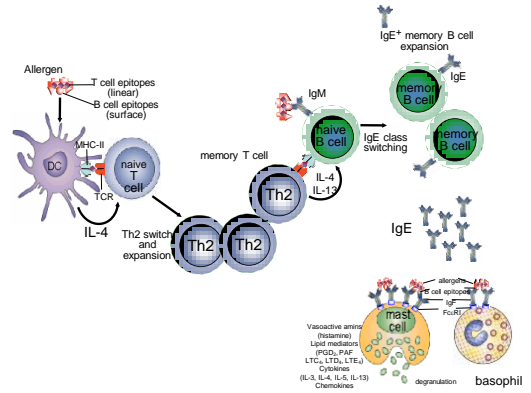


Mechanisms of peripheral tolerance and role of B regulatory cells

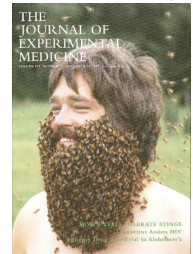
Mübeccel Akdis
Swiss Institute of Allergy and Asthma Research (SIAF)



Which human antigen-specific models are we using?

Beekeepers:

- Show full allergen tolerance Tr1 cells
- 1000x higher allergen-specific IgG4



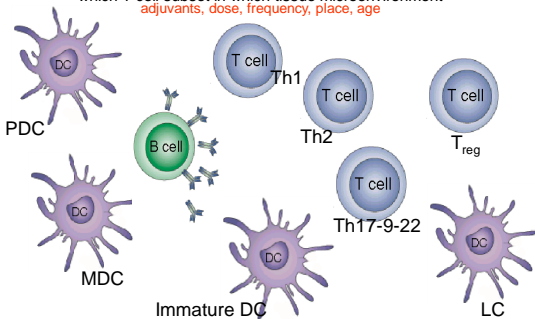
Patients and healthy individuals

allergen-SIT, **biologicals**
blood, **tonsils**,
biopsies of affected tissues,
3D tissue equivalents

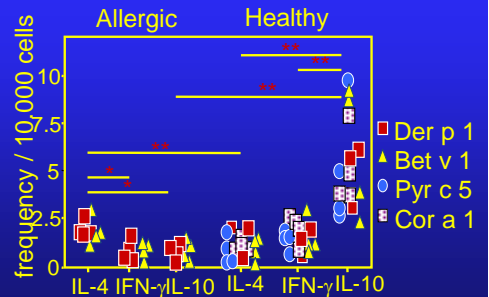
- Meiler 2008, J. Exp. Med.
- Trautmann A 2000, J. Clin Invest.
- Jutel 2001, Nature
- Akdis C 1996, J. Clin. Invest.
- Akdis C 1998, J. Clin. Invest.
- Akdis M 2004, J. Exp. Med.
- Klunker 2009, J. Exp. Med.

It is very difficult to cope with a primed and established immune response

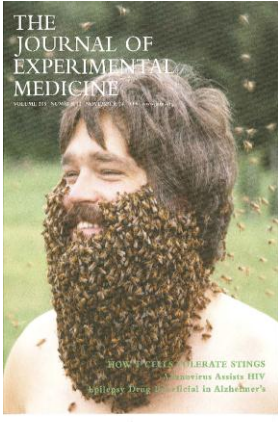
which one will be the first and preferential APC to present the antigen to which T cell subset in which tissue microenvironment
adjuvants, dose, frequency, place, age



Aeroallergen-specific T cell frequency in health and allergy



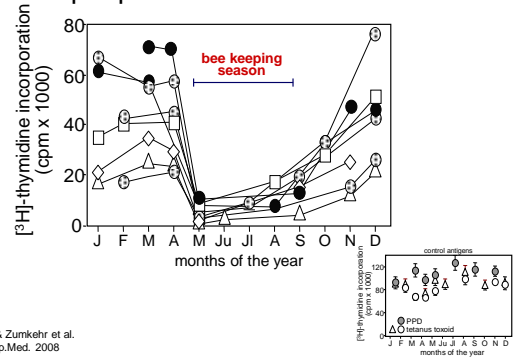
M. Akdis et al. J Exp Med 2004



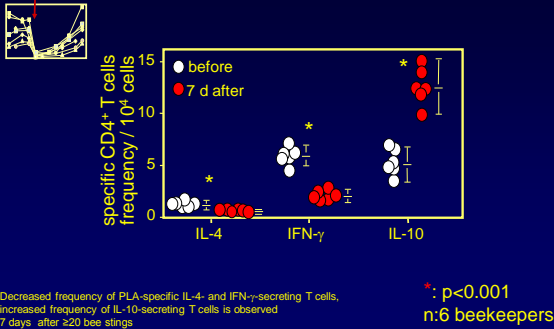
Beekeepers show way to allergen tolerance

The Journal of Experimental Medicine, November 10, 2008

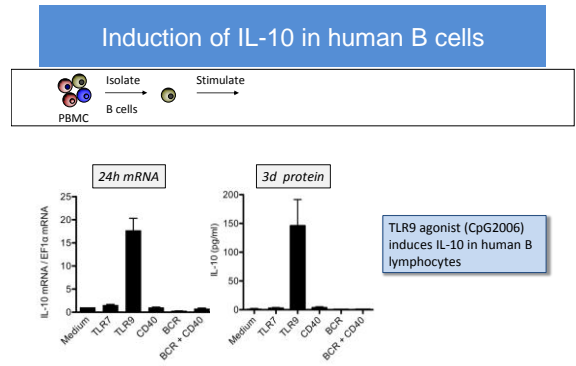
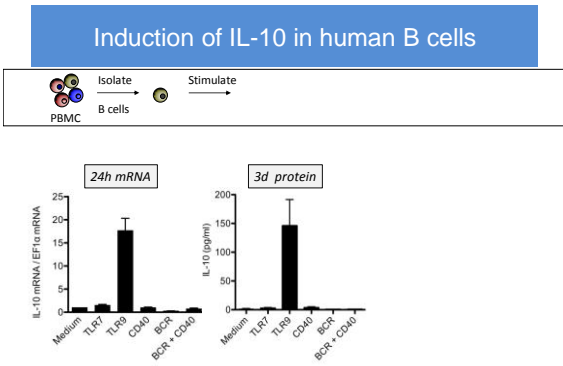
High dose antigen-induced peripheral T cell tolerance



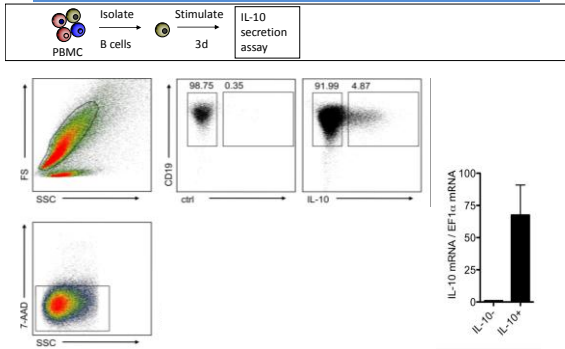
frequency of PLA-specific cytokine secreting T cells before and after live bee stings



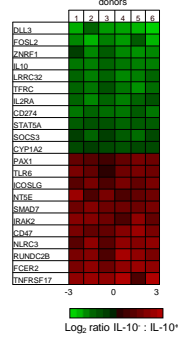
B regulatory Cells in Allergen Tolerance



Sorting of IL-10-secreting B cells

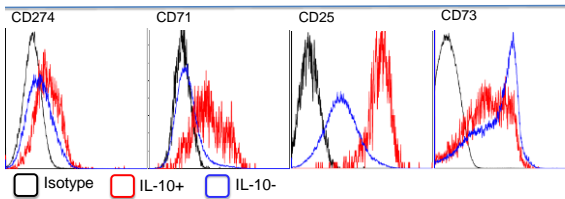


Gene expression in IL-10⁻ vs IL-10⁺ B cells

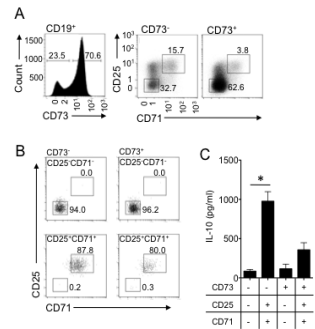


Surface markers upregulated in IL-10⁺ B cells

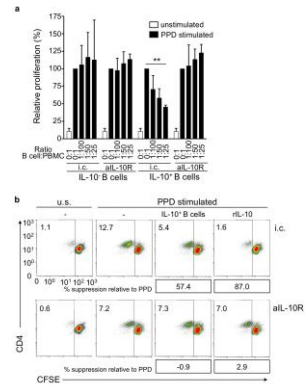
Gene	Expression in IL-10 ⁺ B cells
CD25 (IL-2RA)	↑
CD274 (PD-L1)	↑
CD71 (TFRC)	↑
CD73 (NTSE)	↓



Sorting of CD25⁺CD71⁺ B cells



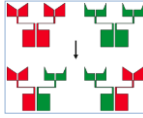
Suppressive capacity of IL-10⁺ B cells



van de Veen et al. Figure 3

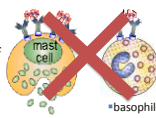
IgG4: A non-inflammatory antibody

- Does not fix complement
- Fab-arm exchange → Functionally monovalent
Prevents formation of immune complexes



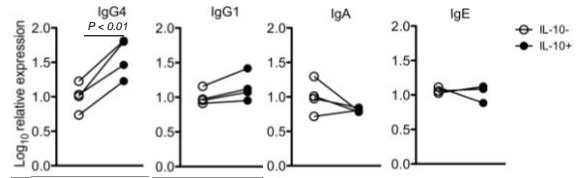
Protective effects in allergy

- Blocking antibody:
 - Compete with IgE for allergen binding
 - Prevent allergen-mediated crosslinking of surface bound IgE

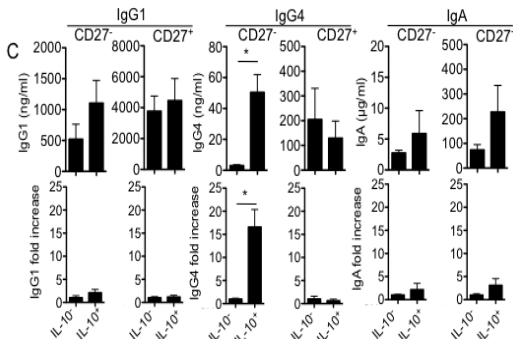


van der Neut Kolfshoten et al., 2007, Science

IL-10-secreting B cells express high levels of IgG4

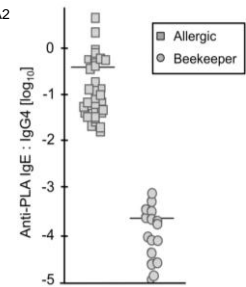


IL-10-secreting B cells express high levels of IgG4



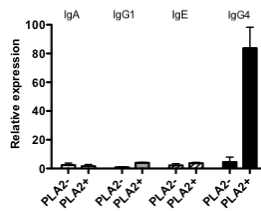
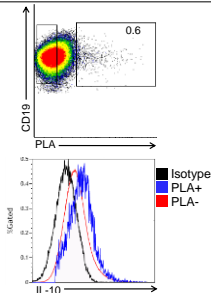
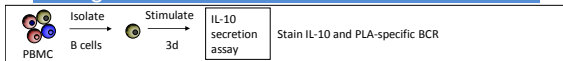
Beekeepers as a human model to study regulatory B cells

- Beekeepers:**
- Develop tolerance to phospholipase-A2 (PLA)¹
 - High PLA-specific IgG4

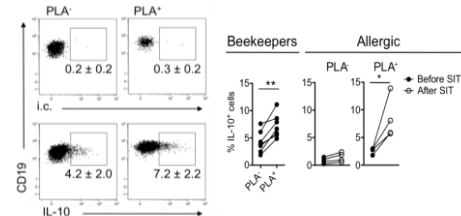


1) Meiler et al., 2008, J Exp Med

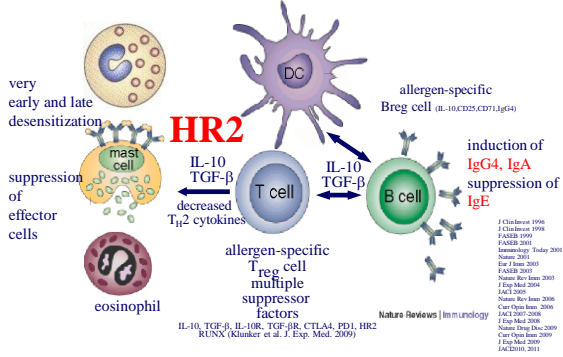
PLA-specific Beekeeper B cells produce higher levels of IL-10 than other B cells



PLA-specific B cells produce higher levels of IL-10 in Beekeepers and in beevenom allergic individuals after SIT

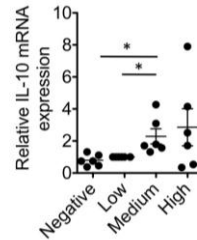
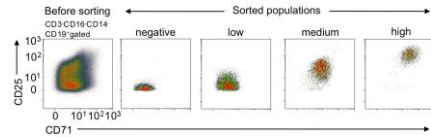


Immune tolerance to allergens in healthy immune response and successful SIT

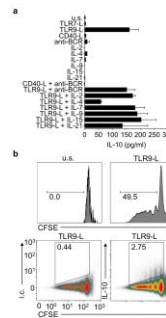
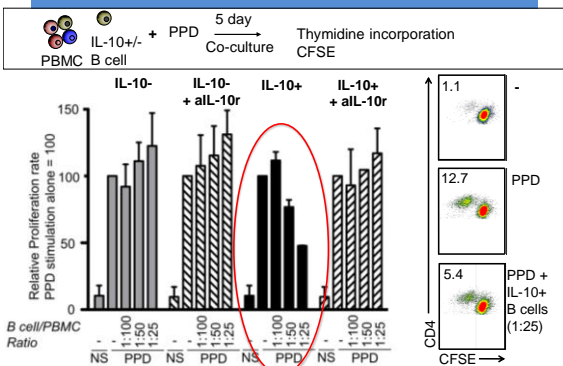


- Willem van De Veen
- Barbara Stanic
- Anna Zalczka
- Stefan Sollner
- Deniz Akdis
- Ozge Soyer
- Flurina Meiler
- Judith Zumkehr
- Sven Klunker
- Beate Ruckert

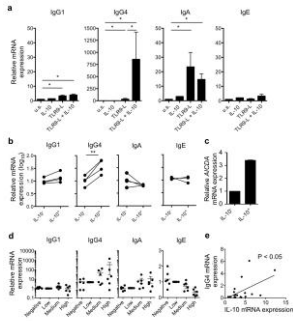
- R. Cramer
C. Rhyner
S. Flückiger
I. Daigle
G. Schnetzler
C. Akdis
- UNI Zürich
T. Kündig
P. Johansen
J. M. Martinez
Gomez
G. Senti



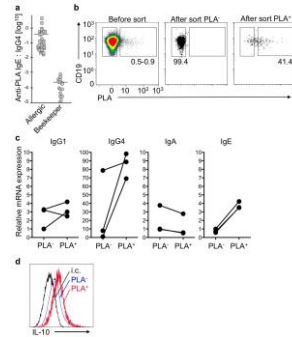
Suppressive capacity of IL-10+ B cells



van de Veen et al. Figure 1



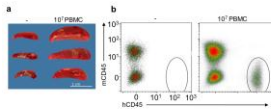
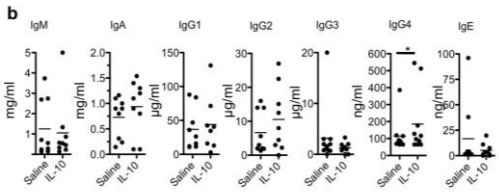
van de Veen et al.
Figure 4



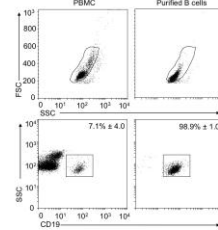
van de Veen et al.



van de Veen et al.
Supplementary figure 1

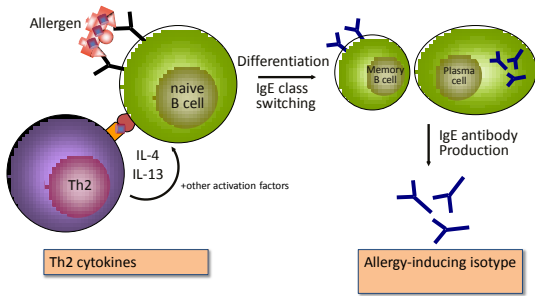


van de Veen et al.
Supplementary figure 3

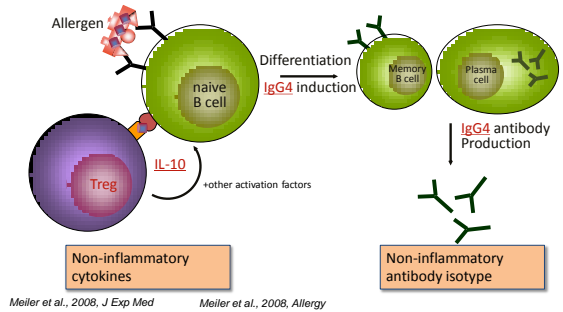


van de Veen et al.
Supplementary figure 4

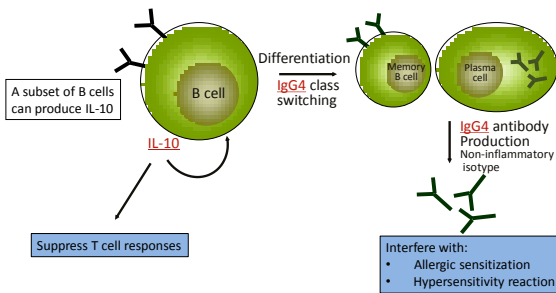
B cells during allergic sensitization



B cells during tolerant response



Aim of study



Summary

- Majority of IL-10+ B cells are CD25^{hi} CD71^{hi} CD274⁺CD73^{low}
- IL-10-secreting B cells suppress antigen-specific proliferation
- IL-10-secreting B cells show elevated IgG4 production
- Beekeepers
 - High levels of PLA-specific IgG4
 - PLA-specific B cells can produce IL-10 and are mainly IgG4-positive

Acknowledgements

SIAF

Supervision
Mübeccel Akdis
Cezmi Akdis

Lab work
Barbara Stanic
Gorkem Yaman
Stefan Söllner
Beate Rückert



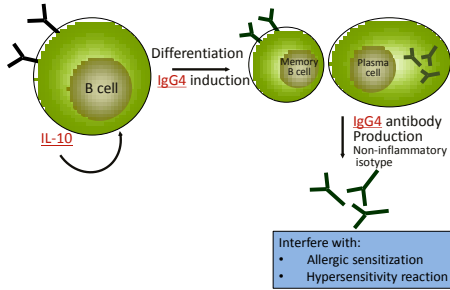
Human Regulatory B cells in Allergic Disease

4th MIM retreat, 4-6 September 2011, Chandolin

Willem van de Veen
Swiss Institute of Allergy and Asthma Research
University of Zürich
Davos, Switzerland

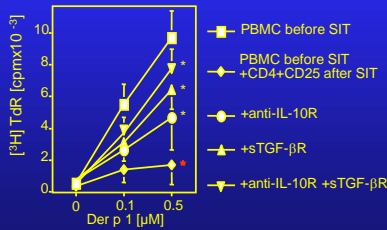


Regulation of IgG4 production



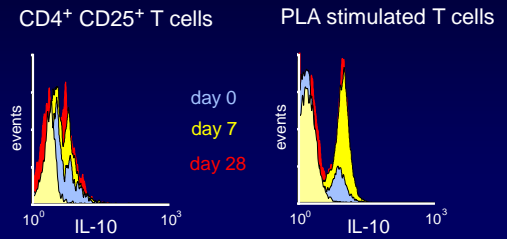
	Allergen-specific T cell response
Healthy	No response
	Th0 response in PBMC and specific T cell clones with low frequency
Allergic	Tr1, particularly IL-10-dominating response with relatively high frequency
	Th2 response with varying quantities of IL-4, IL-5 and IL-13, detectable IL-10 and IFN- γ

IL-10 and TGF- β from Treg cells In peripheral T cell tolerance during aeroallergen SIT



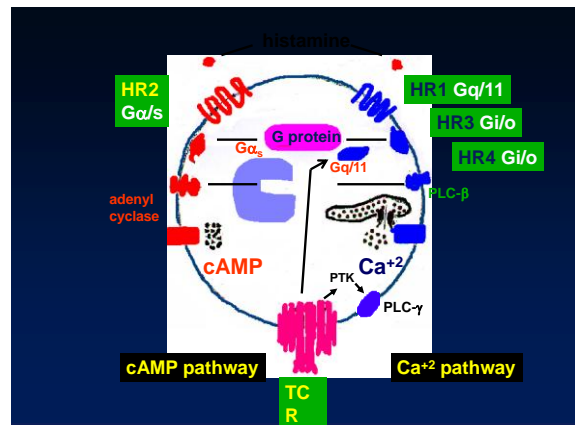
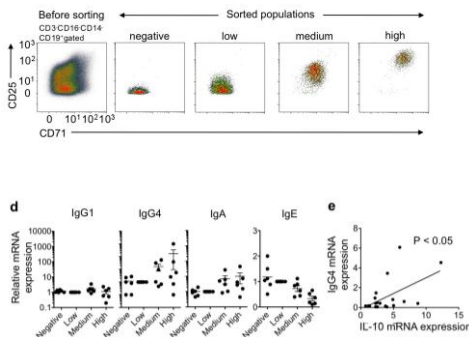
M. Jutel & M. Akdis et al. EJI 2003

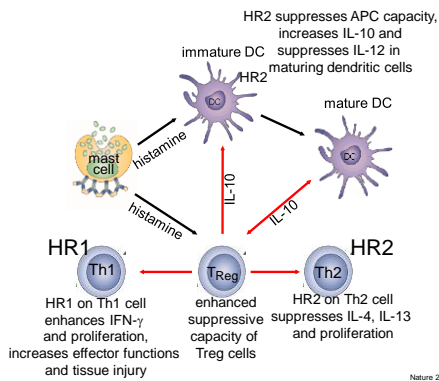
IL-10 production in T cells during specific immunotherapy



Direct demonstration

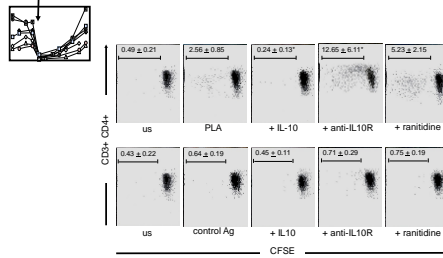
J. Clin. Invest. 1998; 102: 98





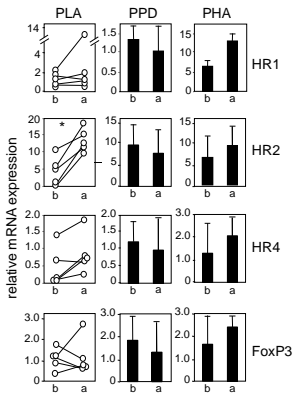
Nature 2001
Curr Opin Immunol. 2002

Breaking of peripheral T cell tolerance by blocking IL-10R and HR2



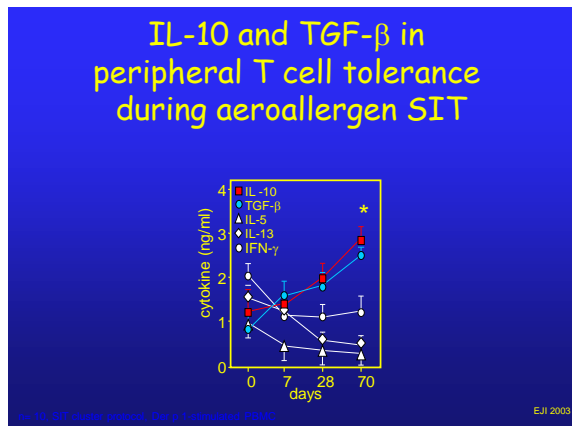
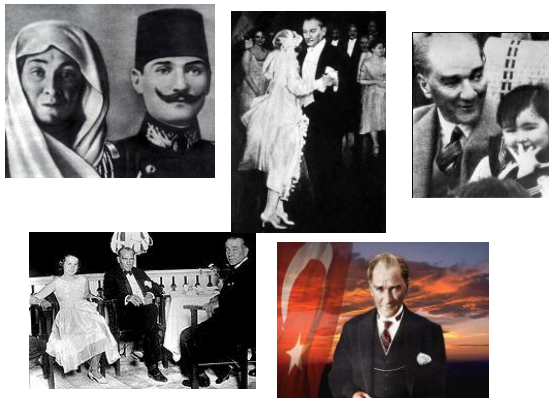
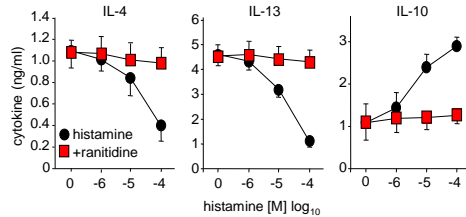
active suppression by IL-10 and histamine via HR2 after multiple bee stings Meiler & Zumkehr et al. J.Exp.Med. 2008

Upregulation of HR2 on allergen-specific T cells by natural bee stings

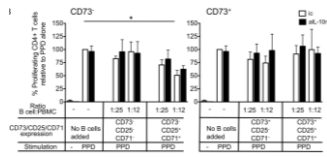


Meiler & Zumkehr et al. J.Exp.Med. 2008

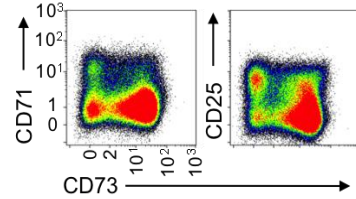
Histamine induces IL-10 production in Th2 cells via HR2



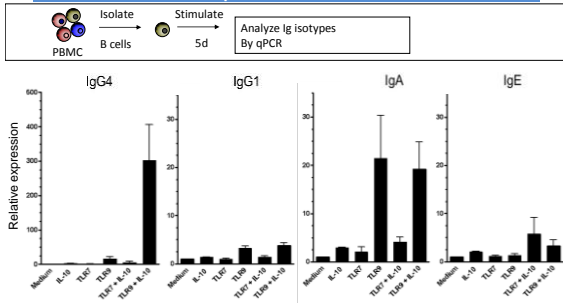
Suppressive capacity of IL-10+ B cells



Sorting of CD25+CD71+ B cells



Regulation of immunoglobulin expression by CpG and IL-10



Regulation of immunoglobulin expression by CpG and IL-10

