Cellular and Molecular Mechanisms of Allergic Diseases

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DAVOS

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Two types of allergic diseases-I

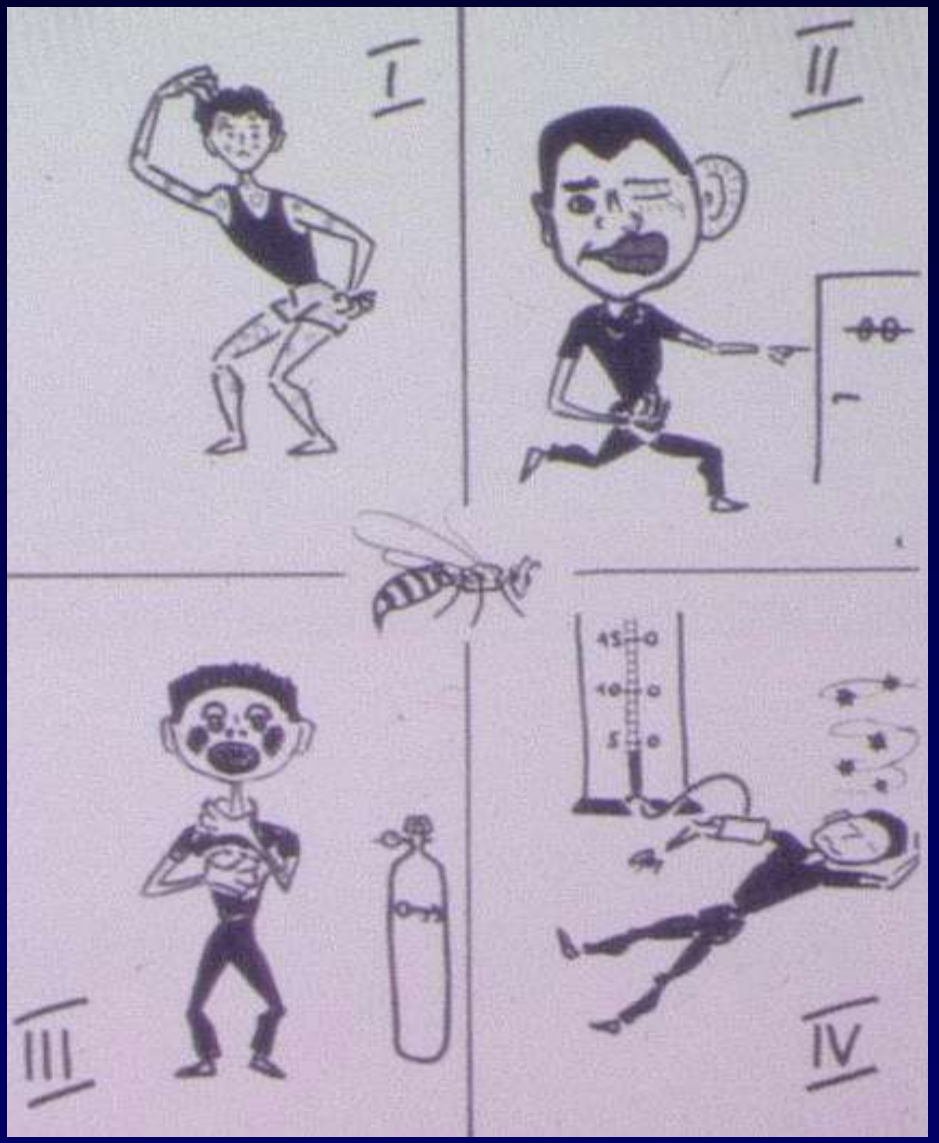
monoallergy (allergic breakthrough)

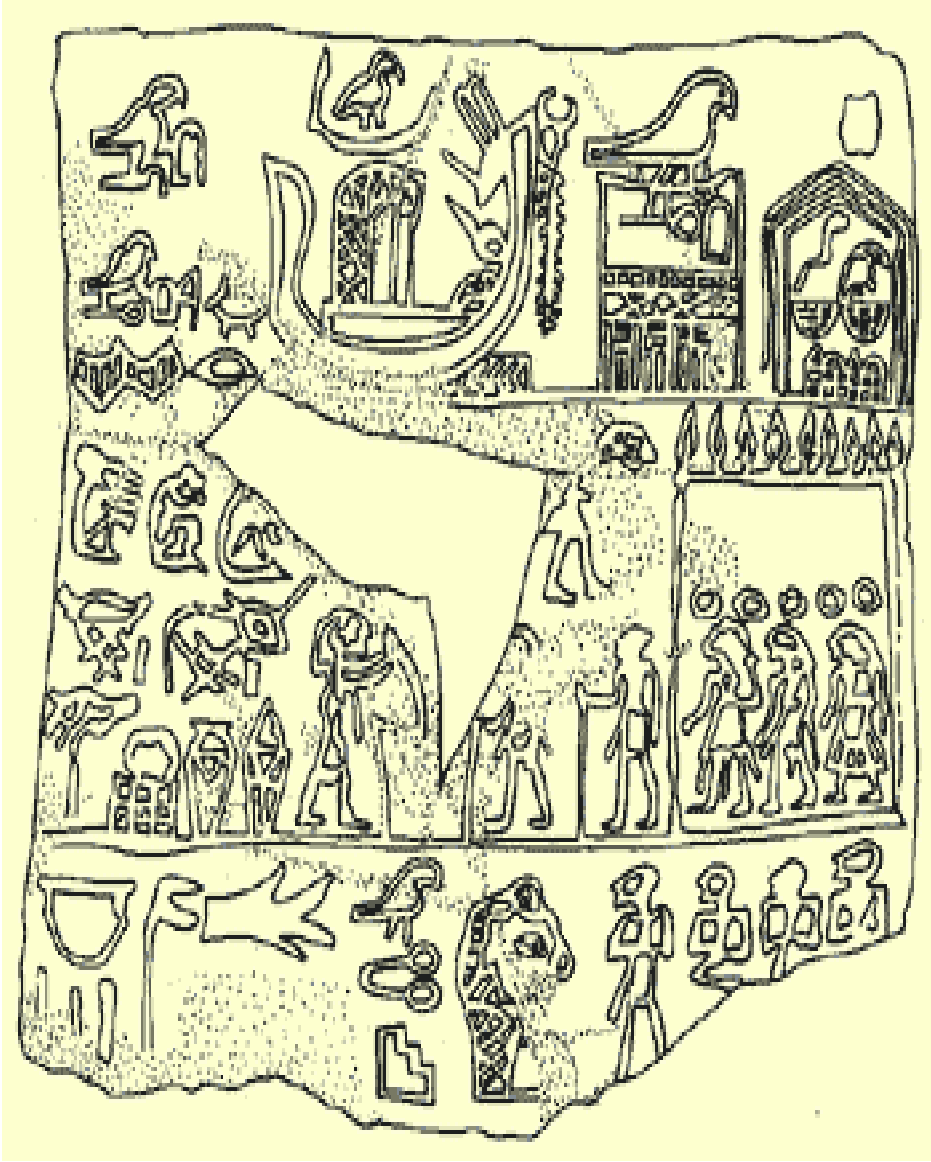
high specific IgE without atopy

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

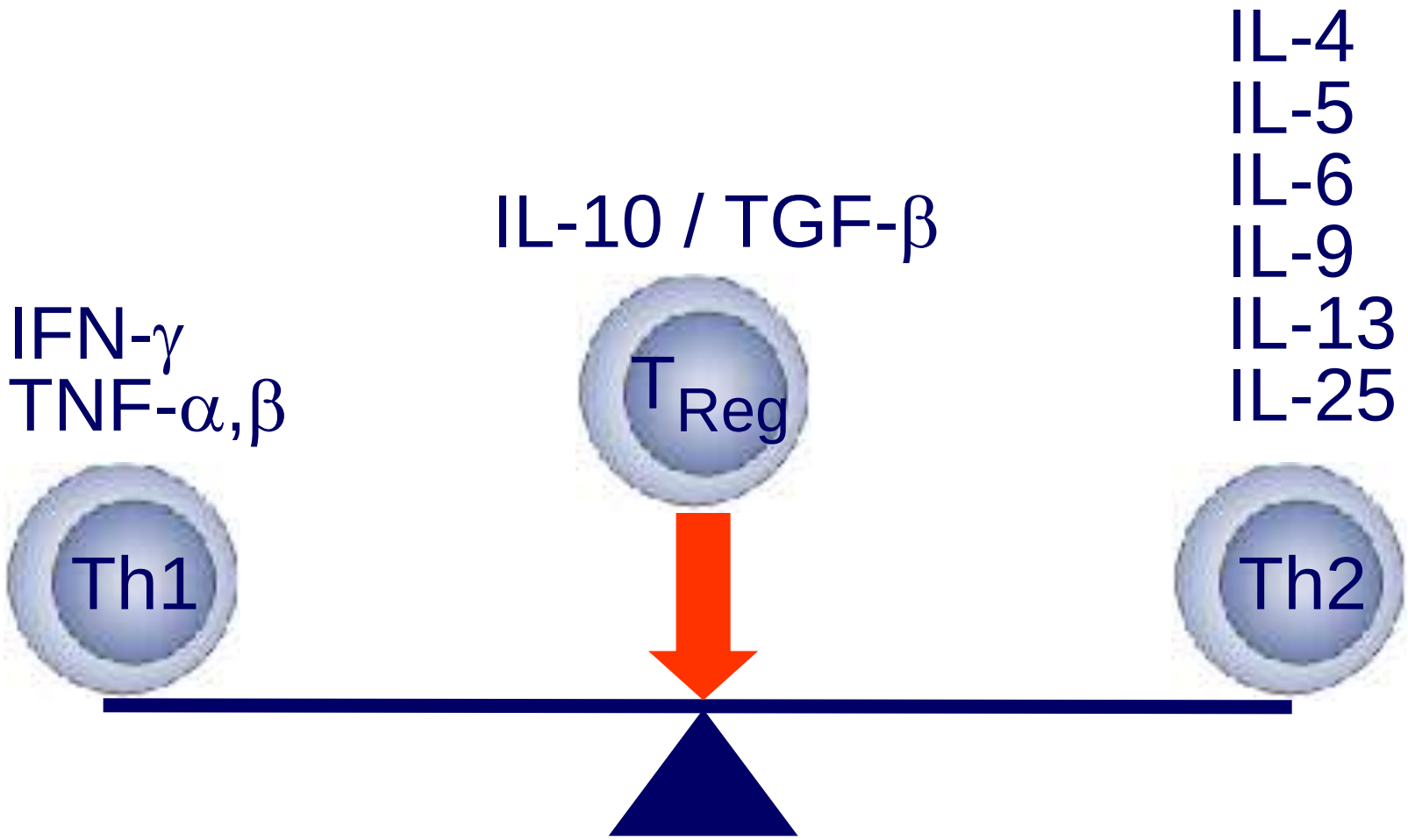
allergic
inflammation

homing

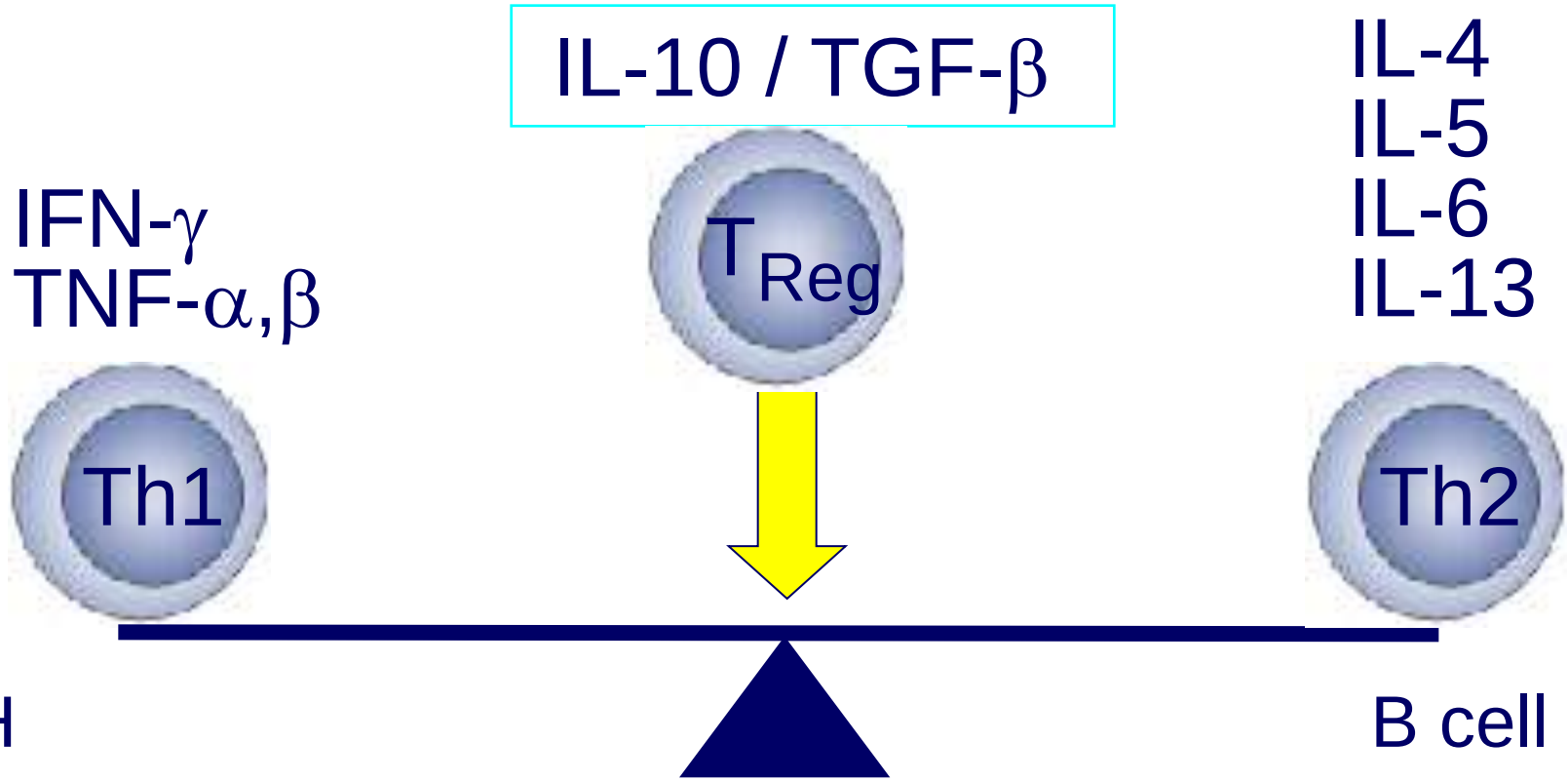
effector
functions

Th1 and Th2 cell balance in disease

Th1 and Th2 cell balance in homeostasis



Major Functions



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

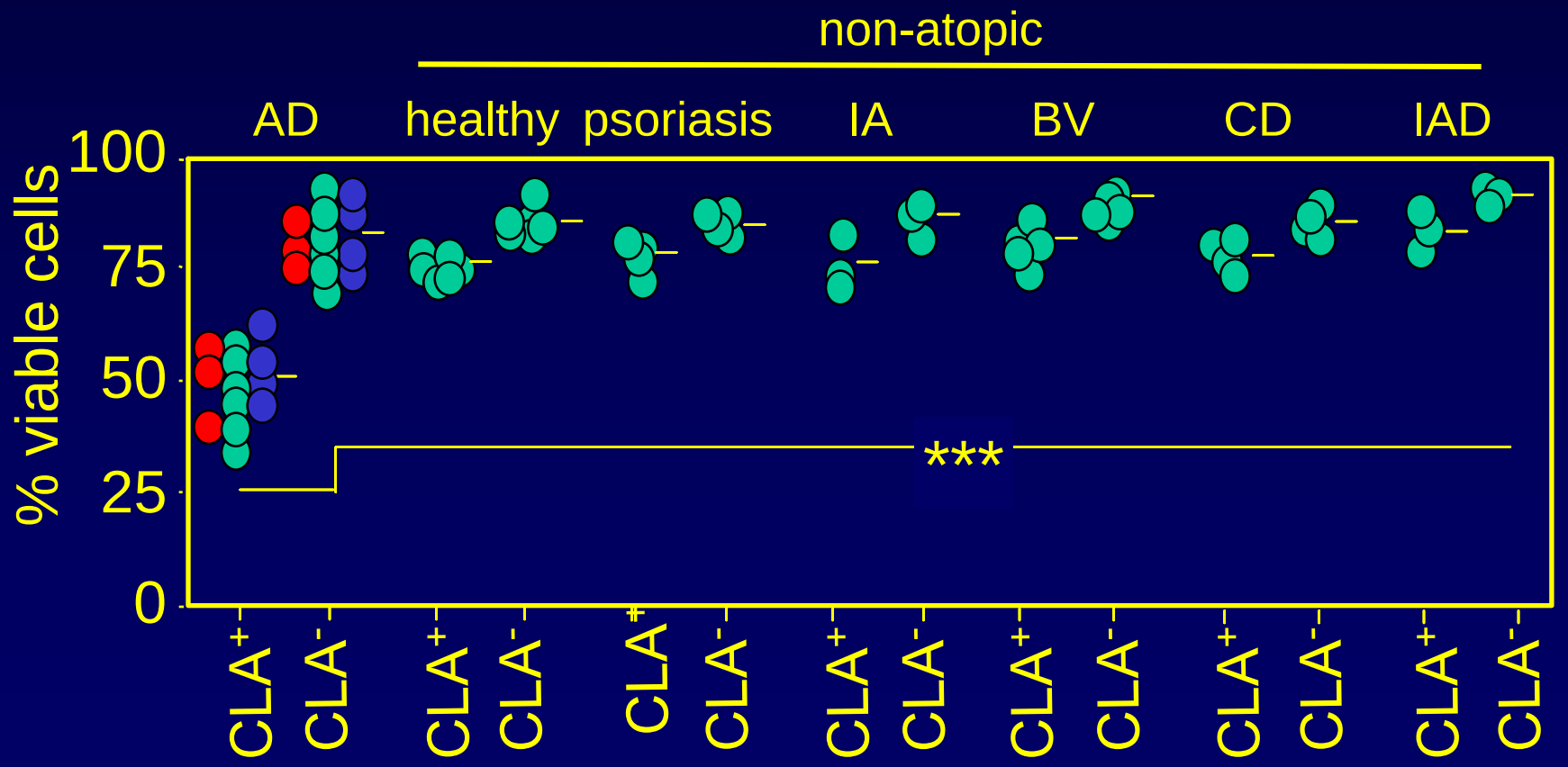
Apoptosis

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)
- Prolonge eosinophil life span (IL-5)

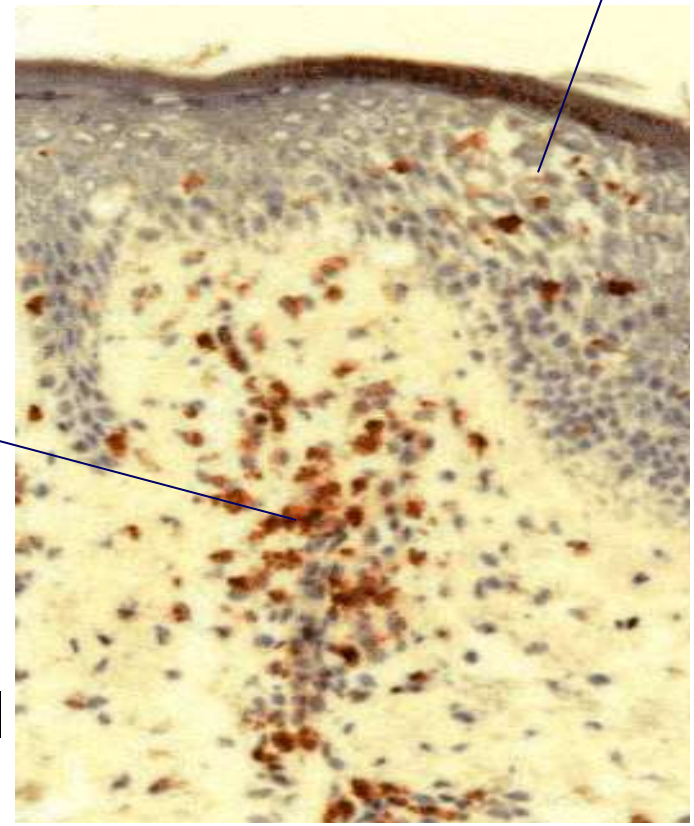
Akdis et al. J. Immunology I997, 1999

Increased death of circulating CLA$^+$ T cells in AD



Histopathology of AD

eczema/spongiosis



effector functions

dermal
mononuclear
cells

70 % T cell
1-3 % Eosinophil
10-20 % Dendritic cell

survival/reactivation

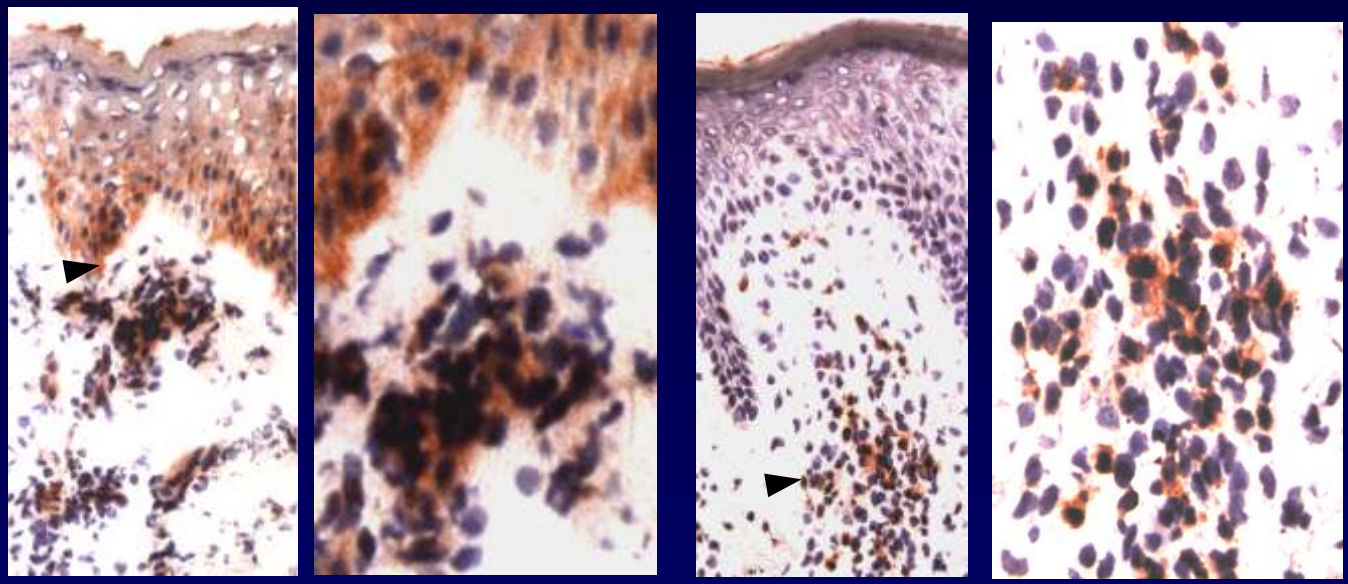
activation/homing

CD4/CD8 ratio: 2

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

Fas

Fas-ligand



Akdis et al. Faseb J 2003

Skin T cells do not die
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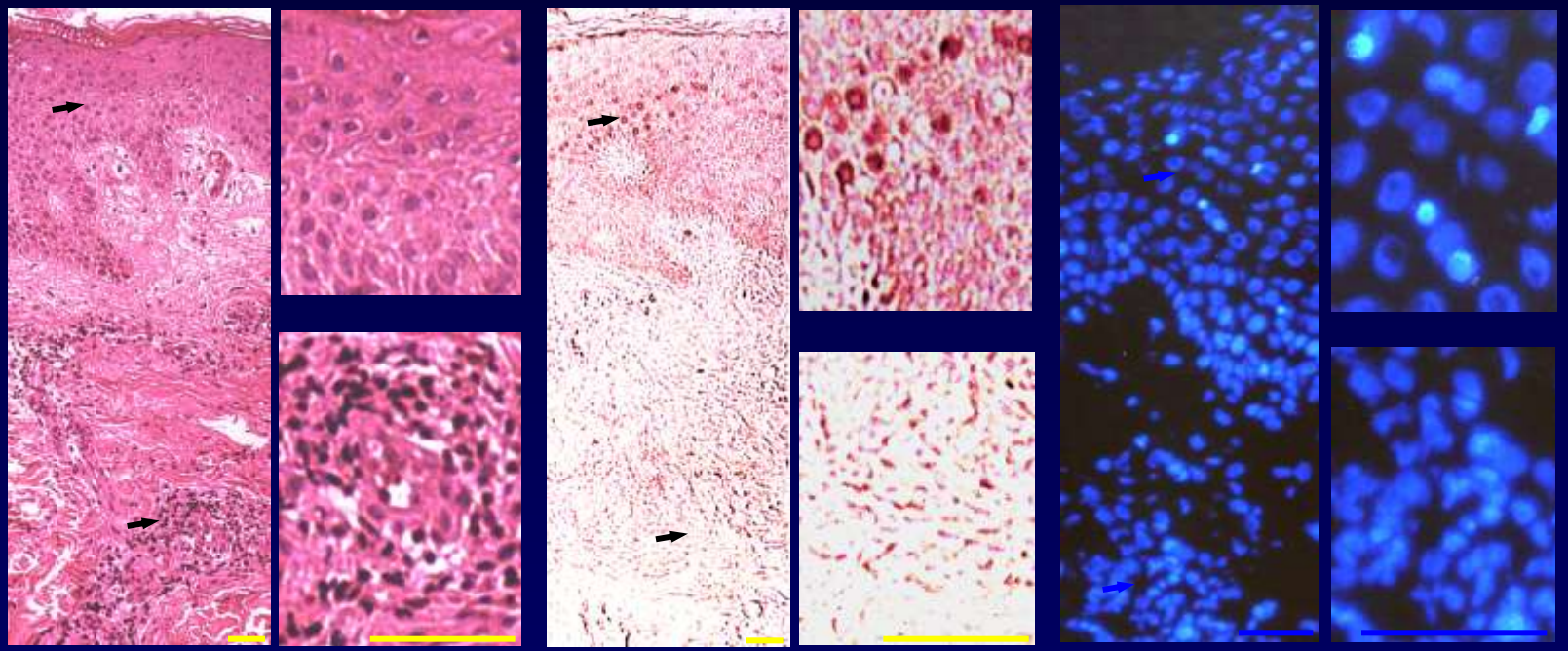
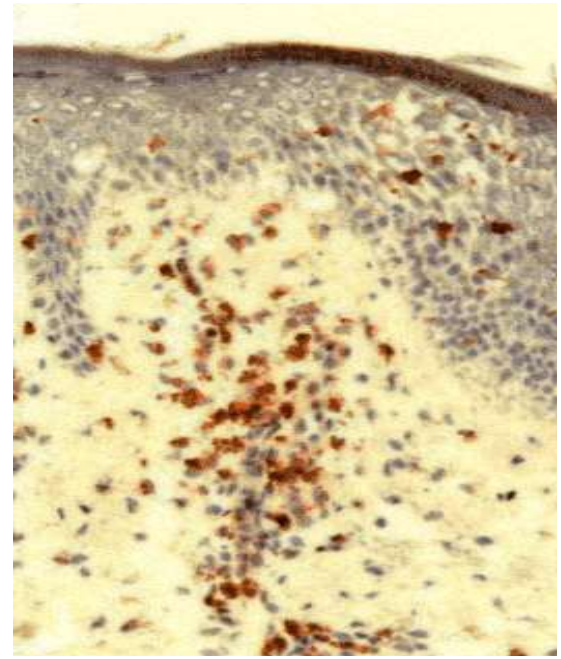
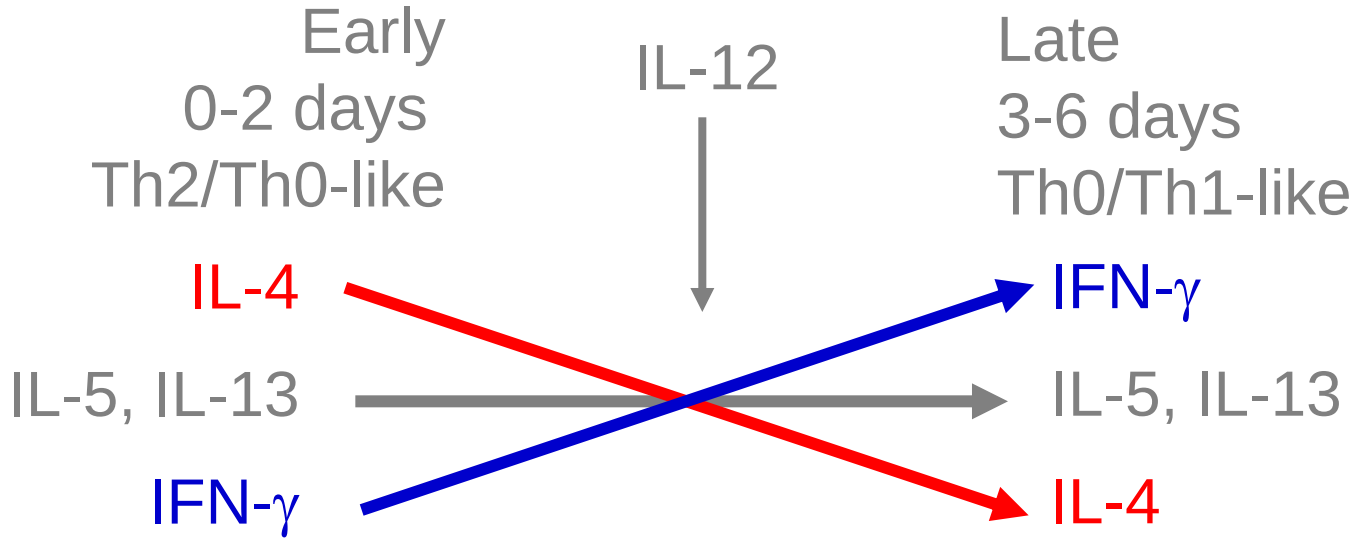


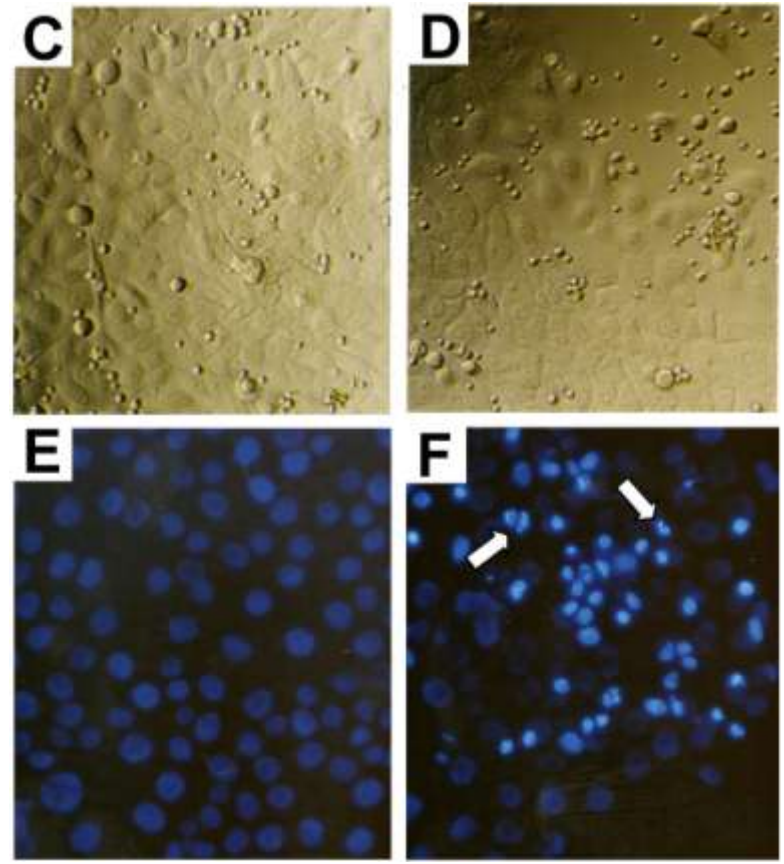
H/E TUNEL Hoechst

Akdis et al. Faseb J 2003




Early
0-2 days
Th2/Th0-like
IL-12
Late
3-6 days
Th0/Th1-like
IL-4
IL-5, IL-13
IFN-γ
IFN-γ
IL-5, IL-13
IL-4

resting T cells



activated T cells

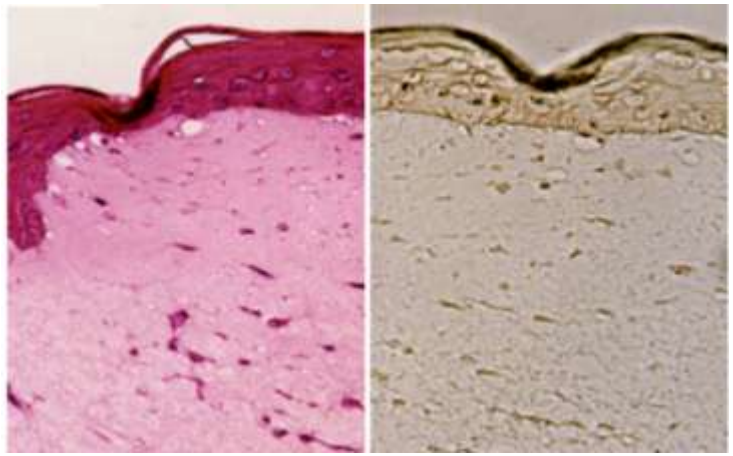
no apoptosis

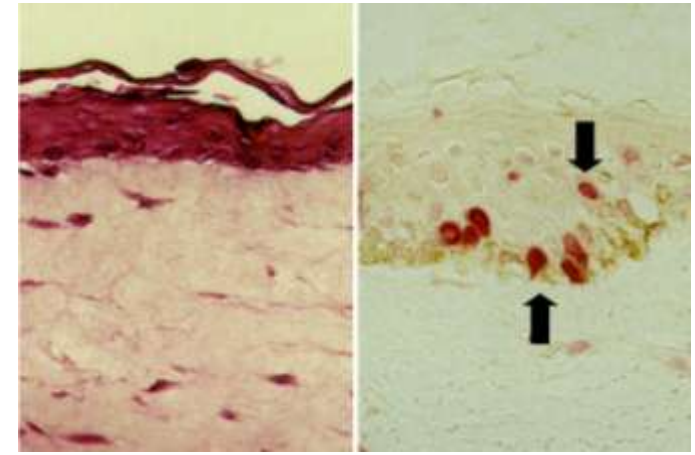
apoptosis

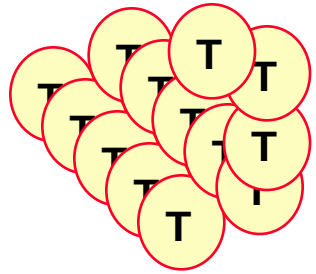
IFN-γ
Fas-ligand
TNF-α

co-cultures

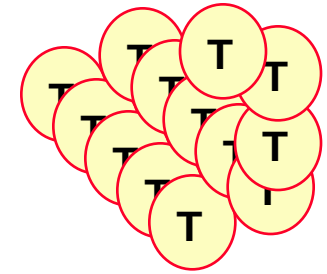
Trautmann et al. J. Clin. Invest. 2000







resting T cells



IFN-γ
Fas-ligand
TNF-α

activated T cells

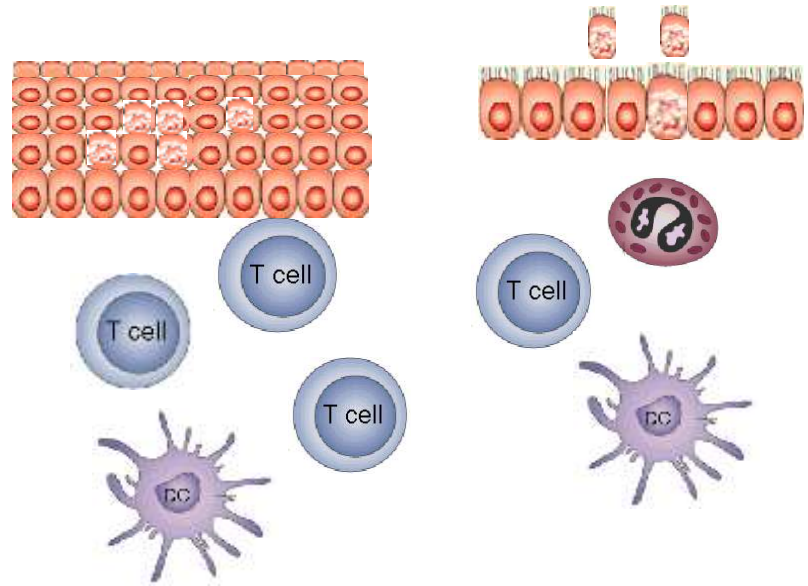
artificial skins

Activation and apoptosis of epithelial cells induced by subepithelial inflammation

Skin Lung

epithelium

subepithelium



counter signals from the epithelial cells augment inflammation

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

key pathogenetic event in atopic dermatitis and asthma

allergy: intolerance to allergens

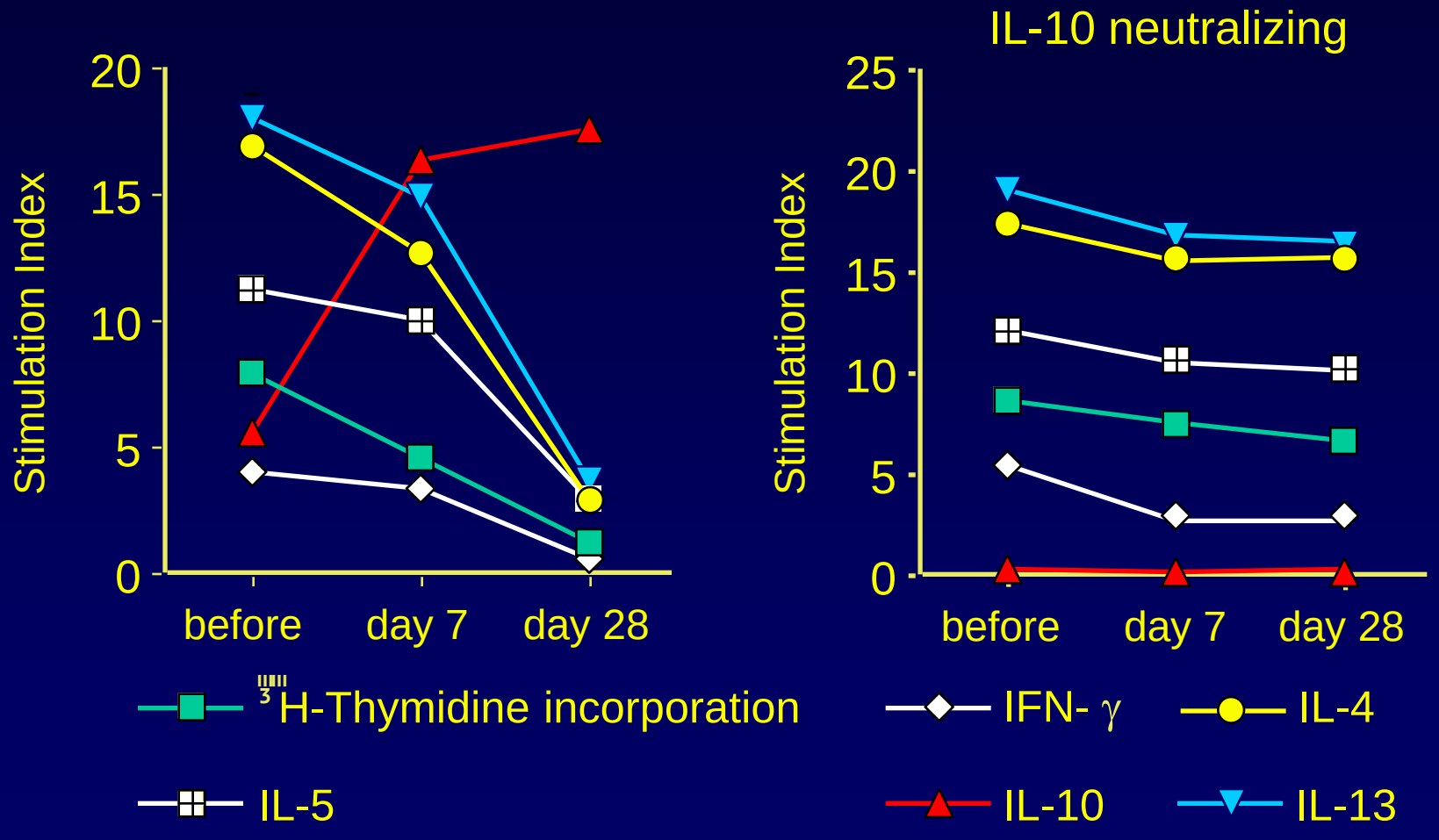
autoimmunity: intolerance to autoantigens

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

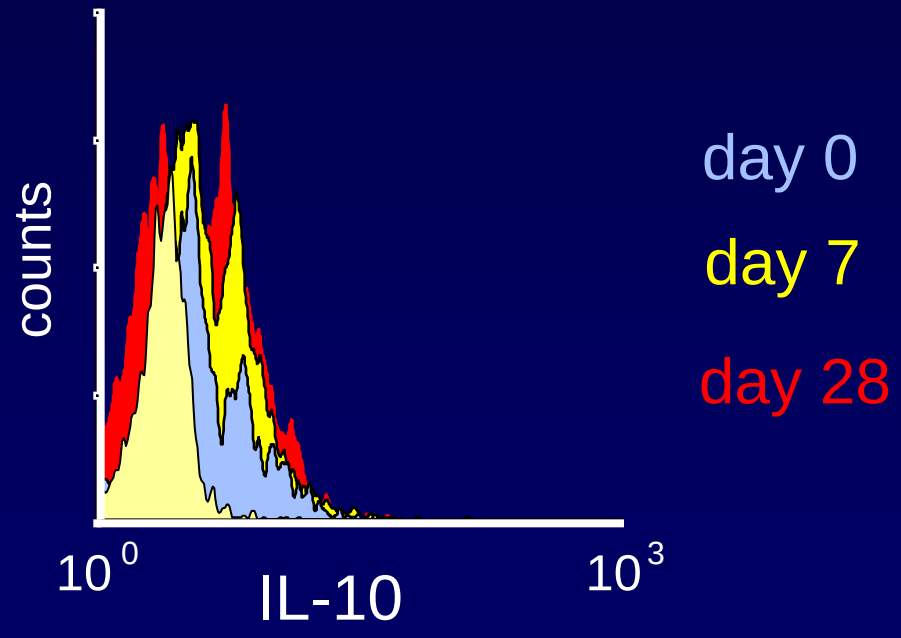
IL-10-induced peripheral T cell tolerance in bee venom specific-immunotherapy



J. Clin. Invest. 1996; 98: 1676
J. Clin. Invest. 1998; 102: 98

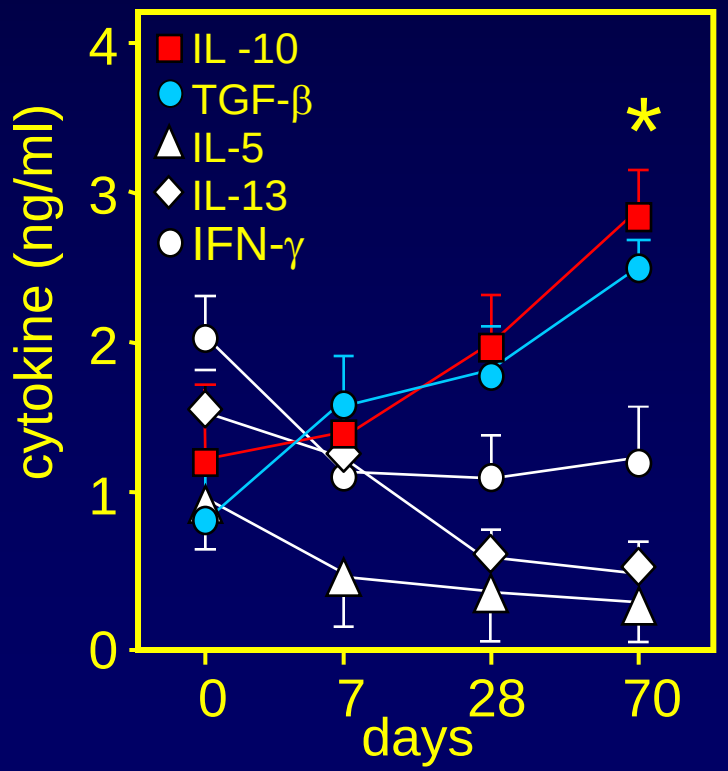
IL-10 production in T cells during specific immunotherapy

$CD4^+$ $CD25^+$ T_{reg} cells



J. Clin. Invest.
1998; 102: 98

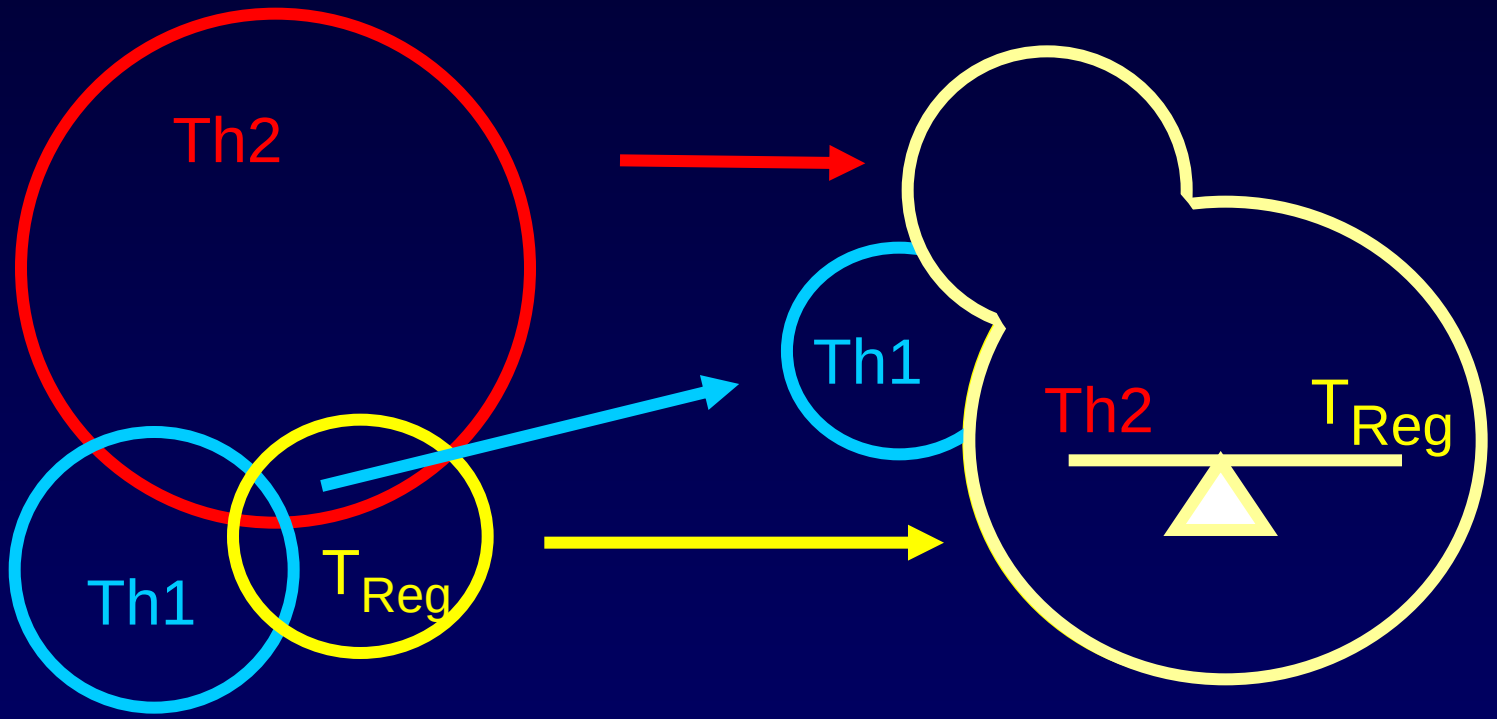
IL-10 and TGF-β in peripheral T cell tolerance during aeroallergen SIT



n= 10, SIT cluster protocol, Der p 1-stimulated PBMC

Jutel et al.

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



before SIT
allergic

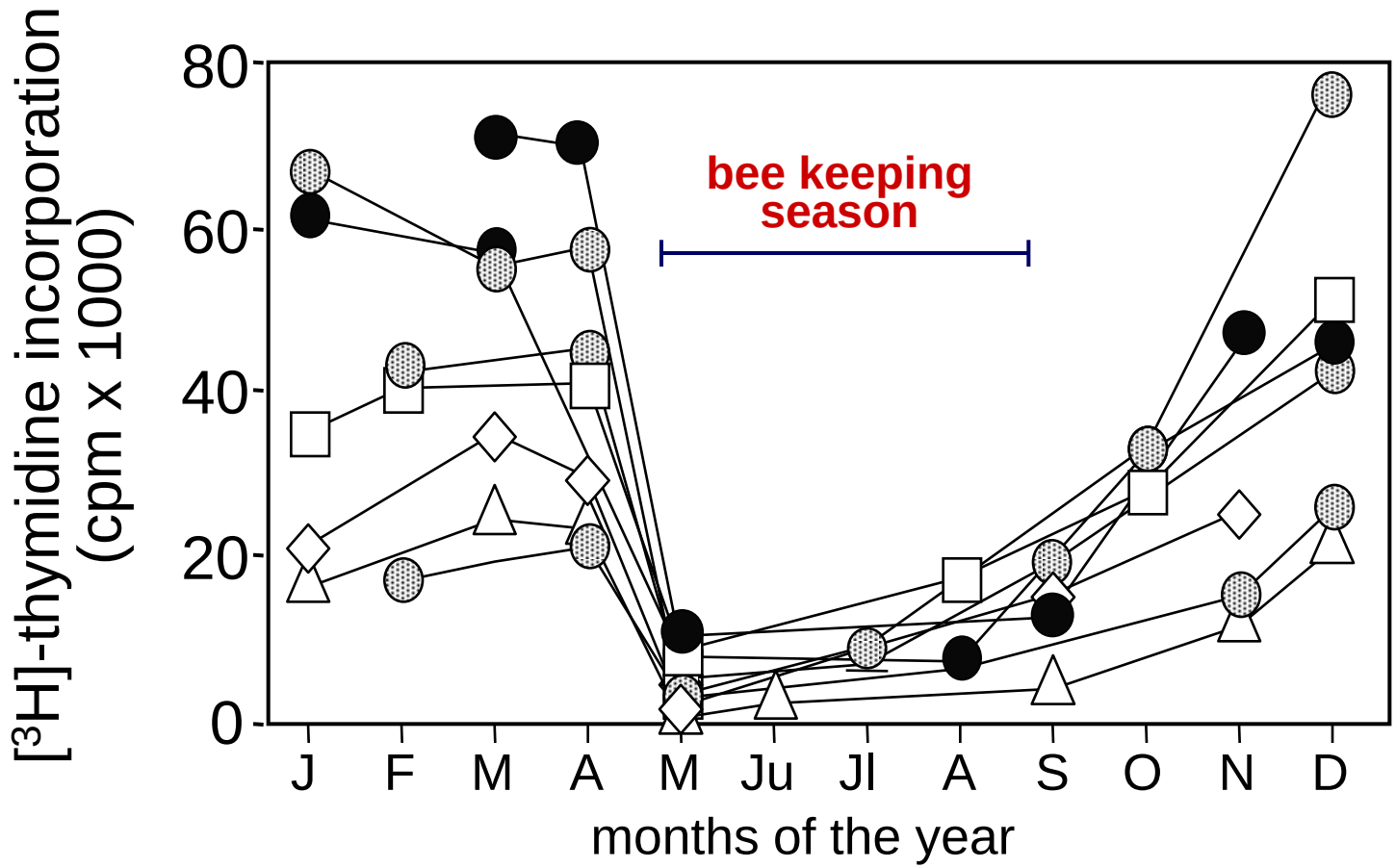
after SIT
healthy

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

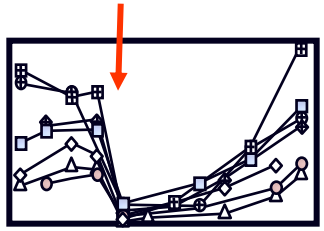
a model for
natural high dose antigen/allergen exposure

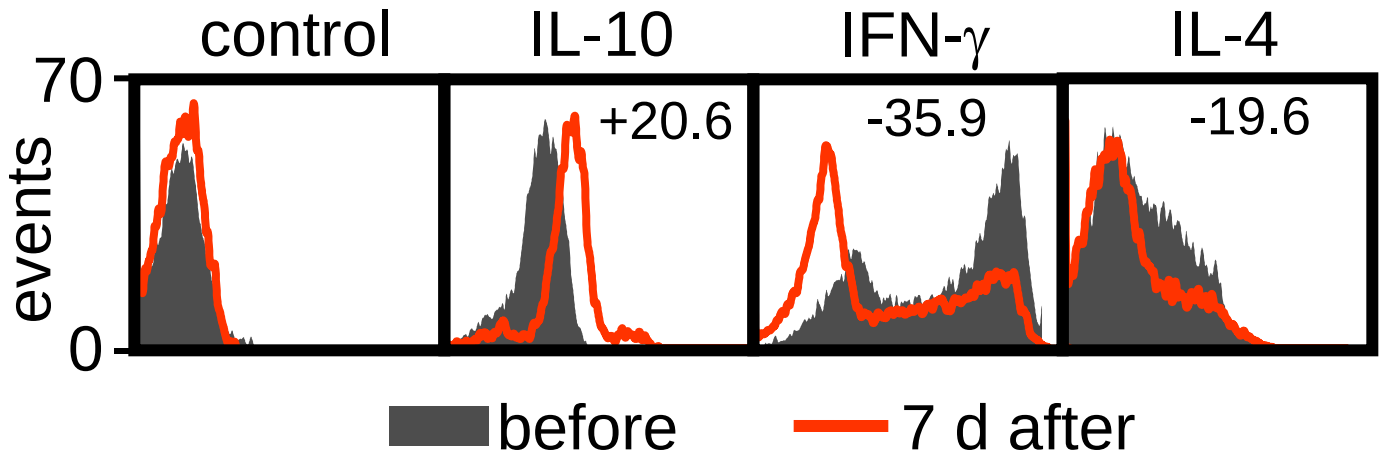
more than 20 bee stings in one week

Antigen-specific peripheral T cell tolerance



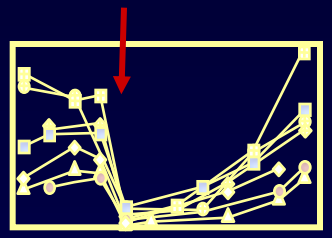
Changes in cytokine profile after bee stings

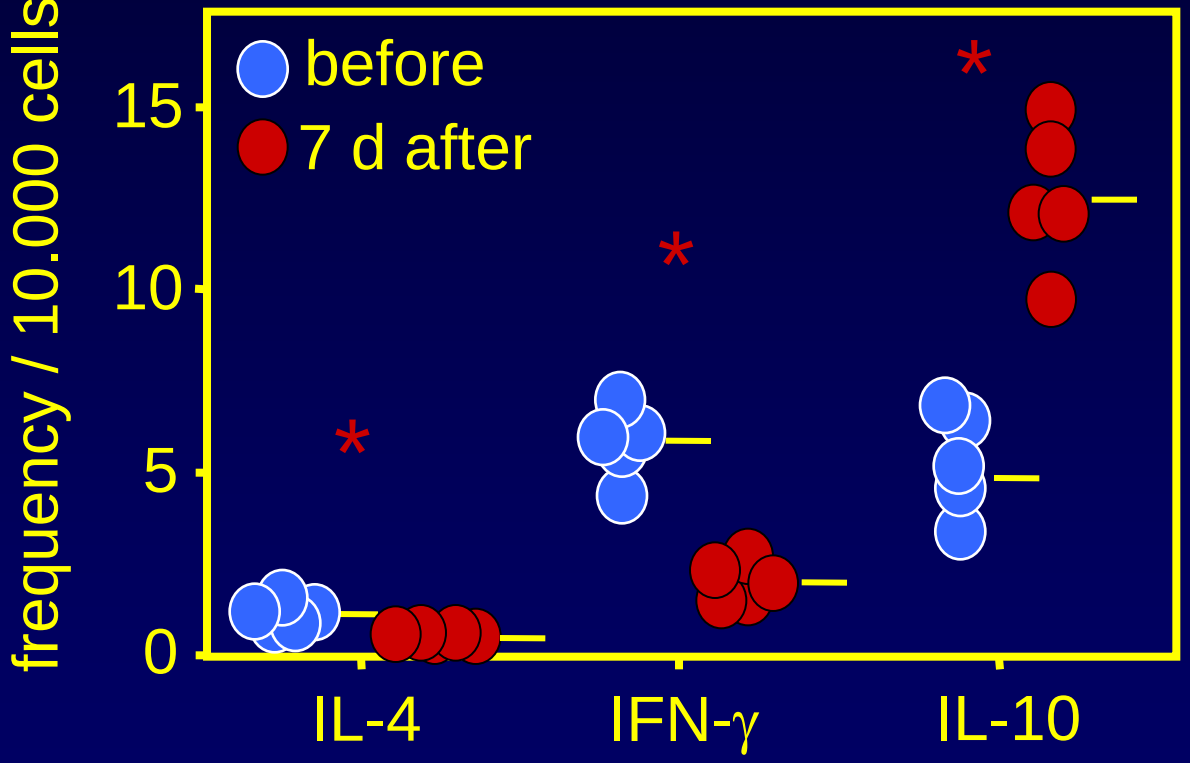




n=6, 5d Ag+7d IL-2 expansion, restimulation anti-CD3/28 4h.

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

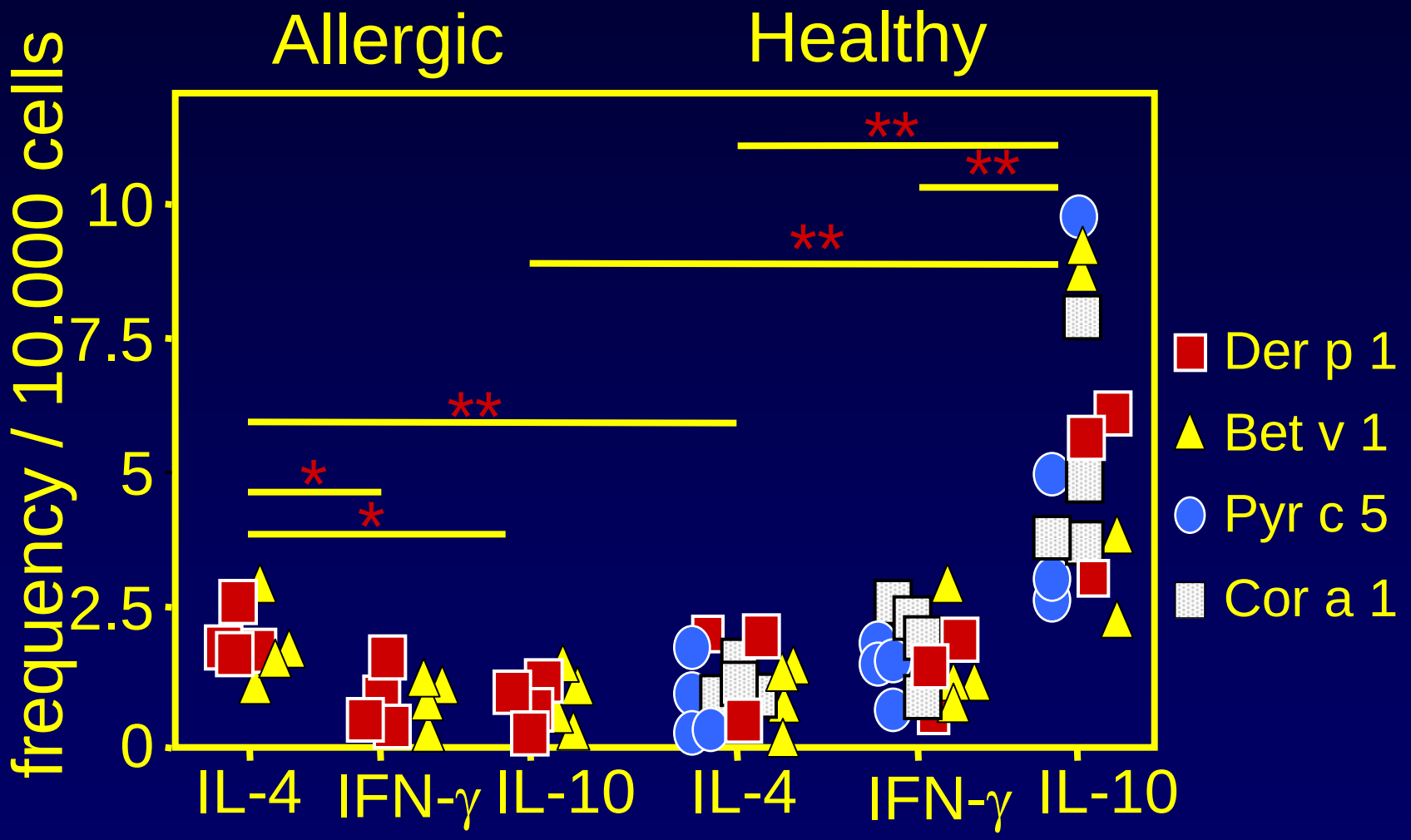




Decreased frequency of PLA-specific IL-4- and IFN-γ-secreting T cells, increased frequency of IL-10-secreting T cells is observed 7 days after ≥20 bee stings

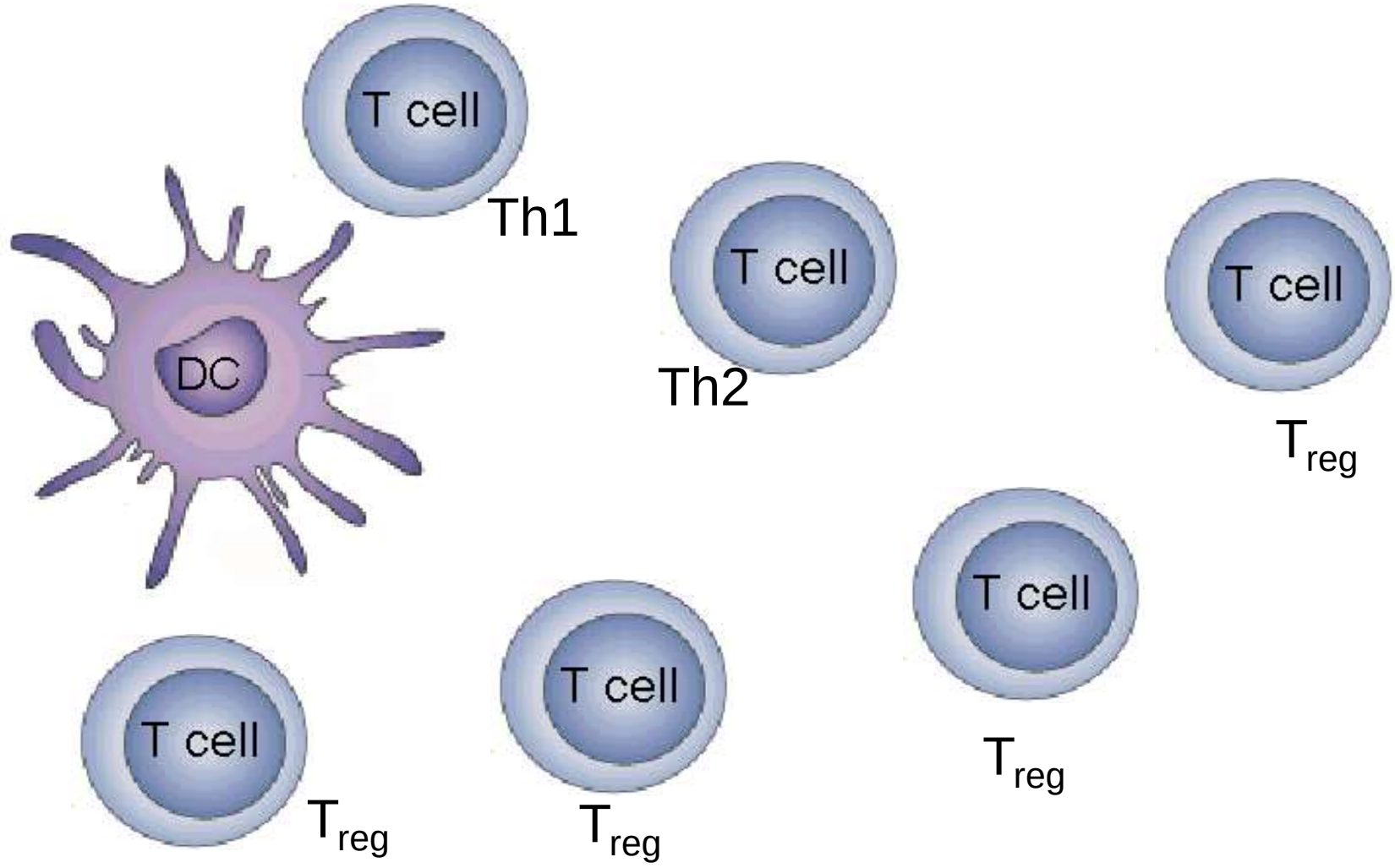
*: $p<0.001$
n:5 beekeepers

Aeroallergen-specific T cell frequency in health and allergy

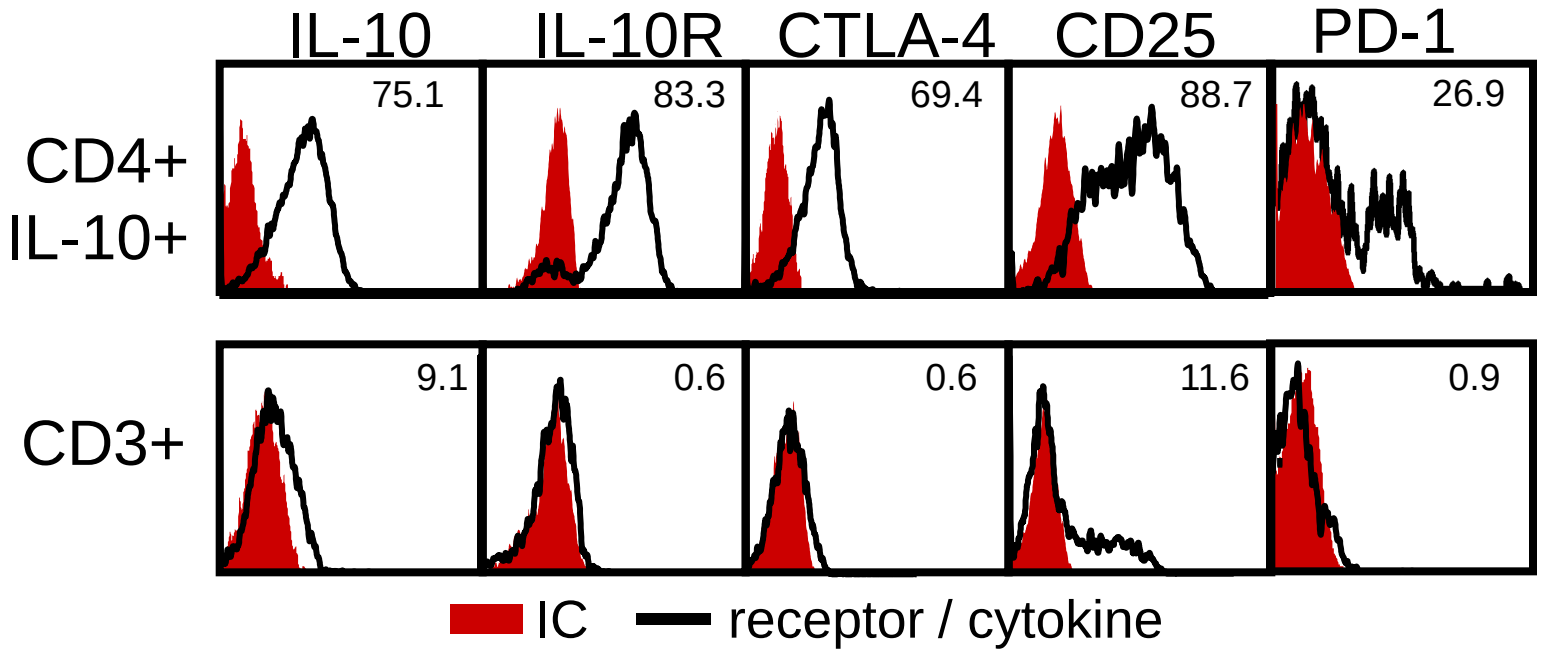


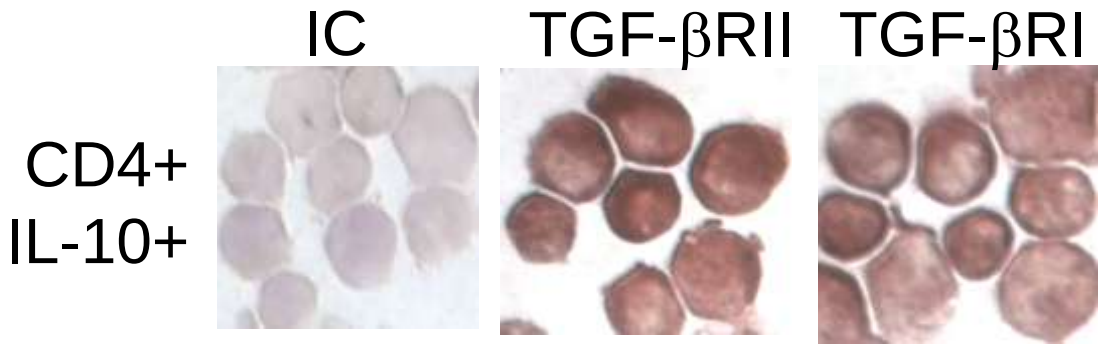
Akdis et al. J Exp Med 2004;199:1567-75

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



T_{Reg} cells in allergy: multiple suppressor factors



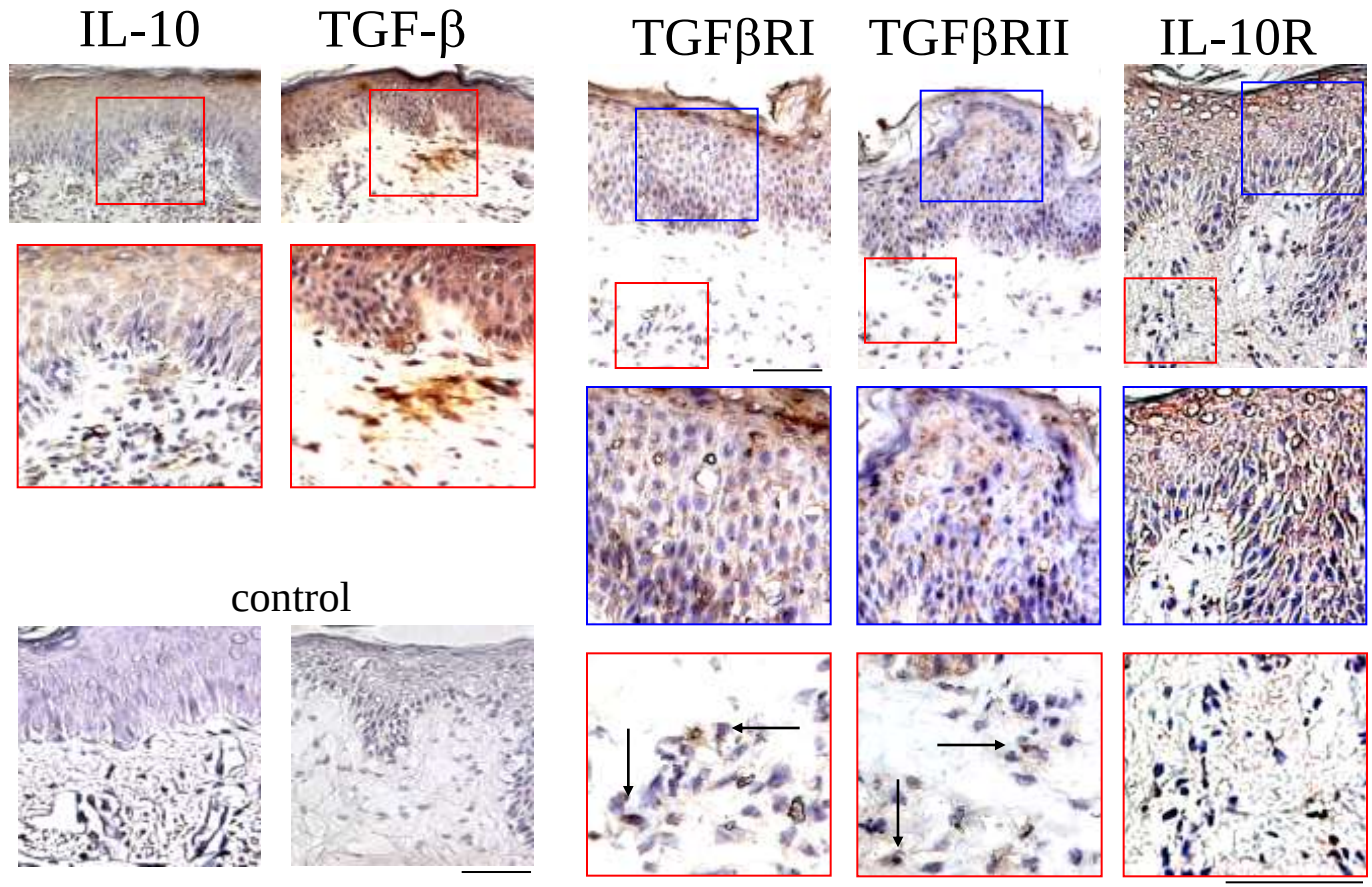


IL-10 suppresses IgE and induces IgG4

J. Clin. Invest.
1998; 102: 98

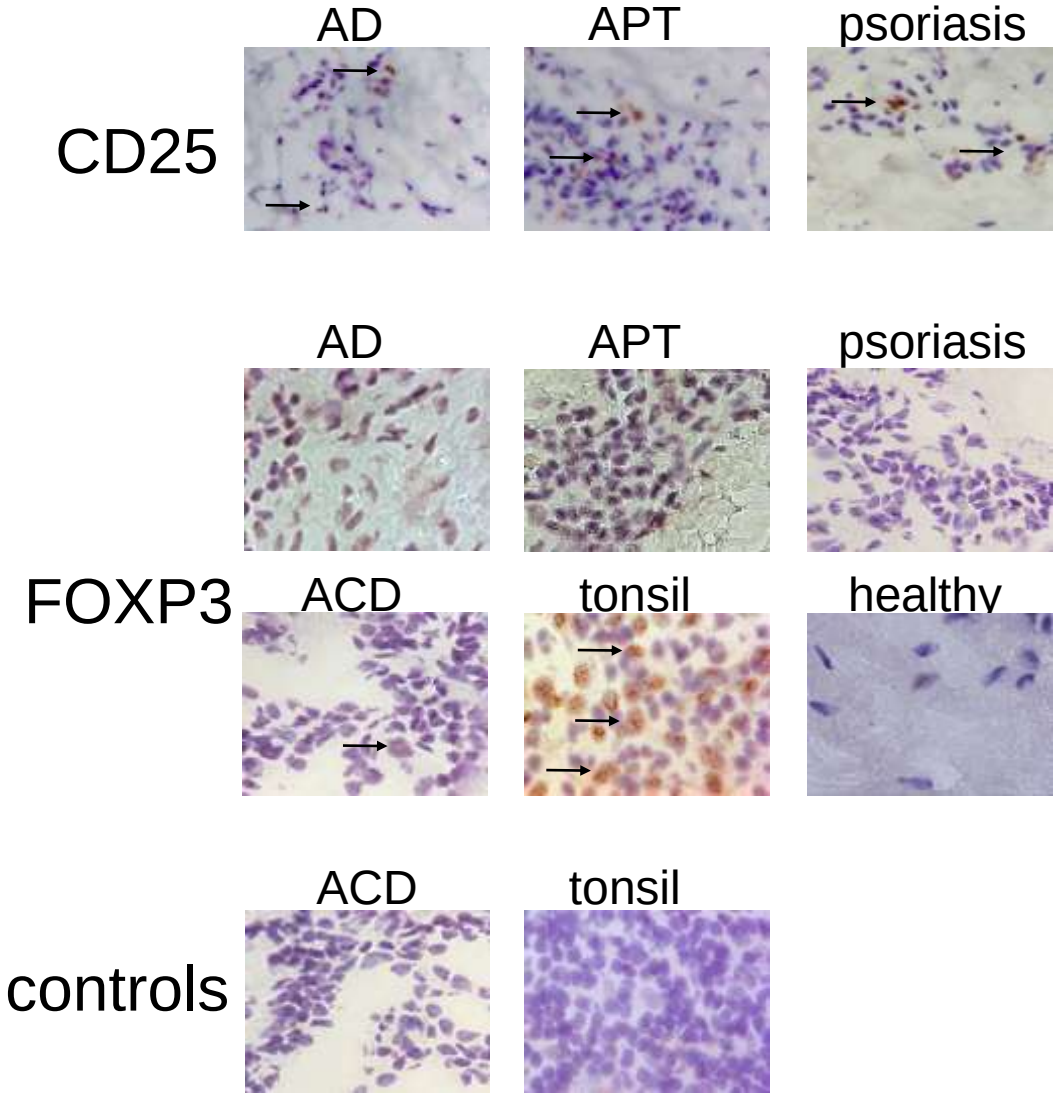
TGF-β
suppresses IgE
and
induces IgA

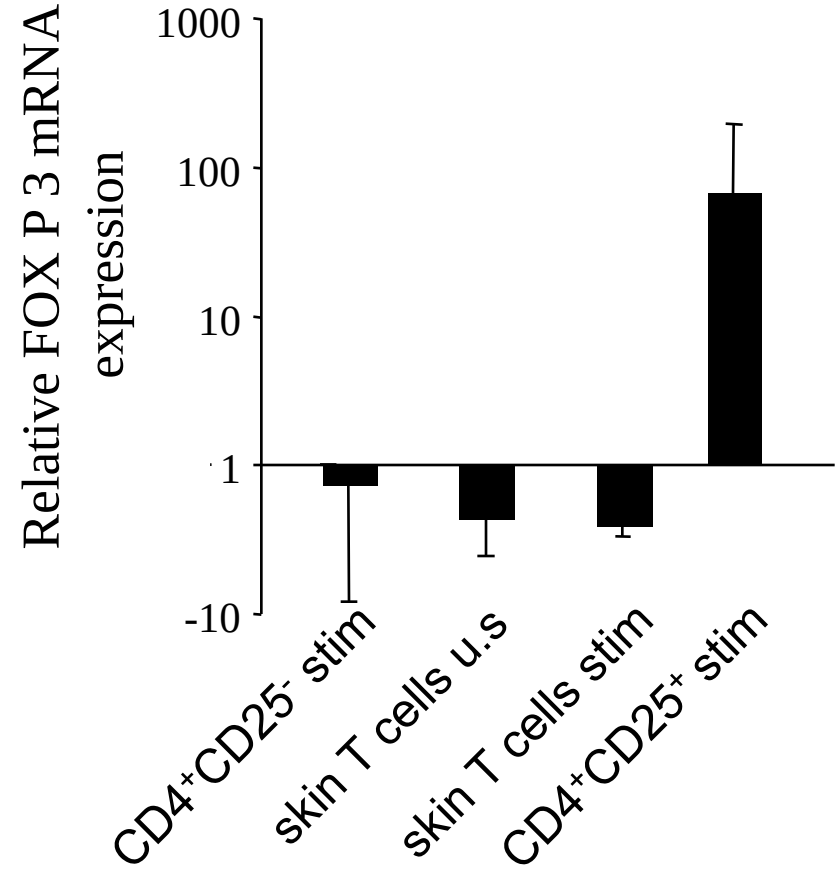
IL-10, TGF-β and their receptors are expressed in AD skin



Verhagen et al. JACI 2006

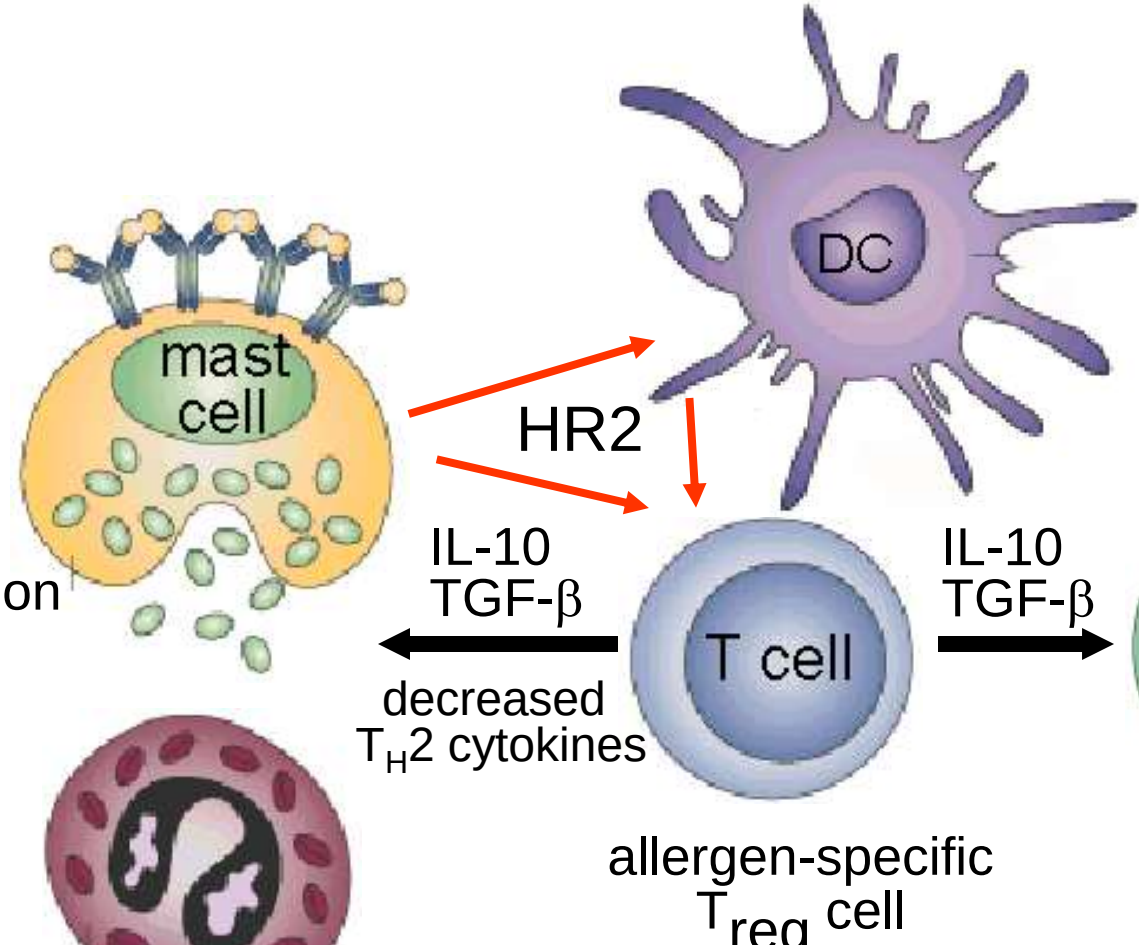
CD4+CD25+FoxP3+ T_{Reg} cell deficiency in atopic dermatitis and psoriasis lesions





Verhagen et al. JACI 2006

T_{Reg} 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

- Axel Trautmann
- Sven Klunker
- Alison Taylor
- Johan Verhagen
- Maya Zimmermann
- Flurina Meiler
- Judith Zumkehr
- Tomasz Basinski

- Reto Crameri
- Carsten Schmidt-Weber

- Cezmi Akdis

Immune tolerance

- 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. Kroczek, Berlin
- M. Colonna, St Louis
- E. Flory, Langen
- S. Viehts, 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

DAVOS

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

SIAF

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 deserts 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 firsthand 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.

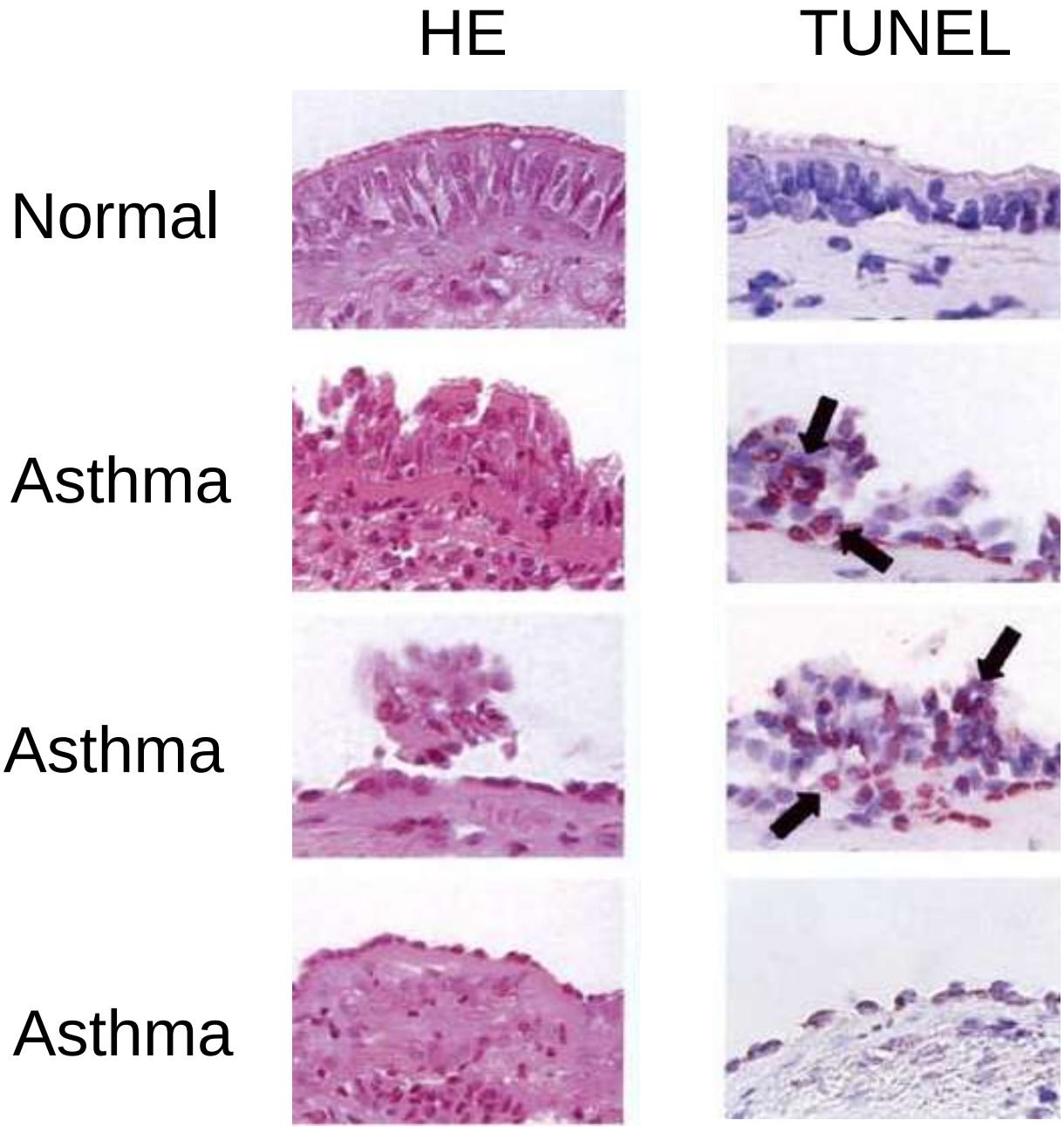
Organisator:
Cezmi Akdis
Organizing comitee:
Carsten Schmidt-Weber
Mübeccel Akdis
Reto Crameri
In:
Davos, congress center
Abstract submission:
15 January 2007 - 15 February 2007
Early registration deadline:
15 December 2006
Meeting style:
Symposium & workshop, practical workshops
Meeting organization:
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
Registration Fee:
500 .- Swiss Francs
Fellows in training: 200.- Swiss Francs

World Immune Regulation Meeting

Special focus on regulatory cells

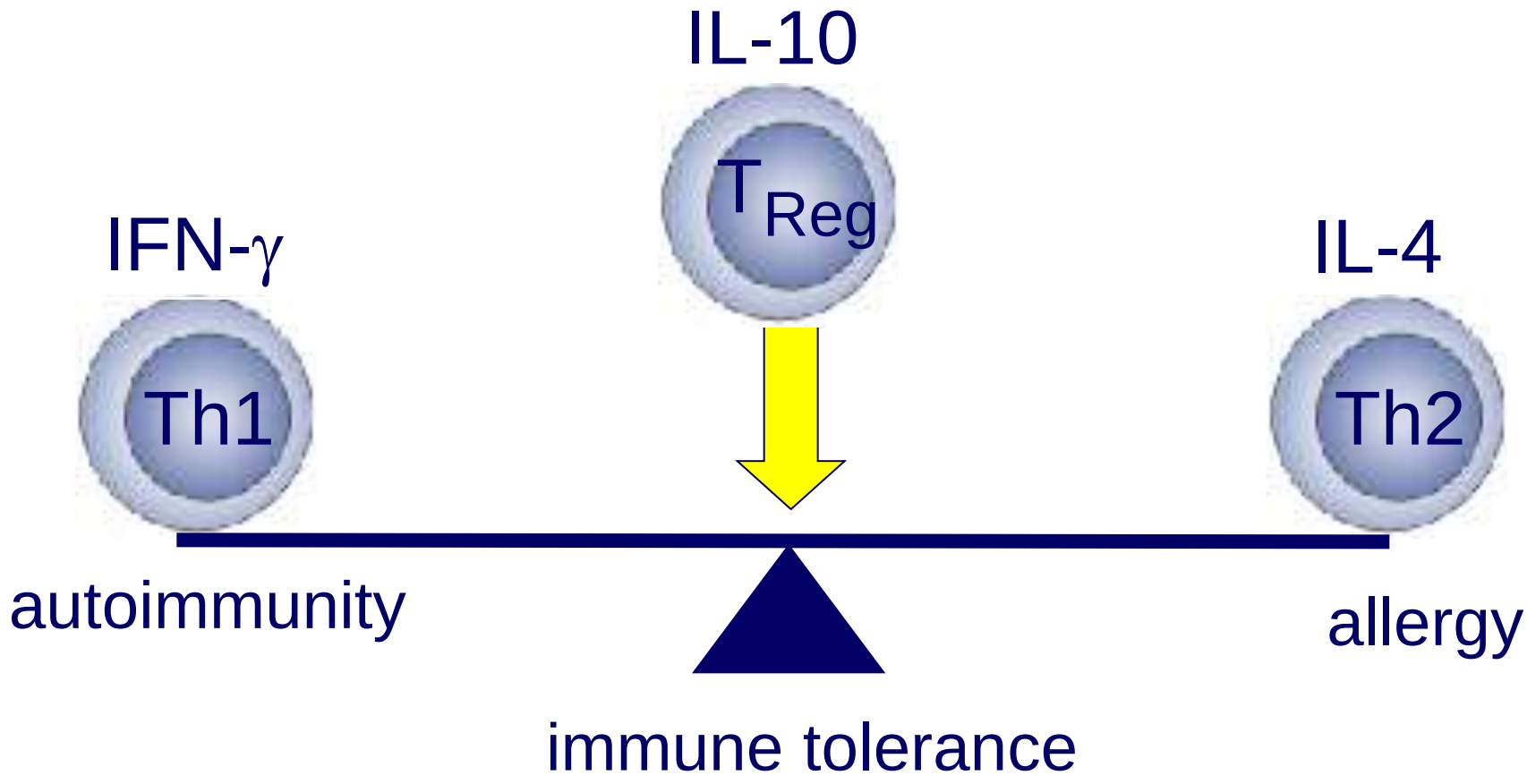
11 - 15 April 2007
Davos - Switzerland

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

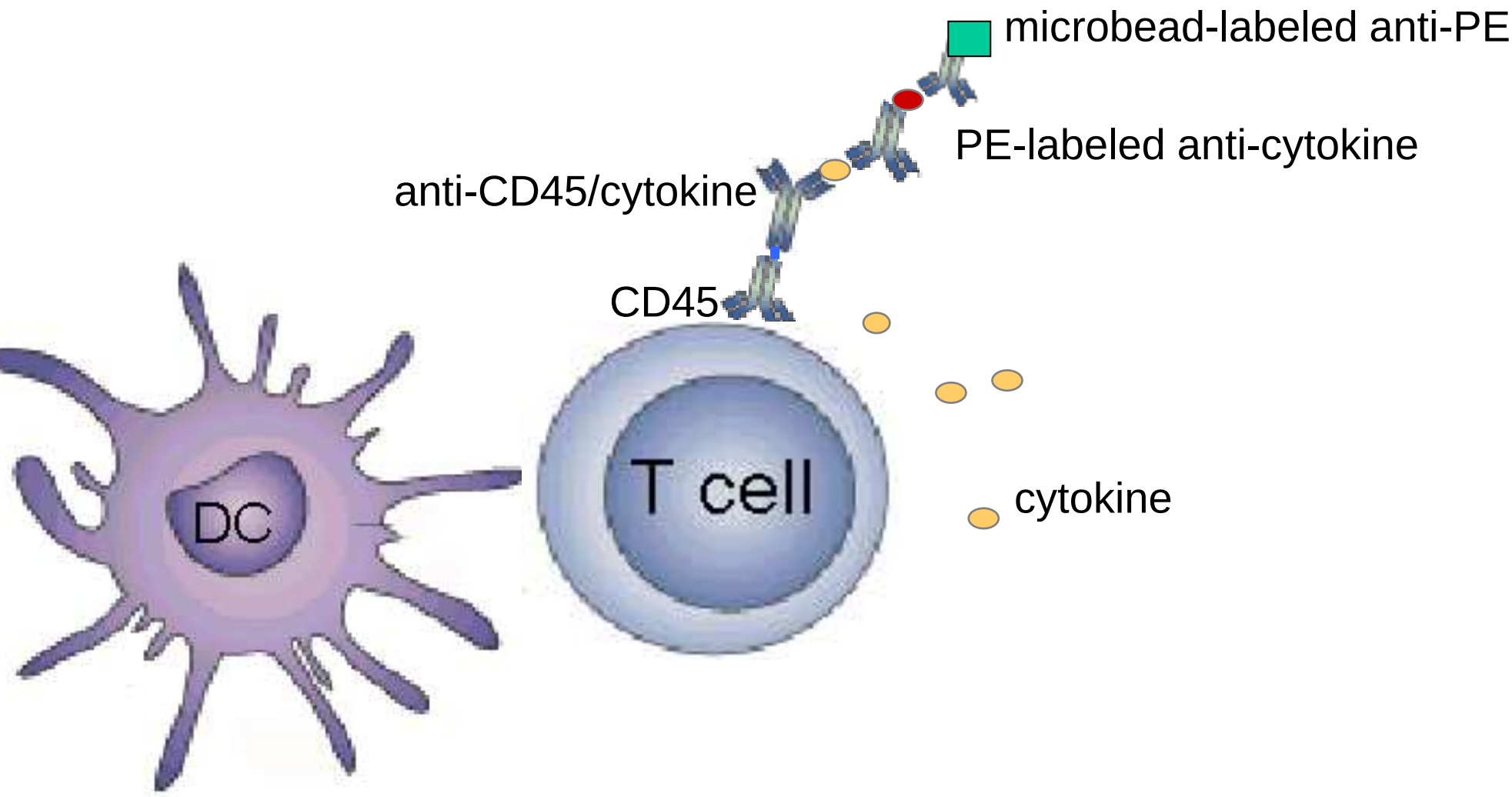


bronchial biopsies

Trautmann et al. 2002, 2005


IL-10
T Reg
IFN-γ
IL-4
Th1
Th2
autoimmunity
allergy
immune tolerance

Purification of allergen-specific cytokine-secreting T cells



Allergic inflammation (late phase)