

# Cellular and Molecular Mechanisms of Allergic Diseases

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(SIAF)

## **Two types of allergic diseases-I**

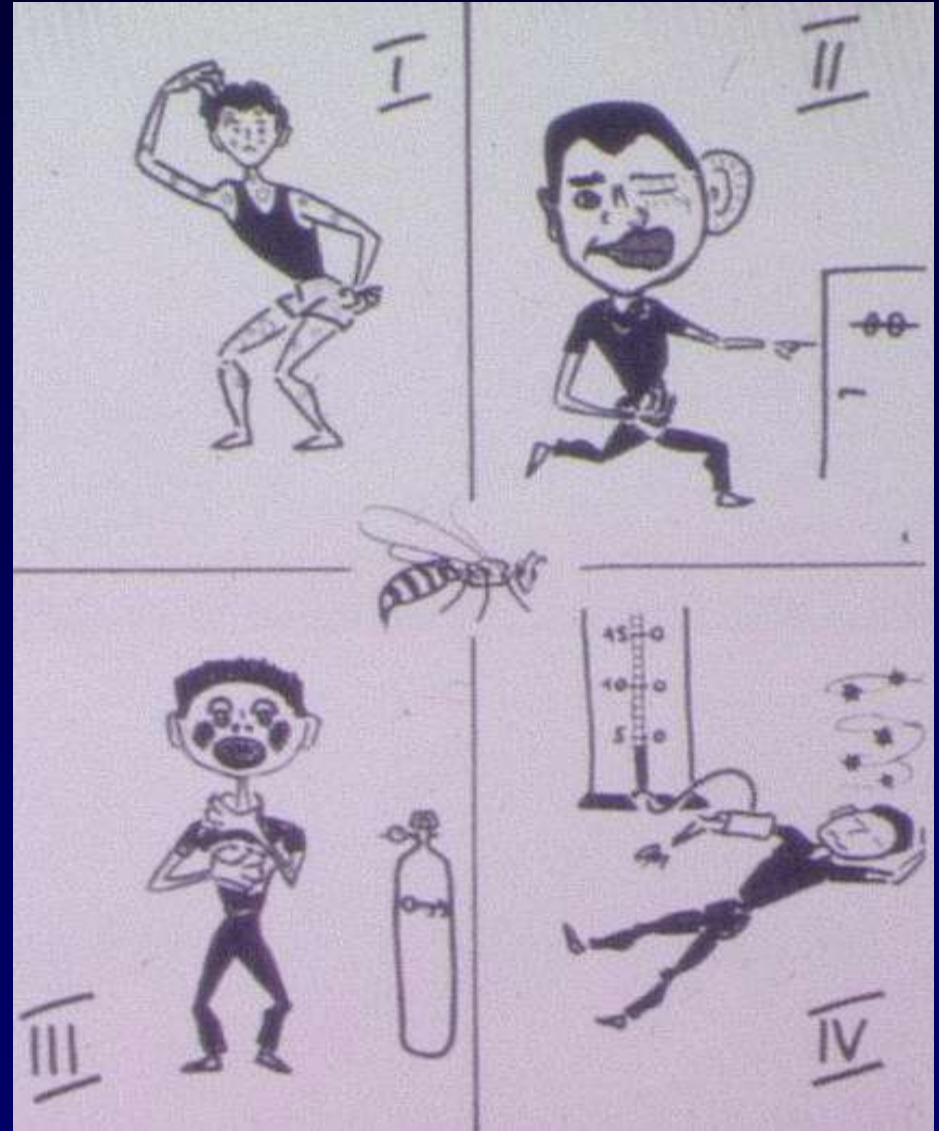
monoallergy (allergic breakthrough)

high specific IgE without atopy

high success of allergen-SIT

in most cases no typical organ involvement  
venom allergy

# Insect venom allergy





The first recorded death from an insect allergy was King Menes of Egypt, who, according to the hieroglyphics on his tomb, died of a wasp sting in 2621 B.C.

# Two types of allergic diseases -II

polyallergic and inflammatory  
atopic diseases (true atopy)

dermatitis, asthma, rhinitis

high total IgE,  
high specific IgE to many allergens,  
eosinophilia



A typical family history of atopy

Emperor Augustus: suffered from bronchial asthma, seasonal rhinitis and atopic eczema

Emperor Claudius: perennial rhinoconjunctivitis

Britannicus: horse dander allergy





King Richard III (1452-1485) used his allergy to strawberries to arrange the murder of Lord William Hastings.

He ate some strawberries and developed acute urticaria.

He then accused Hastings of putting a curse on him, an action that demanded the head of Hastings on a plate.

activation

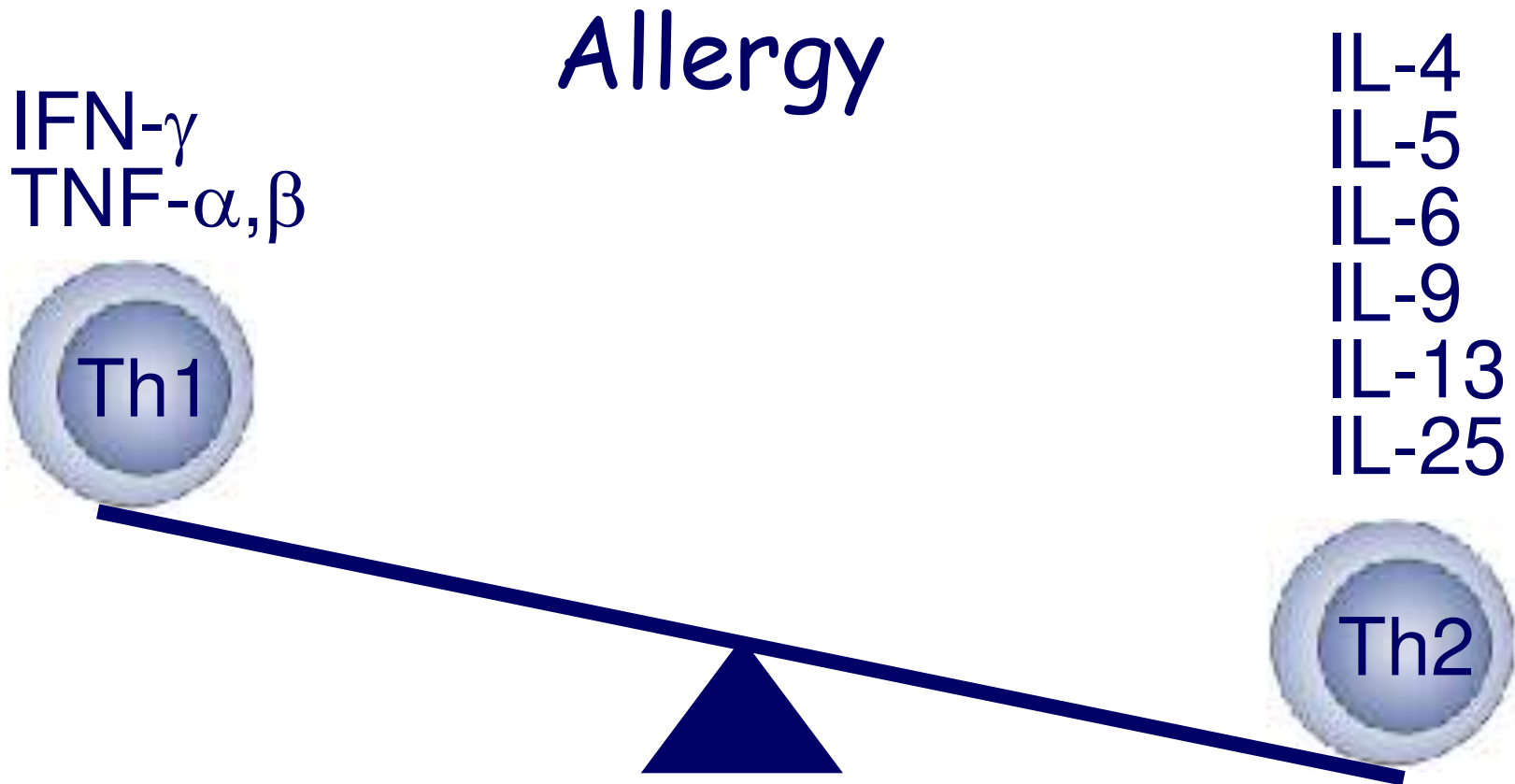
survival  
and  
reactivation

allergic  
inflammation

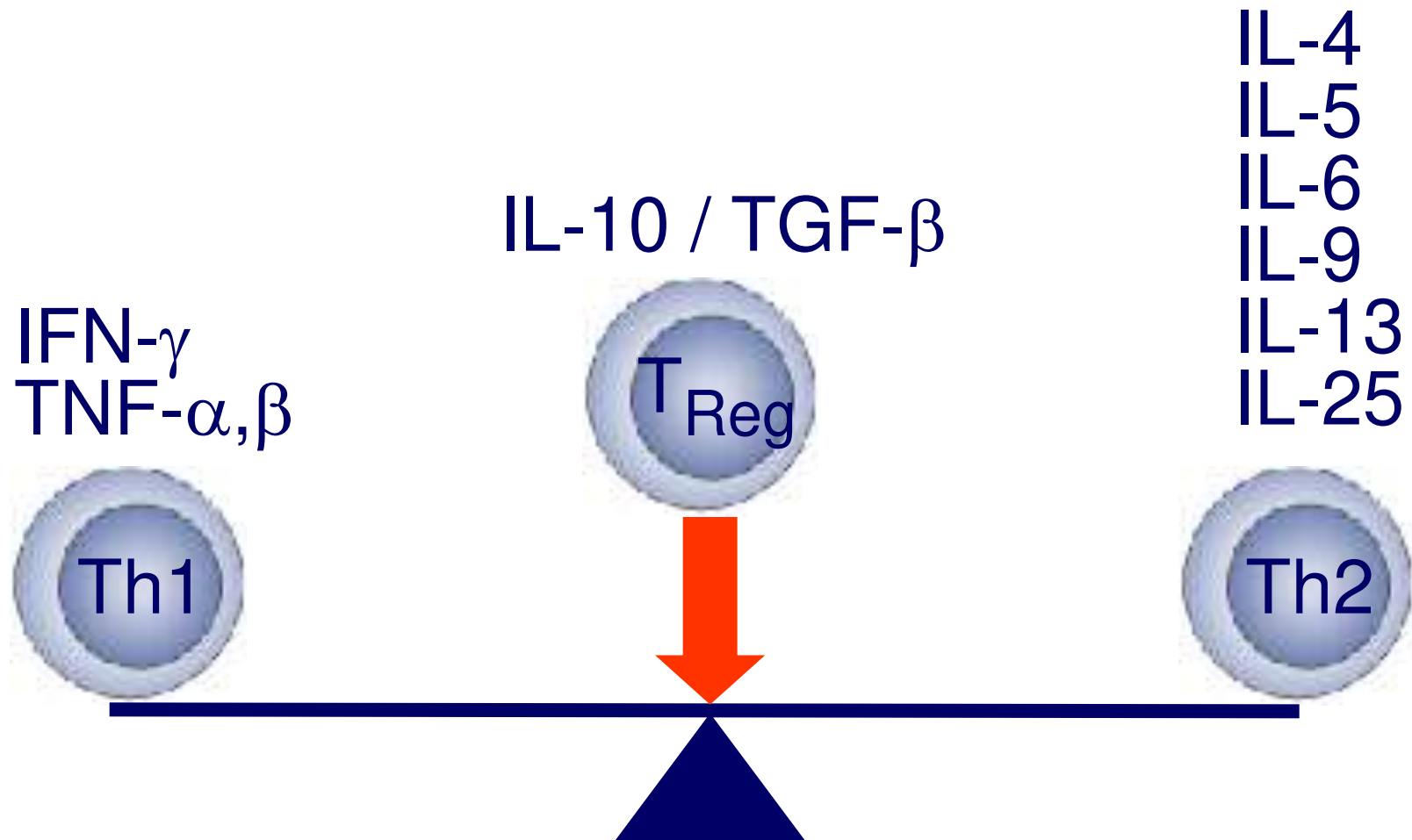
homing

effector  
functions

# Th1 and Th2 cell balance in disease



# Th1 and Th2 cell balance in homeostasis



# Major Functions

IL-10 / TGF- $\beta$

IFN- $\gamma$   
TNF- $\alpha, \beta$



IL-4  
IL-5  
IL-6  
IL-13



DTH  
Macrophage  
activation  
limited B cell  
help/inhibition

inhibition of Th1 Th2 cells  
inhibition of mo/mac  
inhibition of DC maturation

B cell help  
eosinophil  
mast cell stim.  
macrophage  
inhibition

Apoptosis: programmed cell death  
activation-induced cell death

essential mechanism in homeostasis

In atopic dermatitis and asthma, cells  
involved in the pathogenesis show different  
survival and apoptotic properties

Proliferation/  
Survival

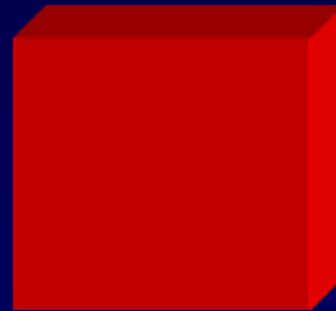
Death

Survival



Apoptosis

Survival



Apoptosis

Survival

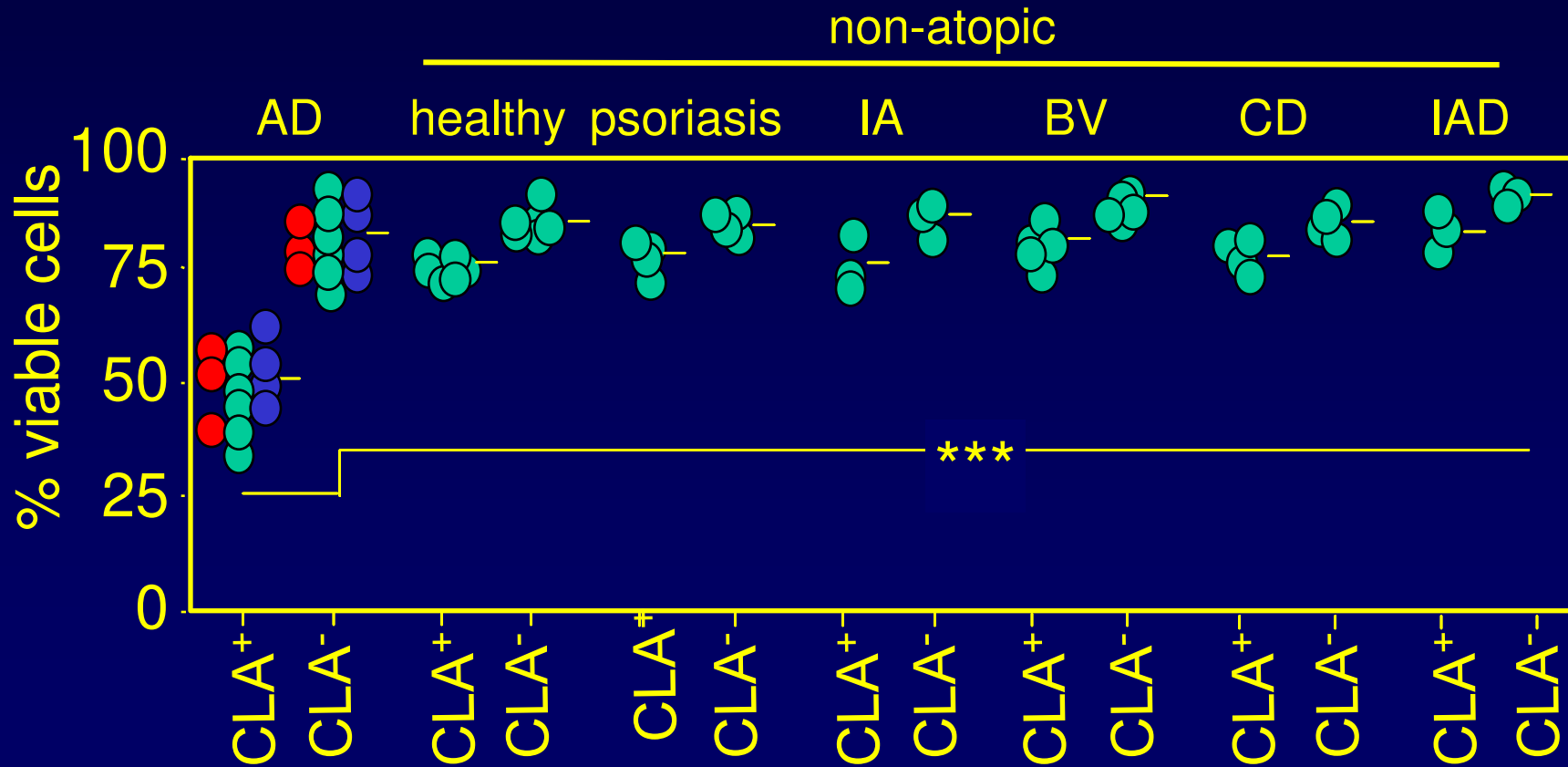


Apoptosis

# Cutaneous lymphocyte-associated antigen-bearing skin homing T cells (CLA+)

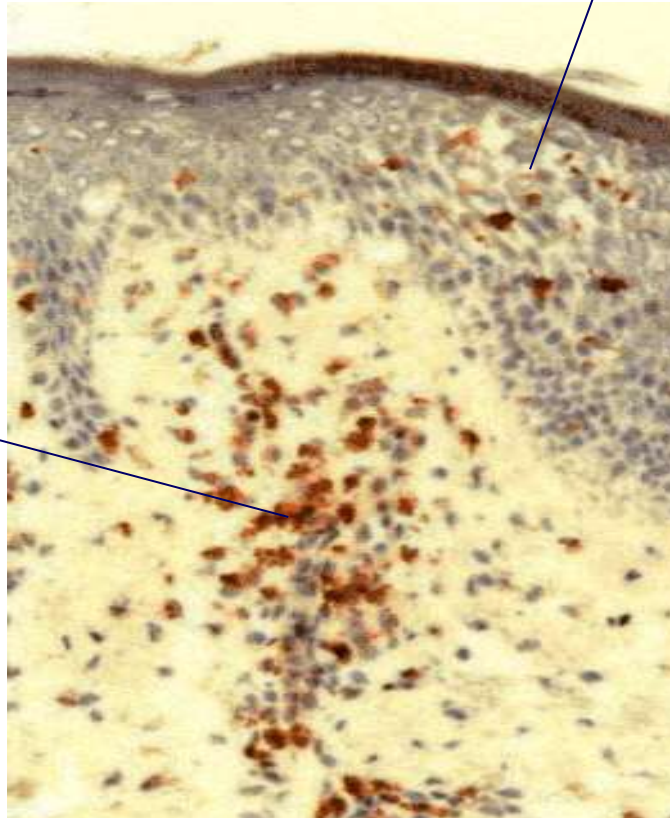
- In vivo activated
- Spontaneously proliferating
- Th2-like cytokine profile (IL-5, IL-13)
- Induce IgE (IL-13)
- Prolonged eosinophil life span (IL-5)

# Increased death of circulating CLA<sup>+</sup> T cells in AD



# Histopathology of AD

eczema/spongiosis



dermal  
mononuclear  
cells

70 % T cell

1-3 % Eosinophil

10-20 % Dendritic cell

CD4/CD8 ratio: 2

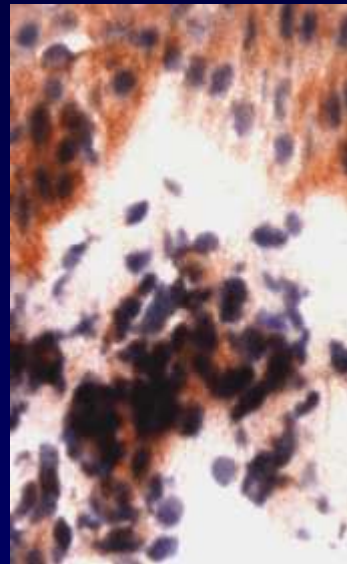
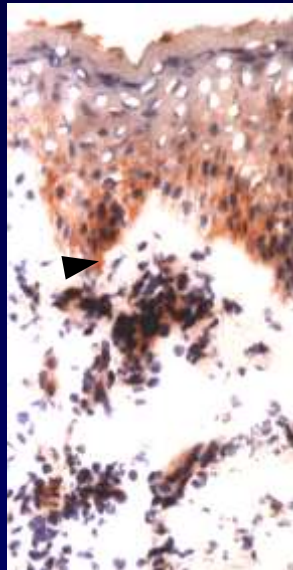
effector functions

survival/reactivation

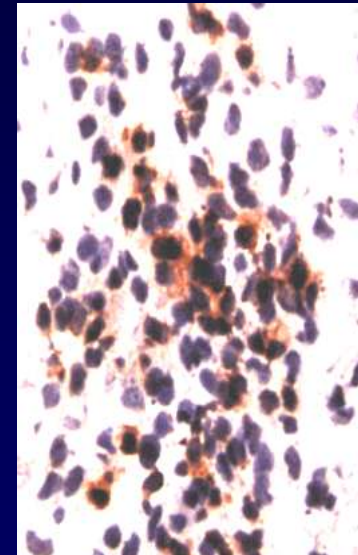
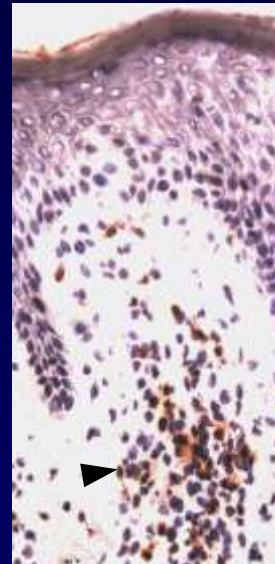
activation/homing

Skin T cells do not die  
although they express  
both Fas and Fas-ligand in AD

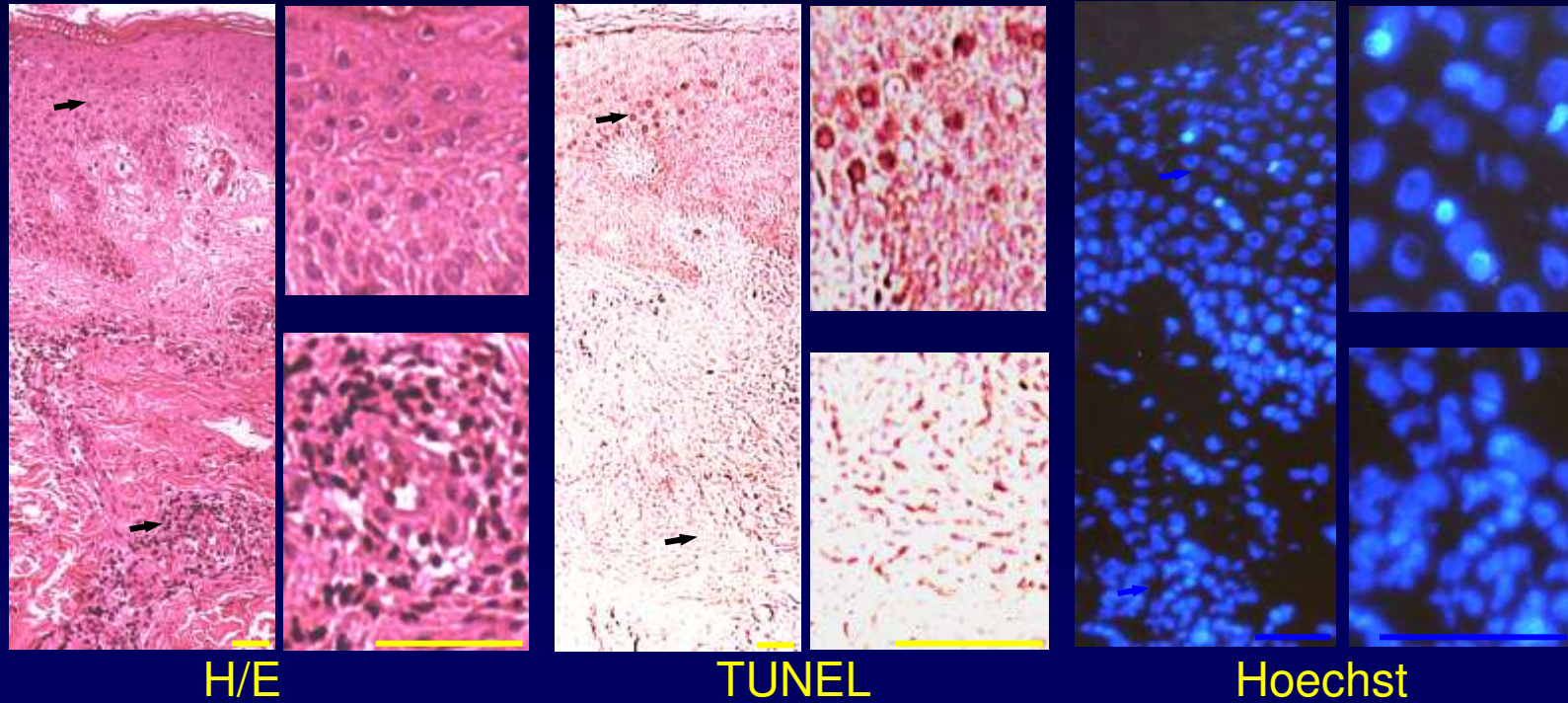
Fas



Fas-ligand

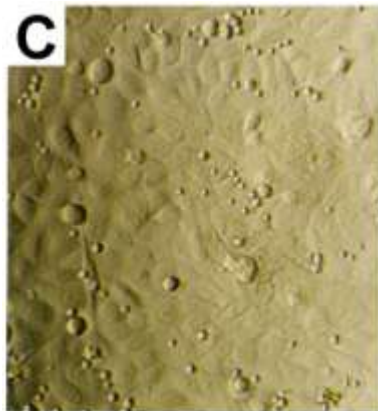


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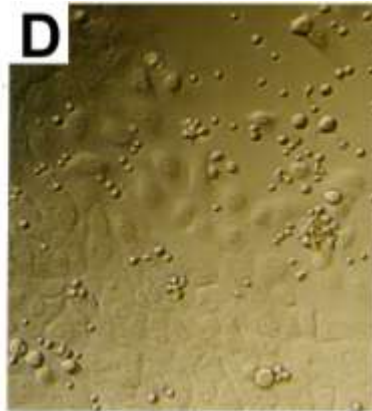




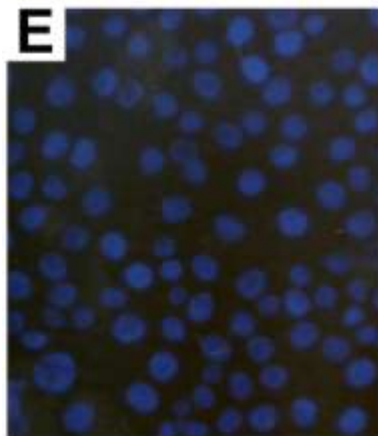
resting T cells



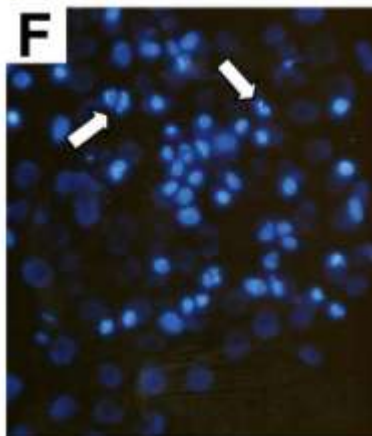
activated T cells



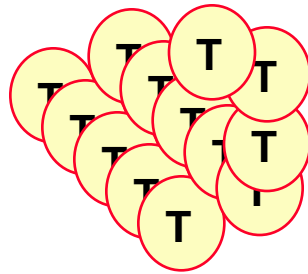
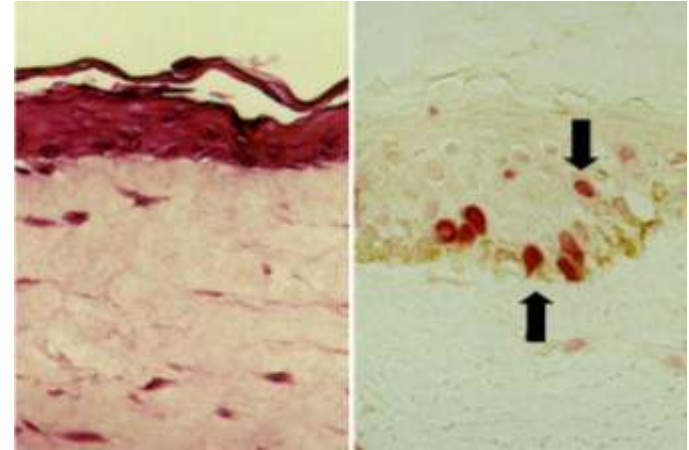
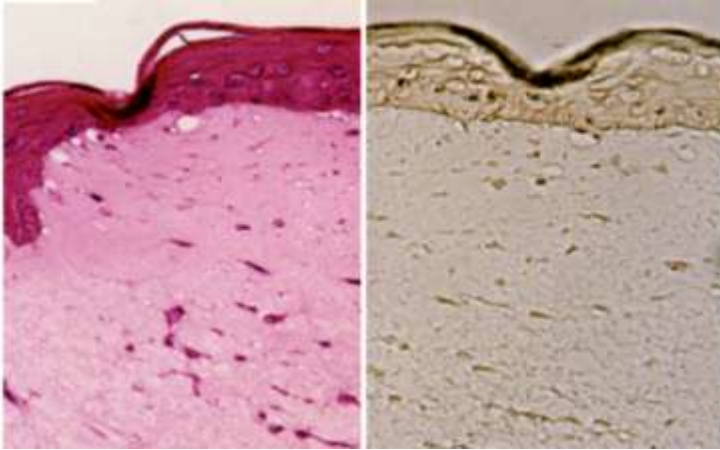
no apoptosis



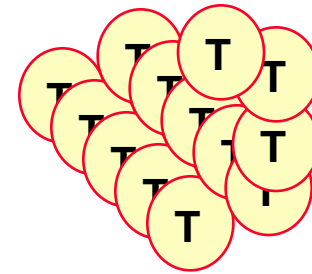
apoptosis



IFN- $\gamma$   
Fas-ligand  
TNF- $\alpha$



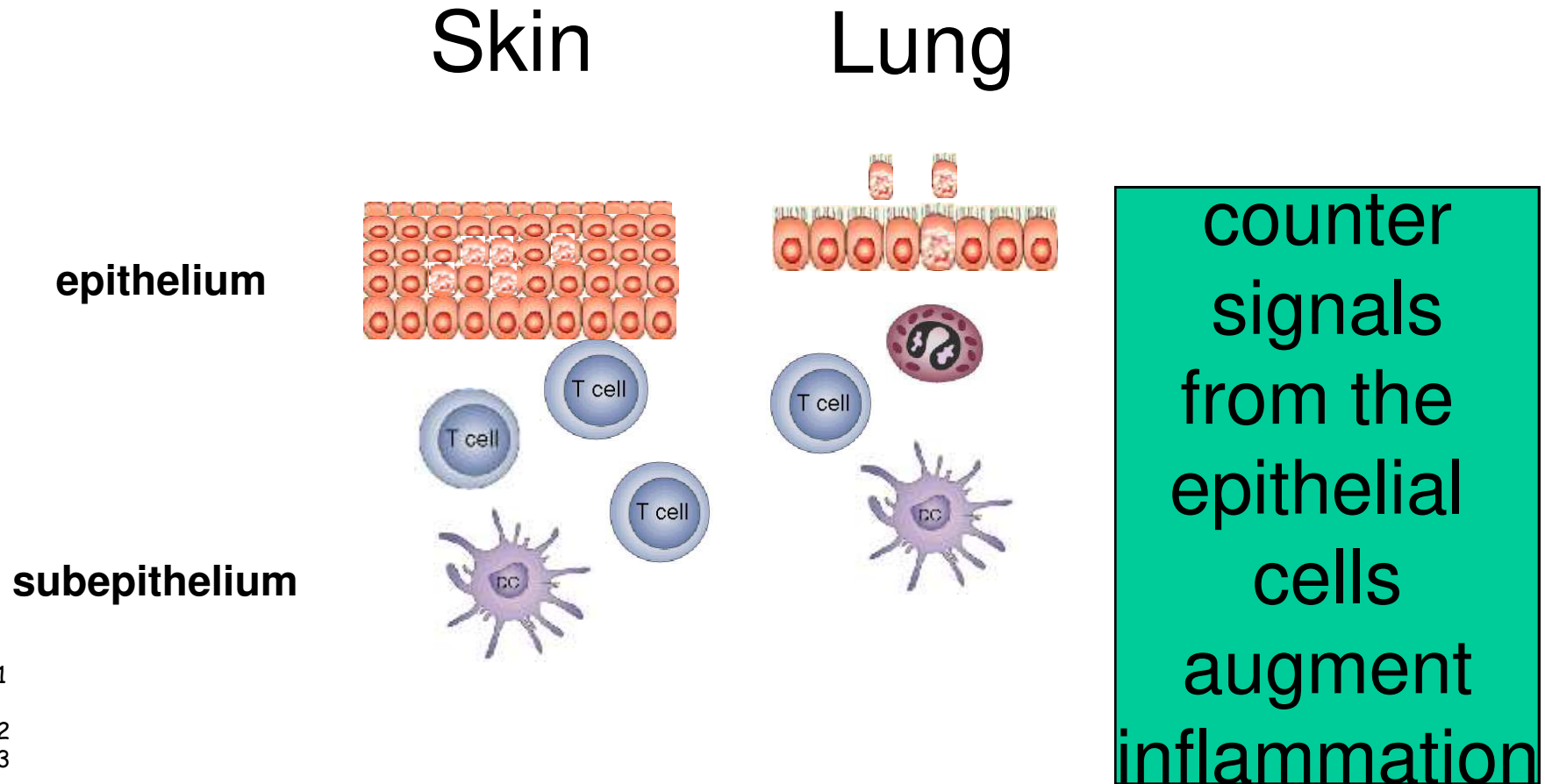
resting T cells



↑ IFN- $\gamma$   
Fas-ligand  
TNF- $\alpha$

activated T cells

# Activation and apoptosis of epithelial cells induced by subepithelial inflammation



key pathogenetic event in atopic dermatitis and asthma

- J Immunol 1997
- J Immunol 1999
- EJI 2000
- J Clin Invest 2000
- Curr Opin Imm 2000
- Trends Imm 2001
- J Allergy Clin Imm 2001
- J Invest Derm 2001
- J Allergy Clin Imm 2002
- J Allergy Clin Imm 2003
- J Immunol 2003
- Faseb J 2003
- Curr Opin Imm 2004
- J Allergy Clin Imm 2005
- J Allergy Clin Imm 2006
- Curr Opin Imm 2006

allergy: intolerance to allergens

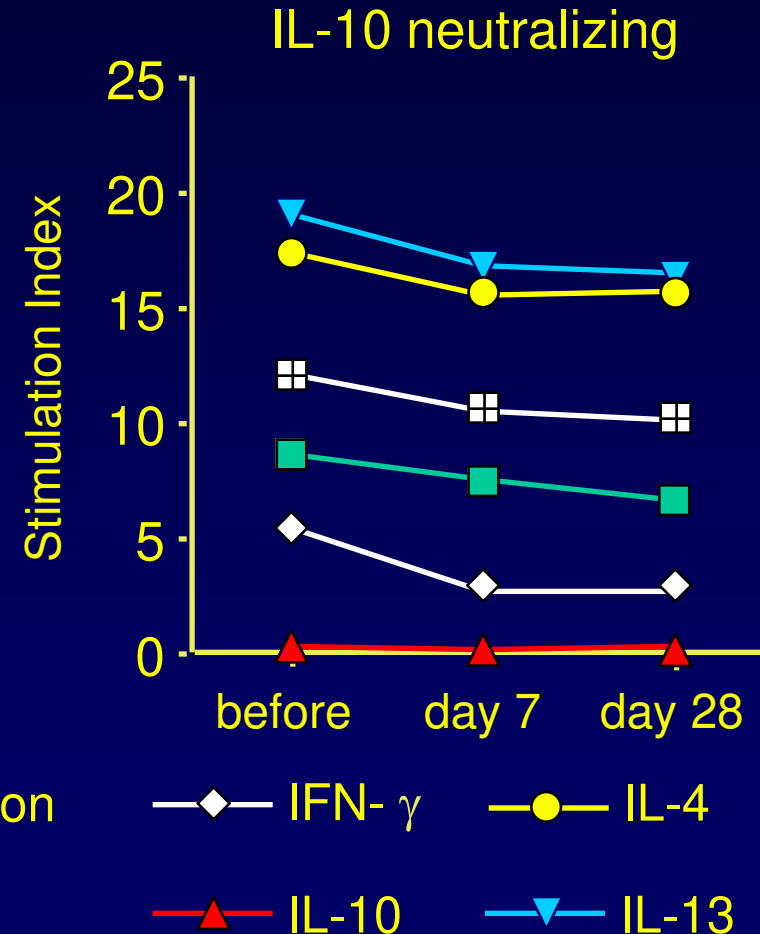
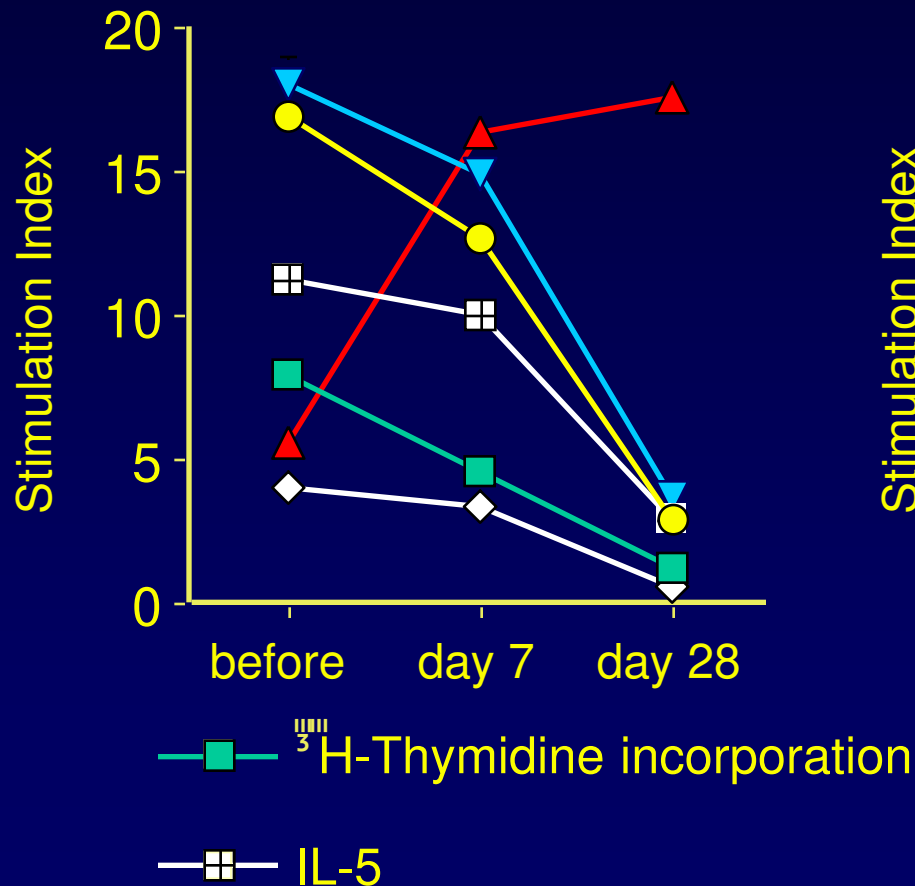
autoimmunity: intolerance to autoantigens

transplantation rejection: intolerance to transplanted organ

chronic infection: neutralization defect of infectious agents because of tolerance

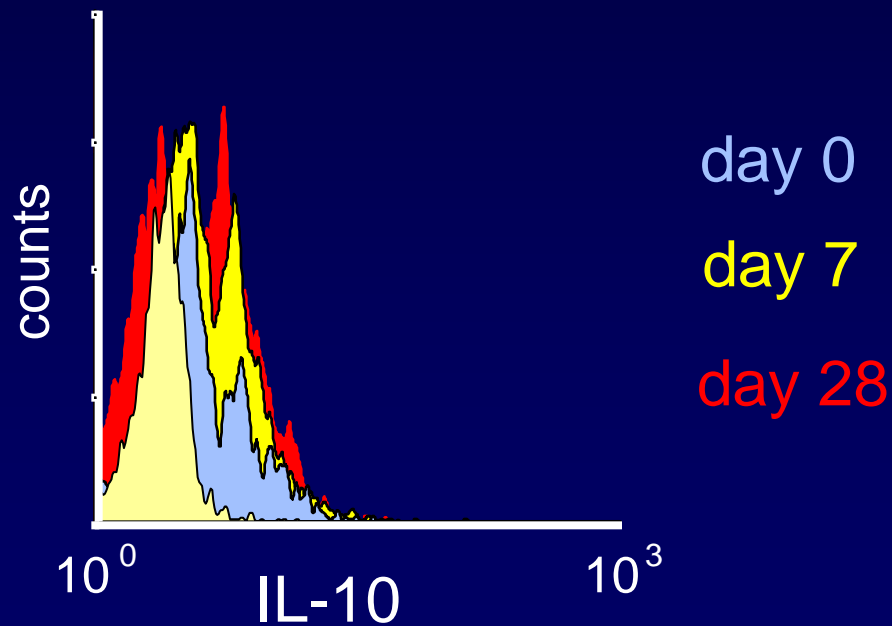
cancer: inappropriate immune response to tumor antigens because of tolerance

# IL-10-induced peripheral T cell tolerance in bee venom specific-immunotherapy

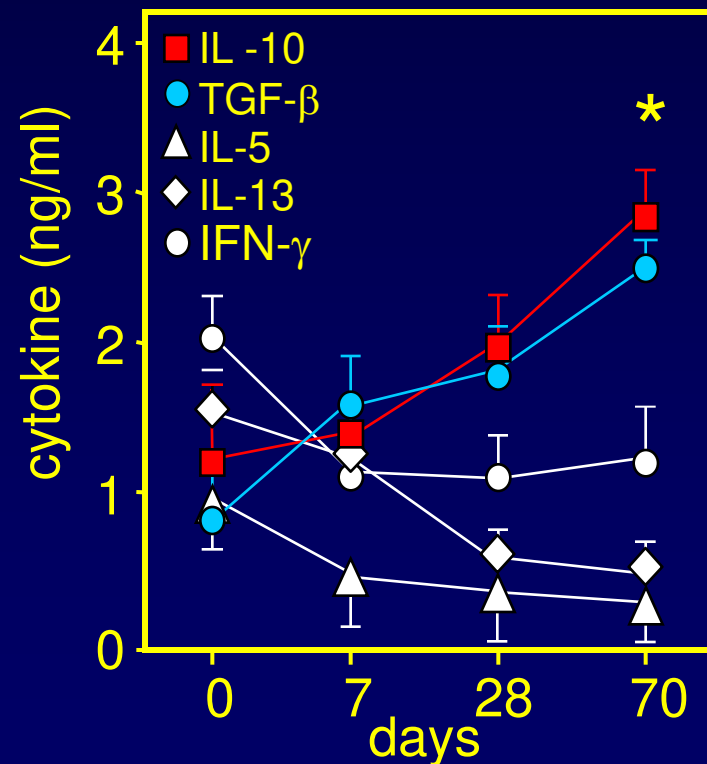


# IL-10 production in T cells during specific immunotherapy

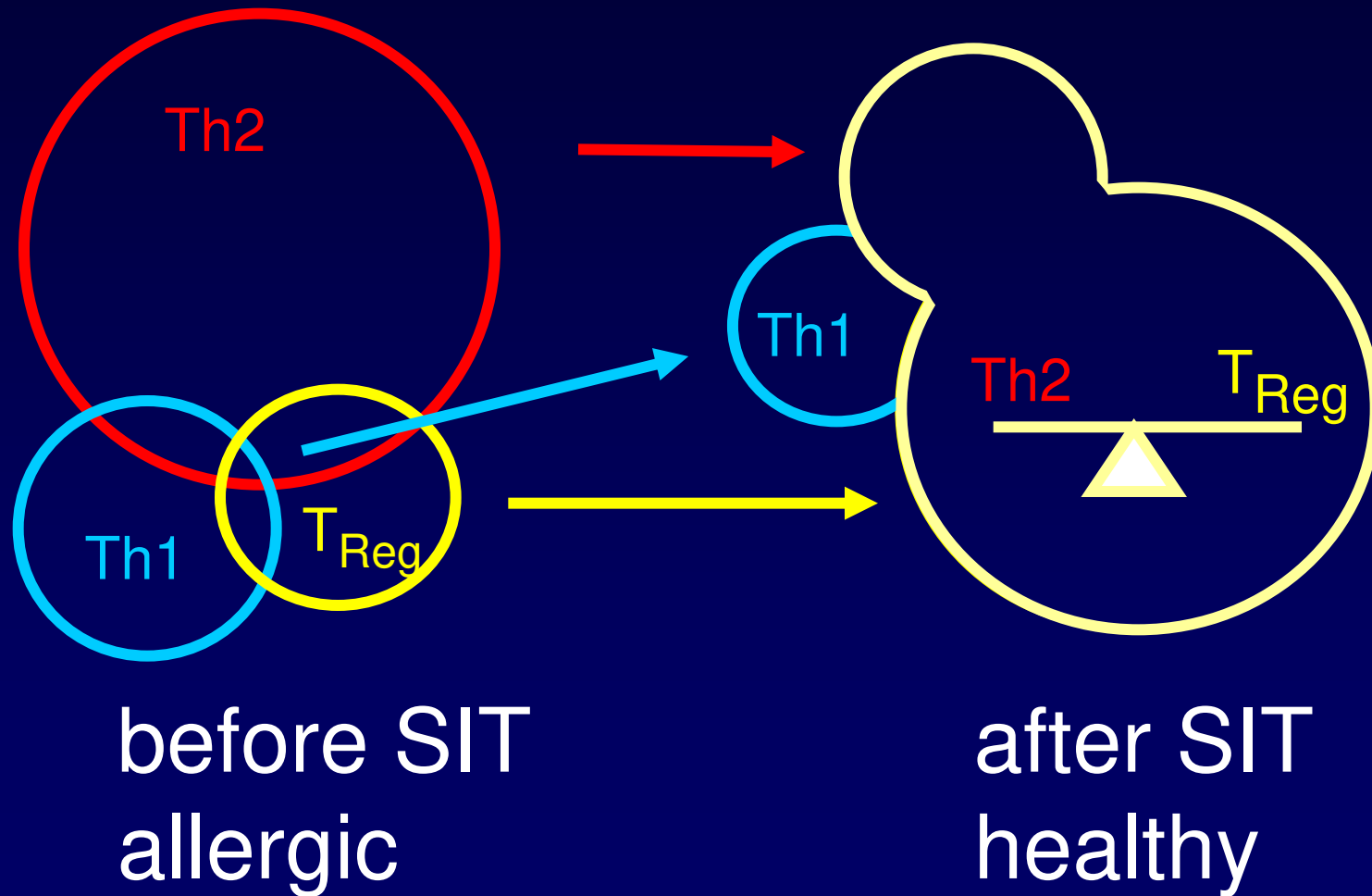
CD4<sup>+</sup> CD25<sup>+</sup> T<sub>reg</sub> cells



# IL-10 and TGF- $\beta$ in peripheral T cell tolerance during aeroallergen SIT



# $T_{Reg}$ cells in allergy: a question of balance



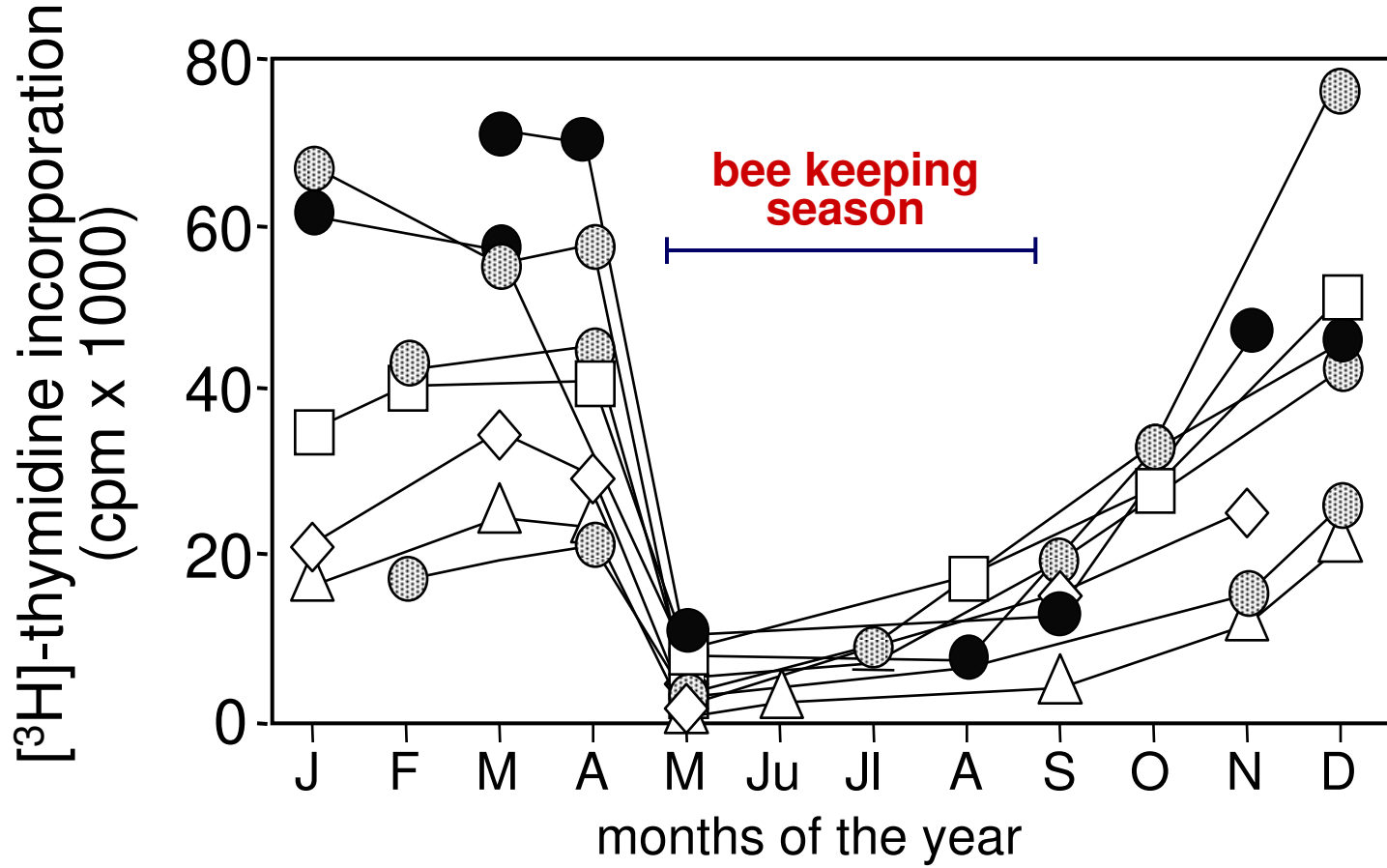
IL-10-mediated peripheral T cell  
tolerance during natural bee stings

a model for  
natural high dose antigen/allergen  
exposure

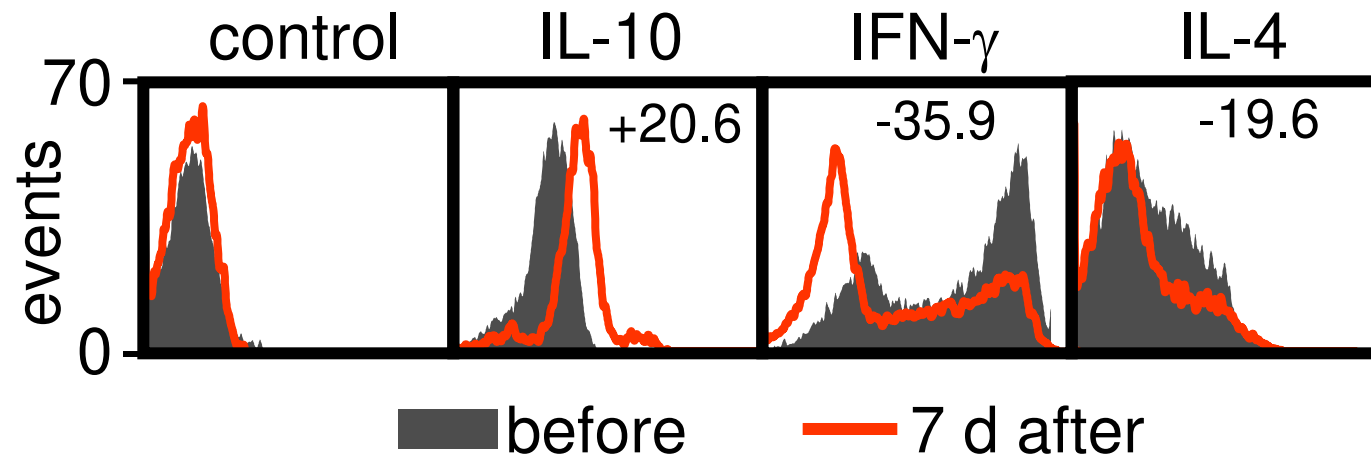
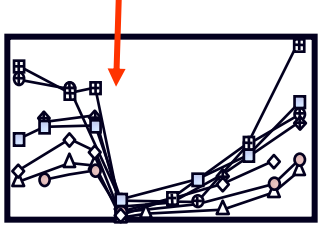
more than 20 bee stings in one week



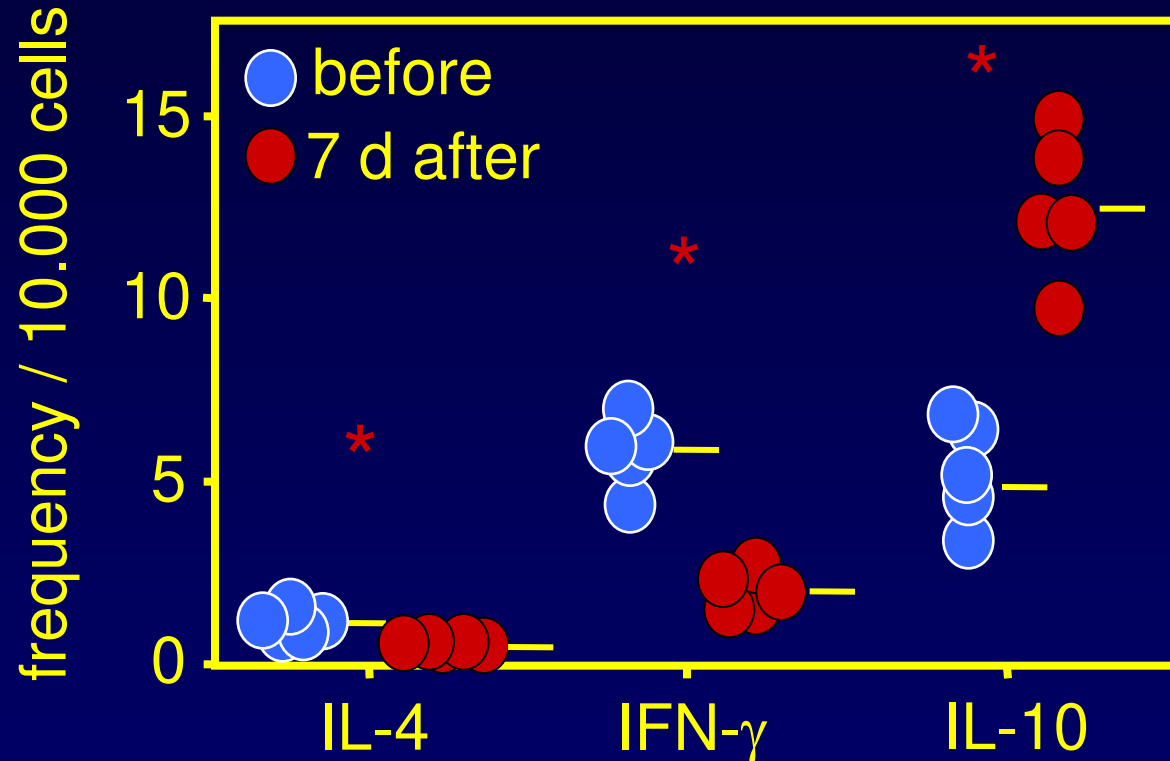
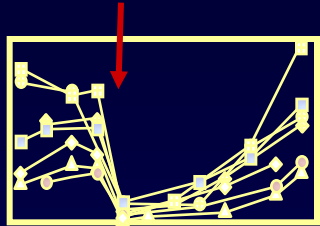
# Antigen-specific peripheral T cell tolerance



# Changes in cytokine profile after bee stings



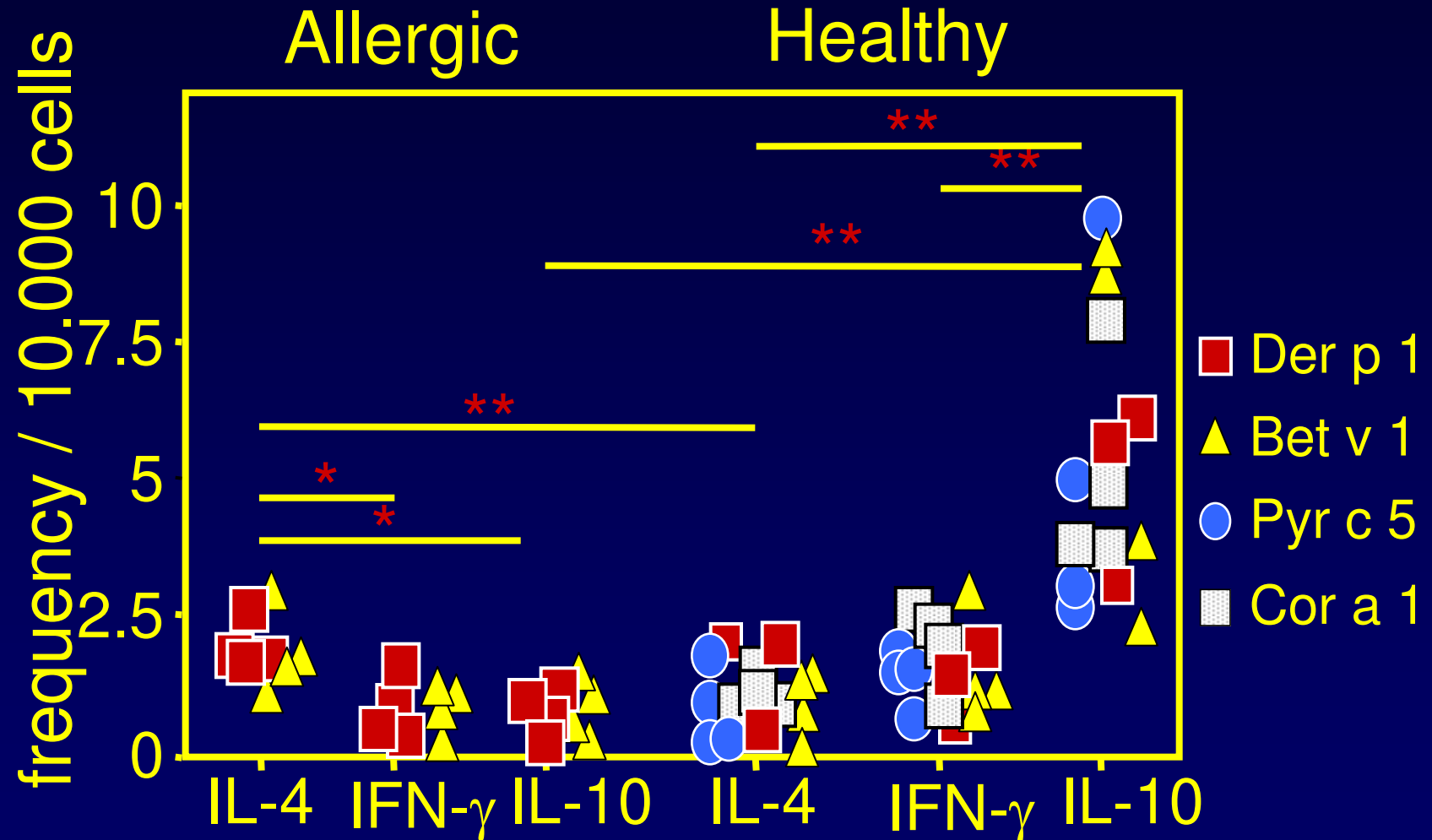
# Frequency of PLA-specific cytokine secreting T cells before and after live bee stings



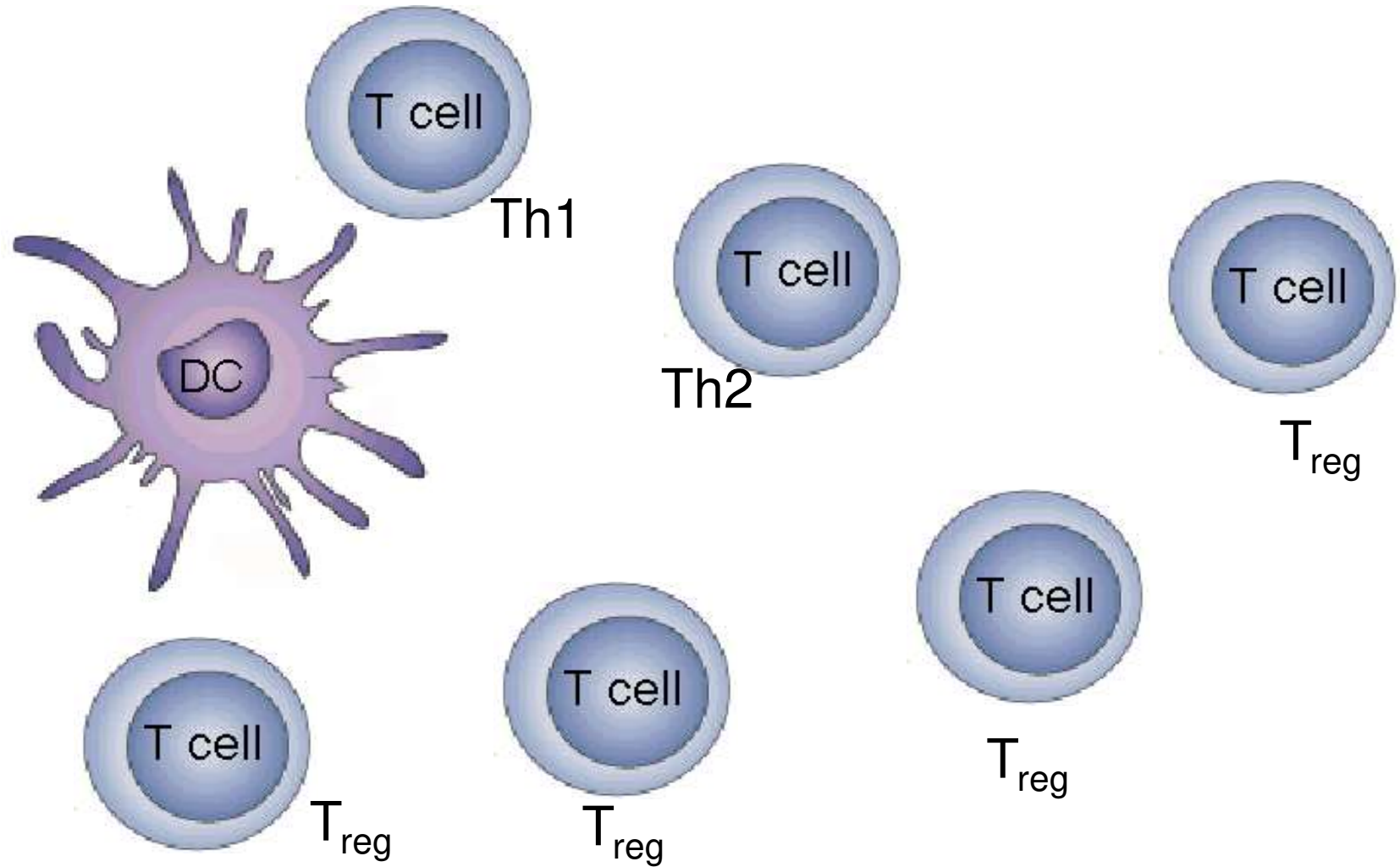
Decreased frequency of PLA-specific IL-4- and IFN- $\gamma$ -secreting T cells, increased frequency of IL-10-secreting T cells is observed 7 days after  $\geq 20$  bee stings

\*: p < 0.001  
n: 5 beekeepers

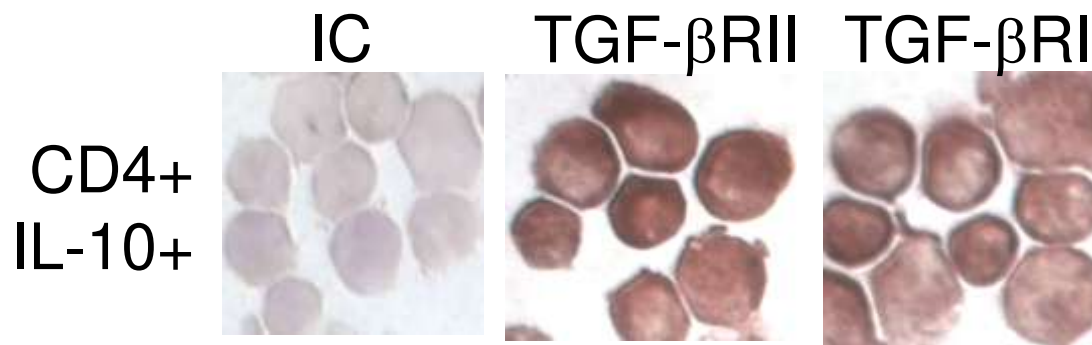
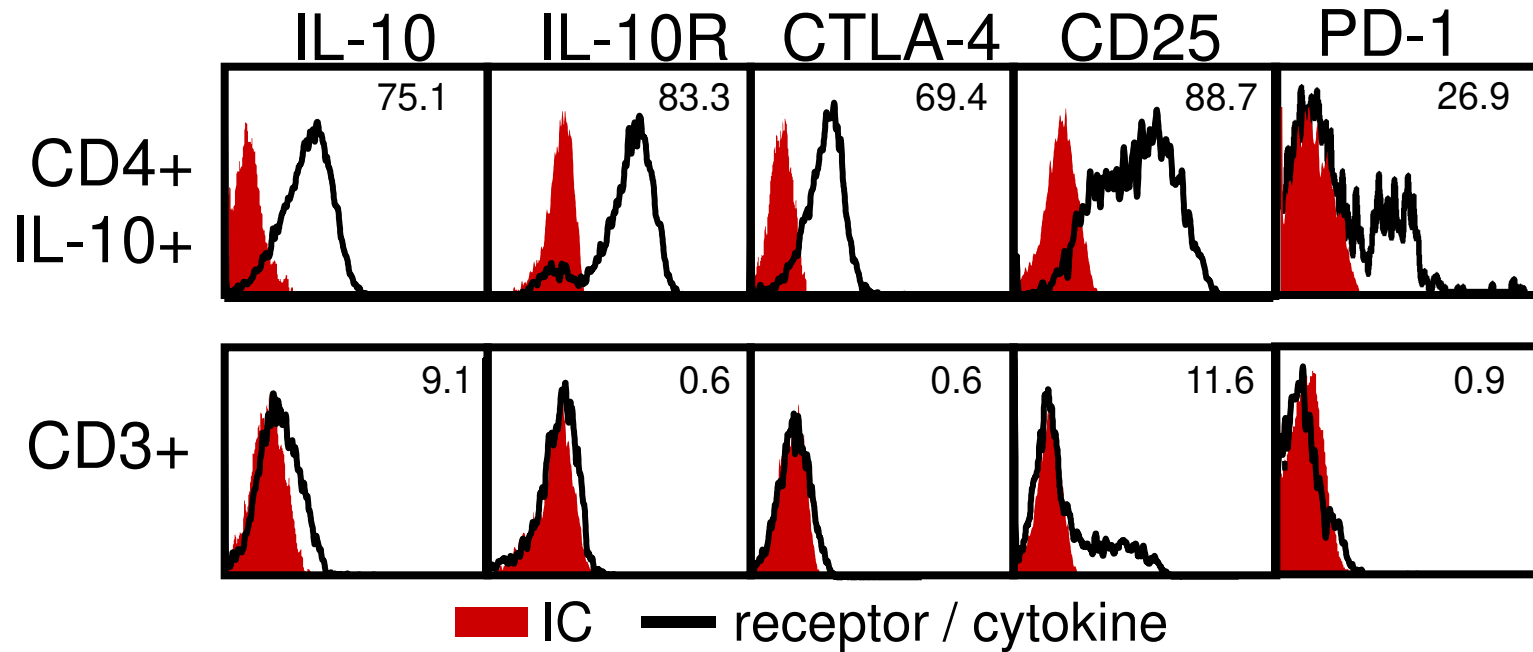
# Aeroallergen-specific T cell frequency in health and allergy



Which one will be the first T cell to contact APC in an ongoing memory response?



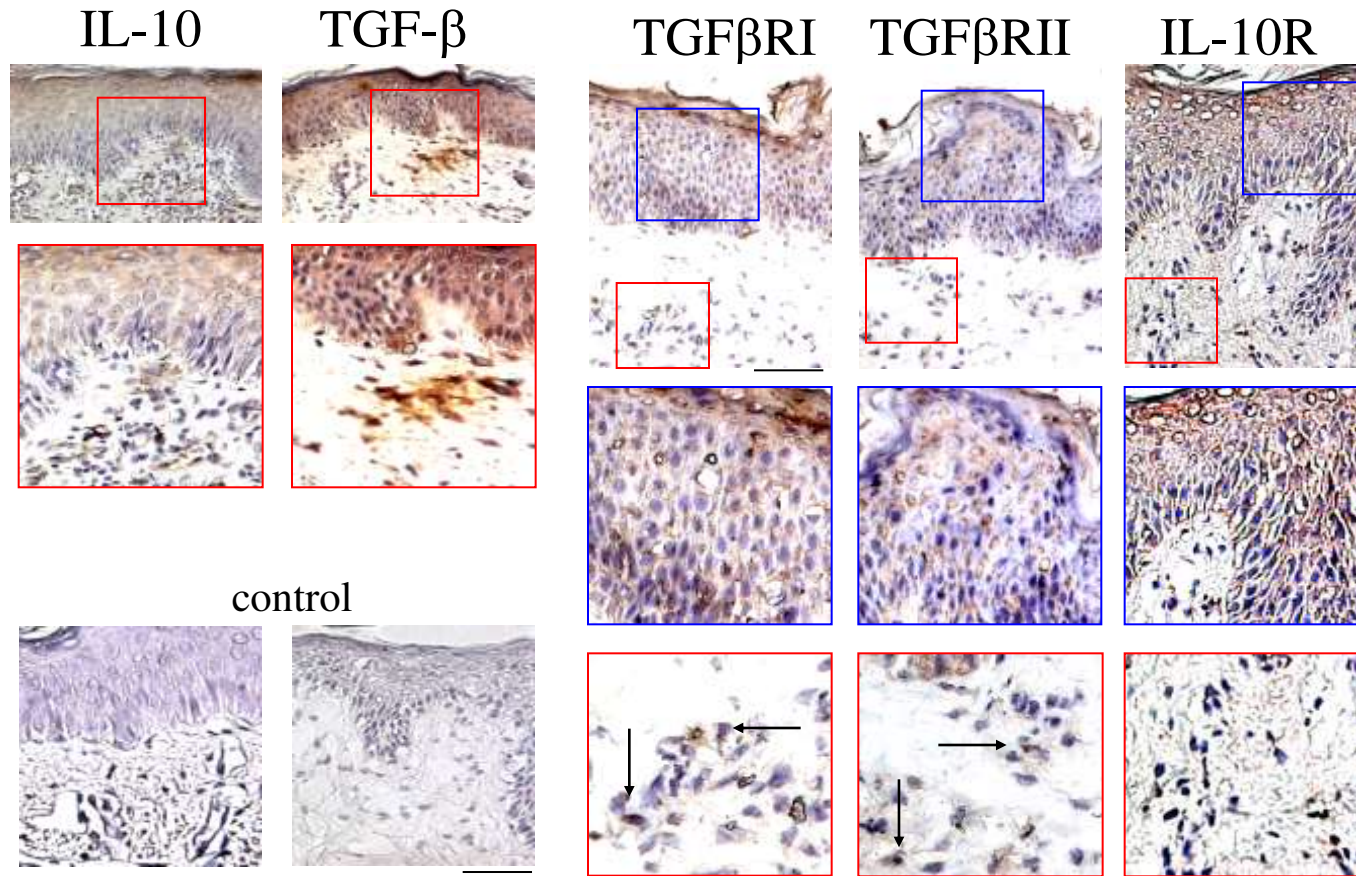
# T<sub>Reg</sub> cells in allergy: multiple suppressor factors



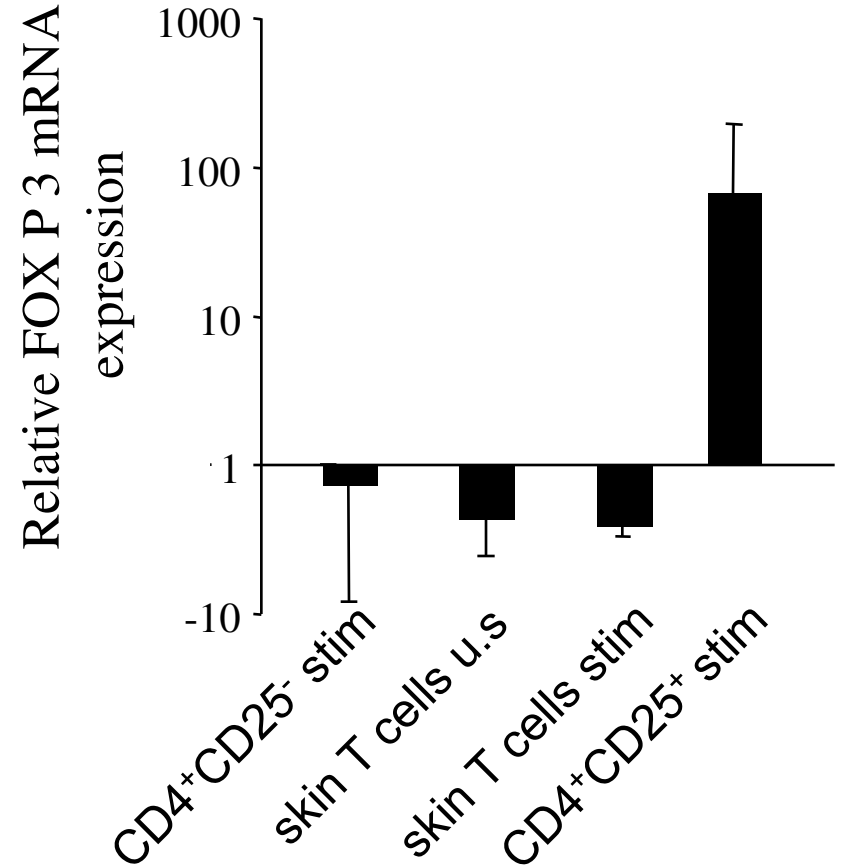
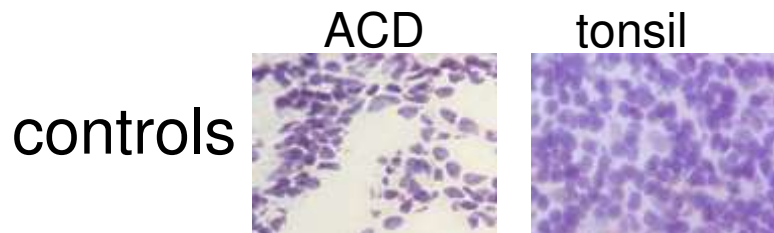
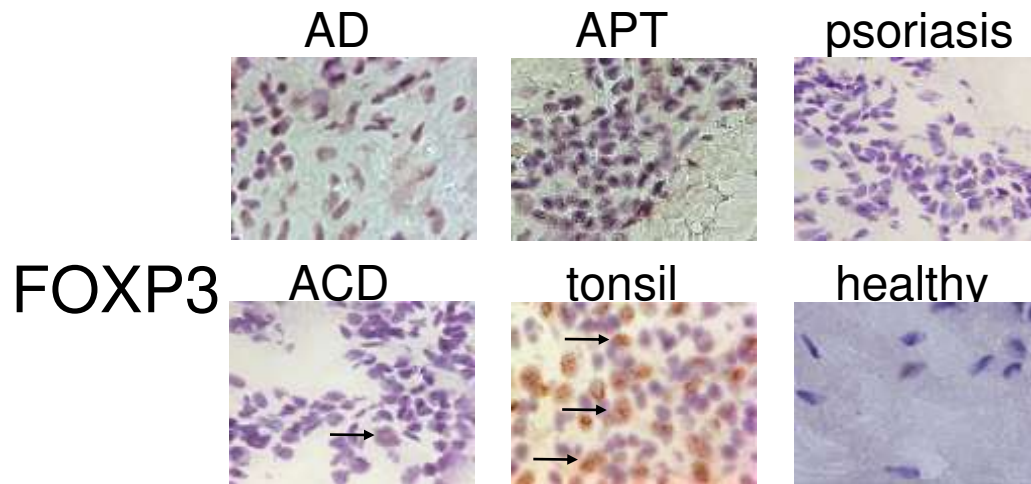
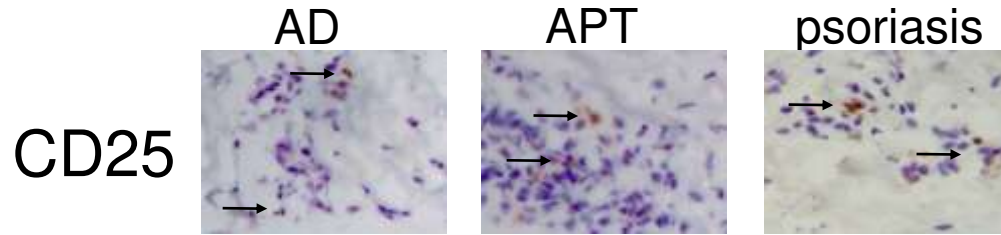
IL-10  
suppresses IgE  
and  
induces IgG4

TGF- $\beta$   
suppresses IgE  
and  
induces IgA

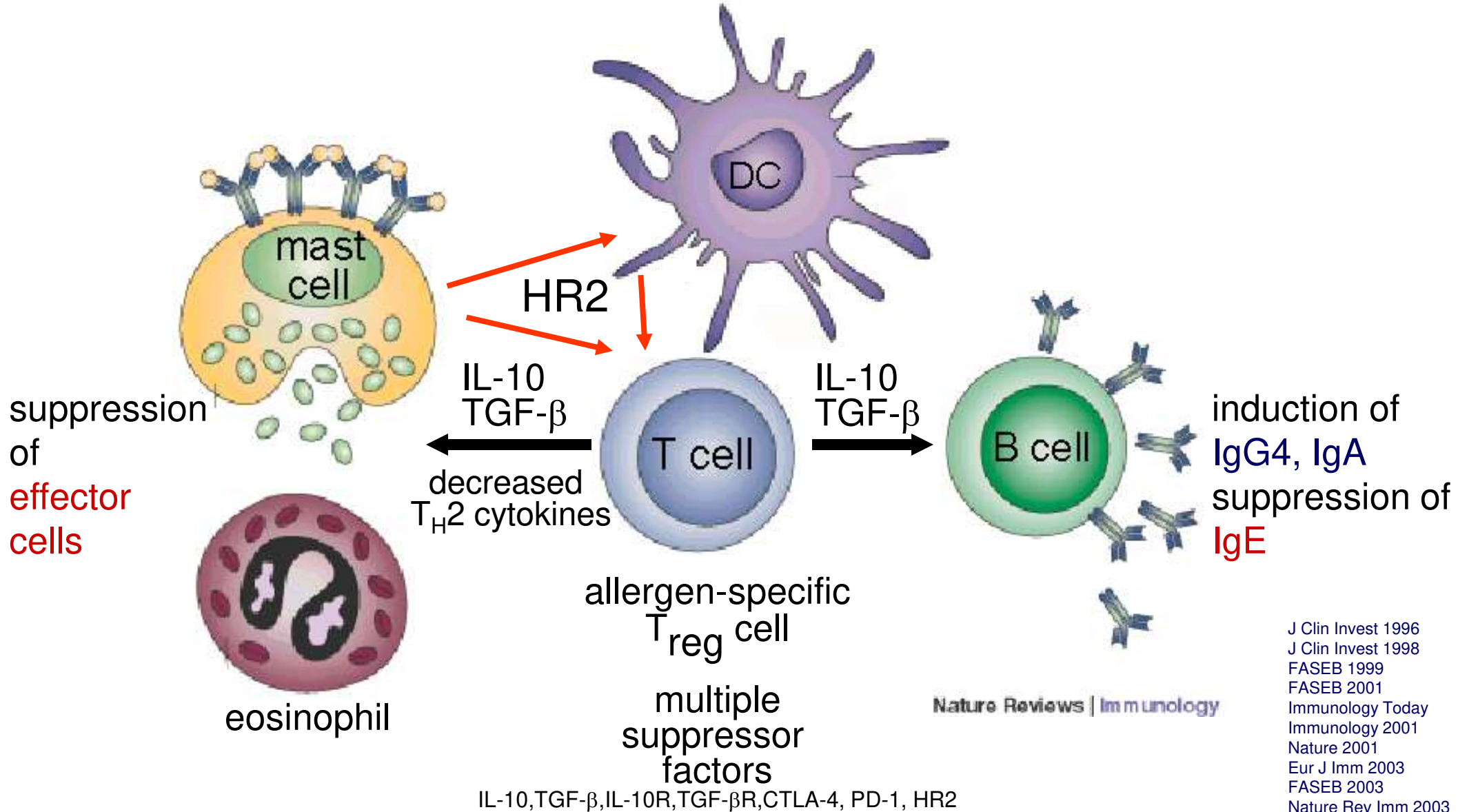
# IL-10, TGF- $\beta$ and their receptors are expressed in AD skin



# CD4+CD25+FoxP3+ T<sub>Reg</sub> cell deficiency in atopic dermatitis and psoriasis lesions



# T<sub>Reg</sub> cells in healthy immune response and successful SIT



J Clin Invest 1996  
 J Clin Invest 1998  
 FASEB 1999  
 FASEB 2001  
 Immunology Today  
 Immunology 2001  
 Nature 2001  
 Eur J Imm 2003  
 FASEB 2003  
 Nature Rev Imm 2003  
 J. Exp. Med 2004

## Immune tolerance

- Axel Trautmann
  - Sven Klunker
  - Alison Taylor
  - Johan Verhagen
  - Maya Zimmermann
  - Flurina Meiler
  - Judith Zumkehr
  - Tomasz Basinski
  
  - Reto Cramer
  - Carsten Schmidt-Weber
  
  - Cezmi Akdis
- U. Müller, Bern
  - B. Wüthrich, Zurich
  - M. Jutel, Wroclaw, SIAF
  - R. Valenta, Vienna
  - E. Jensen-Jarolim, Vienna
  - M. van Hage-Hamsten, Stockholm
  - G. Gavfelin, Stockholm
  - R. Kroczyk, Berlin
  - M. Colonna, St Louis
  - E. Flory, Langen
  - S. Viehls, Langen
  - H. Fiebig, Reinbek
  - C. Heusser, Basel
  - E. Hamelmann, Berlin
  - M. Larchè, London
  - A. Verhoef, London
  - S. Alkan, Minneapolis
  - R. Lauener, Zurich
  - B. Ballmer-Weber, Zurich

## Mechanisms of atopy

- R. Disch
- B. Wüthrich
- P. Schmid-Grendelmeier
- W. Kneist
- M. Schliz
- D. Kleeman
- W. Deglmann
- H. Behrendt,
- C. Traidl-Hoffmann, Munich

## Immune regulation by histamine

- T. Watanabe, Osaka
- R. Koga, Fukuoka

## Philosophy of the meeting

As ever, immune regulation is the hottest issue in basic and clinical sciences. No question that we need to gather and get inspired. With an outstanding list of speakers in this field, „Immune Regulation – Davos“ becomes the key event of the year 2007, being big enough to learn from other disciplines and small enough to personally meet the experts. Davos has been stimulating not only for scientists, but also for other meetings such as the World Economic Forum, held every year in the same conference center. There will be long lunch breaks, allowing to digest attended symposia, to talk with colleagues, while enjoying the winter sports and landscape. The evening sessions will give young researchers the opportunity to meet senior scientists. As at other Davos meetings, we will come together for poster sessions with desserts and drinks providing a relaxed and stimulatory atmosphere for scientific exchange.



## Practical workshops

A practical course on flow cytometric and Treg analysis will be performed at the Swiss Institute of Allergy and Asthma Research. This course will provide first-hand expertise on Treg-analysis facilitating your research. The course is planned both for scientific fellows and technical assistants. It will be an ideal complementation for the theoretical background provided by the meeting and will be supported by flowcytometer experts as well as researchers from SIAF. Several other workshops are being planned and details will be announced on our website.



Organisator:  
**Cezmi Akdis**  
Organizing comitee:  
**Carsten Schmidt-Weber**  
**Mübeccel Akdis**  
**Reto Cramer**  
In:  
Davos, congress center  
Abstract submission:  
15 January 2007 - 15 February 2007  
Early registration deadline:  
15 December 2006  
Meeting style:  
Symposium & workshop, practical workshops  
Meeting organization:  
This meeting is organized by the Swiss Institute of Allergy and Asthma Research (SIAF), a non-profit, University associated foundation SIAF, Obere Str. 22, CH-7270 Davos  
[Treg\\_meeting.Davos@siaf.unizh.ch](mailto:Treg_meeting.Davos@siaf.unizh.ch)  
Registration Fee:  
500.- Swiss Francs  
Fellows in training: 200.- Swiss Francs

**SIAF**



**GALEN**  
Network of Excellence

# World Immune Regulation Meeting

Special focus on regulatory cells

11 - 15 April 2007  
Davos - Switzerland

<http://www.siaf.unizh.ch/WTM/index.html>





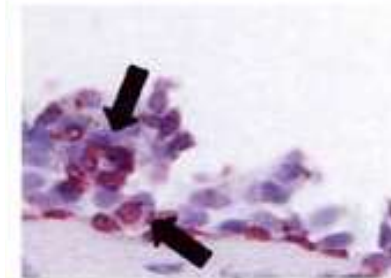
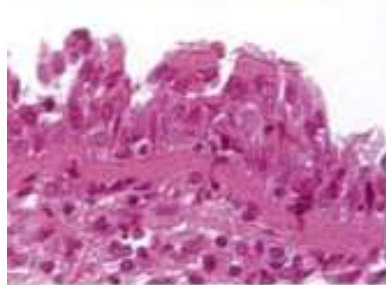
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TUNEL

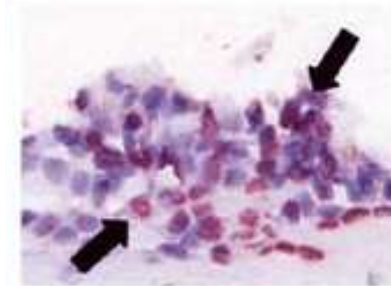
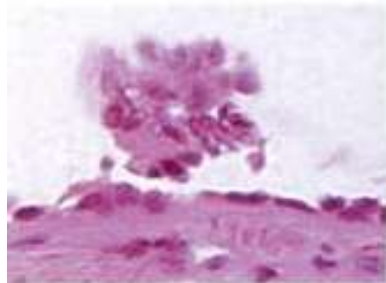
Normal



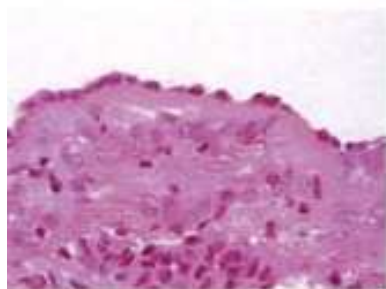
Asthma



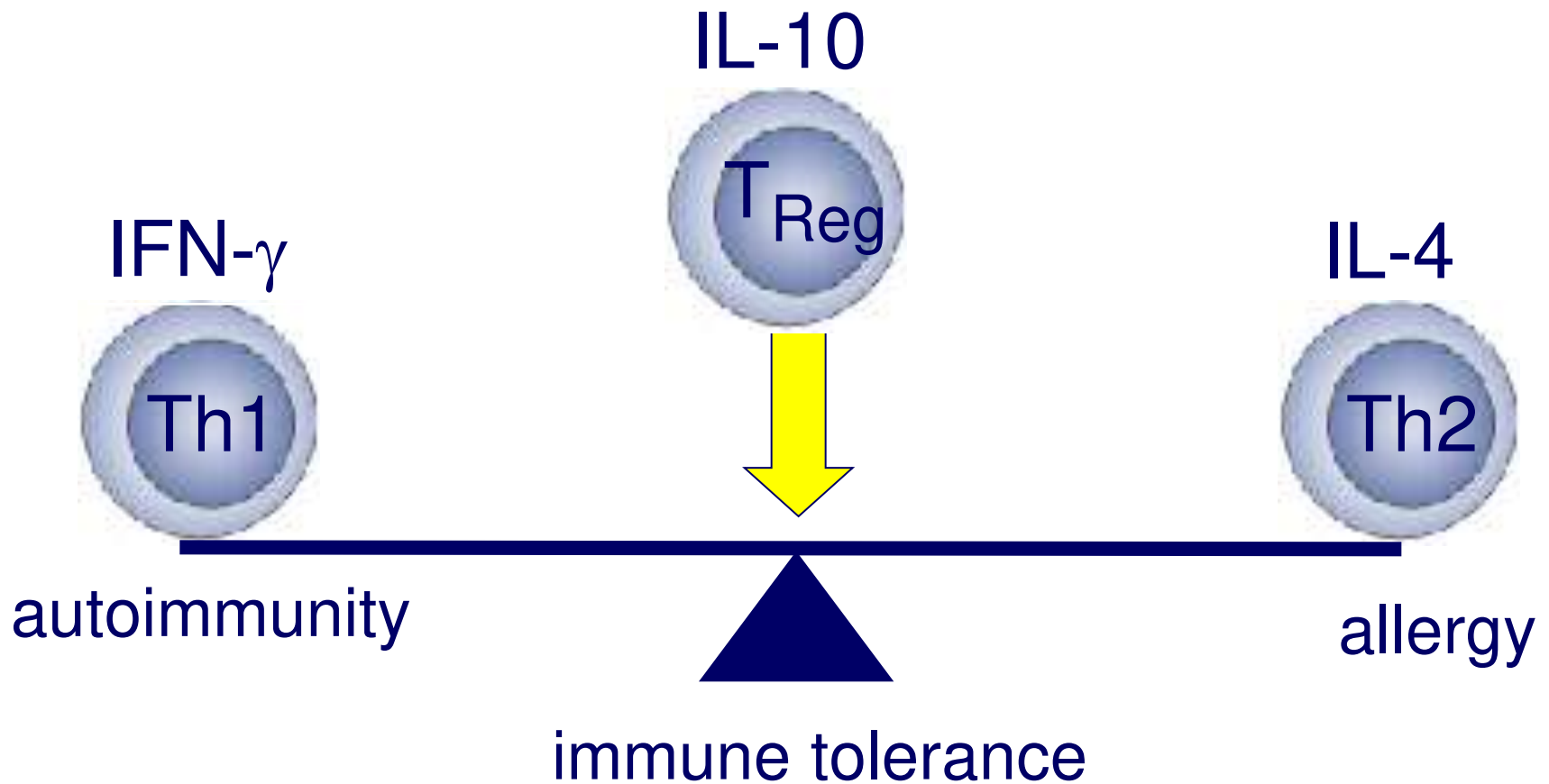
Asthma



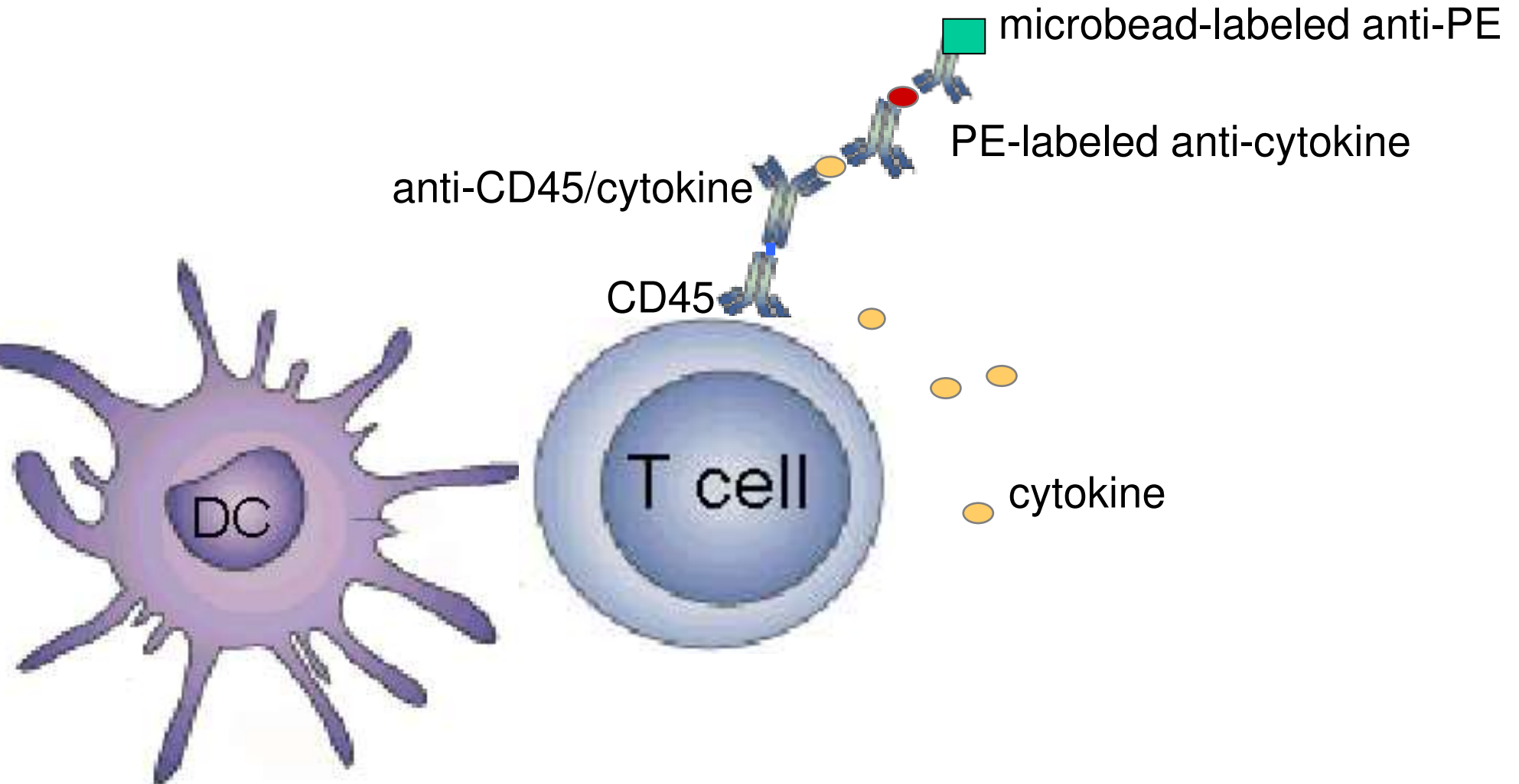
Asthma



TNF- $\alpha$   
IFN- $\gamma$   
Fas-ligand



# Purification of allergen-specific cytokine-secreting T cells



# Allergic inflammation (late phase)

