

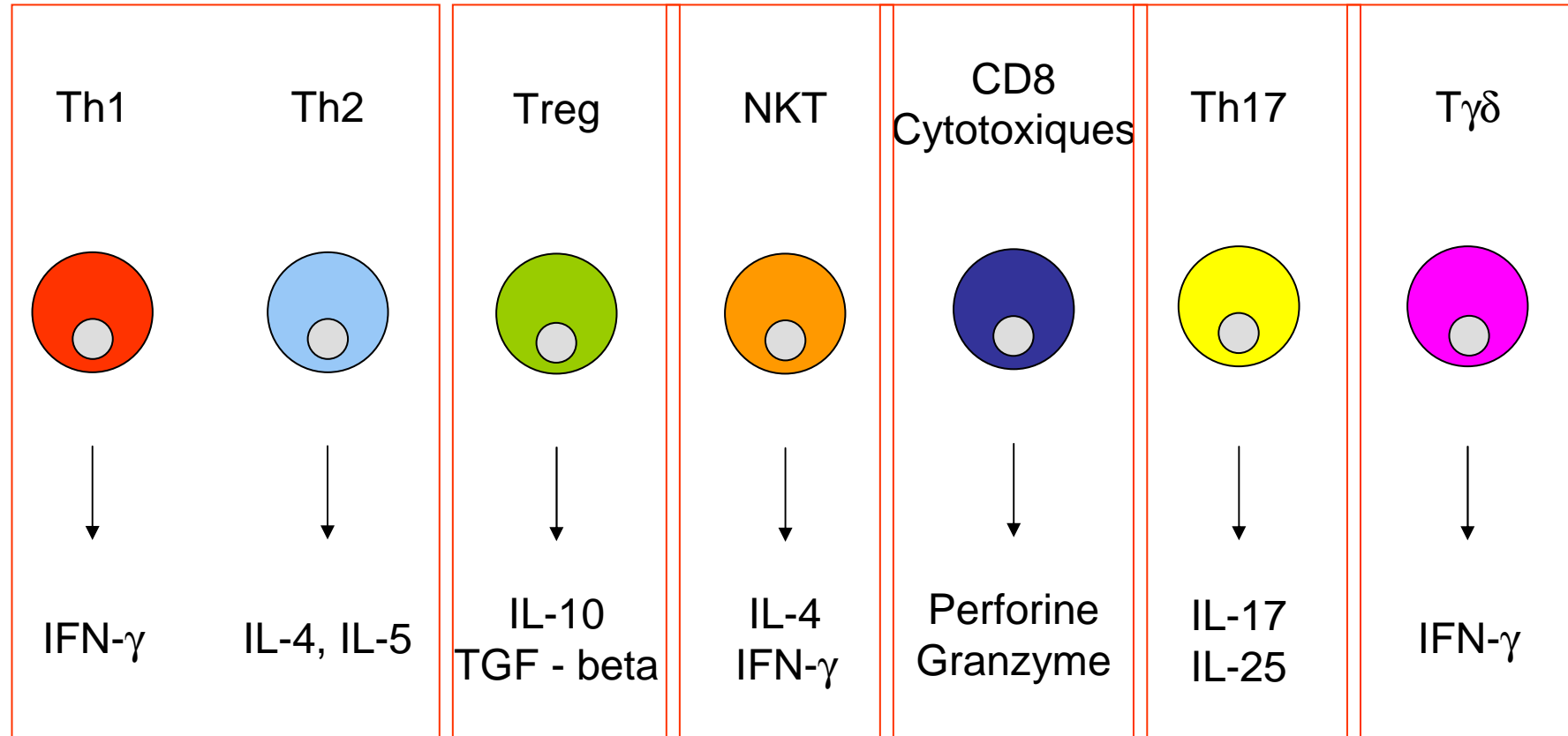
Nouvelles populations lymphocytaires T dans l'asthme

Antoine Magnan

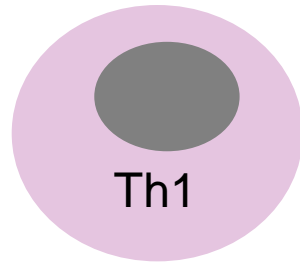


antoine.magnan@inserm.fr

T lymphocytes



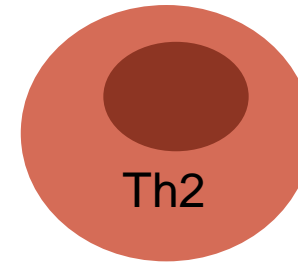
20 years ago: The Th1/Th2 Paradigm



IFN- γ , IL-2, TNF- β

Cytotoxicity, Phagocytosis

Anti-viral
Anti-tumoral
granulomas



IL-4, IL-5,
IL-13, IL-9
IL-10

Antibody production
IgE

Eosinophil activation

Th2 paradigm: validation in animal models

Models of asthma

- IL-4 necessary to the IgE-dependent reaction
- IL-5 necessary to pulmonary eosinophilia

Molecular genetics

Brusselle, Clin Exp Allergy 1994

Foster, J Exp Med 1996

Th2 paradigm validation in humans: comparison with controls

- Bronchial, nasal and skin biopsies
- Broncho-alveolar lavages, blood

- In situ hybridization
- Immunohistochemistry

Th2 paradigm validation in humans: comparison with controls

Th2 deviation in :

- Atopy

Tang, Lancet 1994

- Asthma

Robinson, N Engl J Med 1992

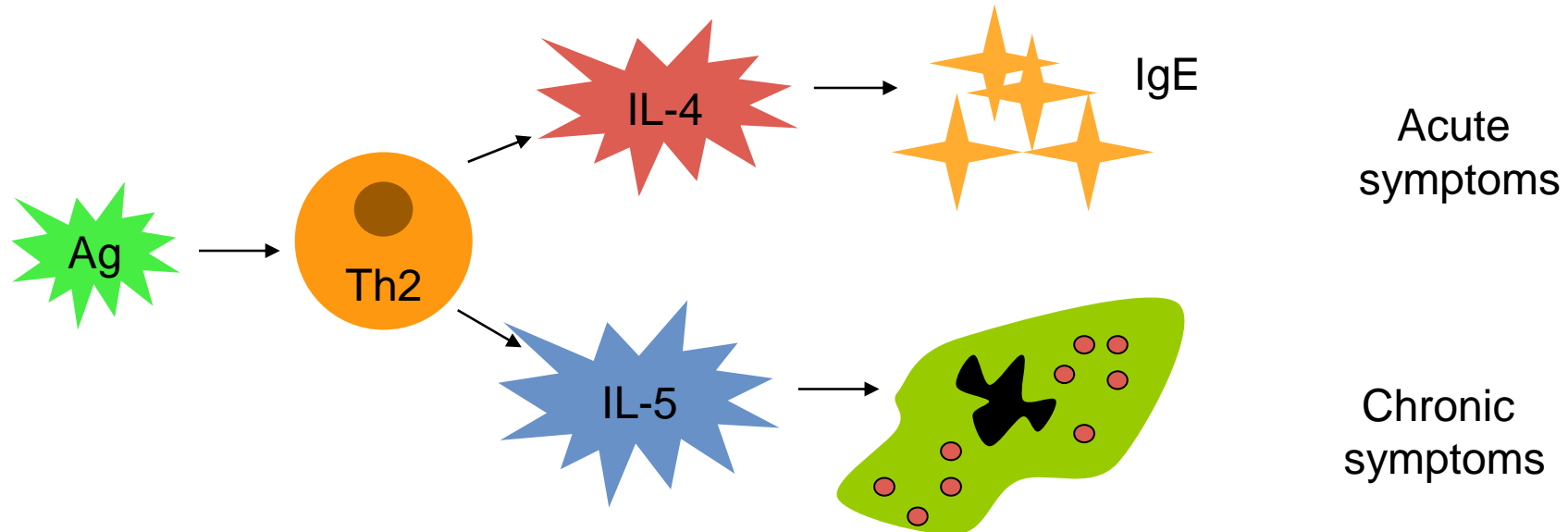
- Atopic dermatitis

Hamid, J Clin Invest 1994

- Allergic rhinitis

*Varney, J Clin Invest
1993*

Allergic response: current dogma

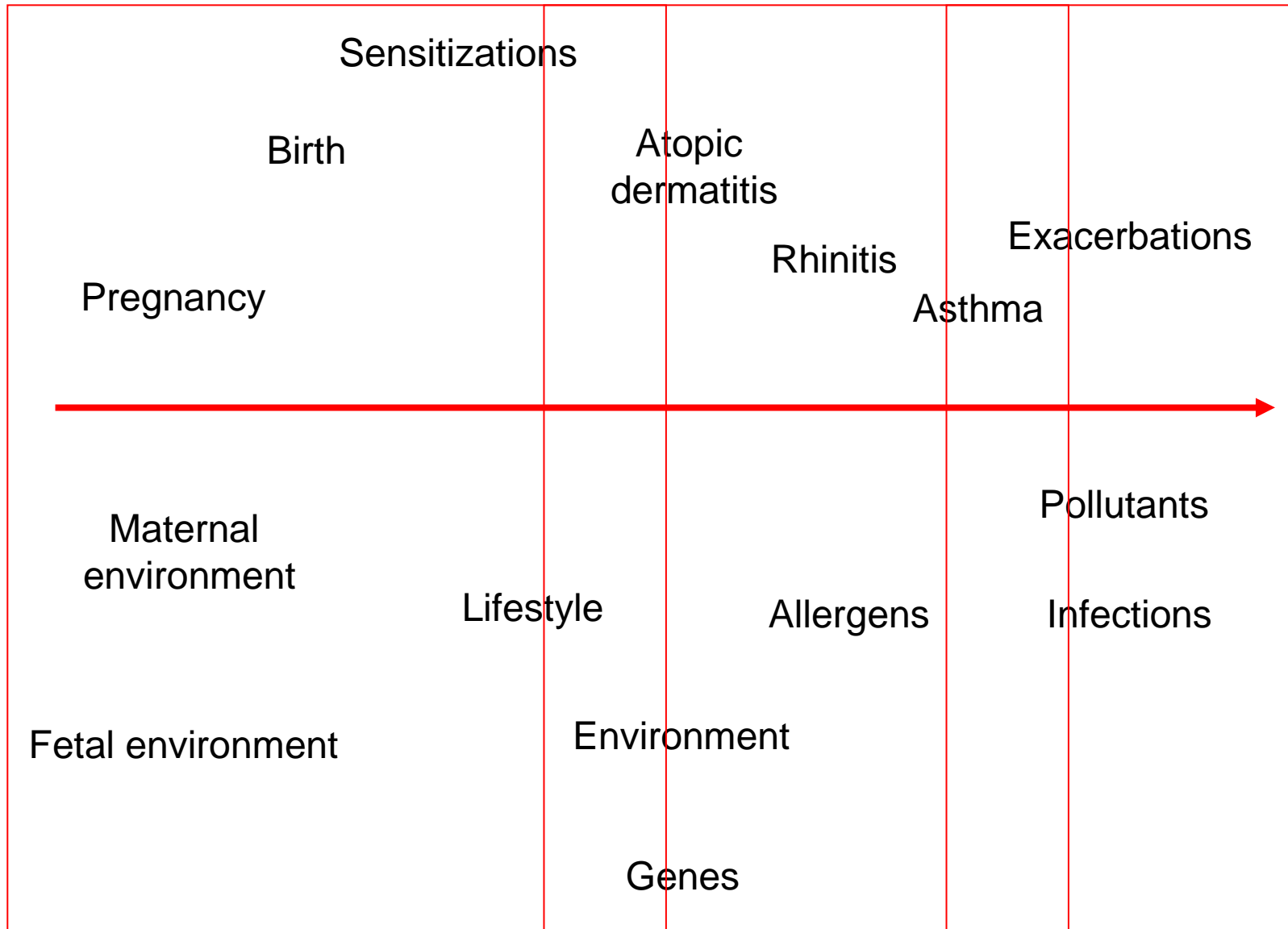


In keeping with the hygiene hypothesis

Demonstrated only in patients compared to controls

Incomplete picture of asthma immunopathology

Natural history of atopy



Limitations of the Th2 paradigm

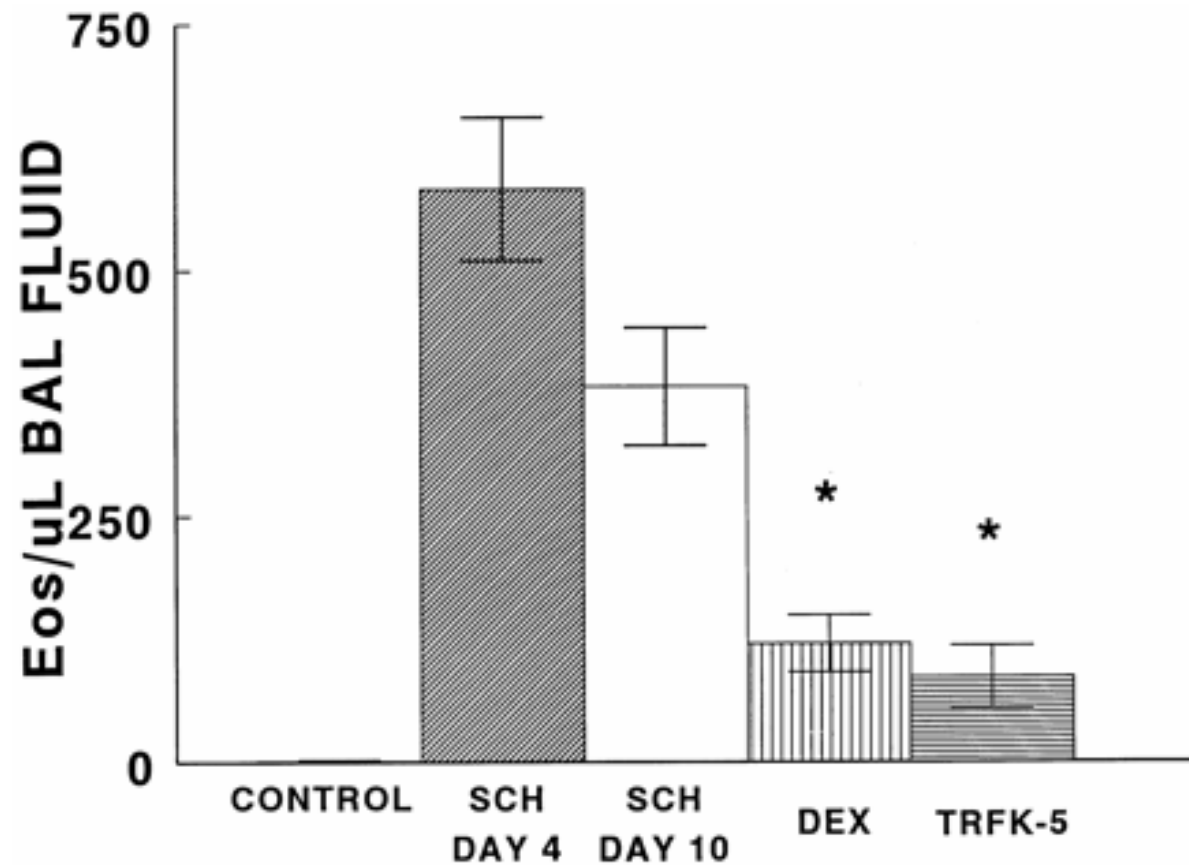
- Failure of anti-Th2 treatments

Leckie, Lancet 2000

- Bronchial hyperreactivity dissociated from eosinophilia

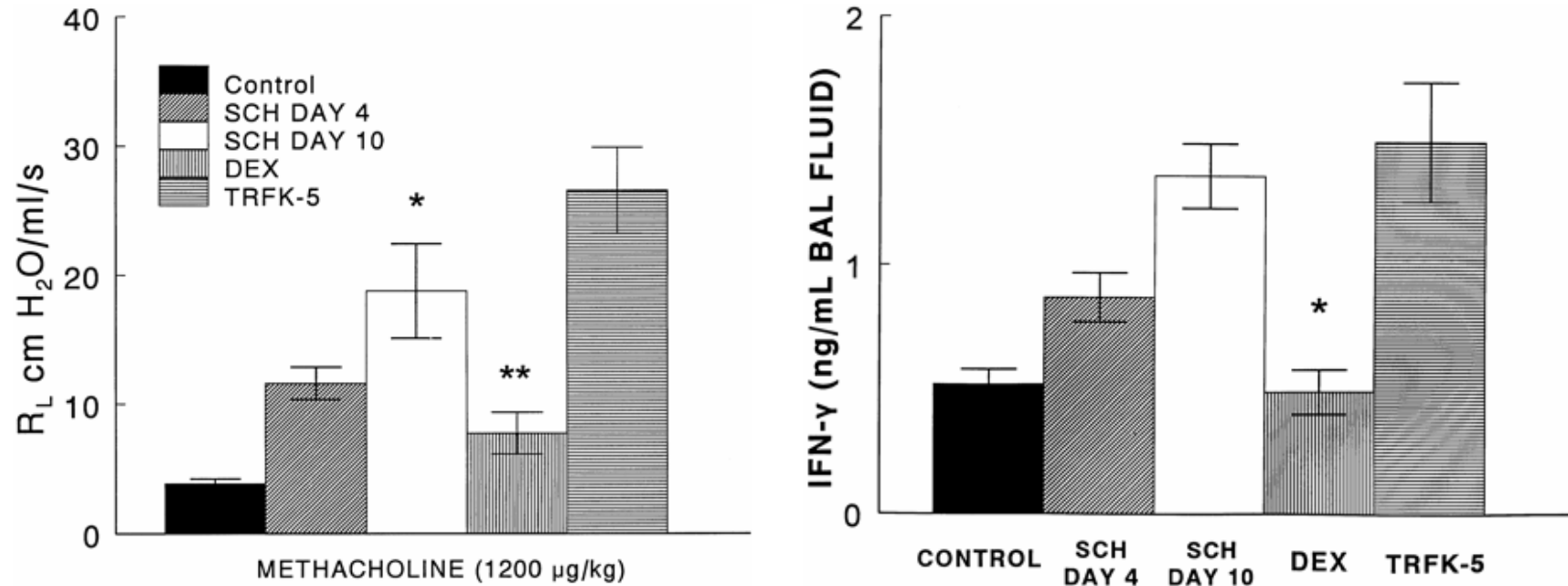
Mathur, Am J Respir Crit Care Med 1999

BHR is dissociated from eosinophilia



Mathur, Am J Respir Crit Care Med 1999, 159: 580

BHR is dissociated from eosinophilia



Mathur, Am J Respir Crit Care Med 1999, 159: 580

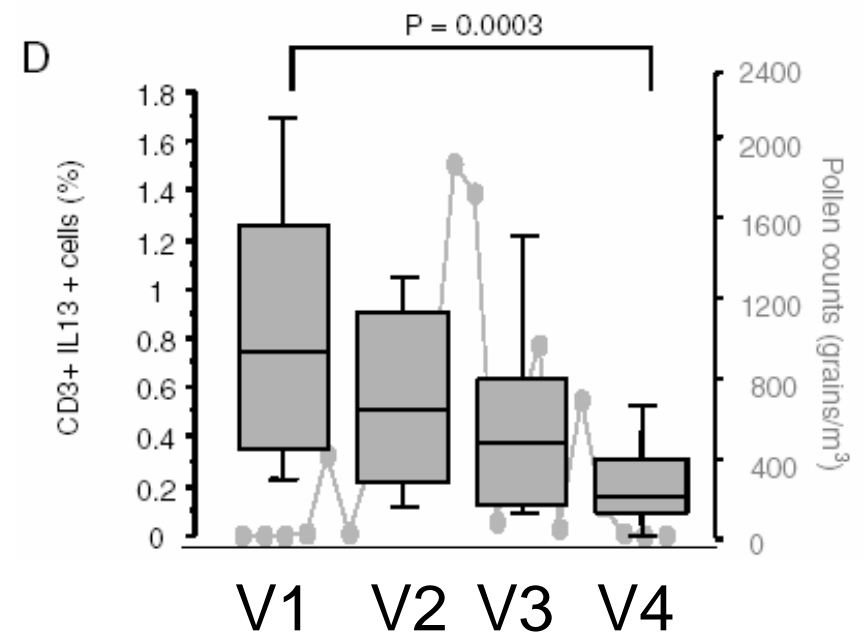
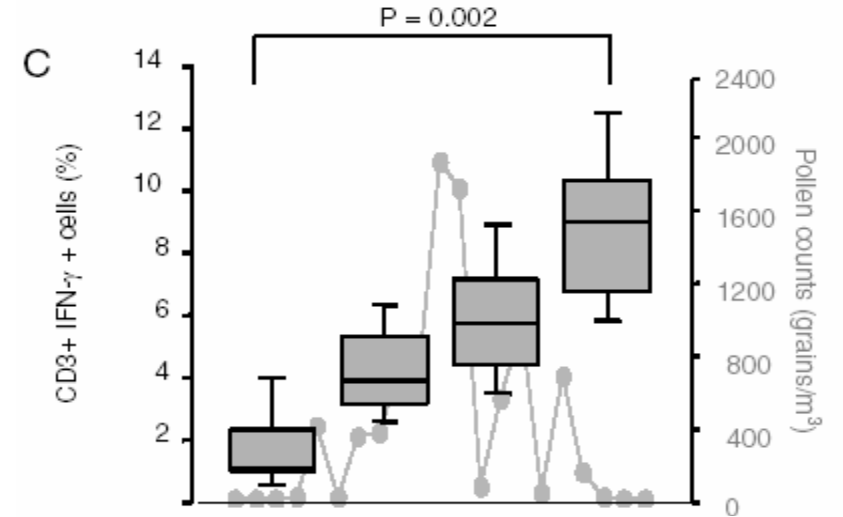
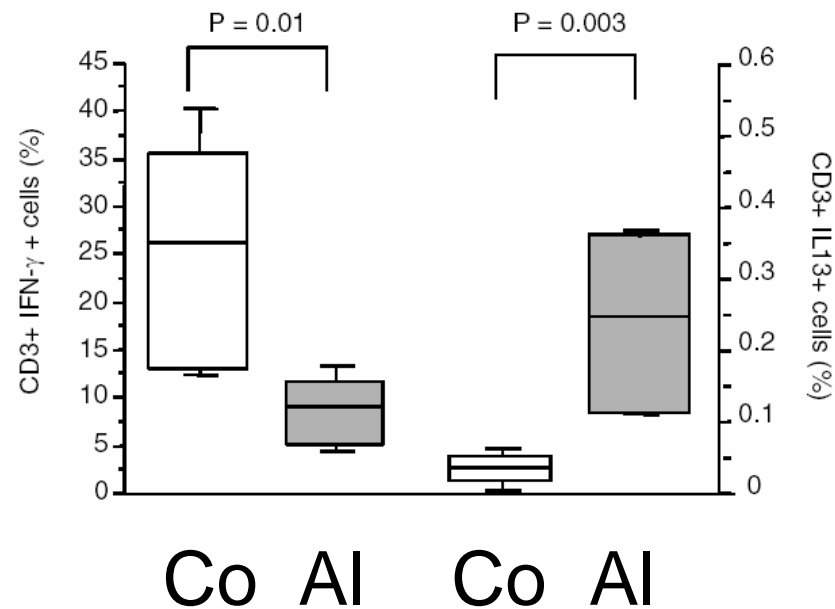
Associated Th1 activation in atopic diseases

IFN- γ in atopic diseases

- Atopic dermatitis
- Rhinitis

Thepen JACI 1996

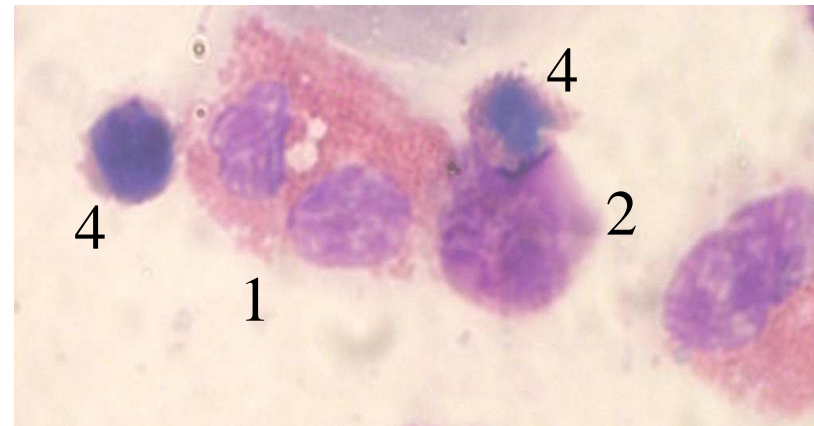
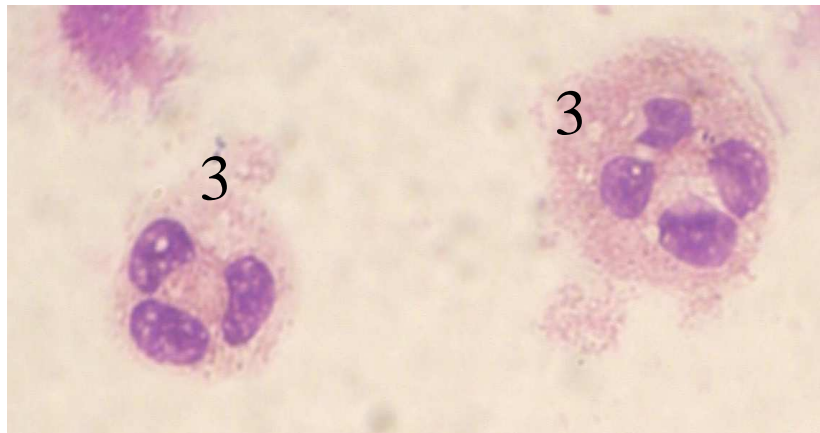
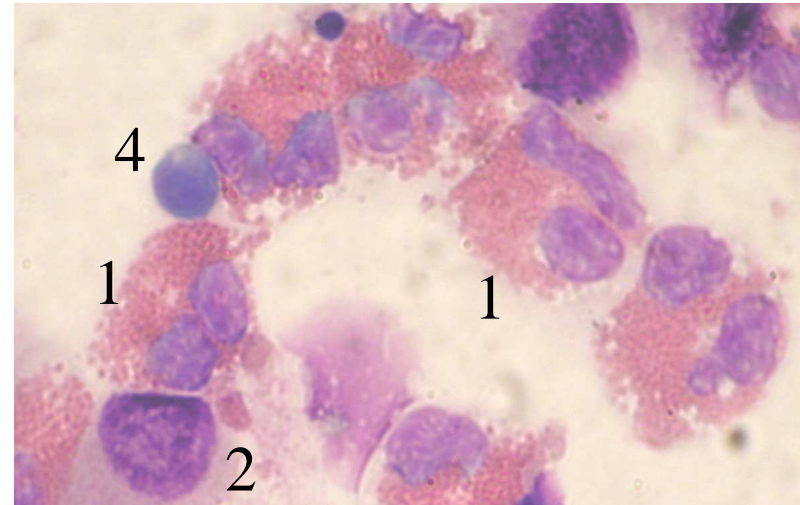
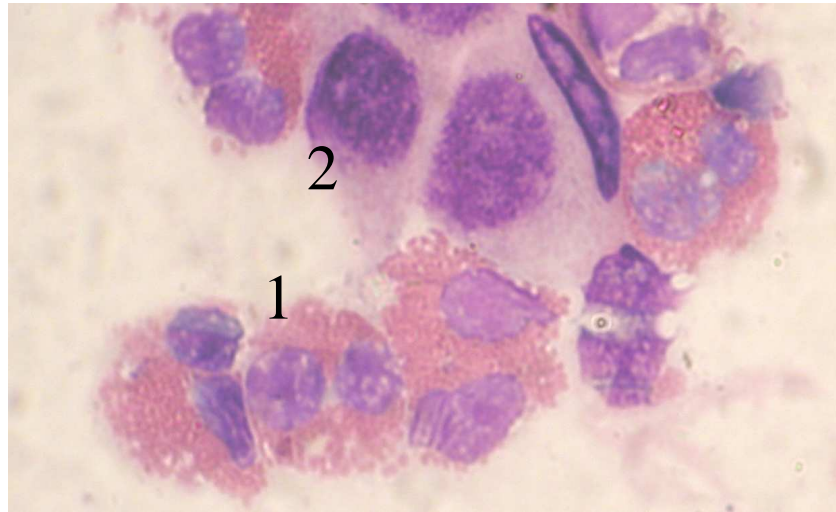
Koscher, Allergy 2006, 61: 35-42



IFN- γ in atopic diseases

- Asthma

	Atopy	Asthma
IL-4 in culture supernatants	112.683 \pm 74.62 (p = 0.006)	220.496 \pm 77.81 (p = 0.136)
IFN- γ in culture supernatants	- 6908.257 \pm 4313 (p = 0.178)	16574.257 \pm 4110.222 (p = 0.003)
IFN- γ producing T cells	- 0.166 \pm 0.0575 (p = 0.005)	0.163 \pm 0.0543 (p = 0.004)
IFN- γ producing CD8+ T cells	- 0.0451 \pm 0.1 (p = 0.672)	0.293 \pm 0.1 (p = 0.005)

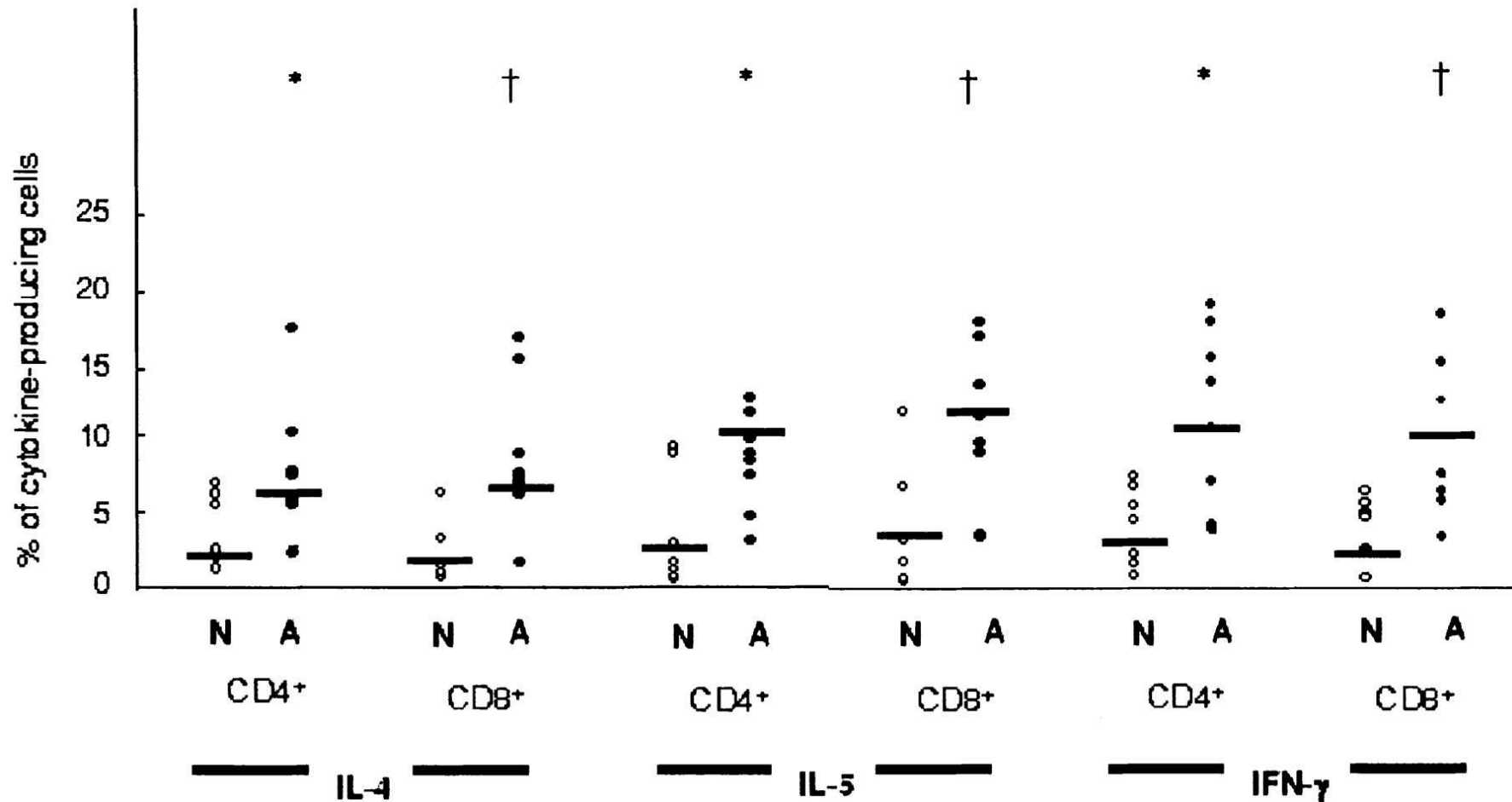


1 = Eosinophile
3 = Neutrophile

2 = Macrophage
4 = Lymphocyte

Magnan, in Aubier, *Pneumologie*, sous presse

T cell cytokines in induced sputum

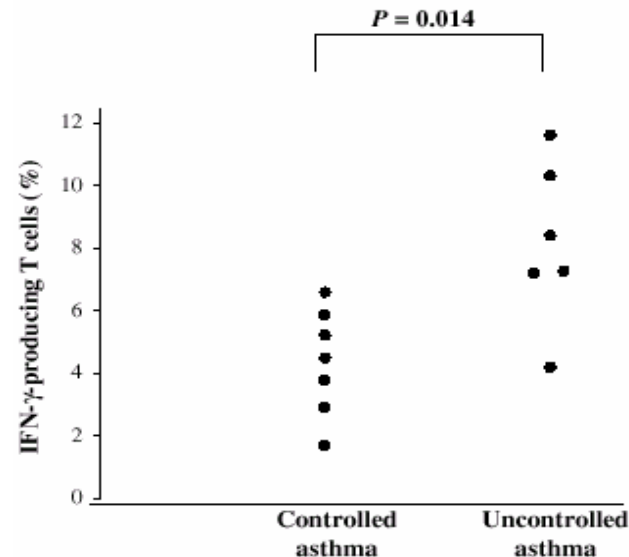


Cho, *Am J Respir Crit Care Med.* 2005, 171: 224-230

Asthma

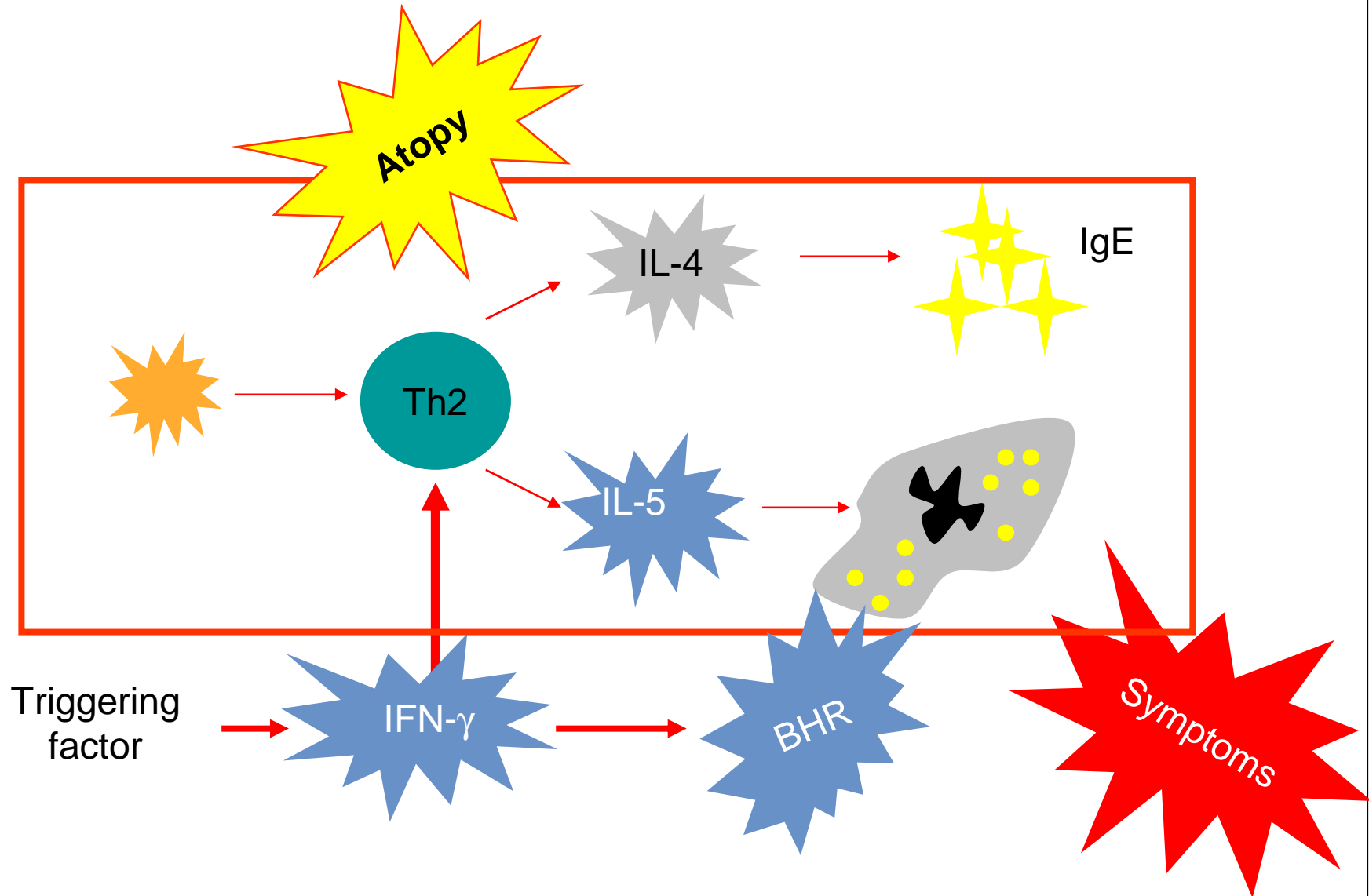
	Controls (n = 19)	Asthma (n = 13)
Cells	1.02 (0.72 – 2.49)	1.29 (0.66 – 1.98)
Lymphocytes	2.5 (1 – 7)	2 (1 – 3)
Eosinophils	0 (0 – 0)	0 (0 -10.75)
Neutrophils	42.5 (28 – 68)	36 (24.7 – 83.5)
macrophages	54 (31 – 64)	25 (9.5 – 68.75)

- After non specific stimulation :
 - More IFN- γ + T cells
 - More IL-13 + T cells

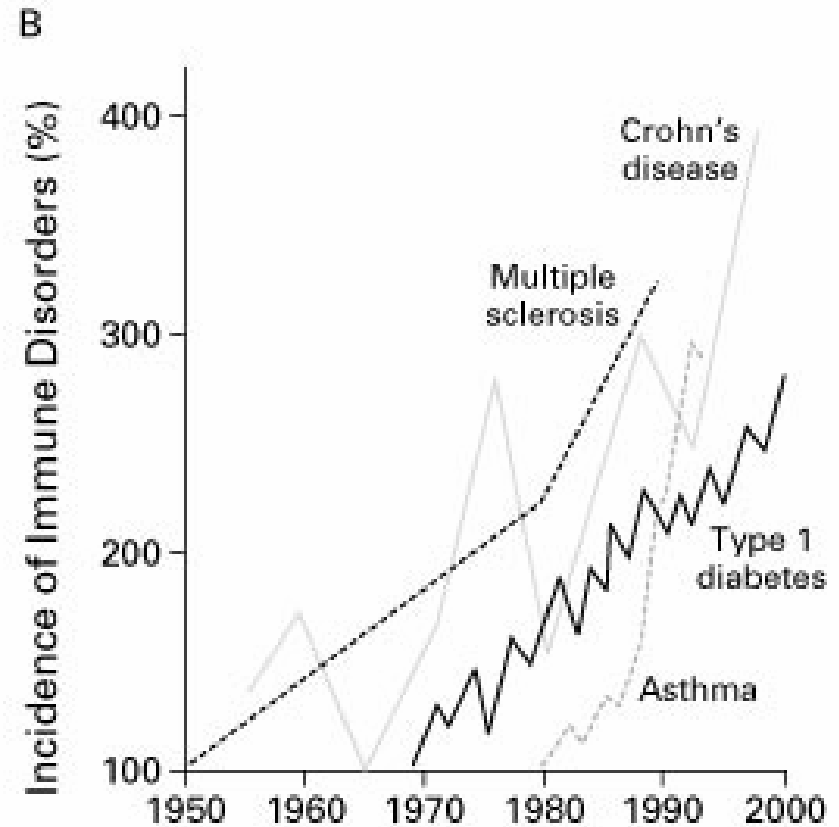
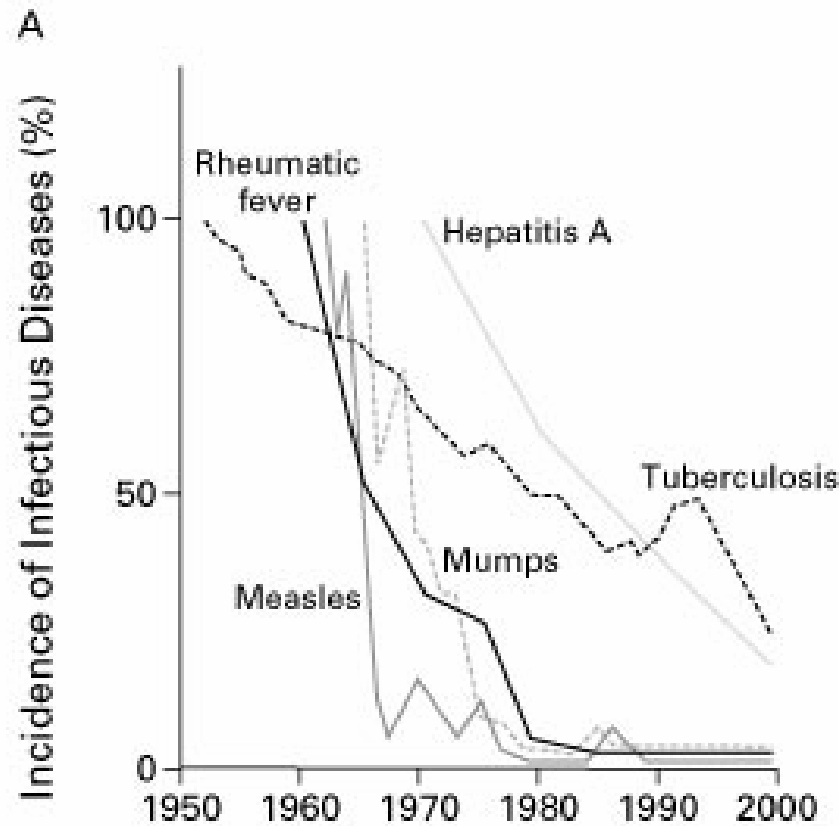


Boniface, Clin Exp Allergy 2003

Allergic response

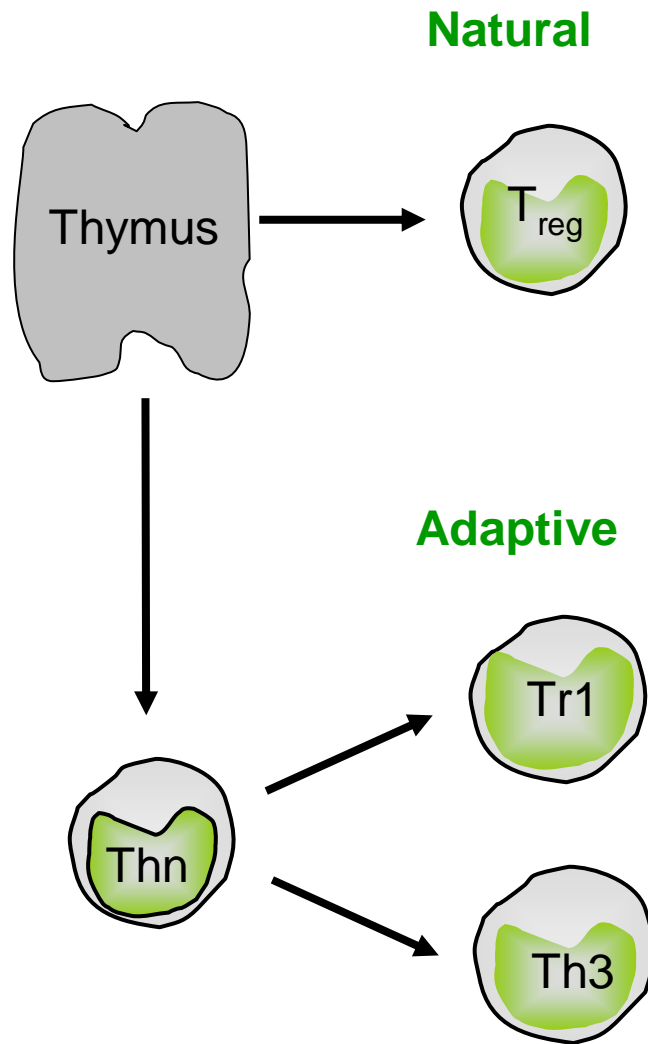


New concept: Treg cell deficiency



Bach, NEJM 2002

Two types of regulatory T cells



Natural

CD4⁺CD25⁺ T cells

Foxp3 transcription factor

Adaptive

Tr1 cells

IL-10

Foxp3?

Th3 cells

TGF- β

Treg cell deficiency in allergy

- Treg cell deficiency in grass pollen and birch pollen + HDM allergic patients

Ling, Lancet 2004
Akdis, J Exp Med 2004

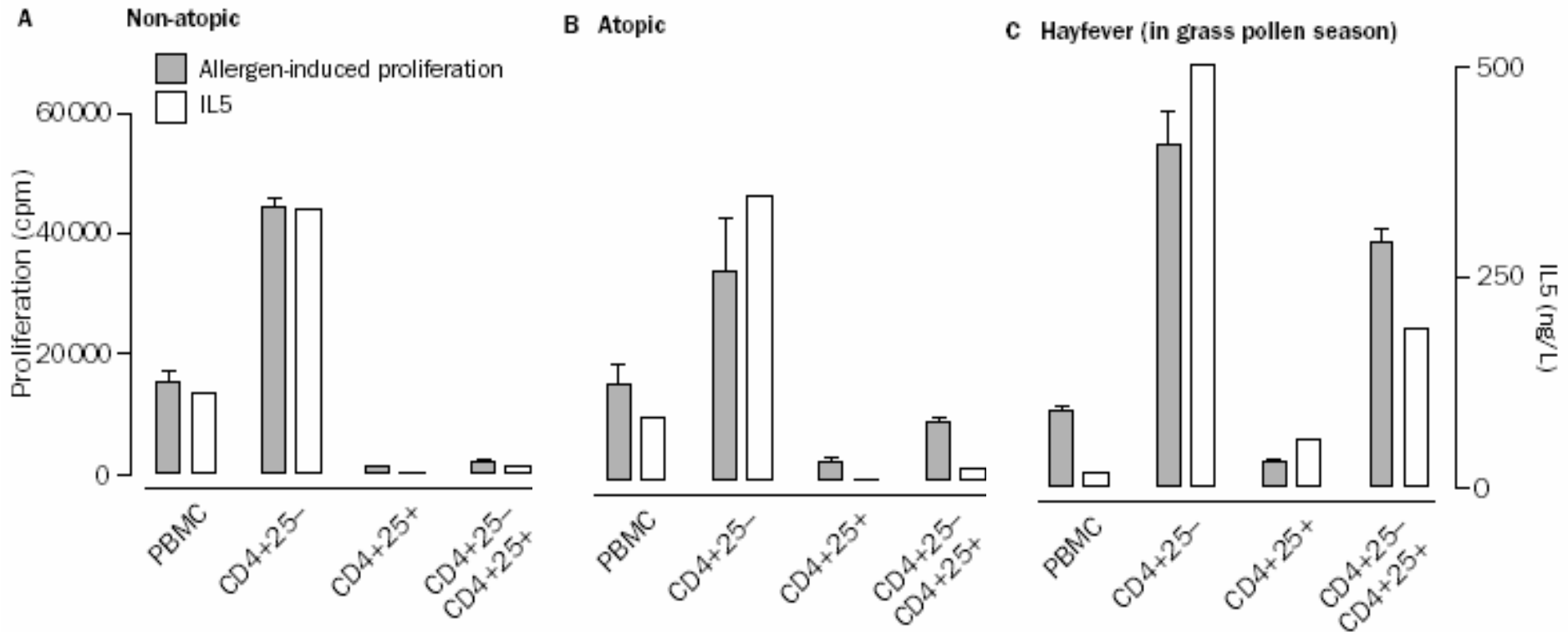
- Treg cell function recovery in milk allergy recovery

Karlsson, J Exp Med 2004

- Treg cells increase during ITS (pollen, HDM, venom)

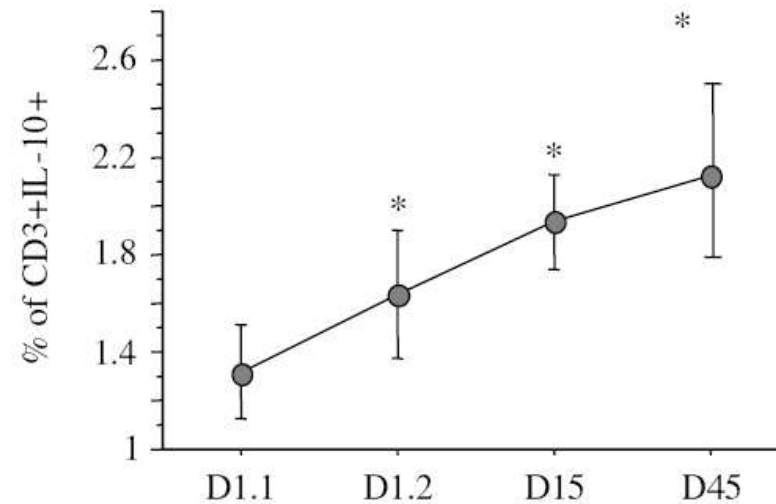
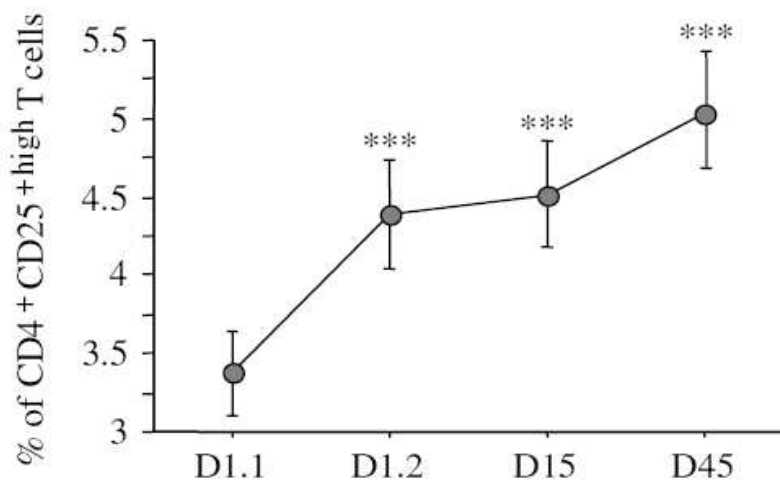
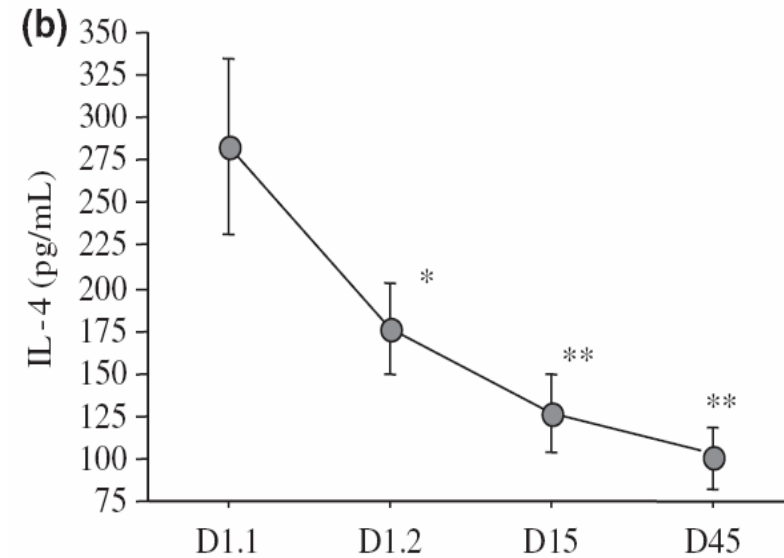
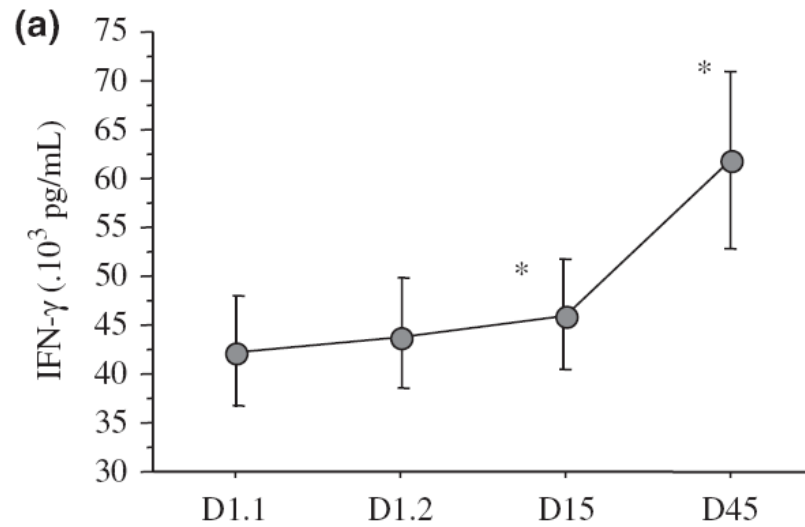
Jutel, Eur J Immunol 2003, Francis, JACI 2003

Treg cell deficiency in allergy

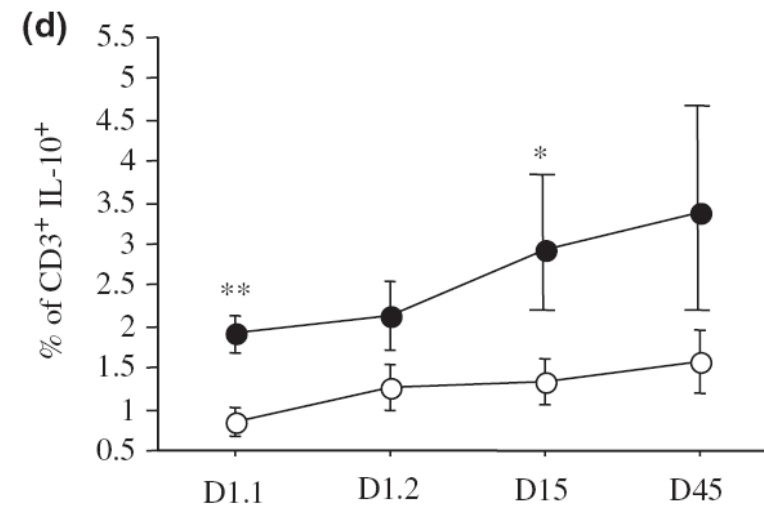
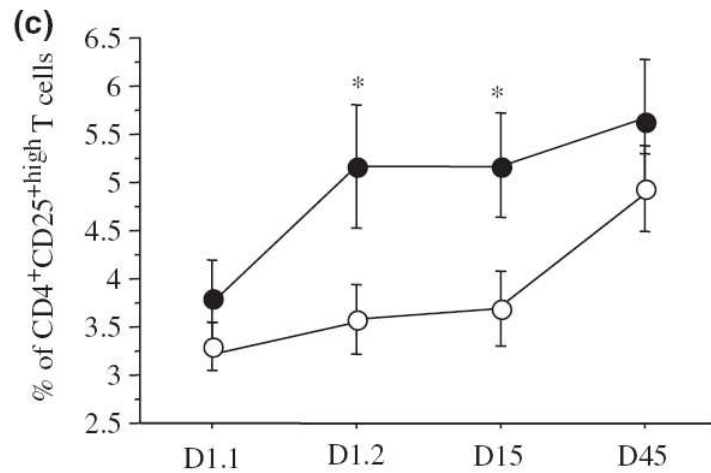
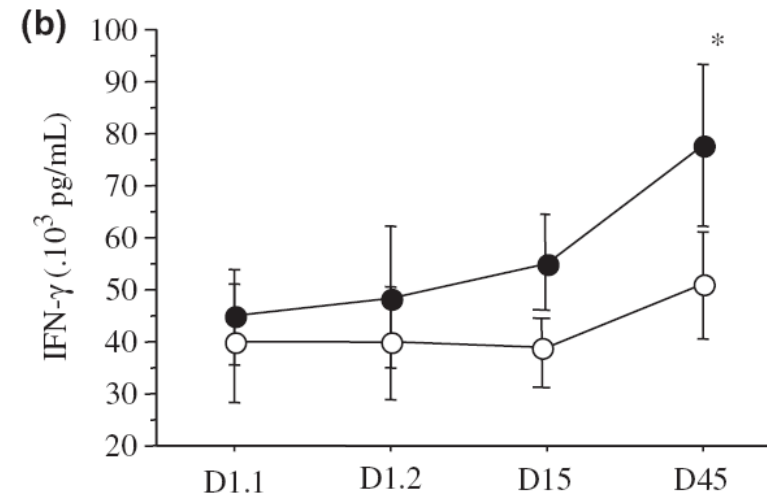
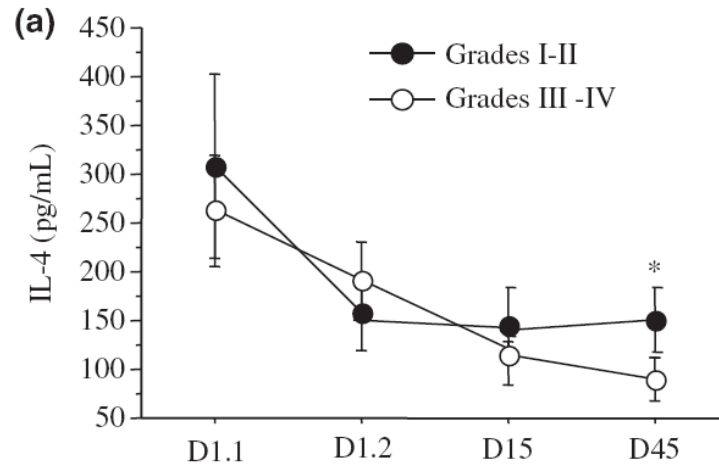


Ling et al. Lancet 2004; 363:608-15.

Allergen specific immunotherapy



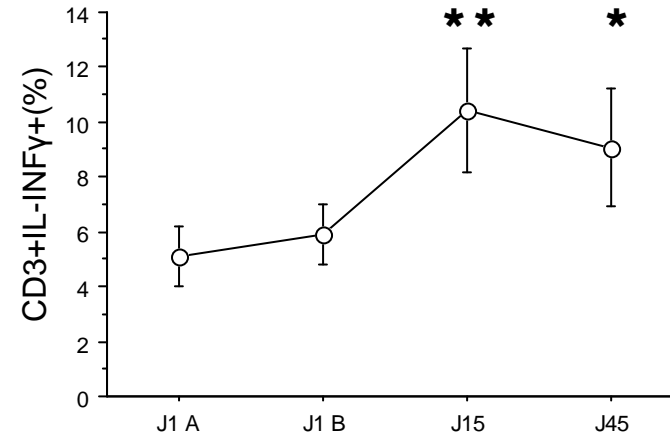
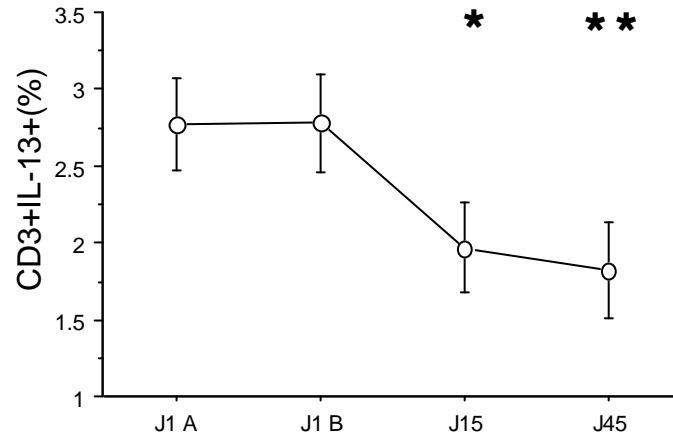
According to the severity of allergy



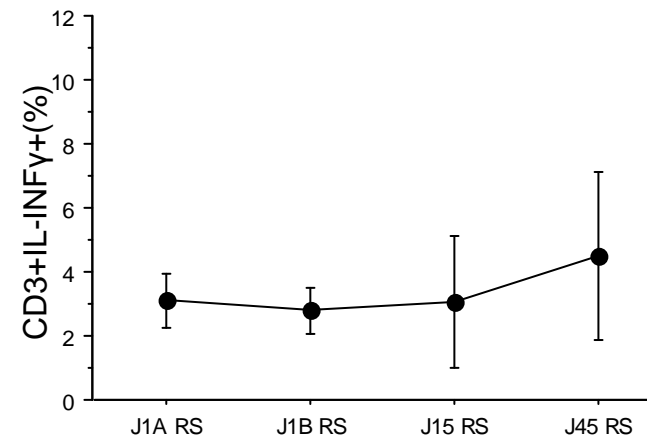
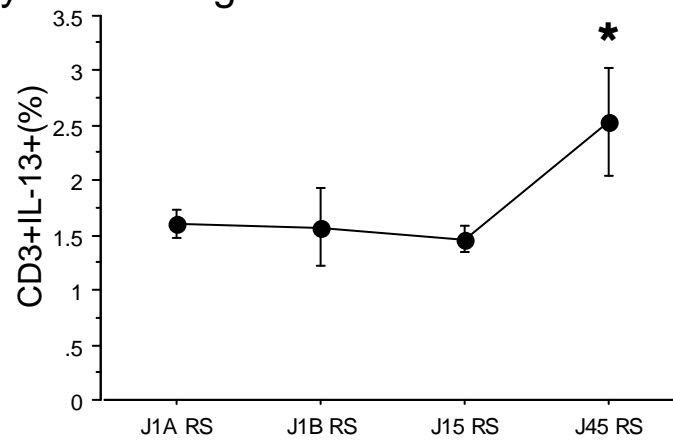
Mamessier, Clin Exp Allergy 2006

According to SIT adverse effects

No anaphylaxis during SIT

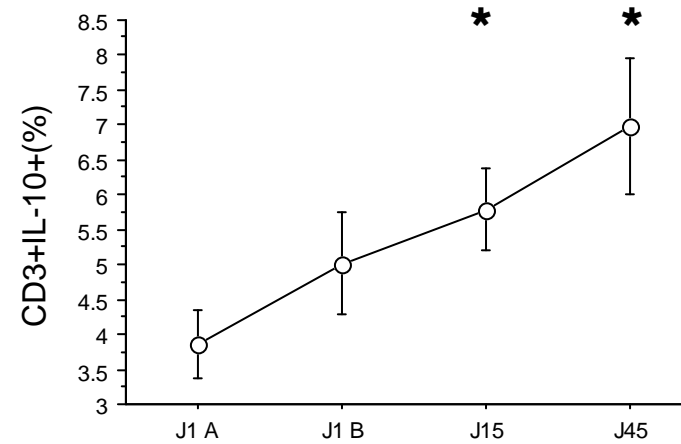
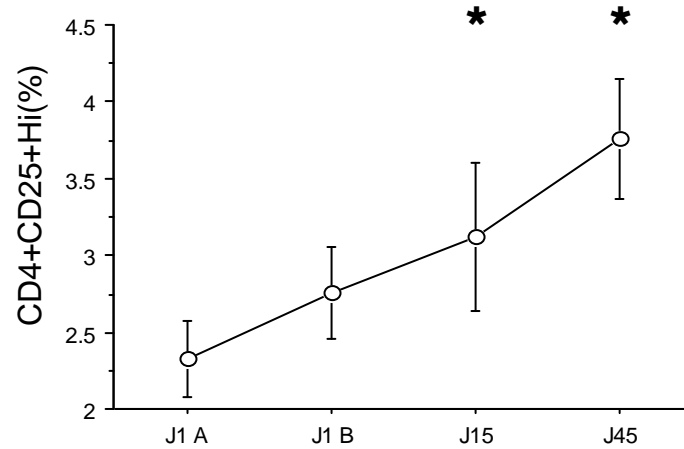


Anaphylaxis during SIT

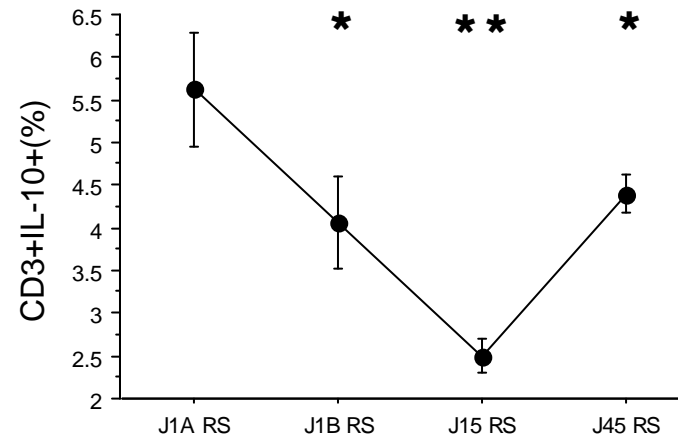
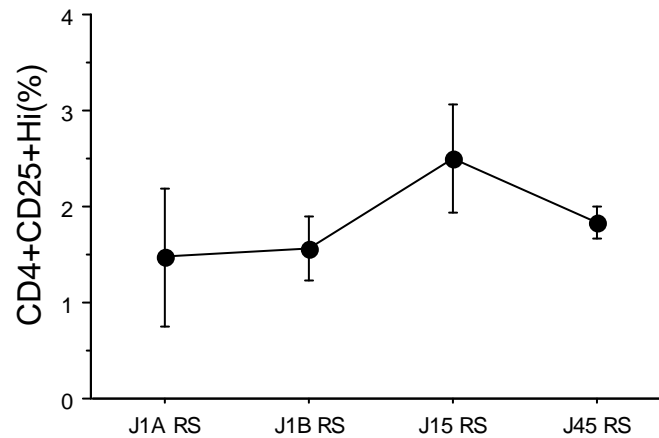


According to SIT adverse effects

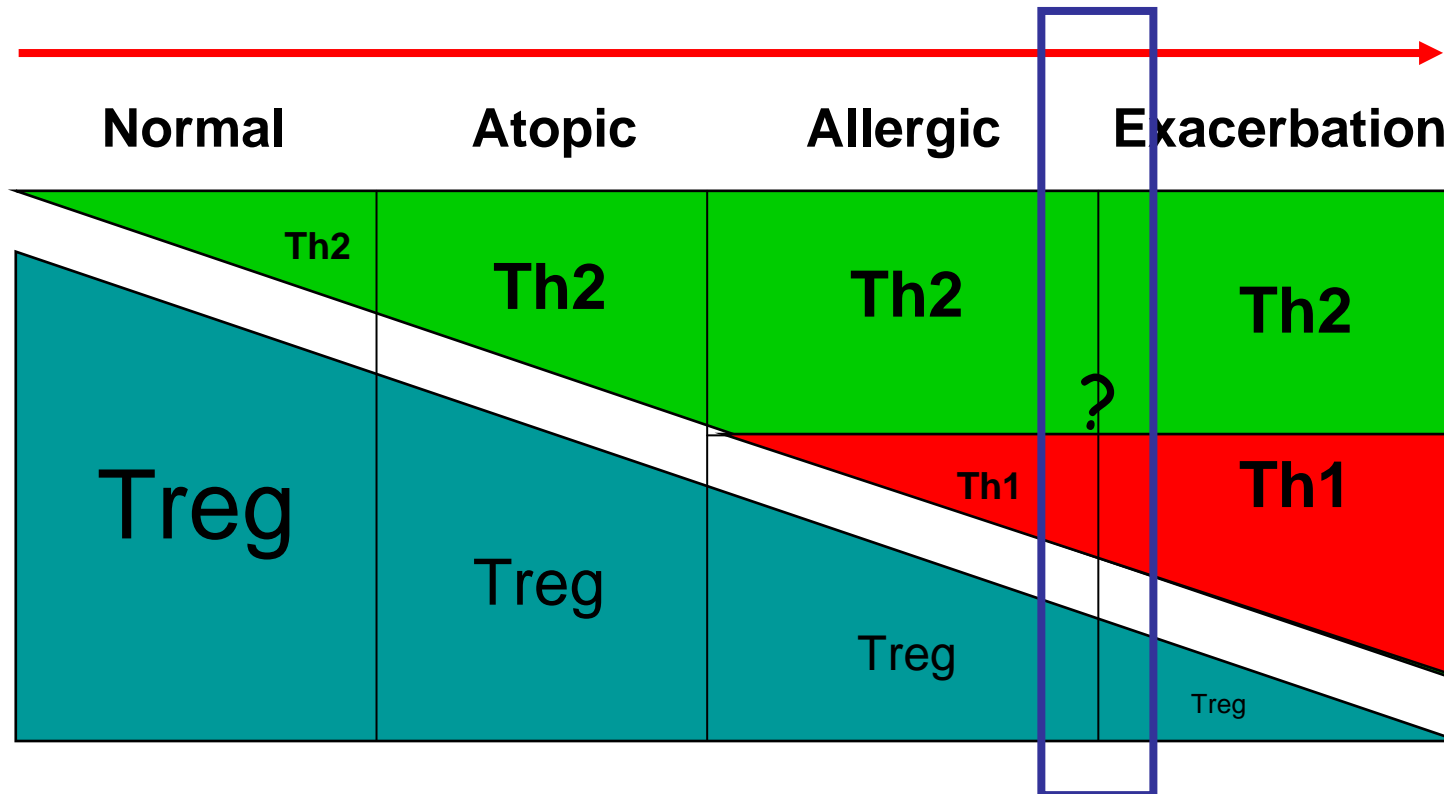
No anaphylaxis during SIT



Anaphylaxis during SIT



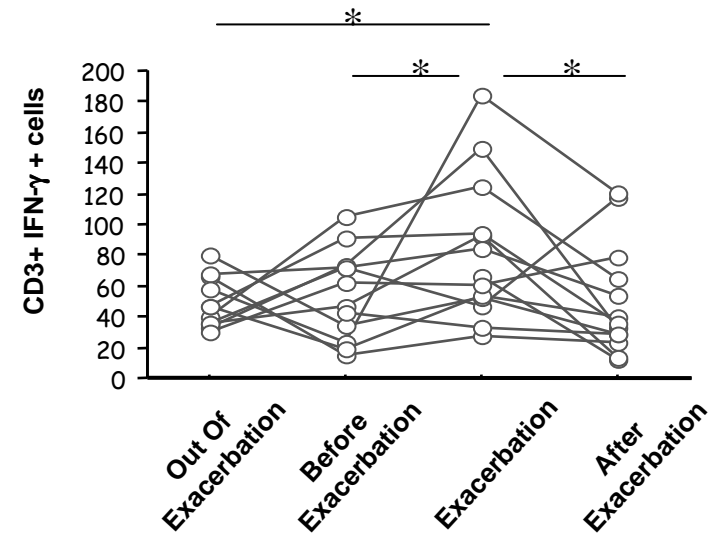
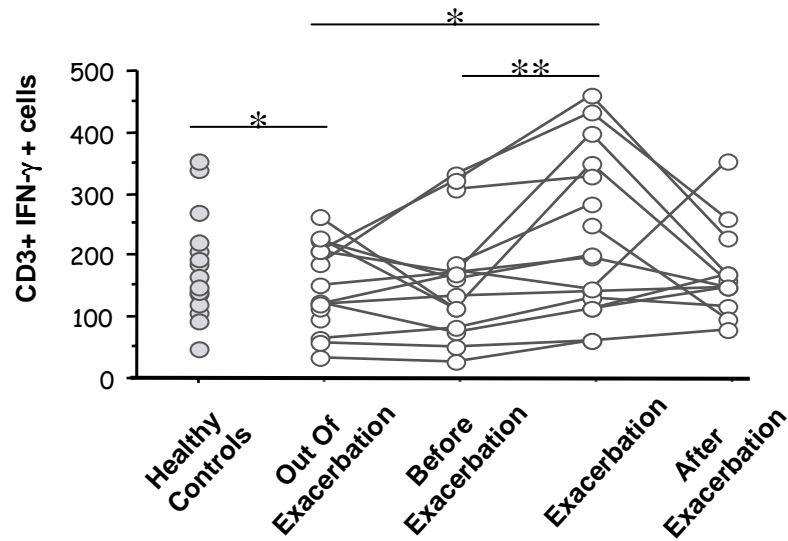
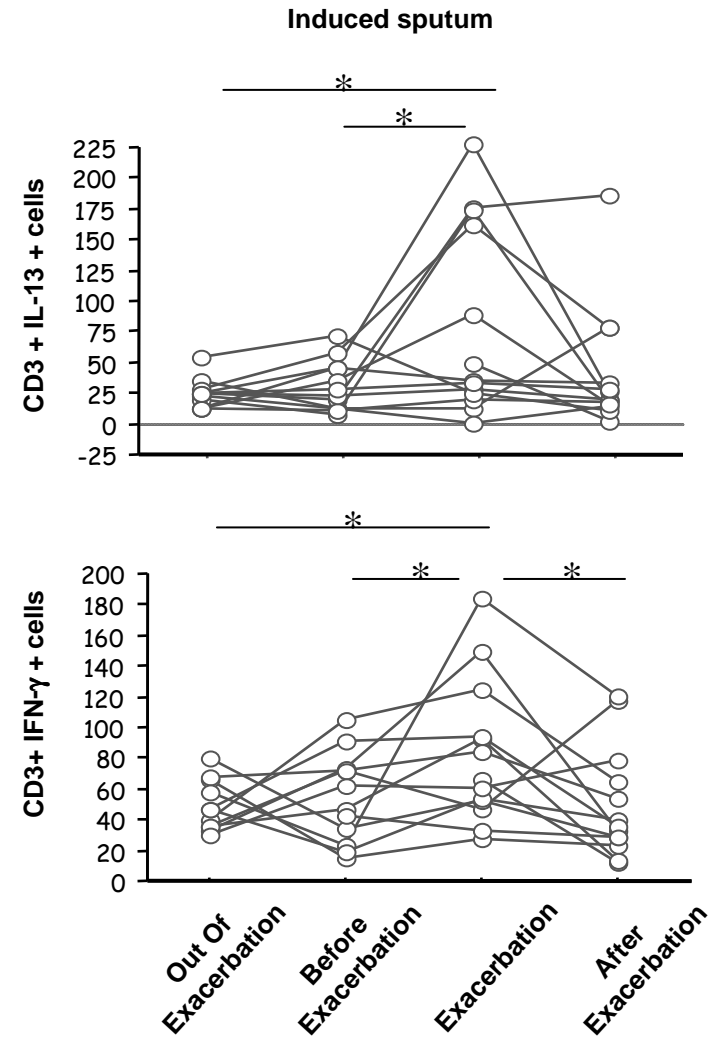
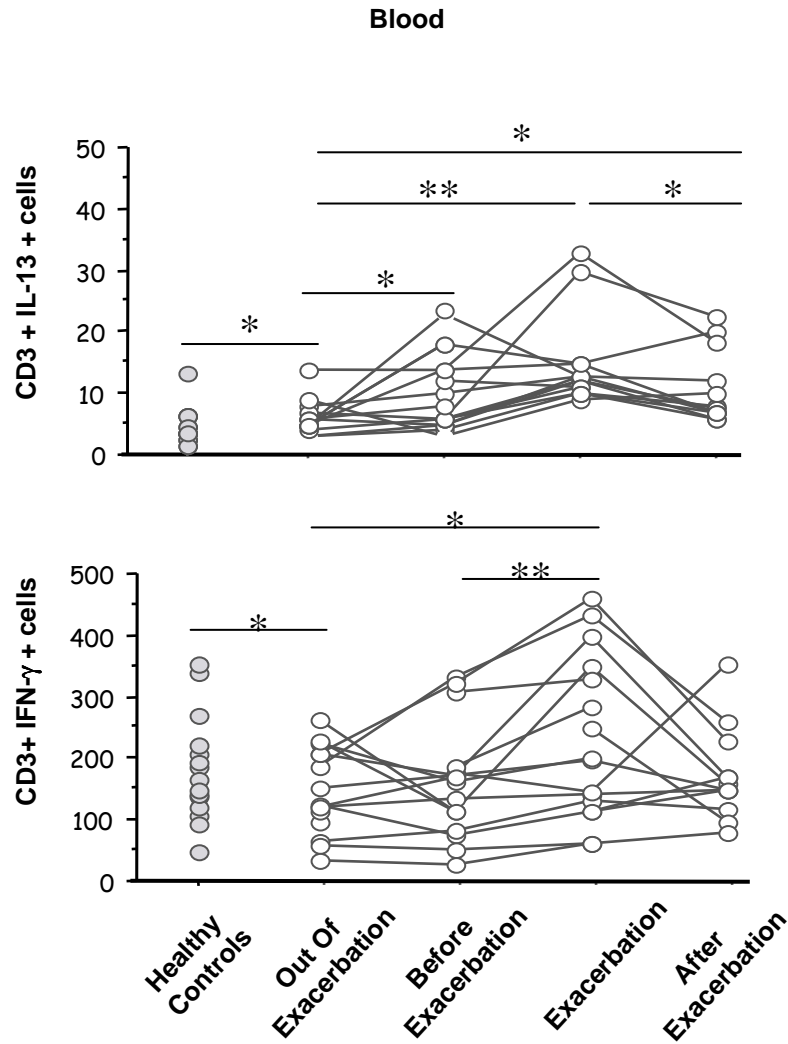
T cell activation in allergy



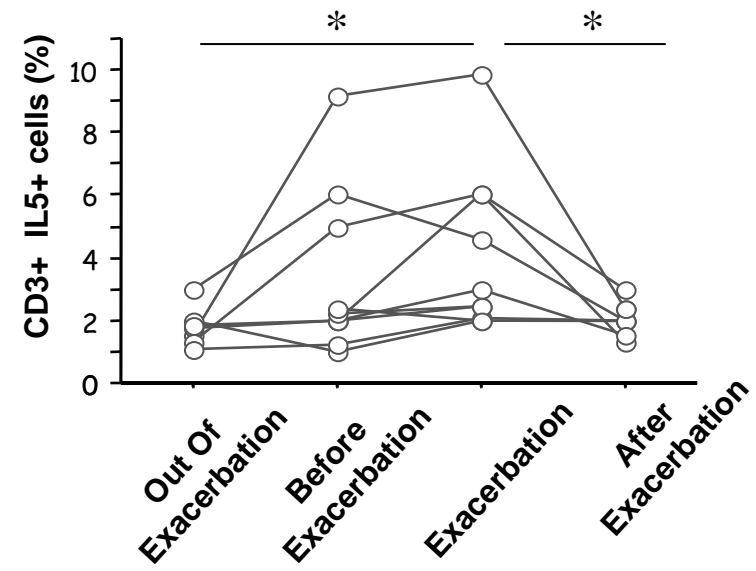
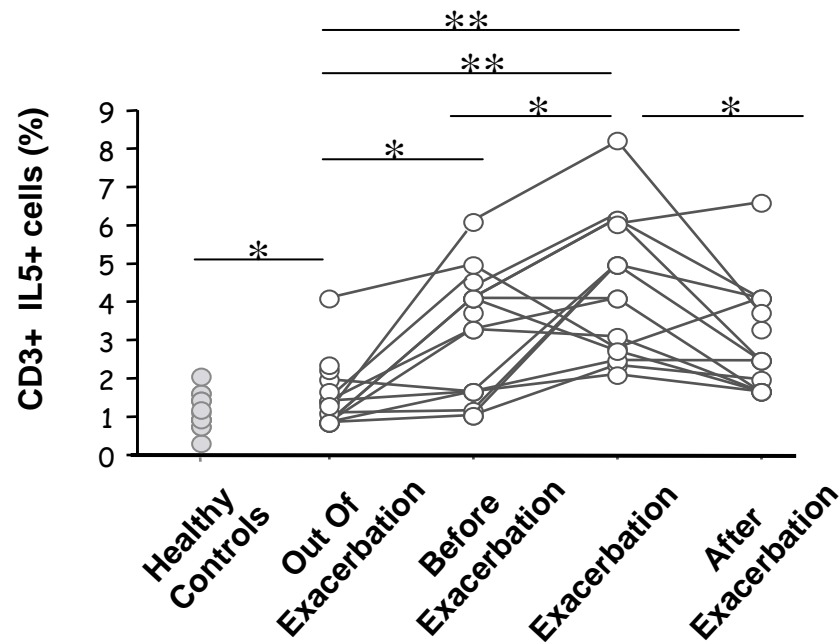
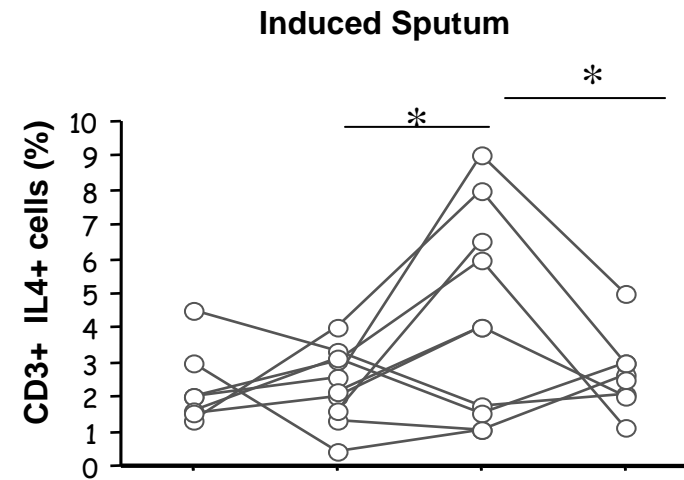
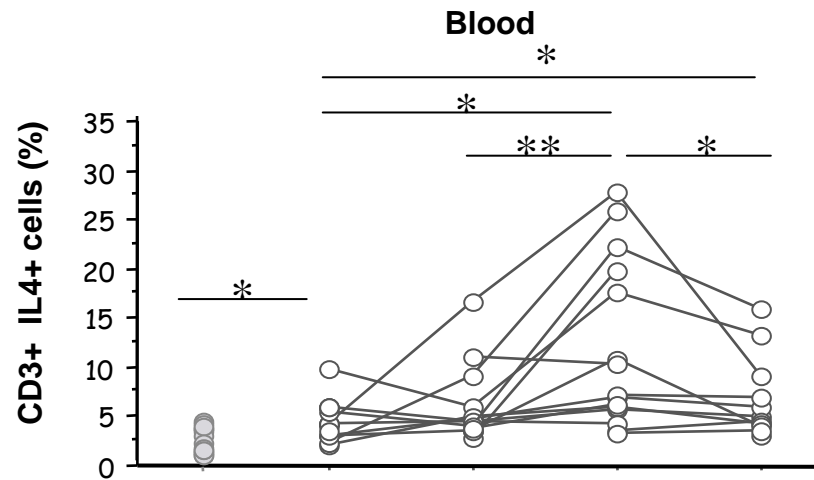
Is deficient tolerance the true paradigm for atopic diseases ?

Magnan A, Humbert M. *Clin Exp Allergy* 2005, 35: 1507-10

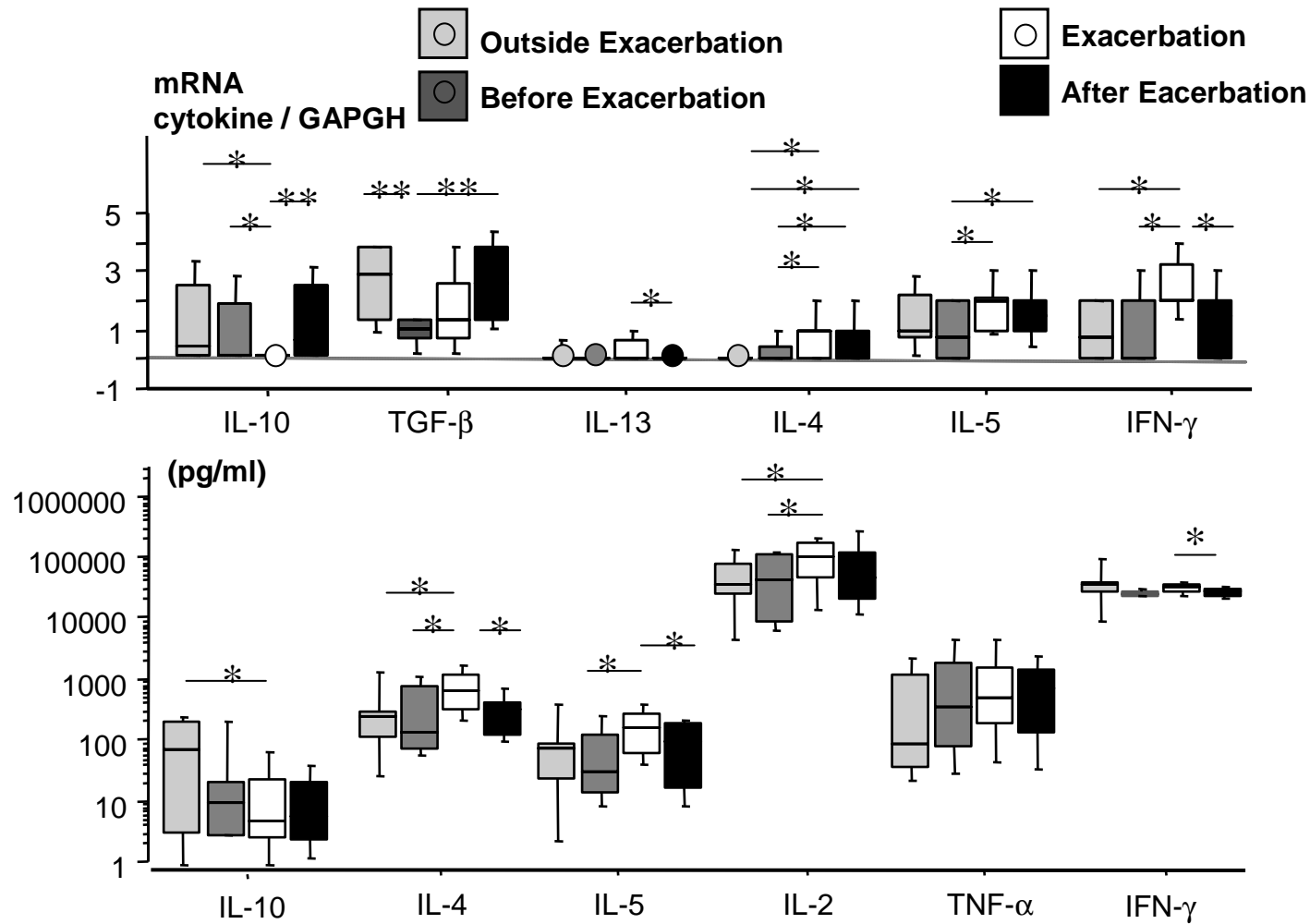
T cell activation during asthma exacerbations



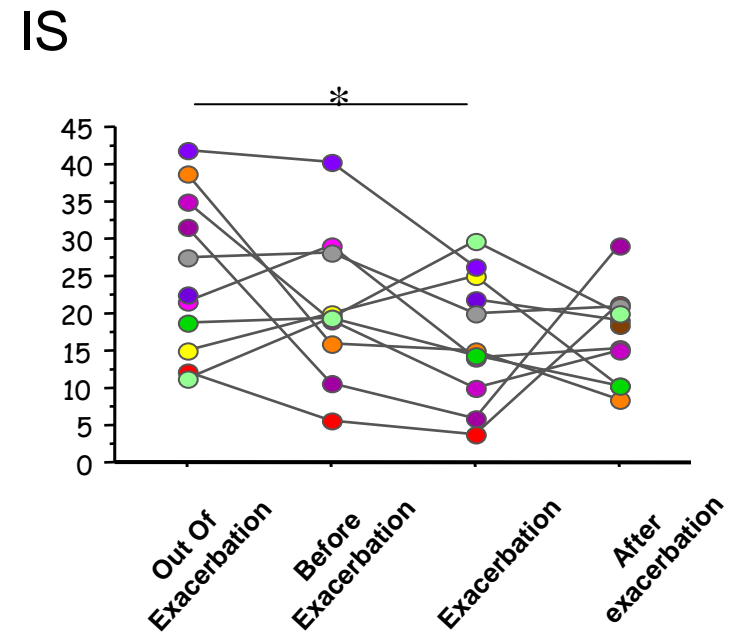
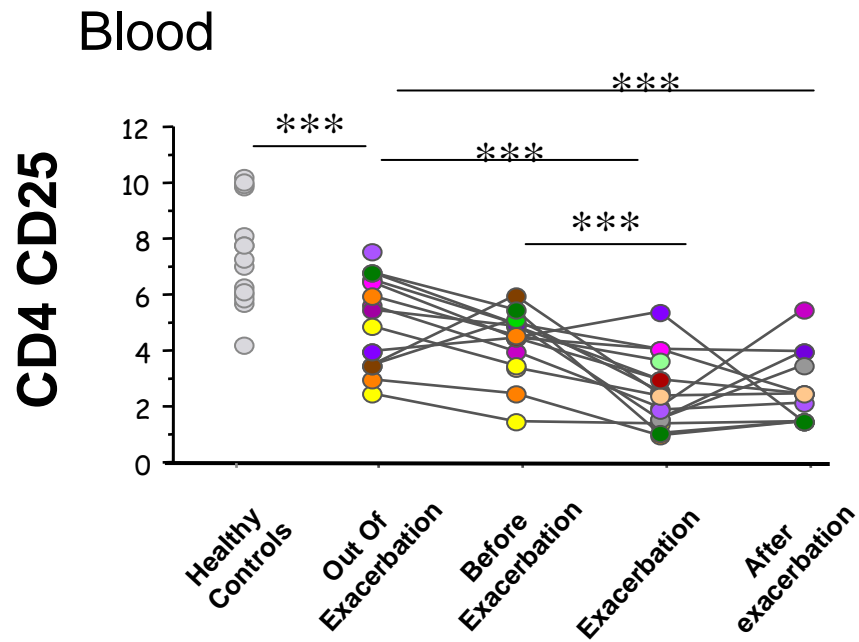
T cell activation during asthma exacerbations



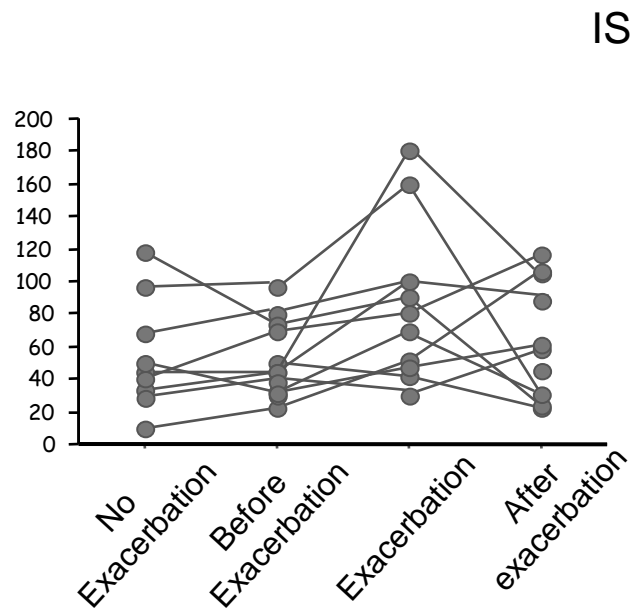
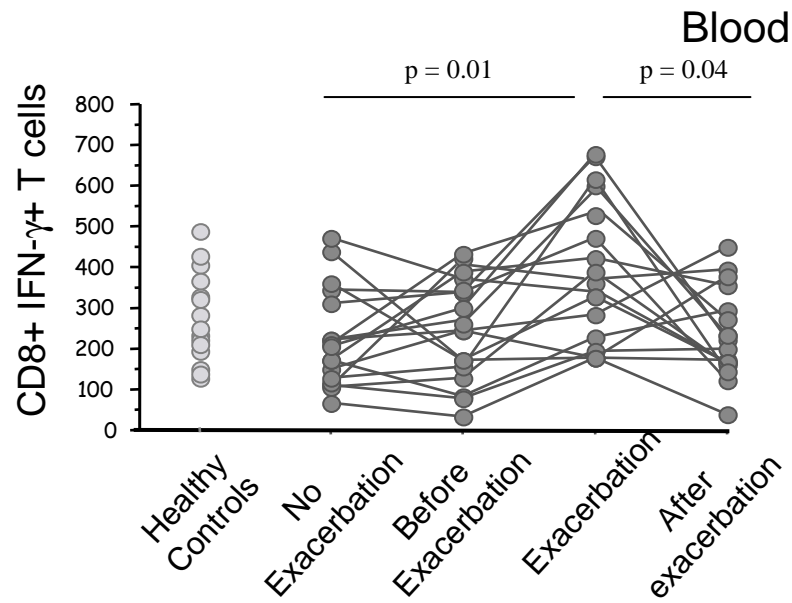
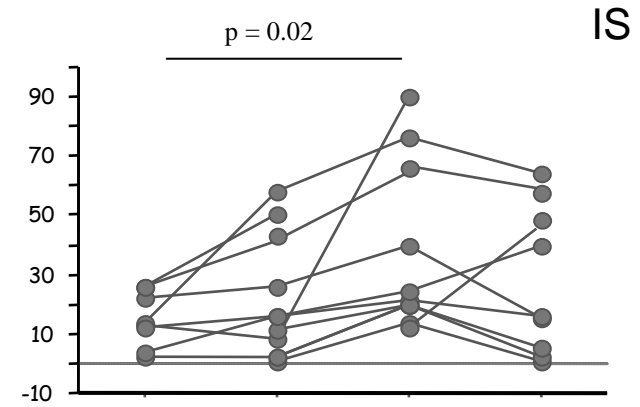
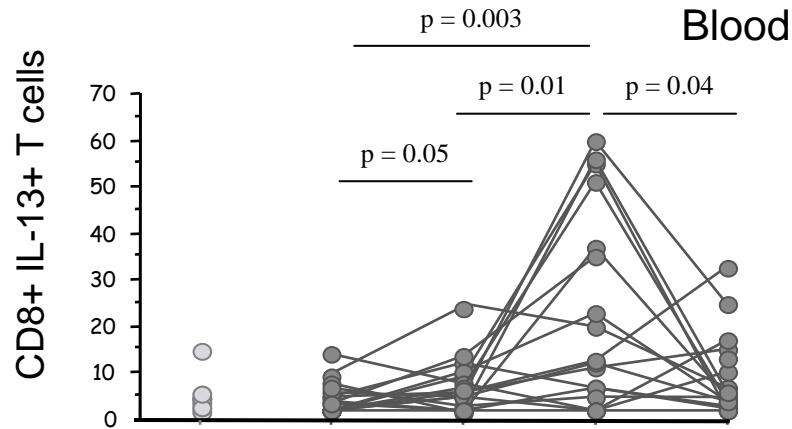
T cell activation during asthma exacerbations



Decrease of Treg cells during exacerbations



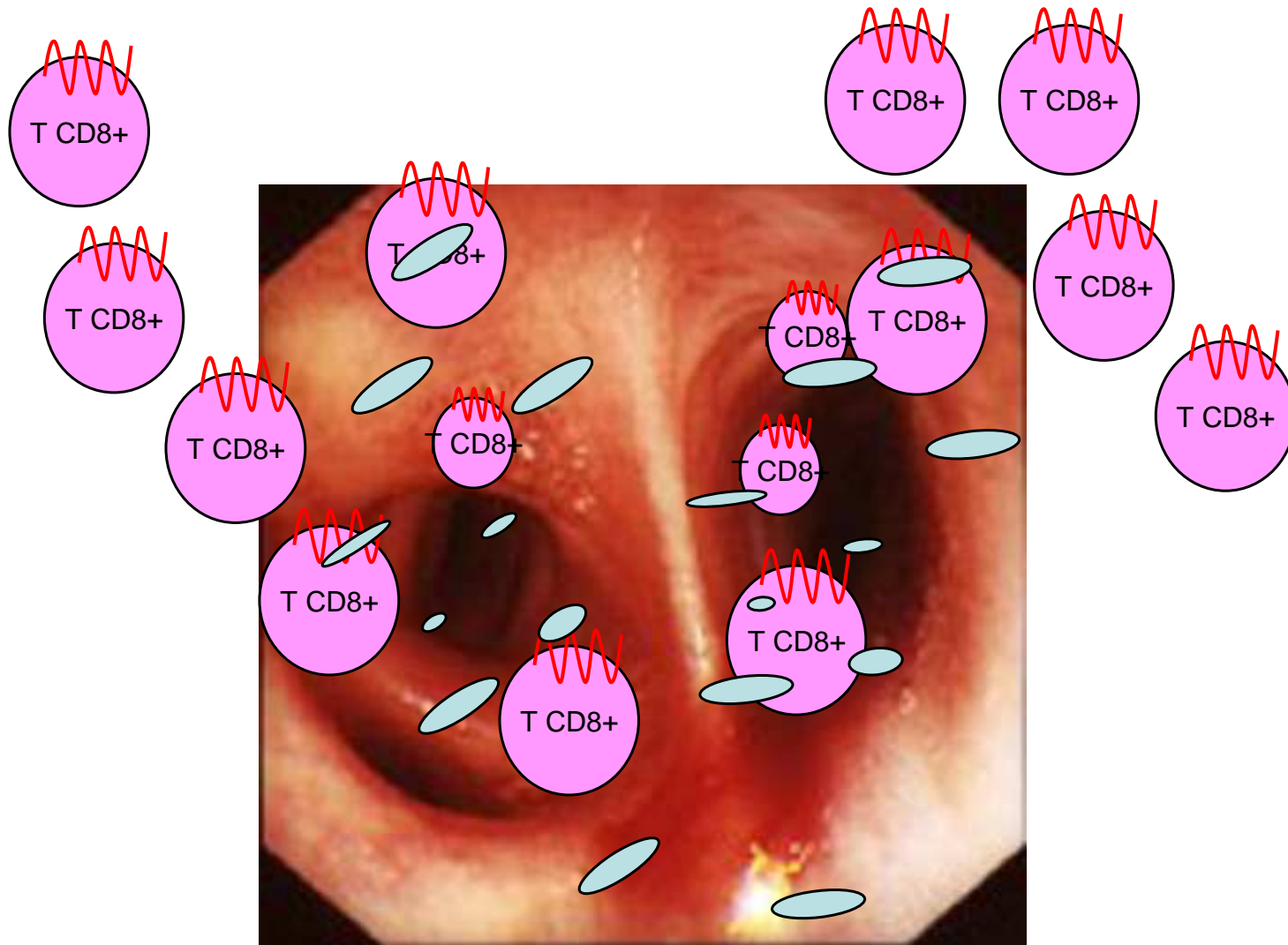
T cell activation during asthma exacerbations



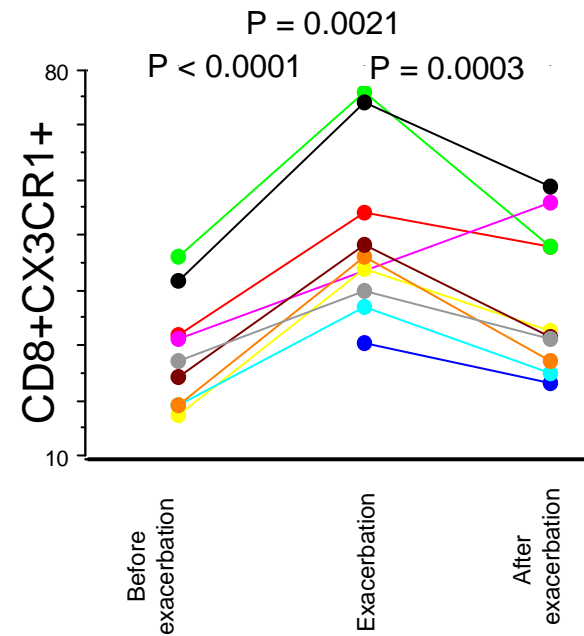
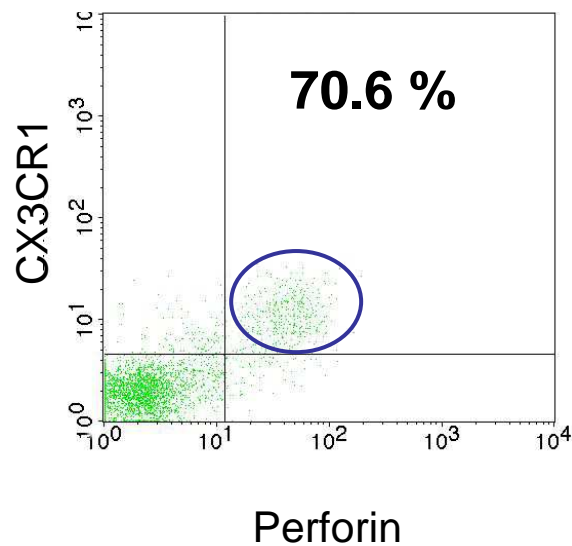
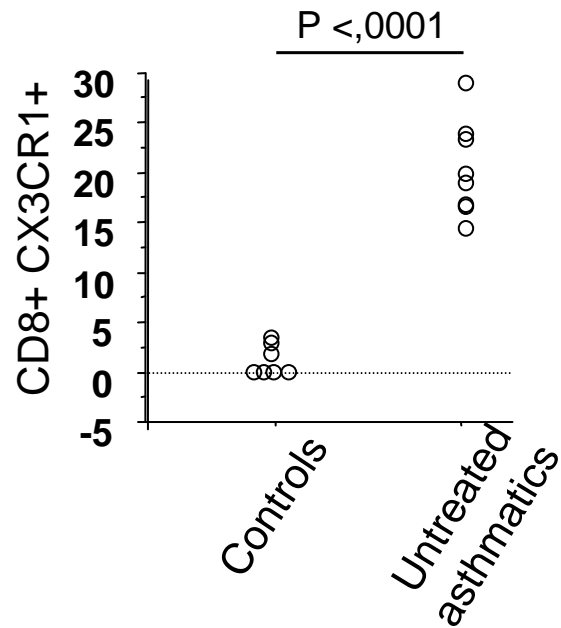
T cell homing



T cell homing



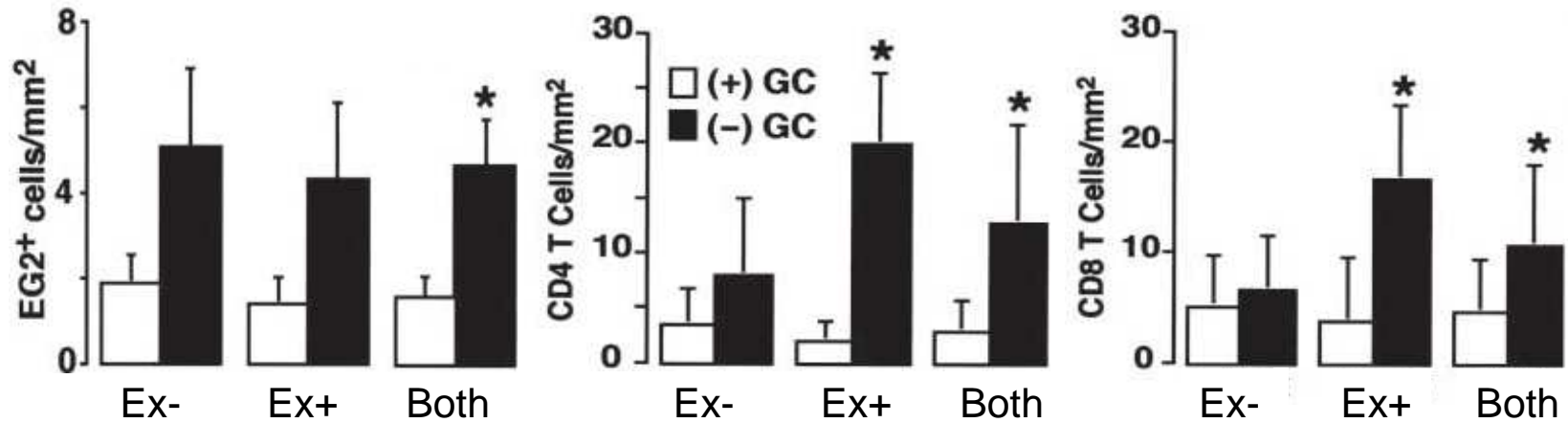
CD8+ cells in exacerbations



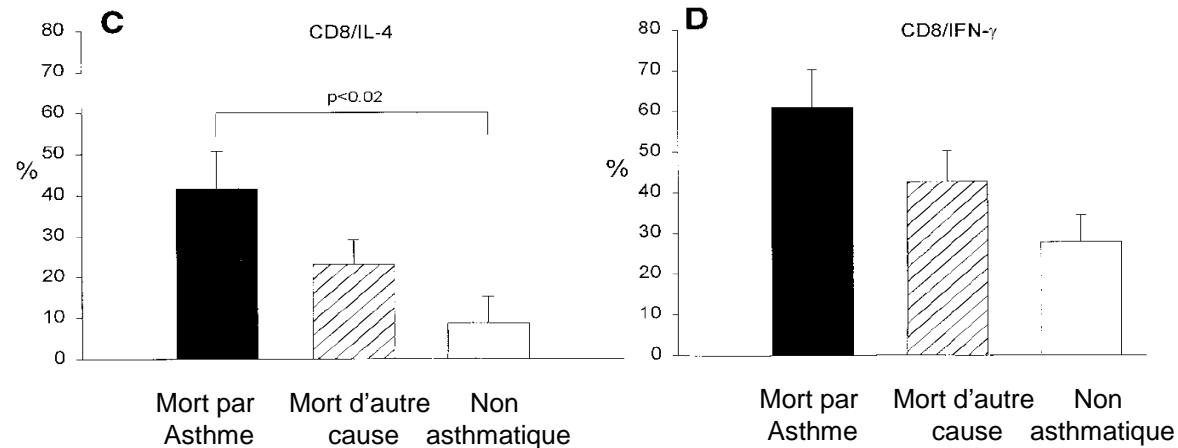
Ghosh, ERS 2006

Projet ANR-06-MIME- CX3CR1CX3CL1Th2
Défi de la recherche en allergologie, FRM 2005

CD8+ cells in exacerbations



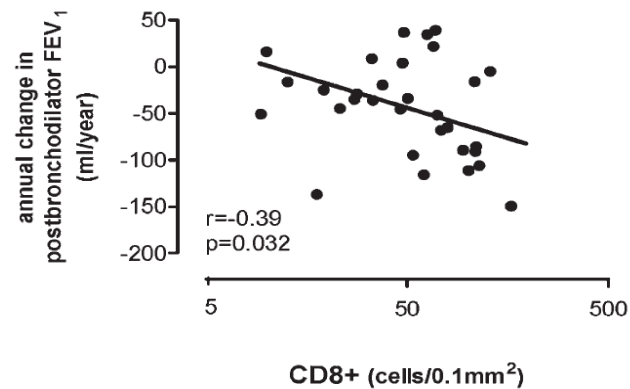
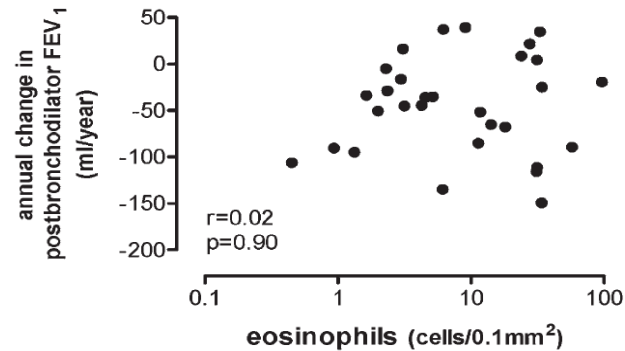
Castro, AJRCCM 2004



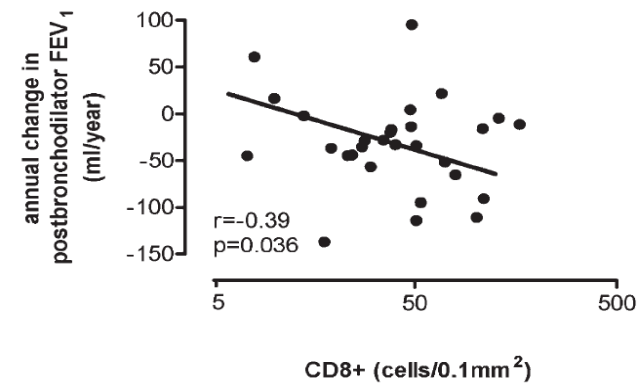
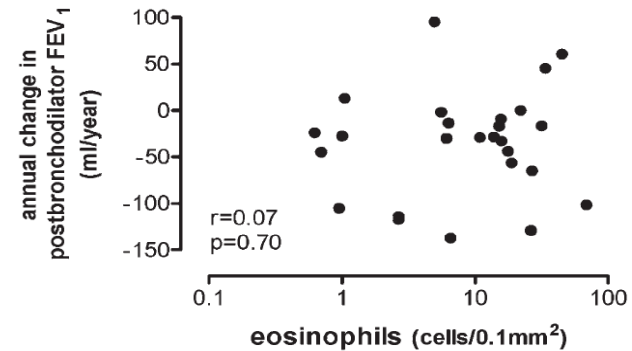
O'Sullivan, Am J Respir Crit Care Med 2001

CD8+ cells in remodelling

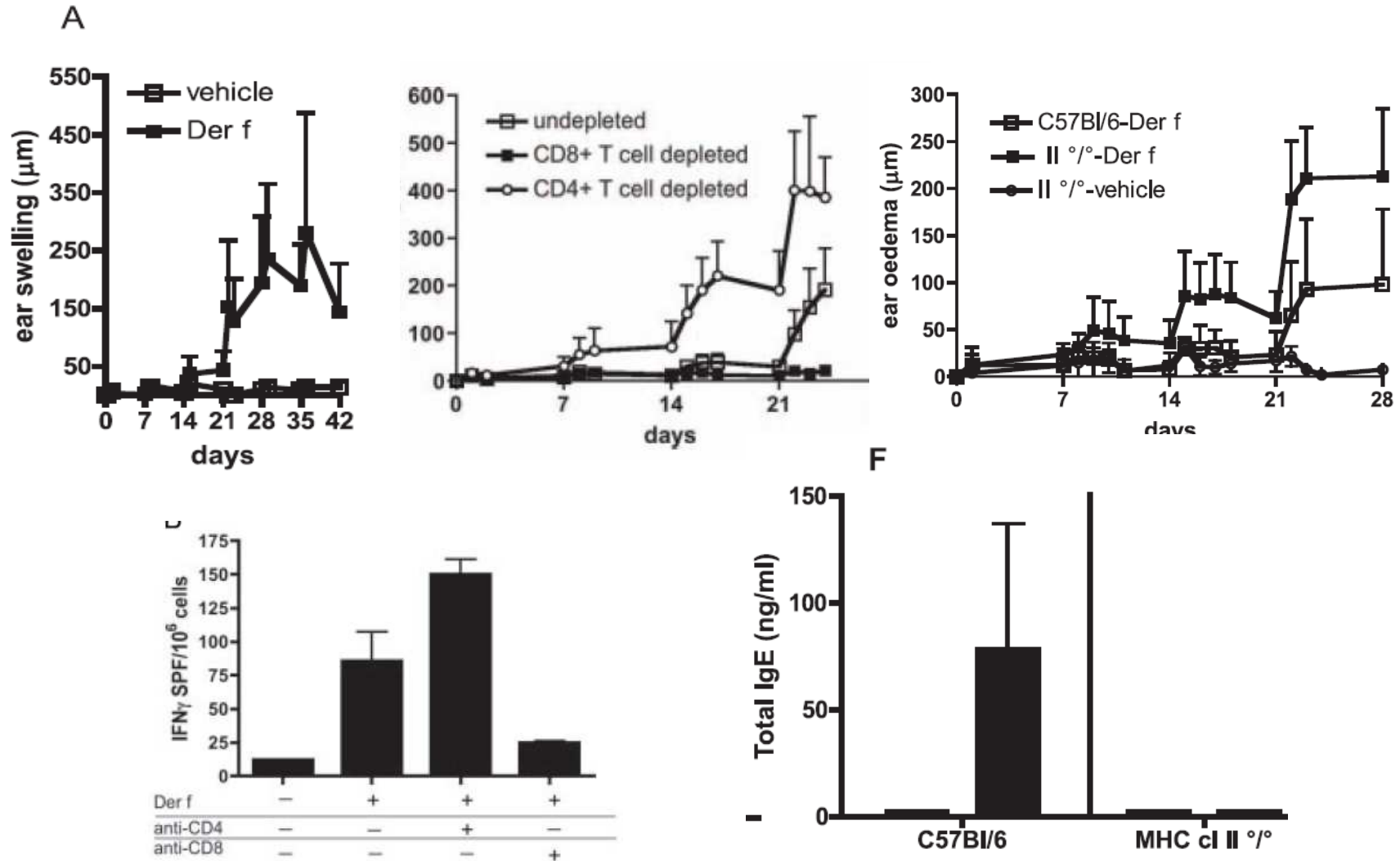
1ere année



7,5 ans

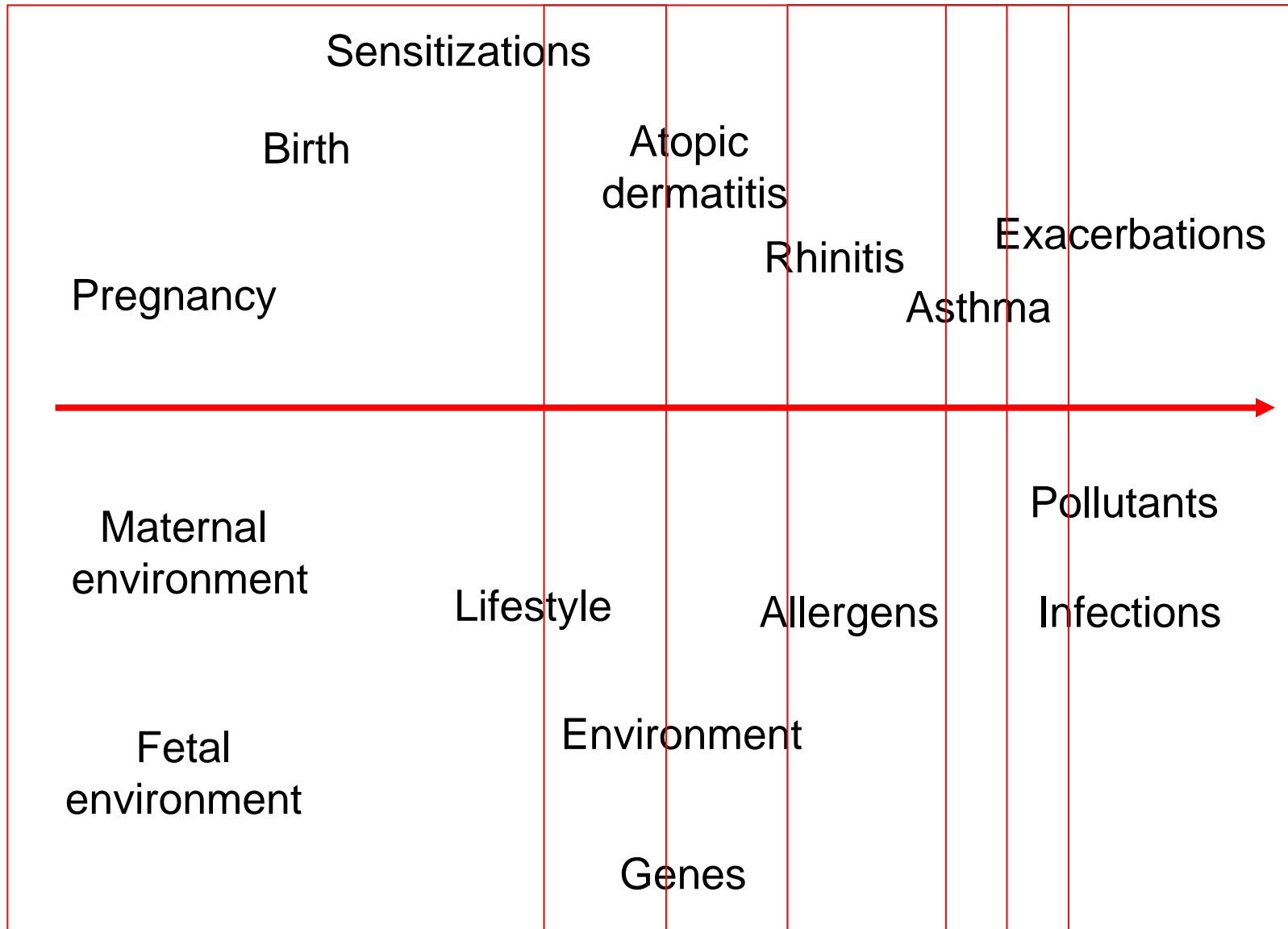


CD8+ cells in atopic dermatitis

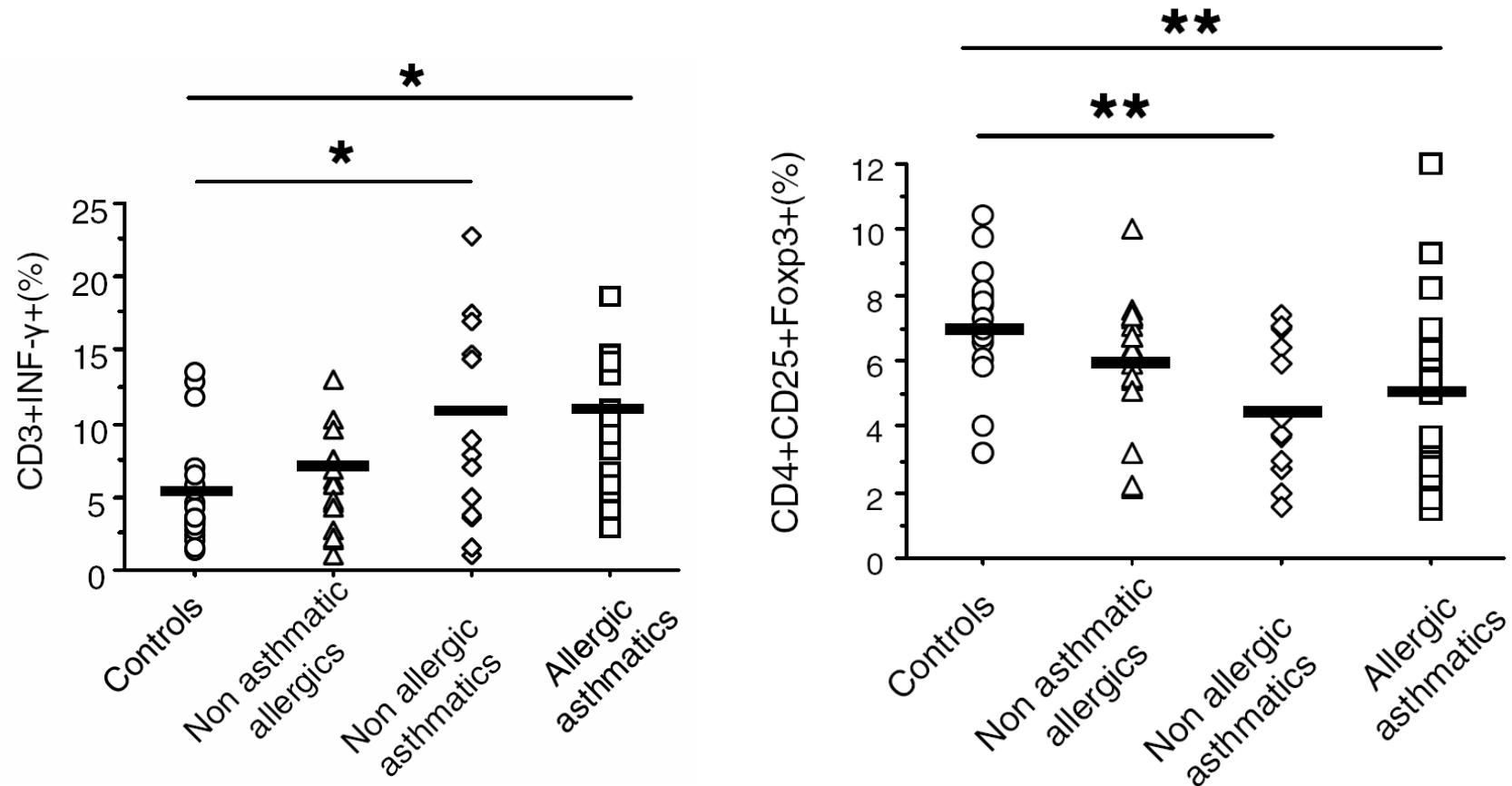


Hennino, Skin infiltrating CD8+ T cells initiate atopic dermatitis lesions, JI 2007

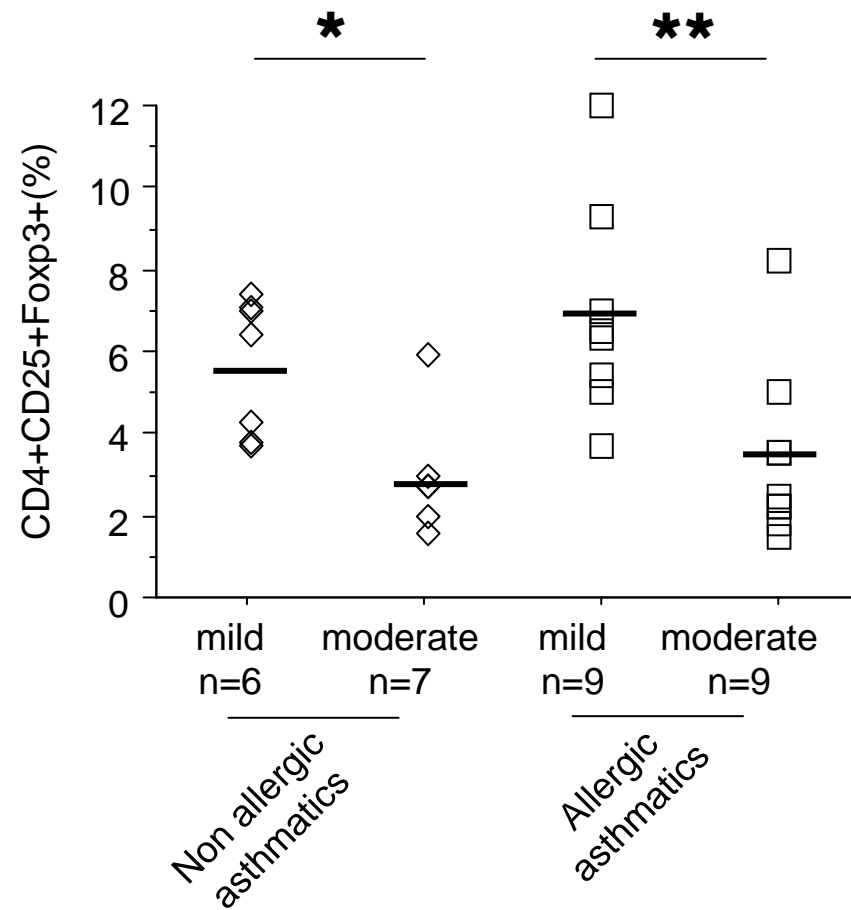
Natural history of atopy



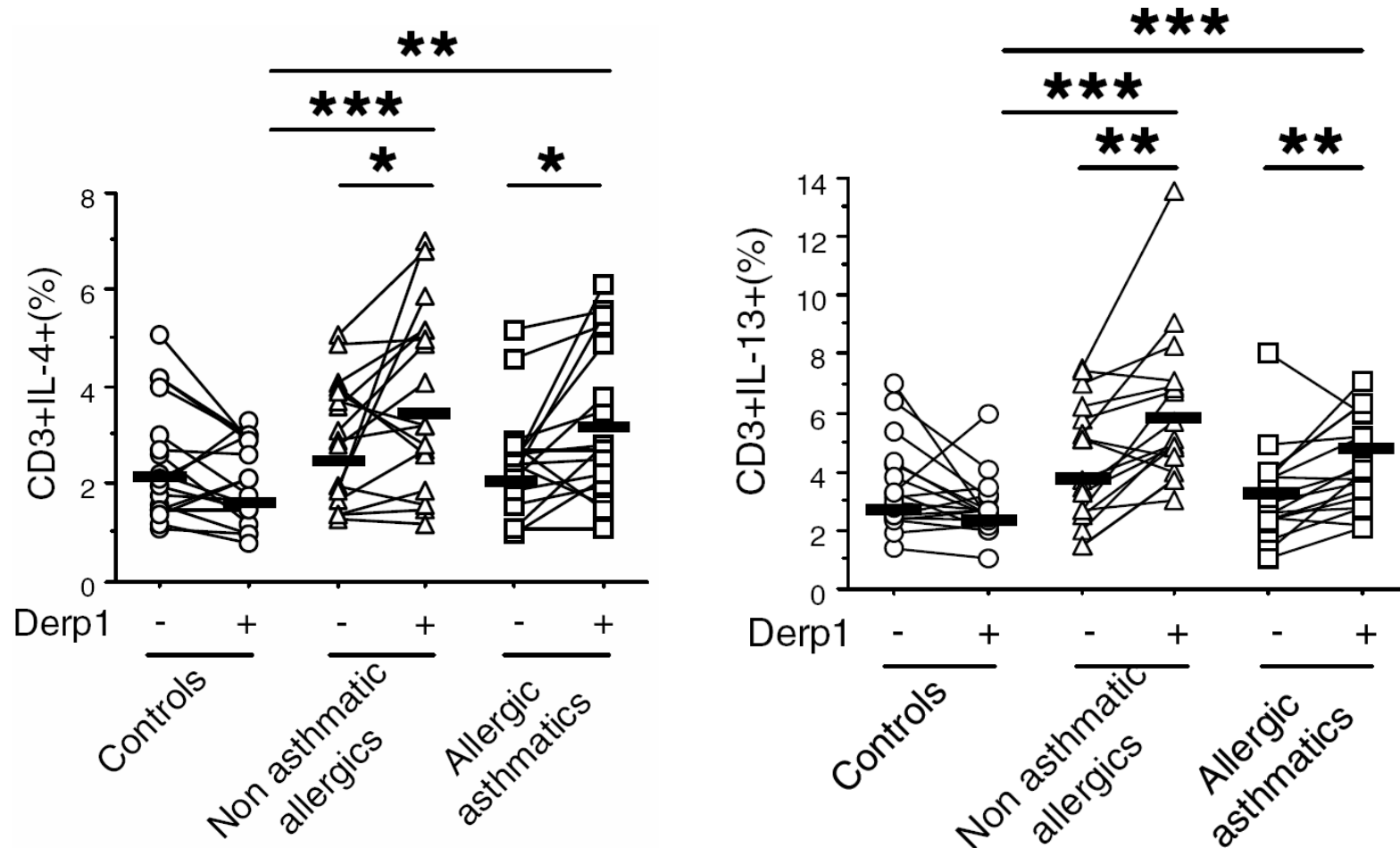
Constitutive Th1/Treg imbalance in asthma



Constitutive Th1/Treg imbalance in asthma

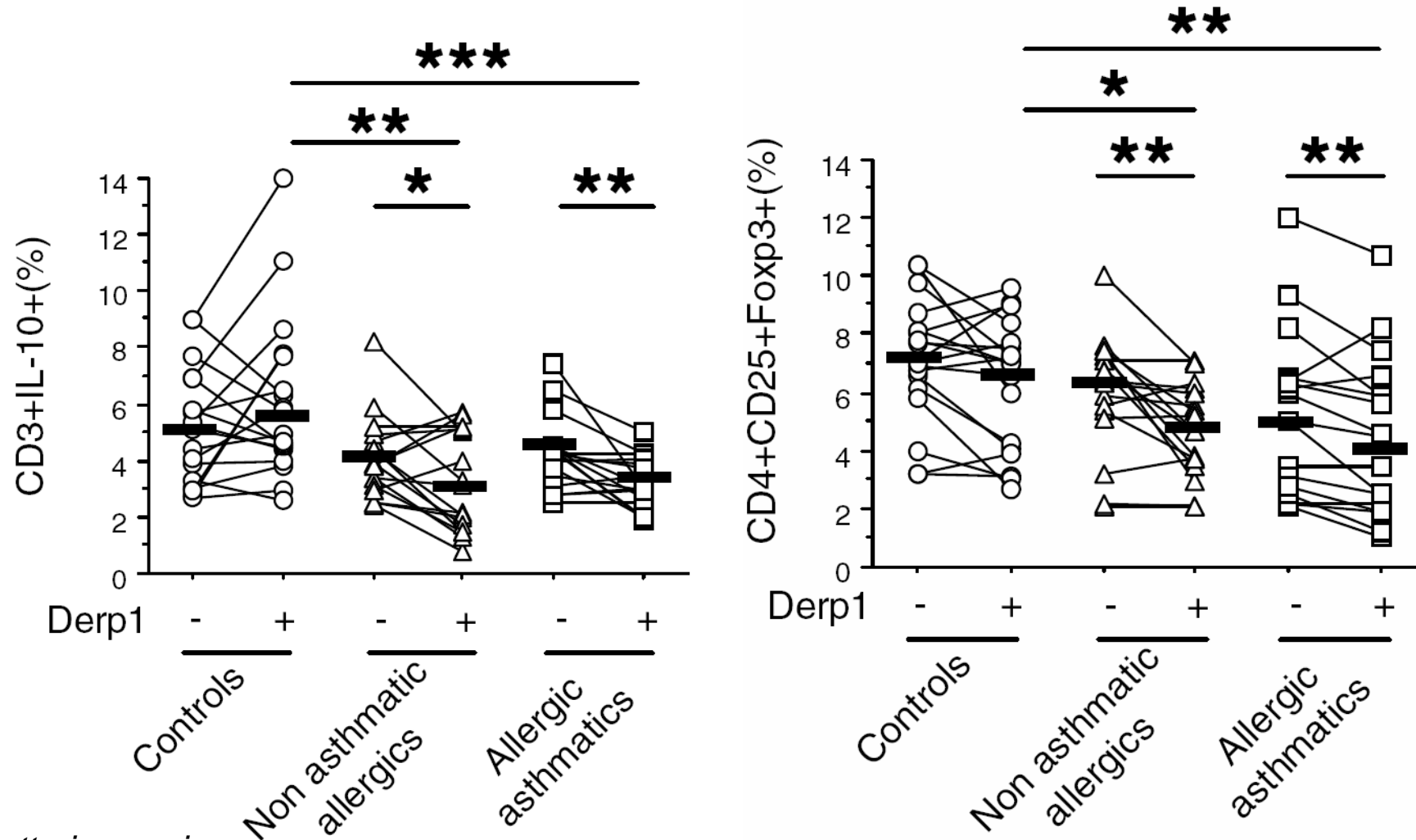


Inducible Th2/Treg imbalance in allergy



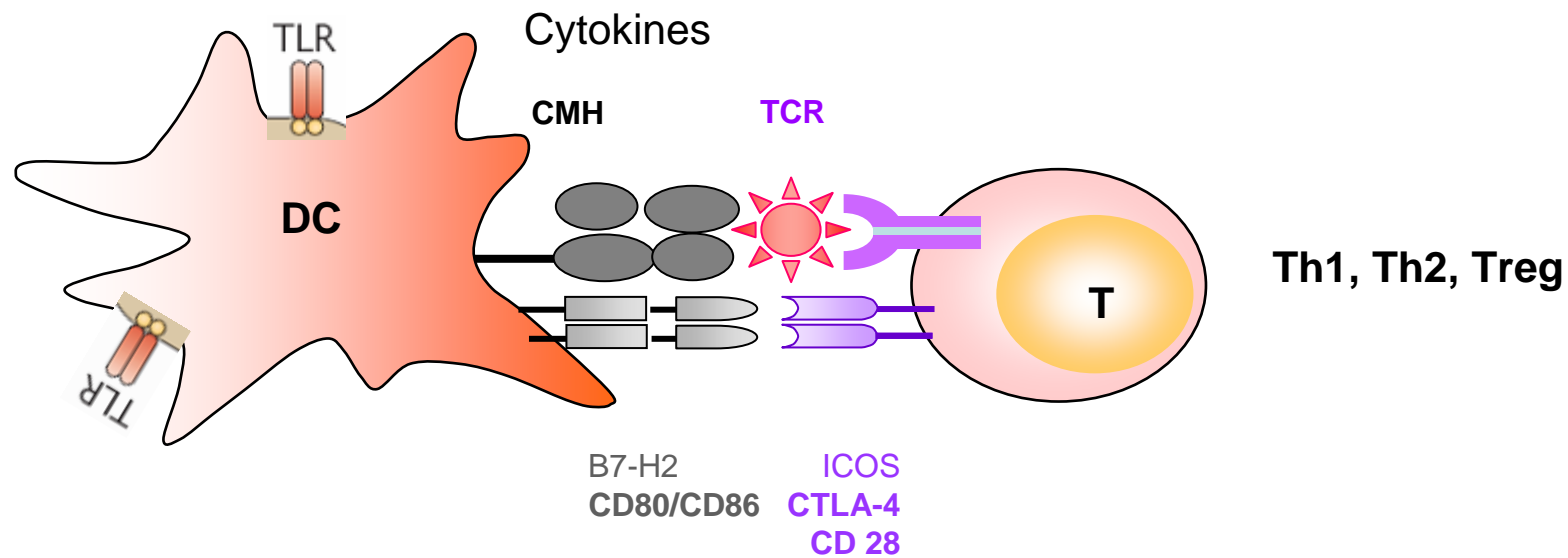
Botturi, soumis

Inducible Th2/Treg imbalance in allergy

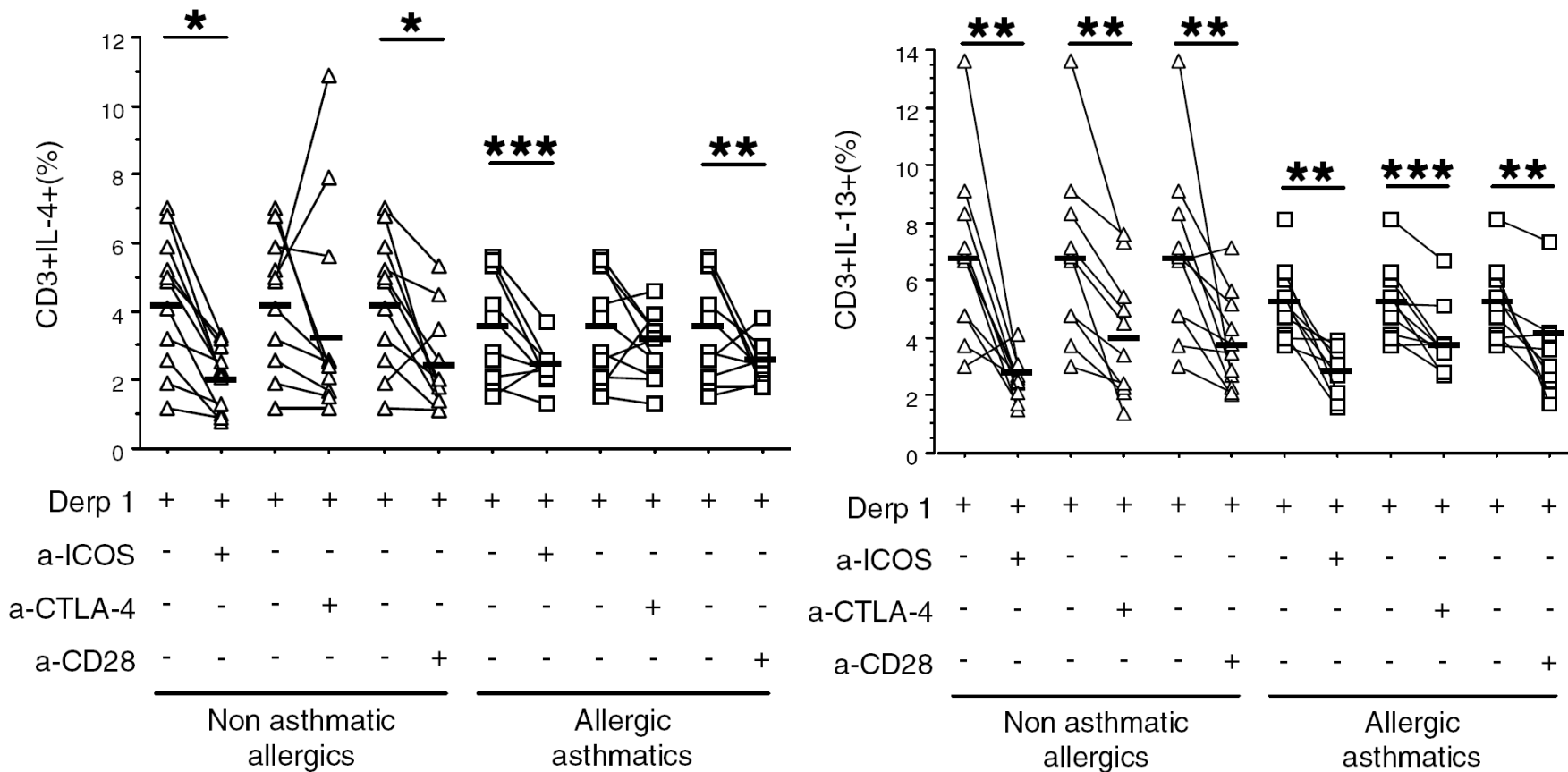


Botturi, soumis

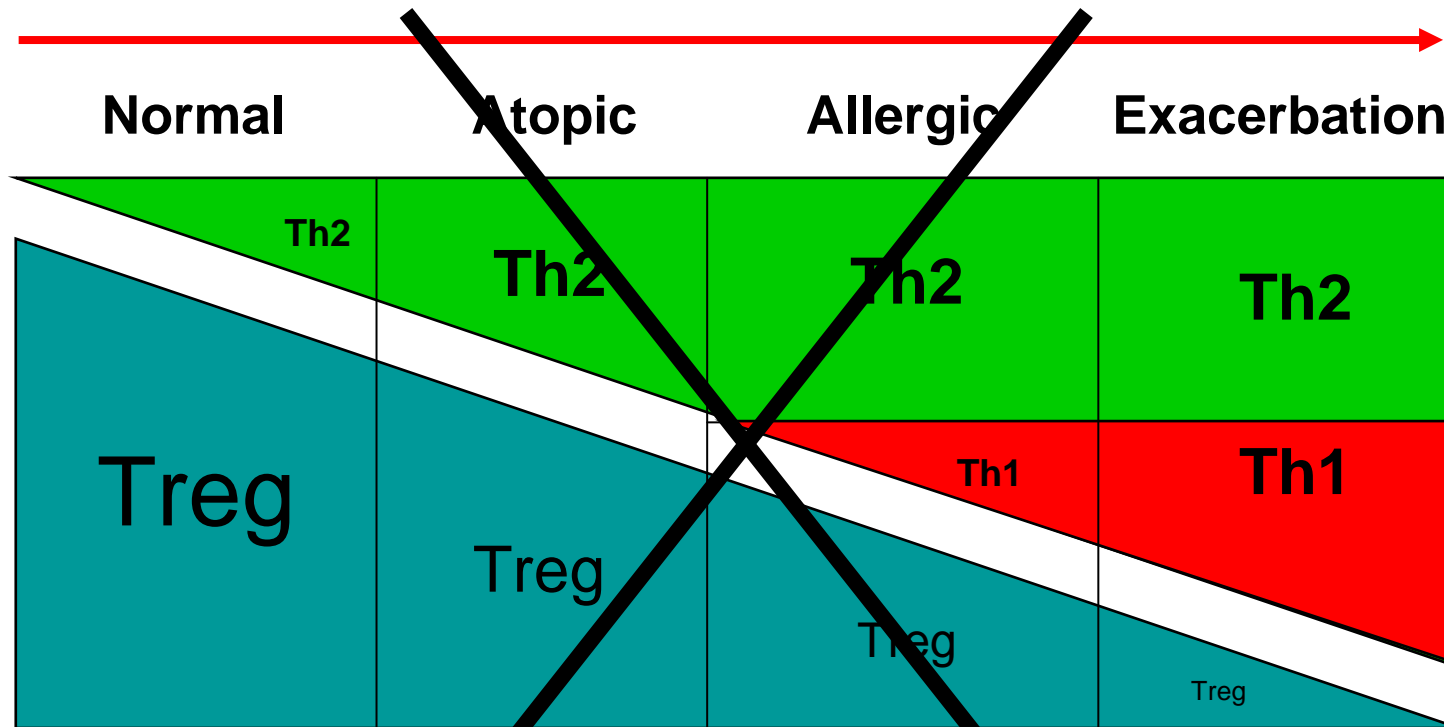
Allergen presentation



Inducible Th2/Treg imbalance in allergy



T cell activation in allergy

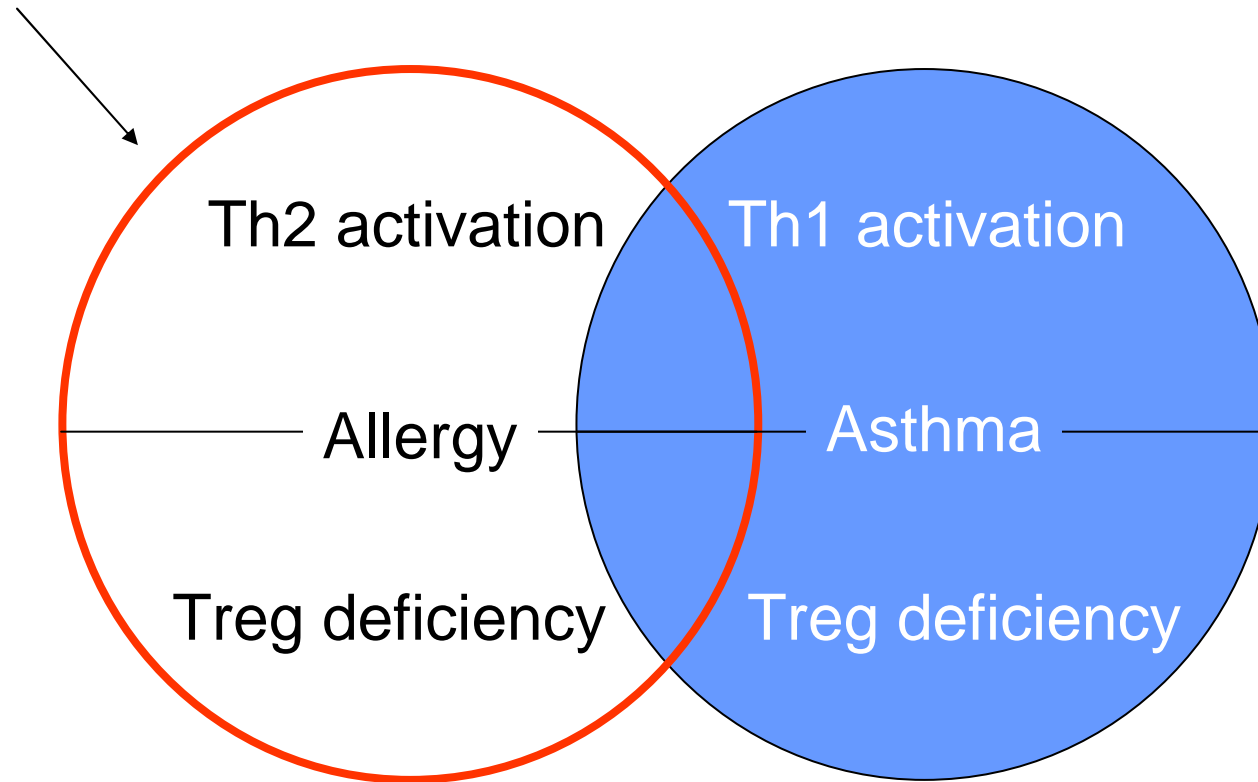


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Magnan A, Humbert M. *Clin Exp Allergy* 2005, 35: 1507-10

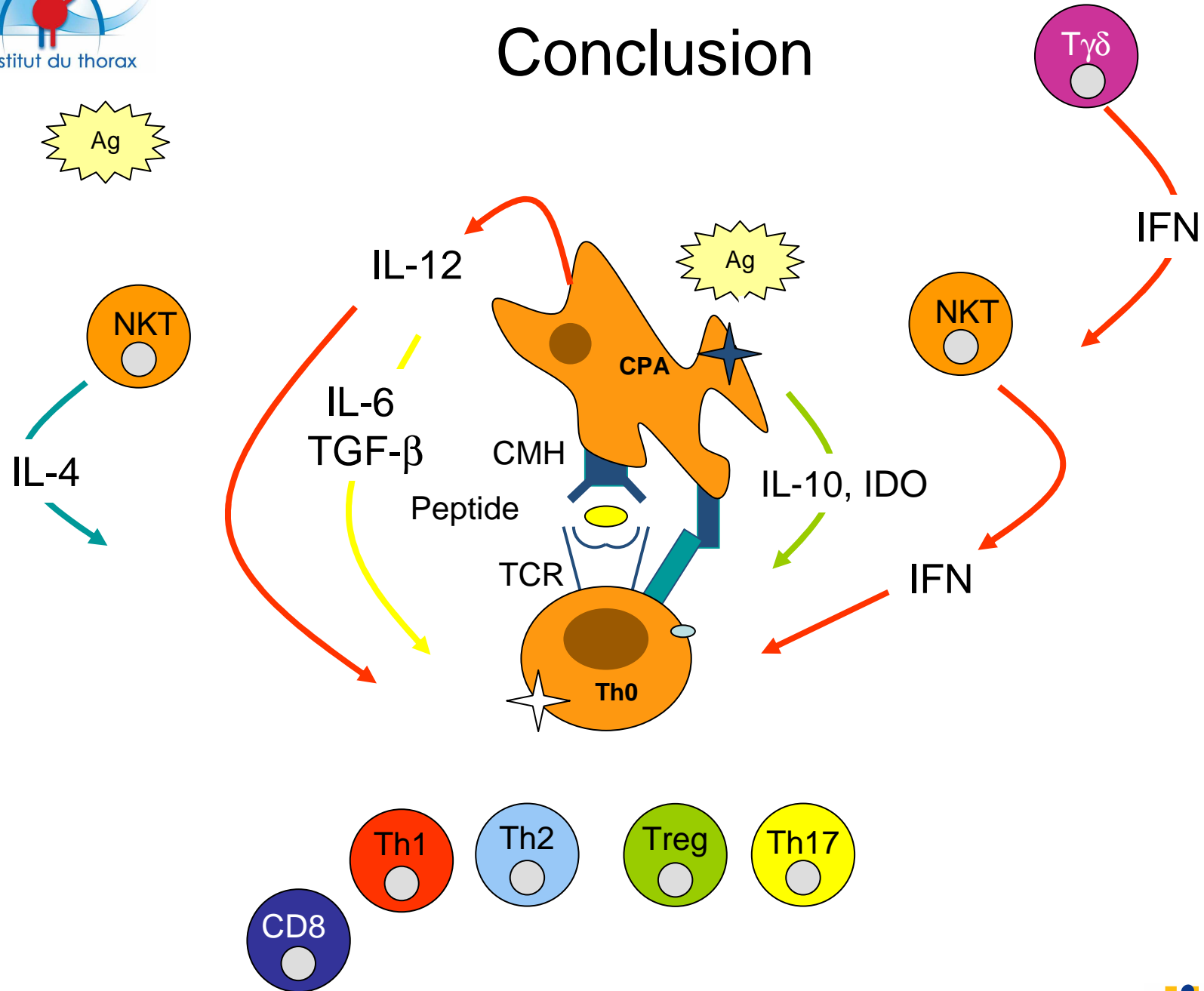
T cell activation in allergy

Allergen stimulation

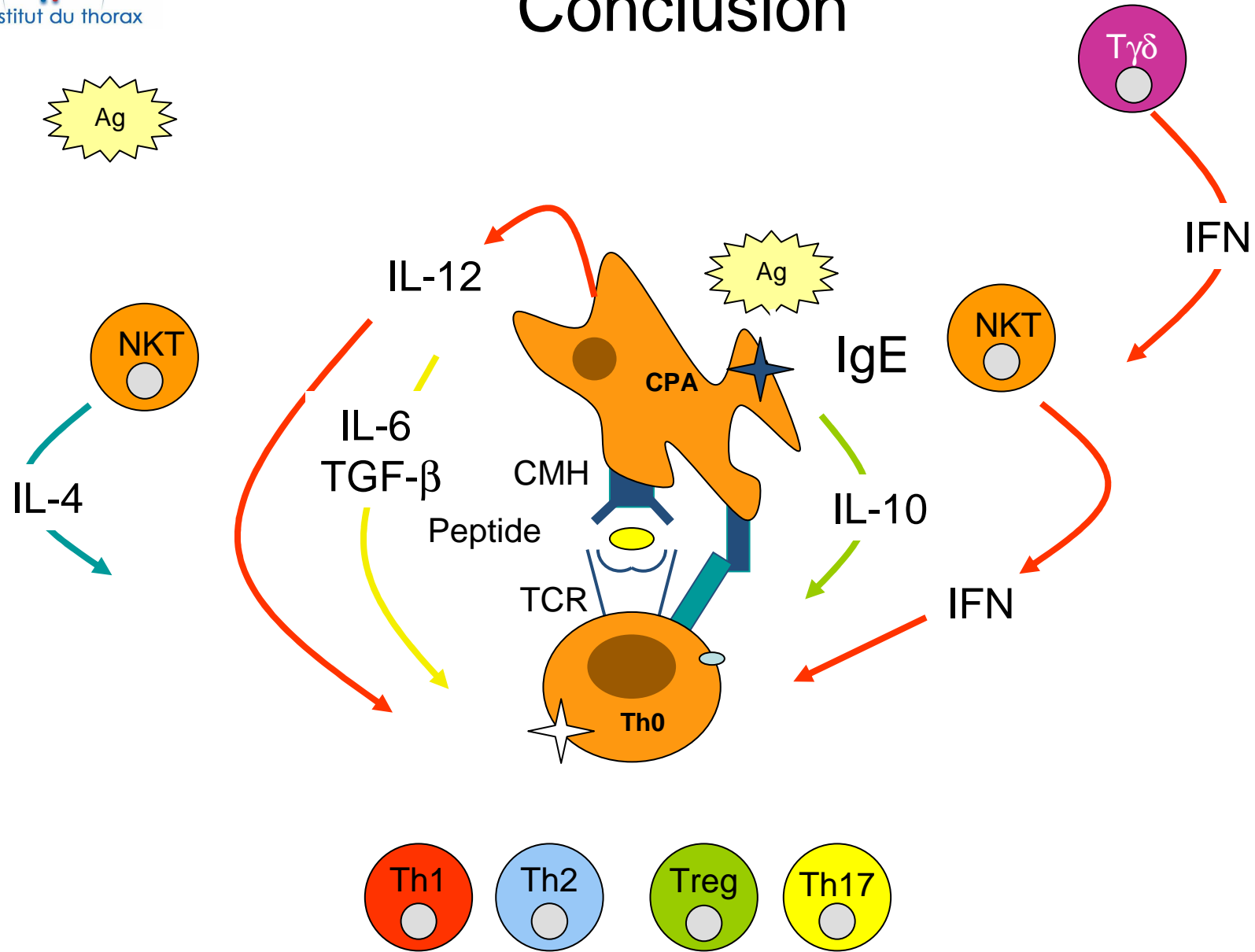


Th2 activation in intrinsic asthma: unknown trigger

Conclusion

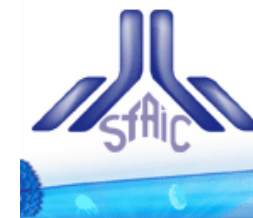


Conclusion



Conclusions

- Investigations in humans are necessary = clinical research and basic research (translational)
- Dynamic approach pivotal:
 - SIT
 - Cypress (seasonal) allergy
 - Cohort studies :
 - Induced sputum (ISEA)
 - identification of relevant subgroups of patients
- Deficient Treg cell activation : cellular therapy ?
- Small T cell populations (NKT, Th17, $\gamma\delta$...): future targets ?



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