How immunology informs the design of immunotherapeutics.

Stephen R Durham

Allergy and Clinical Immunology,

Royal Brompton Hospital and Imperial College London

MRC & Asthma UK Centre in Allergic Mechanisms of Asthma

WAO Cancun Mon Dec 5th 2011

How immunology informs the design of immunotherapeutics.

- Allergen induced early and late nasal responses
- Natural seasonal allergen exposure
  - effects of corticosteroids
- Influence of treatment
  - Immunotherapy
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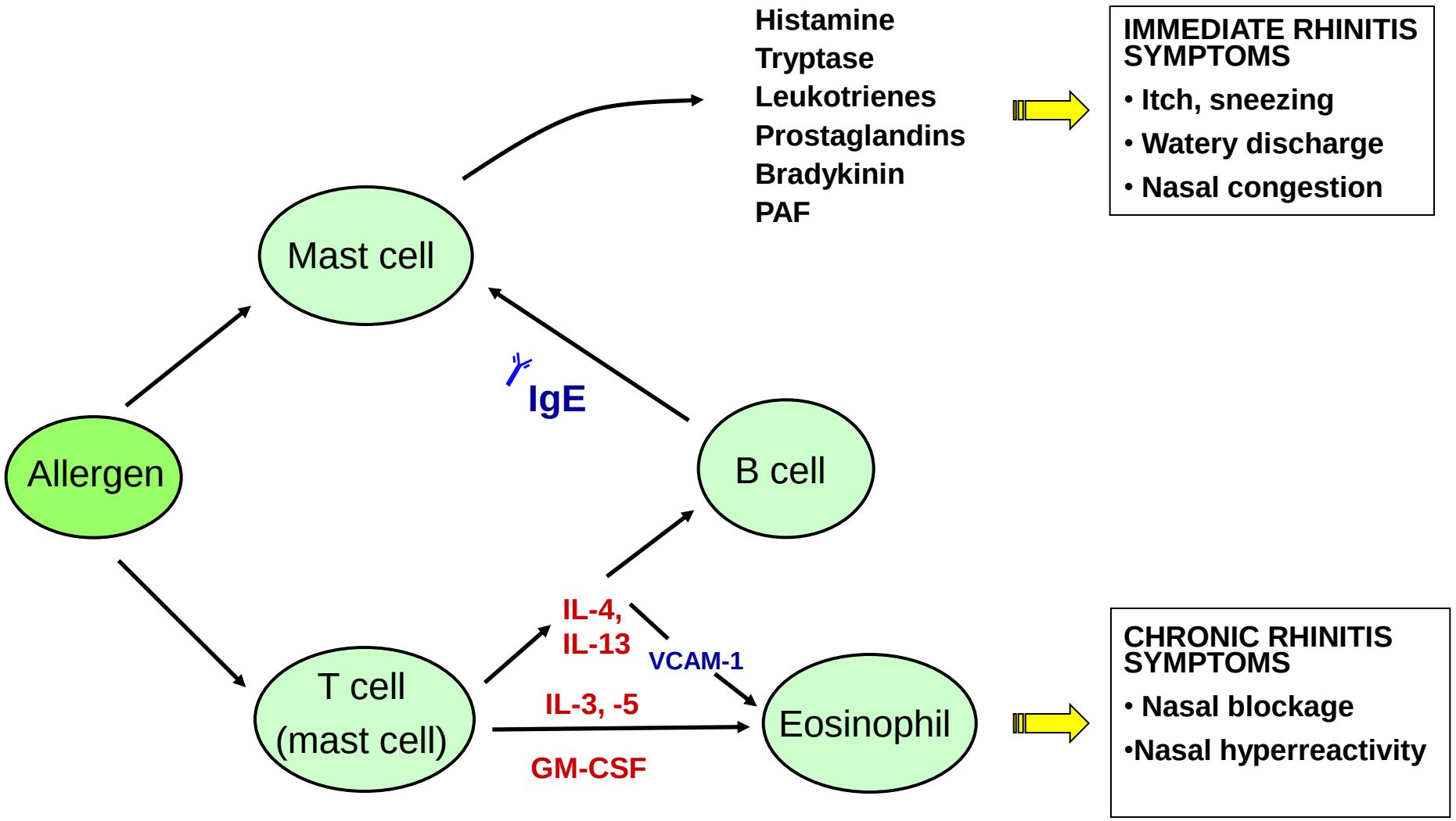
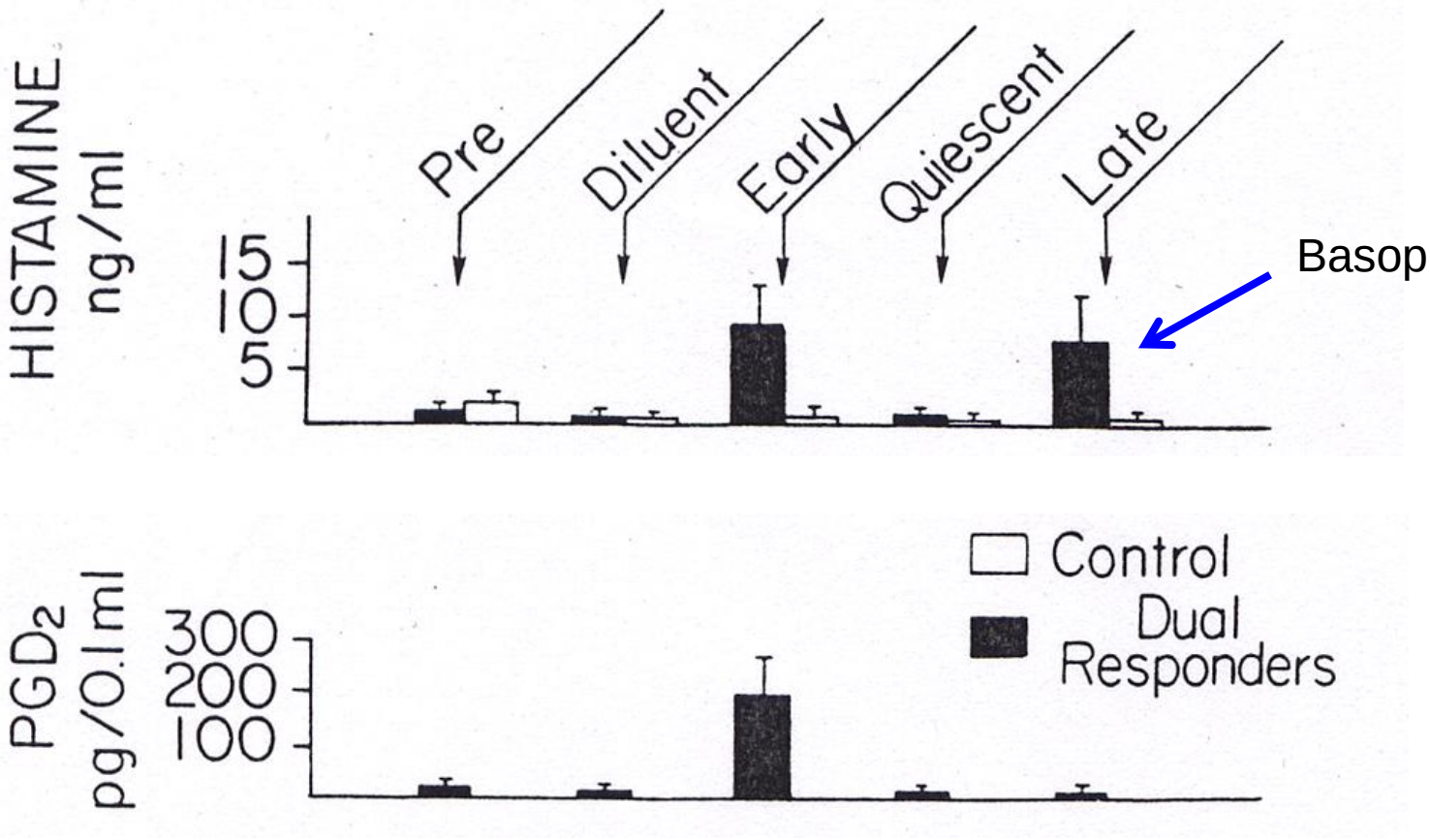
Mechanisms of allergic rhinitis



Inflammatory mediators during allergen-induced nasal responses

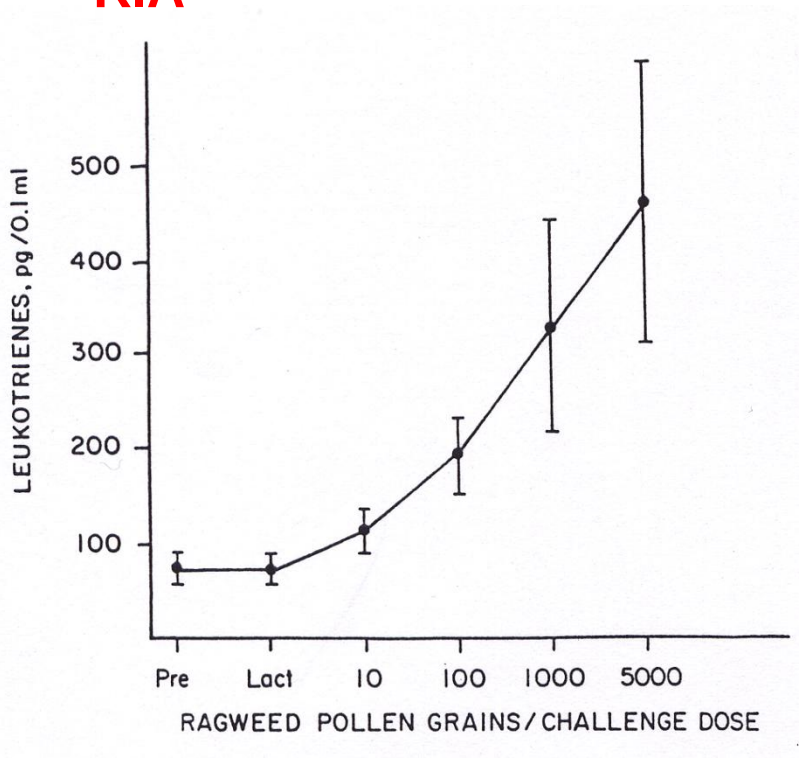
Nasal Fluid



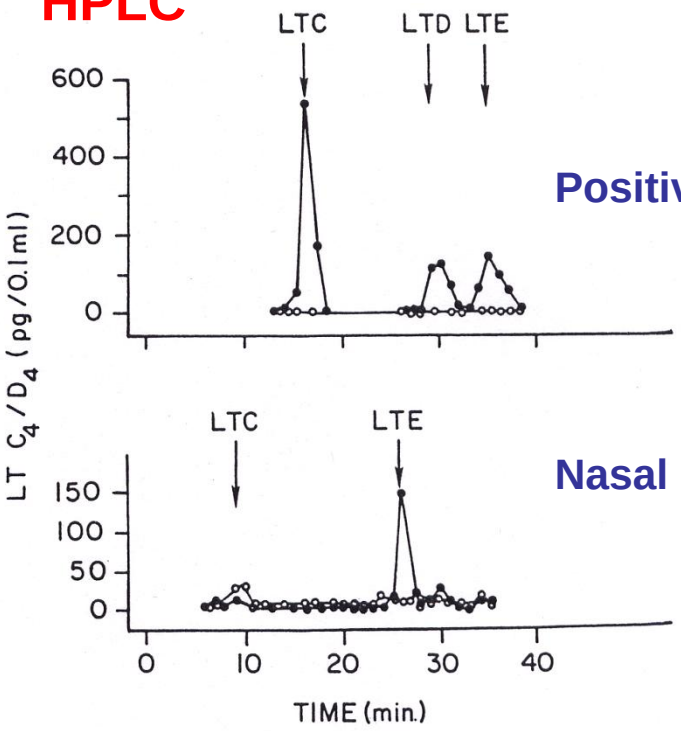
Naclerio RM. New Engl J Med 1985; 313:65-70

Leukotrienes in allergen-induced early nasal responses:

RIA



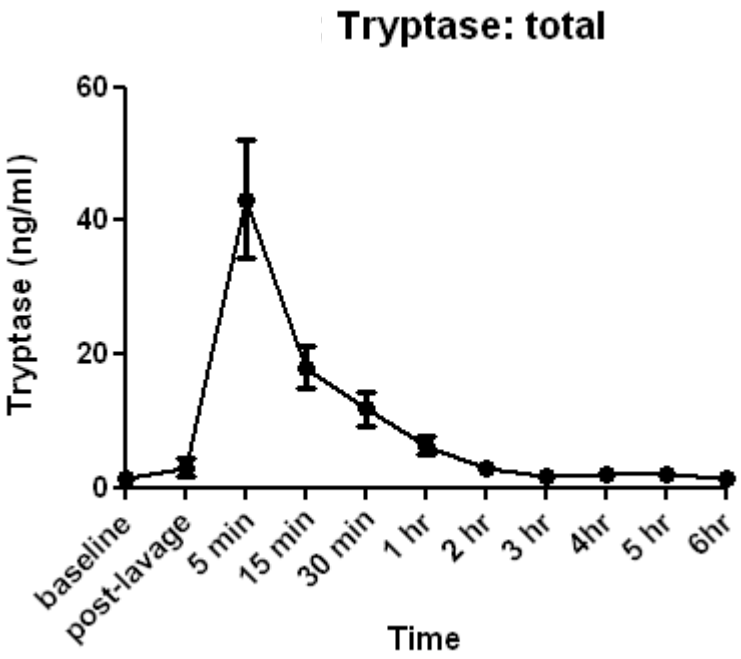
HPLC



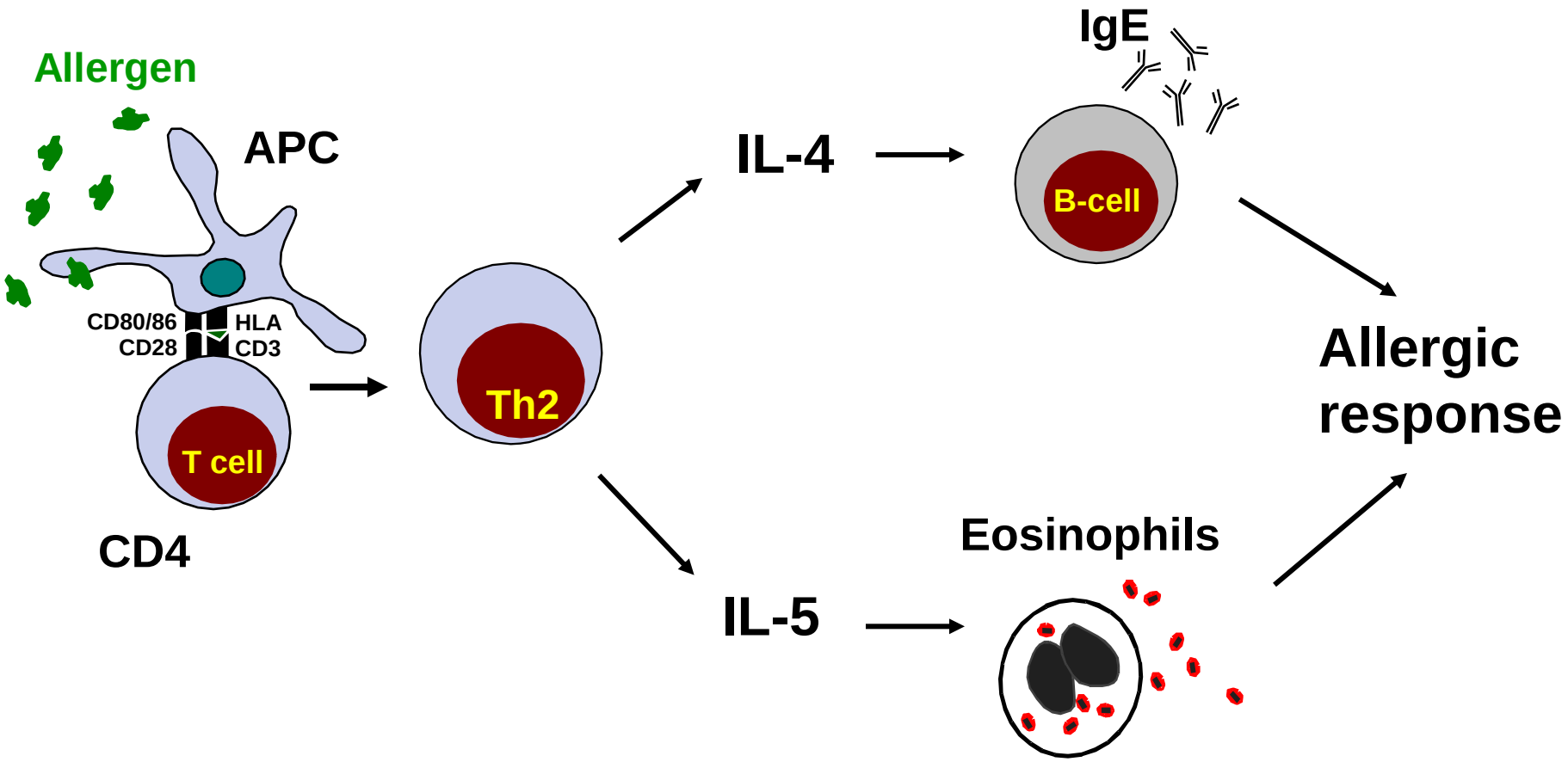
- LTs: Slow-reacting substance of anaphylaxis
- In vitro: Released from mast cells + basophils by Ag-IgE crosslinking
- Nasal lavage, post challenge: levels correlate with symptom scores
- LTC, LTD, LTE present

Creticos PS et al. New Engl J Med 1985; 313:65-70

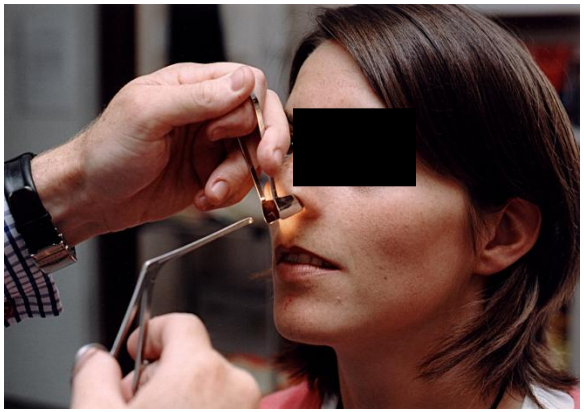
Time course of tryptase in allergen-induced nasal responses: nasal fluid

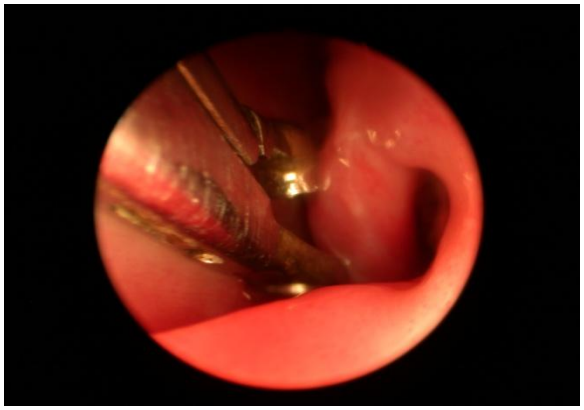


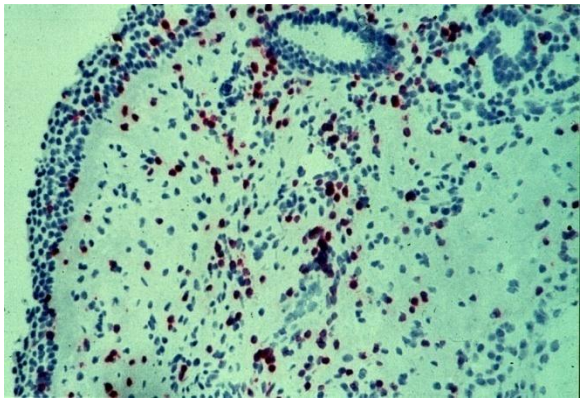
Unpublished data


Allergen
APC
CD80/86
CD28
HLA
CD3
T cell
CD4
Th2
IL-4
IL-5
IgE
B-cell
Eosinophils
Allergic response

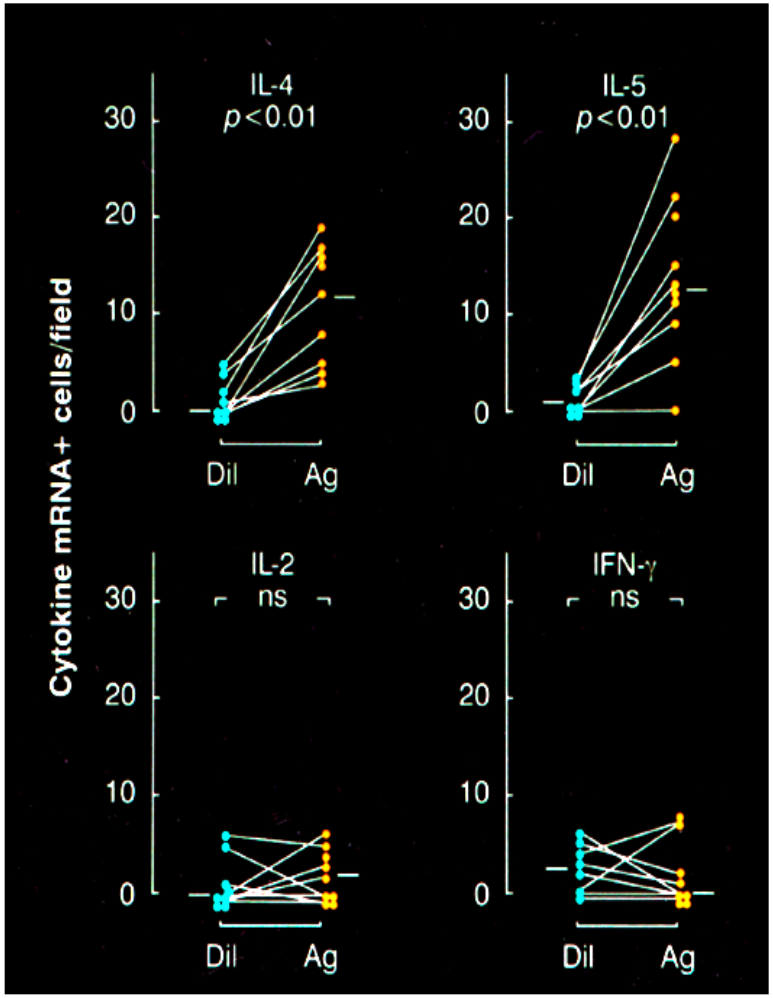
Nasal biopsy

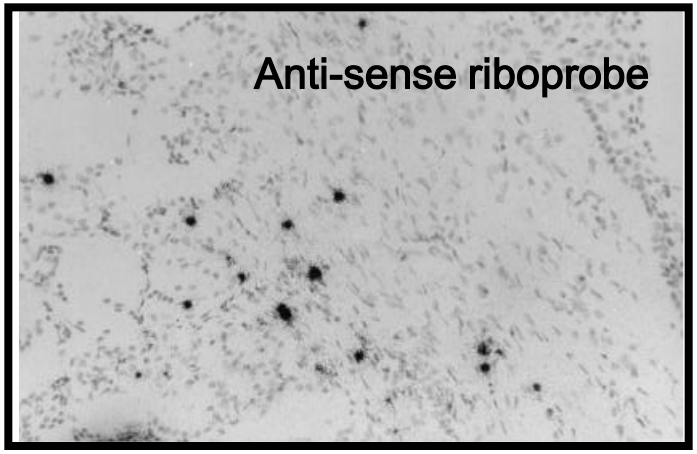


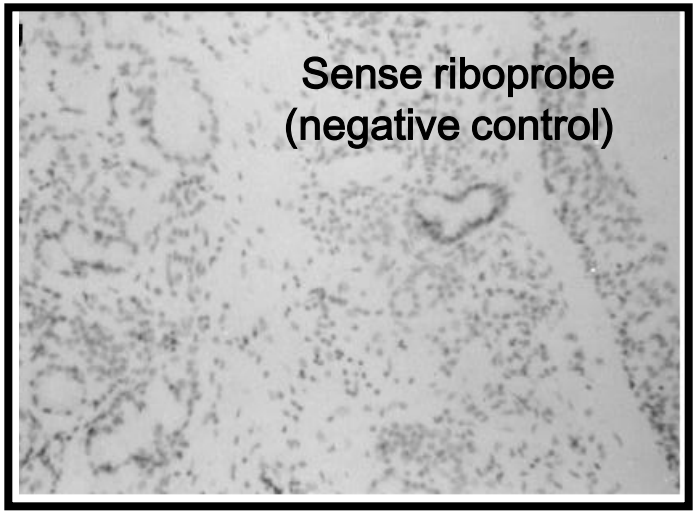




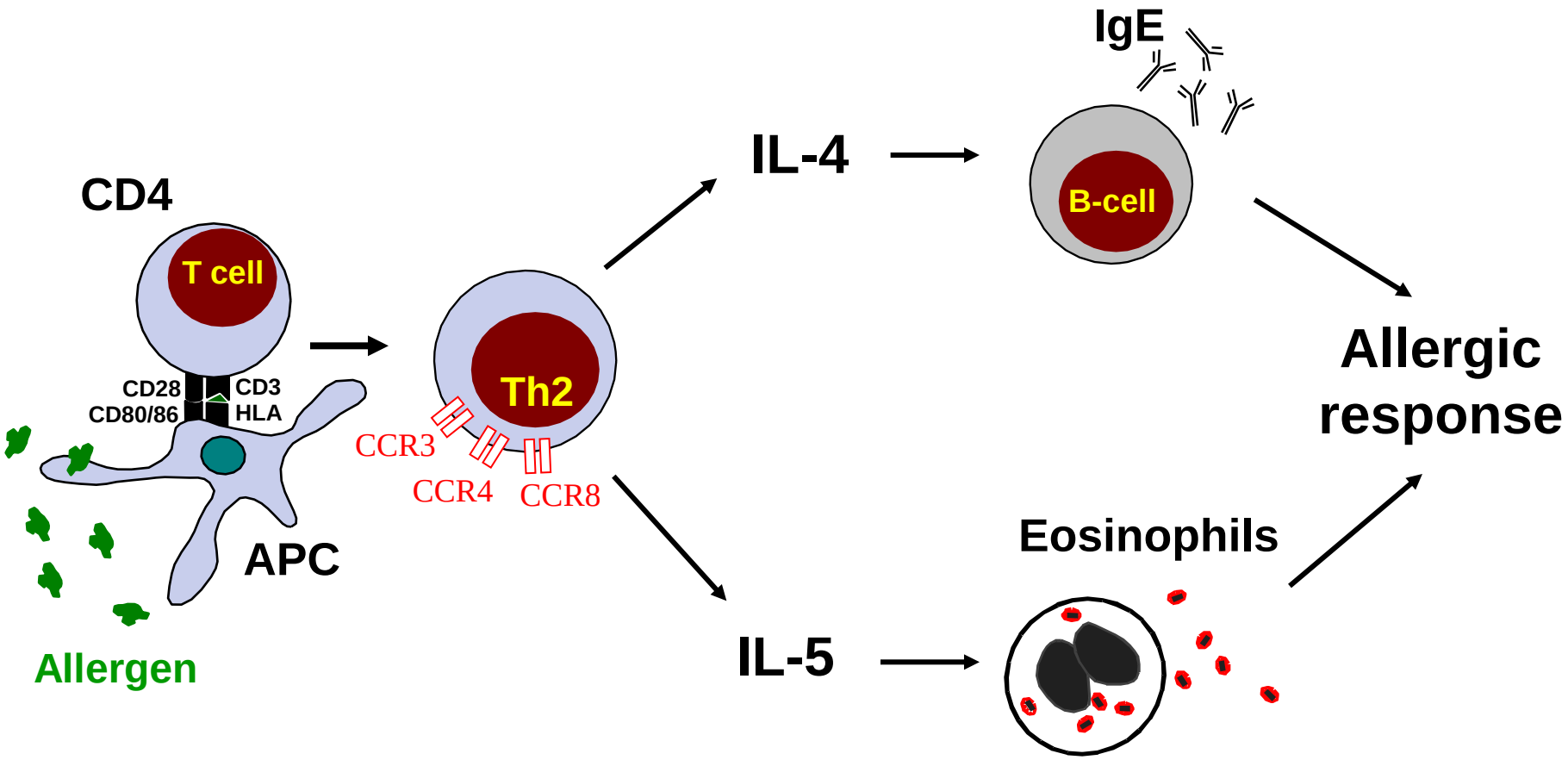
In situ hybridisation studies of nasal mucosa







Durham SR J Immunol 1992; 148: 2390-4


IgE
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T cell
Allergic response
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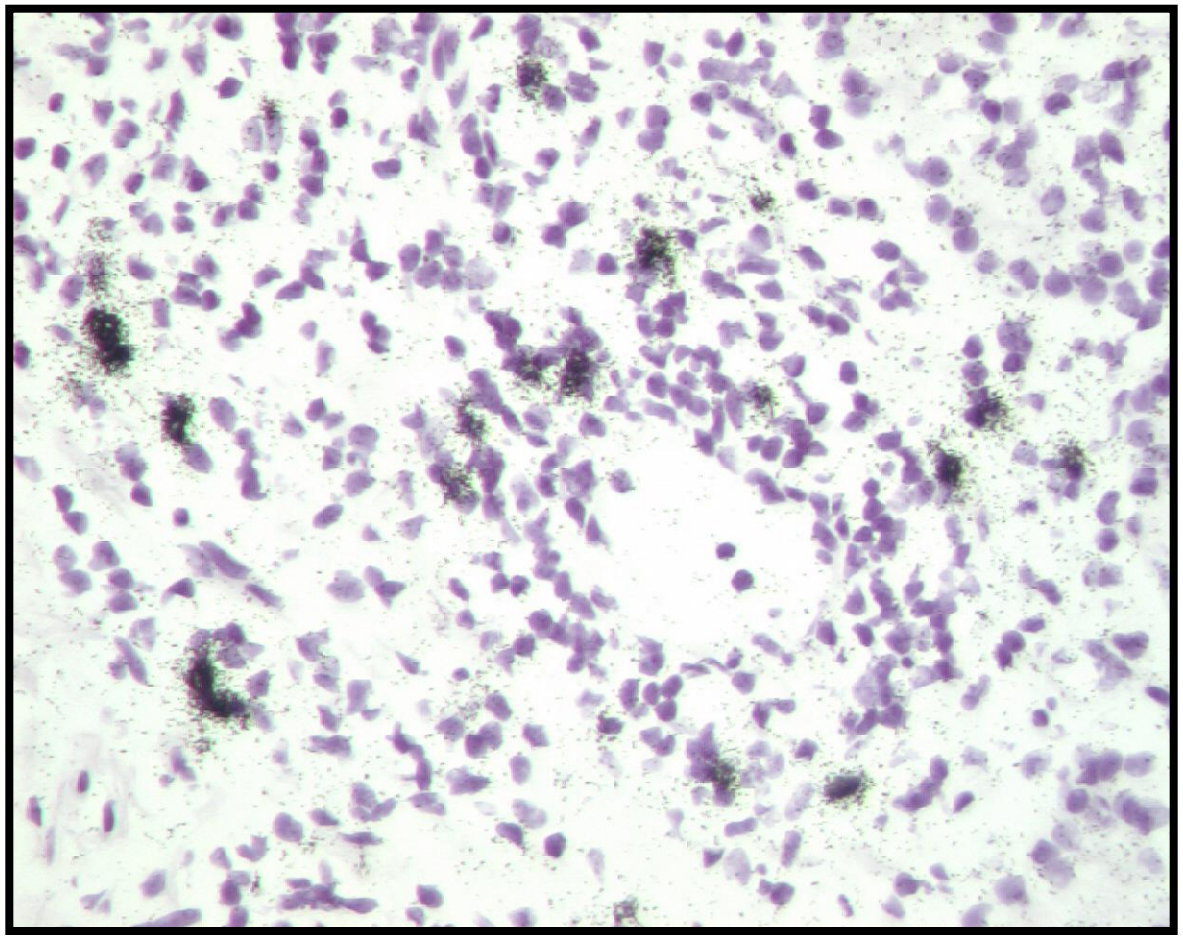
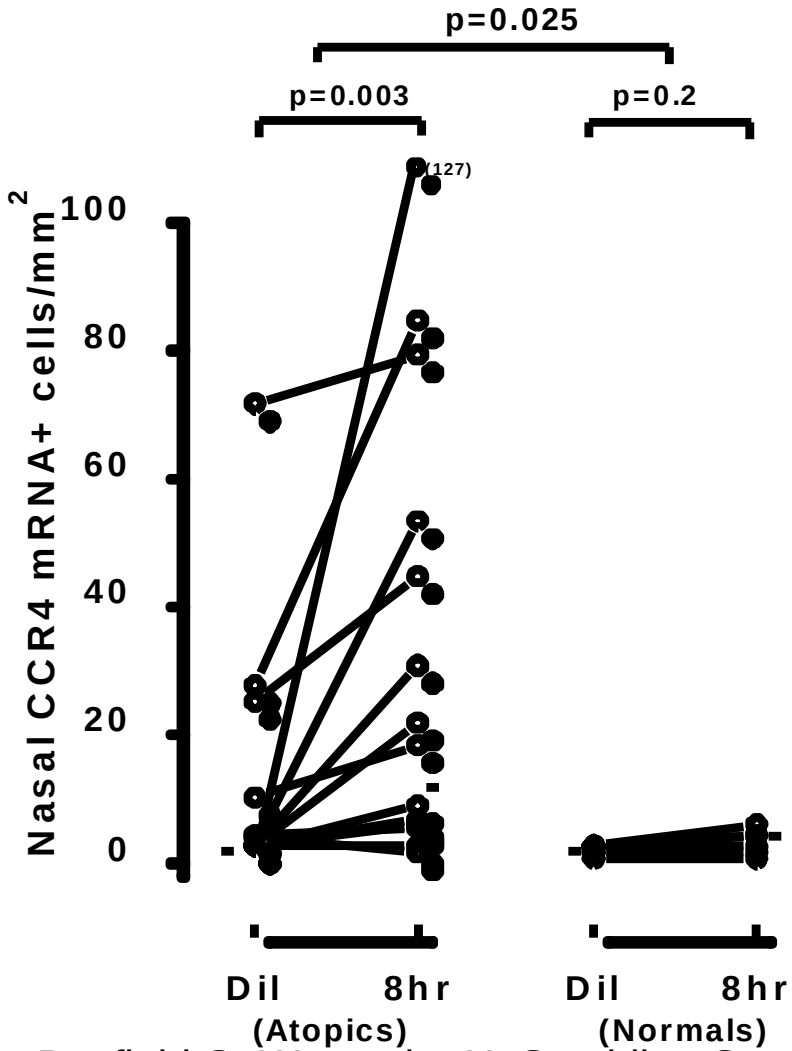
HLA
Th2
CCR3
CCR4
CCR8
APC
Eosinophils
IL-5
Allergen

CCR4 mRNA+ cells in nasal mucosa



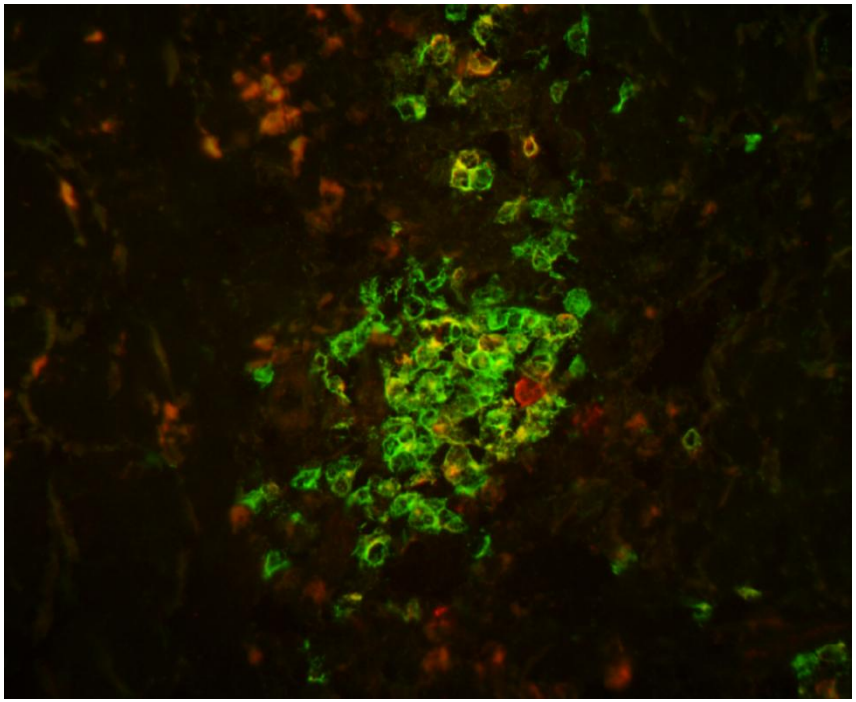
Banfield G, Watanabe H, Scadding G et al Allergy epub Feb 2010

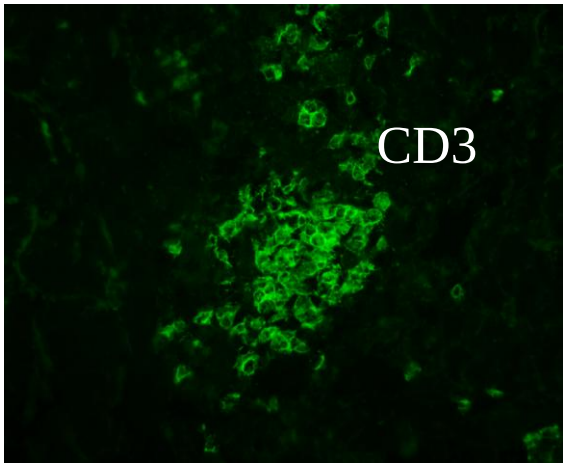
CCR4 mRNA+ cells in the nasal mucosa

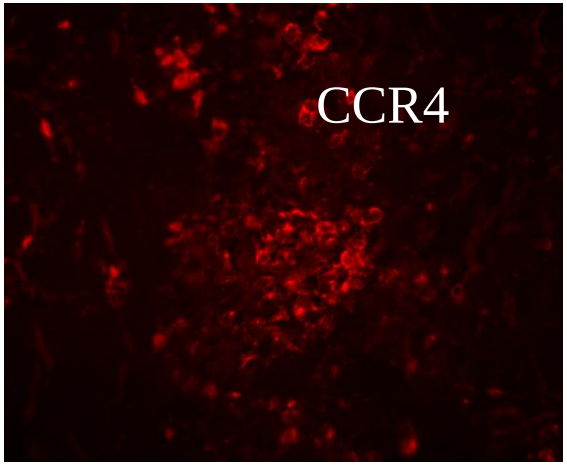


Banfield G, Watanabe H, Scadding G et al Allergy epub Feb 2010

Immunofluorescence for CCR4 and CD3 8hr after allergen challenge







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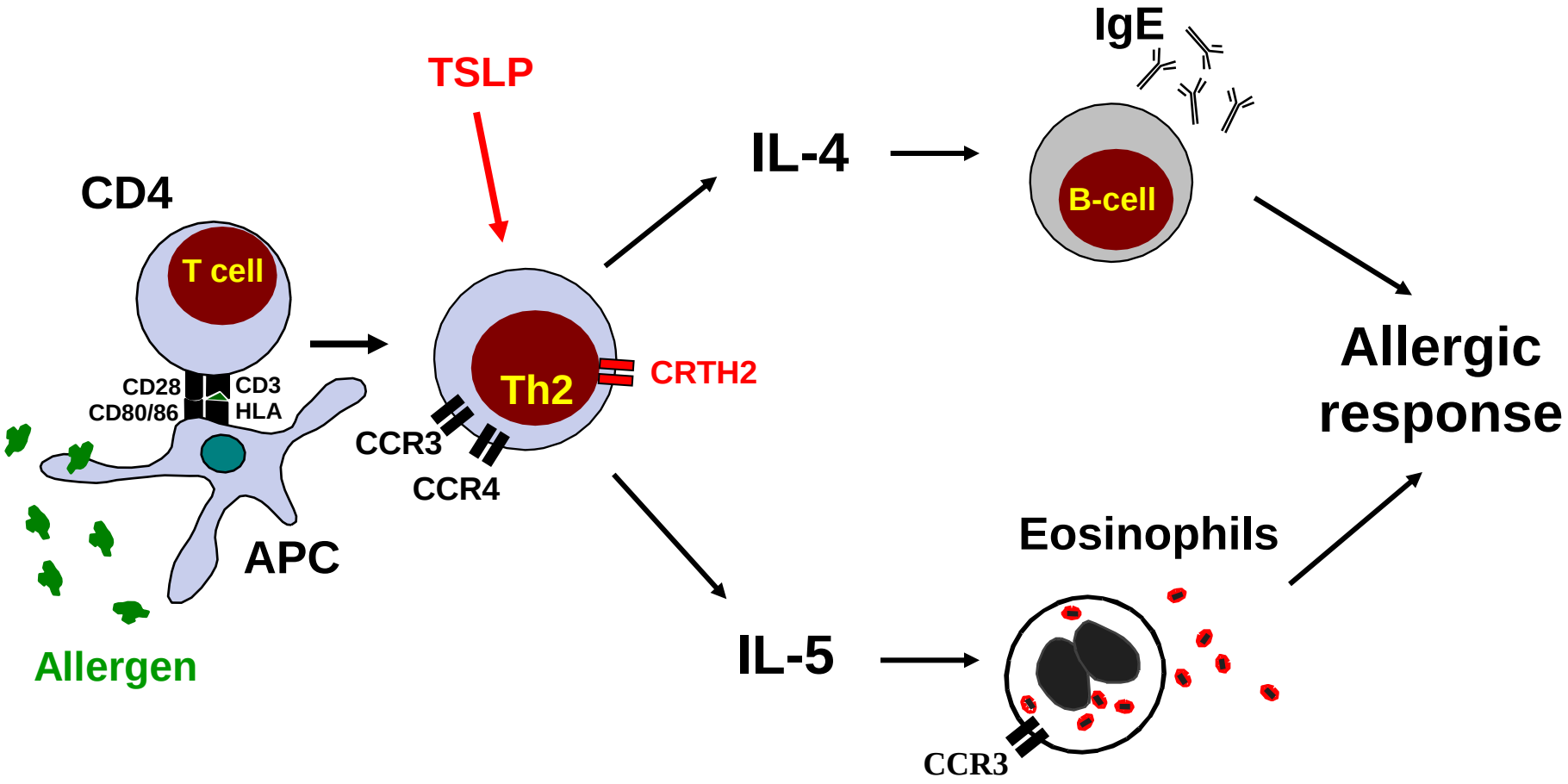
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CRTH2
CCR3
CCR4
Eosinophils
APC
IL-5
Allergen
CCR3

CRTH2 in allergic rhinitis

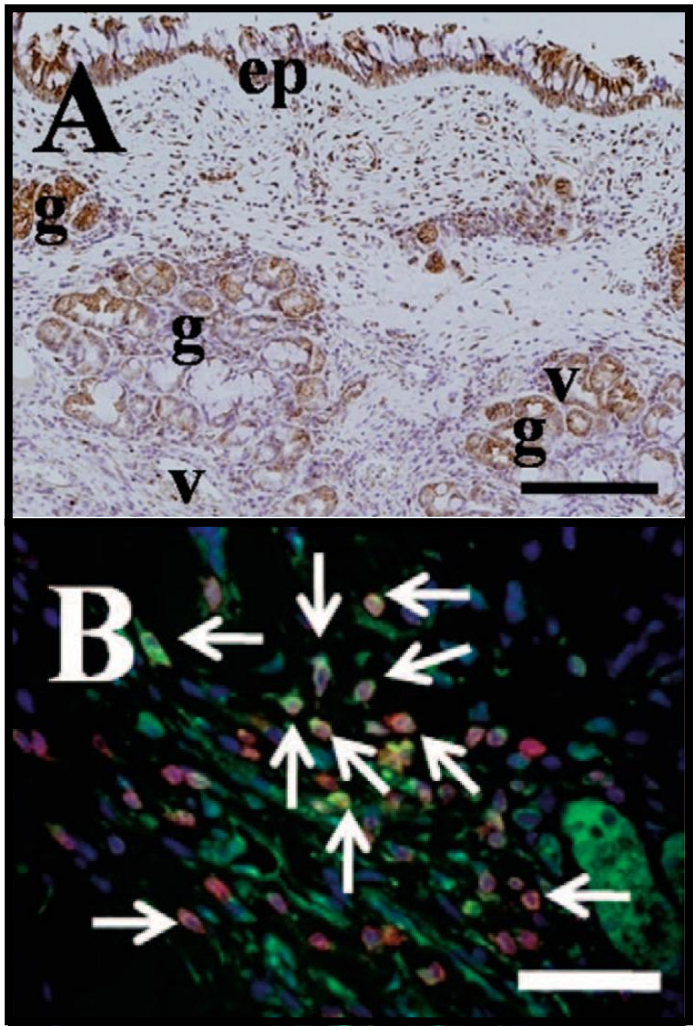
Accumulation of CRTH2-positive leukocytes in human allergic nasal mucosa

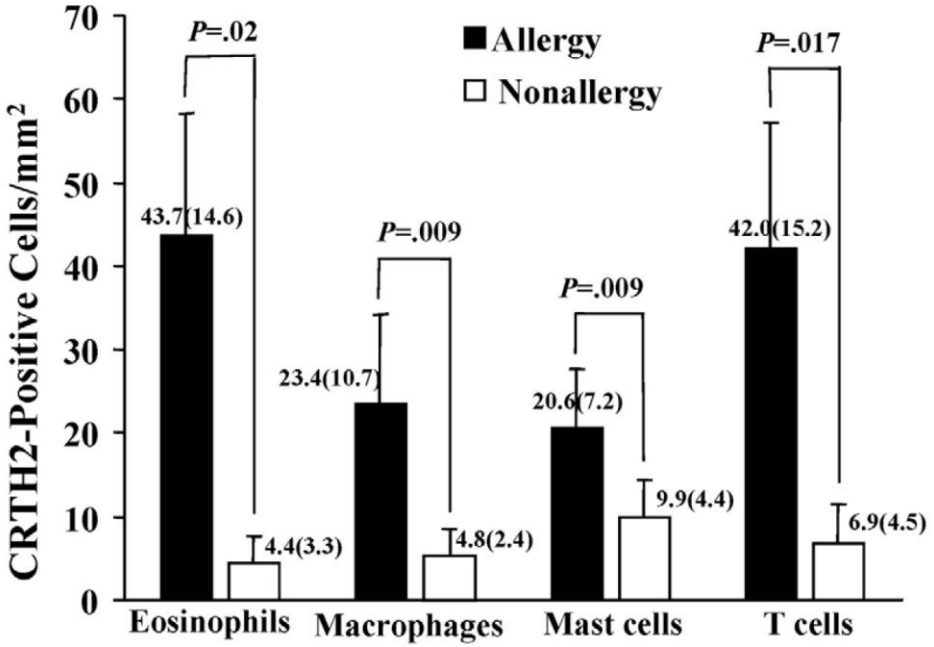
Hideaki Shirasaki, MD, PhD; Megumi Kikuchi, MD, PhD; Etsuko Kanaizumi, MD, PhD; and Tetsuo Himi, MD, PhD

Ann Allergy Asthma Immunol. 2009;102:110–115.

DP2/GPR44/CRTh2 - chemoattractant receptor-homologous molecule expressed on Th2; PGD2-CRTh2 signalling on Th2 cells, eosinophils and basophils induces chemotaxis and up-regulates expression of IL-4, IL-13 and IL-5

CRTH2 in the nasal mucosa in allergic rhinitis





Ann Allergy Asthma Immunol. 2009;102:110–115.

TSLP in allergic rhinitis

Acta Oto-Laryngologica, 2009; 129: 297–301

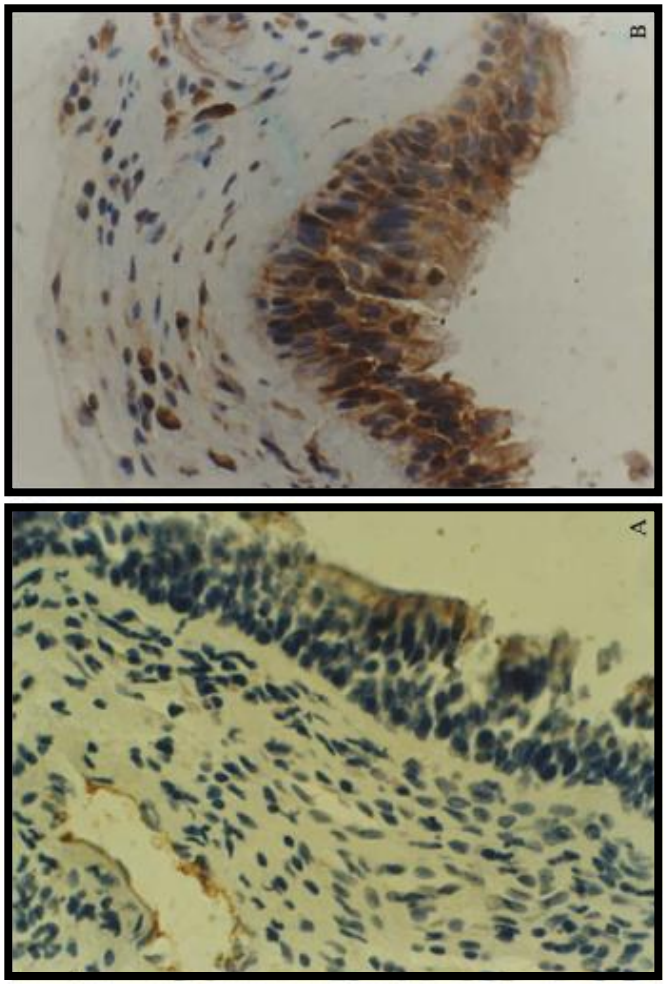
ORIGINAL ARTICLE

Overexpression of thymic stromal lymphopoietin in allergic rhinitis

ZHONGLIN MOU[1], JIAHONG XIA[2], YENONG TAN[1], XIANGDONG WANG[3], YUAN ZHANG[2], BING ZHOU[3], HUABIN LI[3] & DEMIN HAN[3]

[1]*Department of Otolaryngology, Hainan Provincial People's Hospital, HaiKou,* [2]*Department of Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan and* [3]*Department of Otolaryngology Head and Neck Surgery, Tongren Hospital, Capital Medical University, Beijing, China*

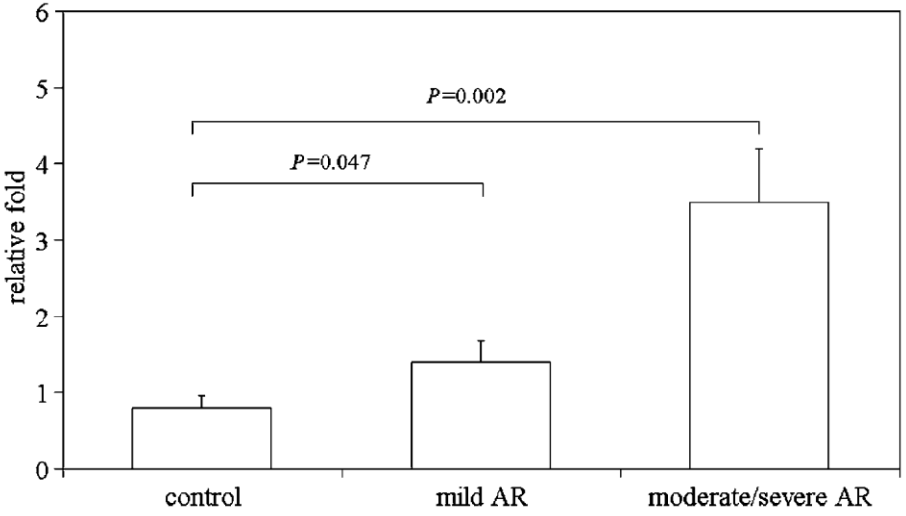
TSLP in the nasal mucosa in allergic rhinitis



Immunochemistry

	−	+	++	+++
AR	0	2	8	6
Control	0	7	3	1

Quantitative RT-PCR



Acta Oto-Laryngologica, 2009; 129: 297–301

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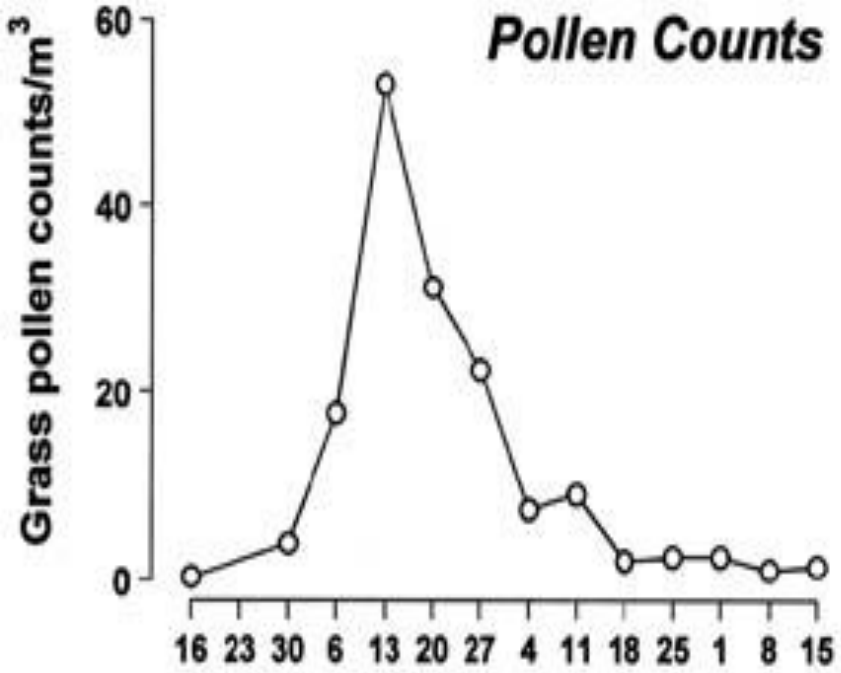
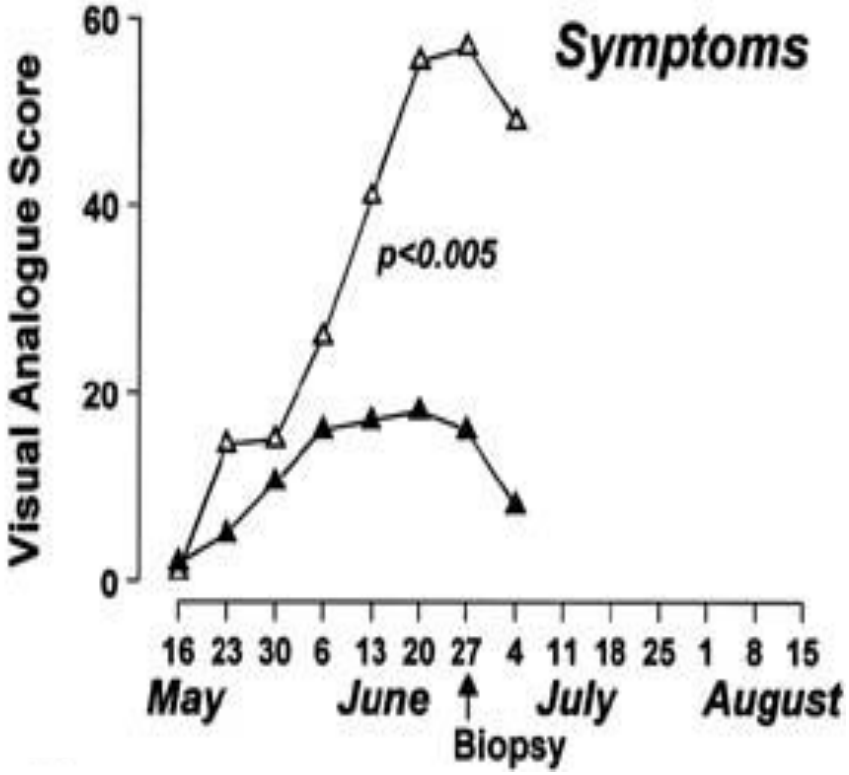
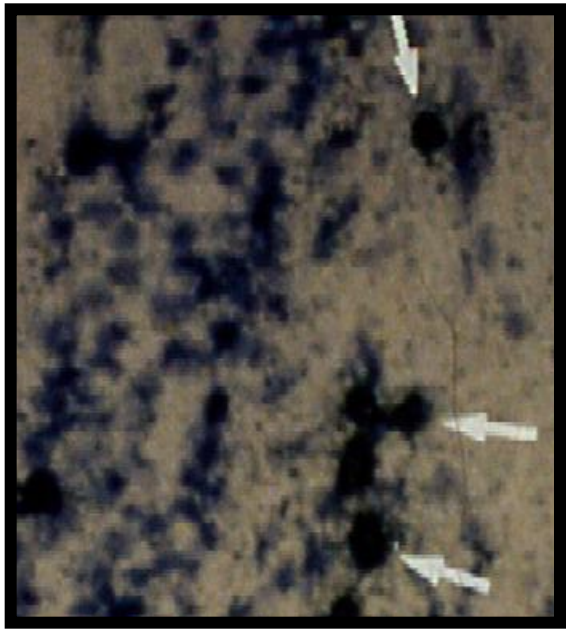
Topical steroid (fluticasone propionate) in hayfever



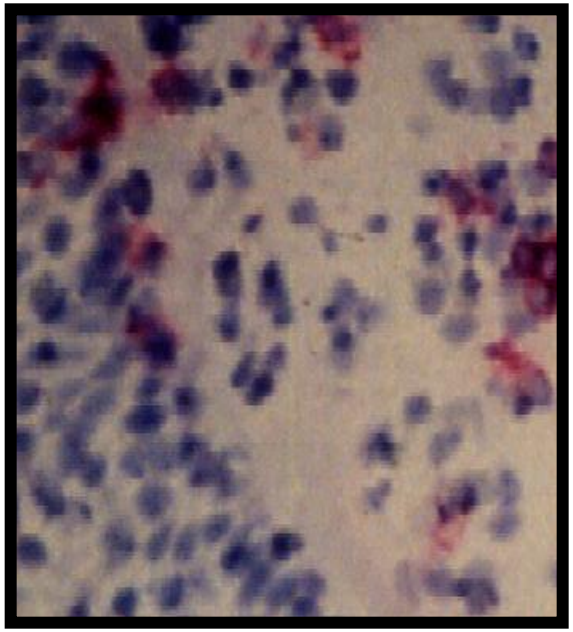


Masuyama K et al, J Allergy Clin Immunol 1998;102:610-7

Immunohistology of nasal mucosa for T and B lymphocytes



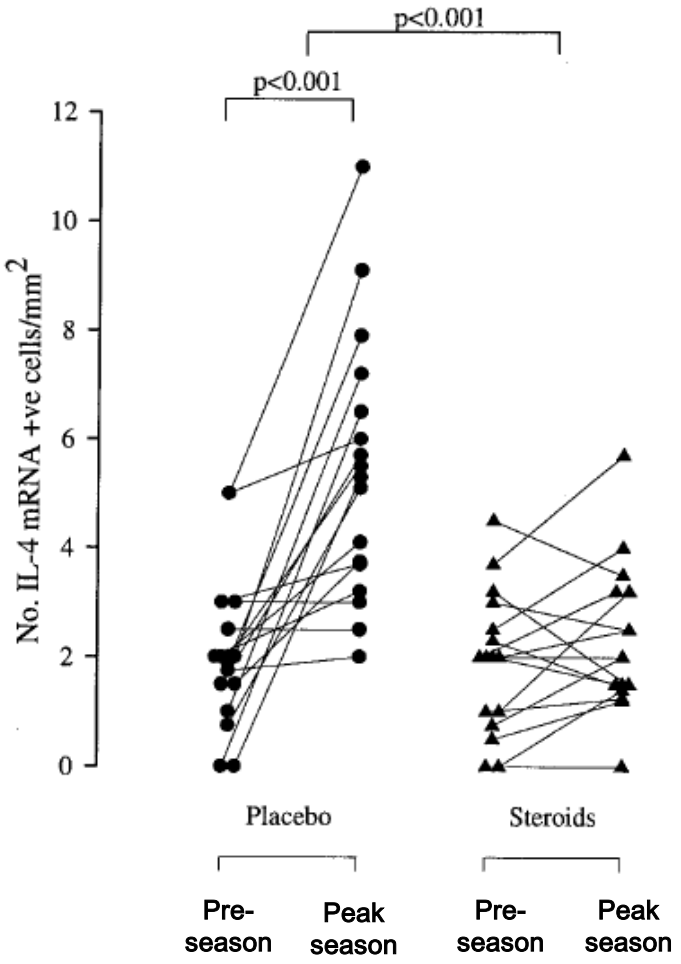
$CD3^+$ T cells
expressing IL-4



$CD20^+$
B cells

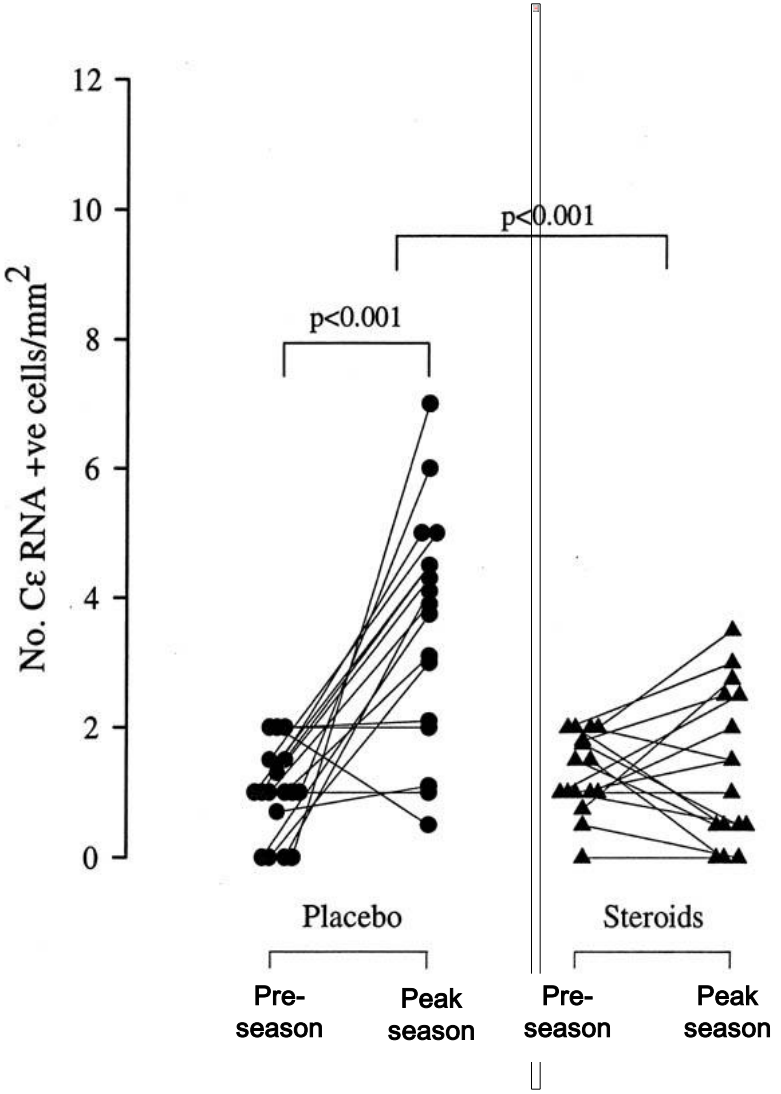
$CD20^+$ B cells
Expressing $C\varepsilon$

Topical steroids inhibit seasonal increases in IL-4 mRNA+ cells



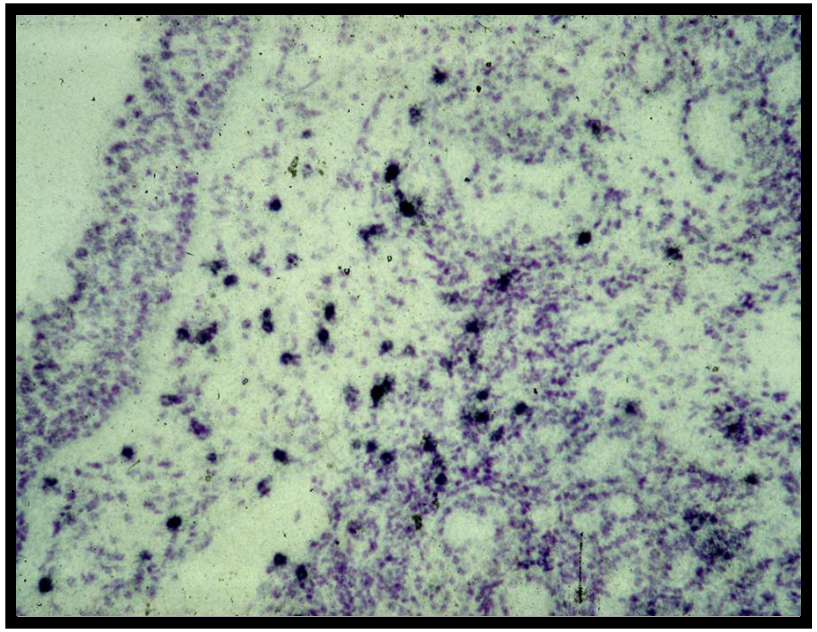
Cameron L et al, J Allergy Clin Immunol 1998; 102: 330-336

Topical steroids inhibit seasonal increases in IgE mRNA+ cells

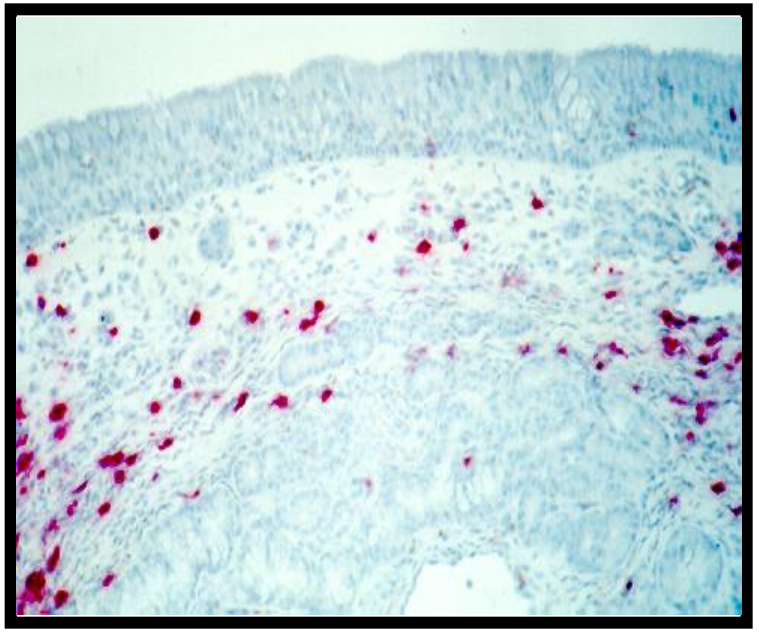


Cameron L et al., J Allergy Clin Immunol 1998;102:610-7

Immunohistology of nasal mucosa for IL-5+ T cells and eosinophils

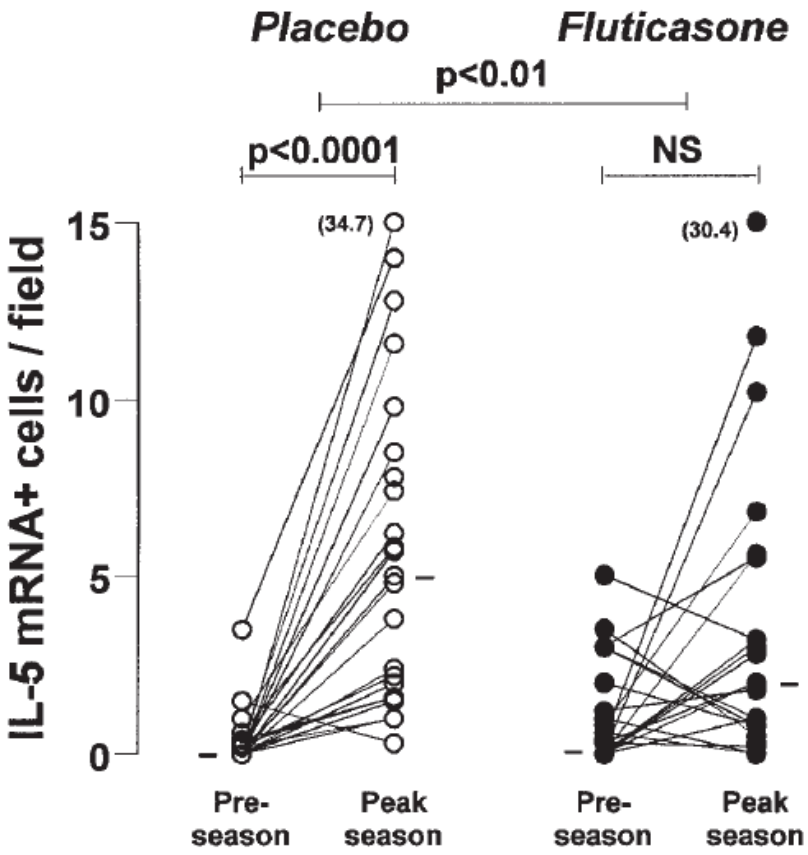


CD3^{+} T cells
expressing IL-5



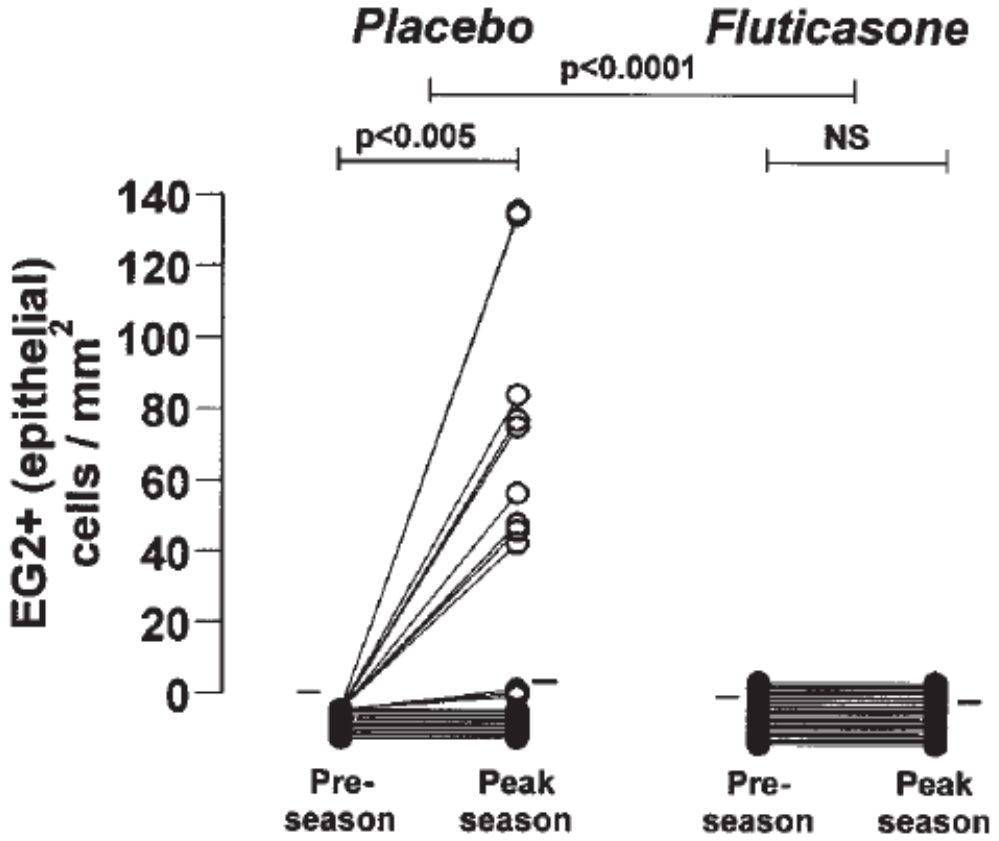
Eosinophils
expressing MBP

Topical steroids inhibit seasonal increases in IL-5 mRNA+ cells



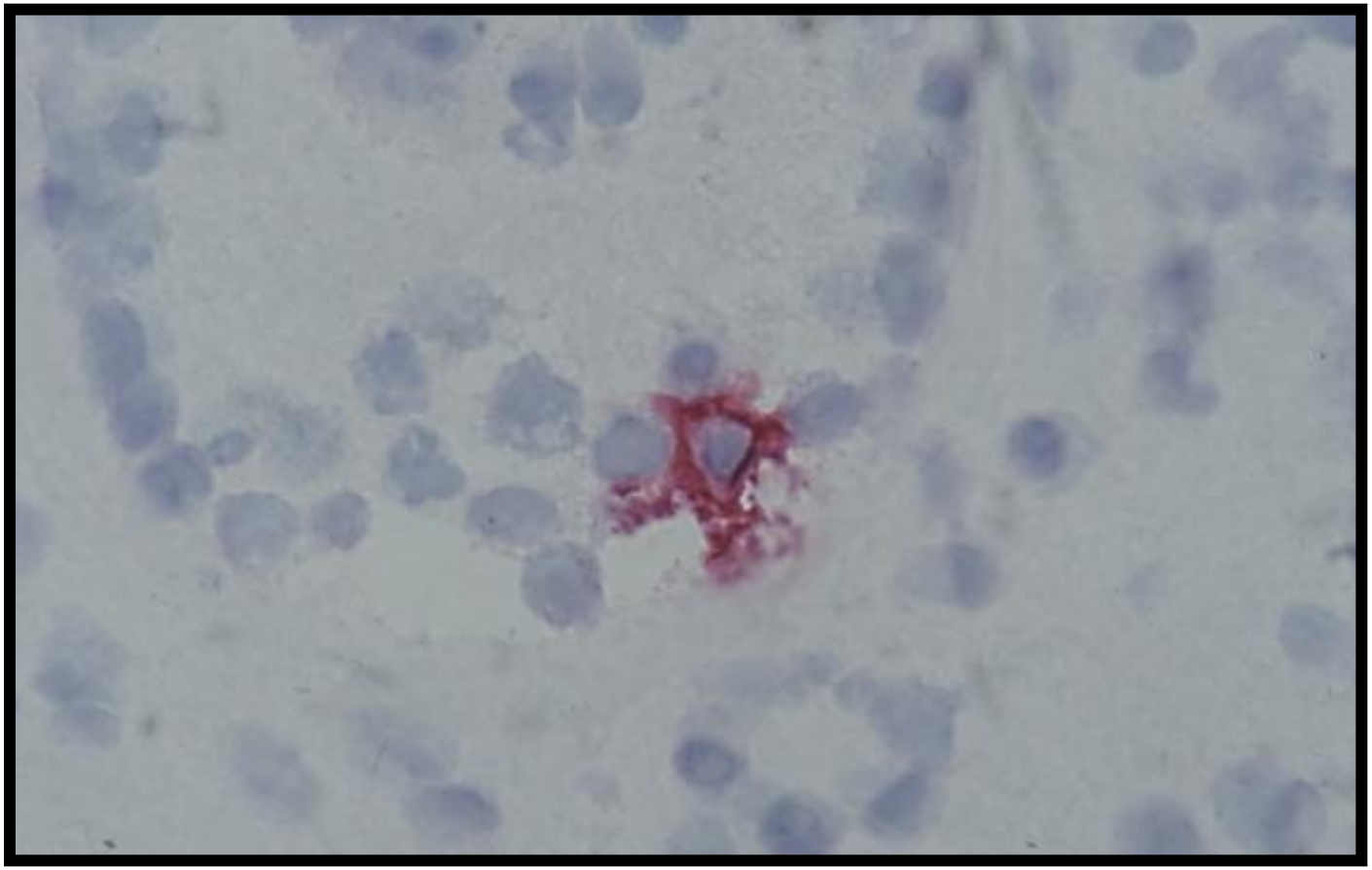
Masuyama K et al., J Allergy Clin Immunol 1998;102:610-7

Topical steroids inhibit seasonal increases in eosinophils



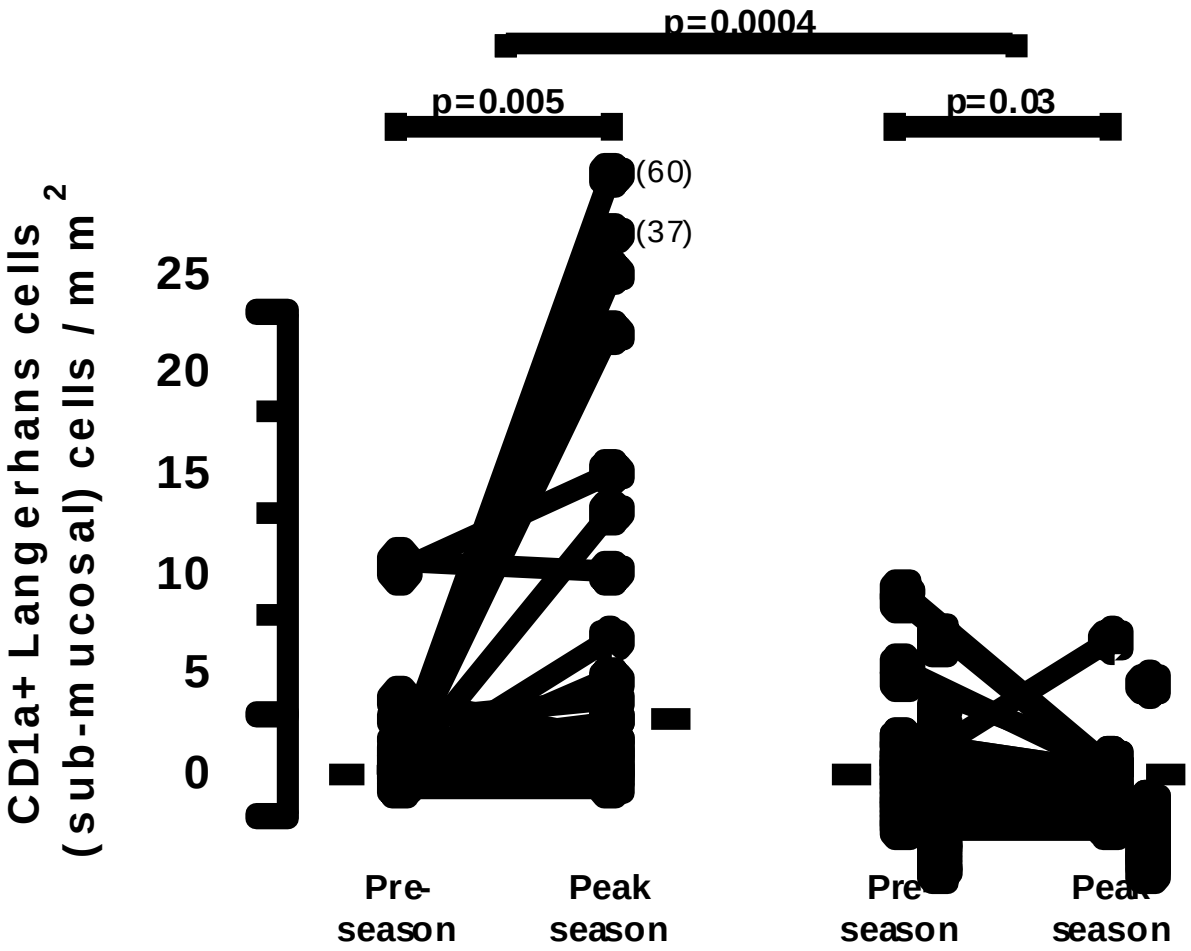
Masuyama K et al., J Allergy Clin Immunol 1998;102:610-7

CD1a^{+} Langerhans cells in nasal mucosa



Till SJ et al., Allergy 2001;56:126-131

Topical steroids inhibit seasonal increases in dendritic cells



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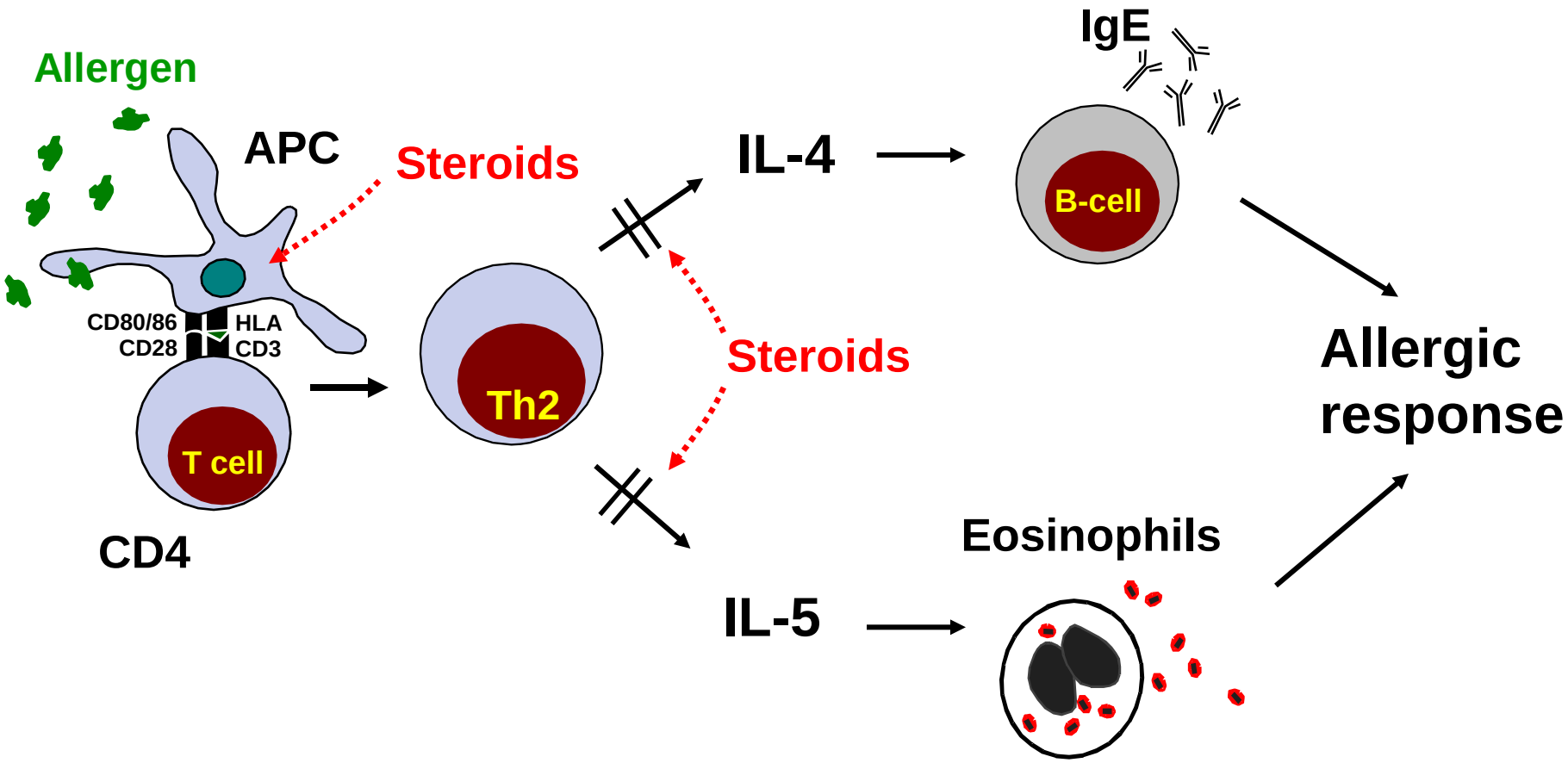
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Allergic response

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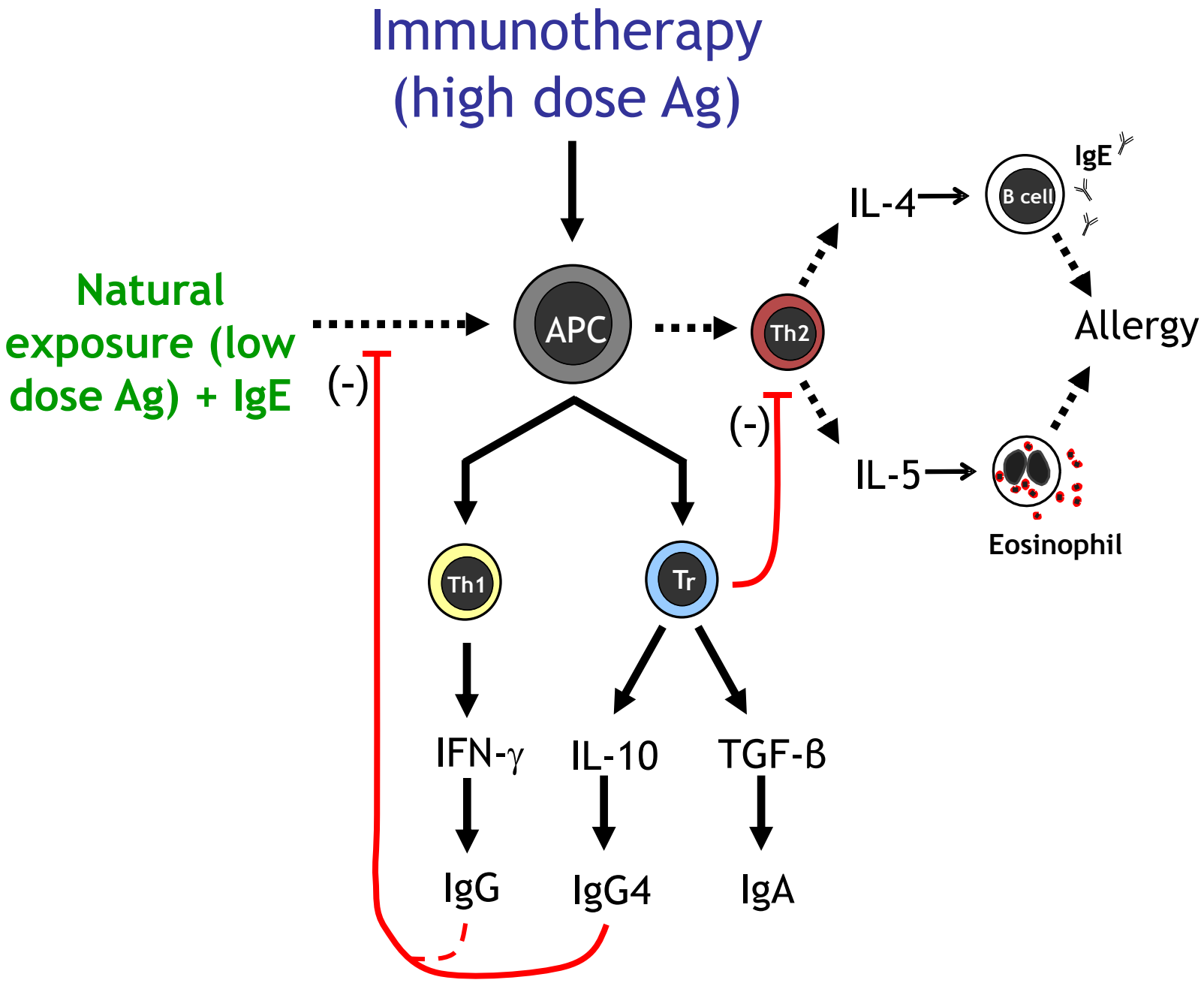
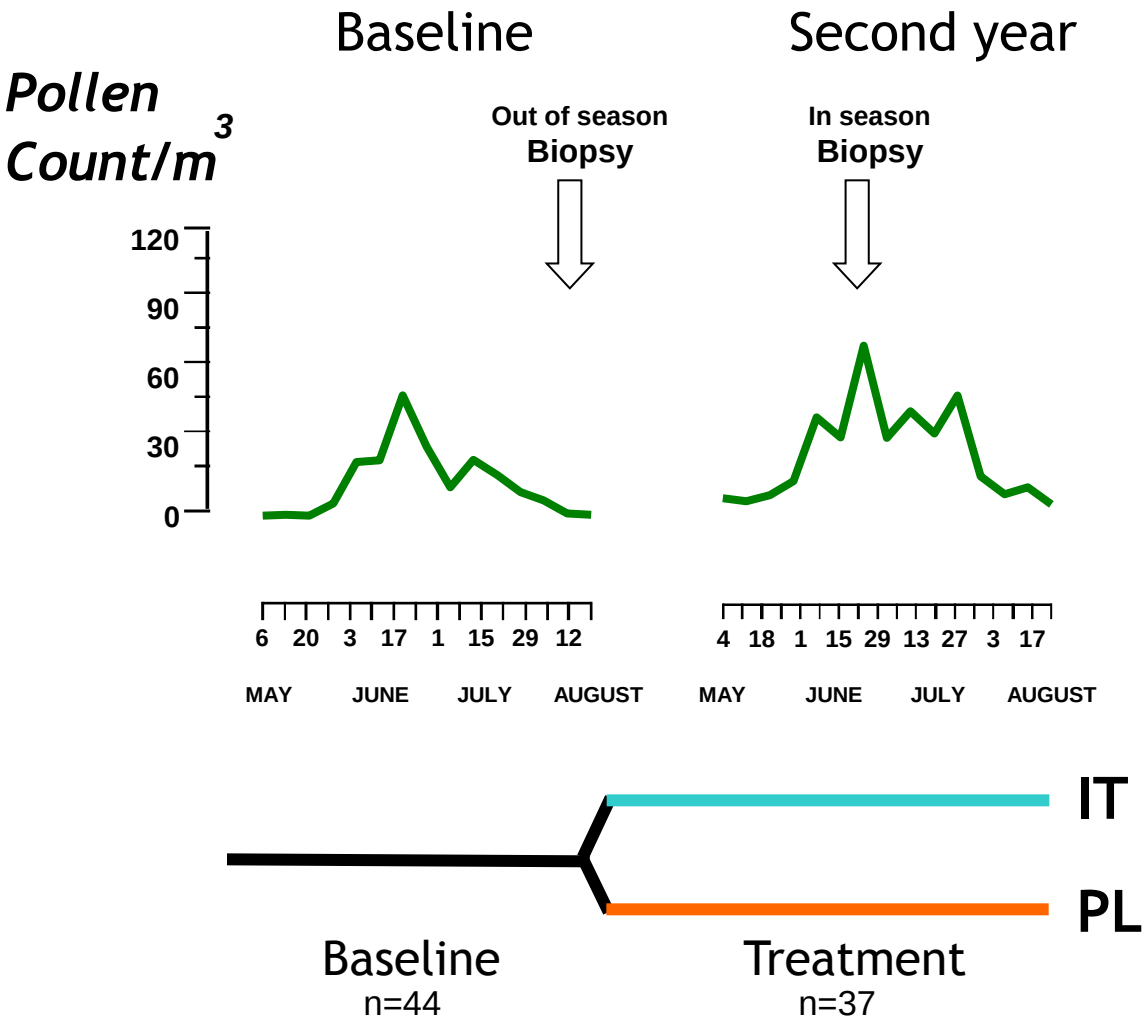


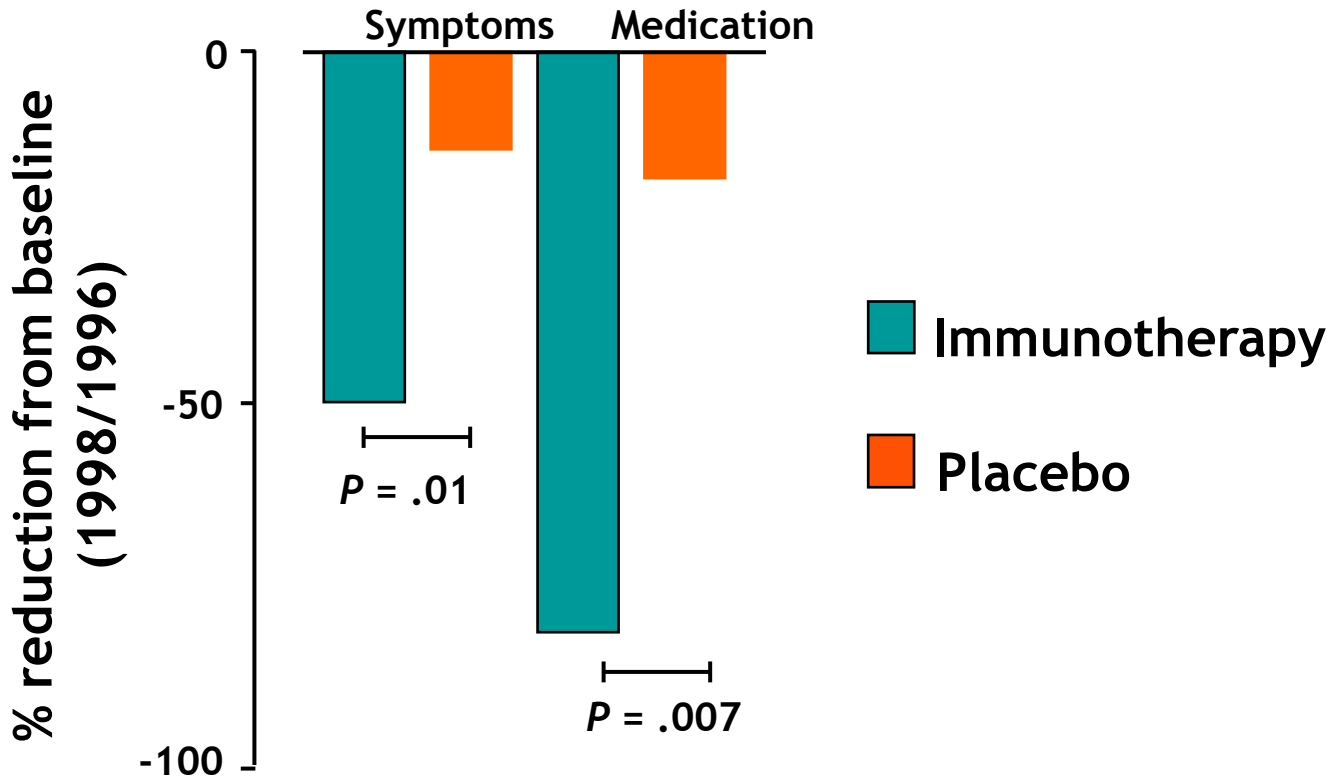
Robinson DS, et al. J Clin Invest 2004;114:1389-97

Grass pollen immunotherapy for seasonal rhinitis/asthma (Alutard SQ *Phleum pratense*)



Walker SM et al., J Allergy Clin immunol 2001;107:87-93

Grass pollen immunotherapy for seasonal rhinitis/asthma



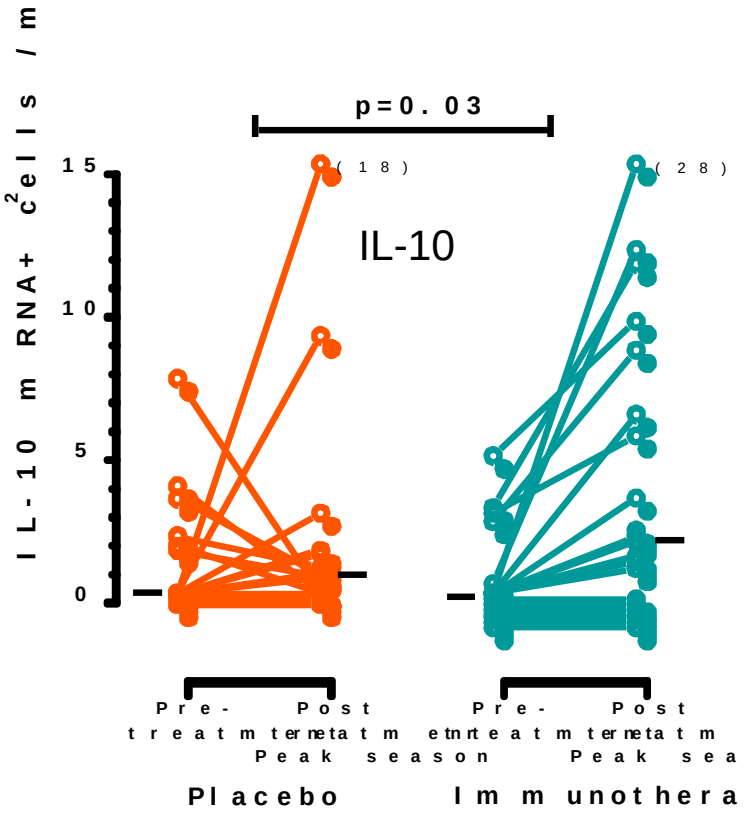
Walker SM et al., J Allergy Clin immunol 2001;107:87-93

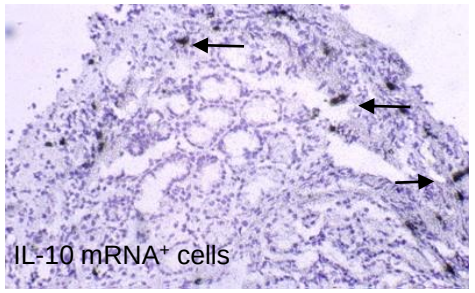
Grass Pollen Immunotherapy Induces Mucosal and Peripheral IL-10 Responses and Blocking IgG Activity[1]

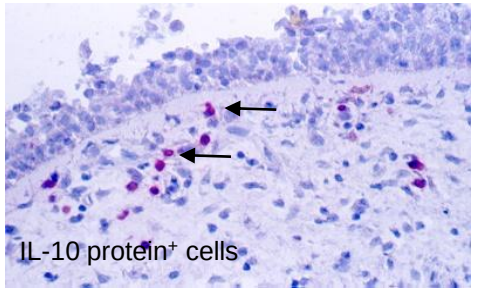
Kayhan T. Nouri-Aria,* Petra A. Wachholz,* James N. Francis,* Mikila R. Jacobson,* Samantha M. Walker,* Louisa K. Wilcock,* Steven Q. Staple,† Robert C. Aalberse,† Stephen J. Till,* and Stephen R. Durham[2]*

J Immunol 2004; 172: 3252-59

Grass pollen immunotherapy: IL-10 in the nasal mucosa

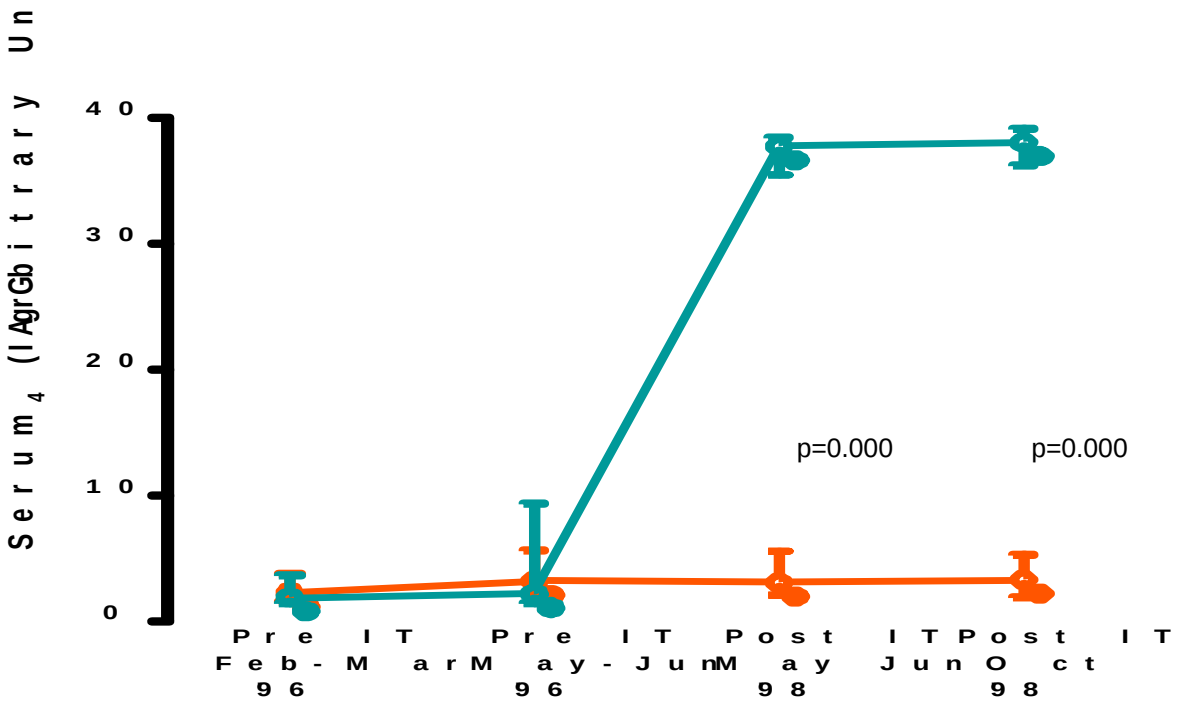






Nouri-Aria K et al J Immunol. 2004; 172:3252-9

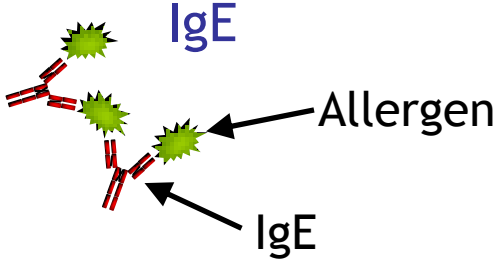
Allergen-specific IgG4



Wachholz P et al J Allergy Clin Immunol 2003; 112, 915-922.

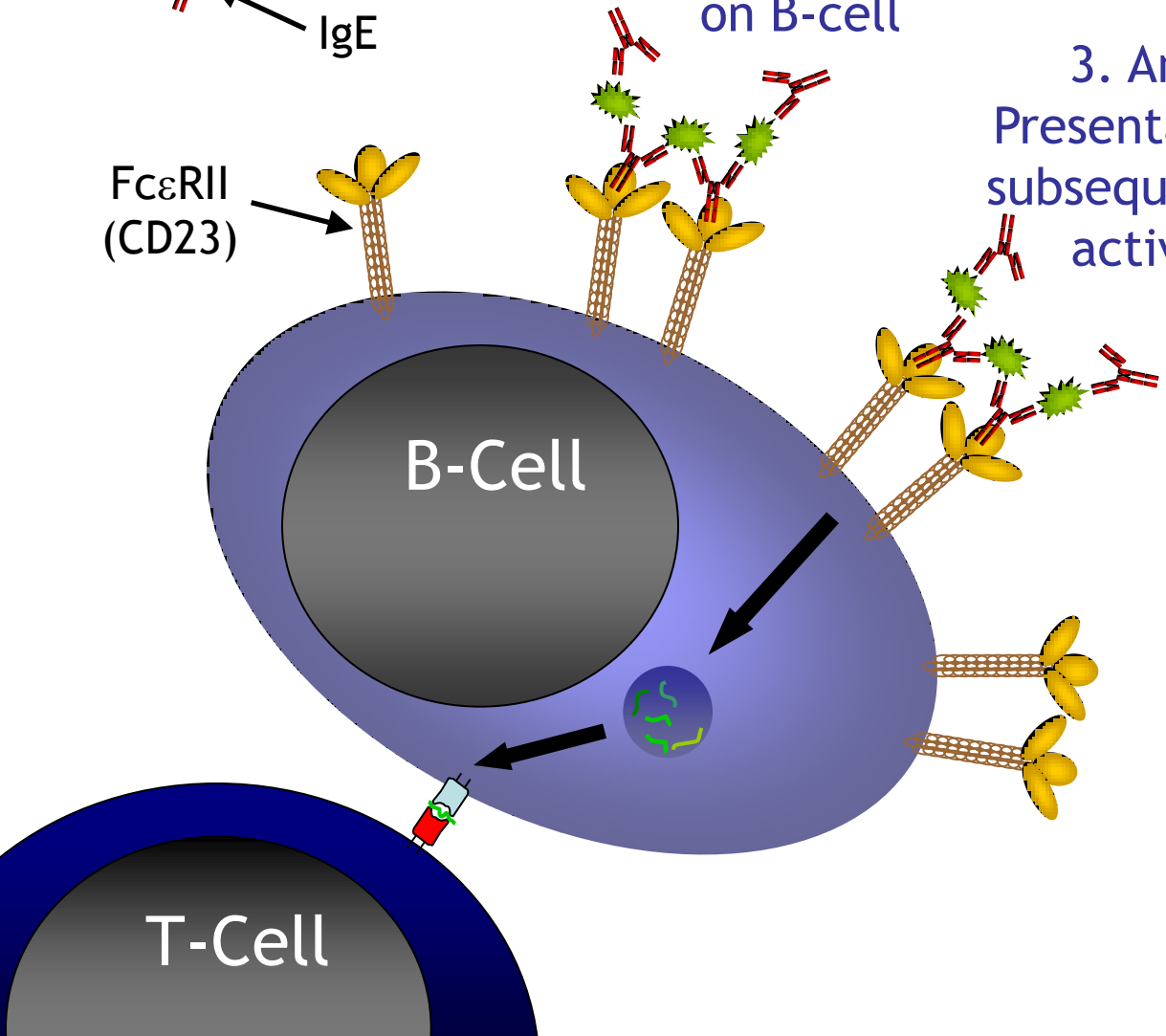
Facilitated Antigen Presentation

1. Allergen forms complexes with IgE

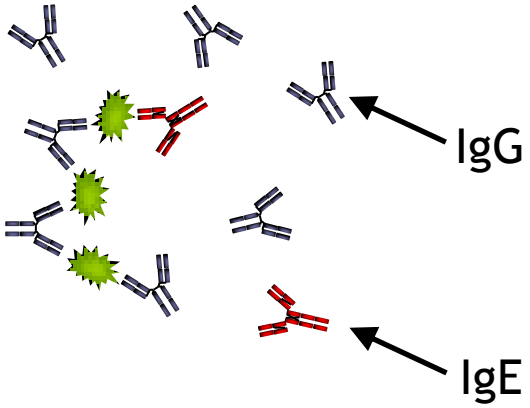


2. Complexes bind FcεRII on B-cell

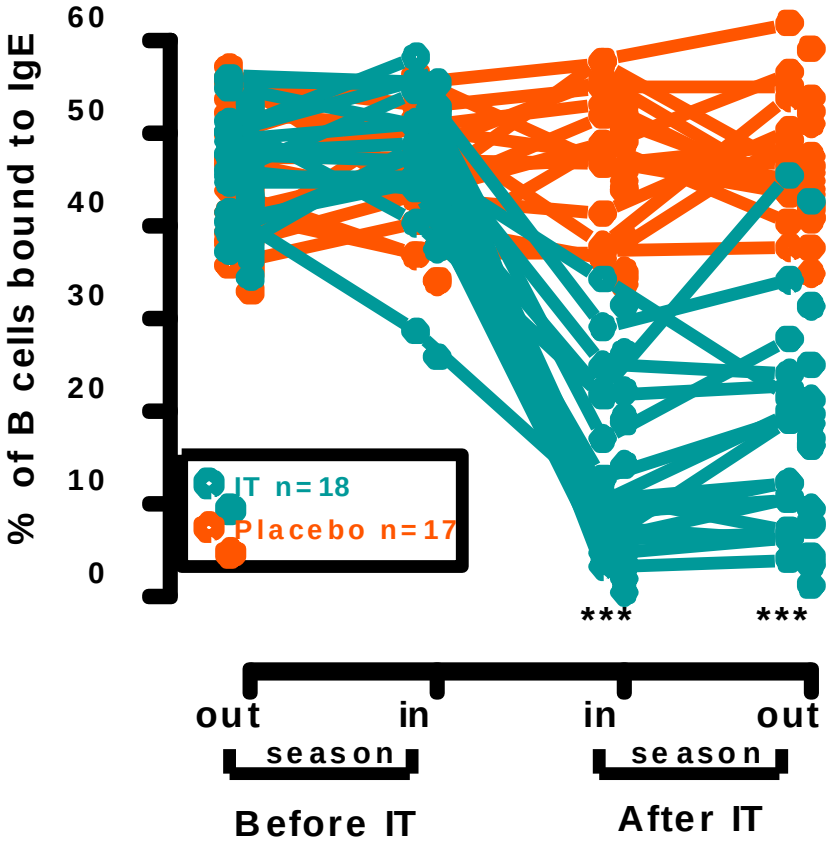
3. Antigen Presentation and subsequent T cell activation



4. Immunotherapy induces IgG antibodies that block IgE binding



Inhibition of allergen-IgE binding to B-cells following immunotherapy



Nouri-Aria KT et al. J Immunol 2004;172:3252-9

How immunology informs the design of immunotherapeutics.

- Allergen induced early and late nasal responses
- Natural seasonal allergen exposure
  - effects of corticosteroids
- Influence of treatments
  - Immunotherapy
  - anti-IgE therapy

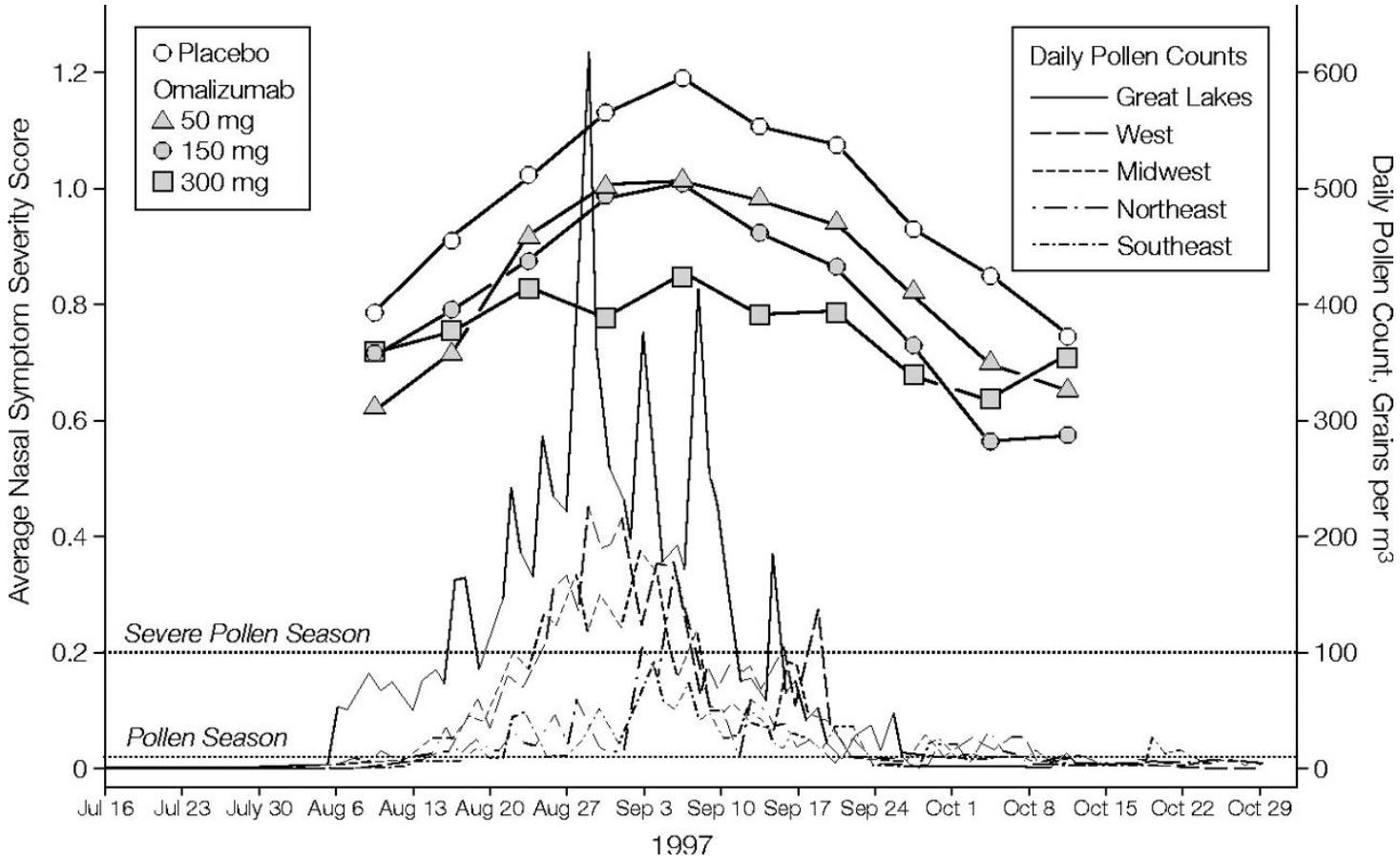
Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomised controlled trial.

Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, McAlary M, Fowler-Taylor A, Racine A, Gupta N, Fick R, Della Cioppa G.

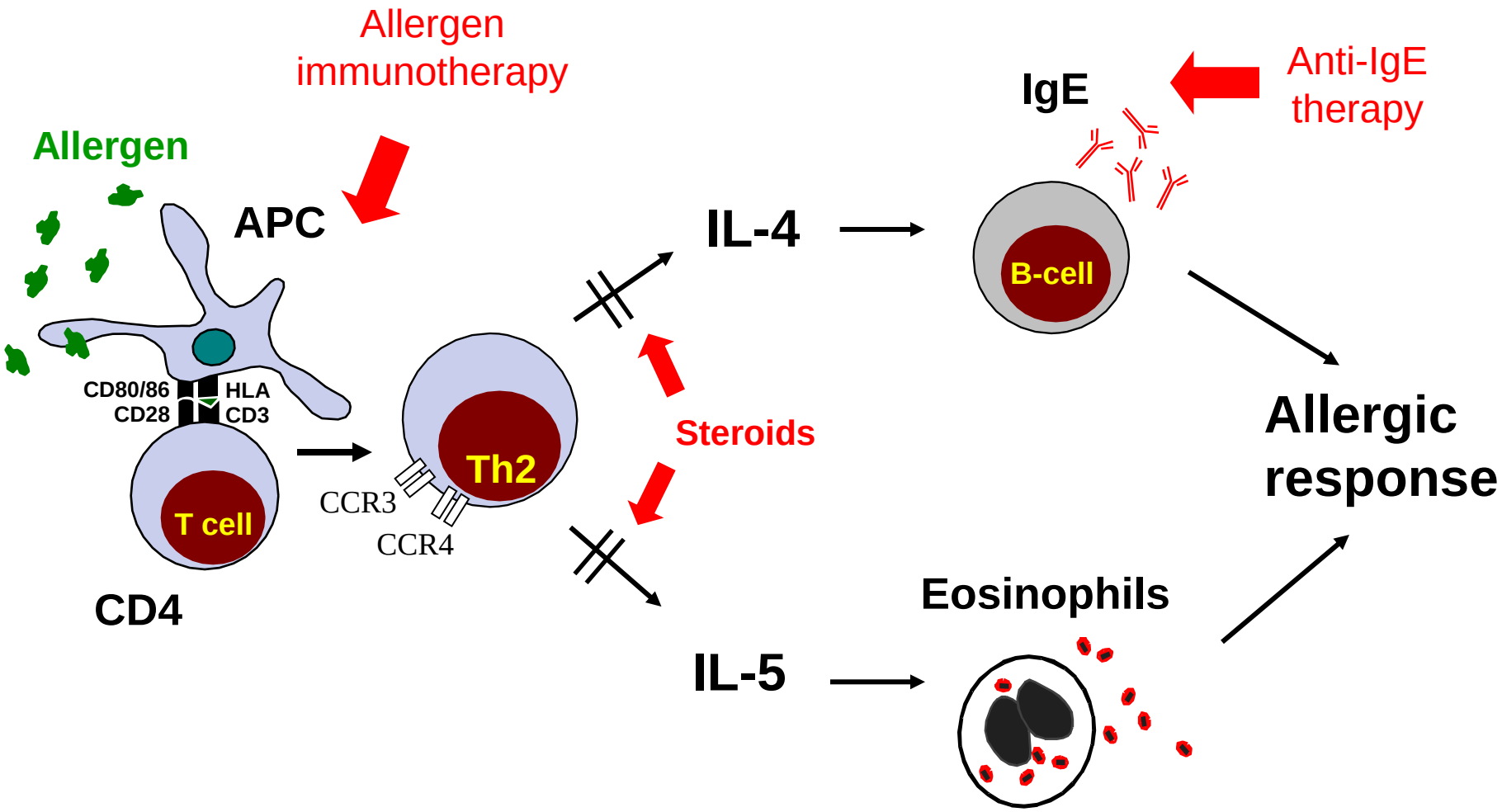
JAMA 2001;286:2956-2967

- 536 patients (959 screened)
- Aged 12-75y
- Moderate/severe symptoms
- IgE 30-700 iu/ml

Nasal Symptoms in the Ragweed Season: Effects of Omalizumab



Casale, T. B. et al. JAMA 2001;286:2956-2967.


Allergen immunotherapy
Allergen
APC
CD80/86
CD28
HLA
CD3
T cell
CD4
Th2
CCR3
CCR4
IL-4
IL-5
Steroids
IgE
Anti-IgE therapy
B-cell
Eosinophils
Allergic response

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