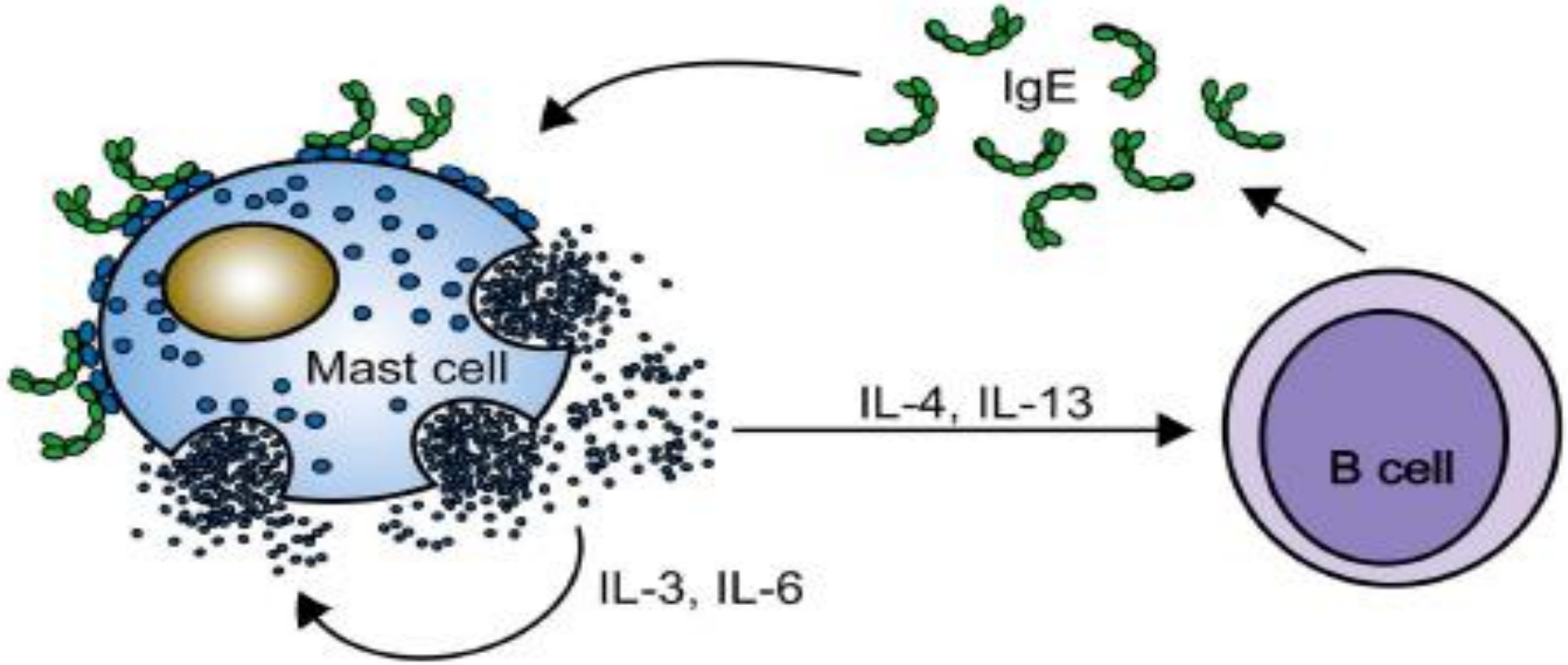
Classical IgE and cytokinergic IgE activation of high affinity IgE receptor on Mast Cells



Bax HJ *et al. Front Immunol*. 2012 ;3:229

Positive feedback between mast cell and B cell mediated by Cytokinergic IgE



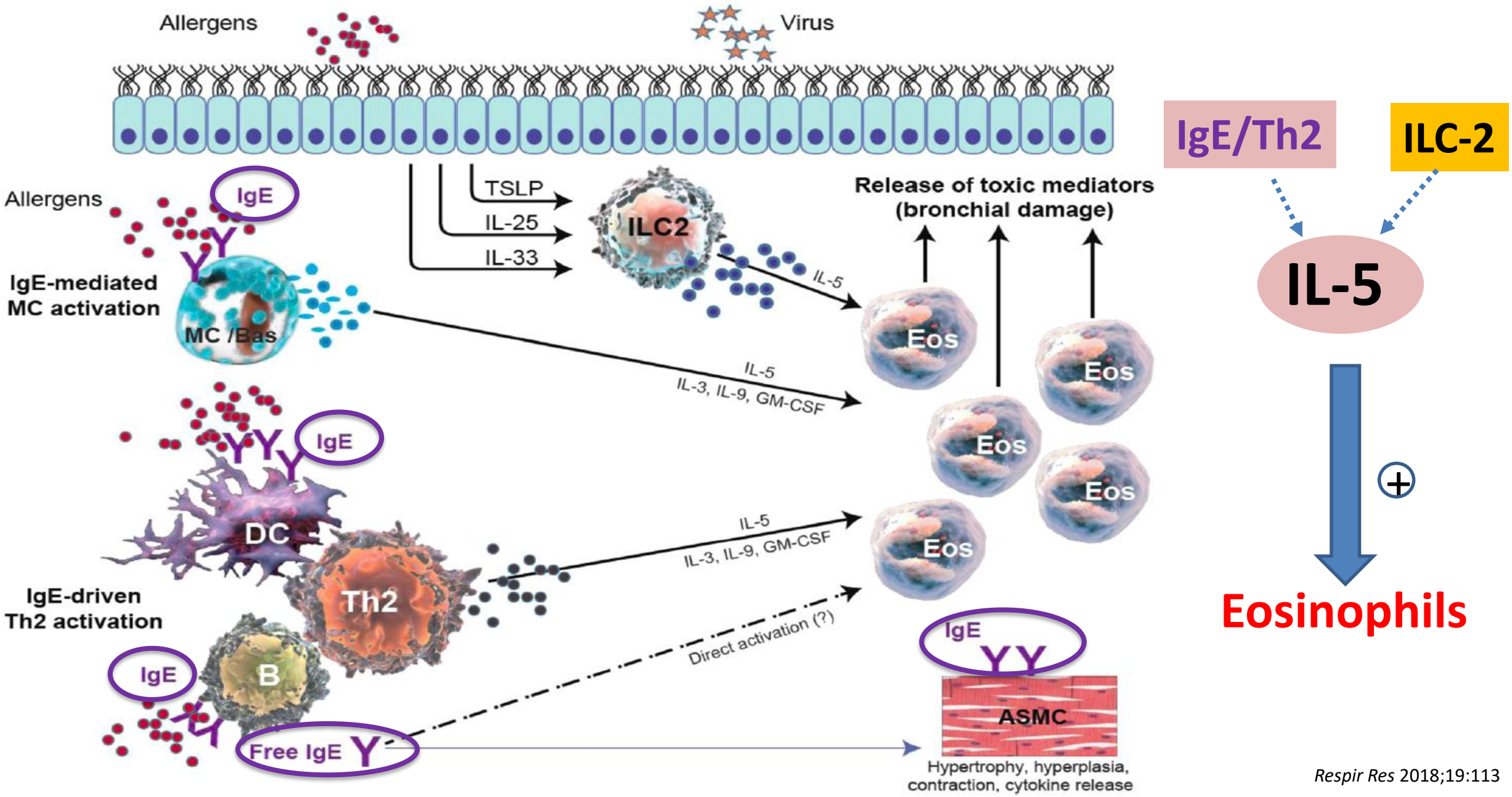
Survival

Class switch to IgE producing cells

Continued production of IgE and cytokines occurs in the absence of antigen

Bax HJ *et al. Front Immunol*. 2012 ;3:229

Role of IgE in Eosinophilic inflammation of asthma



Respir Res 2018;19:113

IgE plays a central role in allergic inflammation asthma

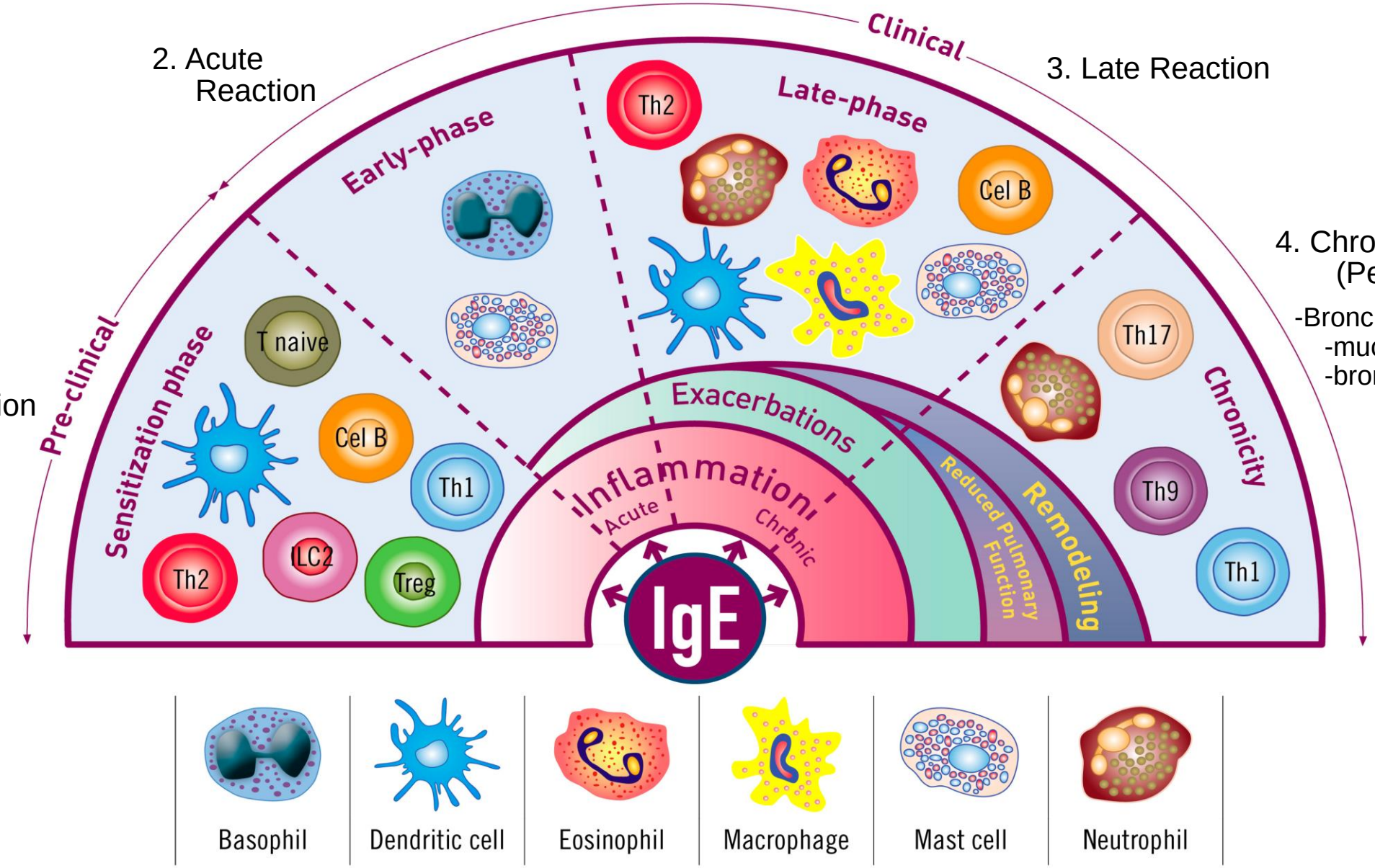
1. Sensitization

2. Acute Reaction

3. Late Reaction

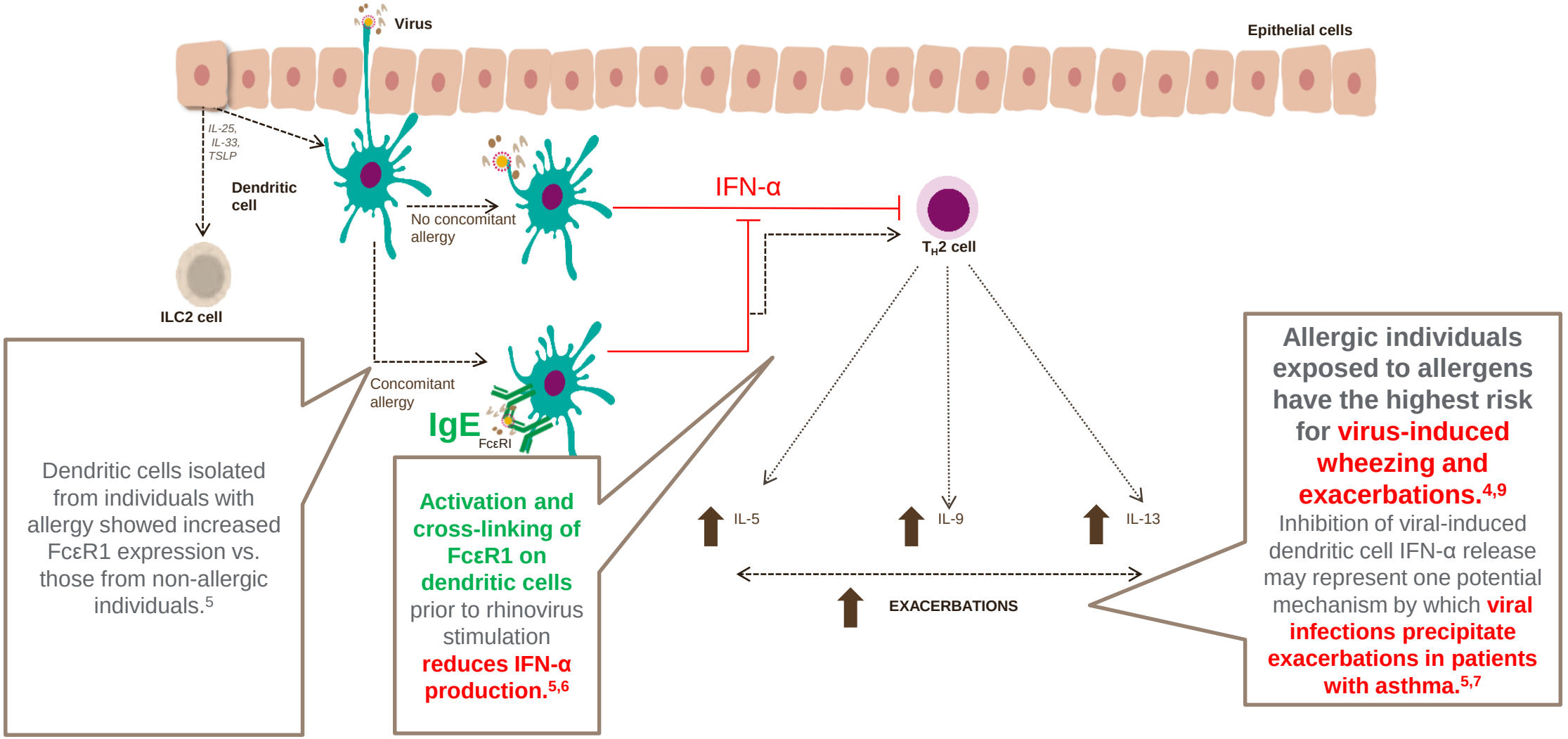
4. Chronic effects (Persistent asthma)

-Bronchial remodeling:
-mucosal
-bronchial smooth muscle



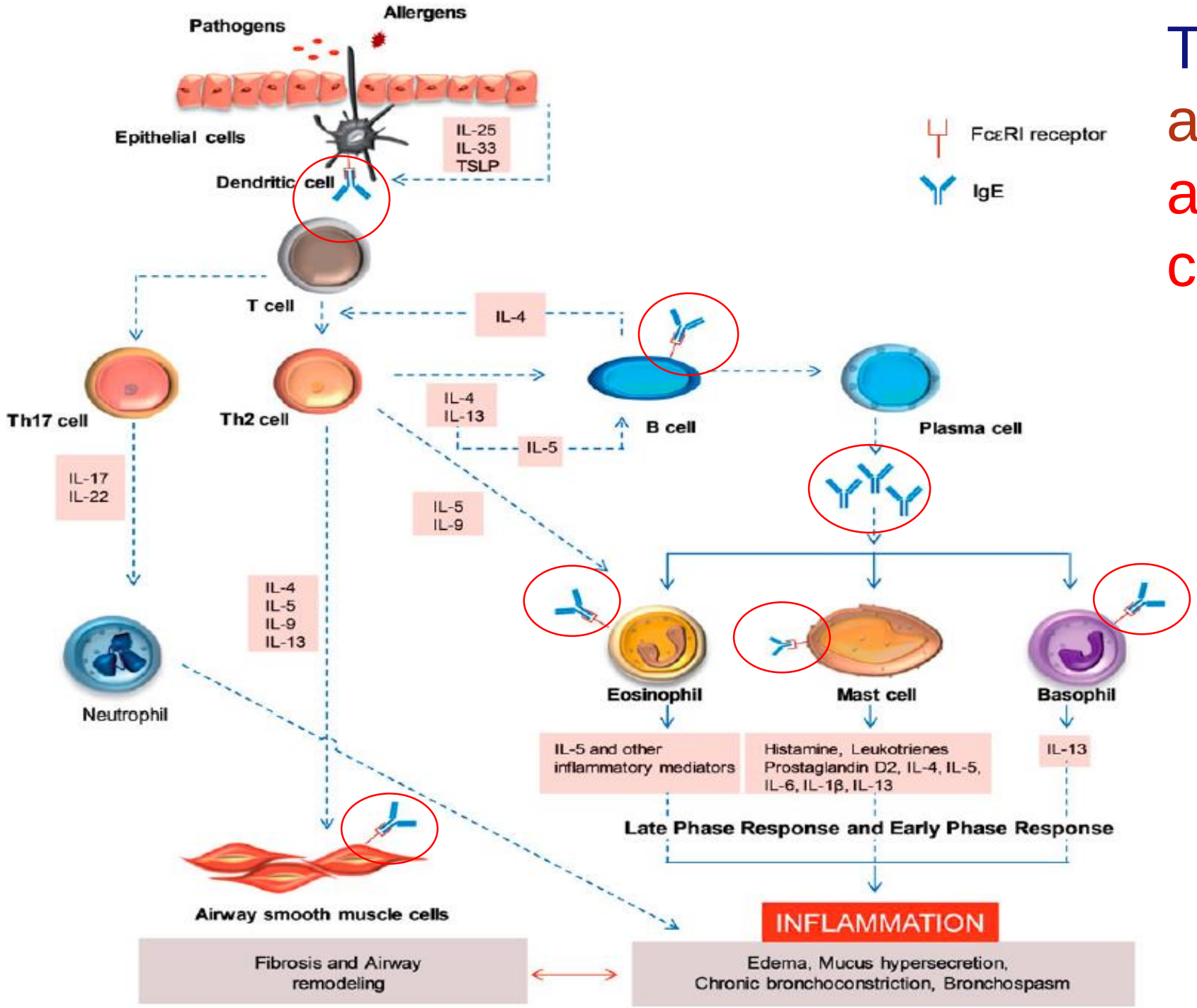
Int. J. Mol. Sci. 2017, 18, 1328; doi:10.3390/ijms18061328

Regulation of viral-induced dendritic cell IFN-α release by IgE in asthma patients



1. Holgate ST. Nature Medicine 2012;18:673–683. 2. Licona-Limon P. et al. Nature Immunology. 2013; 14:536-542. 3. Olin JT & Wechsler ME. BMJ 2014;349:g5517. 4. Busse WW et al. Lancet 2010;376:826-834. 5. Gill MA et al. J Immunology 2010;184:5999-6006. 6. Durrani SR et al. J Allergy Clin Immunol 2012;130:489-495. 7. Pritchard AL et al. J Immunology 2012;188:5898-5905. 8. Rowe RK, Gill MA. Immunol Allergy Clin N Am 2015;35:115-127. 9. Soto-Quiros J et al. J Allergy Clin Immunol 2012;129:1499-1505.

The role of IgE in asthma and the allergic inflammatory cascade



JAMA. 2017;318(3):279-290

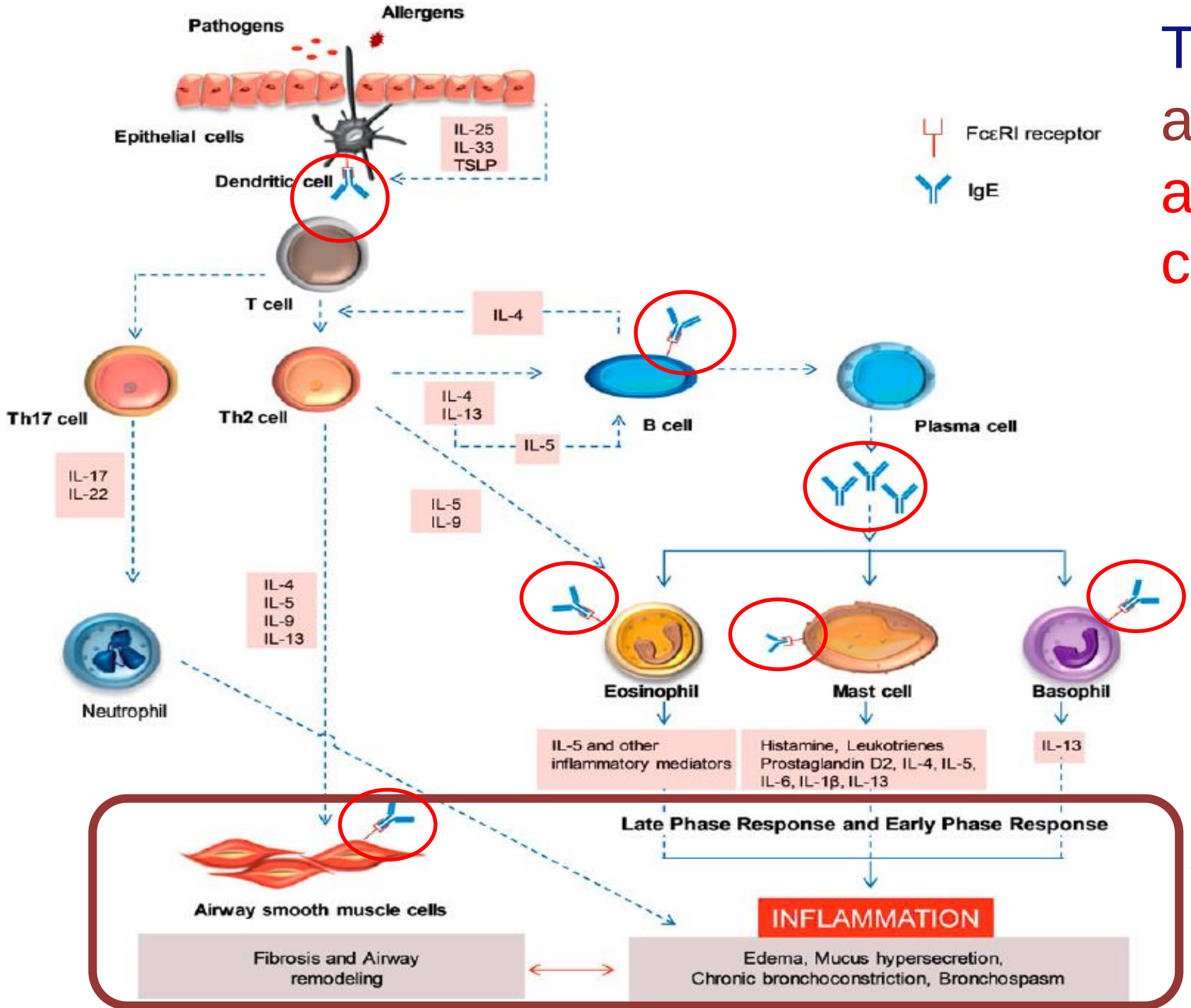
Current Medical Research and Opinion 2017,

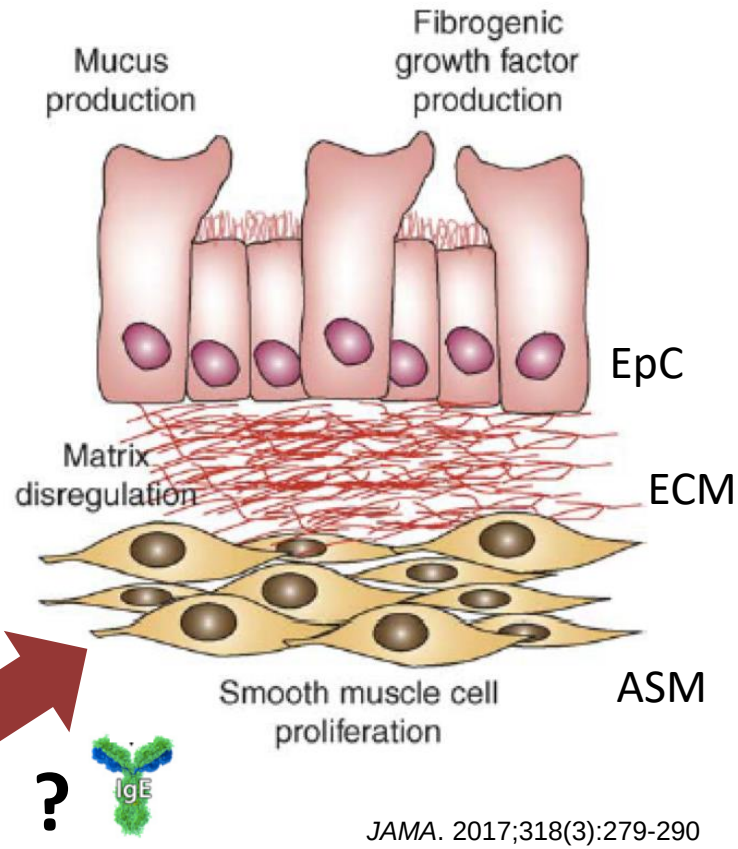
Type 2 Biomarkers and biologics in (severe) asthma

Biomarker	Prognostic	Theragnostic (the ability to predict treatment effect)	Therapeutic Target
Blood eosinophil counts	++	++: Anti-IL5 Anti-IL5R Anti-IL4Rα +: Anti-IgE	Yes
FeNO	++	++: Anti-IL4Rα +: Anti-IgE Anti-IL5 Anti-IL5R	No
Serum total IgE	-	±	Yes Local allergen-specific IgE

Guy Brussel ERS 2019

The role of IgE in asthma and the allergic inflammatory cascade

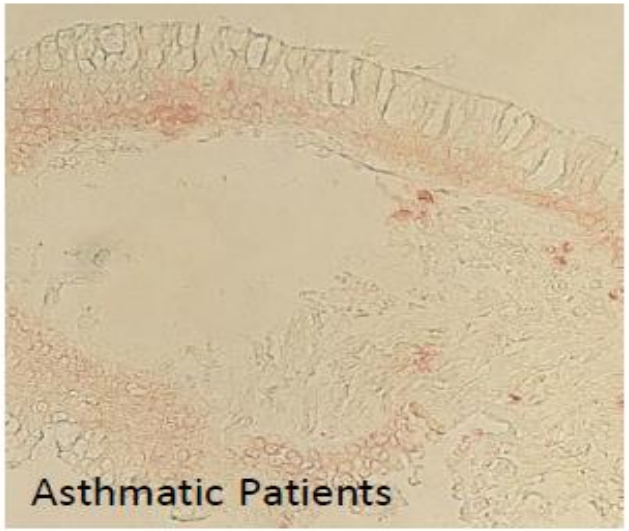


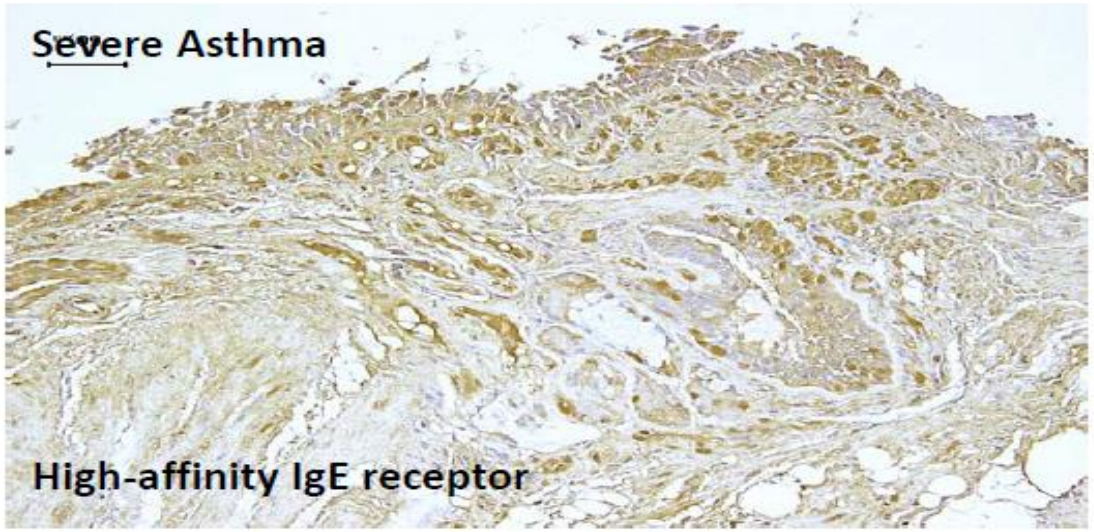


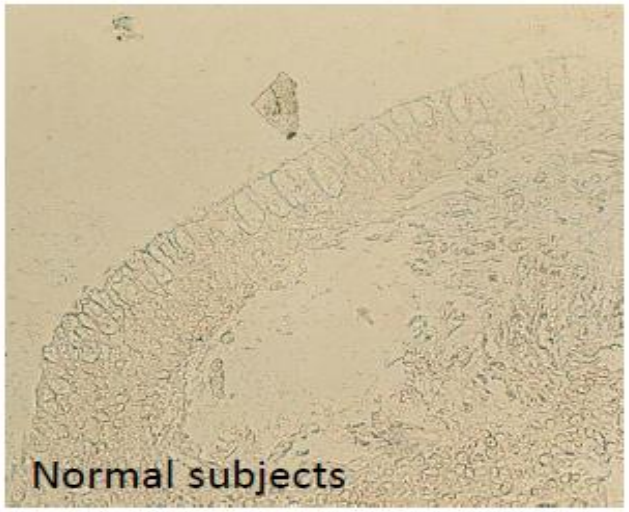
JAMA. 2017;318(3):279-290

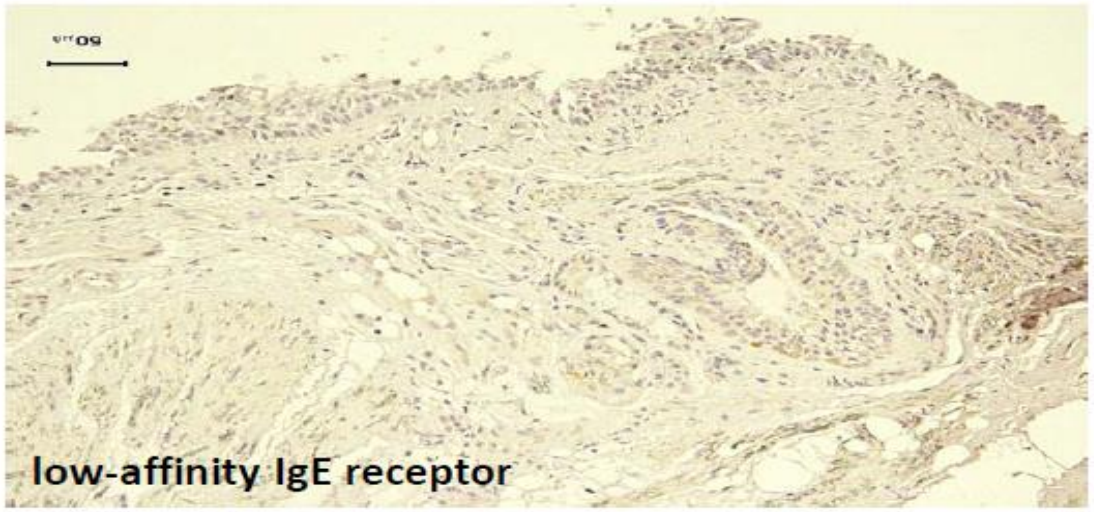
Current Medical Research and Opinion 2017,

Expression of the **High-affinity Receptor for IgE (FcεRIα)** on Bronchial **Epithelial Cells** of Asthmatics



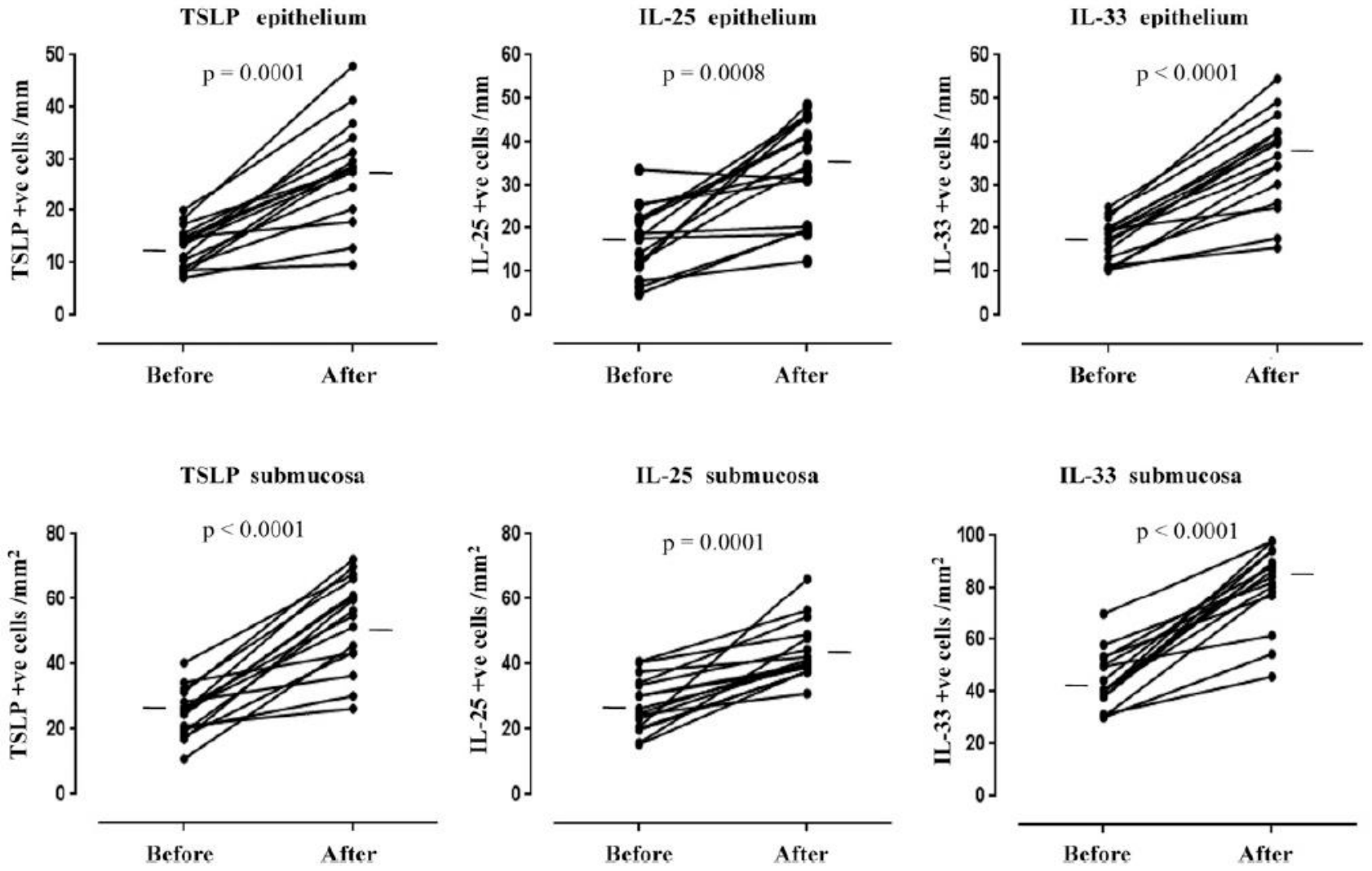






Campbell et al., Am. J. Respir. Cell Mol. Biol. Vol. 19, pp. 92–97, 1998

Increasing alarming production (TSLP,IL-25, IL-33) of airway epithelial cell after allergen challenge in atopic asthma patients



Human Study

J Immunol. 2018 Oct 15;201(8):2221-2231

The Journal of Immunology

Human Airway Smooth Muscle Cells Express the High Affinity Receptor for IgE (Fc εRI): A Critical Role of Fc εRI in Human Airway Smooth Muscle Cell Function

FcRI -chain protein expression by ASM cells

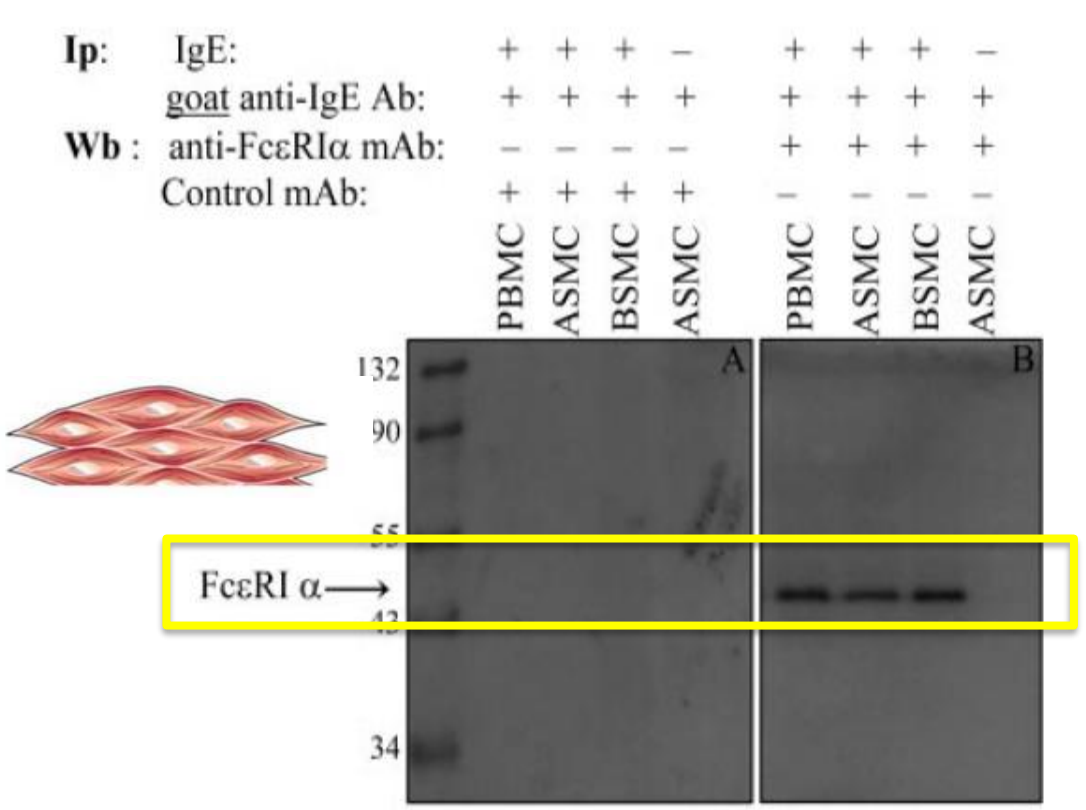
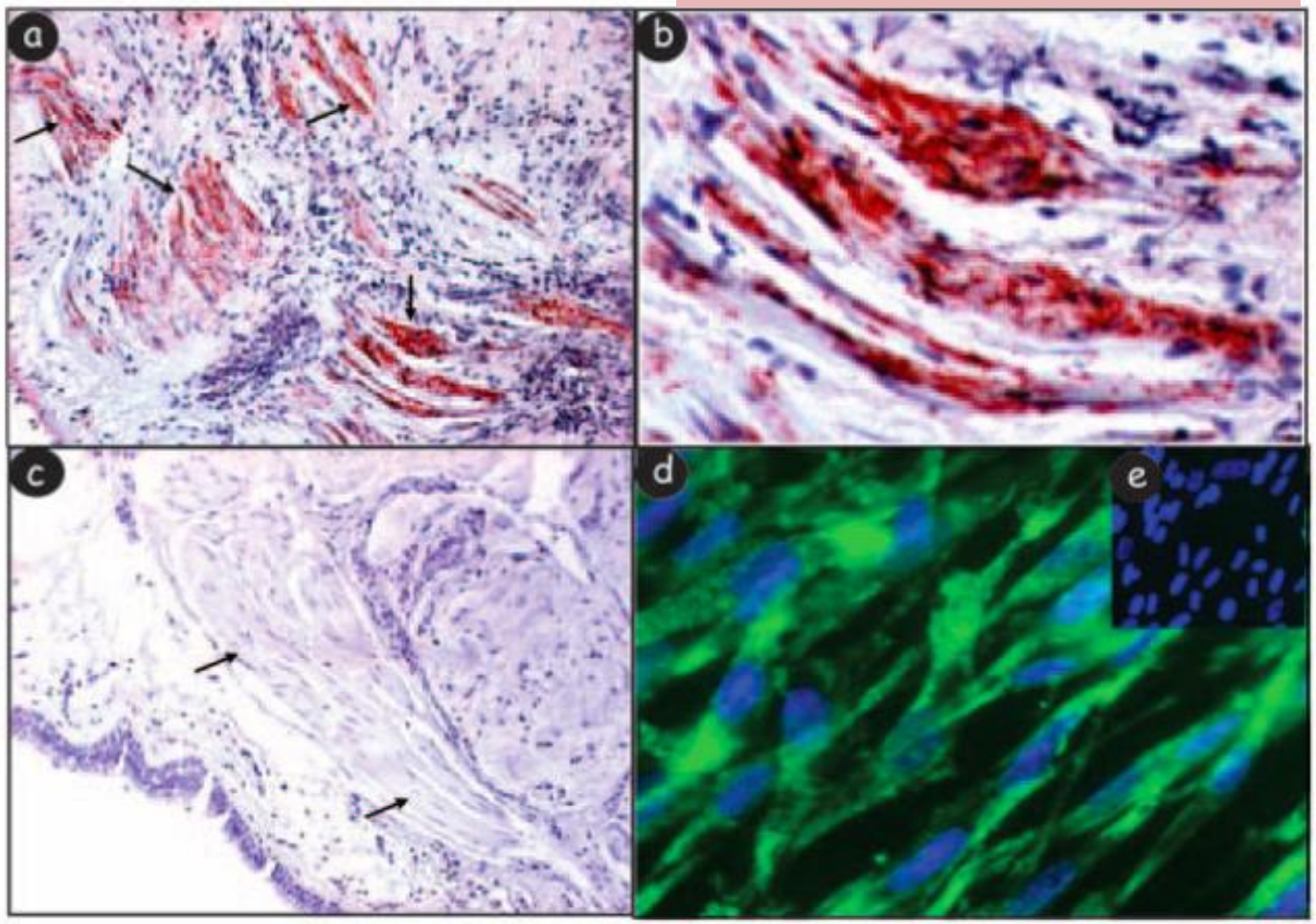


FIGURE 4. FcεRI α-chain protein expression in human B/TSM cells. Cell extract proteins of human PBMC and ASM cells of asthmatic patients or from human B/TSM cells (P2-P5) cultured in serum-free medium were

Ip: Immunoprecipitation, Wb: Western blot

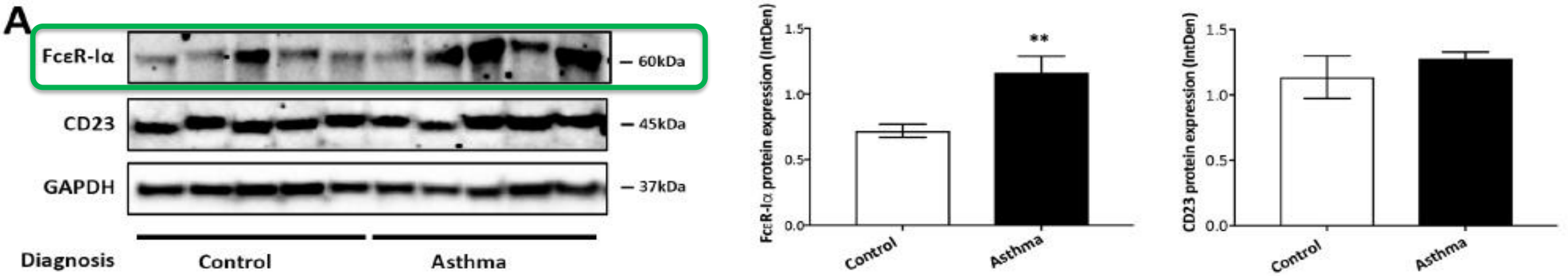
anti-FceRI-chain mAb15–1

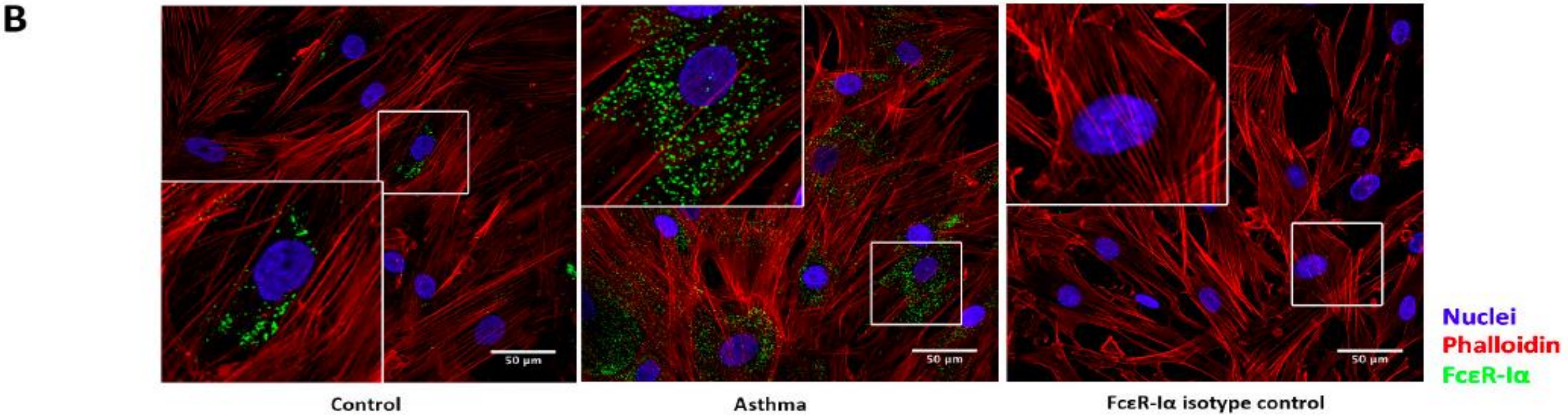


Human Tissue Study

J Immunol 2005; 175:2613-2621

Expression of the High-affinity Receptor for IgE on ASMCs of Asthmatics





Human Tissue Study

GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

Int. J. Mol. Sci. 2019, 20, 875

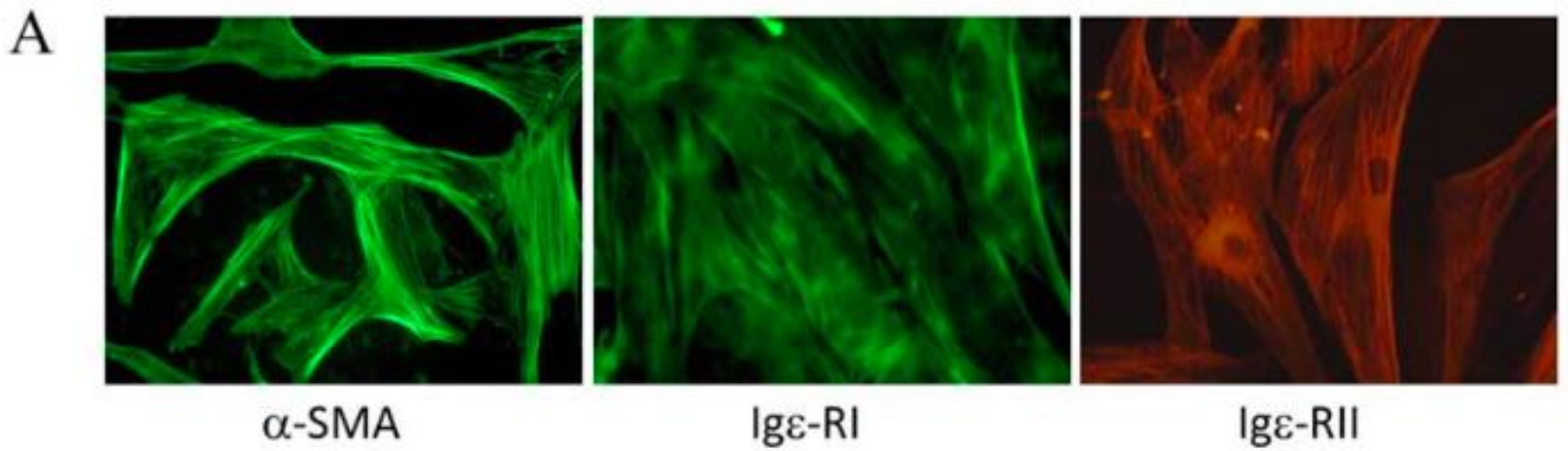
OPEN ACCESS Freely available online

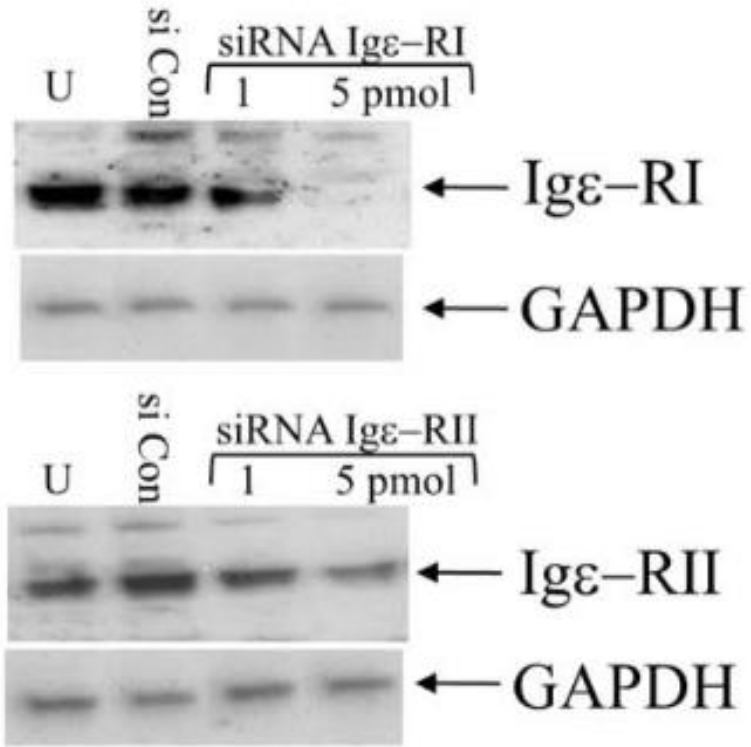
PLOS ONE

The Role of IgE-Receptors in IgE-Dependent Airway Smooth Muscle Cell Remodelling

Michael Roth[1,2]*, Jun Zhong[1], Celine Zumkeller[1], Chong Teck S'ng[1], Stephanie Goulet[1], Michael Tamm[2]

1 Pulmonary Cell Research, Department Biomedicine, University of Basel, Basel, Switzerland, **2** Pneumology, Department Internal Medicine, University Hospital Basel, Basel,





A) ASMC immunofluorescence staining for filamentous a-SMA, Ige-RI and Ige-RII. (B) Immune-blot of Ige-RI and Ige-RII siRNA treatment (48 hours) on protein expression

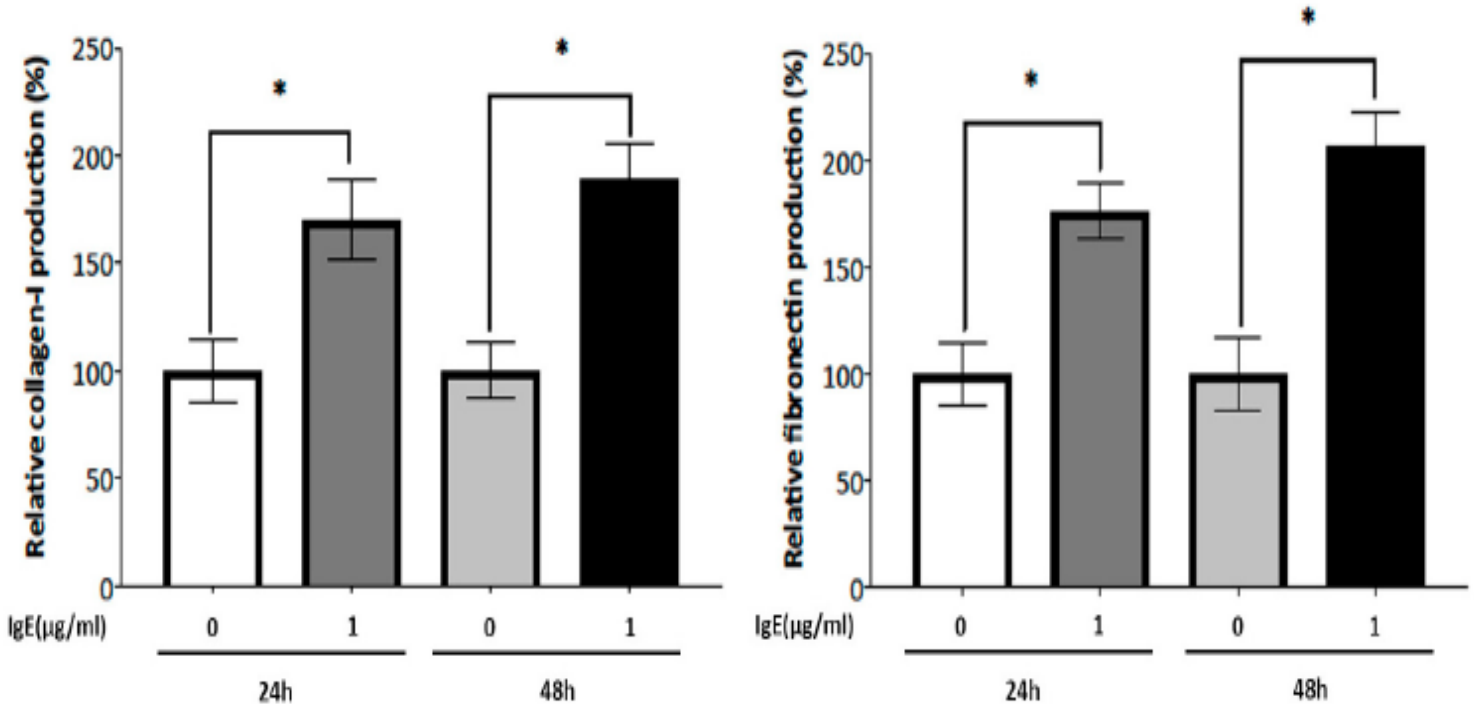
siCon: control siRNA; U: untreated cells;
SiRNA: Small Interfering RNA
GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

Human Tissue Study

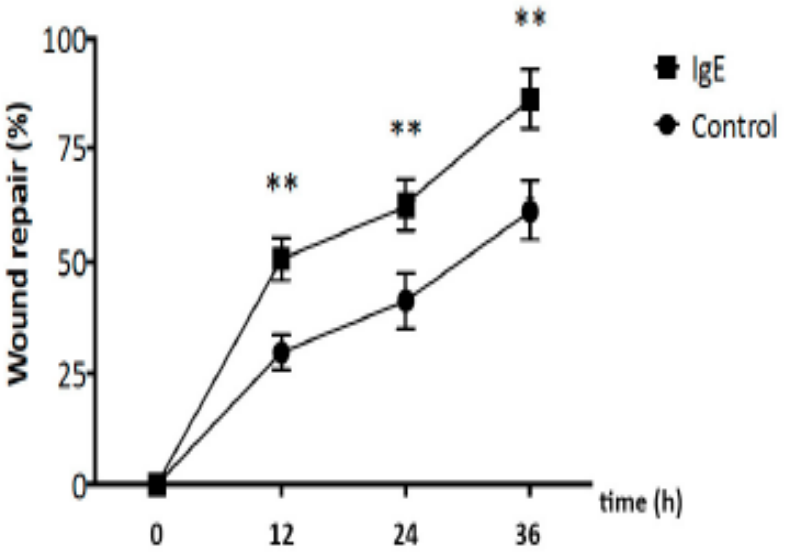
PLoS One. 2013;8:e56015.

IgE stimulated ECM deposition, and ASMC migration in ASMCs of asthmatic patients

* $p < 0.05$



Cell-based ELISA assessed IgE-induced deposition of collagen type-I and fibronectin by asthmatic ASMC at 24 and 48 h.



Cell migration was assessed by measuring the width of a wound at 12, 24, and 36 h in the absence (control) or presence of IgE

Human Tissue Study

Int. J. Mol. Sci. 2019, 20, 875

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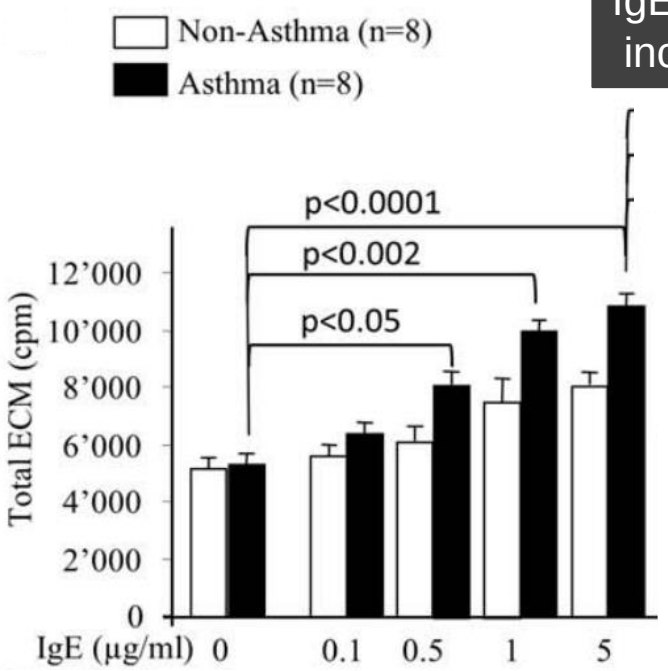
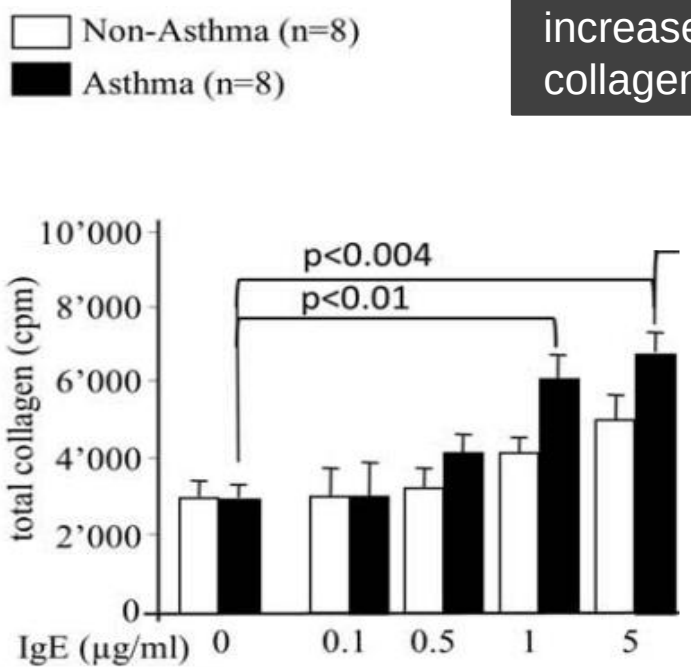
1 Pulmonary Cell Research, Department Biomedicine, University of Basel, Basel, Switzerland, **2** Pneumology, Department Internal Medicine, University Hospital Basel, Basel, Switzerland

IgE induced the increase of ECM



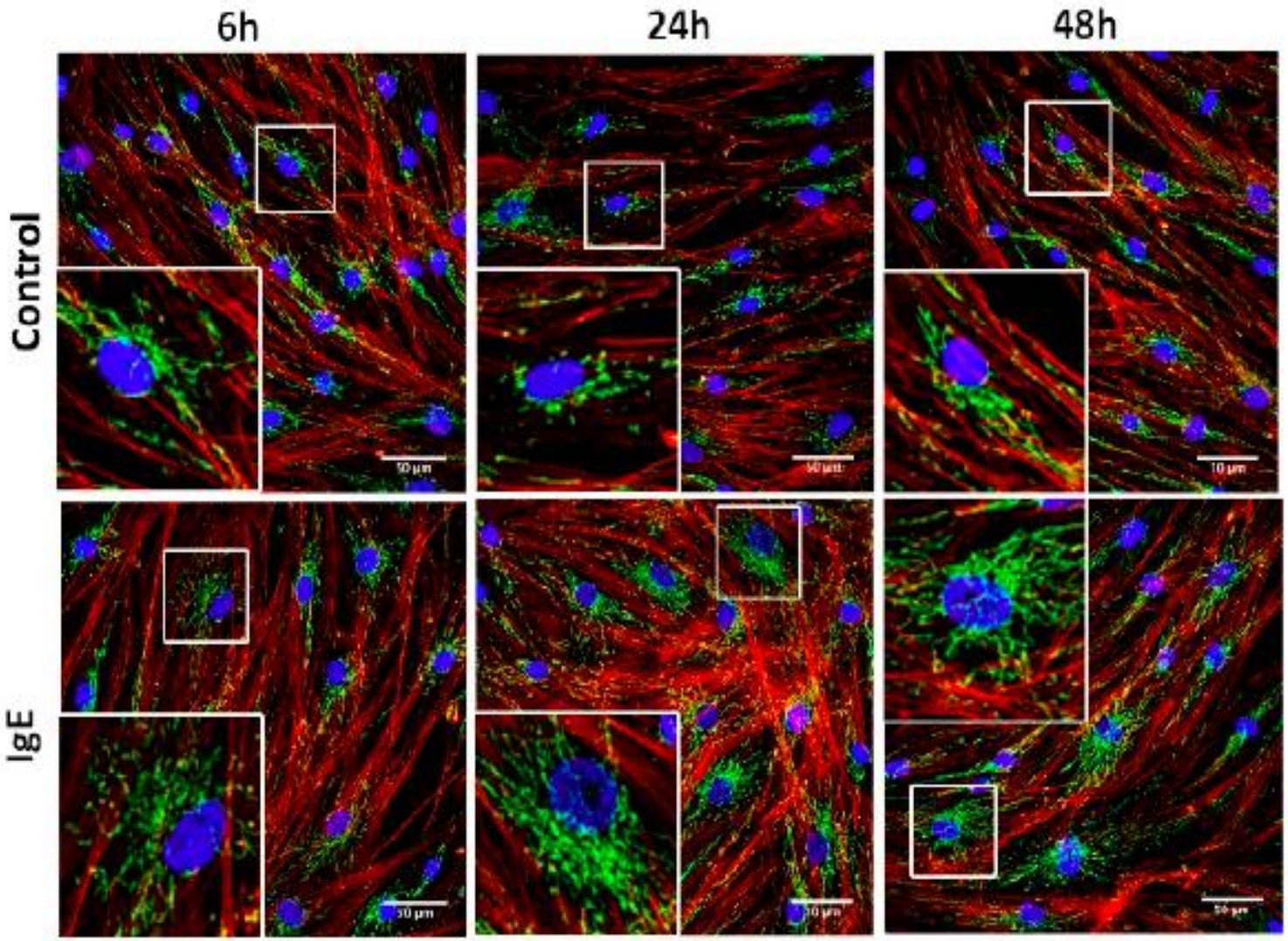
IgE induced the increase of collagen deposition

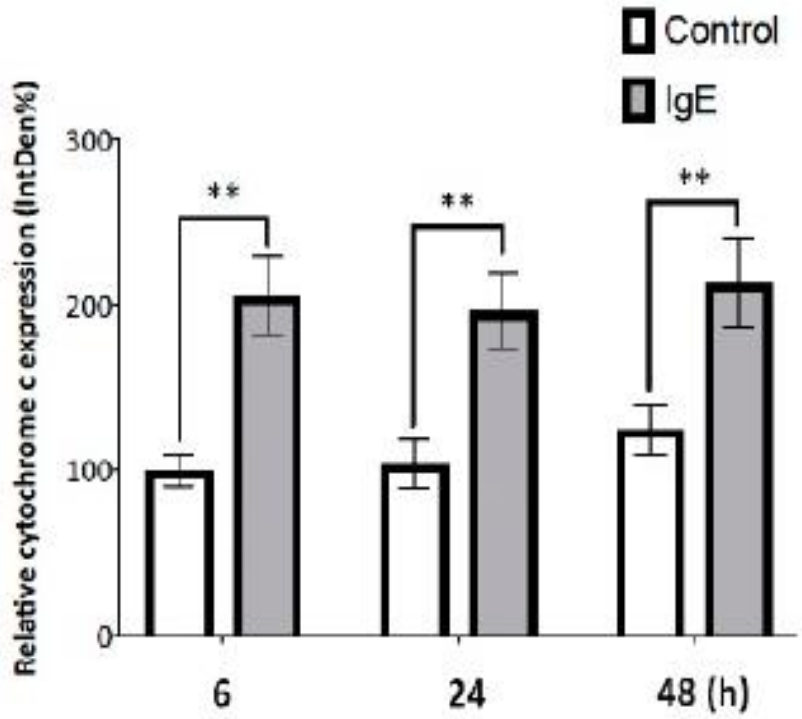


ECM : Extracellular matrix

PLoS One. 2013;8:e56015.

IgE Upregulated the Expression of Mitochondria-Related Genes and Proteins in ASMC

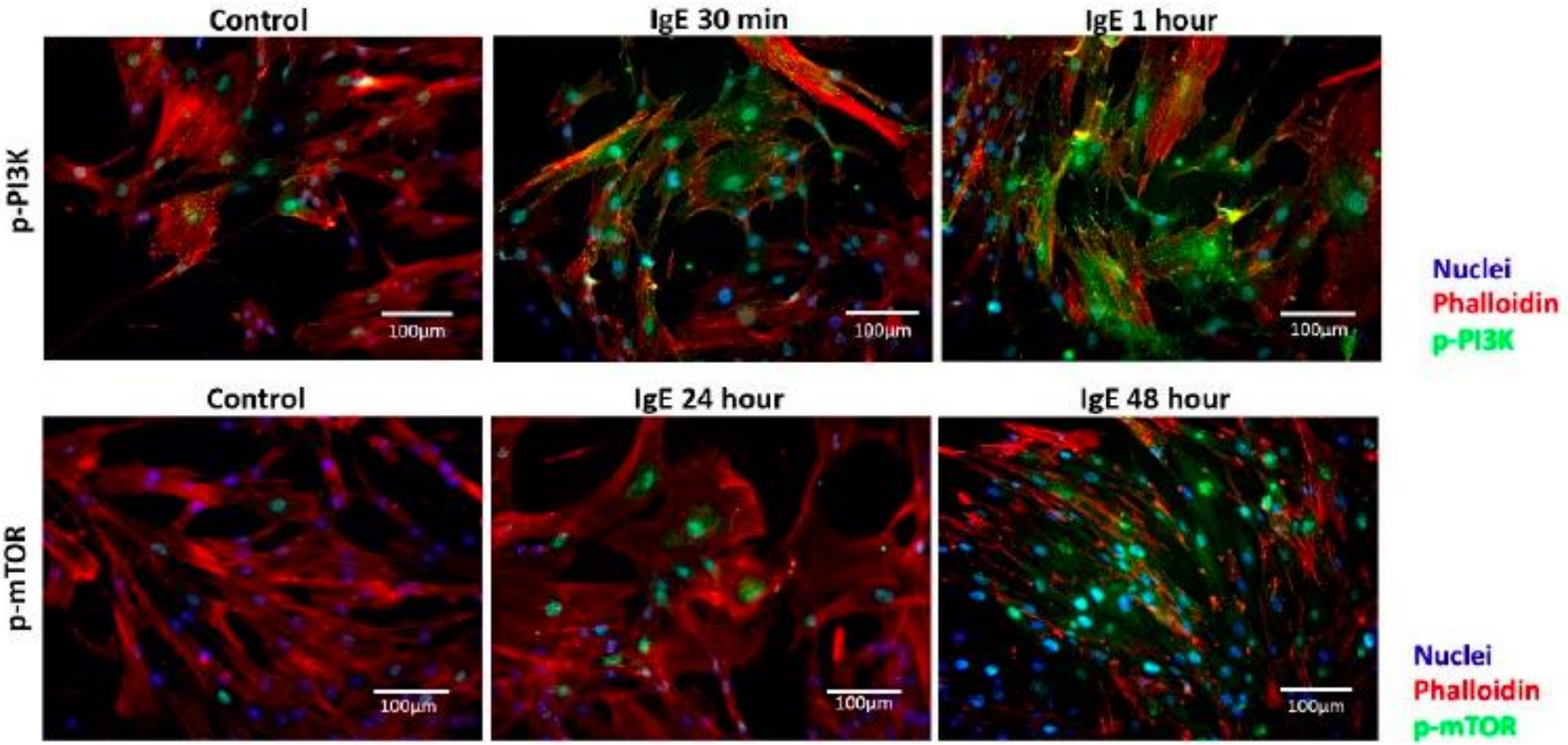




Human Tissue Study

Int. J. Mol. Sci. 2019, 20, 875

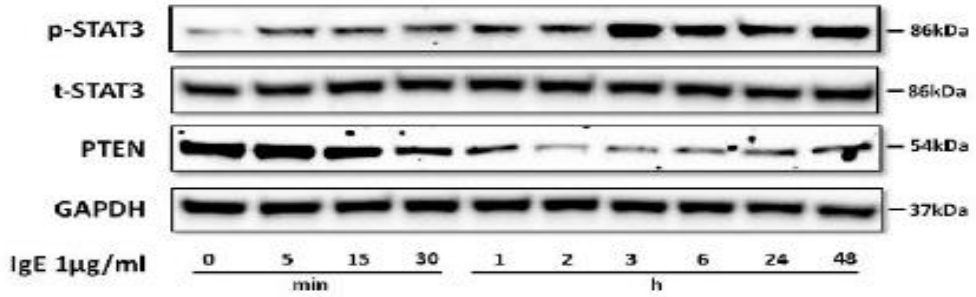
IgE activated PI3K→ AKT → mTOR and STAT3 → microRNA-21-5p, down-regulating PTEN in ASMC

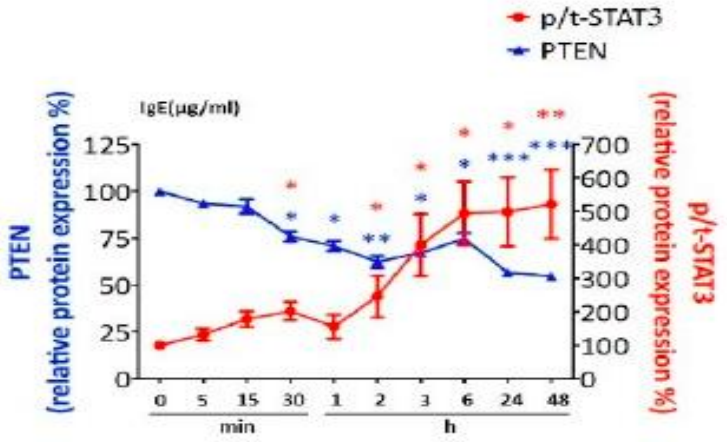


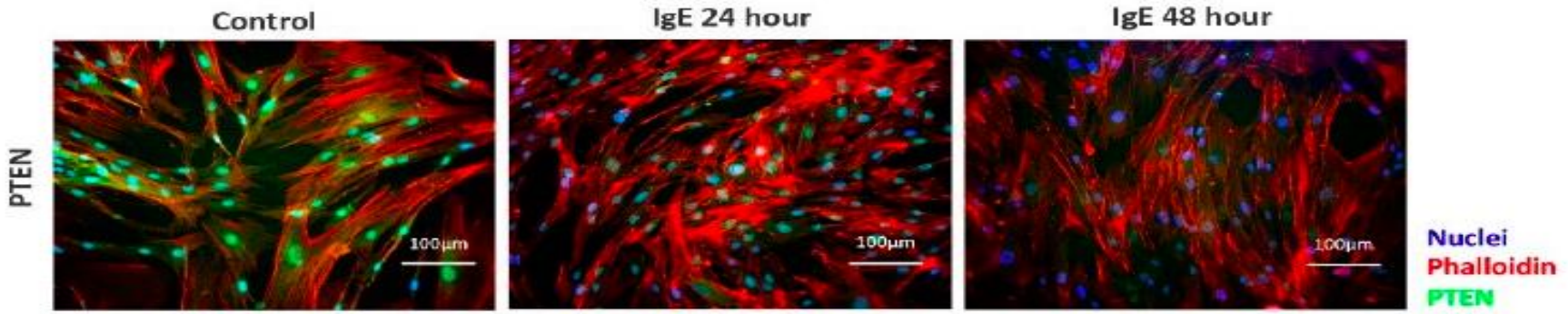
STAT3 signal transducer and activator of transcription
PTEN phosphatase and tensin homolog gene

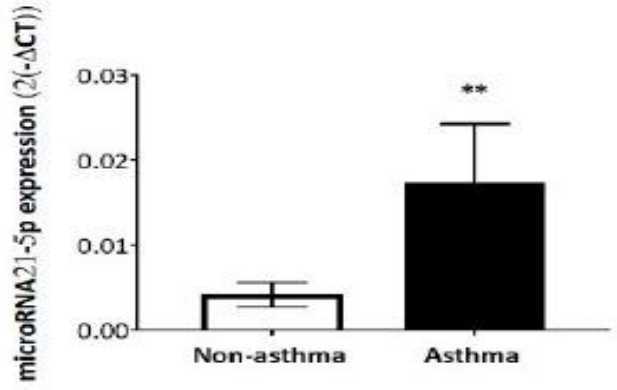
Int. J. Mol. Sci. 2019, 20, 875

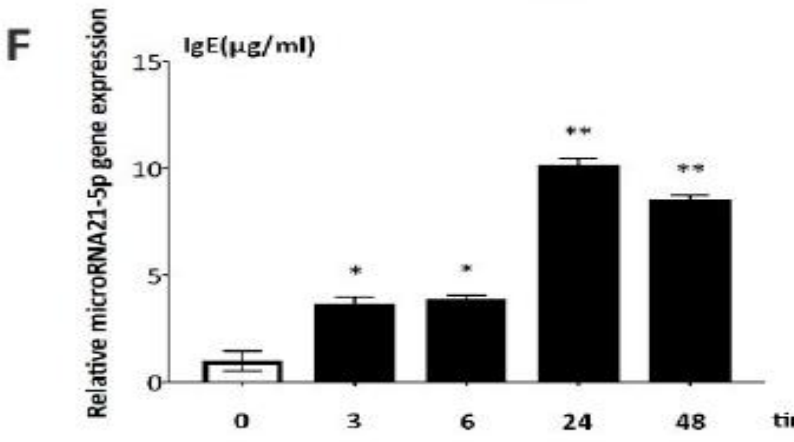
IgE activated PI3K→ AKT → mTOR and STAT3 → microRNA-21-5p, down-regulating PTEN in ASMC









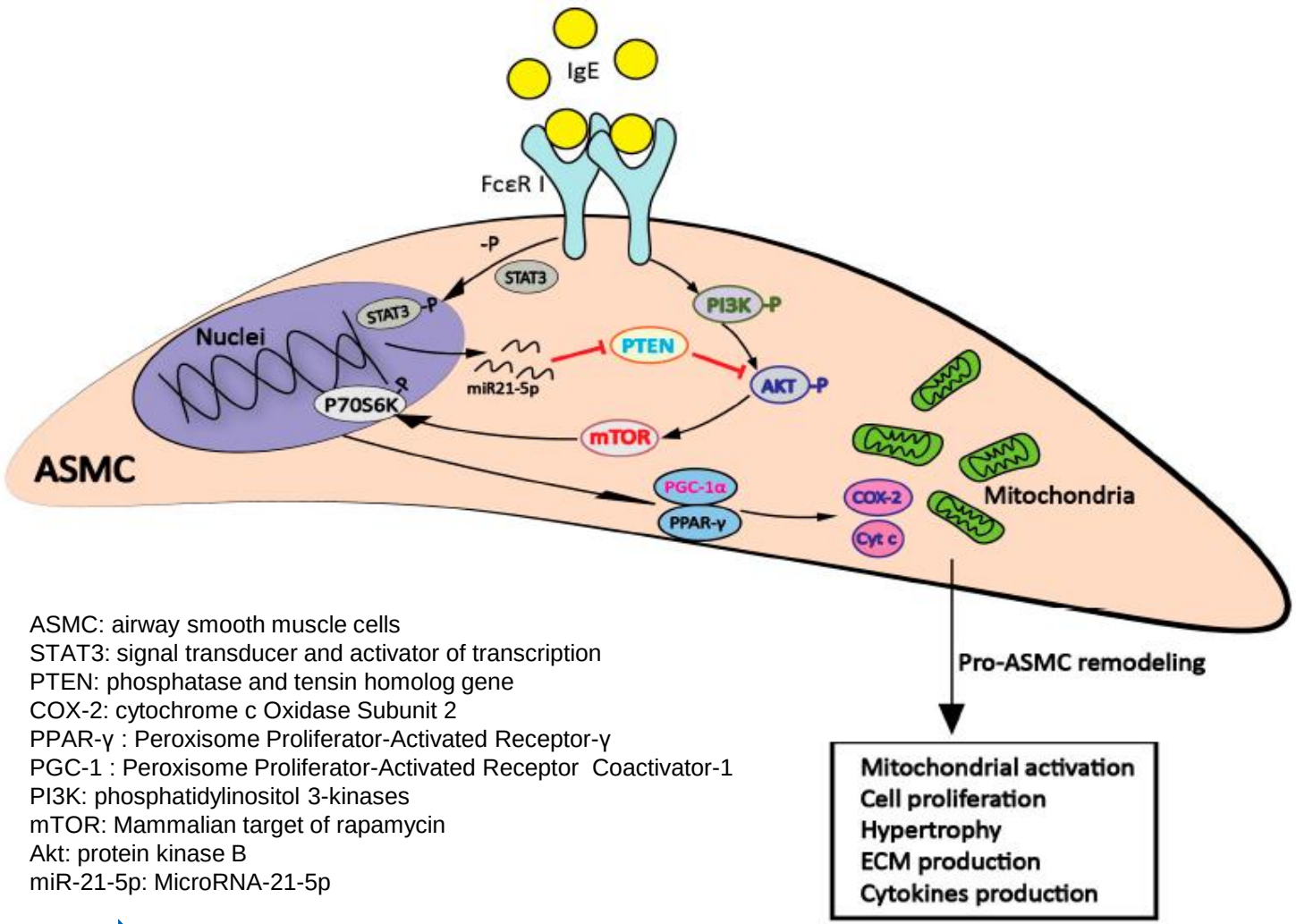


ASMC	airway smooth muscle cells
MAPK	mitogen activated protein kinases
STAT3	signal transducer and activator of transcription
PTEN	phosphatase and tensin homolog gene
COX-2	cytochrome c Oxidase Subunit 2
PPAR-γ	Peroxisome Proliferator-Activated Receptor-γ
PGC-1α	Peroxisome Proliferator-Activated Receptor γ Coactivator-1α

Human Tissue Study

Int. J. Mol. Sci. 2019, 20, 875

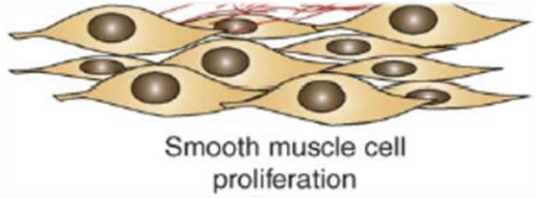
IgE activated two signaling pathways in ASMC cells

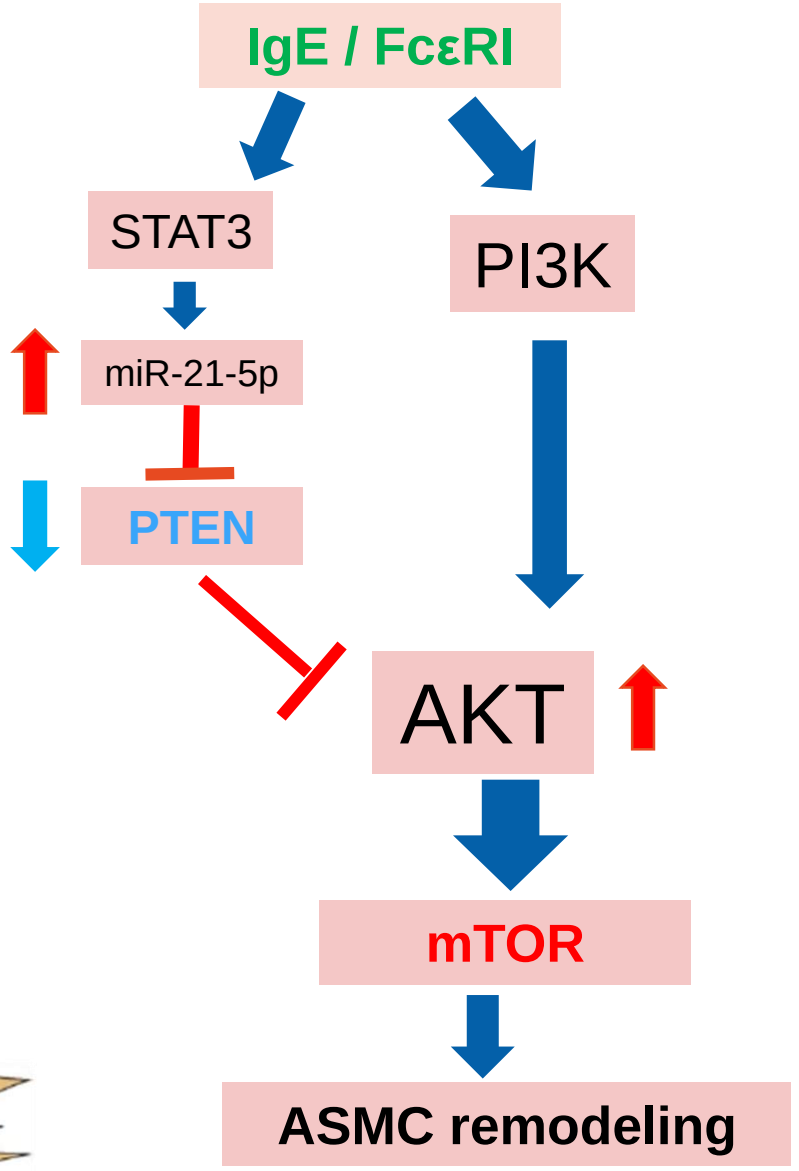


ASMC: airway smooth muscle cells
STAT3: signal transducer and activator of transcription
PTEN: phosphatase and tensin homolog gene
COX-2: cytochrome c Oxidase Subunit 2
PPAR-γ : Peroxisome Proliferator-Activated Receptor-γ
PGC-1 : Peroxisome Proliferator-Activated Receptor Coactivator-1
PI3K: phosphatidylinositol 3-kinases
mTOR: Mammalian target of rapamycin
Akt: protein kinase B
miR-21-5p: MicroRNA-21-5p

Positive Feedback

Negative Feedback





Int. J. Mol. Sci. 2019, 20, 875

Human Tissue Study

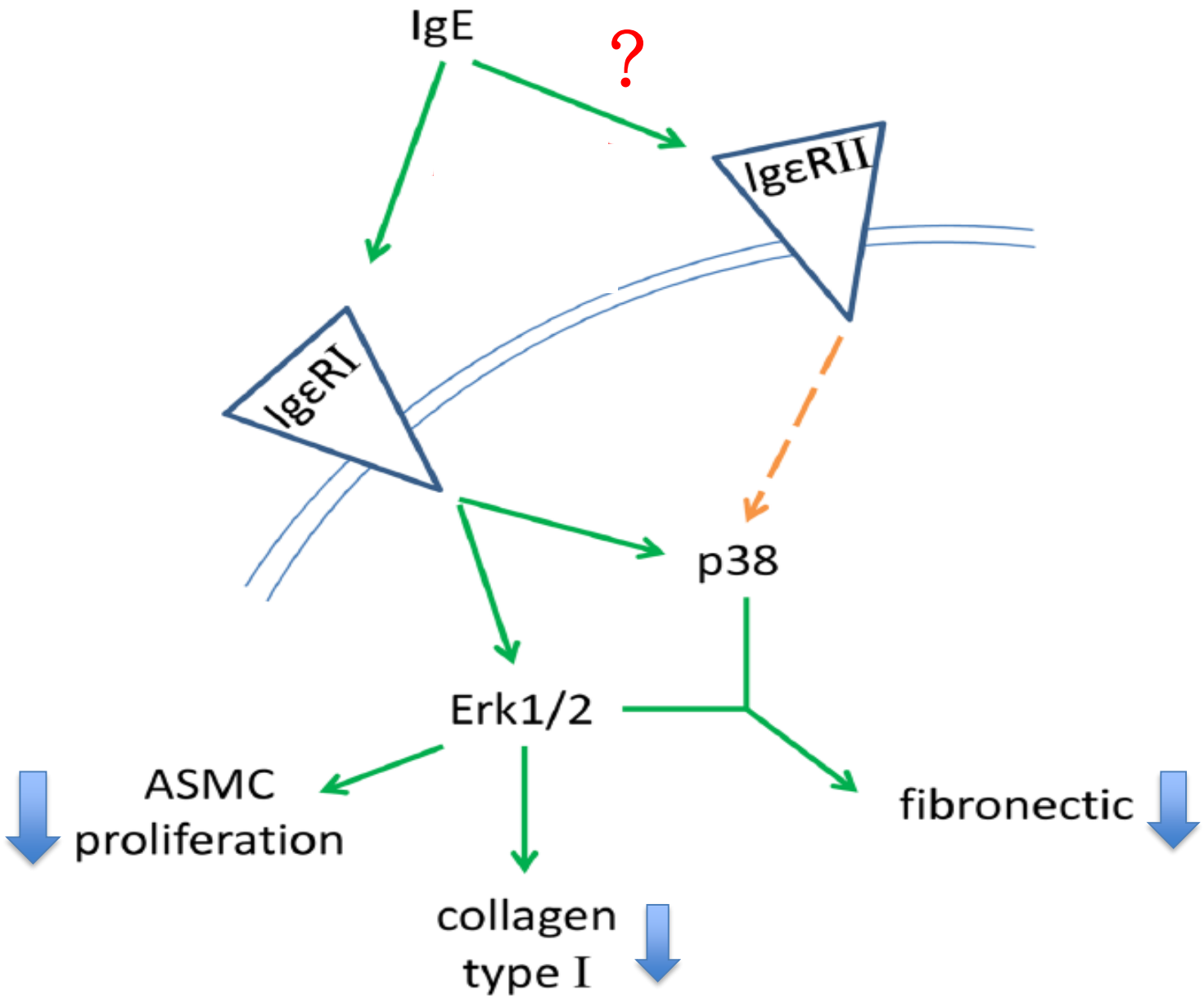


Fig 4. Hypothesized signal pathway for IgE induced airway wall remodeling in human airway smooth muscle cells.

doi:10.1371/journal.pone.0136549.g004

Outlines

- Airway remodeling in asthma
- The role of IgE in airway remodeling of asthma
  - Classical and Cytokinergic IgE
  - IgE plays an important role in severe asthma
  - Effects of IgE on airway smooth muscle cells
- **Evidences of anti-IgE reverse Airway remodeling of asthma**
  - The relationship between omalizumab and related inflammatory mediators
  - The efficacy of omalizumab in reducing blood eosinophils
  - Structure change after omalizumab treatment
  - Lung function improvement after omalizumab treatment

First author [ref.]	Year	Study design	Main findings
Gounni [30]	2005	Experimental study *In vitro* (HASM cells from atopic asthmatics, n=6)	HASM cells express FcεRI (high-affinity IgE receptor) IgE stimulation triggered HASM contraction and IL-4, IL-5, IL-13 and eotaxin release
Kang [70]	2010	Experimental study Murine model of chronic asthma Three groups (control, OVA and omalizumab + OVA)	Omalizumab decreased airway hyperresponsiveness, BALF inflammatory cell counts, BALF IL-5 and IL-13 levels, peribronchial collagen III/V, hydroxyproline and α-smooth muscle actin BALF TGF-β and activin-A levels were not significantly altered in the omalizumab group (although both tended to increase)
Roth [31]	2010	Experimental study *In vitro* (primary HASM cells) Three groups (allergic asthma, COPD and control, n=6 each)	IgE stimulation increased IL-6, IL-8 and TNF-α mRNA synthesis and secretion by HASM cells in all groups Omalizumab inhibited IgE-stimulated cytokine secretion in a dose-dependent fashion
Riccio [64]	2012	Clinical study 11 severely allergic asthmatics 1 year omalizumab	Significant reduction in RBM thickness in bronchial biopsies Reduction of the number of infiltrating eosinophils (not significant)
Hoshino [65]	2012	Clinical study 30 severely allergic asthmatics Randomised 1:1 (omalizumab *versus* conventional therapy for 16 weeks)	Omalizumab decreased WA/BSA, WA percentage and T/√BSA and increased Ai/BSA as assessed by computed tomography Omalizumab decreased percentage of sputum eosinophils and increased FEV_1 and AQLQ scores Changes in FEV_1 and sputum eosinophils correlated with changes in WA percentage
Roth [32]	2013	Experimental study *In vitro* (primary HASM cells) Two groups (allergic asthmatics and nonasthmatics, both n=8)	IgE increased HASM cell proliferation and extracellular matrix and collagen deposition in a dose-dependent manner IgE effects were more prominent in asthmatic tissue Pre-incubation with omalizumab prevented all remodelling effects
Redhu [33]	2013	Experimental study *In vitro* (primary HASM)	IgE-induced proliferation of HASM cells *via* MAPK, Akt and STAT3 signalling pathways
Mauri [72]	2014	Clinical study Severely allergic asthmatics (n=8) 1 year omalizumab Proteomics of bronchial biopsies	Omalizumab downregulated bronchial smooth muscle proteins Among extracellular matrix proteins, galectin-3 correlated best with airway remodelling modulation by omalizumab
Tajiri [66]	2014	Clinical study 31 severely allergic asthmatics 48 weeks omalizumab (assessment at baseline, 16 and 48 weeks)	Omalizumab decreased WA percentage and thickness and increased Ai and Ai/BSA as assessed by computed tomography WA percentage changes significantly correlated with the decrease in $FeNO_{50}$ levels and sputum eosinophils

The main findings of important recent clinical and experimental studies directly associating **IgE or anti-IgE treatment** with features of **airway remodeling**

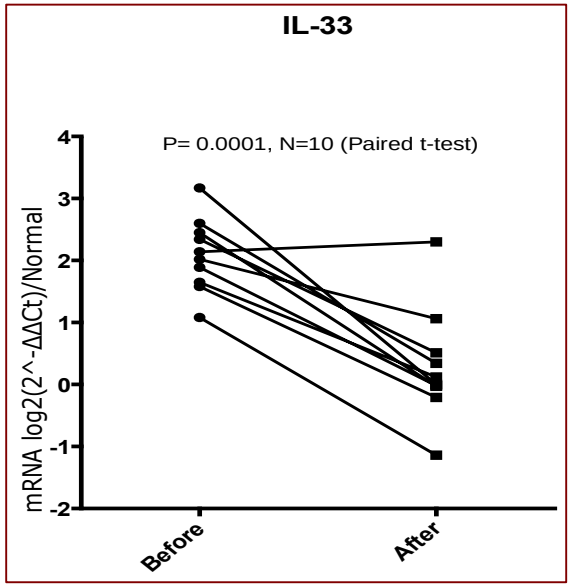
Eur Respir Rev 2015; 24: 594–601

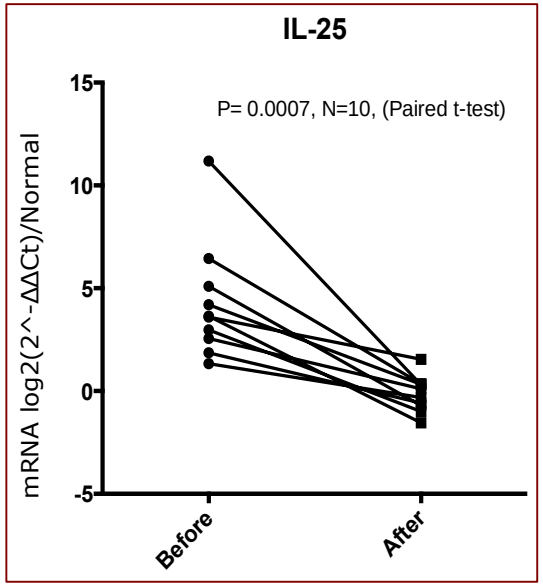
Effects of Blocking IgE

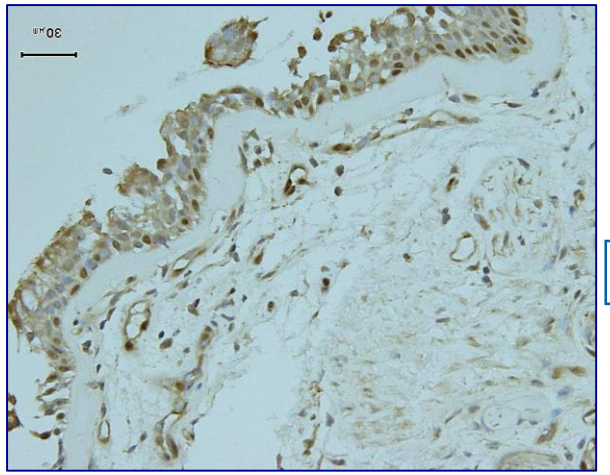
Cell/Effects	Immunomodulatory and antiinflammatory effects of blocking IgE with omalizumab
Mast cells[1] 	• Reduction of FcεRI • Reduction of numbers in lung • Reduction in capacity to release mediators and cytokines
Basophils[2,3] 	• Reduction of FcεRI • Reduction in capacity to release mediators and cytokines
Dendritic cells[4,5] 	• Reduction of FcεRI • Reduction of numbers in lung • Reduction in capacity to activate T cell responses
Eosinophils[6,7] 	• Reduction of numbers in lung
T cells[6] 	• Reduction of total, Th and Tc
B cells[6] 	• Reduction of numbers in lung
Airway remodelling[8,9]	• Reduction of collagen and ECM deposition by SMC *in vitro* • Reduction of proliferation and mediators release

1. Beck LA et al. JACI 2004; 114:527-30
2. Lin H et al. JACI 2004;113:297-302
3. Oliver JM et al. IAAI 2010; 151:275-84
4. Schroeder JT et al. JACI 2010; 124:896-901
5. Chand HS et al. JACI 2010; 125:1157-58
6. Djukanovic R et al. Am J Respir Crit Care Med 2004;170:583-93
7. Takau Y et al. IAAI 2013;161:107-17
8. Zietkowski Z et al. Respiration 2010; 80:534-42
9. Roth M et al. PLoS One 2013; 8:e5601

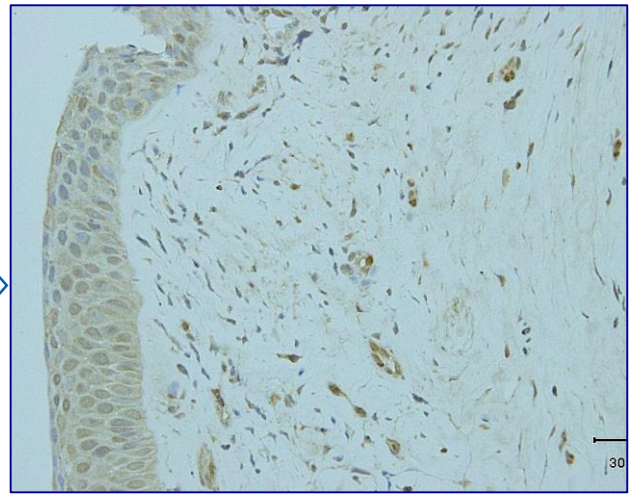
Anti-IgE decreased IL-33, IL-25, TSLP and IL-17A expression in Asthmatic airways







Before



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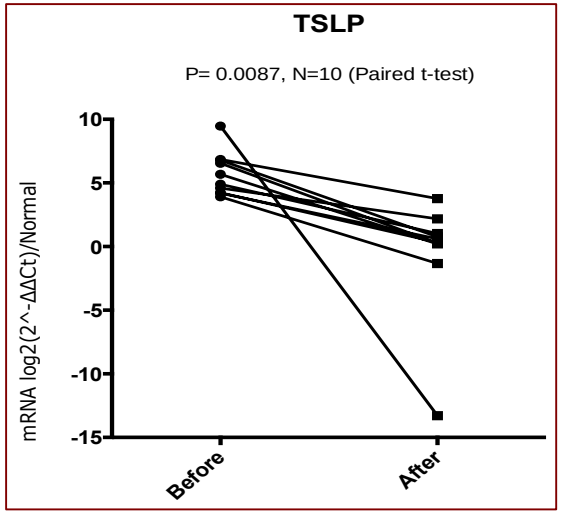
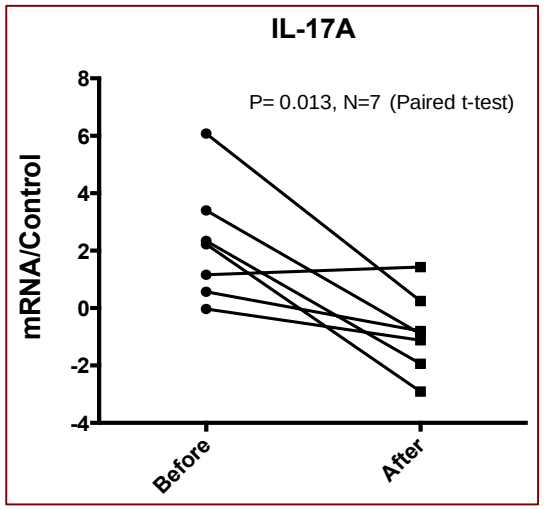
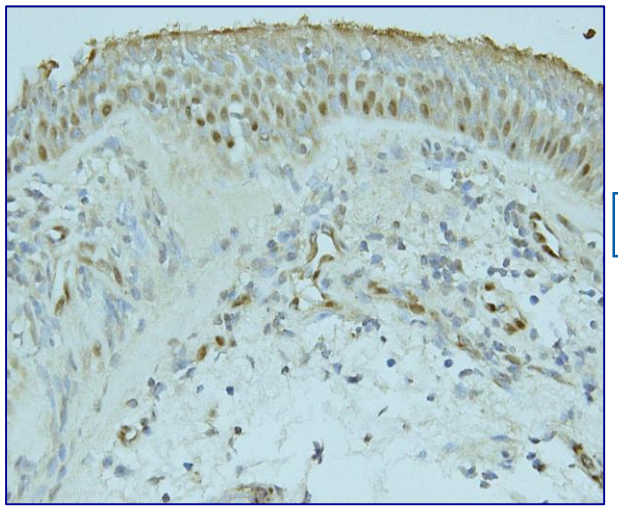
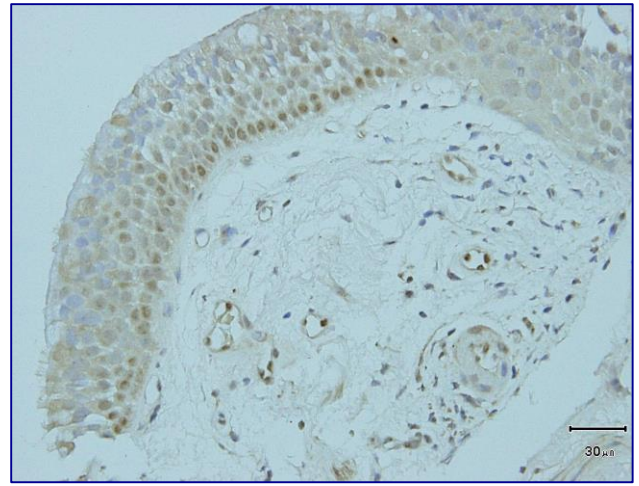








Human Study

Clin Exp Allergy. 2019;49:44–53.

OPEN ACCESS Freely available online

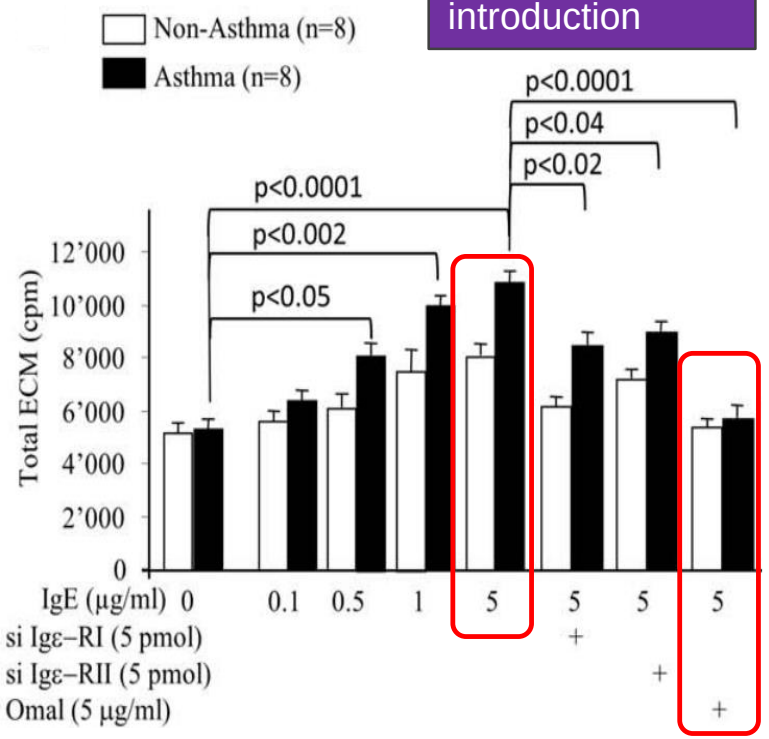
PLOS ONE

The Role of IgE-Receptors in IgE-Dependent Airway Smooth Muscle Cell Remodelling

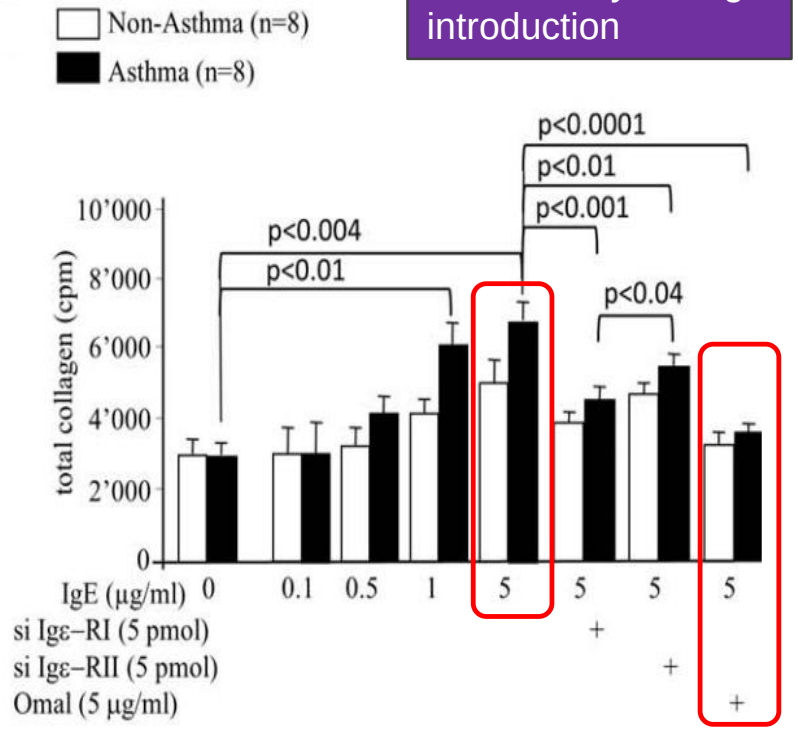
Michael Roth[1,2]*, Jun Zhong[1], Celine Zumkeller[1], Chong Teck S'ng[1], Stephanie Goulet[1], Michael Tamm[2]

1 Pulmonary Cell Research, Department Biomedicine, University of Basel, Basel, Switzerland, 2 Pneumology, Department Internal Medicine, University Hospital Basel, Basel, Switzerland

ECM reduction by anti-IgE introduction



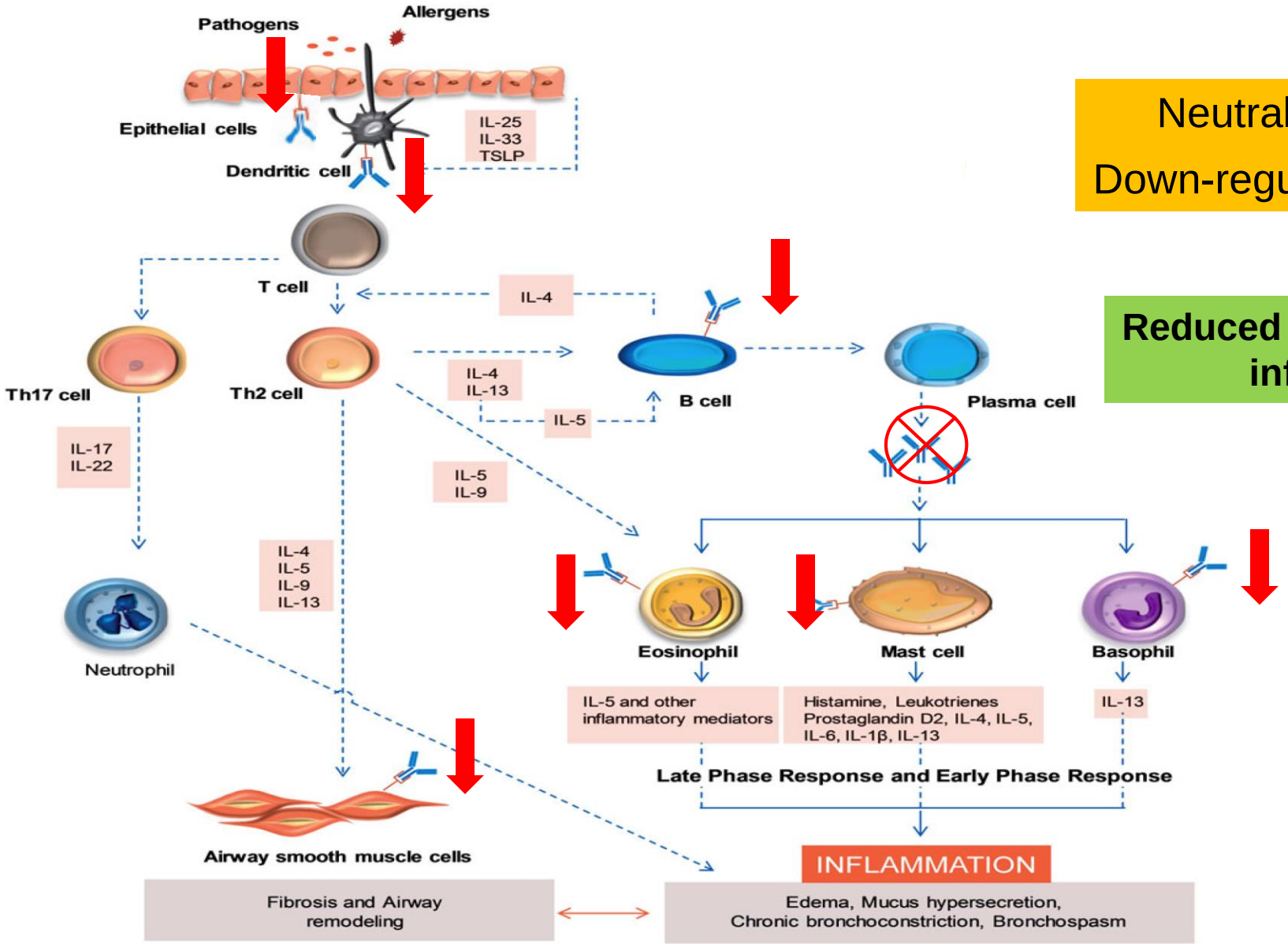
Collagen deposition reduction by anti-IgE introduction



Human Tissue Study

PLoS One. 2013;8:e56015.

Omalizumab mode of action: Reducing levels of circulating free IgE has direct and indirect effects on inflammatory cells



Neutralize free IgE

Down-regulation of FcεRI

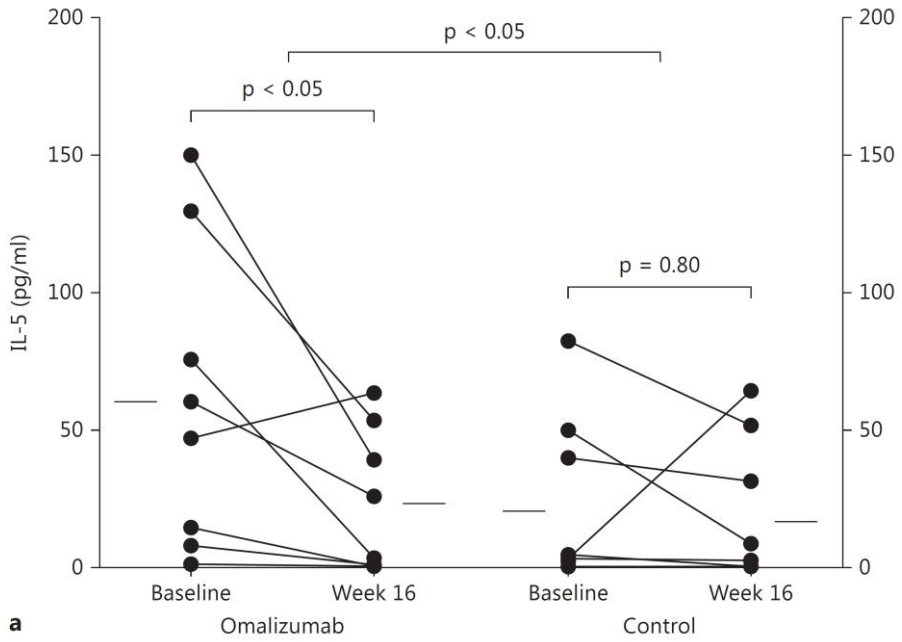
Reduced persistent airway inflammation

Modified from Current Medical Research and Opinion 2017, DOI:10.1080/03007995.2017.1400961

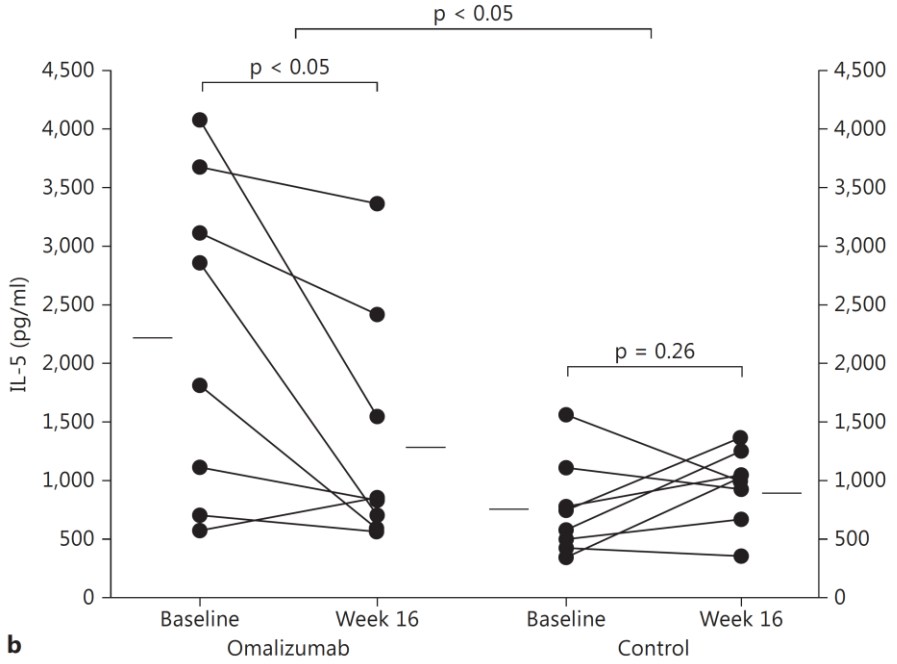
Current Medical Research and Opinion 2017, DOI:10.1080/03007995.2017.1400961
Campbell et al., Am. J. Respir. Cell Mol. Biol. Vol. 19, pp. 92–97, 1998

Ex vivo production of IL-5 by PBMCs decreased significantly after omalizumab treatment

Stimulated with *Df* antigen



Stimulated with ionomycin and PMA

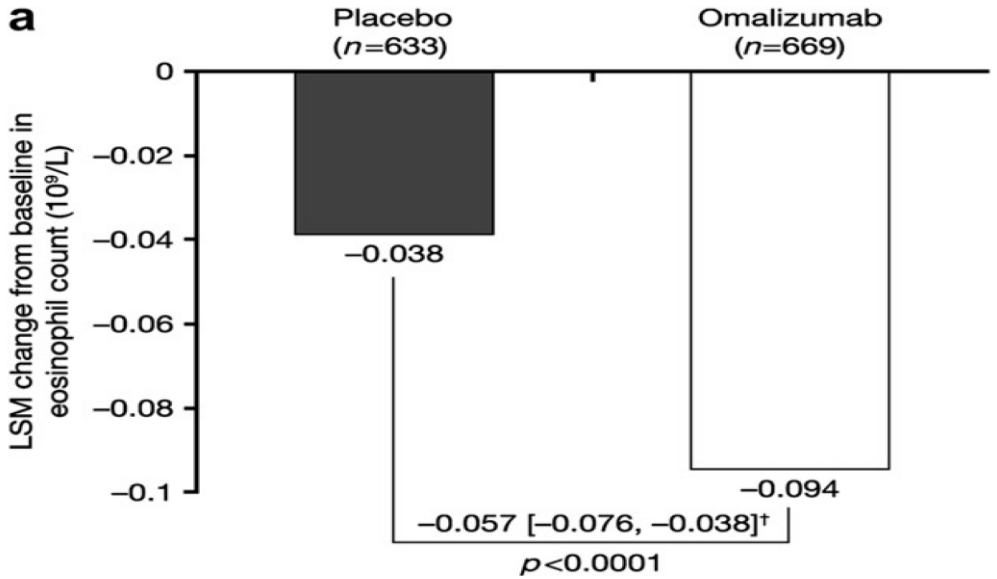


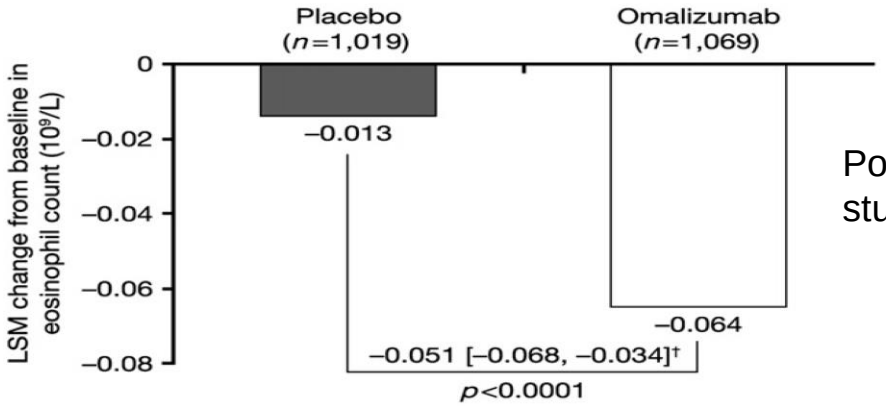
Human Study

Int Arch Allergy Immunol 2013;161(suppl 2):107–117

The longer omalizumab treatment the greater decreased in blood EOS counts

After 16 weeks of omalizumab treatment

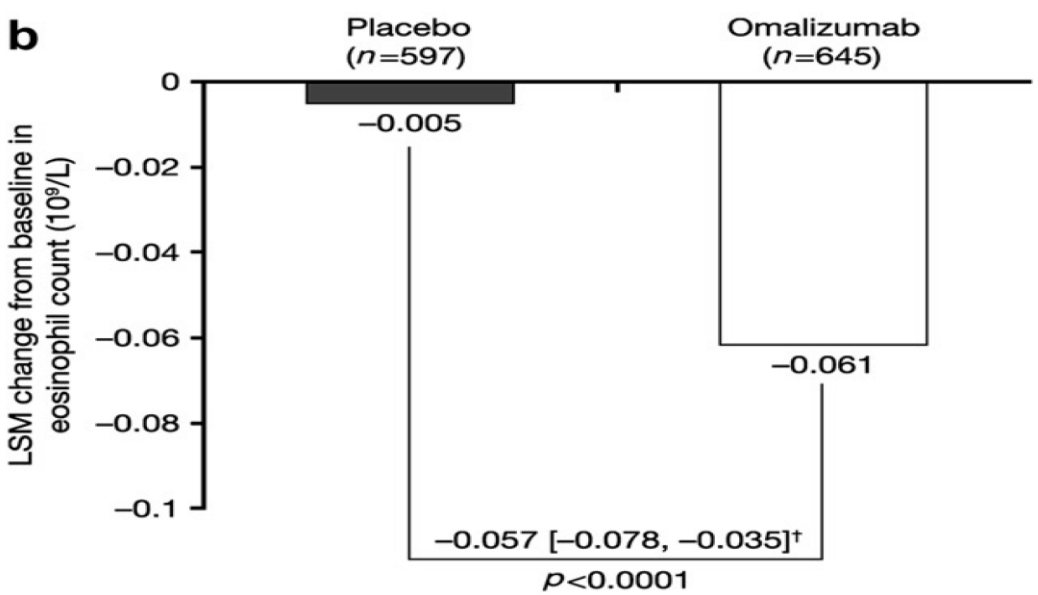




†LSM treatment difference (95% confidence interval)

Pool evidence from 2 studies

After 28 or 32 weeks of omalizumab treatment

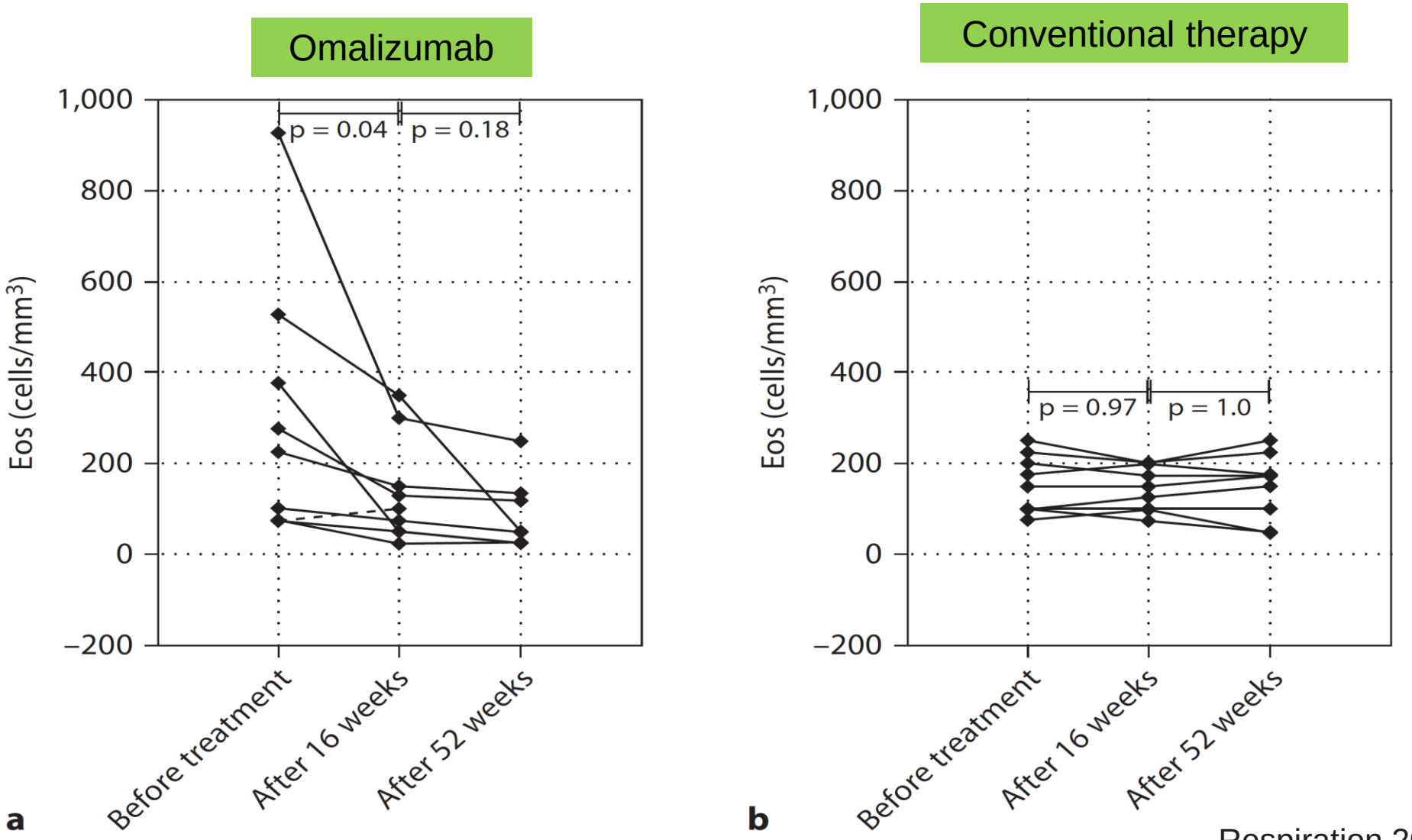


Pool evidence from 3 studies

Human Study

Respiration 2010;80:534–542

The longer omalizumab treatment the greater decreased in blood EOS counts

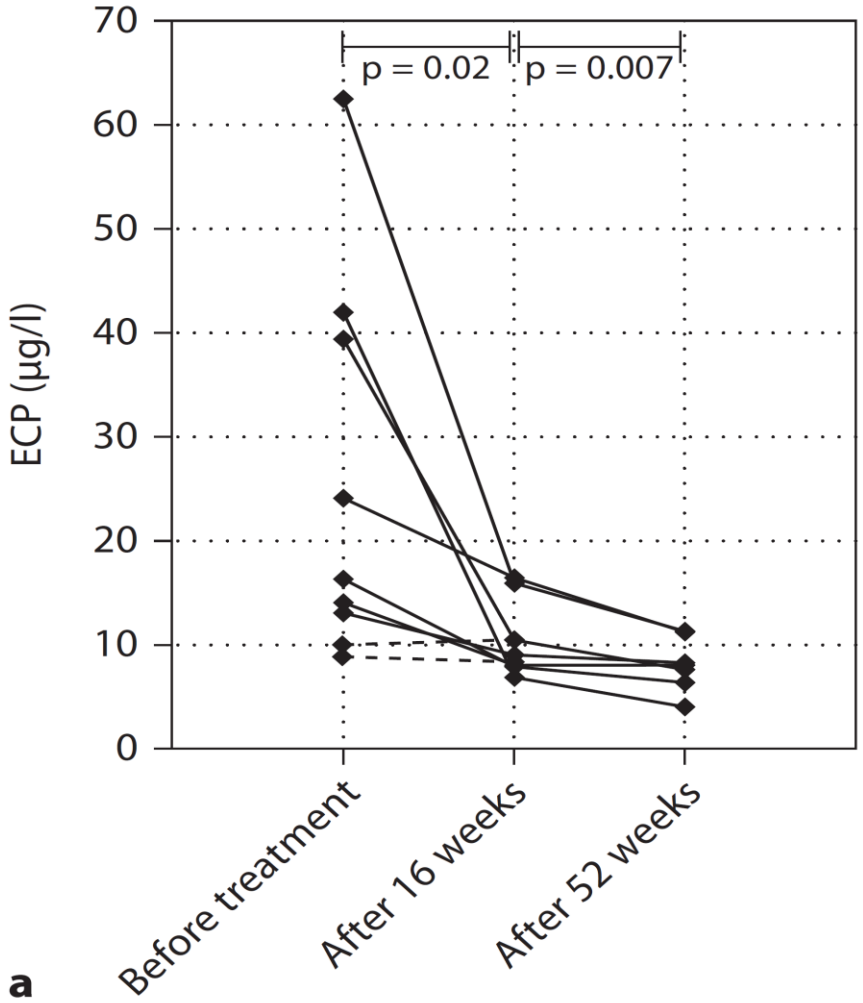


Human Study

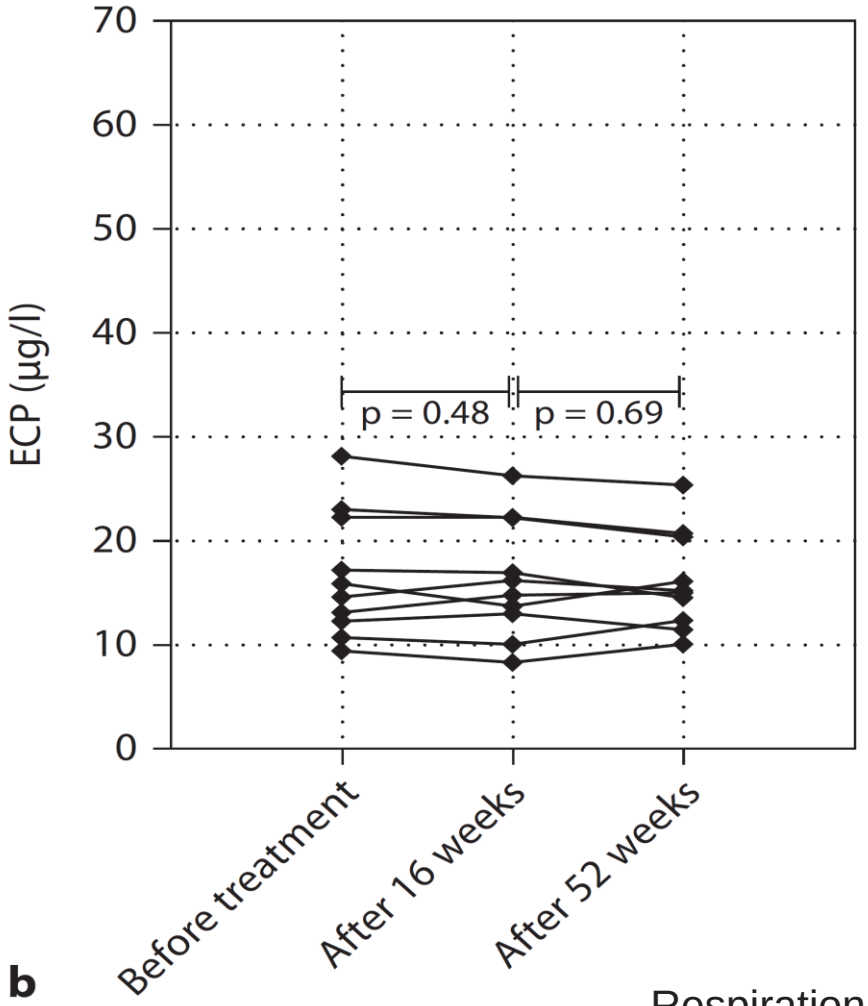
Respiration 2010;80:534–542

Not only EOS counts but ECP decrease significantly after Omalizumab tx

Omalizumab



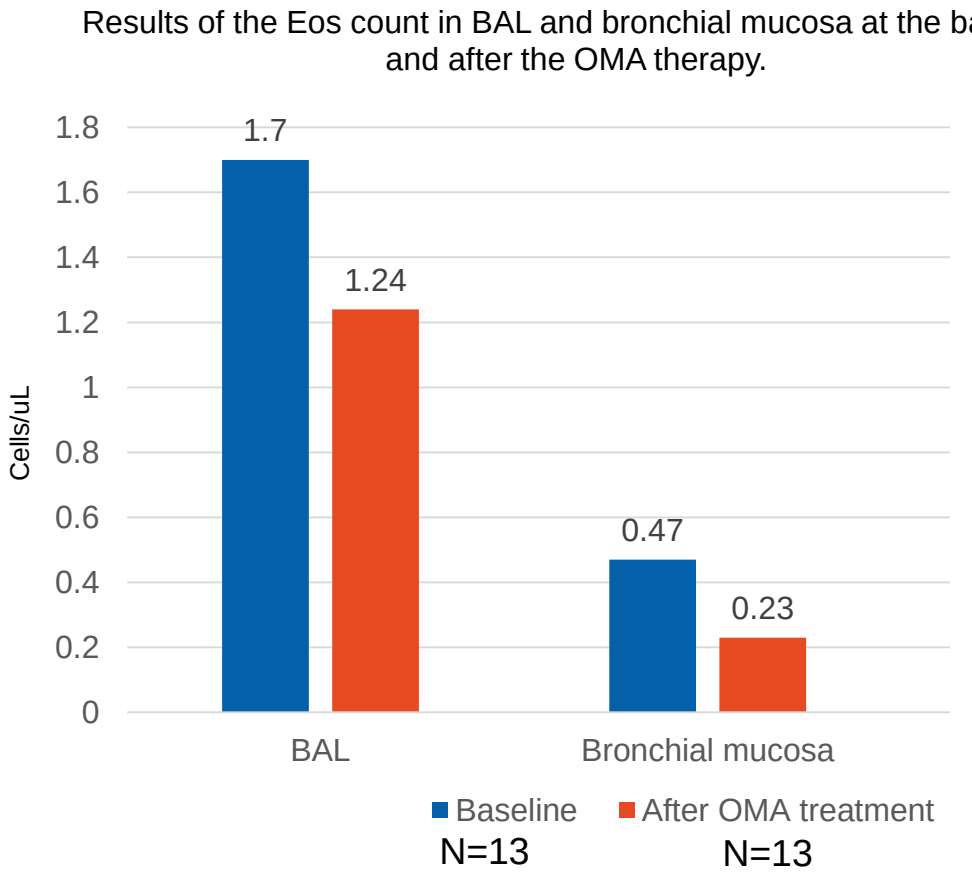
Conventional therapy

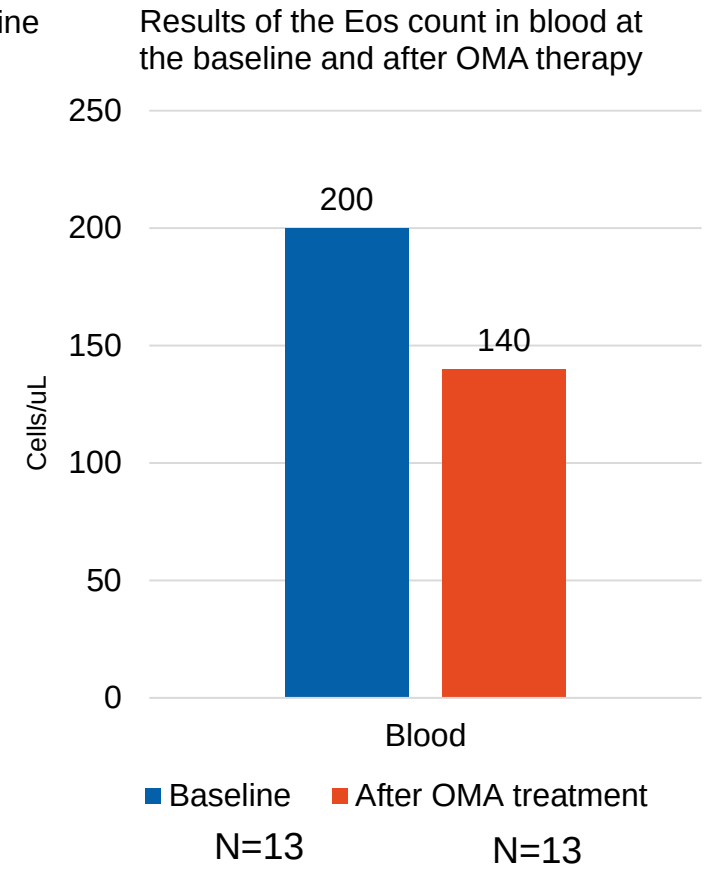


Human Study

Respiration 2010;80:534–542

Omailizumab therapy was also related to the tendency towards reduction of the eosinophil count in blood, BAL and bronchial mucosa



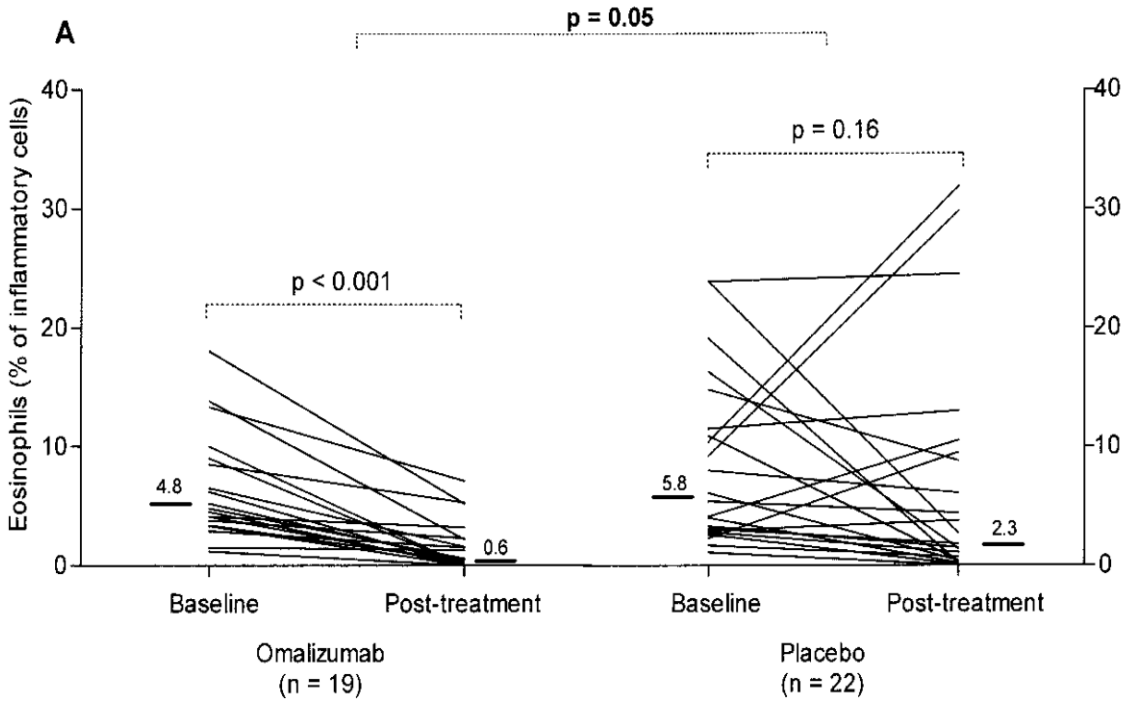


BAL: bronchoalveolar lavage

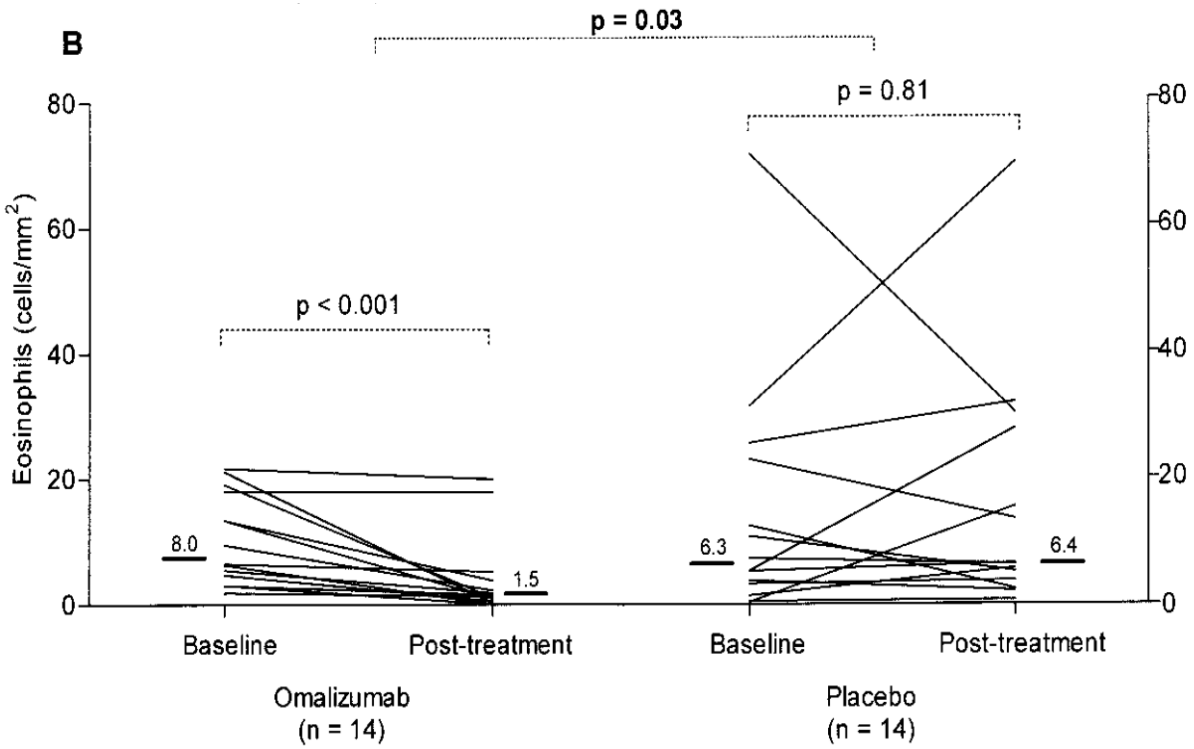
J Asthma. 2019 Mar 23:1-10

IgE blockade decreases eosinophils in sputum and bronchial submucosa in patients with asthma

Percentages of eosinophils in induced sputum



Eosinophil counts in the bronchial submucosa



Human Study

Am J Respir Crit Care Med 2004;170:583–593

ORIGINAL ARTICLE
Airway Diseases

WILEY Allergy

Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma

T. B. Casale[1] | B. E. Chipps[2] | K. Rosén[3] | B. Trzaskoma[3] | T. Haselkorn[4] | T. A. Omachi[3] | S. Greenberg[5,6] | N. A. Hanania[7]

Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma

William Busse, MD[a], Jonathan Corren, MD[b], Bobby Quentin Lanier, MD[c], Margaret McAlary, MS[d], Angel Fowler-Taylor, RPh[d], Giovanni Della Cioppa, MD[e], Andre van As, MD, PhD[d], Niroo Gupta, MD, PhD[d]
Madison, Wis, Los Angeles, Calif, Fort Worth, Tex, East Hanover, NJ, and Horsham, United Kingdom
From [a] the University of Wisconsin; [b] the Allergy Research Foundation, Inc, Los Angeles; [c] the Lanier Education and Research Network, Fort Worth; [d] Novartis Pharmaceuticals, East Hanover; and [e] Novartis Horsham Research Centre, Horsham

J Allergy Clin Immunol. 2001;108:184-190.

The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics

M. Solèr*, J. Matz#, R. Townley¶, R. Buhl+, J. O'Brien§, H. Fox[f], J. Thirlwell[f], N. Gupta**, G. Della Cioppa[f]

Eur Respir J. 2001;18:254-261.

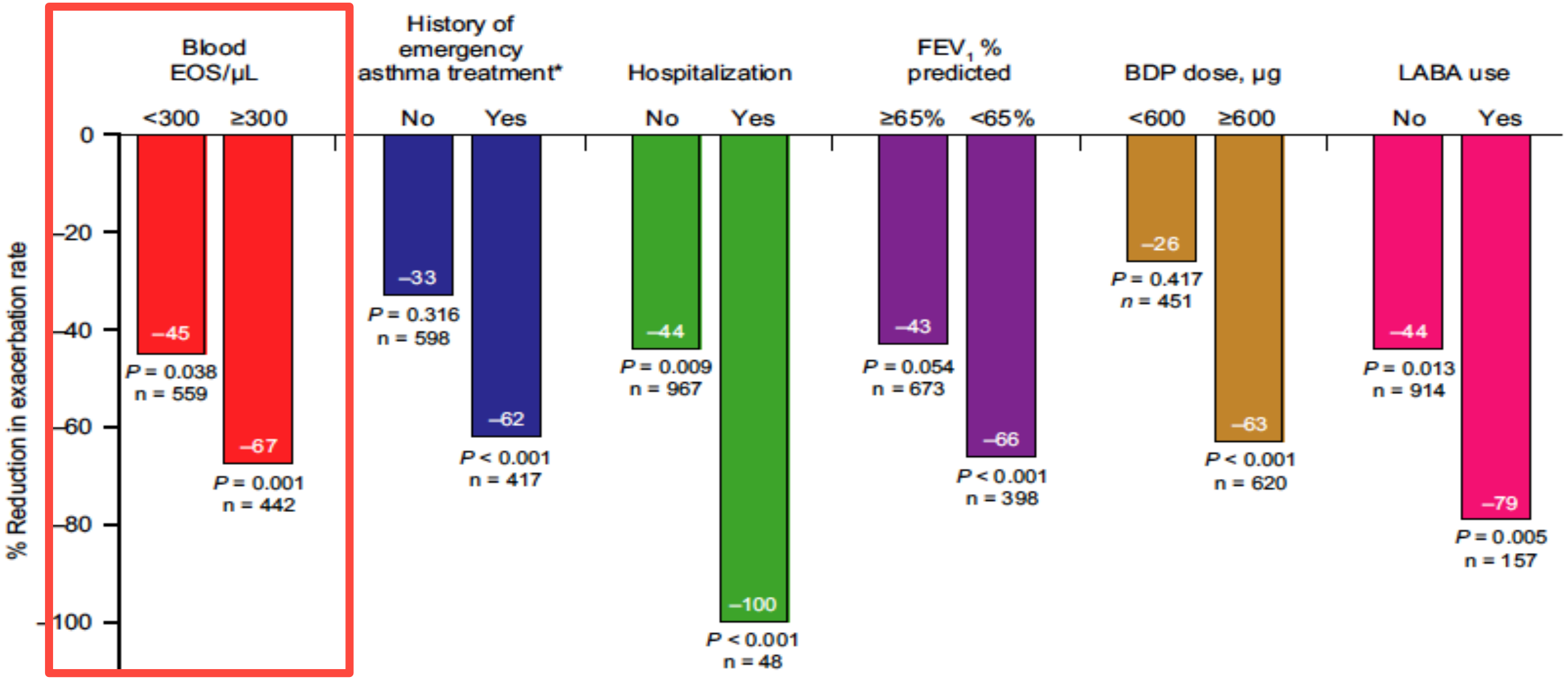
TABLE 1 Baseline demographic and clinical characteristics

Characteristic[a]	Pooled pivotal trials N = 1071	
	Omalizumab n = 542	Placebo n = 529
Age, years, mean (SD)	39.7 (13.8)	39.0 (13.7)
Female, %	55	55
Duration of asthma, years, mean (SD)	20.5 (13.6)	20.8 (14.0)
Prebronchodilator % predicted FEV_1, mean (SD)	65 (12.04)	65 (11.13)
Blood eosinophil count, per µL, geometric mean (SE)	253 (7.0)	274 (7.7)
Serum IgE, IU/mL, geometric mean (SE)	143 (5.29)	144 (5.28)
Inhaled BDP dose, µg, mean (SD)	670.4 (222.2)	672.8 (238.3)
Treated with LABAs at baseline, %	14.0	15.3
Emergency asthma treatment in preceding year, %	41.4	40.8
Hospital admission for exacerbation in preceding year, %	3.3	6.3

BDP, beclomethasone dipropionate; FEV_1, forced expiratory volume at 1 s; IgE, immunoglobulin E; LABA, long-acting beta-agonist.
[a]Percentages based on nonmissing data.

Allergy. 2018;73:490–497.

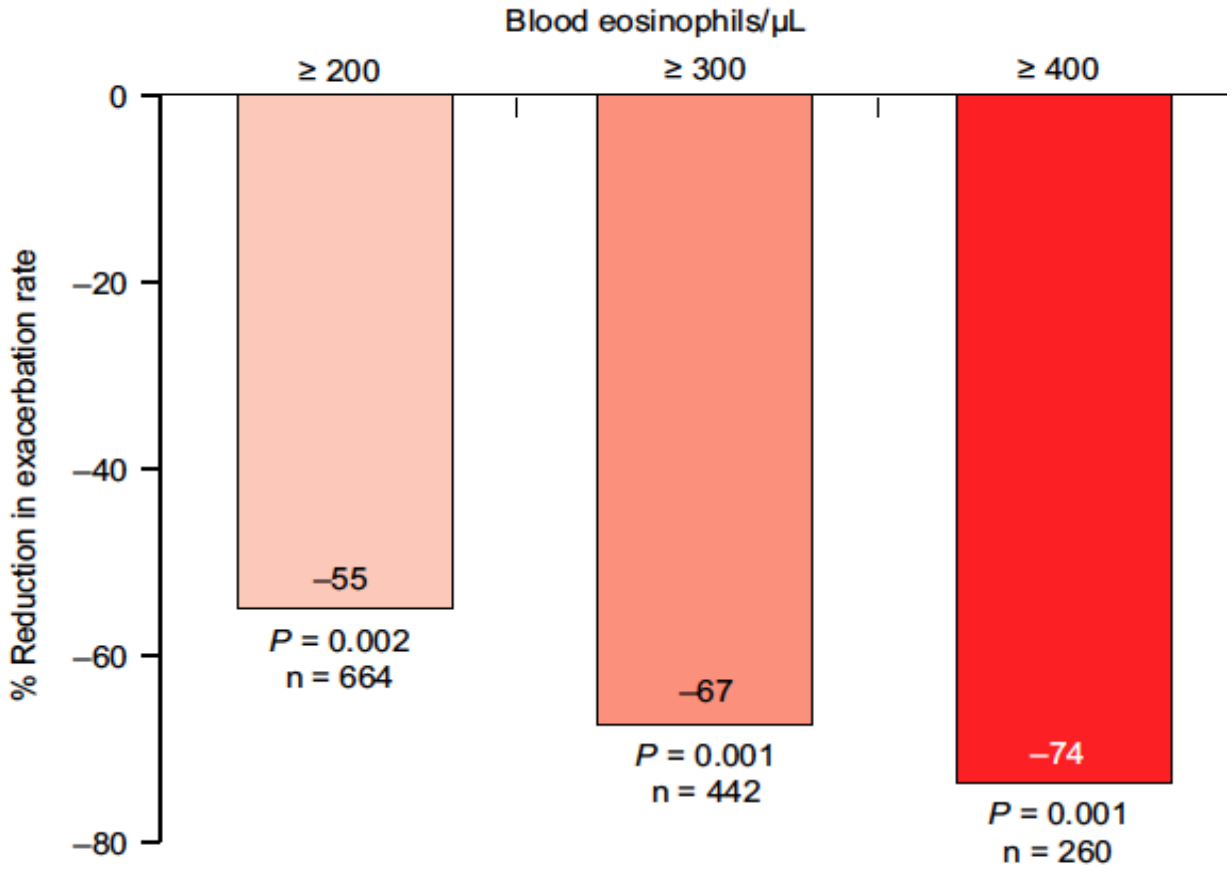
Clinical factors of Asthma patients predict the response of Omalizumab



Allergy. 2018;73:490–497.

Post-hoc study (Phase3)

Blood eosinophil counts predict the efficacy of Omalizumab in asthma AE



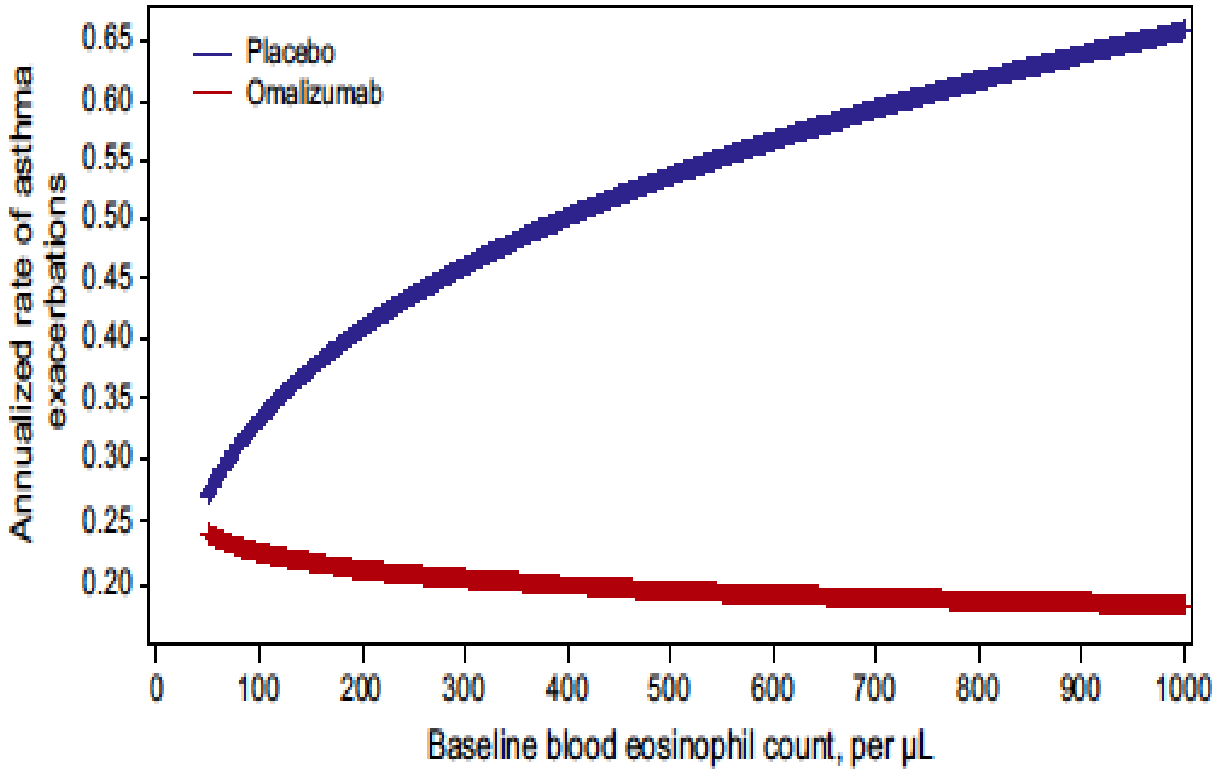


FIGURE 2 Relative percentage change in exacerbation rate by blood eosinophil levels

Allergy. 2018;73:490–497.

Post-hoc study (Phase3)

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Task Force Report

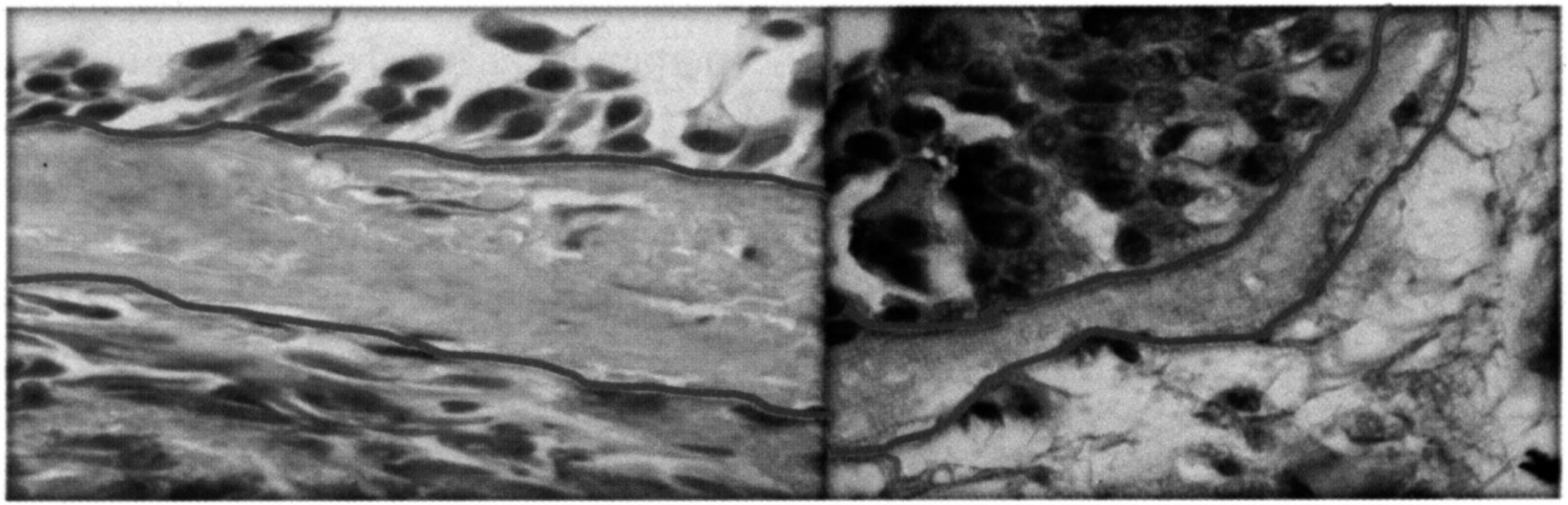
Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline

Recommendations:

1) Suggest using **anti-IL5 and anti IL-5Rα** for severe uncontrolled adult eosinophilic asthma phenotypes
2) Suggest using **blood eosinophil cut-point of ≥ 150/μl to guide anti-IL5 initiation** in adult patients with severe asthma
3) Suggest considering **specific eosinophil (≥ 260 /μl) and FeNO (≥19.5 ppb)** cutoffs to identify adolescents or adults with the greatest likelihood or response to **anti-IgE therapy**
4) Suggest using **inhaled tiotropium** for adolescents and adults with severe uncontrolled asthma despite GINA step 4-5 or NAEPP step 5 therapies
5) Suggest a trial of **chronic macrolide therapy** to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype
6) Suggest using **anti-IL4/13** for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels.

Fernando Holguin et al. ERJ 2019 in press

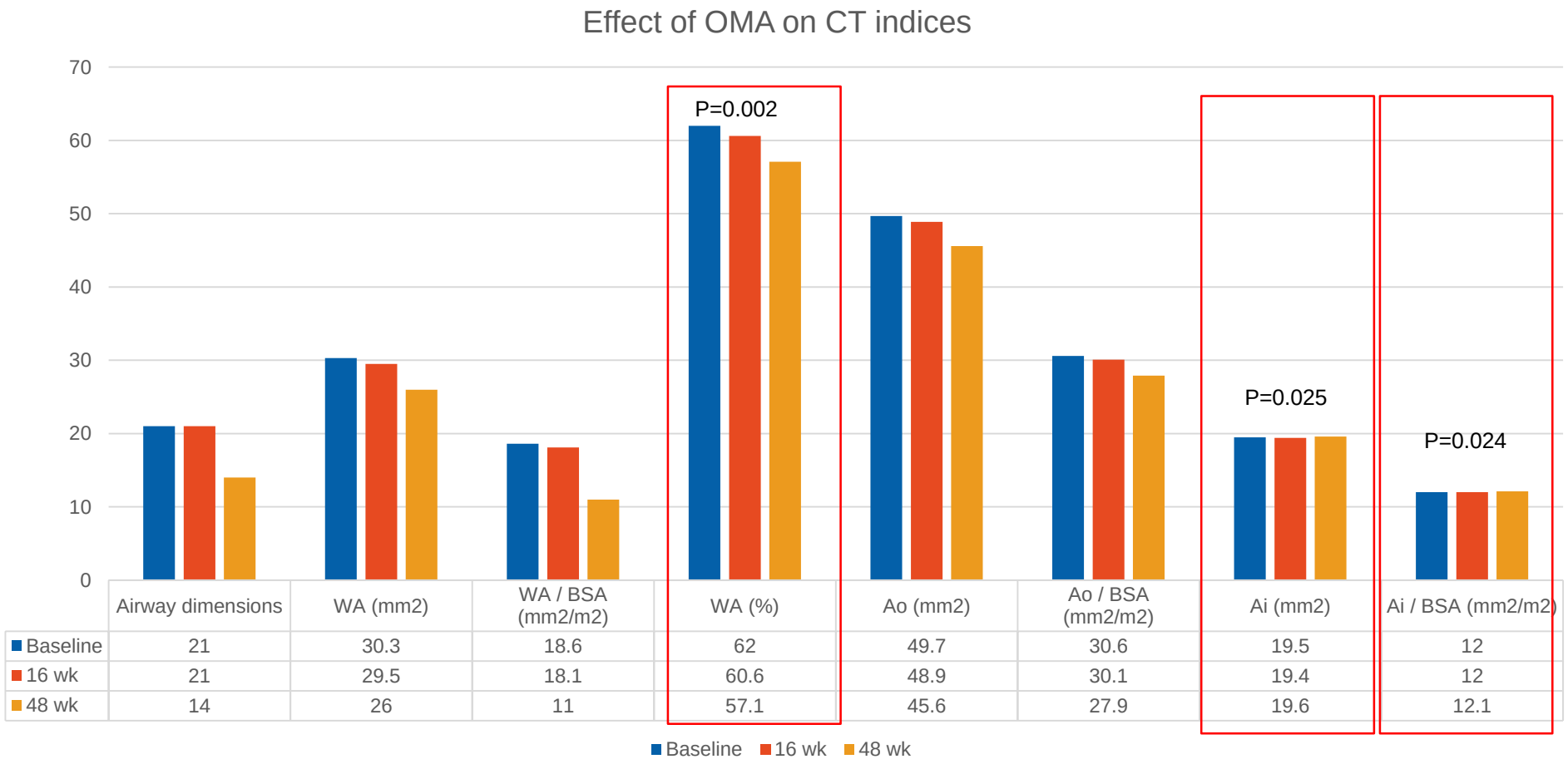
Omalizumab results a decreased of basement membrane thickness after 12 months treatment



Human Study

G. Pelaia et al., *Asthma: Targeted Biological Therapies*, DOI 10.1007/978-3-319-46007-9_4
Riccio *et al. Int. J. Immunopathol. Pharmacol. 2012;25(2):475-484,*

Omalizumab results a significant decreased of bronchial wall thickness after 48 weeks treatment



	Airway dimensions	WA (mm2)	WA / BSA (mm2/m2)	WA (%)	Ao (mm2)	Ao / BSA (mm2/m2)	Ai (mm2)	Ai / BSA (mm2/m2)
Baseline	21	30.3	18.6	62	49.7	30.6	19.5	12
16 wk	21	29.5	18.1	60.6	48.9	30.1	19.4	12
48 wk	14	26	11	57.1	45.6	27.9	19.6	12.1

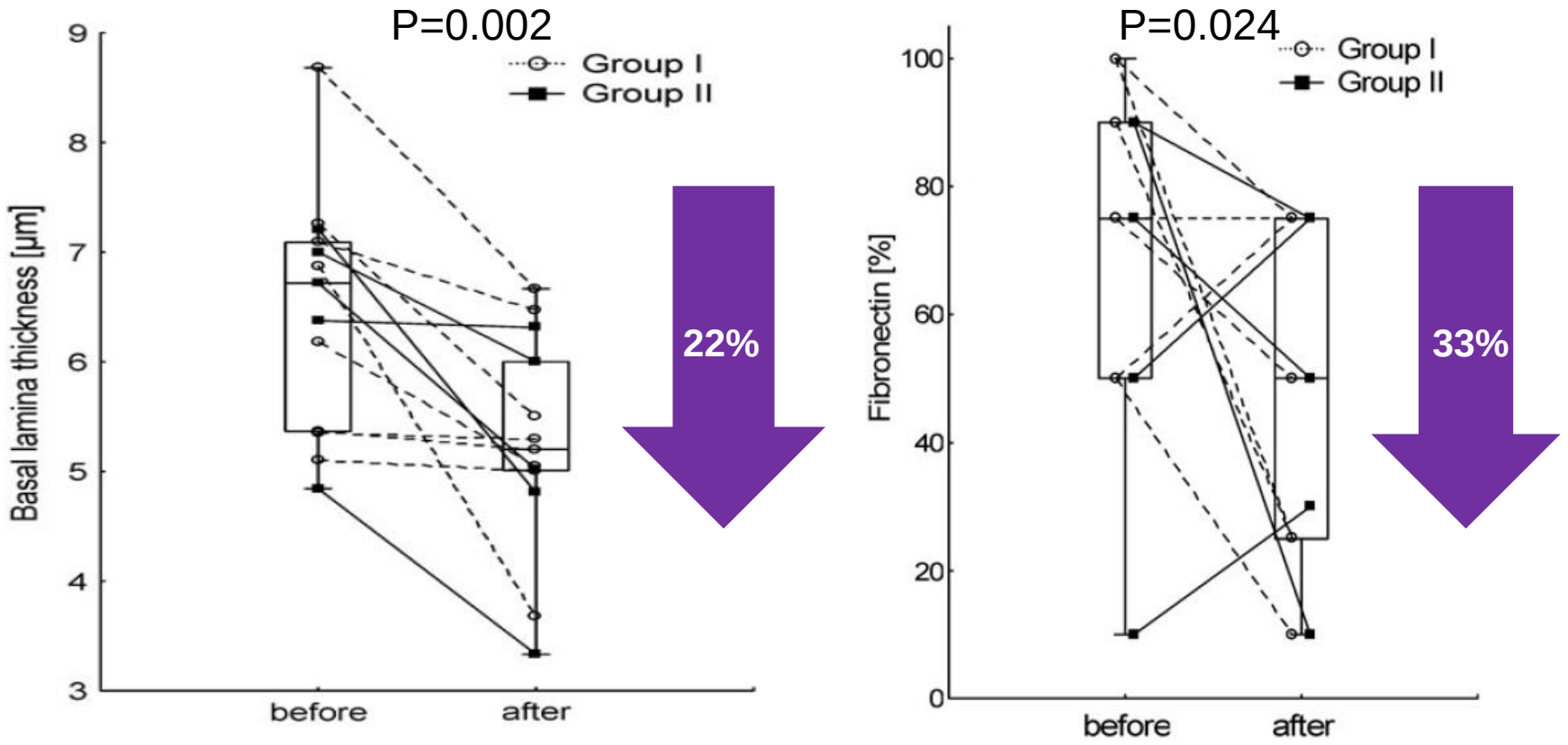
P value for baseline vs 48 weeks by paired t test.

Ai, luminal area; Ao, outer area of bronchus; BSA, body surface area; CT, computed tomographic; WA%, percentage of wall area equal to wall area divided by outer area of bronchus multiplied by 100; WA, wall area.

Human Study

Ann Allergy Asthma Immunol 2014;113: 470-475

Omalizumab decrease unfavorable structural airway changes in allergic asthmatics: decreasing the fibronectin deposit and thickness of the basal lamina.

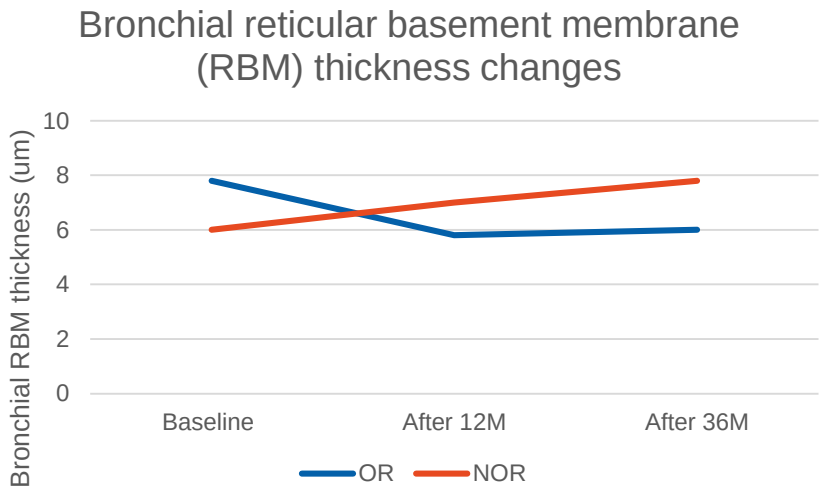


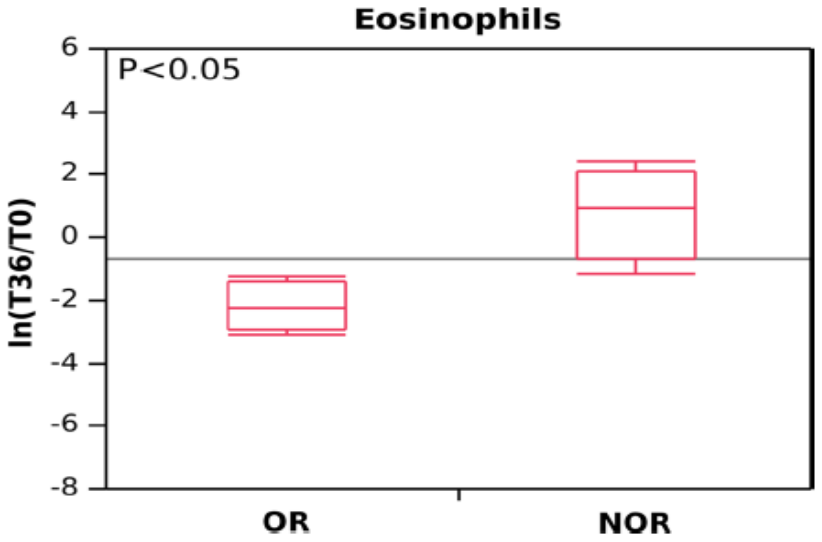
Group 1: Patients who manifested one exacerbation episode at the maximum during treatment with omalizumab, n=8)
Group 2: Patients demonstrated a minimum of two exacerbations, n=5.

Human Study

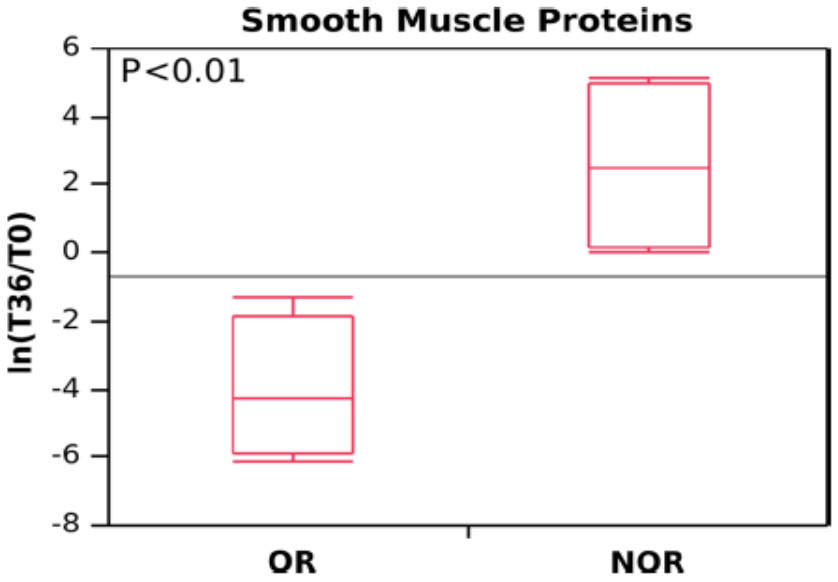
J Asthma. 2019 Mar 23:1-10

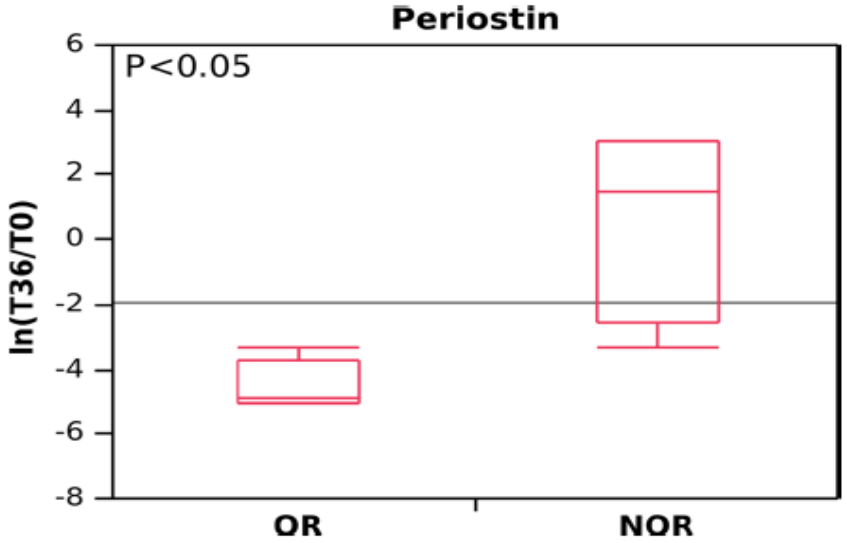
Omalizumab may exert disease-modifying effect on airway remodeling





OR: OMA responder
NOR: Non-OMA responder





Human Study

G. Pelaia et al., *Asthma: Targeted Biological Therapies*, DOI 10.1007/978-3-319-46007-9_4
Riccio *et al. Clin Transl Allergy (2017) 7:6,*

Improvement of FEV1 after omalizumab introduction

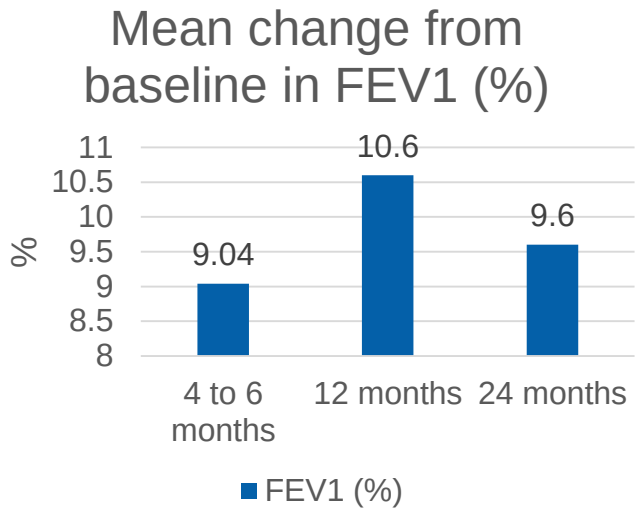
Change of FEV_1 predicted

Cochrane

Study or subgroup	Omalizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Moderate to severe asthma						
Busse 2011	208	211	0.92 (0.8776)		44.0 %	0.92 [-0.80, 2.64]
NCT00096954	159	174	4.9 (1.9311)		9.1 %	4.90 [1.12, 8.68]
Ohta 2009	158	169	2.77 (1.08)		29.1 %	2.77 [0.65, 4.89]
Subtotal (95% CI)	**525**	**554**			**82.2 %**	**2.01 [0.76, 3.27]**
Heterogeneity: $Chi^2 = 4.28$, df = 2 (P = 0.12); I^2 =53%						
Test for overall effect: Z = 3.14 (P = 0.0017)						
2 Severe asthma						
INNOVATE	209	210	2.8 (1.379)		17.8 %	2.80 [0.10, 5.50]
Subtotal (95% CI)	**209**	**210**			**17.8 %**	**2.80 [0.10, 5.50]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.03 (P = 0.042)						
Total (95% CI)	**734**	**764**			**100.0 %**	**2.15 [1.01, 3.30]**
Heterogeneity: $Chi^2 = 4.54$, df = 3 (P = 0.21); I^2 =34%						
Test for overall effect: Z = 3.70 (P = 0.00022)						
Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.61), I^2 =0.0%						

-10 -5 0 5 10

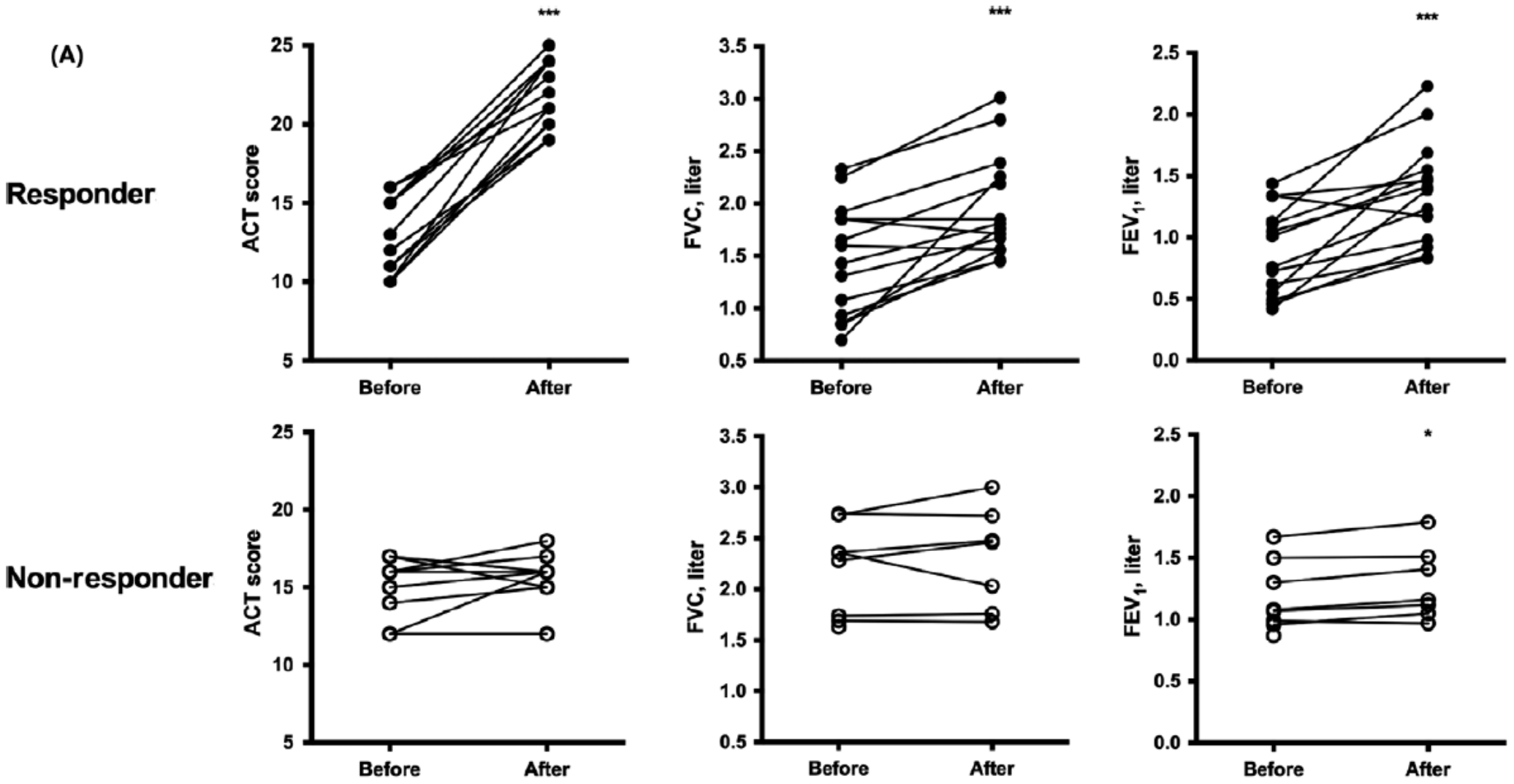
Favours Placebo Favours Omalizumab



Normansell R *et al. Cochrane Database Syst Rev*. 2014 Jan 13;1:CD003559

J ALLERGY CLIN IMMUNOL PRACT, 2017. Expert Rev Clin Immunol. 2019 Feb 14:1-17

Improvement of ACT and lung function after 4 months omalizumab treatment



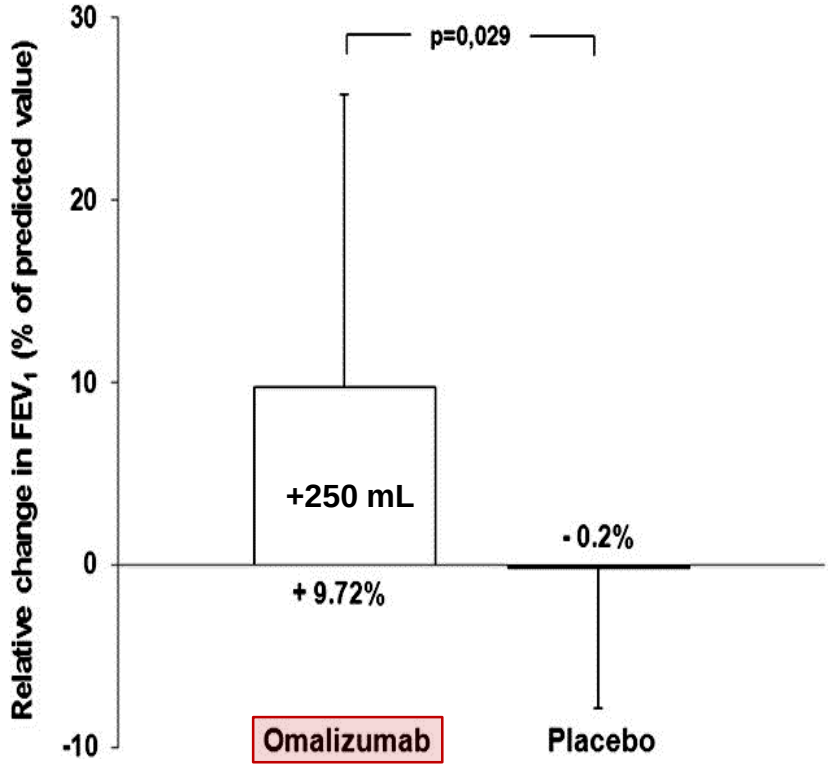
Each dot represents an individual patient. *$P < 0.05$, **$P < 0.01$ ***$P < 0.001$

Human Study

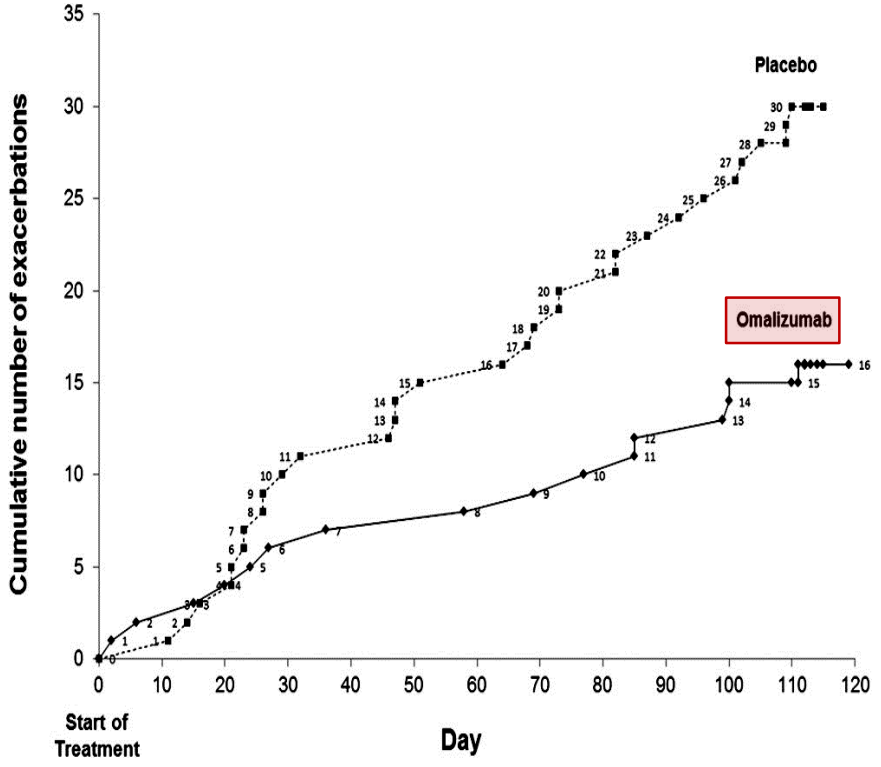
Clin Exp Allergy. 2019;49:44–53

Omalizumab improves lung function and reduces exacerbations in patients with severe non-atopic asthma

Change in FEV_1



Exacerbations



Garcia G *et al. Chest*. 2013 Aug;144(2):411-9

Human Study

Case 67 y/o woman

CC: wheezing at night and dyspnea on exertion (Walk distance <100 m)

S/S: night time awaking(+), cough with scanty whitish sputum

dyspnea on exertion, talk in sentences (+)

frequent watery rhinorrhea (+)

PH: Previous diagnosed as asthma s/p tx

but loss f/u for 7 years without tx

Diagnosed Asthma since she was 20+ year-old without control

PH: Allergic rhinitis (+) under anti-histamine tx at LMD

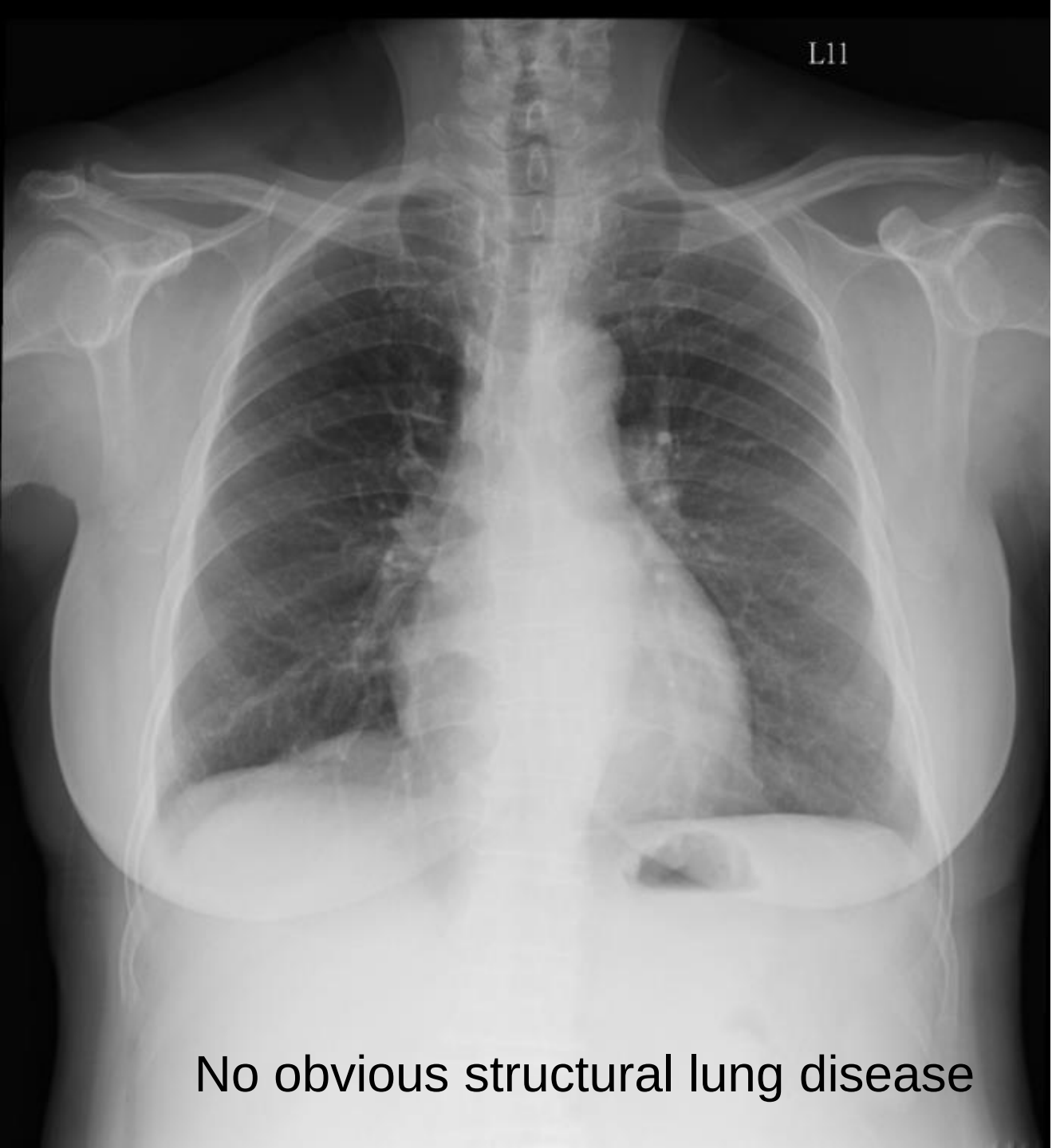
Atopic eczema since childhood but improving after 20 year-old

Drug allergy: pyrin

Occupation: Farmer (雲林斗六)

Nonsmoker (denied secondhand smoke exposure),

No pet or animal exposure



No obvious structural lung disease

[PE]
BH: 150.3 cm , BW: 62.2 Kg **BMI:27.2**
Clear consciousness
BS: bilateral wheezing, diffuse
HS: no murmur
No leg edema
Nasal polyposis (-)
Non-stop Runny nose (+)

Walk distance **<100 m**
(走去照CXR 就需要停下來)

[Current medication of LMD]

Montelucast 1# HS
Dextromethorphan 1# bid po
Procaterol 1# bid po
Aminophylline 1# tid
Fenoterol prn use

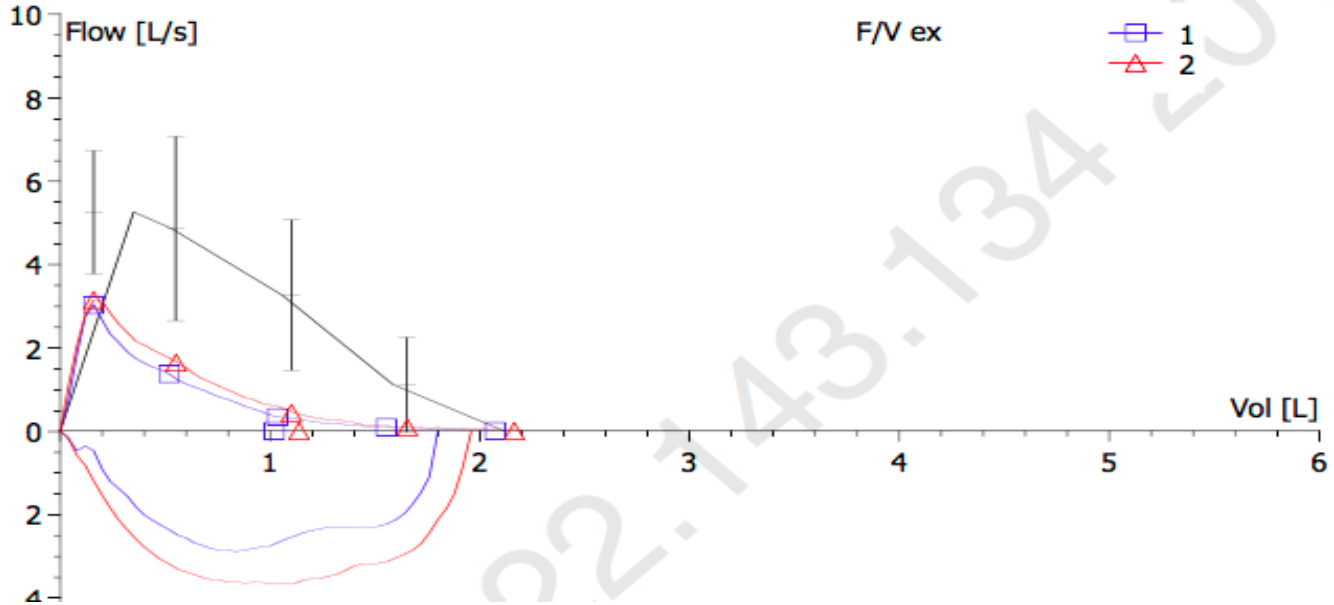
No ICS use !

Lung function test

Flow-Volume

	Pred	Pre	%(P/Pred)	Post	%(Po/Pred	Chg%
FVC	2.12	2.07	97.9	2.16	102.2	4.39
FEV 1	1.75	1.02	58.2	1.14	65.0	11.69
FEV1%F		49.15		52.58		6.99
MEF 75	4.86	1.37	28.1	1.64	33.7	19.90
MEF 50	3.26	0.33	10.1	0.43	13.2	30.30
MEF 25	1.11	«	«	«	«	«
MFEF						
PEF	5.25	3.02	57.6	3.14	59.9	3.94
MVV	78.43					

Date
Time



Previous lung function: 2009/4 (NTUH)
FEV1/FVC: 58%
FEV1: **56%**
FVC: 81%
BDT(+): **22%**

No IgE data and allergy panel ?

Lab data 2015.12 (asthma AE)

檢驗項目	檢驗值	單位	參考值
RBC	4.55	M/μL	3.78~4.99
HB	14.2	g/dL	10.8~14.9
HCT	40.6	%	35.6~45.4
MCV	89.2	fL	80~100
MCH	31.2	pg	26~34
MCHC	35.0	g/dL	31~37
PLT	289	k/μL	150~361
RDW-CV	12.1	%	11.9~14.5
PS	-		
WBC	12.04	k/μL	3.54~9.06
Blast	0.0	%	0~0
Promyl.	0.0	%	0
Myelo.	0.0	%	0
Meta	0.0	%	0
Band	0.0	%	0-5(2019/7/1變更，舊參考區間2012/10/2~2019/7/1為0)
Seg	59.6	%	38.3~71.1
Eos.	6.6	%	0.2~7.3
Baso.	0.2	%	0.2~2
Mono.	4.4	%	2.7~7.6
Lym.	29.2	%	21.3~50.2
Aty.Lym.	0.0	%	
PlasmaCell	0.0	%	0
Normobl.	0.0		0
PS	-		

檢驗項目	檢驗值	單位	參考值
Phadiotop	3.90(Class=3)		
牛毛	NA		
Der p (屋塵蹣)	1.13(Class=2)		
Der f (粉塵蹣)	3.86(Class=3)		
Blomia tropicalis (熱帶五爪蹣)	20.2(Class=4)		
cockroach,German (德國蟑螂)	0.03(Class=0)		
Mixes(animal) (混合動物毛皮)	0.07(Class=0)		
黴菌過敏原篩檢	0.06(Class=0)		
貓毛皮屑	NA		
狗毛皮屑	NA		
馬毛	NA		
IgE	152	KU/l(IU/ml)	0~100

Atopic

Blood eosinophil: 6.6% (794 cells/uL)
Allergy test (+) : mites (+)
IgE :152 IU/ml

氣喘控制測驗 (ACT™)

以下的測驗可幫助有氣喘的人 (12 歲或 12 歲以上) 評估氣喘的控制程度。

請在每個問題，圈選出適當的分數。
總共有五個問題。

您可將每個題目回答的分數相加，算出氣喘控制測驗的總分。請務必將此結果和您的醫師或護士討論。

請翻頁以確定您的分數所代表的意義。

了解您的氣喘分數

步驟 1 請在每個問題，圈選出您的分數，並將分數寫在右邊空格內。請儘可能誠實作答，這將幫助您和醫師討論您氣喘的實際狀況。

						分數
第 1 題	在過去 4 週中，您的氣喘有多常讓您無法完成一般的工作、課業或家事？					
	1 總是如此	2 經常如此	3 有時如此	4 很少如此	5 不曾如此	1
第 2 題	在過去 4 週中，您多常發生呼吸急促的情形？					
	1 一天超過 1 次	2 一天 1 次	3 一週 3 至 6 次	4 一週 1 至 2 次	5 完全沒有發生過	1
第 3 題	在過去 4 週中，您多常因氣喘症狀 (喘鳴、咳嗽、呼吸急促、胸悶或胸痛) 而讓您半夜醒來或提早醒來？					
	1 一週 4 次或 4 次以上	2 一週 2 至 3 次	3 一週 1 次	4 過去四週 1 或 2 次	5 完全沒有發生過	1
第 4 題	在過去 4 週中，您多常使用急救性藥物或噴霧型藥物 (例如：Albuterol® (舒坦寧®)、Ventolin® (泛得林®)、Berotec ® (備勞喘®)或 Bricanyl (撲可喘®) 等氣喘藥物)？					
	1 一天 3 次或 3 次以上	2 一天 1 或 2 次	3 一週 2 至 3 次	4 一週 1 次或更少	5 完全沒有使用過	1
第 5 題	在過去 4 週中，您對您氣喘控制程度的評價為何？					
	1 完全沒有受到控制	2 控制不好	3 稍微受到控制	4 控制良好	5 完全受到控制	1

了解您的氣喘分數

步驟 2 請將分數相加，來得到您的總分

步驟 3 請翻頁以確定您的分數所代表的意義

總分 **5**

How about the "Asthma control" in this patient ?

- Daytime symptoms-->**Can't work** due to symptoms
- Frequent Asthma AE →**ER visit (～2 times/last year)**
- Nighttime symptoms (dyspnea, cough, chest tightness/wheezing every night) **醒來1-2次/night**
- Frequent **SABA use: 2-3 times/day**

A. Symptom control		**Level of asthma symptom control**		
In the past 4 weeks, has the patient had:		**Well-controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms more than twice a week?	Yes ☑ No ☐	None of these	1-2 of these	3-4 of these
• Any night waking due to asthma?	Yes ☑ No ☐			
• Reliever needed for symptoms* more than twice a week?	Yes ☑ No ☐			
• Any activity limitation due to asthma?	Yes ☑ No ☐			

B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best, then periodically for ongoing risk assessment

ASSESS PATIENT'S RISKS FOR:

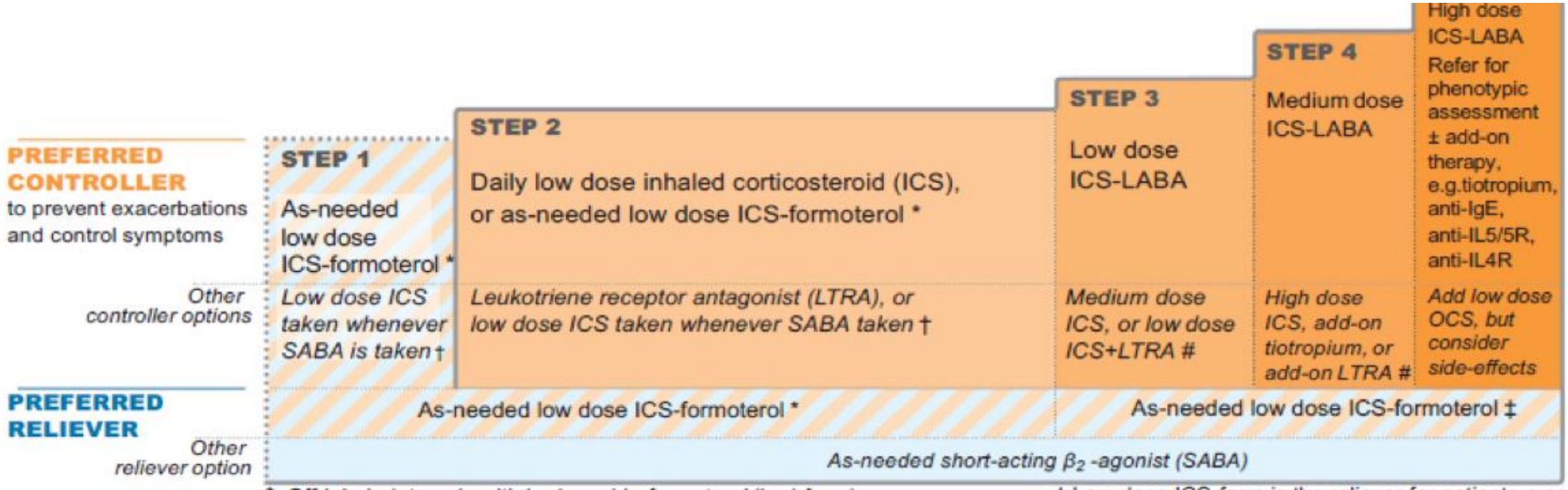
- Exacerbations
- Fixed airflow limitation
- Medication side-effects

Dx: Uncontrolled asthma

1.Give high dose ICS/LABA (Budesonide/Formoterol 2puff Bid/SMART) for asthma control

2. Asthma education and exposure survey

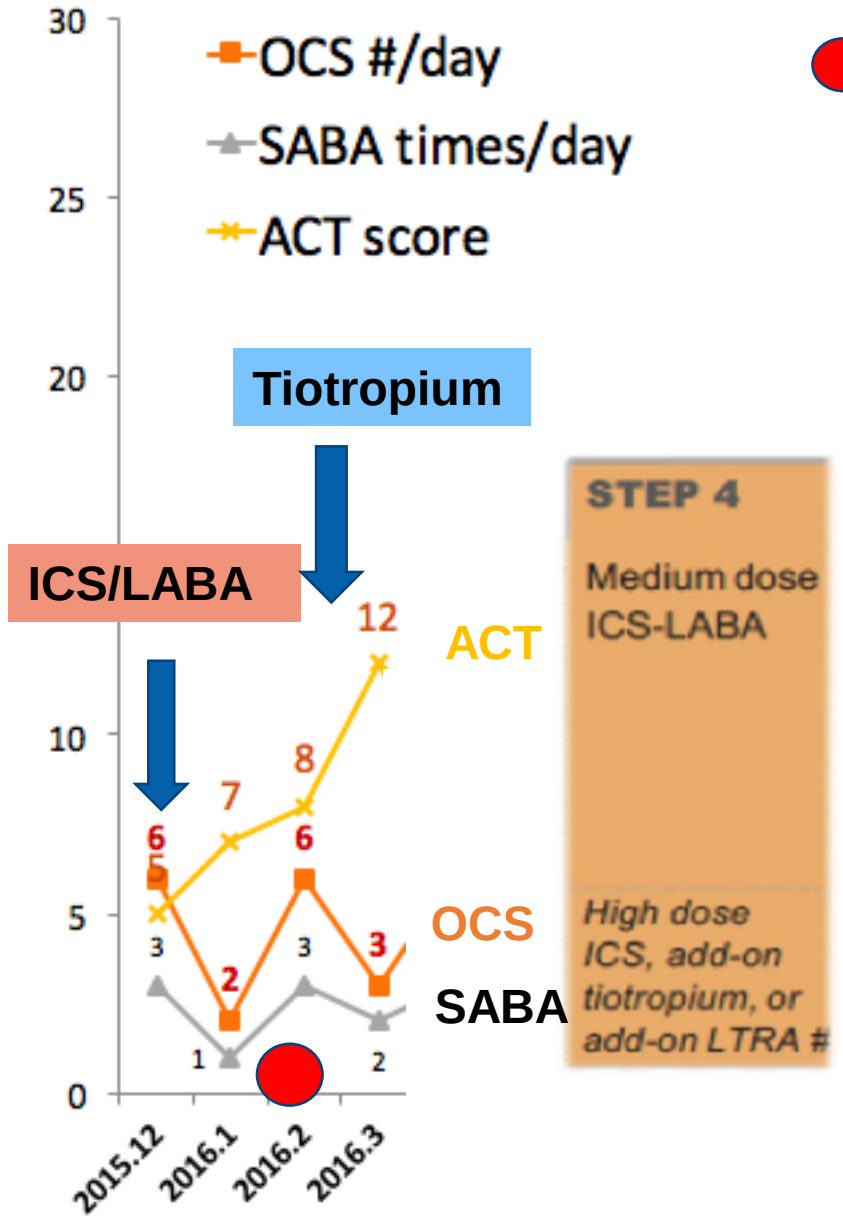
3. Survey comorbidities of asthma , check device technique



 2019 GINA guideline

Tx: high dose ICS/LABA

Added on Tiotropium



PFT:FEV1/FVC:52.58%, FEV1:65%, FVC:102.2%

1. Check inhaler technique of device →OK
2. Poor adherence? →No ,use Inhaler and correct dose every day
3. Special exposures (smoking (x) , allergen mite (v)
4. Occupational or environment change→ No
5. Comorbidities :

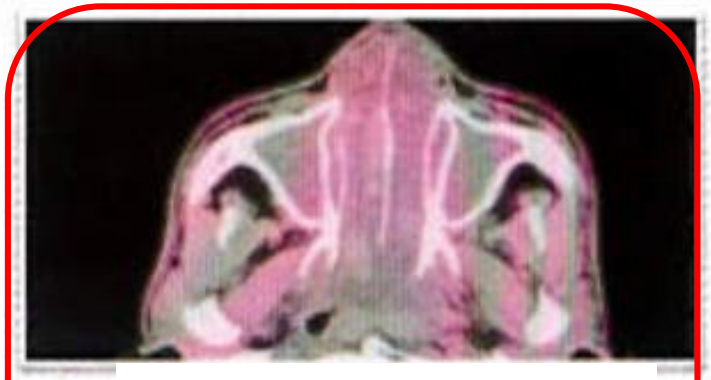
Comorbid Conditions commonly associated with Asthma

Atopic dermatitis

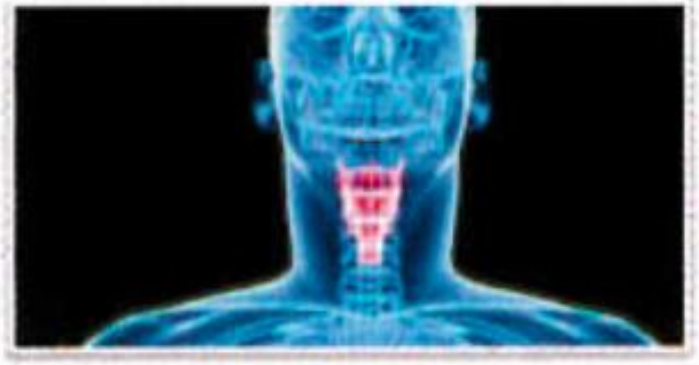
GERD

Obesity

Obstructive sleep apnea



Allergic rhinitis
Nasal polyposis

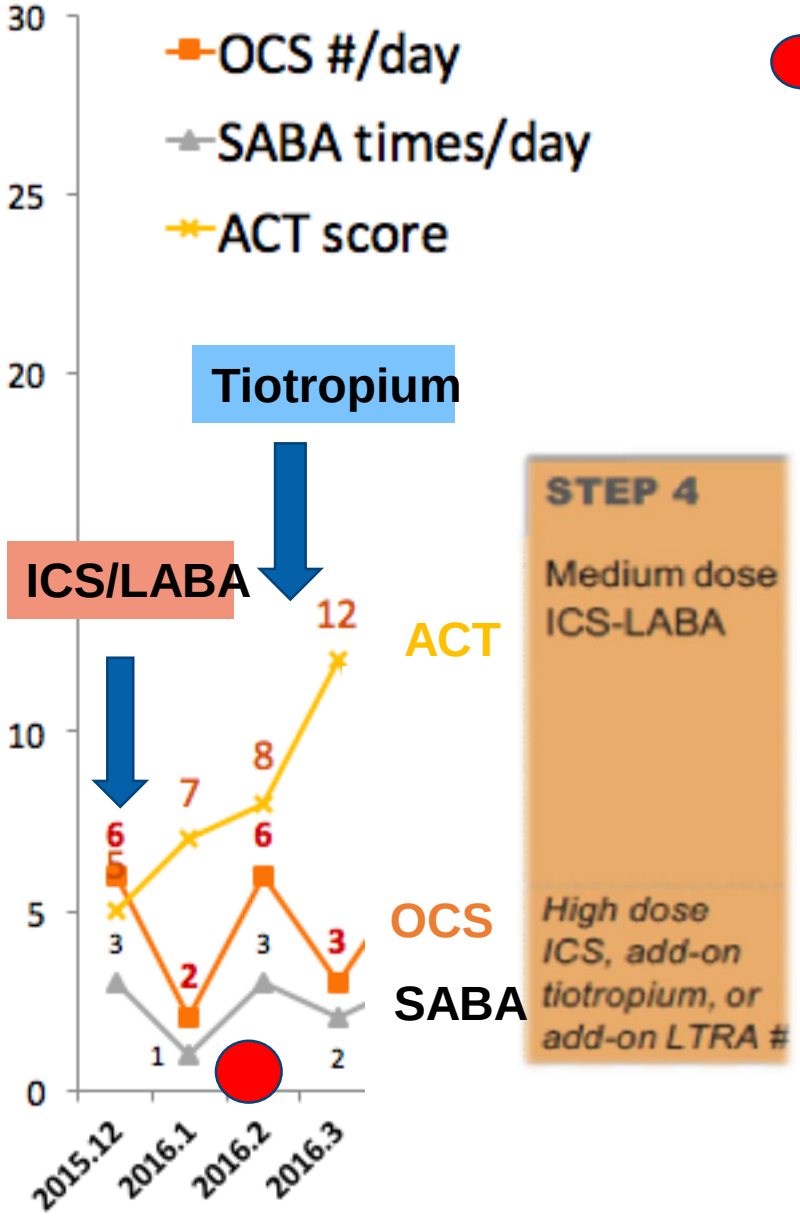


Vocal cord dysfunction

Boulet LP. *Eur Respir J.* 2009;33(4):897-906; Galli E, et al. *Allergy Asthma Proc.* 2007;28(5):540-543; Porsbjerg C, Menzies-Gow, A. *Respirology.* 2017;22(4):651-661.

Under high dose ICS/LABA

Added on Tiotropium



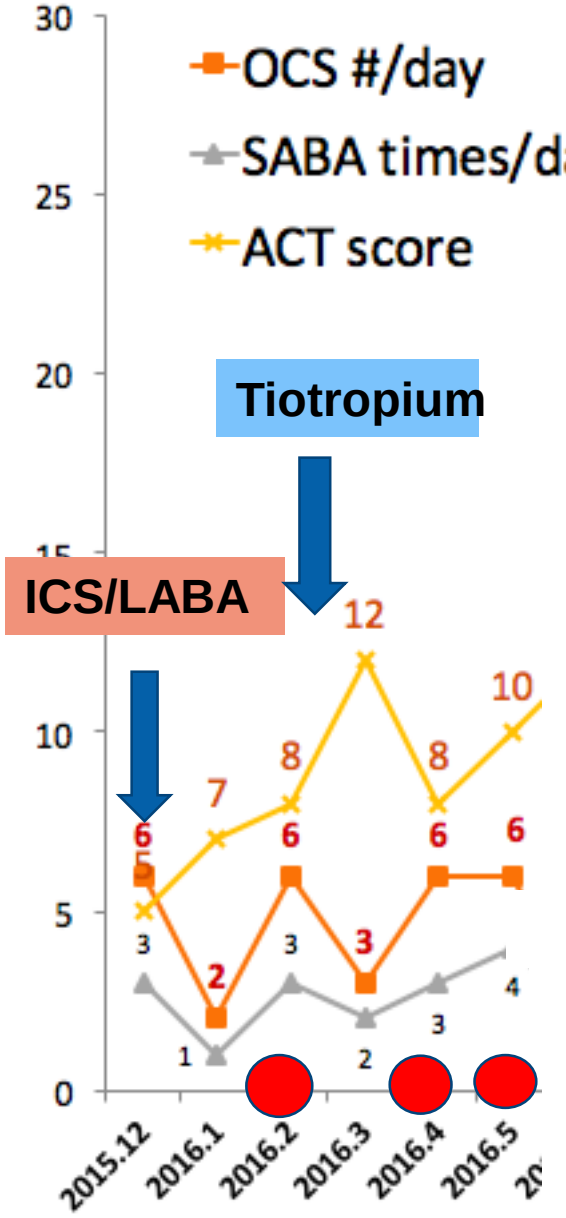
Asthma AE

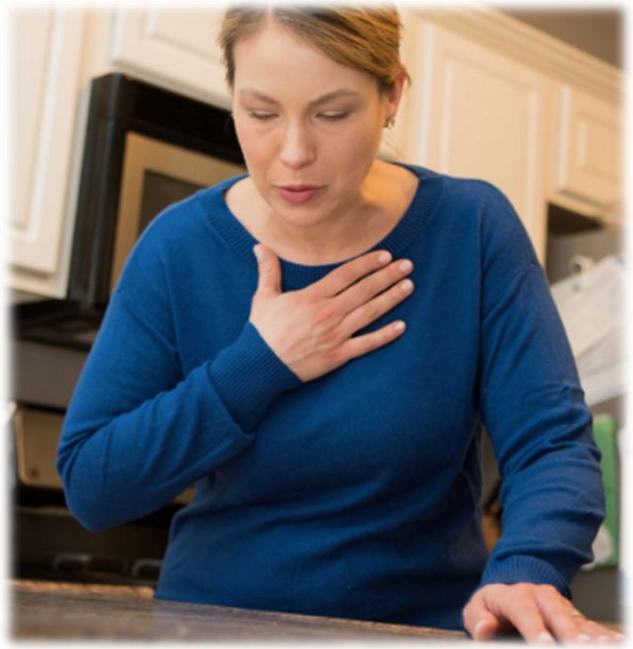
PFT:FEV1/FVC:52.58%, FEV1:65%, FVC:102.2%

1. Check inhaler technique of device →OK
2. Poor adherence? →No ,use Inhaler and correct dose every day
3. Special exposures (smoking (x) , allergen (v)
4. Occupational or environment change→ No
5. Comorbiditis :

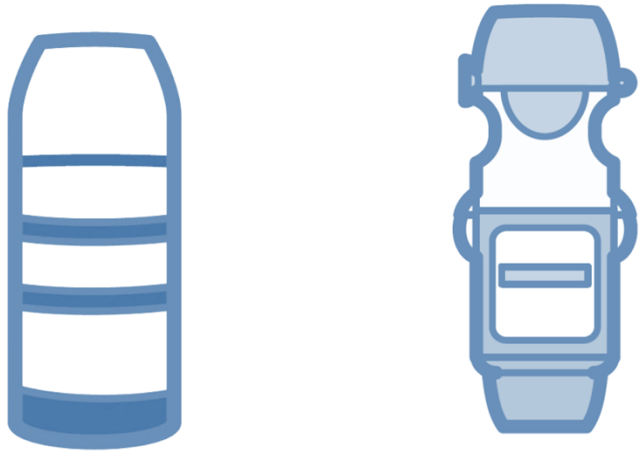
- **GERD: acid-reflux after oral intake: Esomeprazole use (V)**
- **Allergic rhinitis (V): Levocetirizine, Fluticasone nasal spray (V)**
- **Obesity[BMI=27.2(V)]: Weight loss**
- **Atopic eczema: mild**

Still exacerbation under high dose ICS/LABA + Tiotropiu





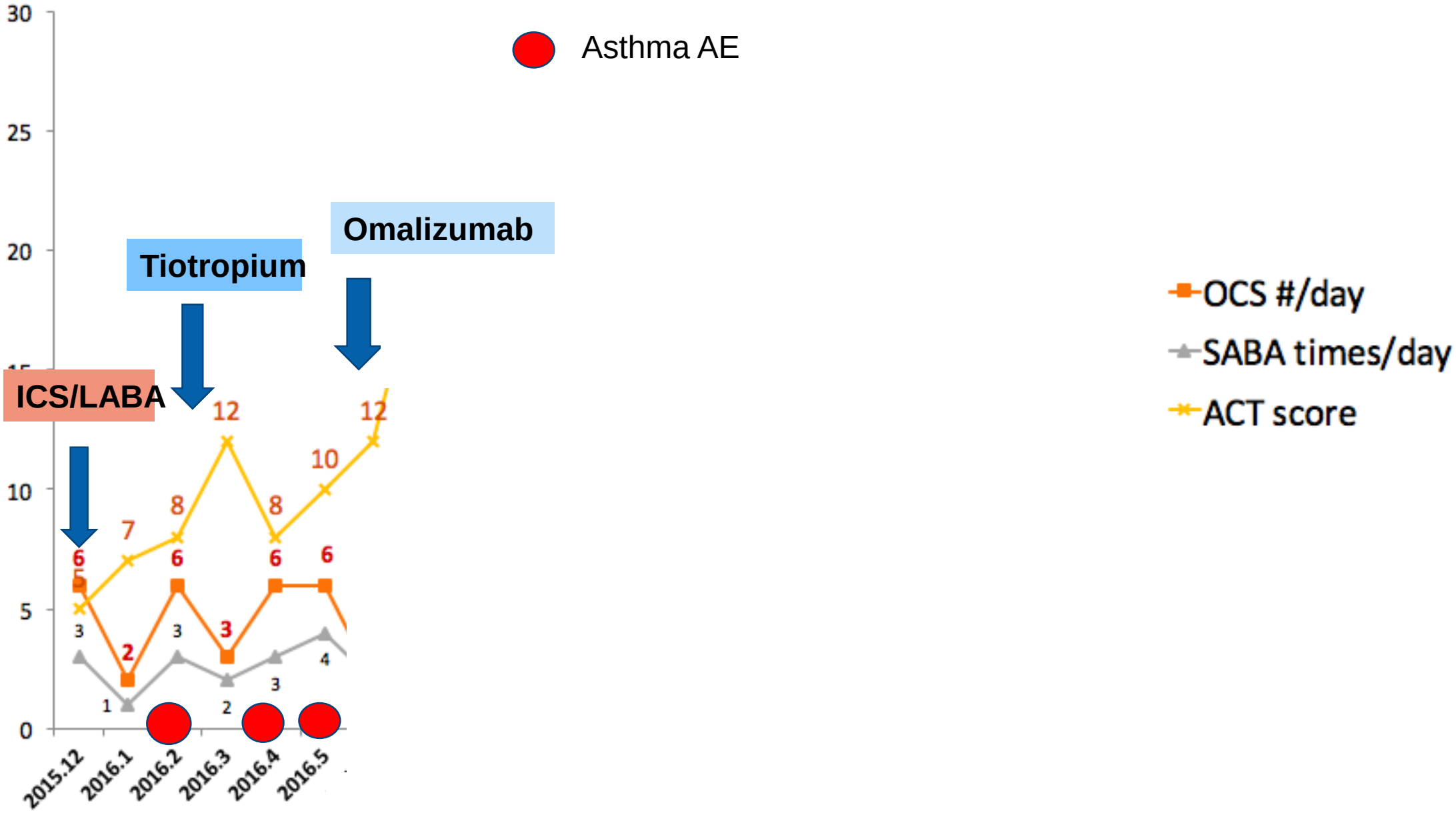
(示意圖, 非當事人)



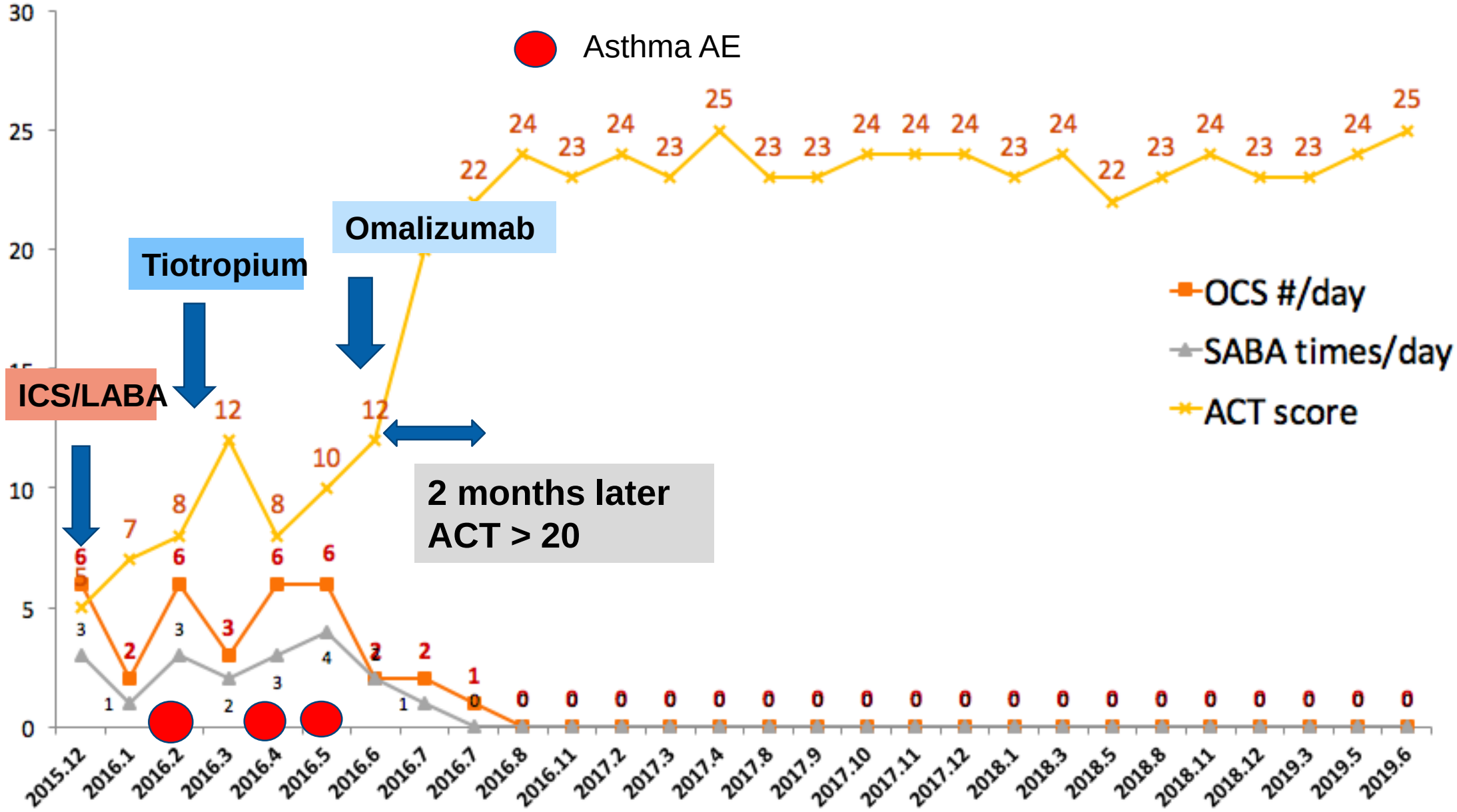
- **Optimize treatment** (check and correct inhaler technique and adherences switch to maintenance and reliever therapy if available)
- **Treat comorbidities** and modifiable risk factors
- **Asthma education**
- **Consider non-pharmacological therapy,** e.g. smoking cessation, exercise, weight loss mucus clearance, influenza vaccination
- **Consider non-biologic add-on therapy (e.g. LABA, Tiotropium, LM/LTRA macrolide)**

GINA 2018

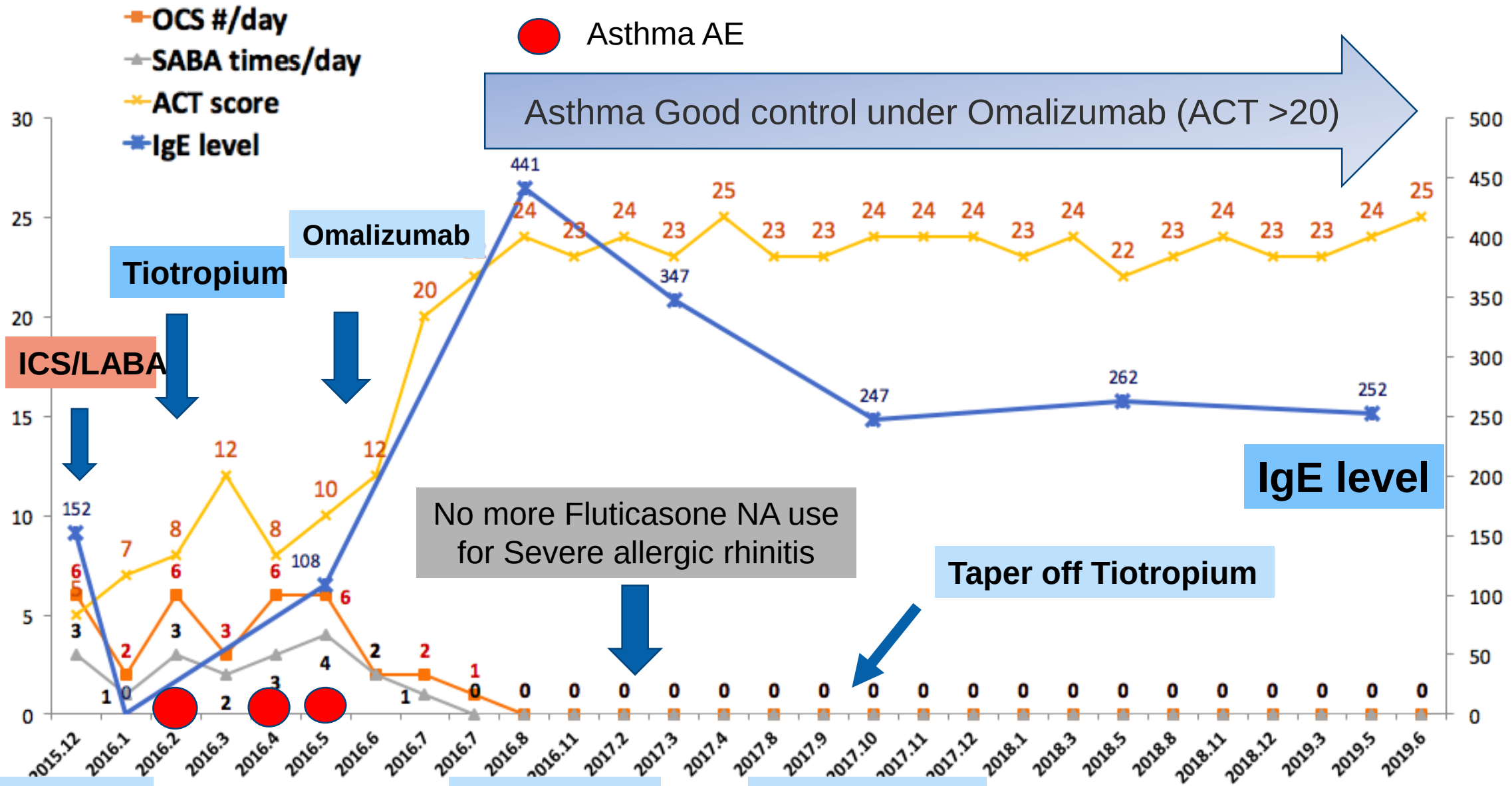
high dose ICS/LABA + Tiotropium added Omalizumab



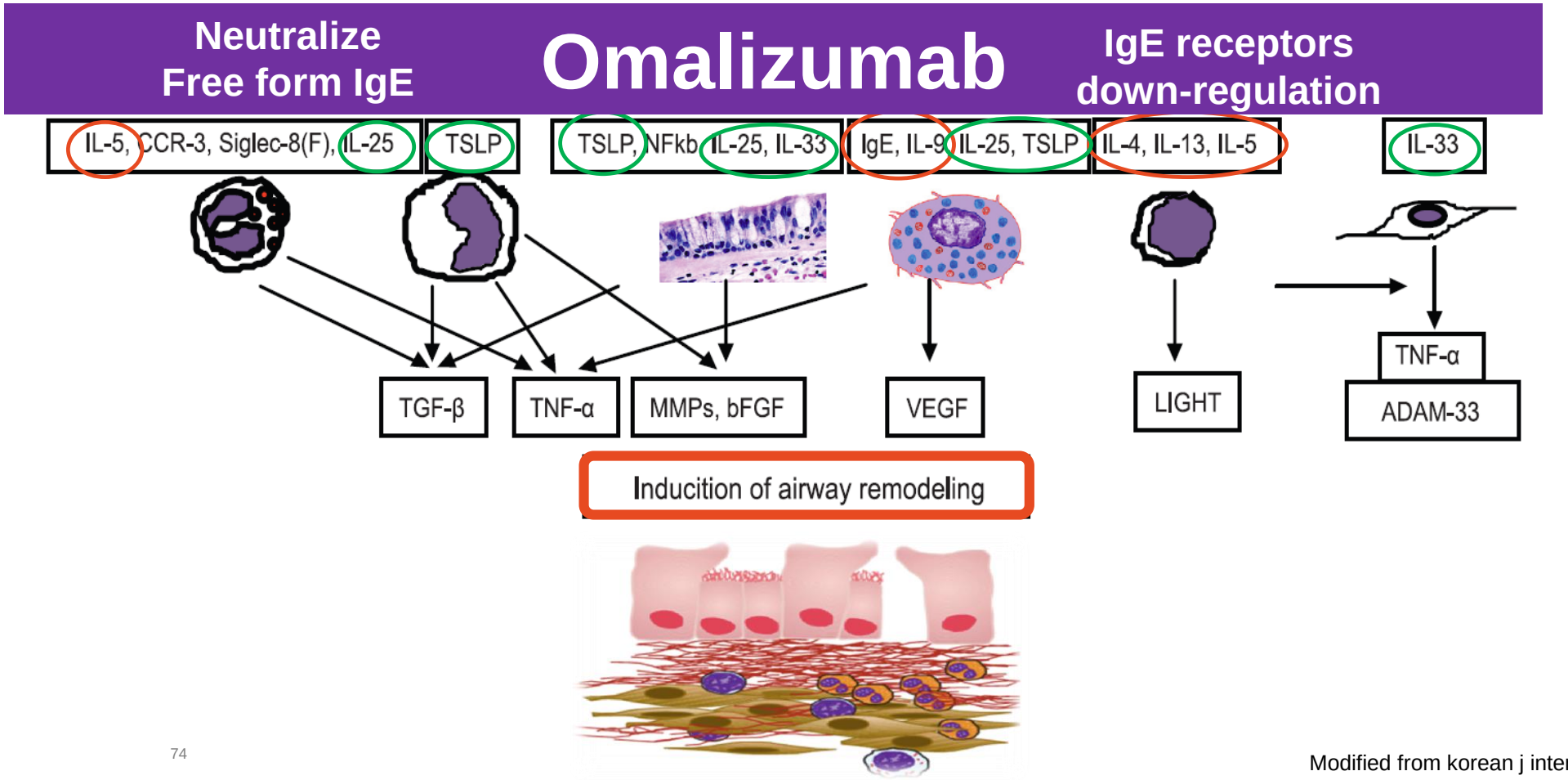
high dose ICS/LABA + Tiotropium added Omalizumab



high dose ICS/LABA + Tiotropium added Omalizumab



Omalizumab blocking Inflammatory cells and mediators related to reverse airway remodeling



Modified from korean j intern med 2011;26:367-383

Conclusions

- **Airway remodeling:**
  - Repeated airway Injury, chronic Inflammation and Immune-mediated Event (Viral Infection)
  - Thickening of the lamina reticularis
  - Structural changes : epithelium, submucosa, smooth muscle, and vasculature of the airway
- **IgE** plays an important role in allergic severe asthma as well as airway remodeling process
  - IgE affect inflammatory cells from **sensitization to chronic phase** in allergic asthma
  - IgE can directly interact with **ASMC** **and** **Epithelium** to cause **structure changes and stimulate related cytokines** production of airway remodeling
- **Anti-IgE** offer disease-modifying effect and improved lung function
  - By inhibiting IgE mediated cytokine and chemokine release (IL-4, IL-5, IL-13, GM-CSF, IL-25, IL-33, TSLP etc.)
  - Anti-IgE ameliorates of tissue remodeling process.
  - Real evidences show Omalizumab improve lung function and symptoms, reduce AE rates

Thank you ! NTUH-YL branch Yen-Fu Chen. Email: yenfu1228@gmail.com