

# Role of Tissues in Immune Regulation

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# WHAT IS CHRONICITY? AN IMMUNOLOGICAL PERSPECTIVE

## ROLE OF TISSUES IN IMMUNE TOLERANCE

J Immunol 1997  
 J Immunol 1999  
 EJI 2000  
 J Clin Invest 2000  
 J Allergy Clin Immunol 2001  
 J Invest Dermatol 2001  
 J Allergy Clin Immunol 2002  
 J Allergy Clin Immunol 2003  
 J Immunol 2003  
 Trends 2003  
 Curr Opin Immunol 2004  
 JACI 2005  
 JACI 2006  
 Curr Opin Immunol 2006  
 JACI 2007/2008  
 Basinski et al. JACI 2009  
 Meyer et al. JACI 2010, 2012  
 Zimmermann JACI 2011  
 Soyka JACI 2012  
 Reboreo JACI 2012  
 Chakrabarti, Wanka 2013

# AN AGREEMENT BETWEEN THE TISSUES AND THE IMMUNE SYSTEM FOR CHRONICITY

Body surfaces: Skin 0.5%  
 Mucosas 99.5%

Lung: 100 m<sup>2</sup>  
 Gut: 300 m<sup>2</sup>  
 1<sup>1/2</sup> Tennis court

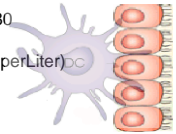


1 Ton food per year mixed with water = 12\*0.6\*60\*24\*365\*80 = 3'027'456'000 liters

10<sup>14</sup> bacteria  
 1 kg  
 2000 species

10 billion particles (3 per Liter)

1 kg



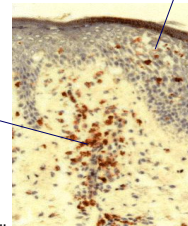
Only one cell layer between life and death  
 0.03 mm thick



# T CELL EPITHELIUM INTERACTION RULES OF ACTIVATION AND CELL DEATH OF EPITHELIUM

## Histopathology of AD

dermal mononuclear cells



eczema/spongiosis

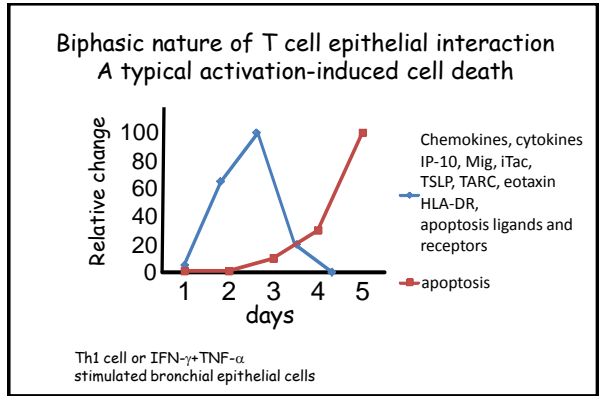
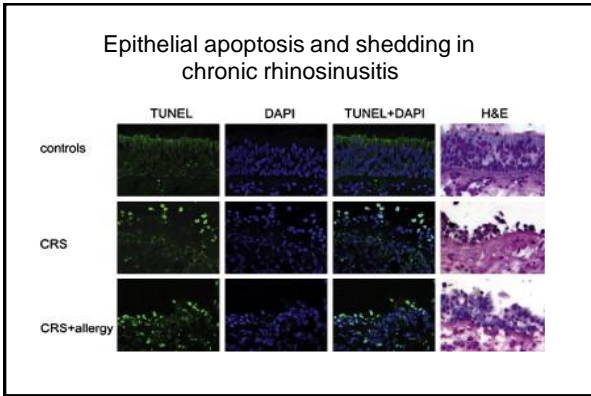
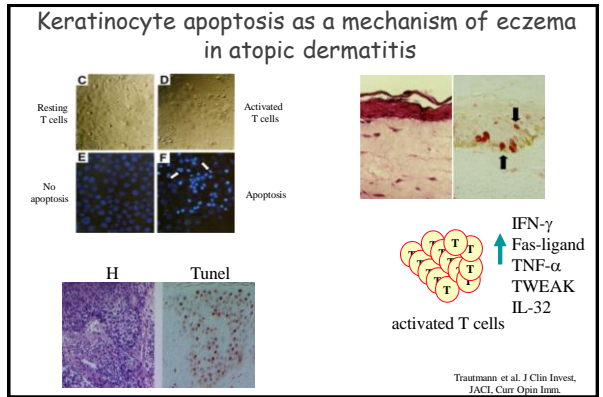
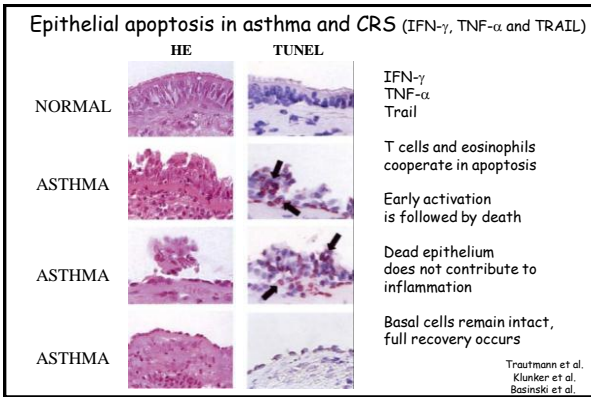
effector functions

70 % T cell  
 1-3 % eosinophil  
 10-20 % dendritic cell

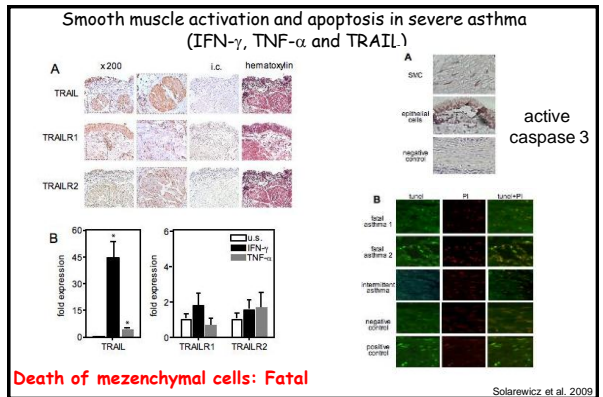
activation/  
 organ  
 migration

survival/reactivation

J Immunol 1997  
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# MEZENCHYMAL CELL DEATH AND FATAL ASTHMA



## RULES OF ANGIOGENESIS AND REMODELLING IN CHRONICITY

## Angiogenesis and remodeling

Rules of angiogenesis:

Blocked during severe inflammation

Induced during low level inflammation

Induced during remissions and healing

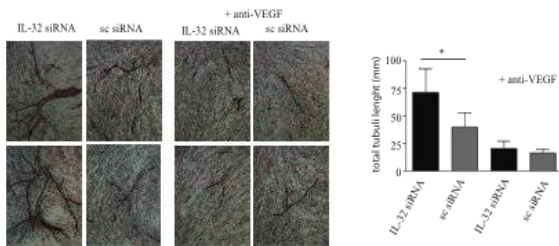
Blocked by high dose proinflammatory cytokines

Induced mainly by VEGFA, PlGF, PDGF

Inhibited by IL-32 (Meyer et al. JACI 2012)

Rules for chronicity, feed, revascularize, never bleed

## Angiogenesis and remodeling



IL-32 downregulates VEGF and PDGF and angiogenesis

CKCARE

Norbert Meyer JACI 2012

## EPITHELIAL BARRIER VERSUS PERMISSIVENESS

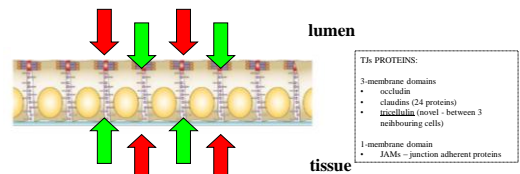
Epithelial tight junctions  
(Epithelial permissiveness for allergens etc.)

Drainage of inflammation

## Tight junctions (TJs) T cells and airway epithelium

-Closed tight junctions: preventive and protective

-Open tight junctions: to drain inflammation, but allow allergen, toxin accessibility



**Defective epithelial barrier function in asthma**

Chang Xiao, et al.  
 The Journal of Allergy and Clinical Immunology  
 Volume 128, September 2011, Pages 549–556.e12

•The bronchial epithelial barrier in asthma is compromised. This defect may facilitate the passage of allergens and other agents into the airway tissue, leading to immune activation and may thus contribute to the end organ expression of asthma.

**Tight junction defects in patients with atopic dermatitis**

Anna De Benedetto, et al.  
 The Journal of Allergy and Clinical Immunology  
 Volume 127, March 2011, Pages 773–786.e7.

• An impairment in tight junctions contributes to the barrier dysfunction and immune dysregulation observed in AD subjects and that this may be mediated in part by reductions in claudin-1.

**Defective epithelial barrier in chronic rhinosinusitis: The regulation of tight junctions by IFN- $\gamma$  and IL-4**

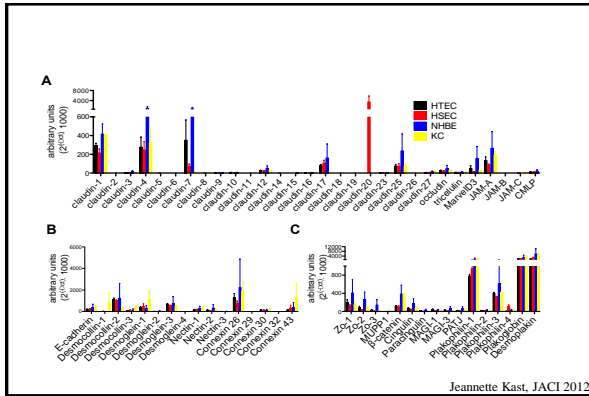
Michael B. Soyka et al.

A defective epithelial barrier was found in patients with CRS with nasal polyps along with a decreased expression of TJ proteins.

**The broad spectrum of interepithelial junctions in skin and lung**

Jeannette I. Kast et al.

TJ network is complex and involves many proteins



Jeannette Kast, JACI 2012

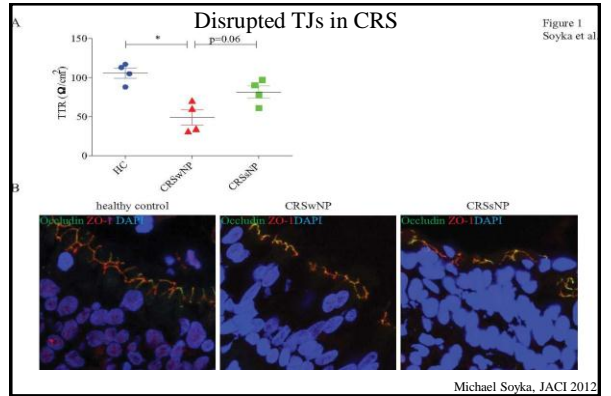
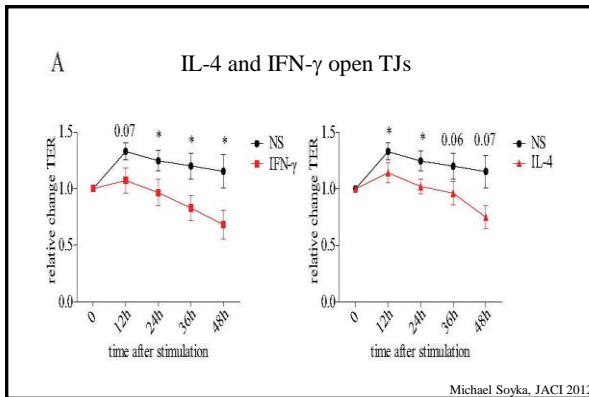


Figure 1 Soyka et al

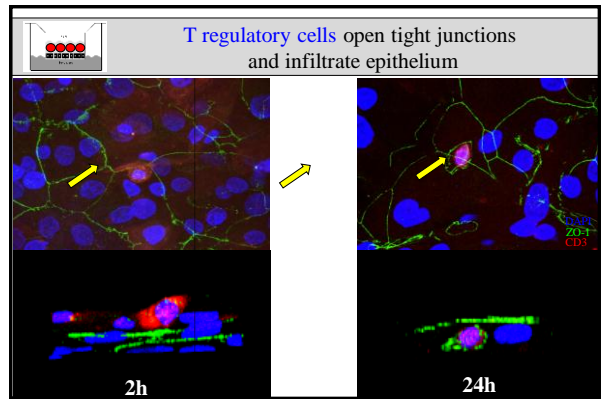
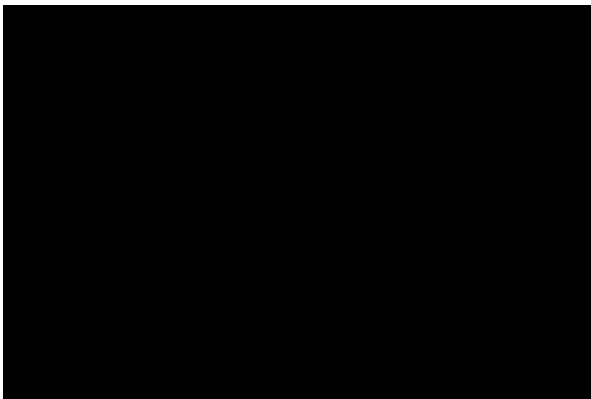
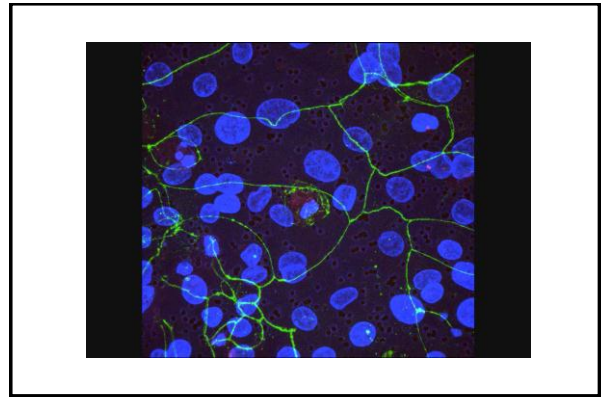
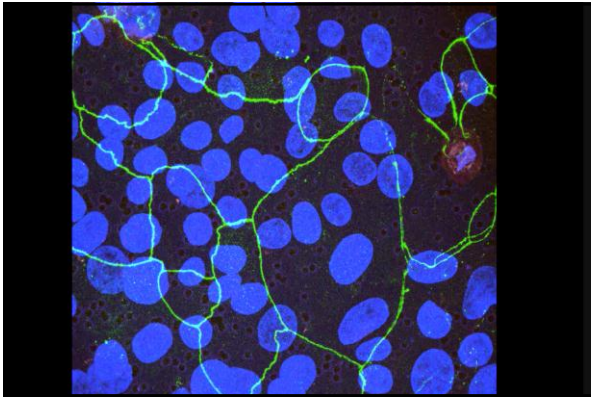
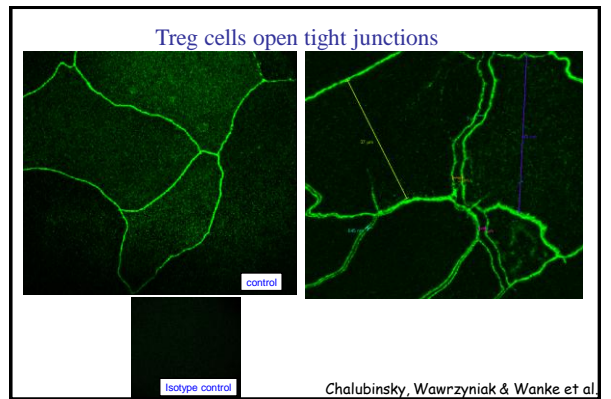
Michael Soyka, JACI 2012

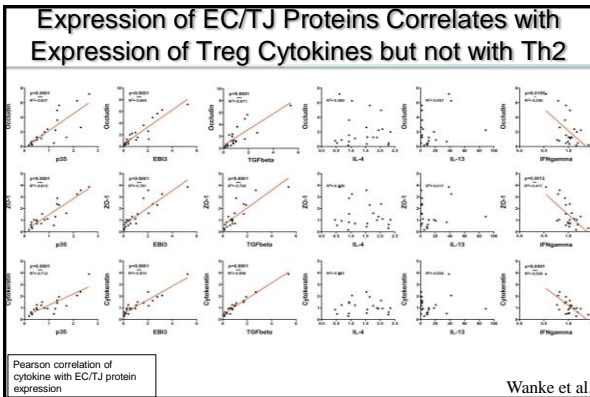
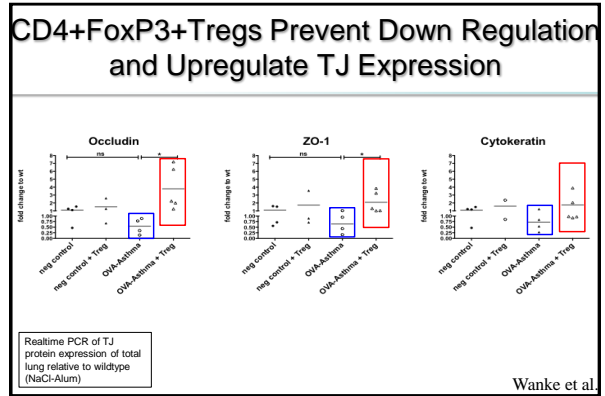
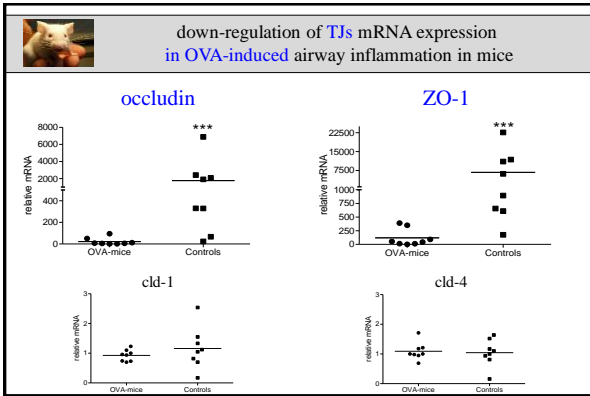
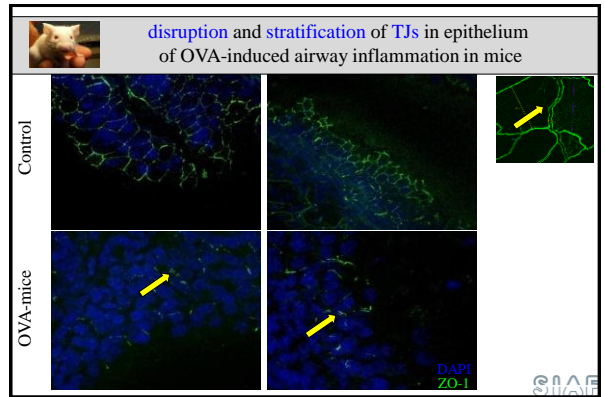
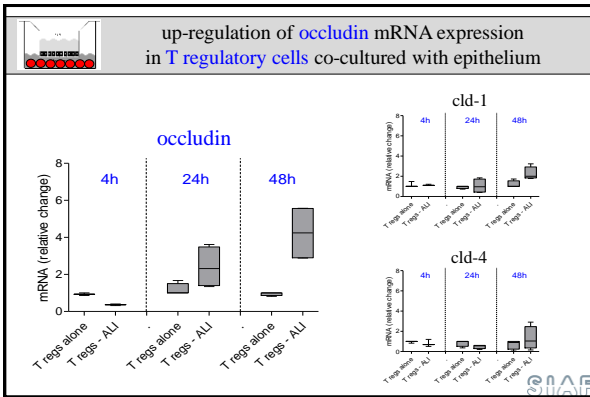


Michael Soyka, JACI 2012

<u>Opening of TJs</u>	<u>No effect on opening of TJs</u>	<u>Epithelial regeneration</u>
IL-4, IL-13	IL-10	Treg cells
IFN- $\gamma$ (apoptosis)	IL-17	EGF (recovery)
TNF- $\alpha$ (apoptosis)	IL-2	
LPS	IL-21	
TGF- $\beta$	IL-23	
	IL-25	
	IL-33	
	EGF (closing)	

# Treg cells open tight junctions and regenerate epithelium



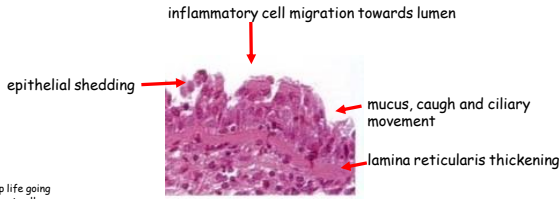


**KEEP AWAY  
WASH AWAY  
&  
SUPPRESS**

## Tissue factors that contribute to immune tolerance

Quae medicamenta non sanant, ferrum sanat,  
quae ferrum non sanat, ignis sanat

Hippocrates



Keep life going  
Tolerate allergens  
Keep tissues as  
intact as possible  
Minimize tissue injury

keep away, wash away, suppress

## RULES OF AGREEMENT BETWEEN THE IMMUNE SYSTEM AND TISSUES

- KEEP BUSY AND LOW LEVEL INFLAMED (D)
- DO NOT KILL THE BASAL EPITHELIAL CELLS
- KILL HIGHLY ACTIVATED SUPRABASAL EPITHELIAL CELLS (D)
- DRAIN INFLAMMATION IF NECESSARY
- IN PRINCIPLE DO NOT ATTACK MESENCHYMAL TISSUES, RESPECT IMMUNE PRIVILEGE
- DO NOT ATTACK VASCULATURE, NEVER BLEED
- REGENERATE AND REMODELL THE TISSUES (D)
- MAKE A PHYSICAL BARRIER BETWEEN DISEASE INDUCING FACTORS AND CELLS OF THE IMMUNE SYSTEM (D)
- SUPPORT ANGIOGENESIS, DO NOT ALLOW NECROSIS



EAACI-WAO  
World Allergy & Asthma Congress  
22 - 26 June 2013  
Milan, Italy

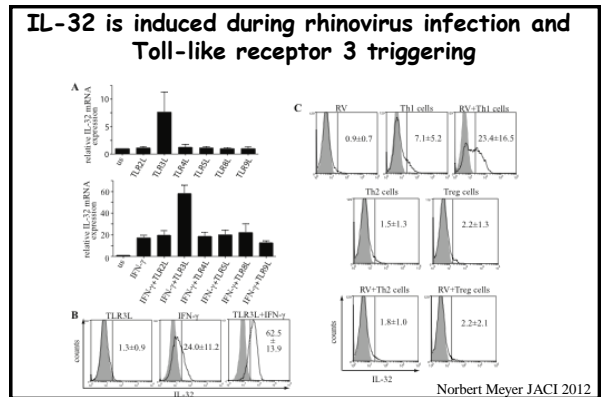
**EAACI-WAO Congress 2013**

Allergy, a Global Health Challenge

Save the date!

Abstract Submission Deadline: 21 January 2013

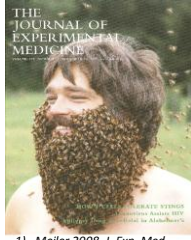
[www.eaaci-wao2013.com](http://www.eaaci-wao2013.com)



## Which human antigen-specific models are we using?

### Beekeepers:

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

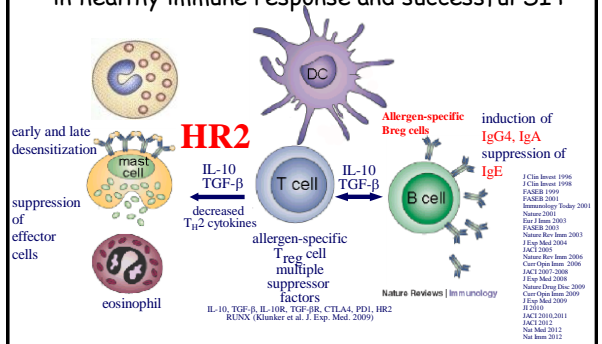


- Meiler 2008, *J. Exp. Med.*
- Trautmann A 2000, *J. Clin. Invest.*
- Jutel 2001, *Nature*
- Akdis C 1996, *J. Clin. Invest.*
- Akdis M 2004, *J. Exp. Med.*
- Klunker 2009, *J. Exp. Med.*

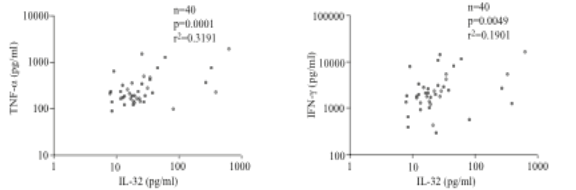
### Patients and healthy individuals

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

## Immune tolerance to allergens in healthy immune response and successful SIT



## Serum IL-32 correlates with TNF-α and IFN-γ



Norbert Meyer JACI 2012

## Mechanisms of Immune Tolerance to Allergens

### Tissue factors that contribute to immune tolerance

