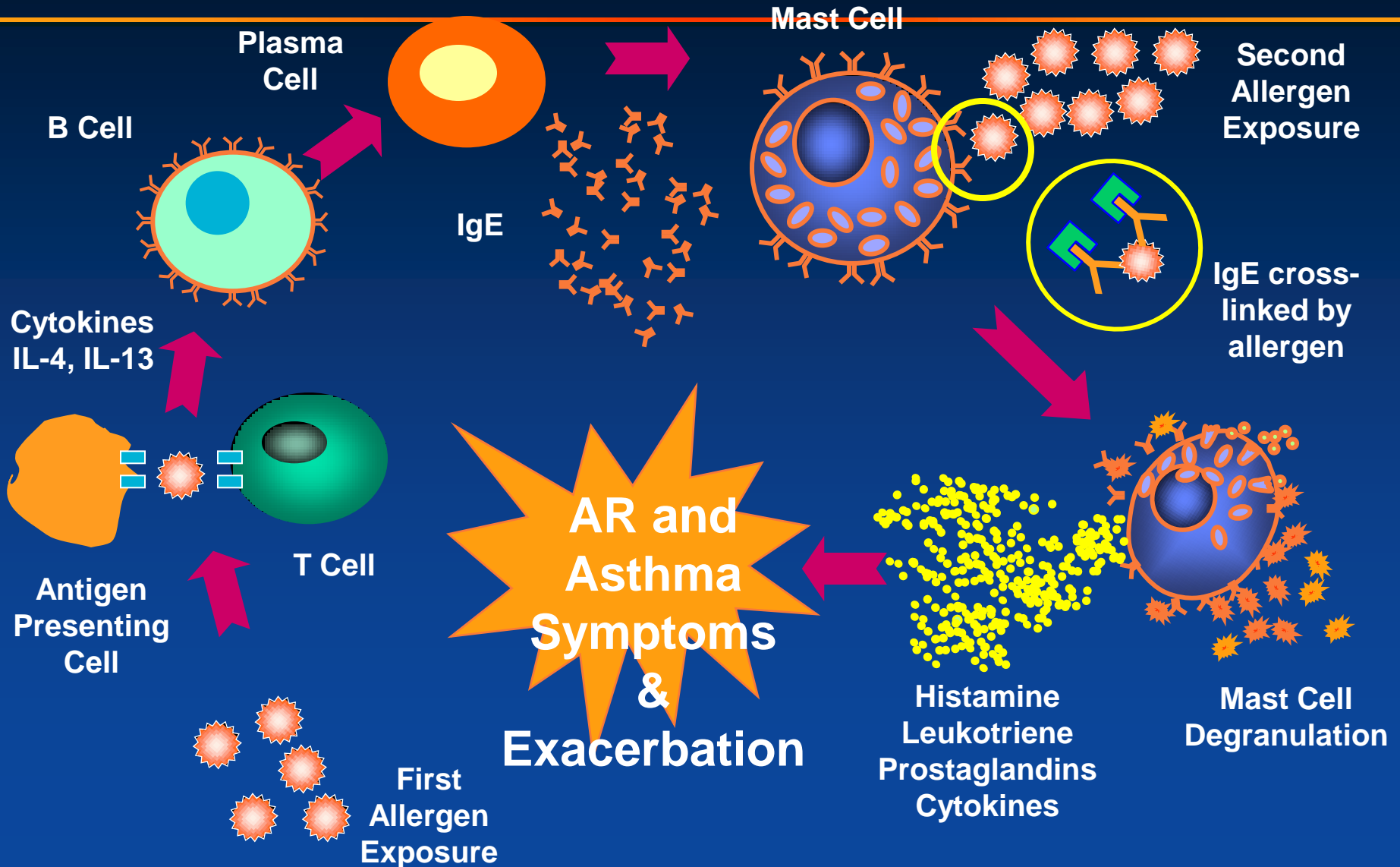


# Role of IgE and IgE receptors in allergic airway inflammation and remodeling

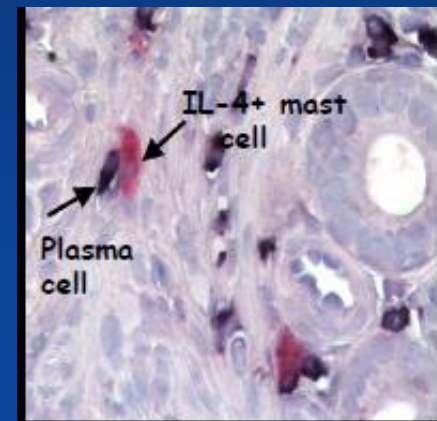
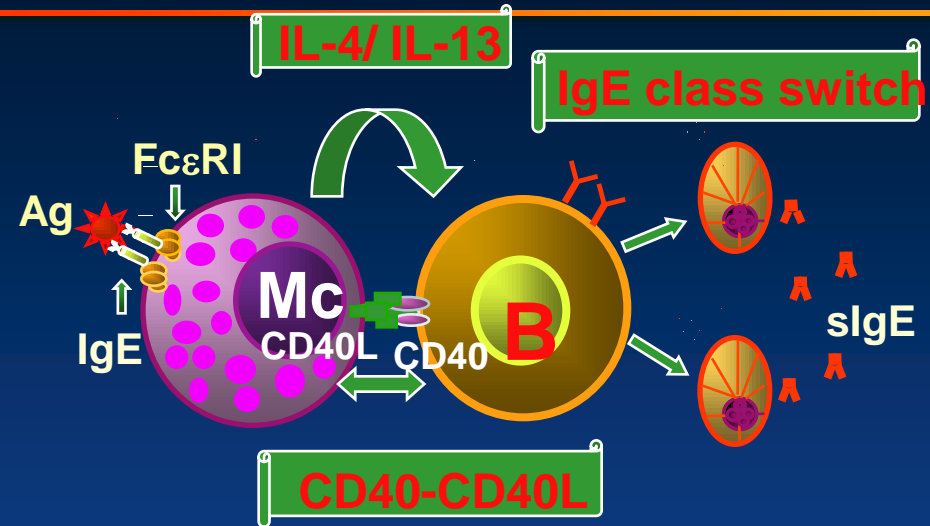
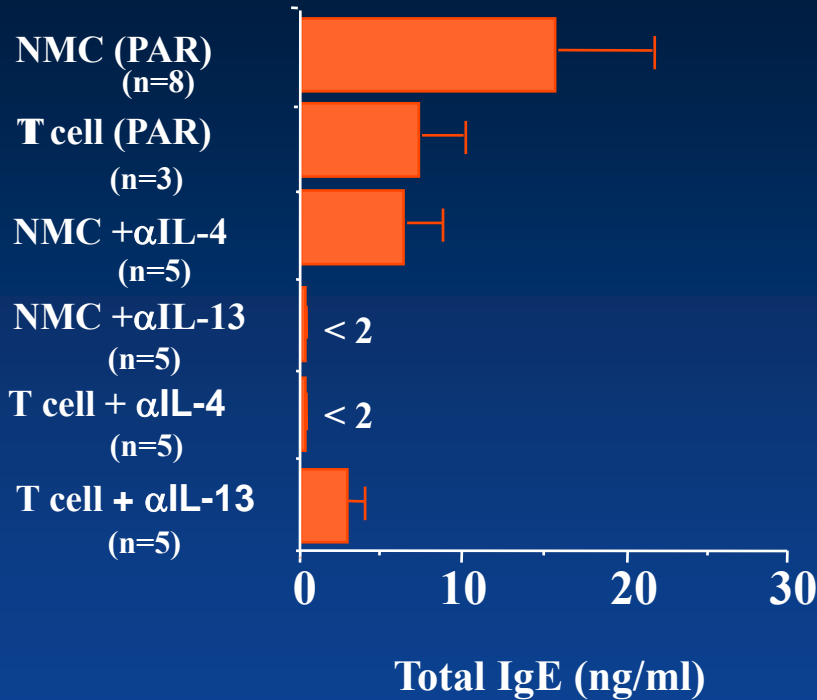
---

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Prof. Div of Allergy, Dept of Pediatrics  
Nippon Medical School  
Tokyo, Japan  
pawankar.ruby@gmail.com*

# The Allergic Inflammatory Cascade

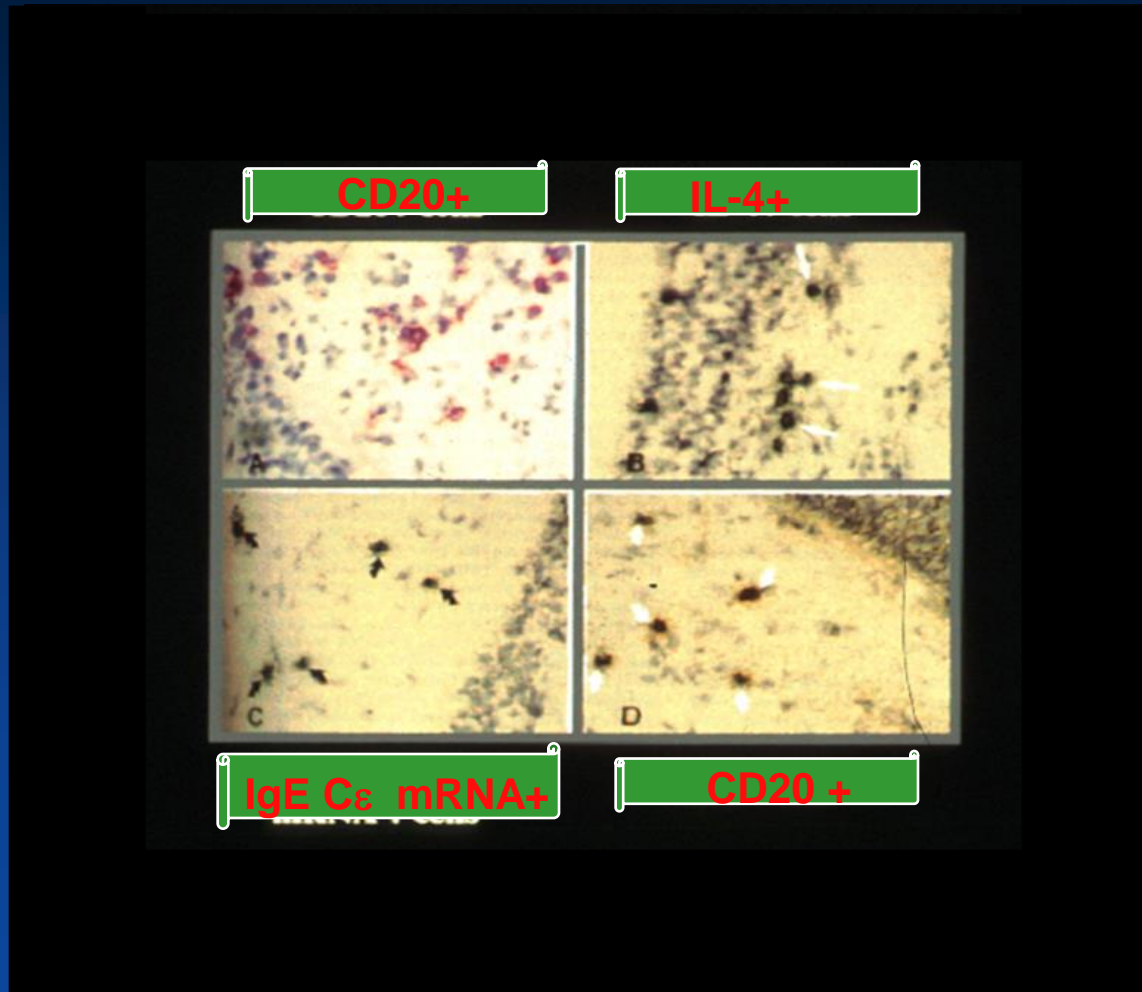


# Mast cells can induce IgE synthesis in B cells



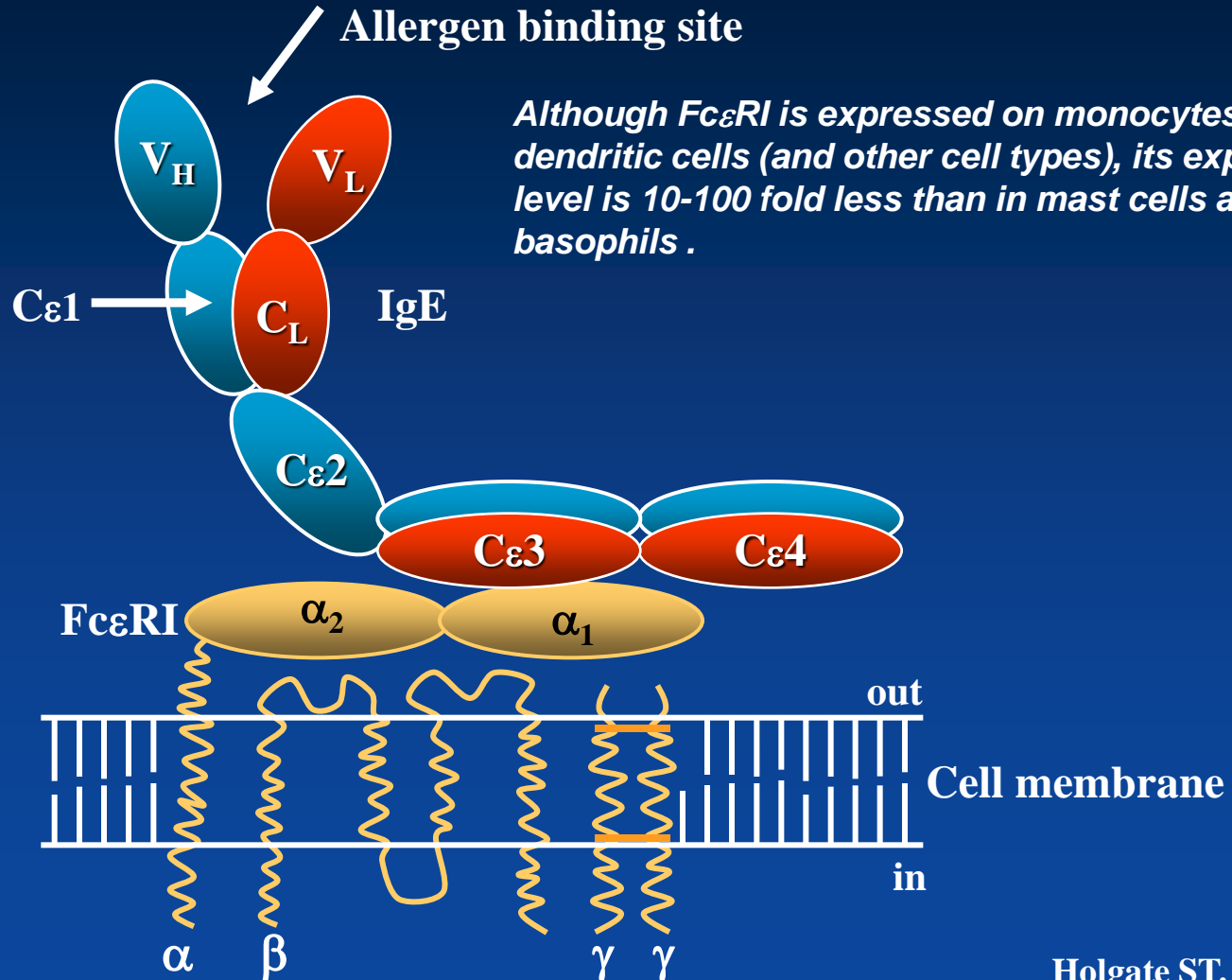
*Pawankar R et al. J Clin Invest*  
*Pawankar R et al, Clin Exp Allergy*  
*Pawankar R. Curr Opin Allergy Immunol,*

# IgE is locally produced in the target organ

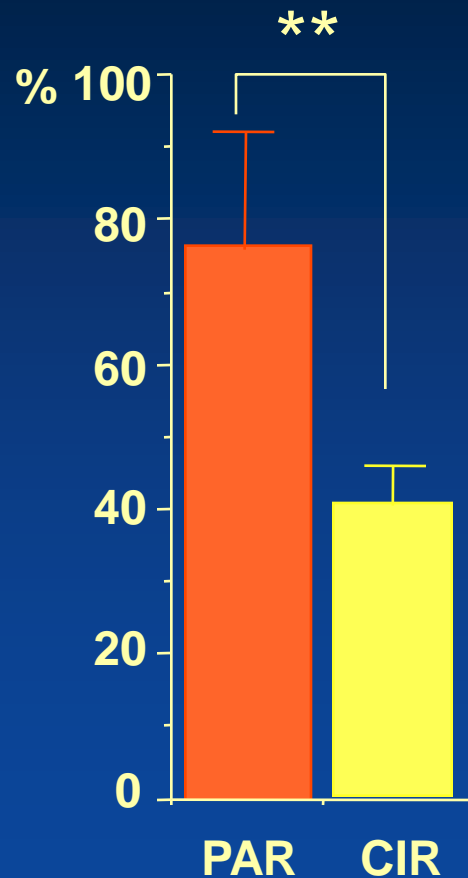


# Binding of IgE to high-affinity (FcεRI) receptor

Twenty-five years later the receptors that mediate the binding of IgE to cells were described.

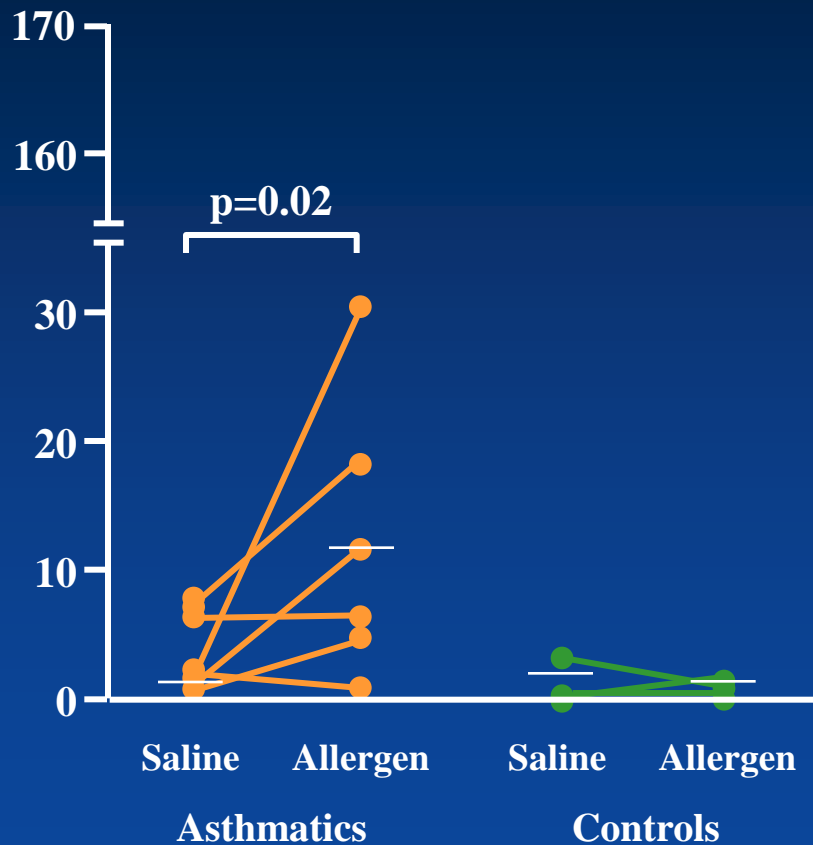


# Fc epsilon RI expression in NMC

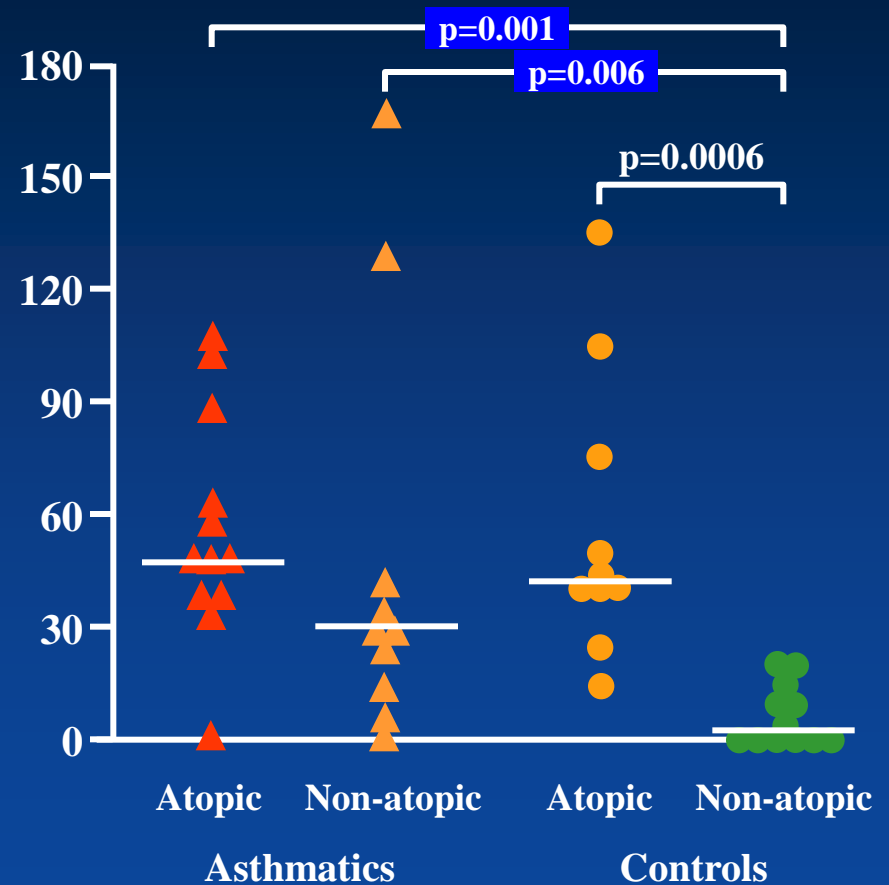


# High-affinity IgE receptor-bearing cells in atopic and non-atopic asthma

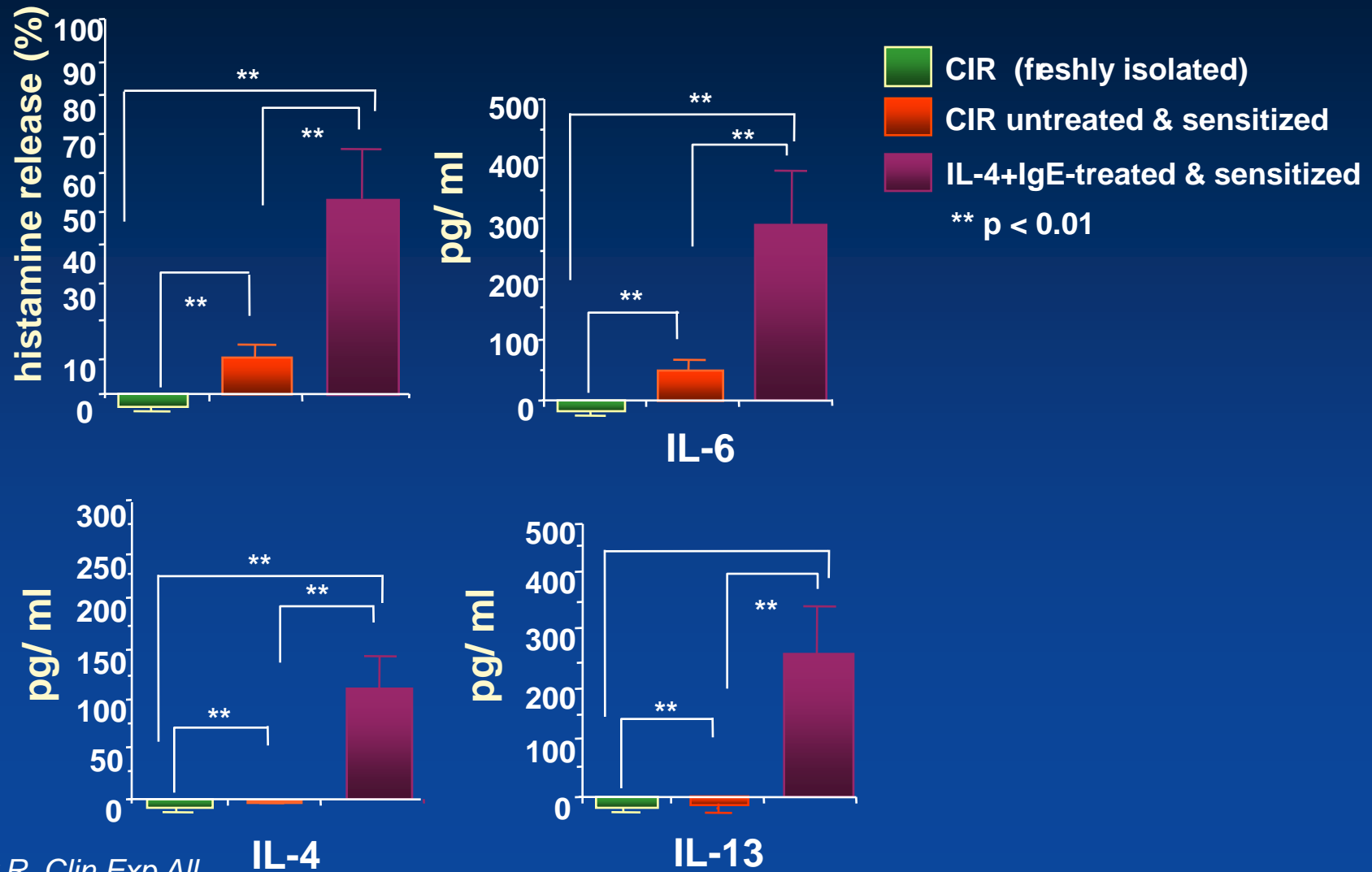
$Fc\epsilon RI\alpha$  mRNA+ cells ( $\times 10^6$  cells)  
– obtained from 120mL BAL



$Fc\epsilon RI+$  cells/mm<sup>2</sup>

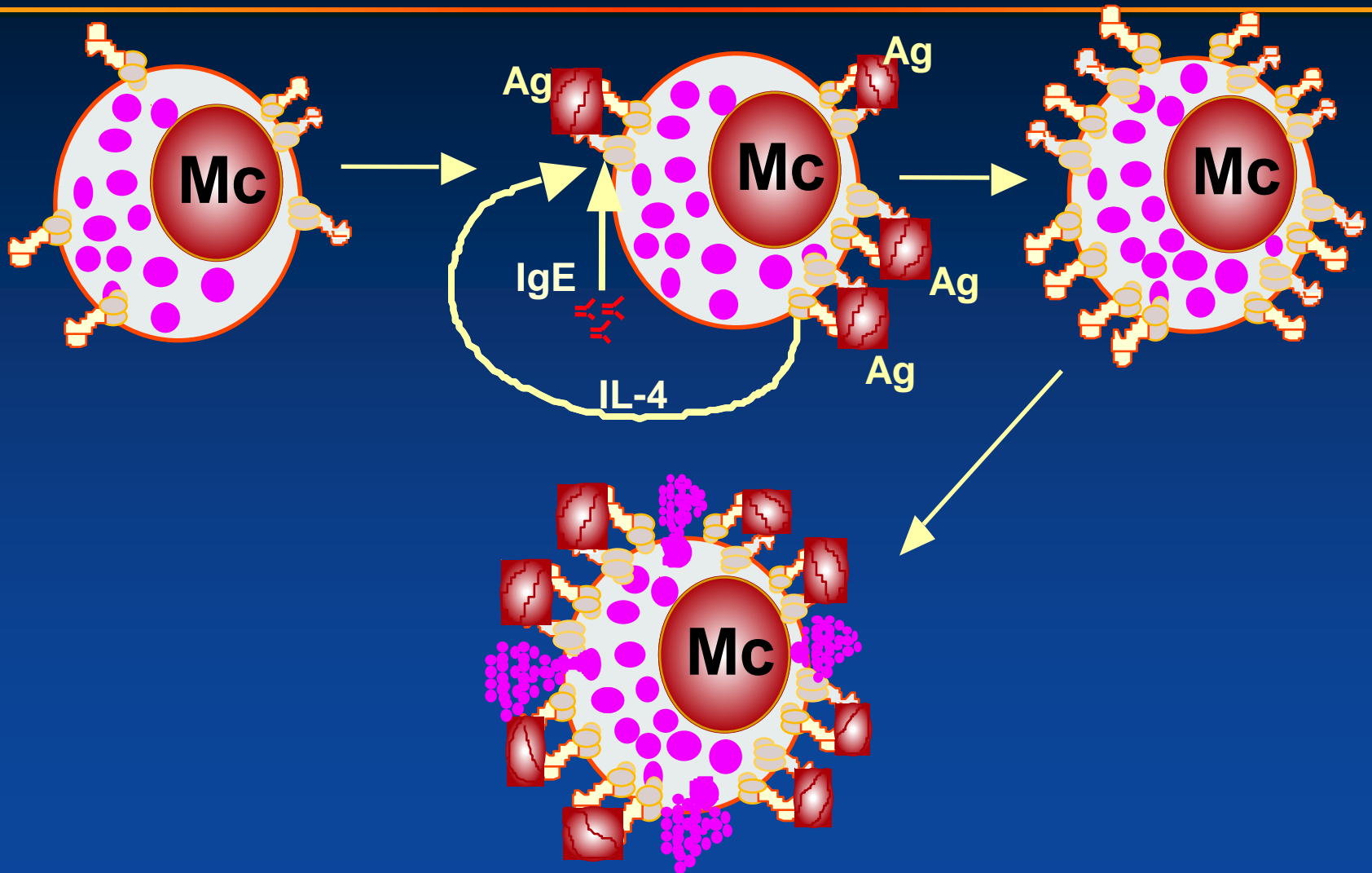


# IL-4 + IgE enhance mediator release from NMC





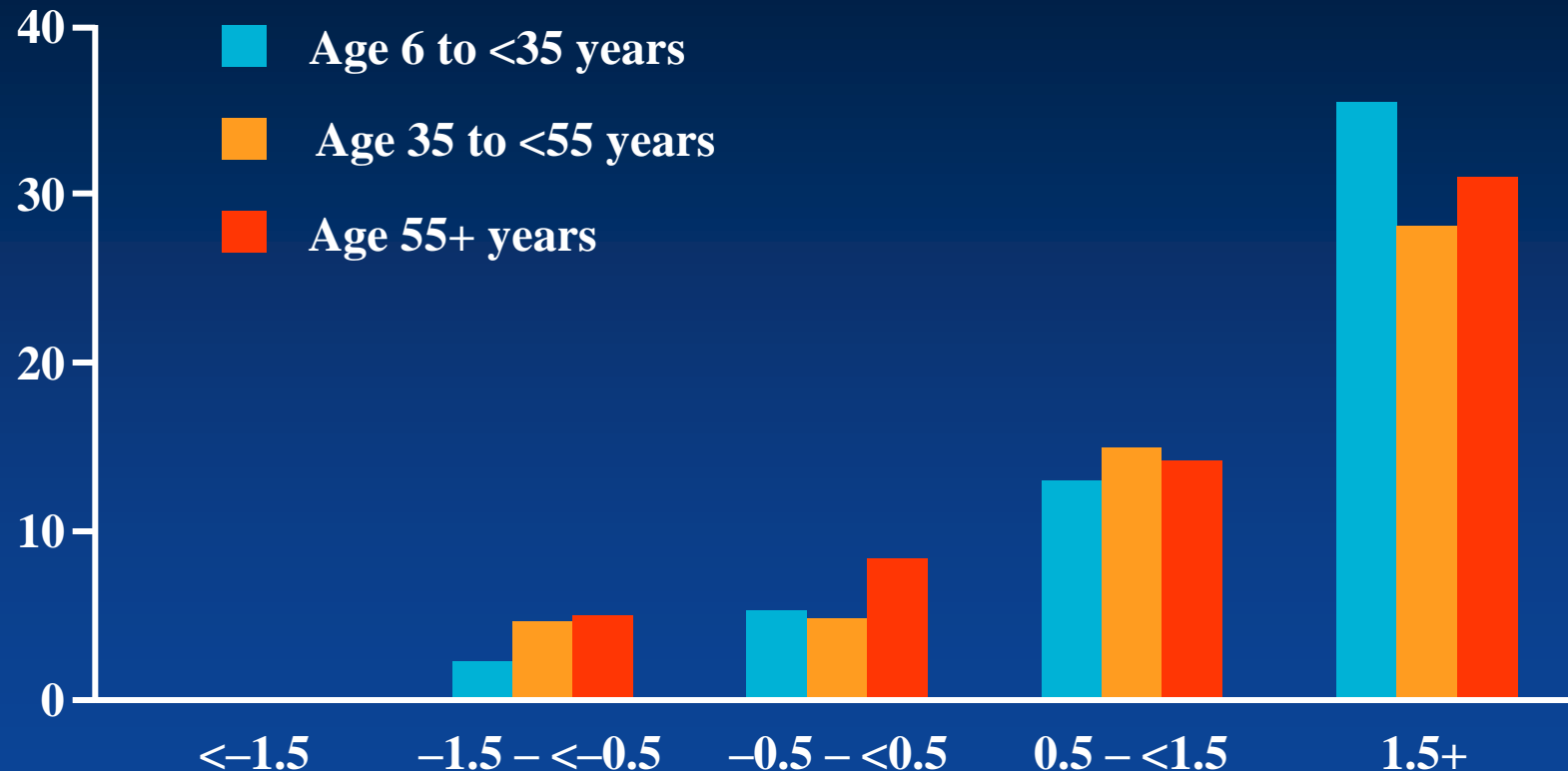
# Mast cell-IgE-IgE receptor axis



# The prevalence of asthma is related to the level of serum IgE standardized for age and sex

Prevalence of asthma (%)

n = 2657 of the general population with self-reported asthma or allergic rhinitis



*In all age groups, there was a highly significant trend for prevalence to increase with increasing Z scores ( $p < 0.0001$ ).*

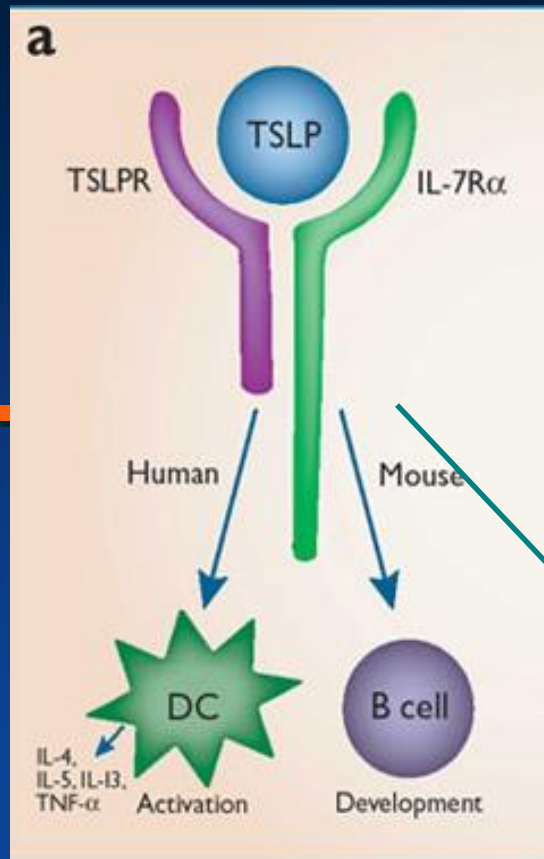
# **FcεRI-mediated Thymic Stromal Lymphopoietin Production by IL-4-primed Human Mast Cells**

---

# Function of Thymic stromal lymphopoietin (TSLP)

Induction of  $T_H2$ -attracting chemokines CCL17, CCL22

Priming of naïve  $T_H2$  cells to produce  $T_H2$  cytokines



Promotion of development of B220+ IgM+ immature B cells from pre-B cells

A weak comitogen for T cell proliferation

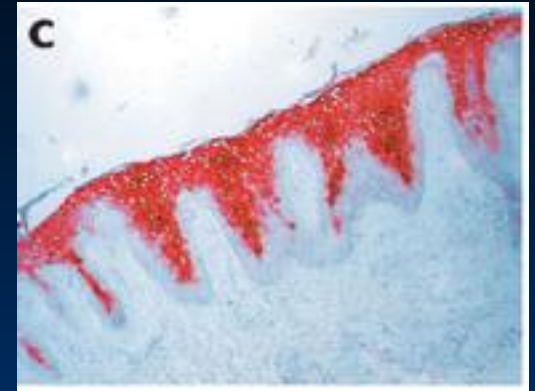


CD4+T cell development

# TSLP as a key initiator of allergic inflammation

## Humans

TSLP is expressed in epithelial cells of patients with atopic dermatitis



The number of cells within the bronchial epithelium and submucosa expressing mRNA for TSLP are significantly increased in asthmatics as compared with controls.

## Mice

Skin-specific overexpression of TSLP results in an atopic dermatitis-like phenotype.

Lung-specific overexpression of TSLP induces asthma-like airway inflammation.

TSLPR KO mice fail to develop an inflammatory lung response to inhaled antigen.

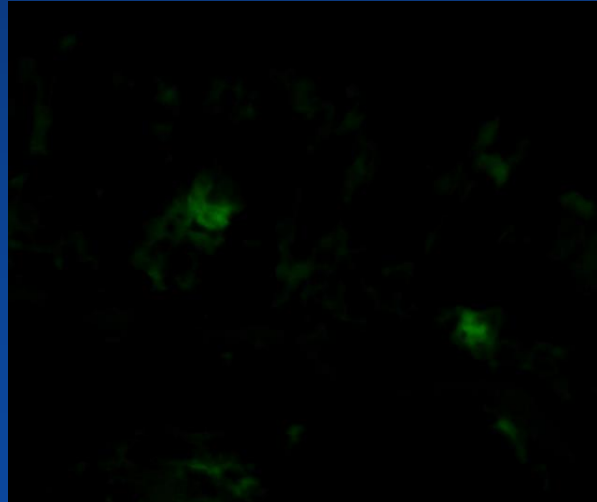
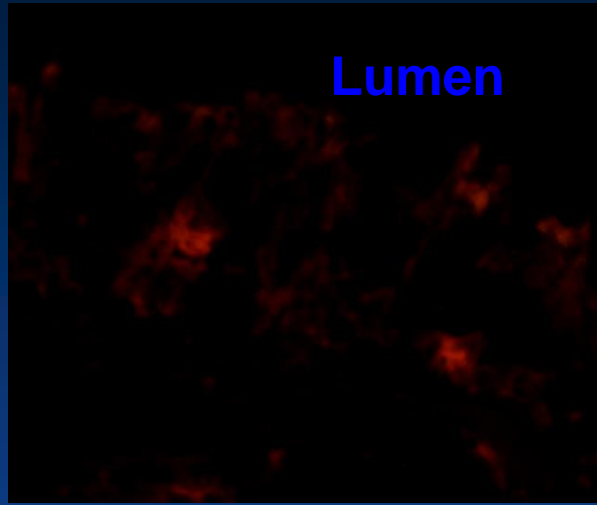
# TSLP expression by human bronchial mucosal mast cells of asthmatic patients

**TSLP**

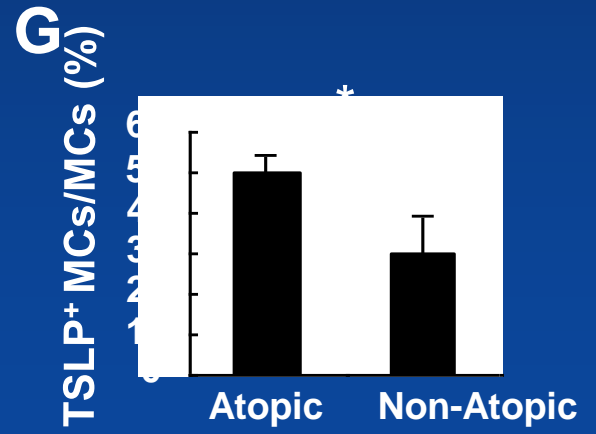
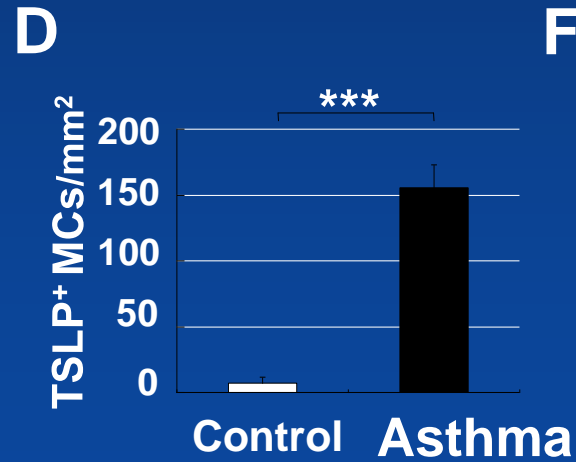
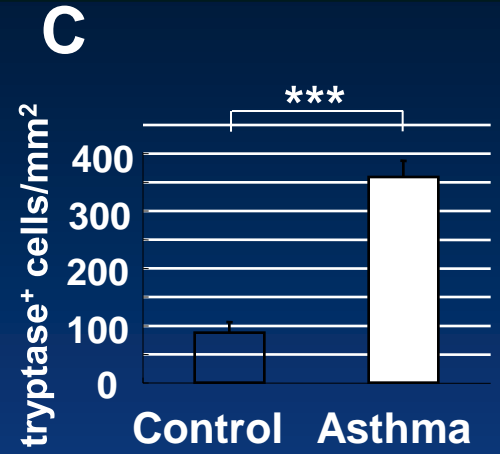
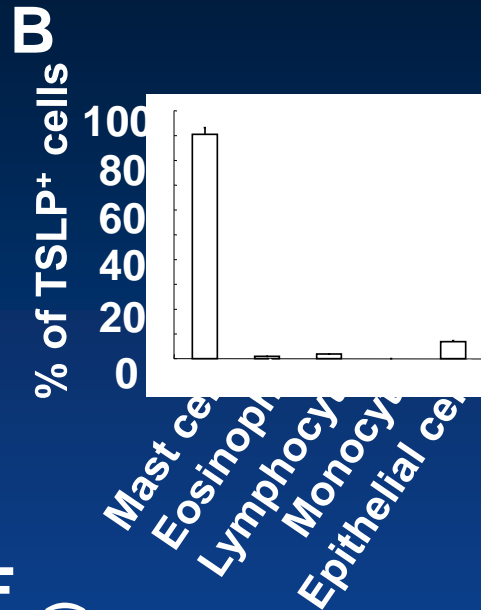
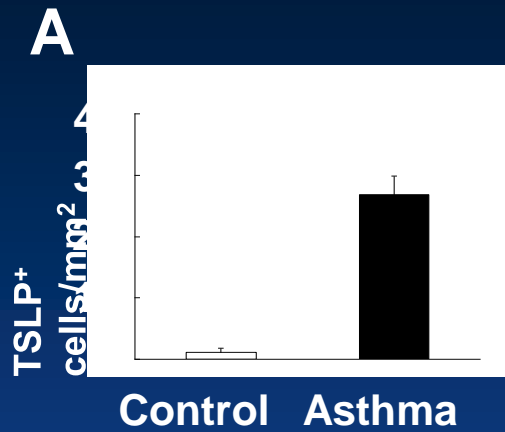
Lumen

**Merged**

**Tryptase  
(mast cells)**

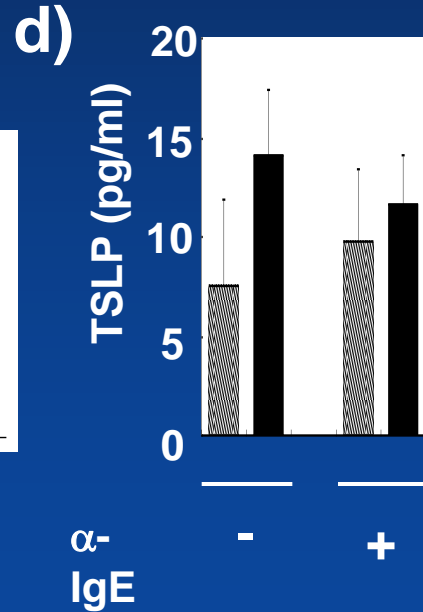
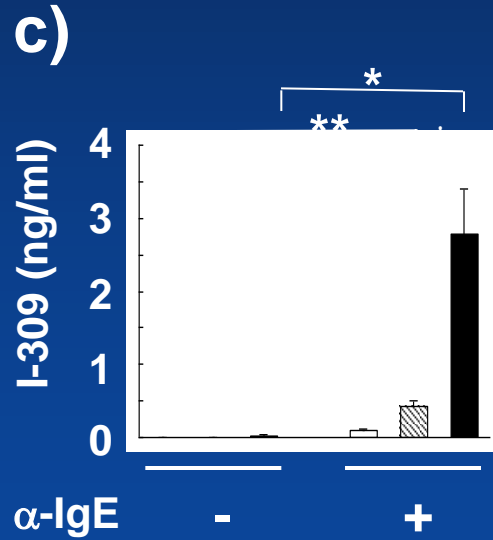
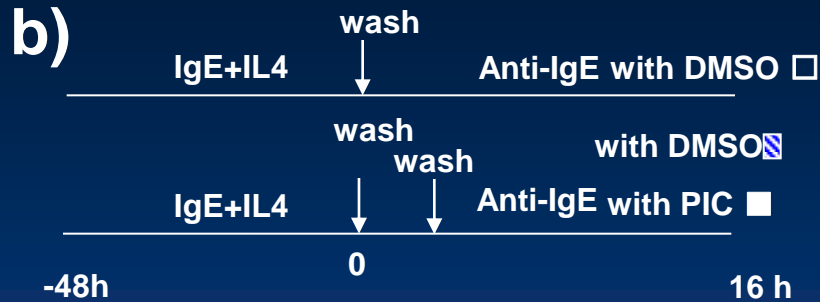


# Significant increase in number of TSLP<sup>+</sup>Tryptase<sup>+</sup> cells in the airways of asthmatic patients



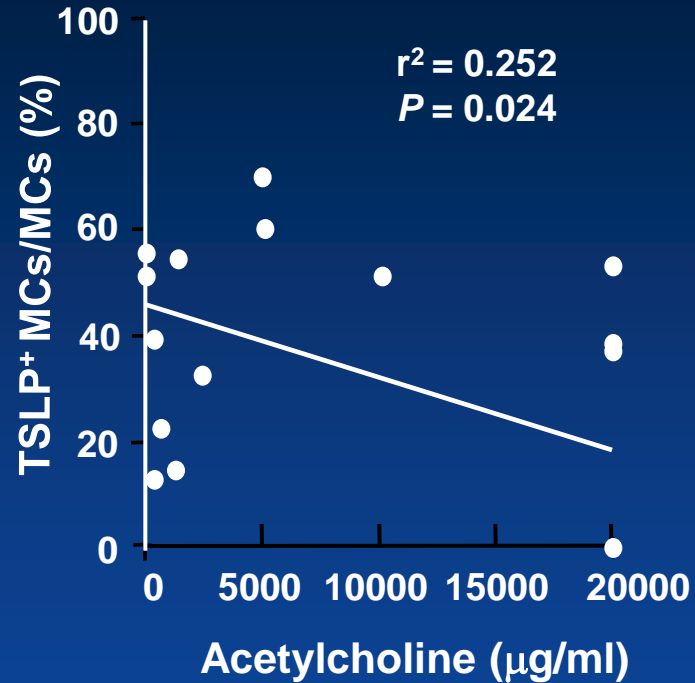
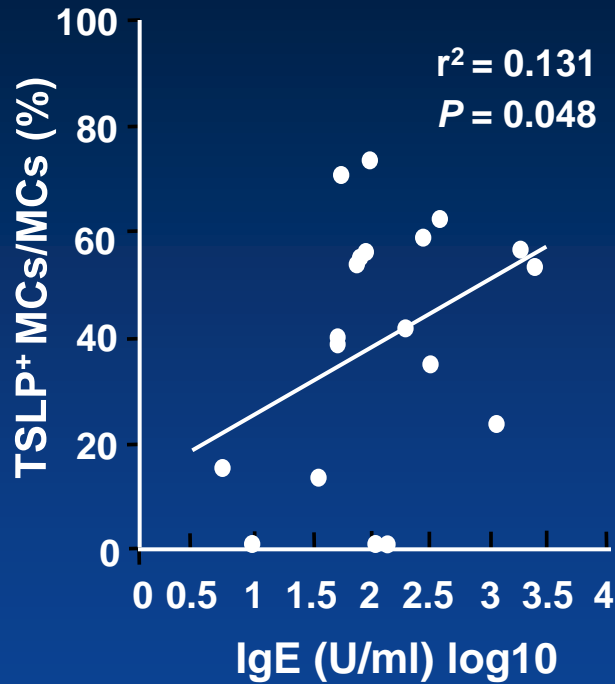
# TSLP production by human mast cells following aggregation of Fc $\epsilon$ RI in the presence of IL-4

1

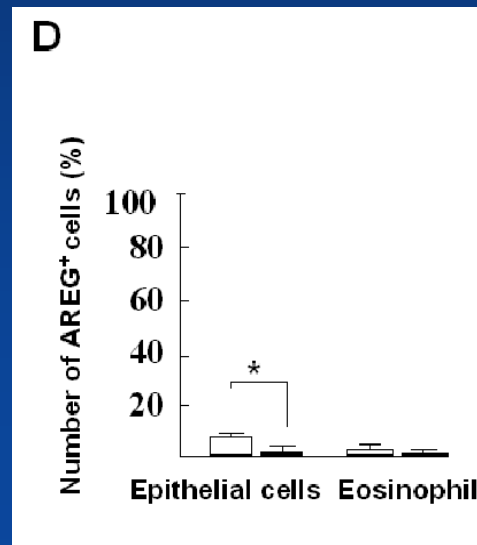
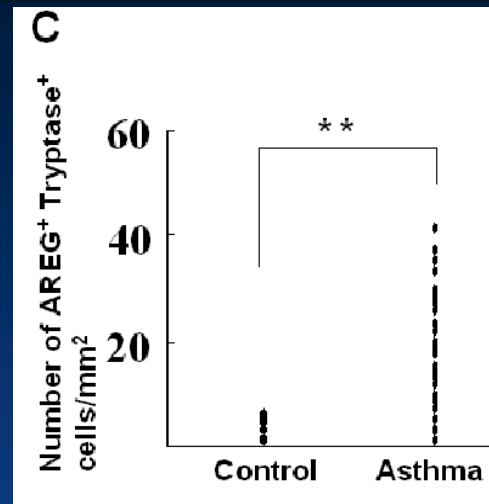
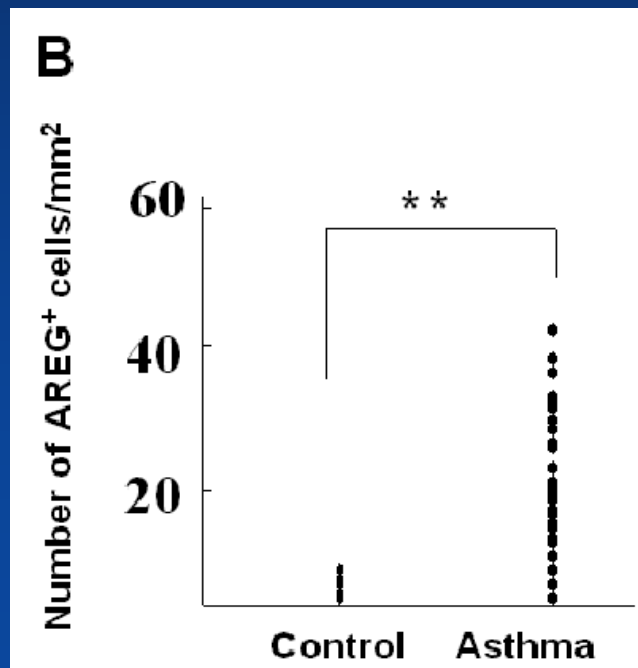
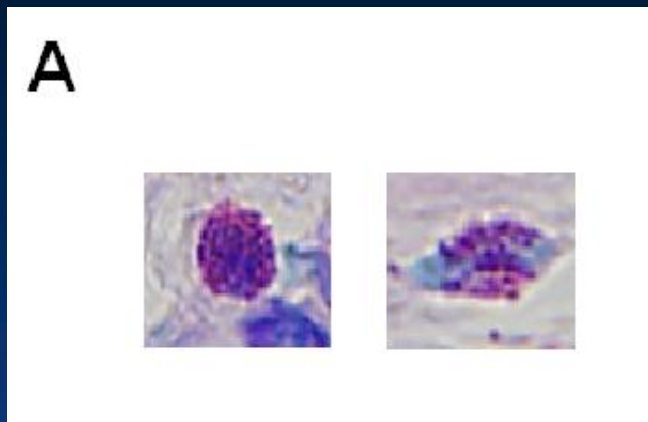




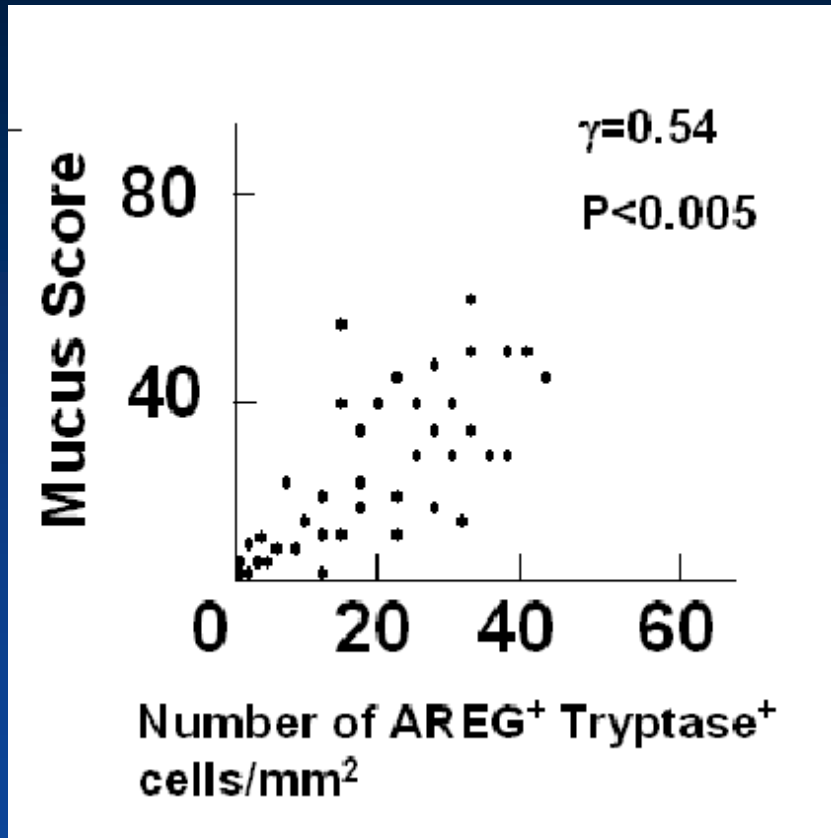
# Correlation of % of TSLP<sup>+</sup> cells in mast cells with the serum IgE level, and hyperresponsibility in asthmatic patients and controls



# The number of AREG<sup>+</sup> tryptase<sup>+</sup> cells increases in bronchial mucosa of subjects with asthma



# Correlation between AREG<sup>+</sup> tryptase<sup>+</sup> cells with the extent of goblet cell hyperplasia in the airways of asthmatic subjects



$$\text{Mucus score} = n_1 + 2n_2$$

Grade 1

Goblet cell height epithelial layer  $< (1/3)$

Grade 2

Goblet cell height epithelial layer  $> 1/3$

$n_1$ ; Grade 1-cell count

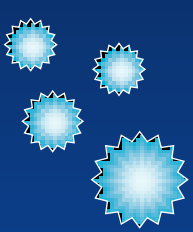

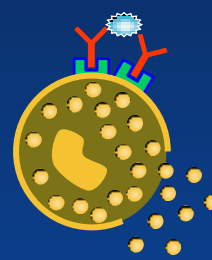
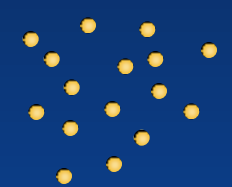
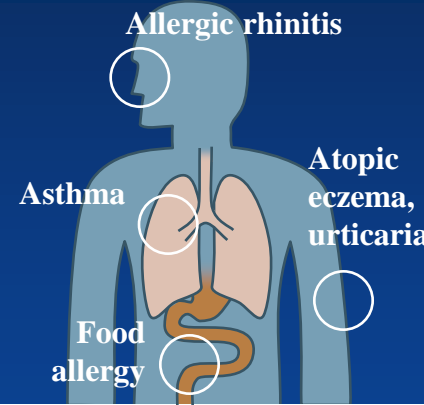
$n_2$ ; Grade 2 cell count

(Tokuyama K et al Am J Physiol 1990)

# Rationale for anti-IgE therapy

Anti-IgE stops IgE binding to effector cells

Mechanism

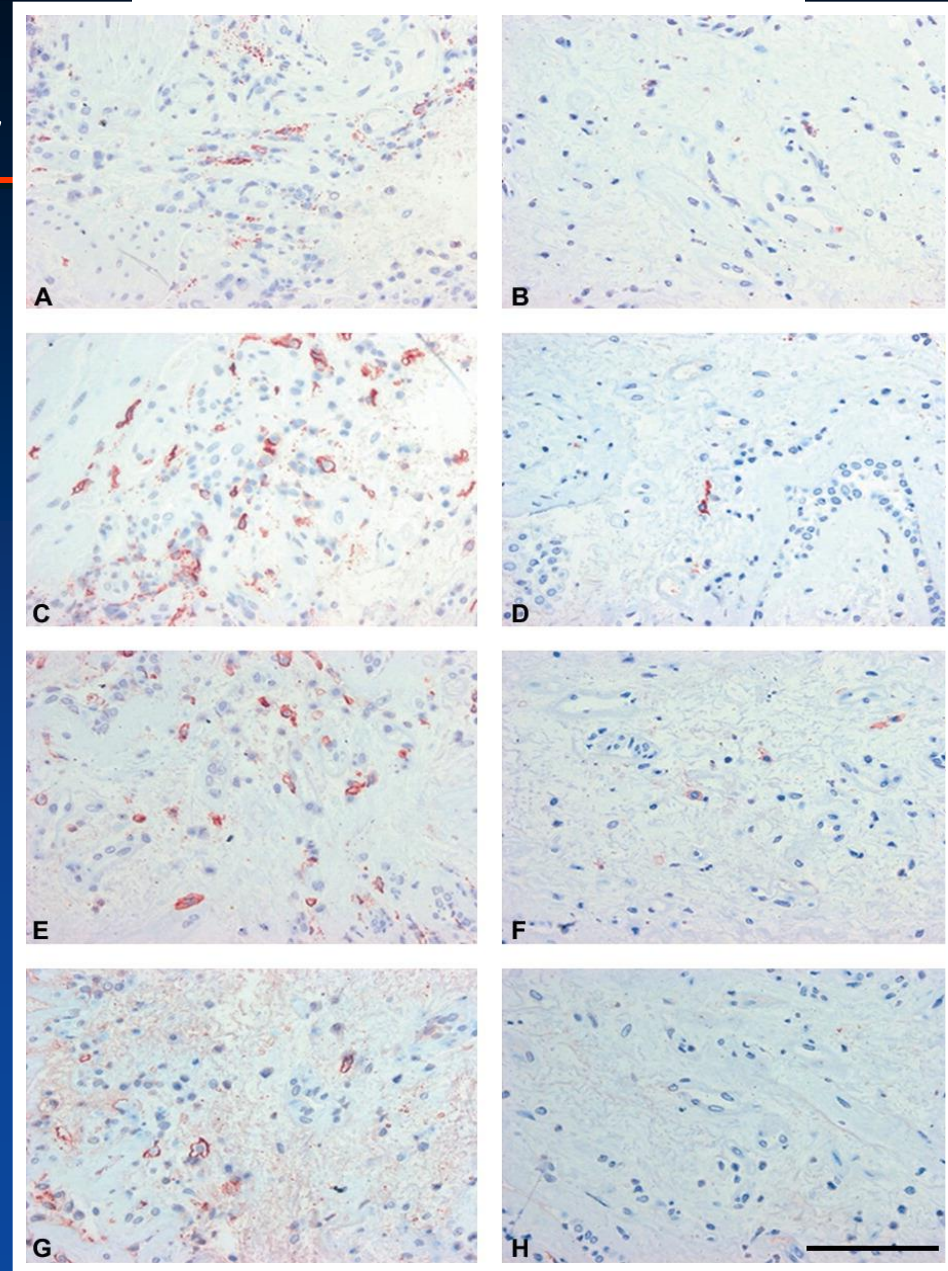
	Allergen	IgE synthesis	Mast cell degranulation	Inflammatory mediators	Clinical symptoms
					
Treatment	Allergen avoidance	Hypo-sensitization	Mast-cell stabilization: cromones, isoprenaline	Mediator antagonists: antihistamines, antileukotrienes	Late-phase inhibitors: steroids

Adapted from Roitt J. Essential Immunology 1994

**Immunohistochemical staining of bronchial biopsy specimens before (left) and after (right) 16 weeks of omalizumab treatment.**

**Representative sections show staining with antibody against:**  
**ECP (A and B)**  
**Cell-surface IgE (C and D)**  
**High-affinity IgE R (E and F)**  
**IL-4 (G and H)**

**Djukanović R, et al. Am J Respir Crit Care Med 2004;170:583-93.**



# Mechanisms of Action of Omalizumab



- ◆ Reduces serum levels of free IgE
- ◆ Down-regulates expression of IgE receptors (FceRI) on mast cells and basophils.
- ◆ In the airways of patients with allergic asthma, it reduces FcεRI+ and IgE+ cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers.

*Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. J Allergy Clin Immunol 2005;115(3):459-65.*

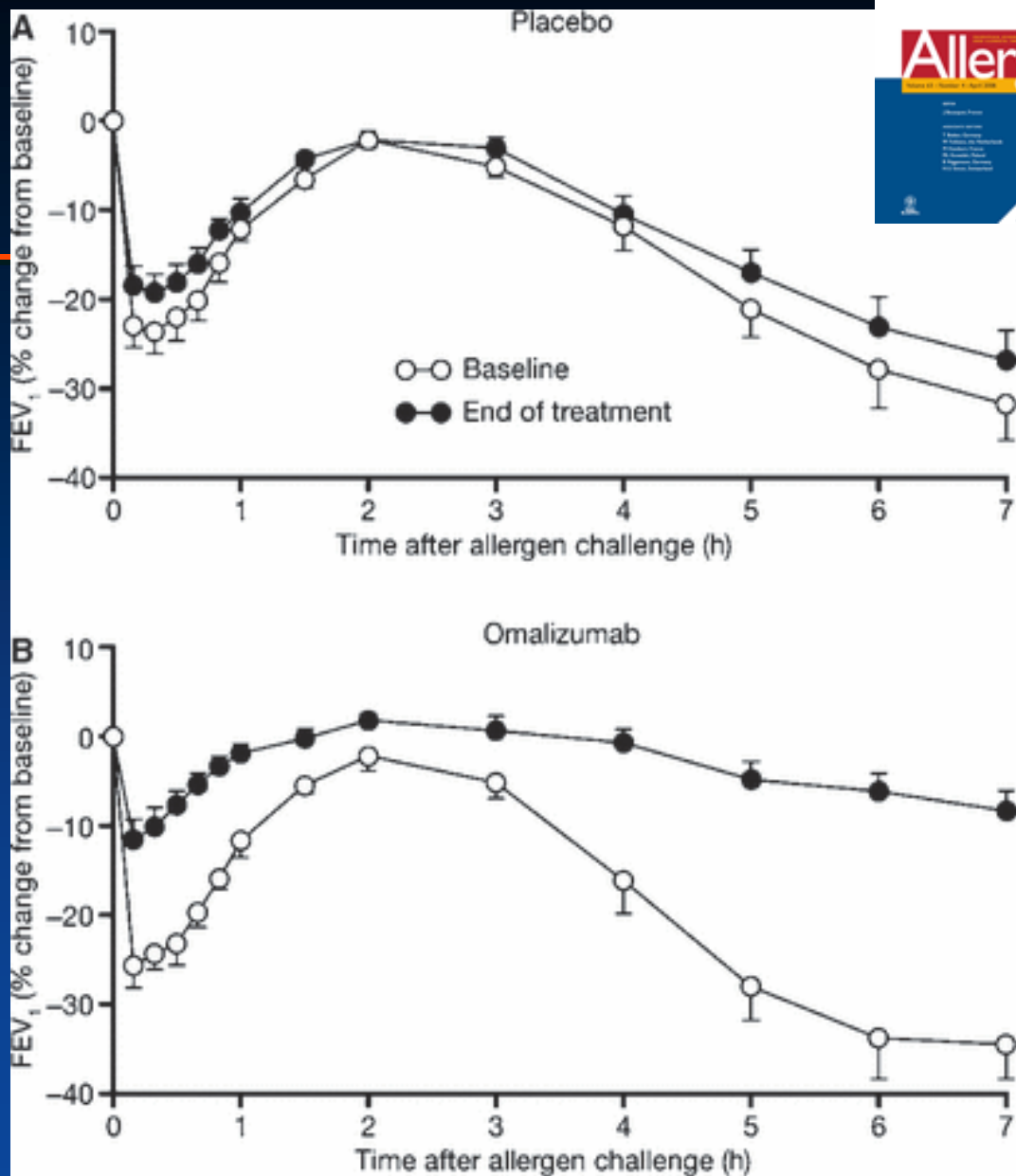
# Mechanisms of action of omalizumab (cont'd)



- ◆ The reductions in circulating levels of IgE resulting from omalizumab treatment leads to reductions in FcεRI expression on mast cells, basophils and dendritic cells.
- ◆ This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia, levels of GM-CSF, IL-2, IL-4, IL-5 and IL-13.
- ◆ It may also reduce allergen presentation to T-cells and the production of Th2 cytokines.

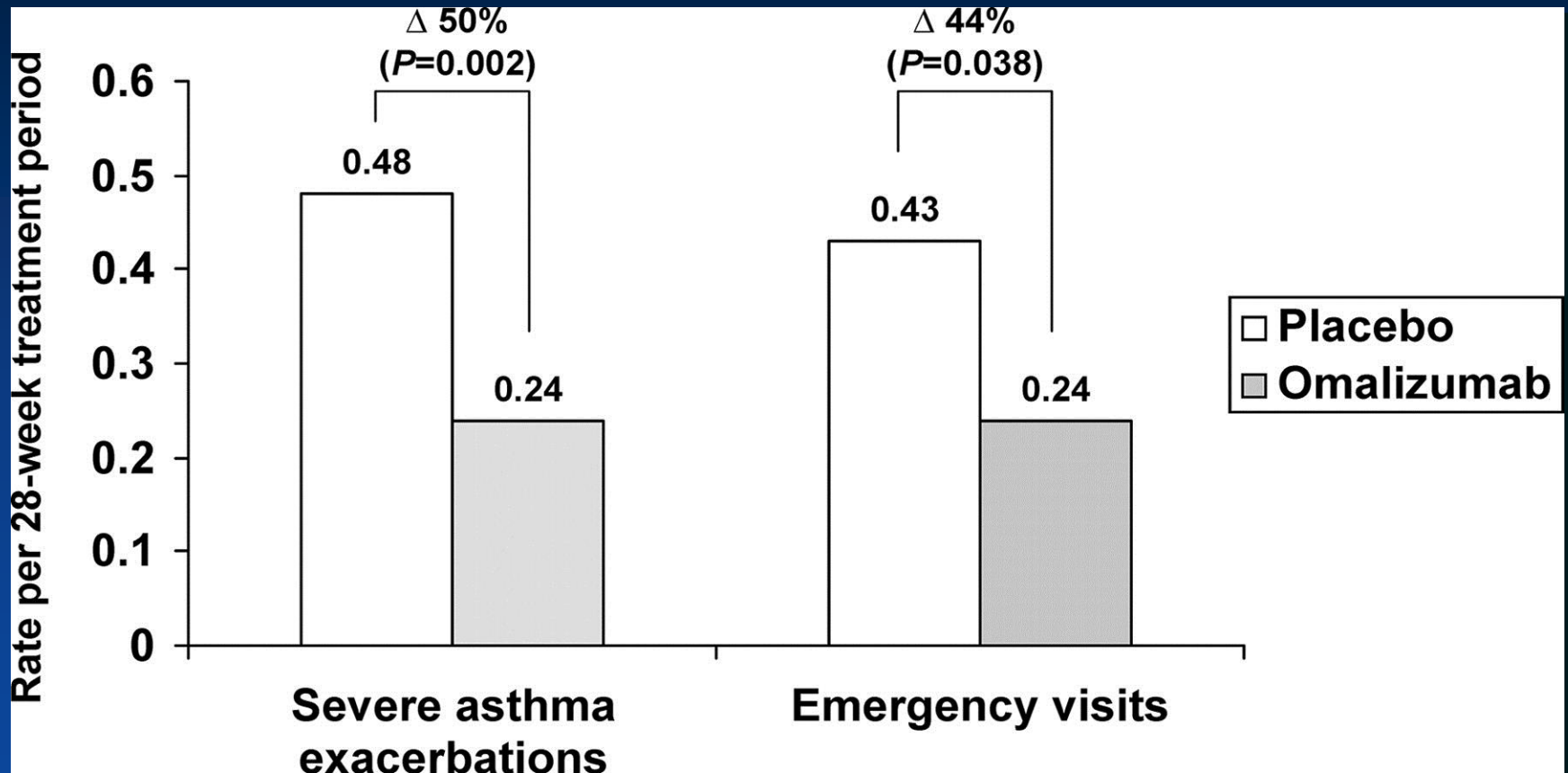
*Holgate S, et al. Allergy 2009;64(12):1728–36.*

Forced expiratory volume in 1 second as a percentage of baseline in the placebo (A) and omalizumab (B) groups.





# Effect of add-on therapy with omalizumab in patients with severe persistent asthma whose asthma was inadequately controlled by therapy with high-dose ICSs plus a LABA



Humbert M, et al. Allergy 2005; 60:309–16

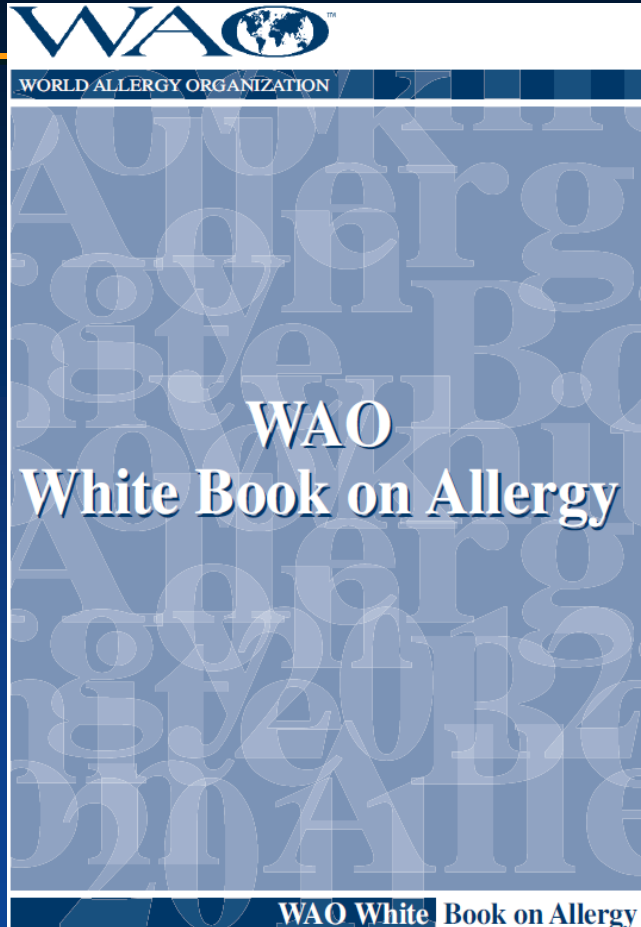
# *Conclusion*

## **Benefits of Anti-IgE in atopic disease**

- ◆ Effectively reduces the incidence of allergic asthma exacerbations while decreasing the need for steroids
- ◆ Improves asthma-specific QoL and reduces the incidence of hospitalizations
- ◆ Can simplify the control of asthma with only once or twice monthly injections
- ◆ Controls the symptoms of SAR, reducing the requirement for concomitant medication
- ◆ Has a good long-term safety profile

# WAO White Book on Allergy

## Allergic Diseases as a Global Public Health Issue



### Authored by:

- International expert allergists and clinical immunologists; has been compiled for publication under the supervision of the
- WAO Education Council.

### Purpose:

To serve as a major resource in explaining allergic diseases, their prevalence, management, and the importance of adequate service provision for allergy patients.

*Edited by Professors Ruby Pawankar, Stephen T. Holgate, G. Walter Canonica, and Richard F. Lockey*

[http://www.worldallergy.org/UserFiles/file/WAO-White-Book-on-Allergy\\_web.pdf](http://www.worldallergy.org/UserFiles/file/WAO-White-Book-on-Allergy_web.pdf)

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