

3rd International Conference and
Exhibition on
**Clinical & Cellular
Immunology**

September 29 - October 01, 2014
Baltimore, USA

Immune mechanisms implicated in
the tolerance induction to food
allergens in children

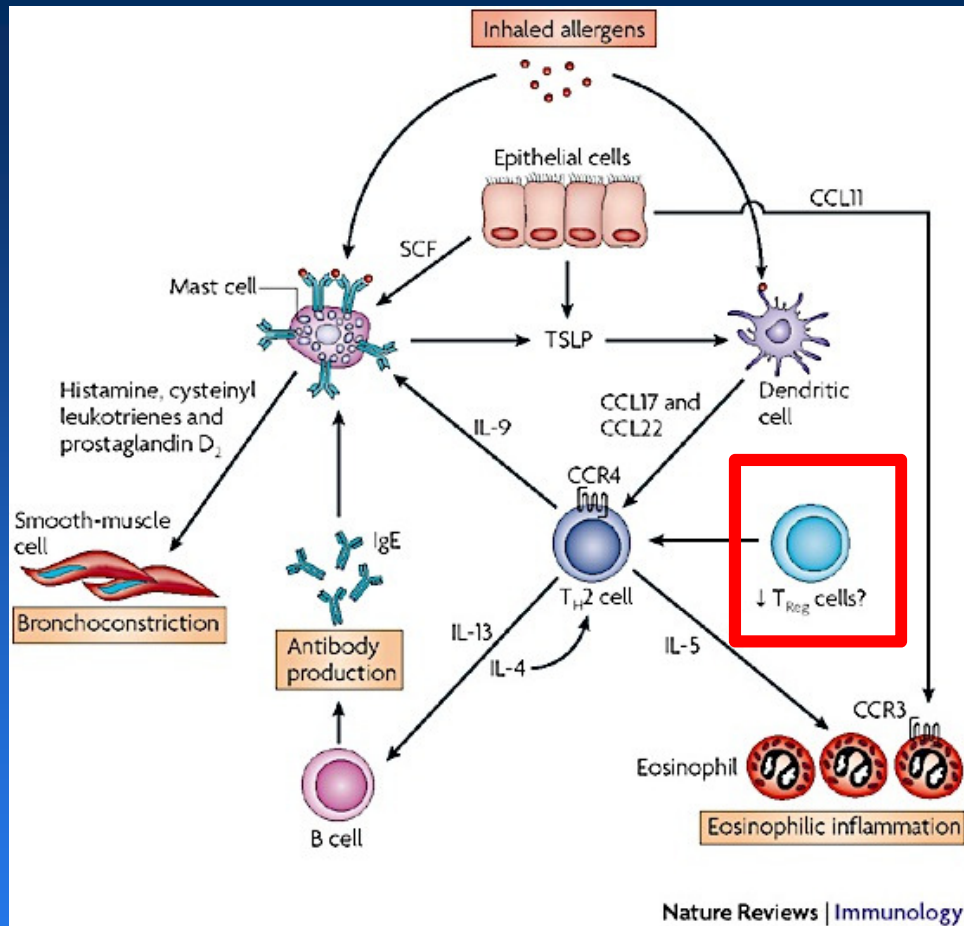
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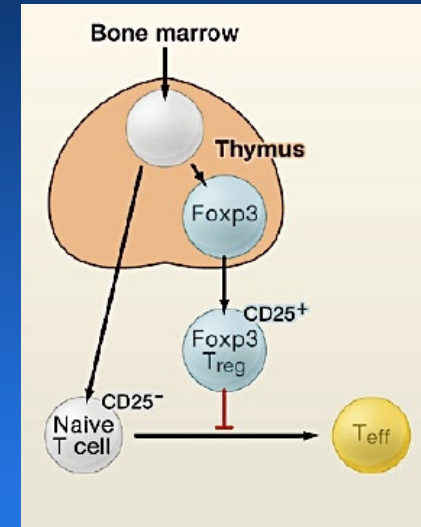


Allergy is caused by a reaction of the immune system against substances that are normally innocuous

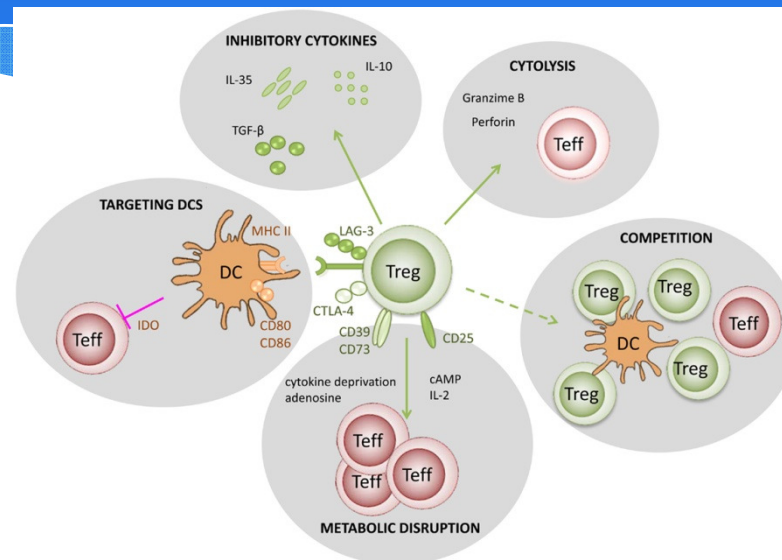
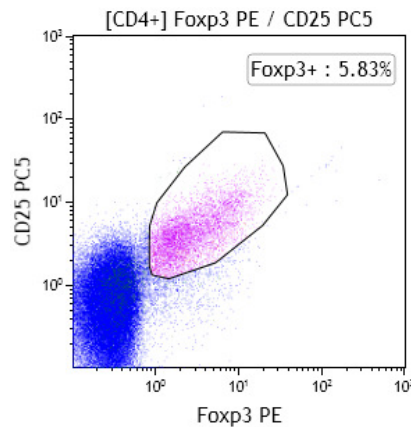
Allergy

Regulatory T cells (Treg) → Subpopulation of CD4+ T cells with a suppressive activity

- Treg are identified as CD4+CD25+Foxp3+ cells
- Treg are considered a crucial component of immune system for preserving peripheral tolerance and the correct immune homeostasis

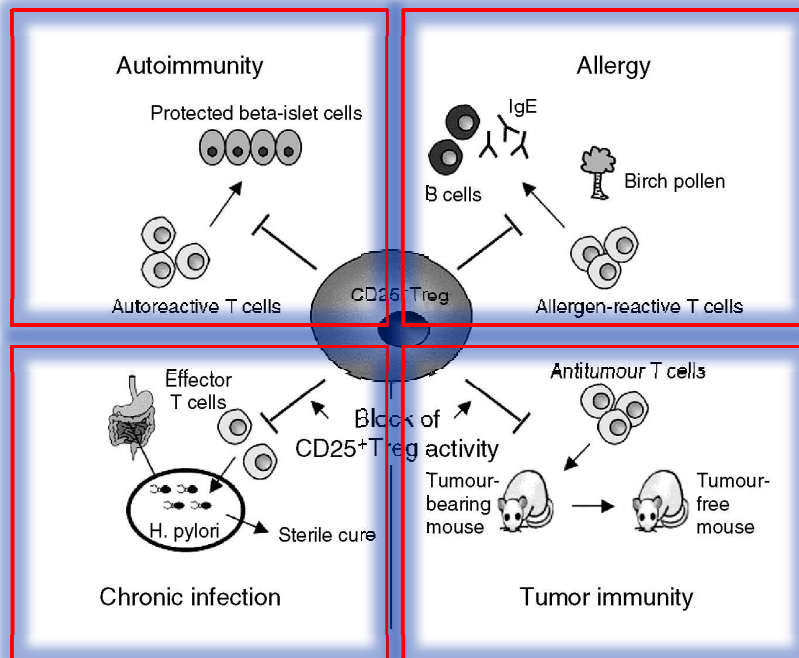


Treg cells



Células Treg

Treg cells play a crucial role preserving the **Immune Homeostasis**

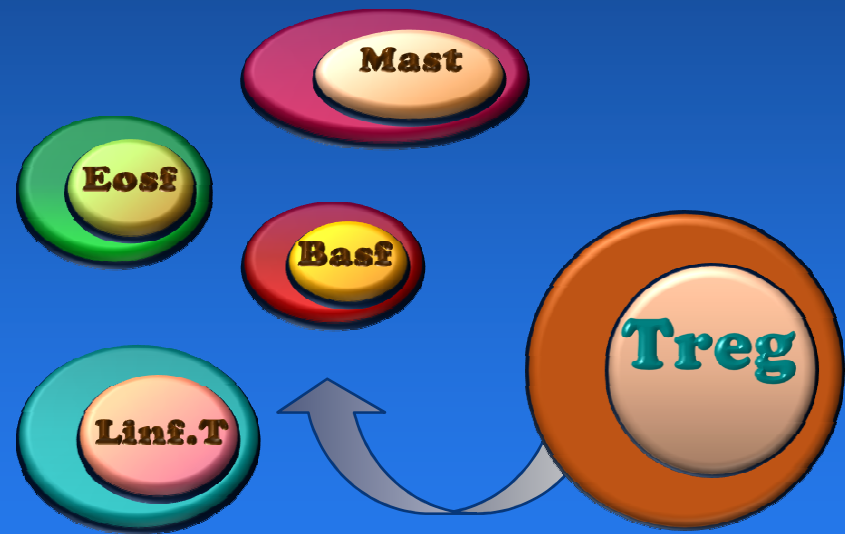
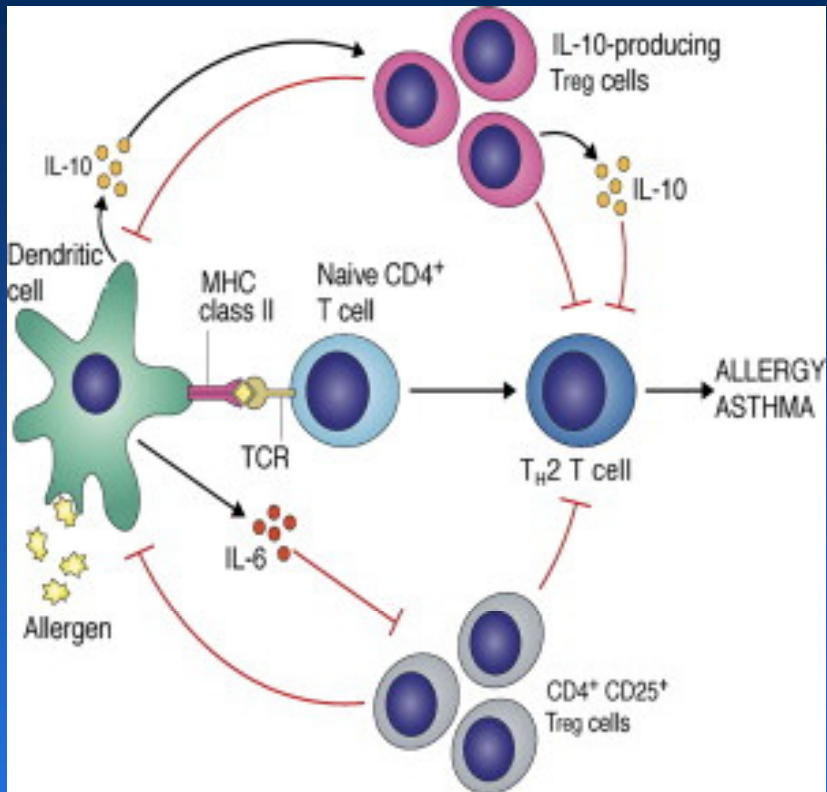


Treg induce tolerance to self-antigens (autoimmune dis.) and non-self antigens (transplant)

Treg induce tolerance to allergens and reduce inflammation

Treg have a dual role in infections, reducing the inflammation but also reducing specific responses.

Treg inhibit immune responses to tumour antigens, promoting tumour growth.



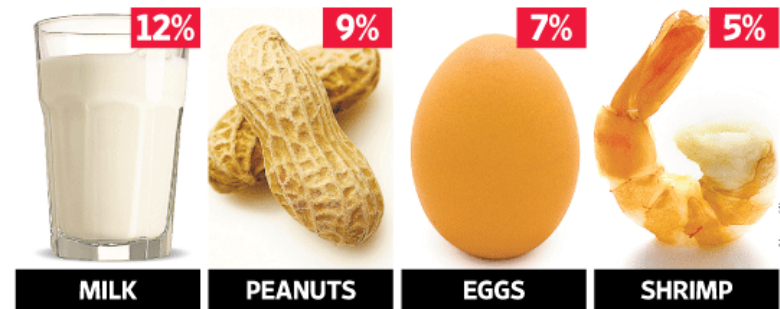
Treg cells

Food Allergy

- estimated prevalence of > 5% in children
- most frequent reason for anaphylactic reactions

A Possible Overreaction

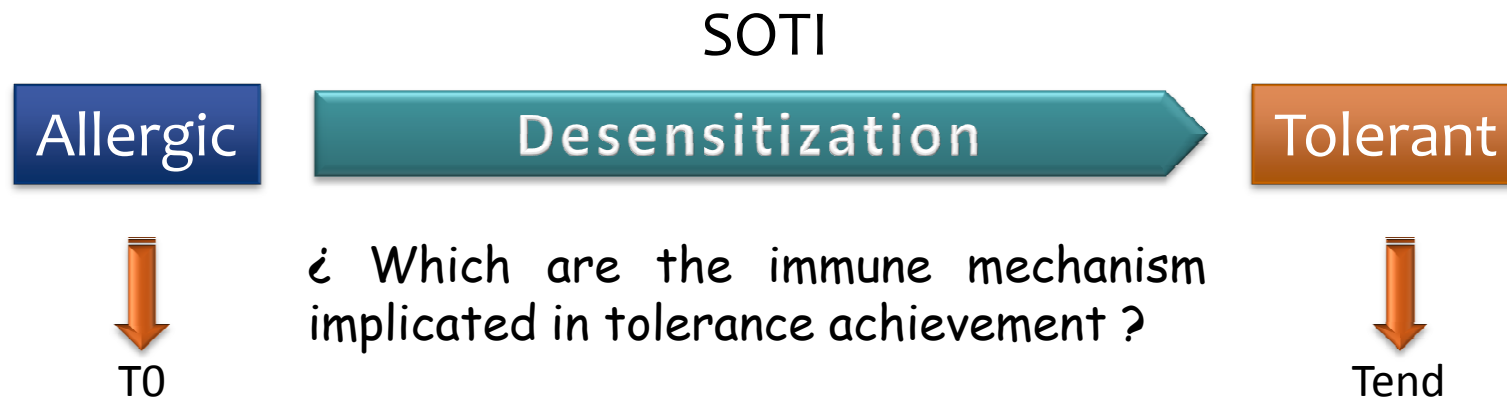
The percentage of children under 18 whose blood samples tested positive for antibodies to these foods. But since the tests only indicate the presence of antibodies and not an actual allergic reaction, the percentages may be high.

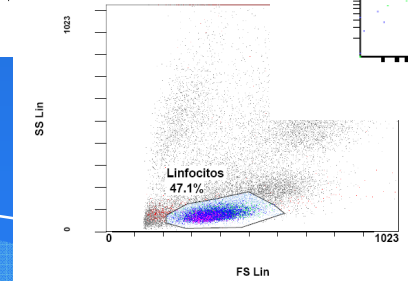
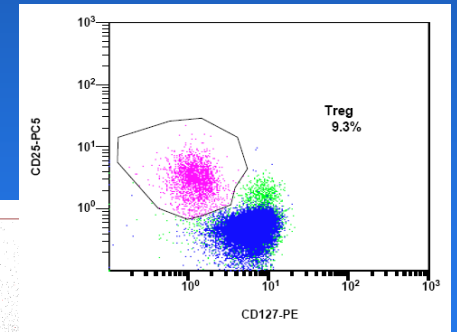
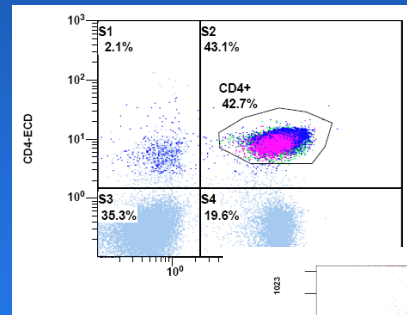
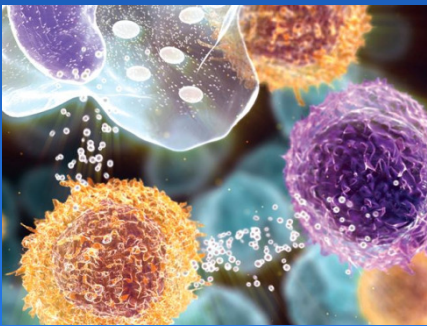
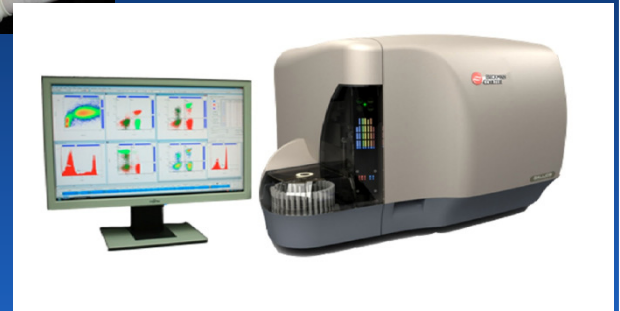
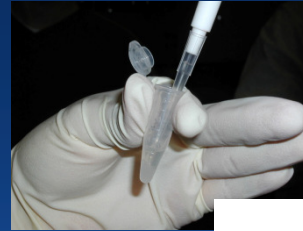


Source: Centers for Disease Control and Prevention, 2005-2006

Precedents

- In most of the cases Food Allergy could be reverted in Children (SOTI)
- Children have a preserved thymic function and a high plasticity of the immune system
- Thymic generation of Treg (suppressive) cells could be related with the tolerance achievement





Methods

19 Children with Egg allergy + 12 Healthy Controls

Specific Oral Tolerance Induction (SOTI)

Oral administration of increasing amounts of a food allergen to achieve clinical tolerance

Powdered pasteurized egg mixed with juice or milkshakes

- Day 1: 1 → 3 → 9 → 18 (Total: 31 mg)
- weekly increases until 10 g of powdered egg (1 egg)
- Tolerance of 10 g → desensitised
- Normal diet



SOTI

Immune changes after SOTI

ALLERGY → TOLERANCE

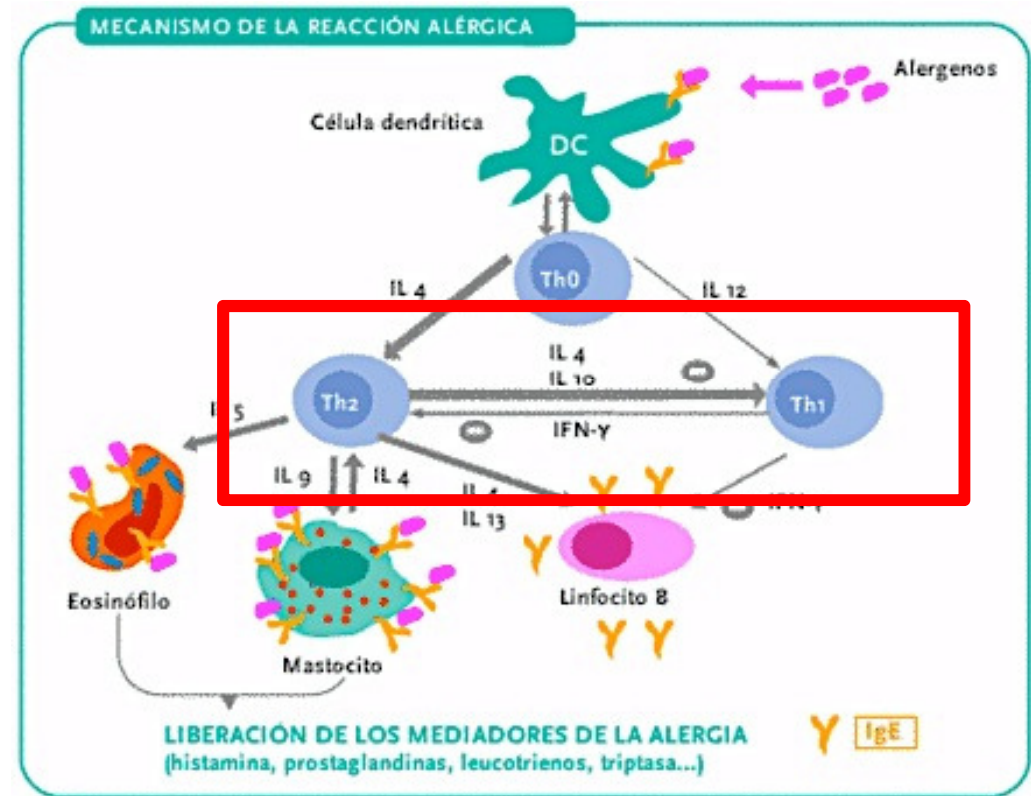
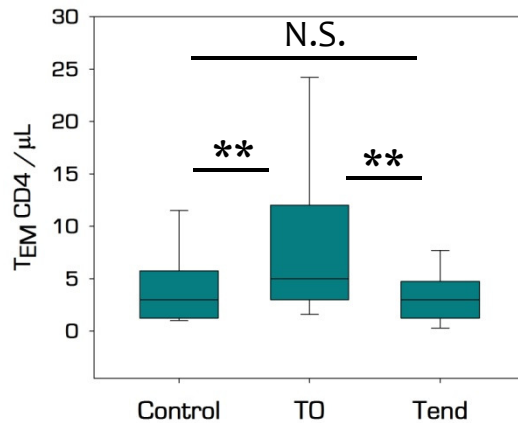
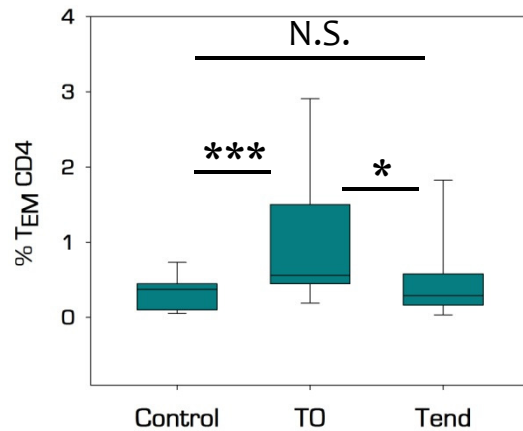
16/19 (84,2%) Desensitized
9,7 weeks

	Percentage			Cells/ μ L		
	T0	Tend	<i>p</i>	T0	Tend	<i>p</i>
Monocytes	5.63 (4.91-7.38)	6.54 (4.95-7.93)	0.723	327 (263-475)	383 (286-506)	0.717
Basophils	1.26 (0.91-1.87)	1.18 (0.74-1.57)	0.985	71 (52-86)	75 (52-87)	0.655
Granulocytes	49.40 (42.8-55.4)	48.31 (40.8-52.1)	0.179	2624 (1772-3911)	2499 (2096-3207)	0.334
Neutrophils	84.17 (74.3-87.7)	84.06 (76.4-90.2)	0.642	2084 (1530-3337)	1982 (1744-2654)	0.281
Eosinophils	14.36 (10.9-23.6)	14.25 (8.9-20.0)	0.796	339 (231-660)	460 (274-631)	0.427

Immune changes after SOTI

	Percentage			Cells/ μ L		
	T0	Tend	p	T0	Tend	p
Total Lymphocytes	40.1 (30.9-45.4)#	41.1 (35.5-43.3)#	0.673	2217 (1750-2818)	2533 (2030-2892)	0.312
CD4+ T cells	39.9 (34.7-42.7)	41.2 (37.6-42.4)	0.279	804 (697-1090)	942 (881-1220)	0.144
CD8+ T cells	24.4 (21.5-26.7)	22.2 (20.4-25.4)	0.565	548 (390-695)	600 (453-703)	0.668
NK cells	9.39 (6.9-10.2)	8.07 (7.2-10.8)	0.768	185 (153-270)	204 (152-260)	0.775
NKT cells	1.22 (0.9-2.1)	1.44 (1.0-1.8)	0.678	33 (20-48)	38 (22-44)	0.910
B cells	15.2 (12.5-18.6)	15.8 (13.4-18.1)	0.972	353 (203-507)	375 (287-493)	0.668
CD4+ T cells						
Naive	57.1 (52.9-62.6)	58.1 (50.4-68.8)	0.638	477 (382-625)	621 (478-758)	0.058
Memory	34.2 (29.2-36.4)	30.6 (25.6-36.8)	0.488	287 (242-410)	329 (253-418)	0.315
Activated	3.92 (3.0-4.8)	3.92 (2.3-5.8)	0.348	36 (26-48)	41 (27-73)	0.183
Effector	0.56 (0.45-1.5)	0.29 (0.16-0.58)	0.128	5 (3-12)	3 (1.2-4.7)	0.027*
RTEs	42.4 (39.2-49.2)	43.5 (40-56.1)	0.463	368 (277-489)	514 (404-650)	0.033*
CD38⁺CD45RO⁻	42.6 (31.4-51.7)	50.4 (42.6-57.6)	0.084	353 (263-596)	638 (415-718)	0.008*
CD8+ T cells						
Naive	57.5 (51.7-63.6)	57.6 (51.3-65.6)	0.920	303 (254-372)	327 (286-365)	0.775
Memory	24.8 (16.6-25.6)	22.6 (16.1-28.4)	0.826	140 (79-193)	150 (115-231)	0.433
Activated	4.18 (2.0-6.7)	6.68 (2.4-8.3)	0.282	22 (11-44)	51 (13-63)	0.073
Effector	14.5 (3.9-22.1)	15.5 (10.8-20.3)	0.776	76 (22-125)	95 (59-134)	0.410
RTEs	55.9 (46.1-58.6)	51.5 (48.2-61.4)	0.739	270 (227-316)	322 (263-355)	0.541

Effector CD4+ T cells



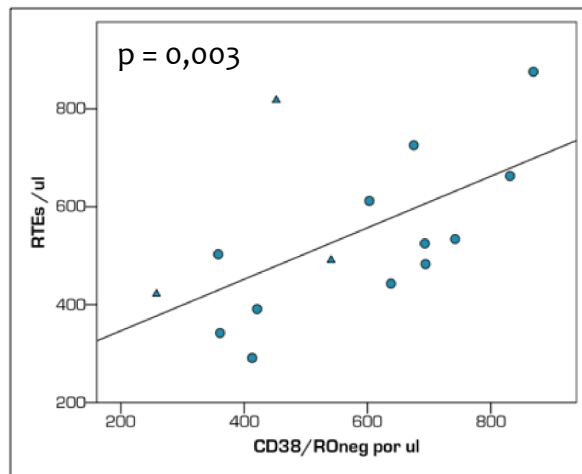
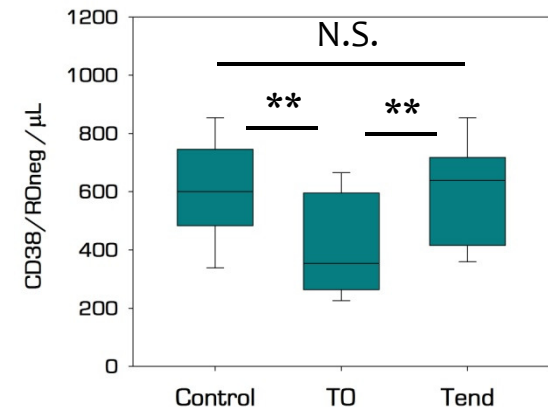
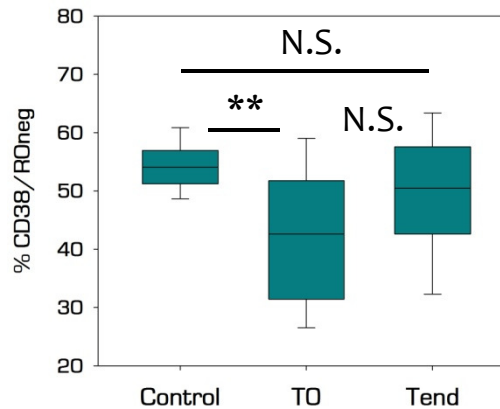
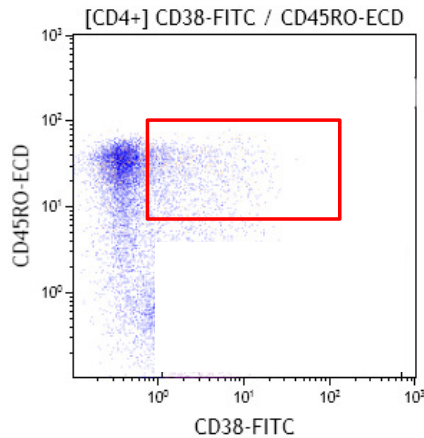
T effector cells are increased in allergic children and decrease markedly after SOTI

New CD4 subset

European Journal of
Immunology

CD38 identifies a hypo-proliferative IL-13-secreting CD4⁺ T-cell subset that does not fit into existing naive and memory phenotype paradigms

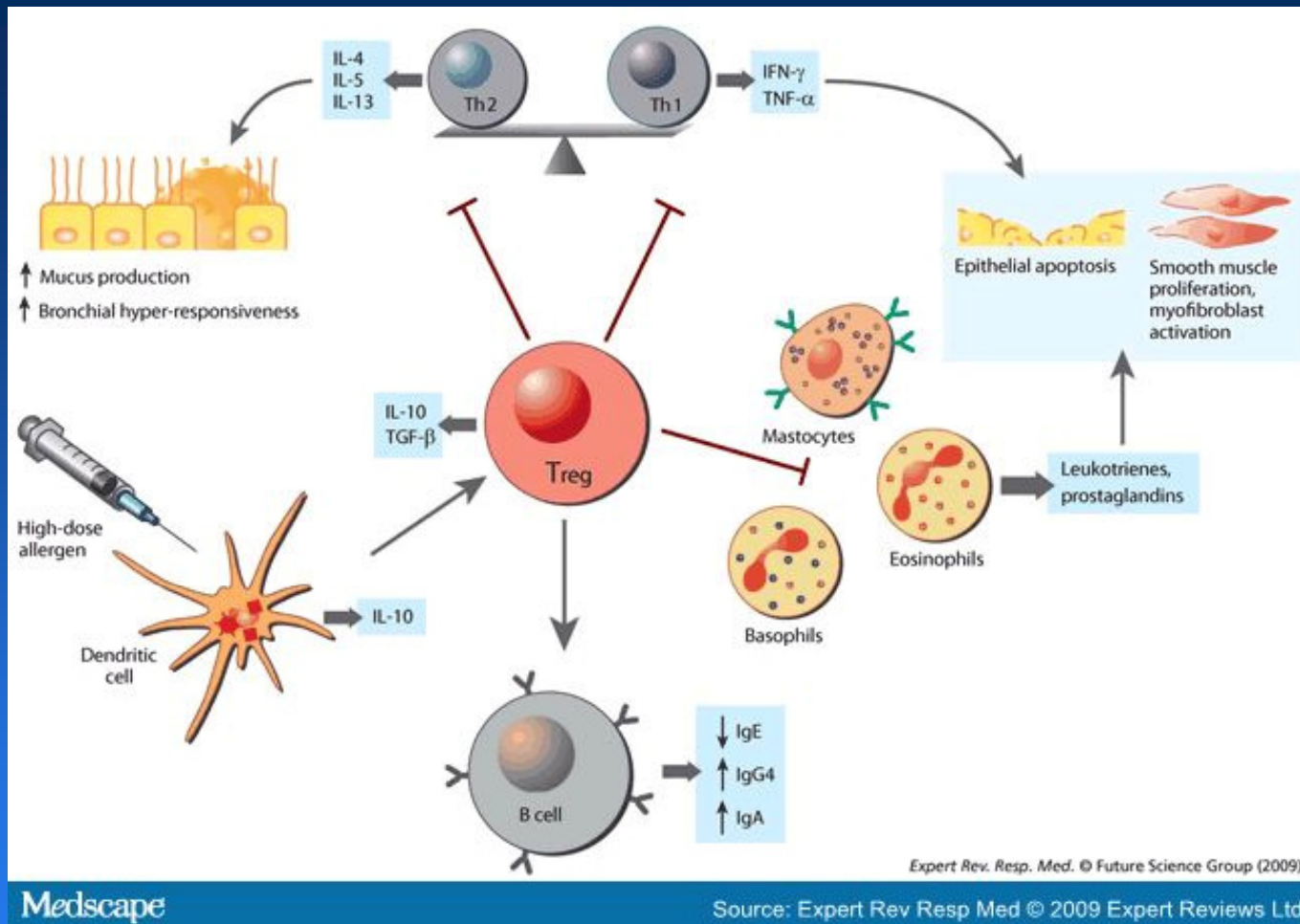
Karen Scalzo-Inguanti and Magdalena Plebanski



CD38/ROneg cells have a hypo-proliferative phenotype

These cells are diminished in allergic children and are recovered with the desensitization

Pediatric Allergy and Immunology (2012). 23(7): 648-53



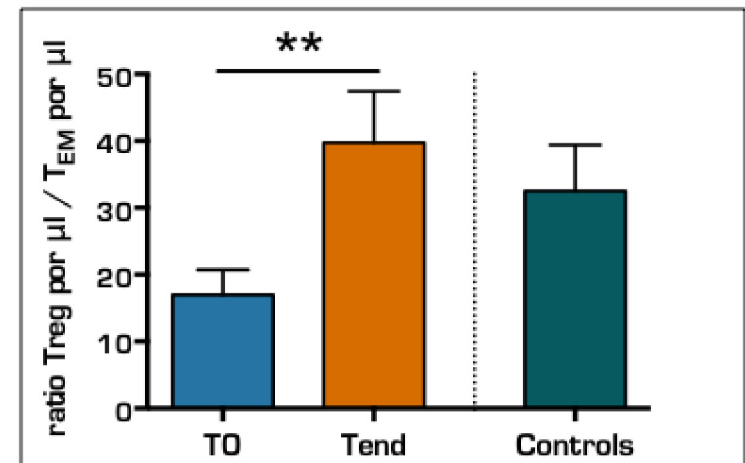
Are Treg cells responsible of the control of effector cells in the acquisition of tolerance ?

Treg cells

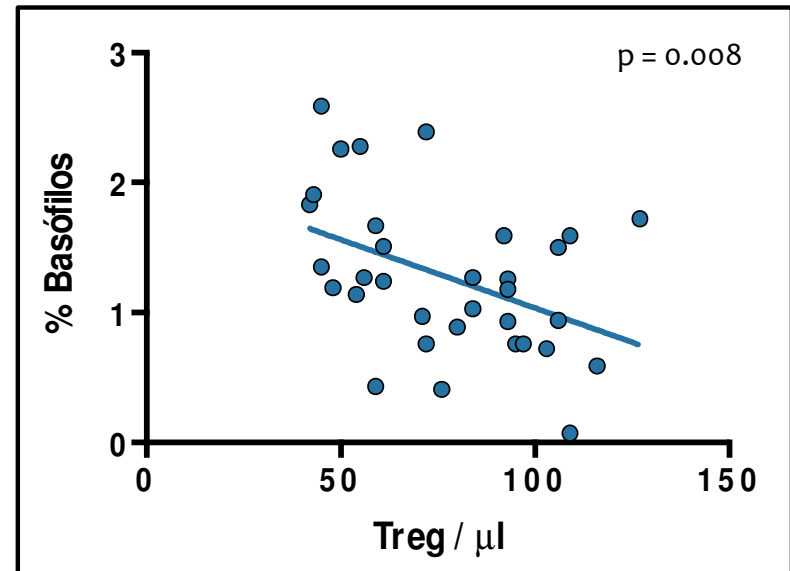
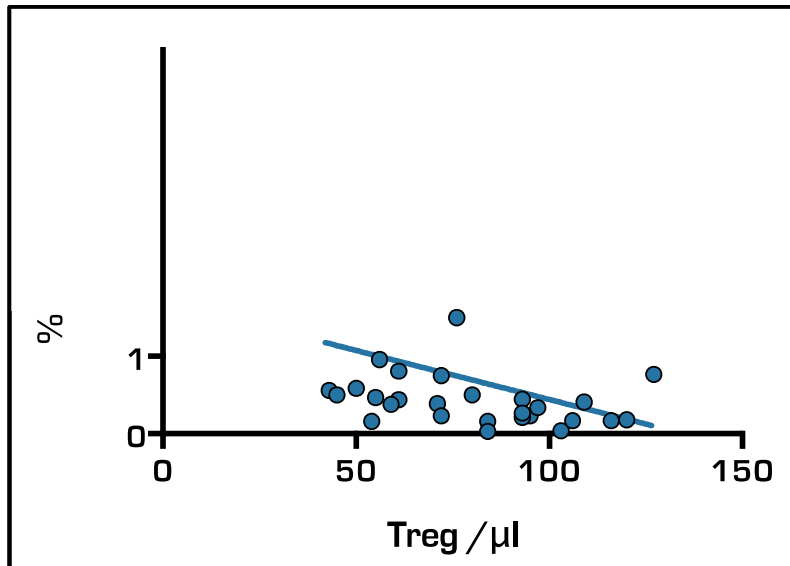
	Percentage			Cells/ μ L		
	T0	Tend	<i>p</i>	T0	Tend	<i>p</i>
Treg Cells	7.89 (7.11-9.99)	8.42 (7.41-9.81)	0.010*	73 (49-93)	84 (61-105)	0.037*
Naïve Treg	48.35 (43.7-55.2)	51.88 (44.5-55.6)	0.948	34 (24-49)	39 (32-59)	0.064
Suppressive Treg	52.21 (45.4-56.5)	48.64 (45.0-56.1)	0.879	35 (26-48)	43 (31-55)	0.031*

SOTI → Increases Treg values

The balance Treg/effector is reestablished



Treg cells



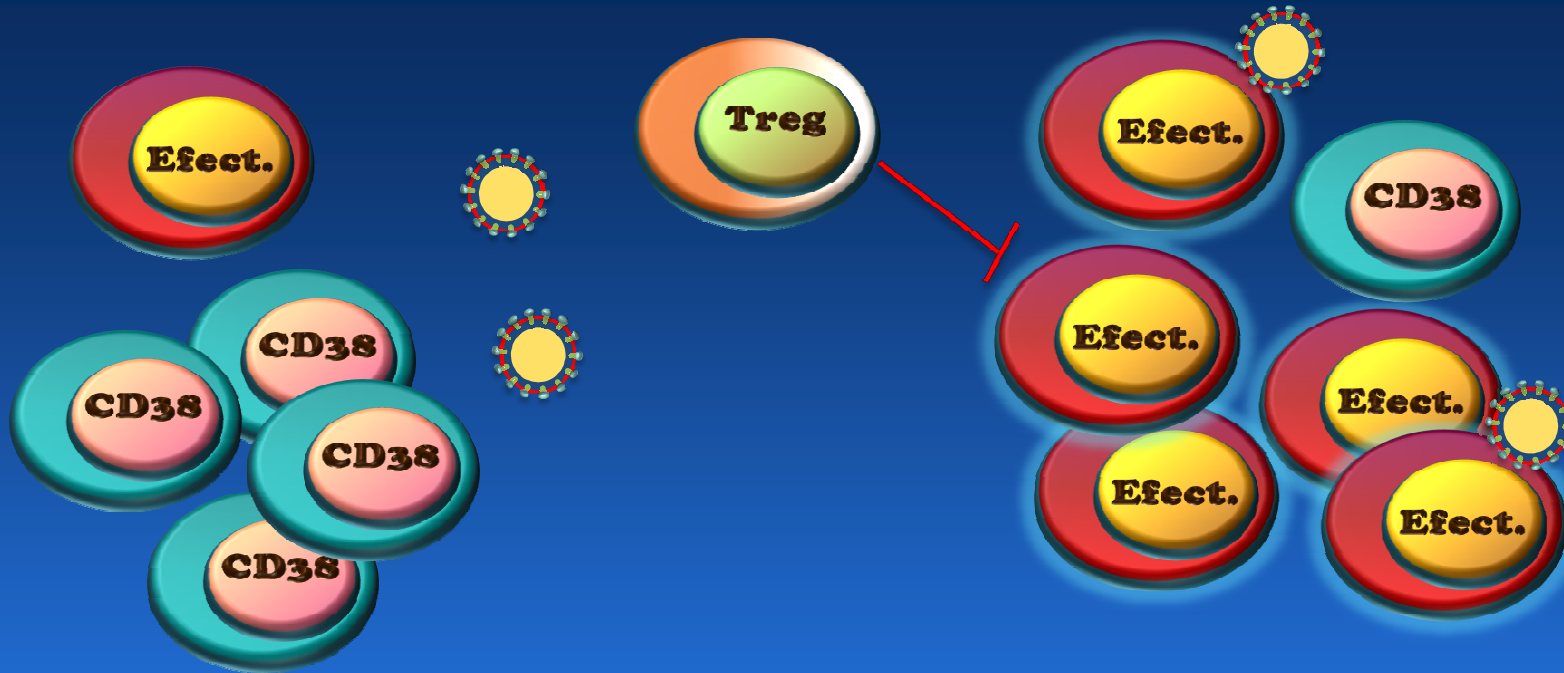
Increased values of circulating Treg cells are related with a decrease in the effector cells associated with allergic symptoms

IgG / cytokines

Immunoglobulins			
	T0	Tend	p
IgE (total) (kU/L)	738 (282-1578)	772 (329-1550)	0.900
IgE white	8.18 (3.6-14.2)	9.51 (4.1-15.1)	0.792
IgE ovalbumin	4.63 (3.0-12.4)	4.61 (1.7-7.9)	0.290
IgE ovomucoid	6.08 (2.2-12.8)	8.30 (2.6-17.8)	0.725
IgG white (mg/L)	5.02 (3.2-7.0)	20.8 (8.2-44.5)	0.027*

Cytokines			
	T0	Tend	p
IL-12	37.95	12.68	0.068
IFN-γ	156.1	87.48	0.036
IL-17A	267.1	235.53	0.006
IL-2	110.32	66.70	0.041
IL-10	31.19	24.09	0.025
IL-9	73.26	58.97	0.021
IL-22	417.26	370.45	0.028
IL-6	0.34	1.93	0.180
IL-13	112.58	161.85	0.657
IL-4	77.84	52.16	0.097
IL-5	64.12	30.20	0.028
IL-1β	129.41	94.41	0.059
TNF-α	24.67	12.71	0.046

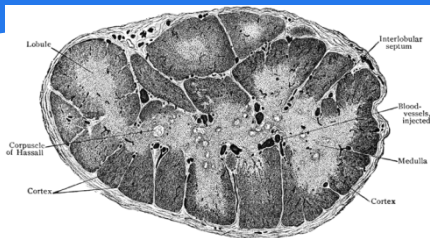
SOTI \rightarrow Decreases “allergic” cytokines



TOLERANCE

ALLERGY

SOTI



Thymus

Negative Selection



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