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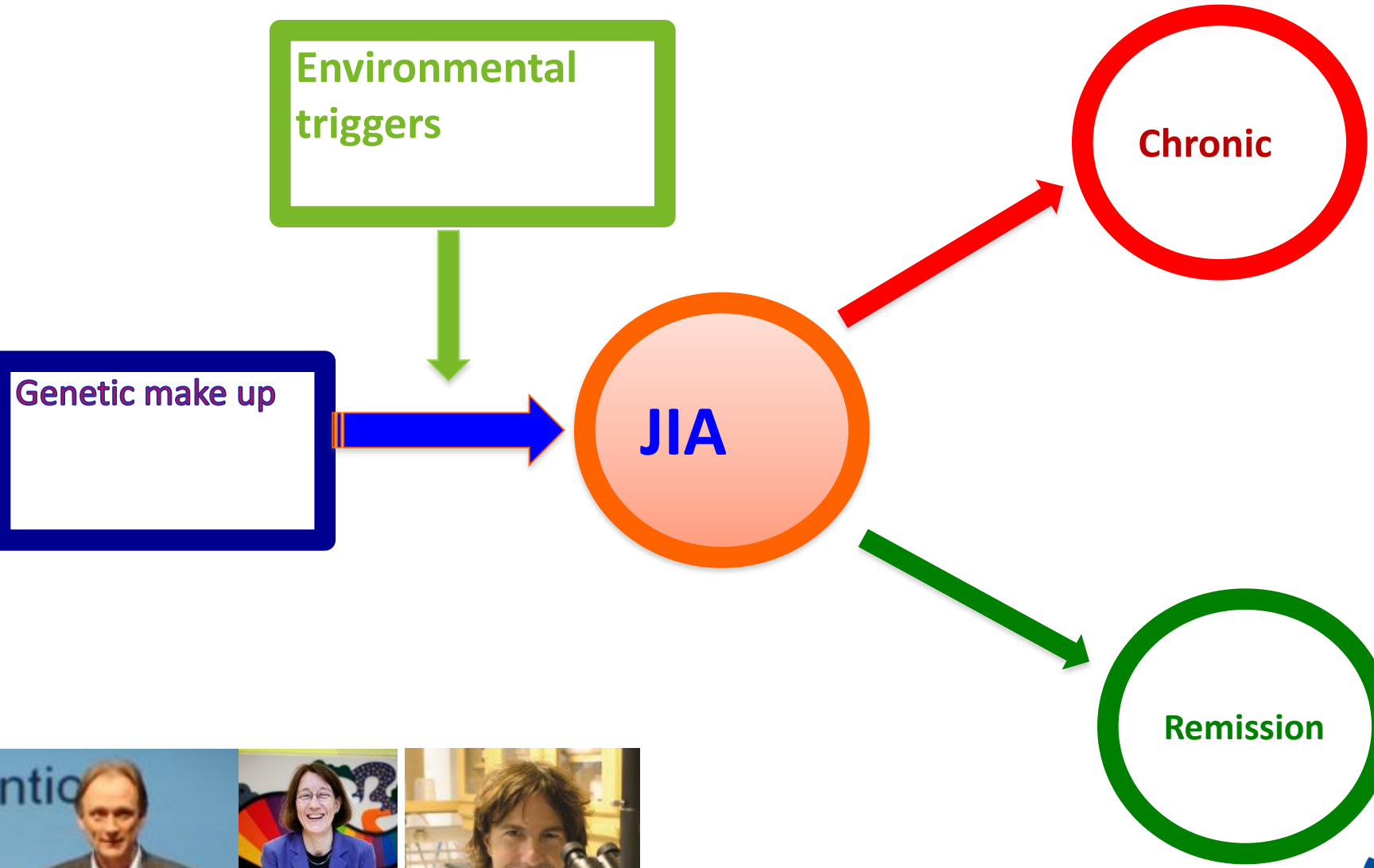
Pathogenesis of Rheumatic diseases, especially JIA

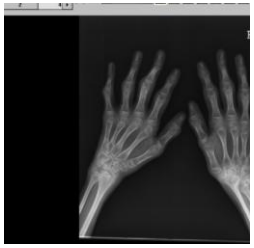
Nico Wulffraat, dept pediatric immunology&reumatology

JIA pathogenesis, the big unknown



Subtypes of Juvenile Idiopathic Arthritis (JIA)

- Non-remitting: poly



- Self-limiting: oligo

- Auto-inflammatory: systemic

JIA, a balancing act between inflammation and regulation

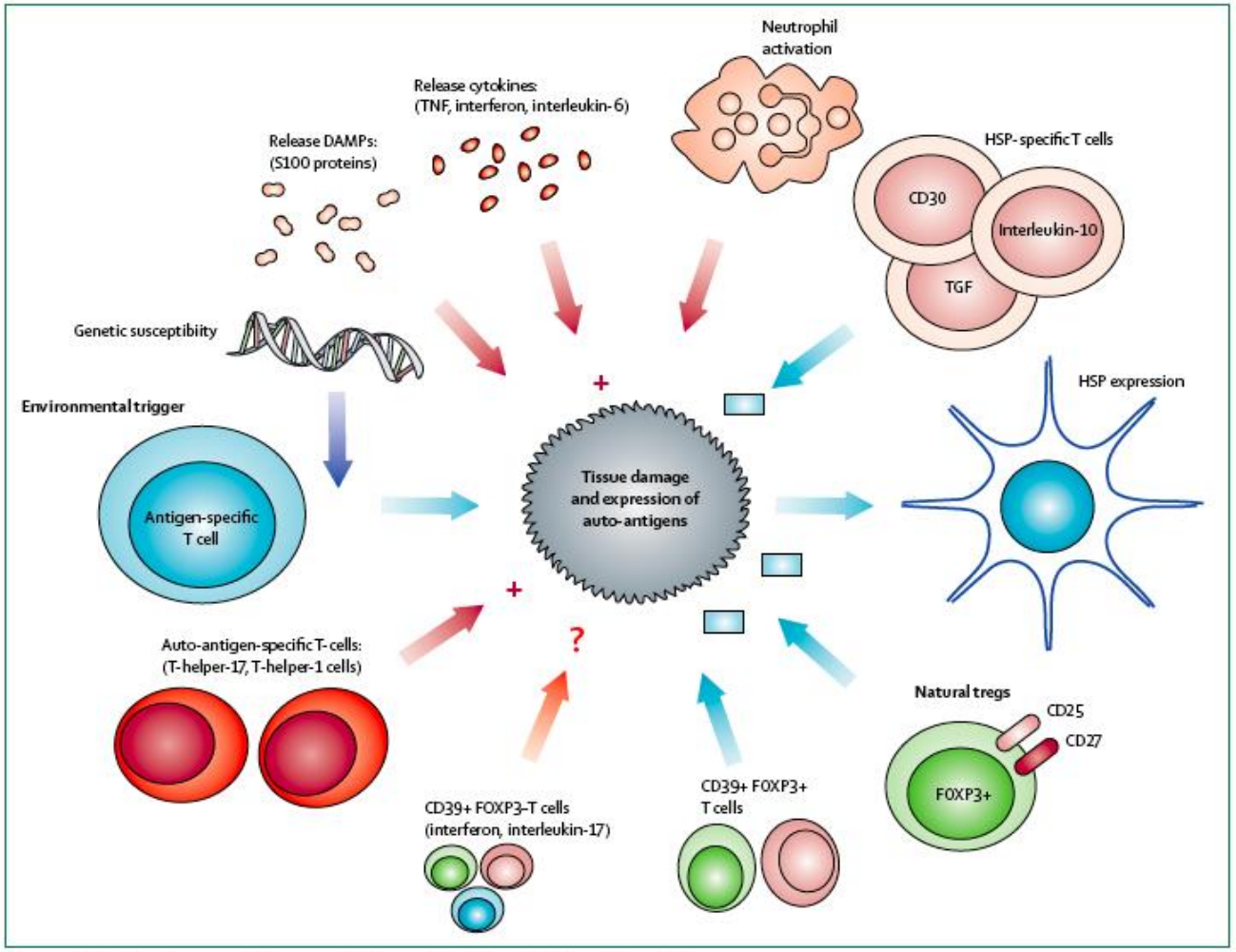
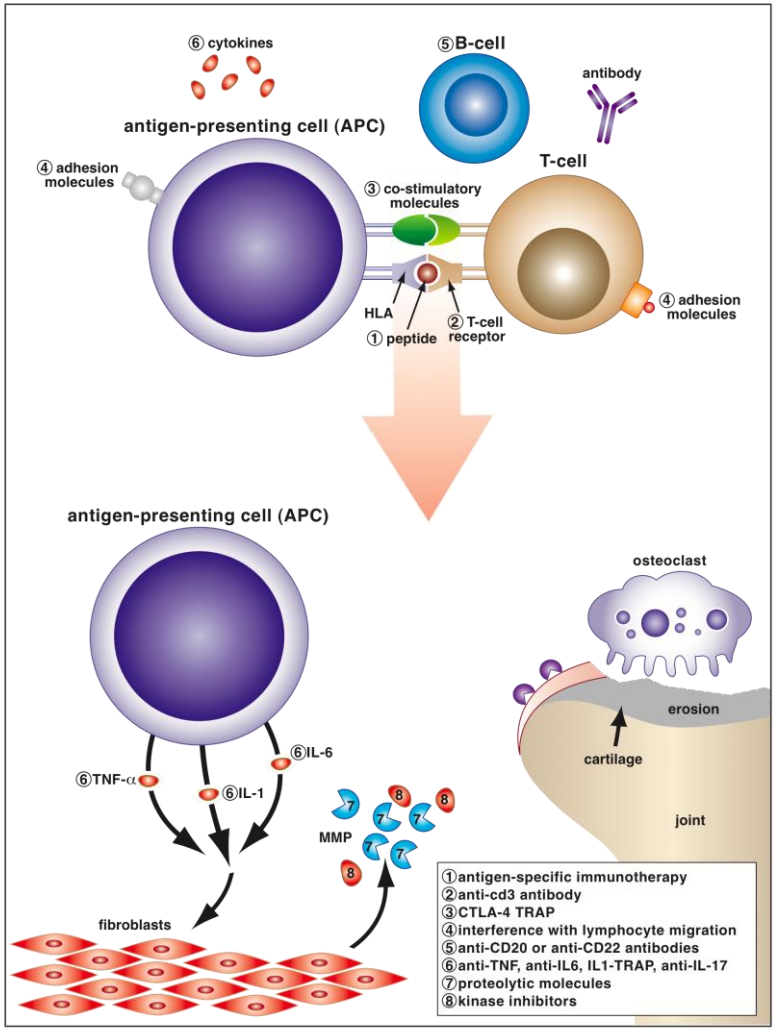


Figure 1: The balance between tolerance and inflammation in juvenile idiopathic arthritis

Prakken et al ***Lancet*** *2011*

Possible Interventions

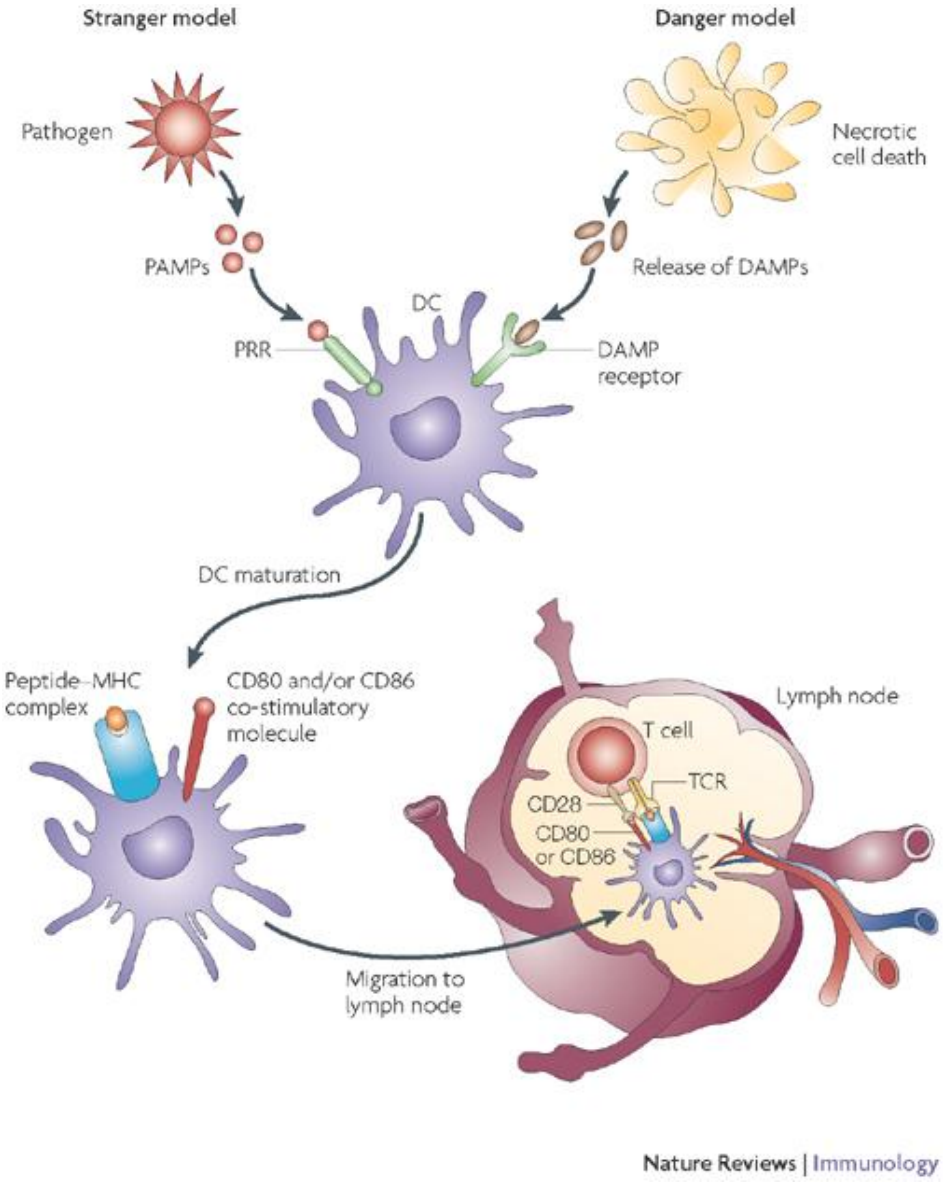


Prakken et al ***Lancet*** *2011*

The crucial question

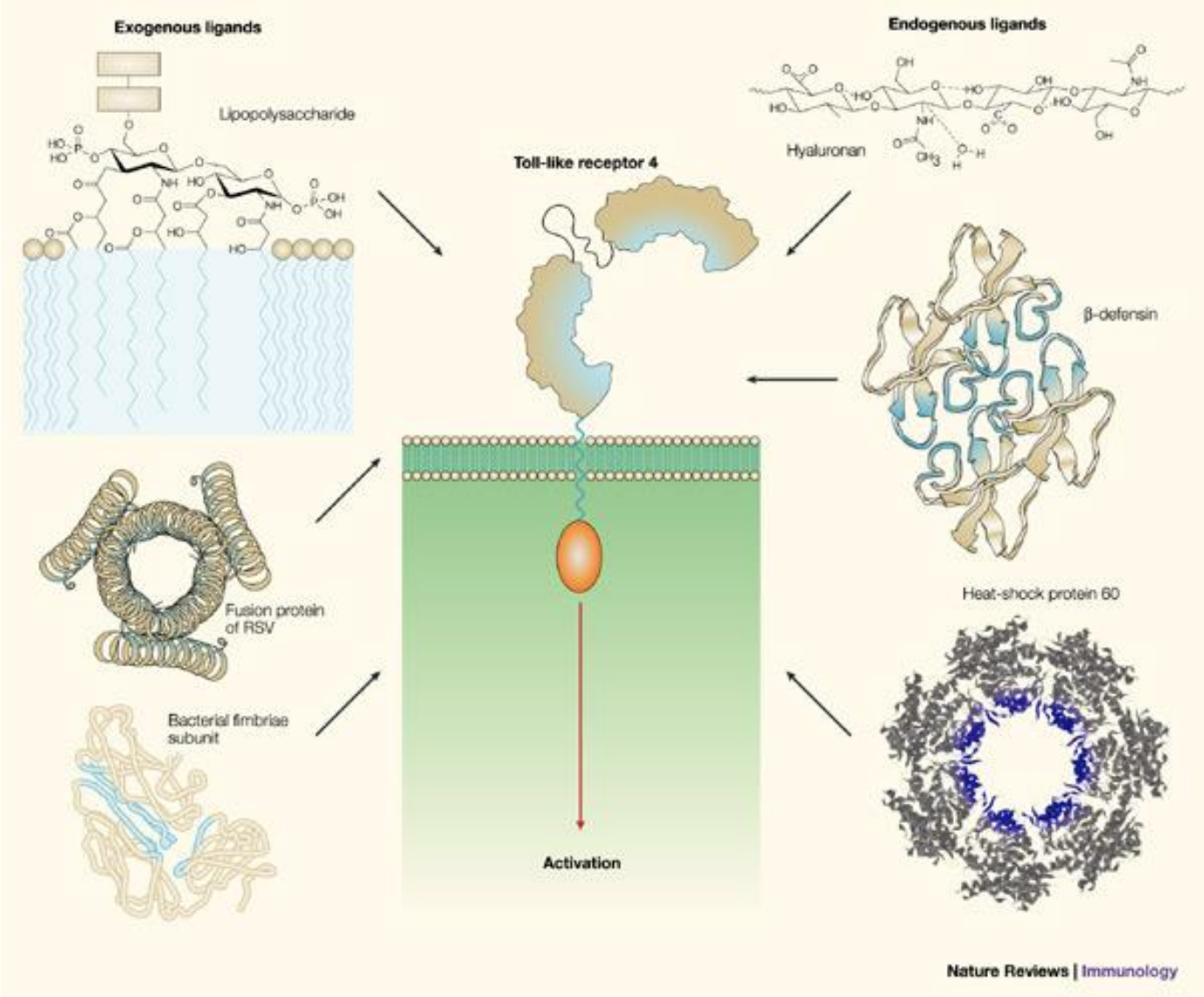
Why doesn't everybody develop autoimmunity?

PAMP & DAMP: STRANGER & DANGER



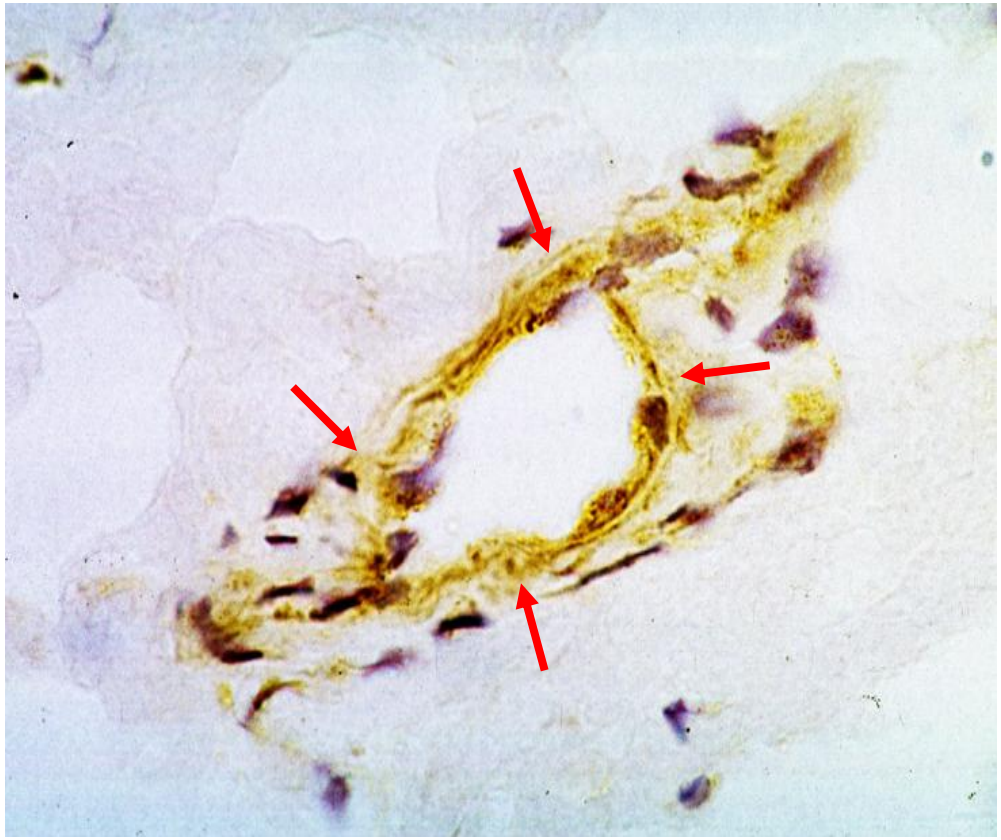
From: Kono & Rock *Nature Reviews Immunology 2008*

Exogenous and Endogenous ligands



Seung-Yong Seong and Polly Matzinger, Nature Rev Immunol 2004

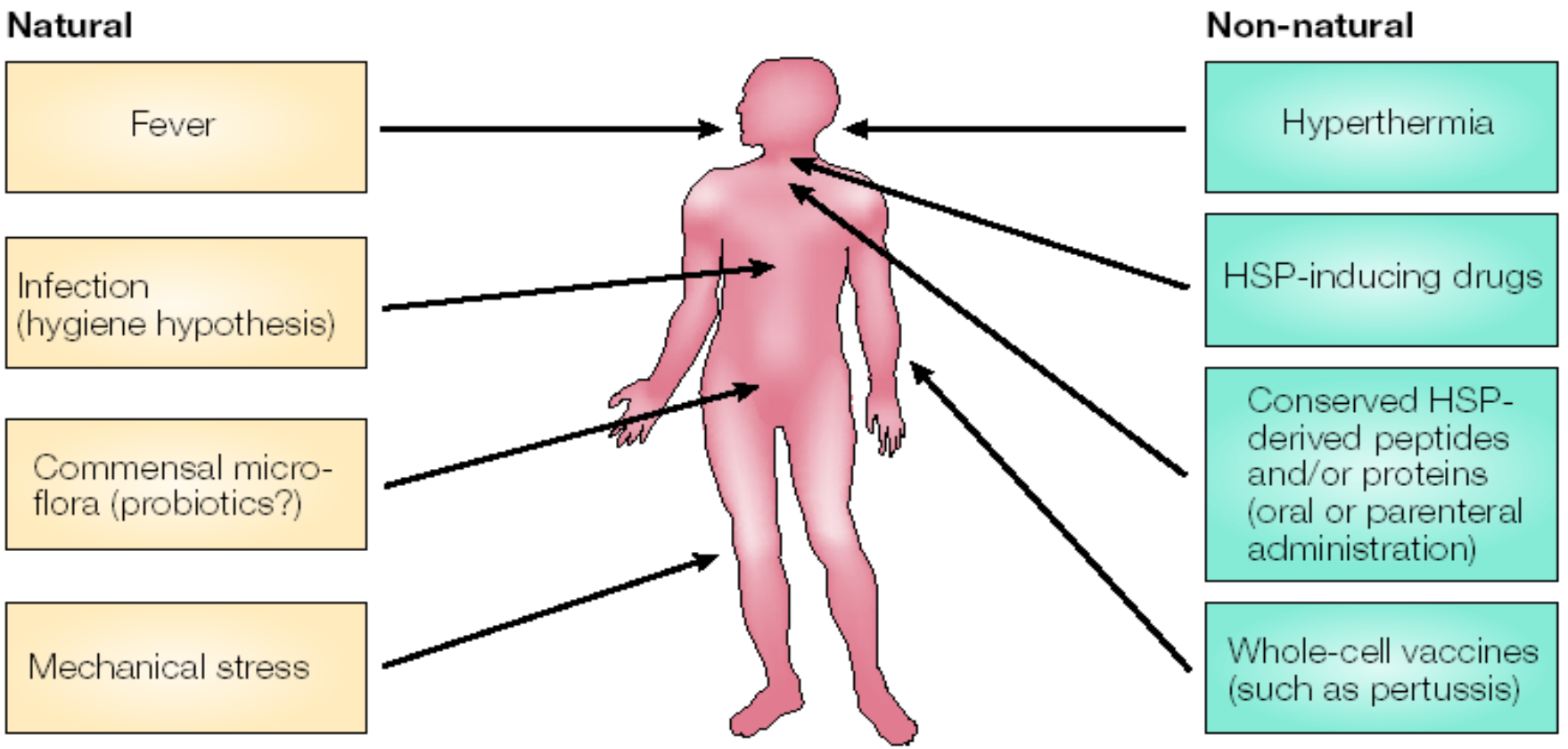
Target antigen in arthritis: Heat shock proteins



- Highly conserved
- Immune dominant
- Stress proteins

(van Eden & Prakken Nature Rev Immunol 2005)

Triggering factors in hsp-induced immune regulation



Van Eden, van der Zee & Prakken Nature Rev Immunol 2005

Hsp's: highly conserved immunogenic stress proteins:

Causing autoimmunity through antigenic mimicry?

Autoimmunity = Immune deficiency of immune regulation

Self-recognition is physiologic

JIA pathogenesis

Role of the innate immune system

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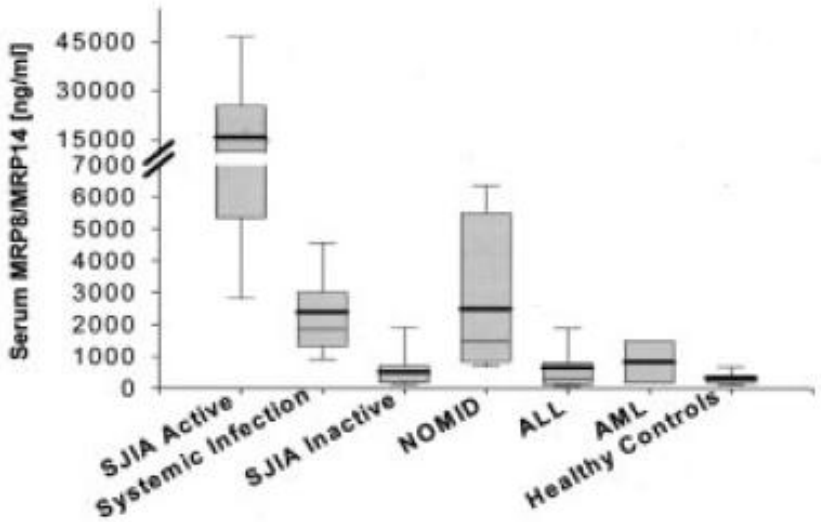
S100A (=MRP) are DAMP proteins

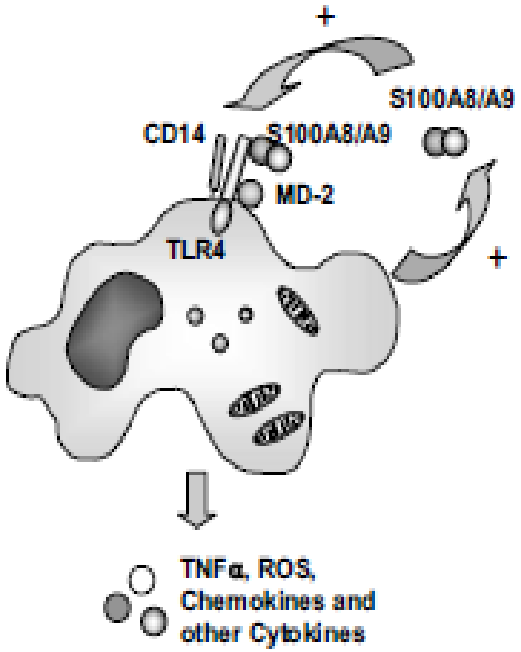
- Activate human monocytes through TLR4
- Differentiate monocytes into mature DC
- Promote Th17 differentiation (IL6 mediated)
- Cause crystal induced inflammation (gout)
- Enhance inflammation during influenza A virus infection
- Elevated in systemic inflammation (SJIA)



Frosch et al. A & R 2009 Mar;60(3):883-91

MRP8/14 (S100A8/A9): DAMP proteins

- Biomarker of Inflammation
- Phagocyte activation marker
- Stable in serum



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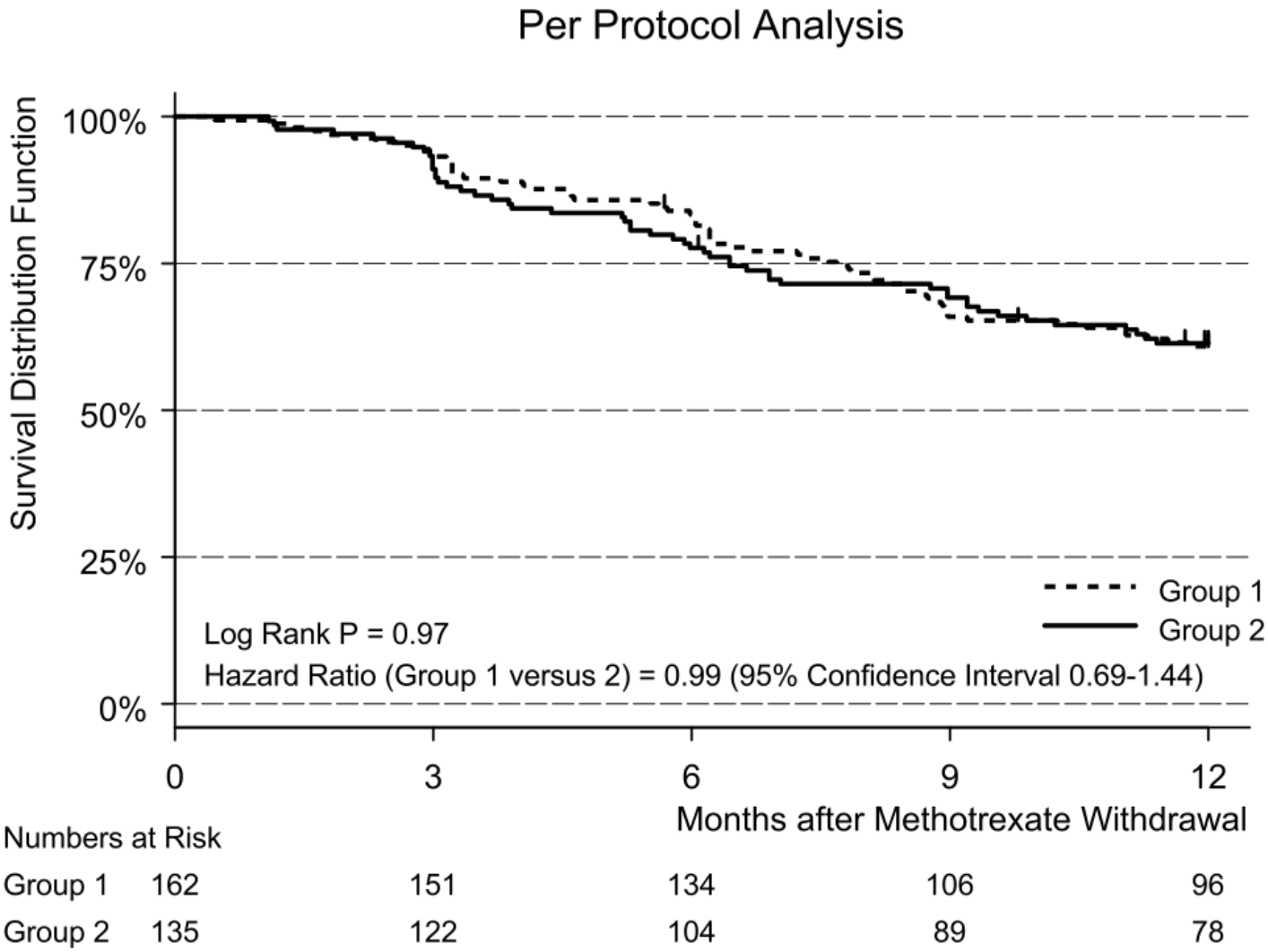
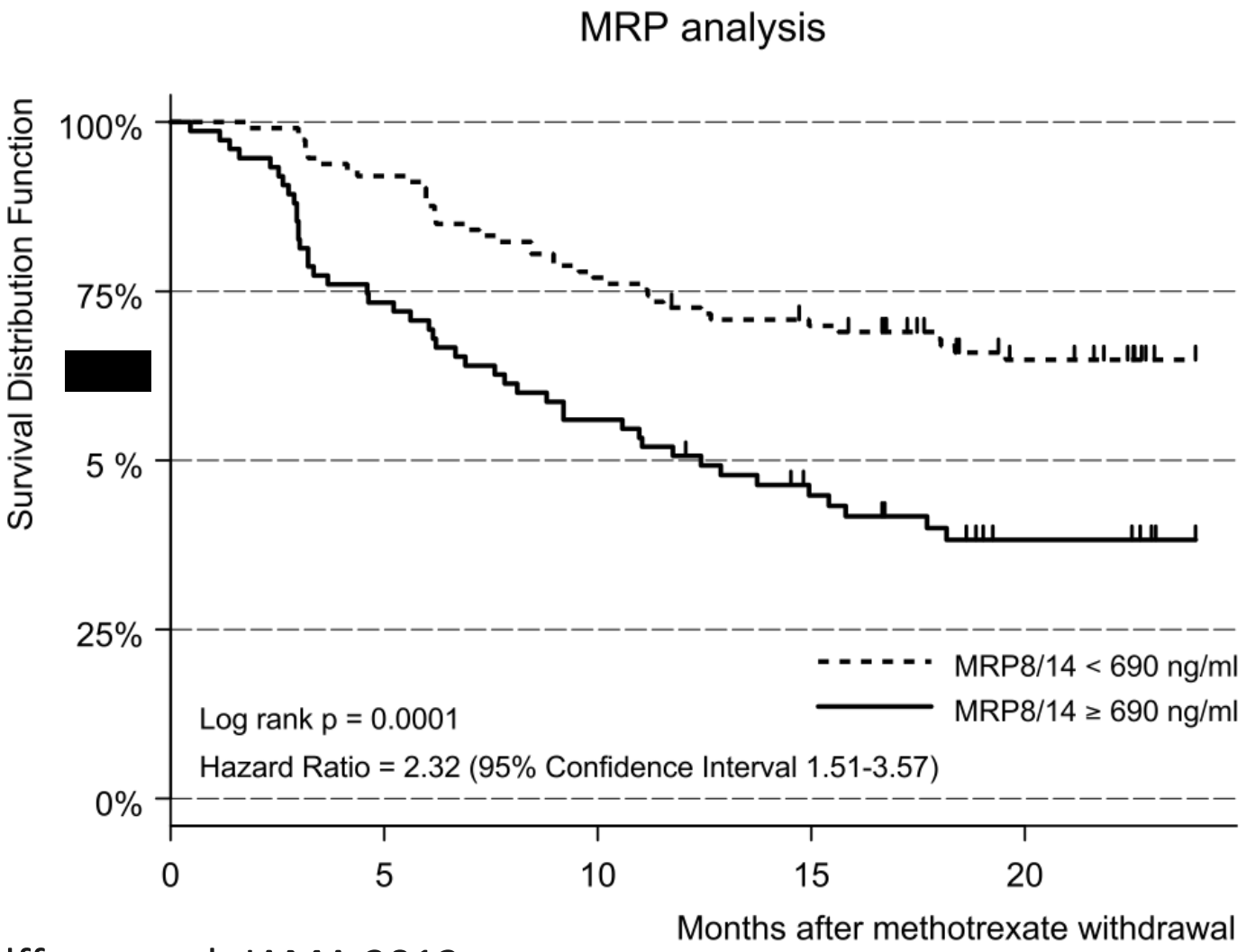
Universitätsklinikum
Münster




Longer treatment with MTX does not decrease the risk of relapse



MRP8/14: detecting the difference between clinical and true remission



Foell, Wulffraat et al, JAMA 2012

JIA pathogenesis

Role of the adaptive immune system:
A balance between pro- and anti-inflammatory signals

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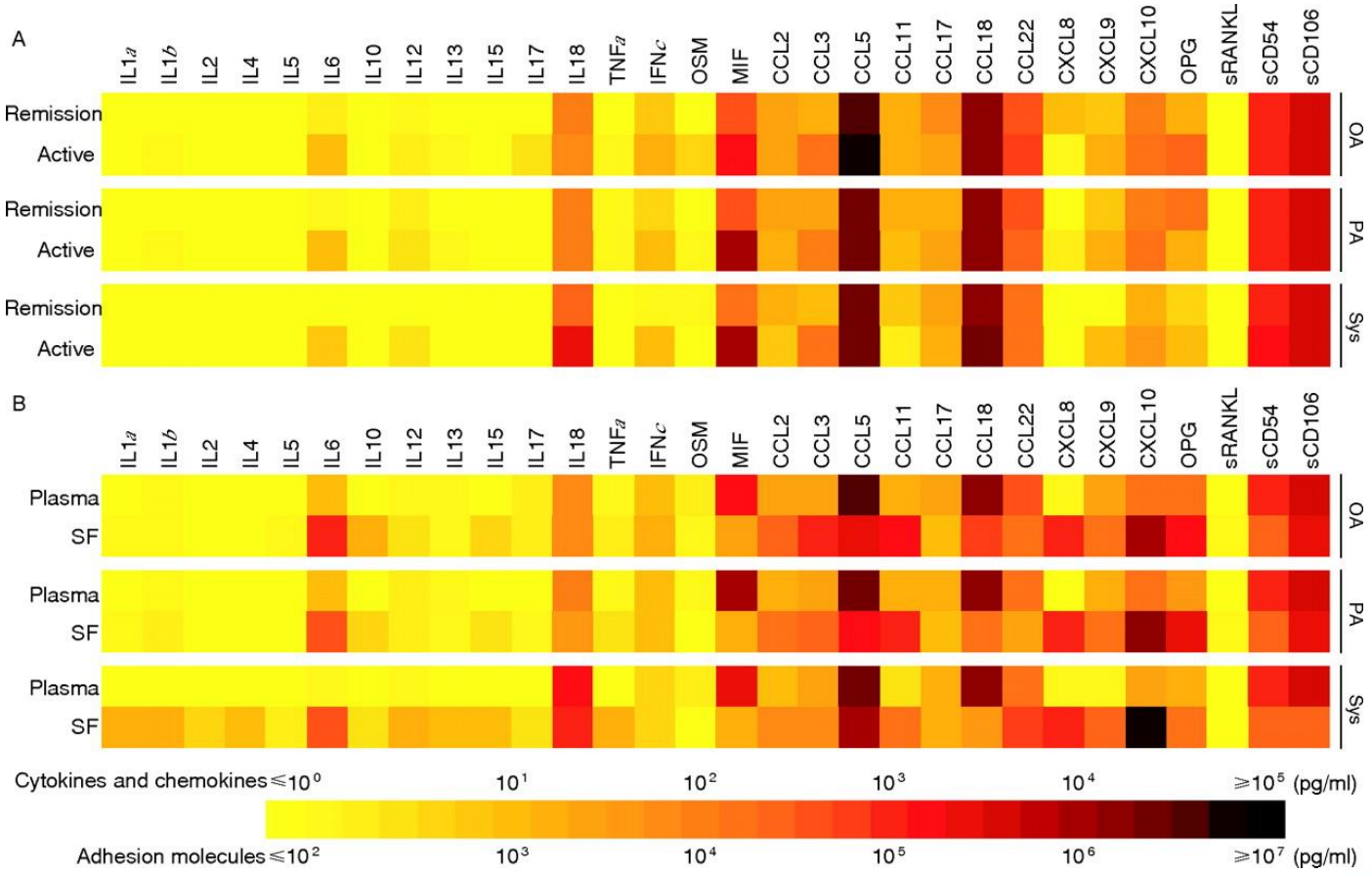
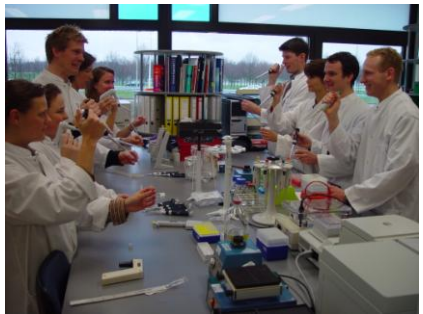
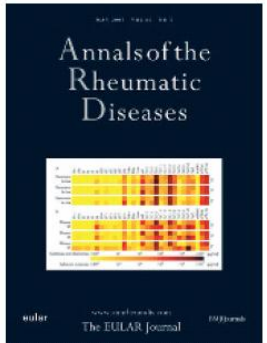
Cyto-omics of Juvenile Idiopathic Arthritis



de Jager, W. et al. ARD 2007;66:589-598
de Jager et al A&R 2009





What happens when Tregs are absent?

An experiment of nature: IPEX syndrome

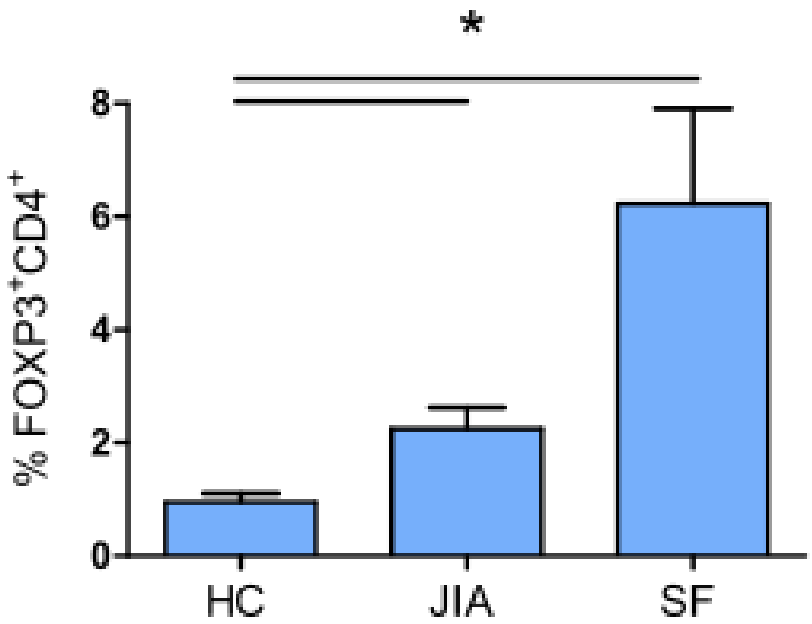
- **FOXP3 mediates immune suppression during infections, autoimmunity, cancer**
- **FOXP3 mutation causing absence of T regs**
- **Loss of immune inhibitory functions**
- **Causing dermatitis, refractory diarrhea, autoimmune endocrinopathy (IDDM, thyroiditis)**
- **Treatment: stem cell transplantation**

Two types of T regulatory cells in remitting JIA

- **Natural CD4+FOXP3+ Treg cells** (de Kleer et al *J.Immunol* 2004,*Blood 2006* Ruprecht et al *J.Exp Med 2005, Wehrens Blood 2011)*

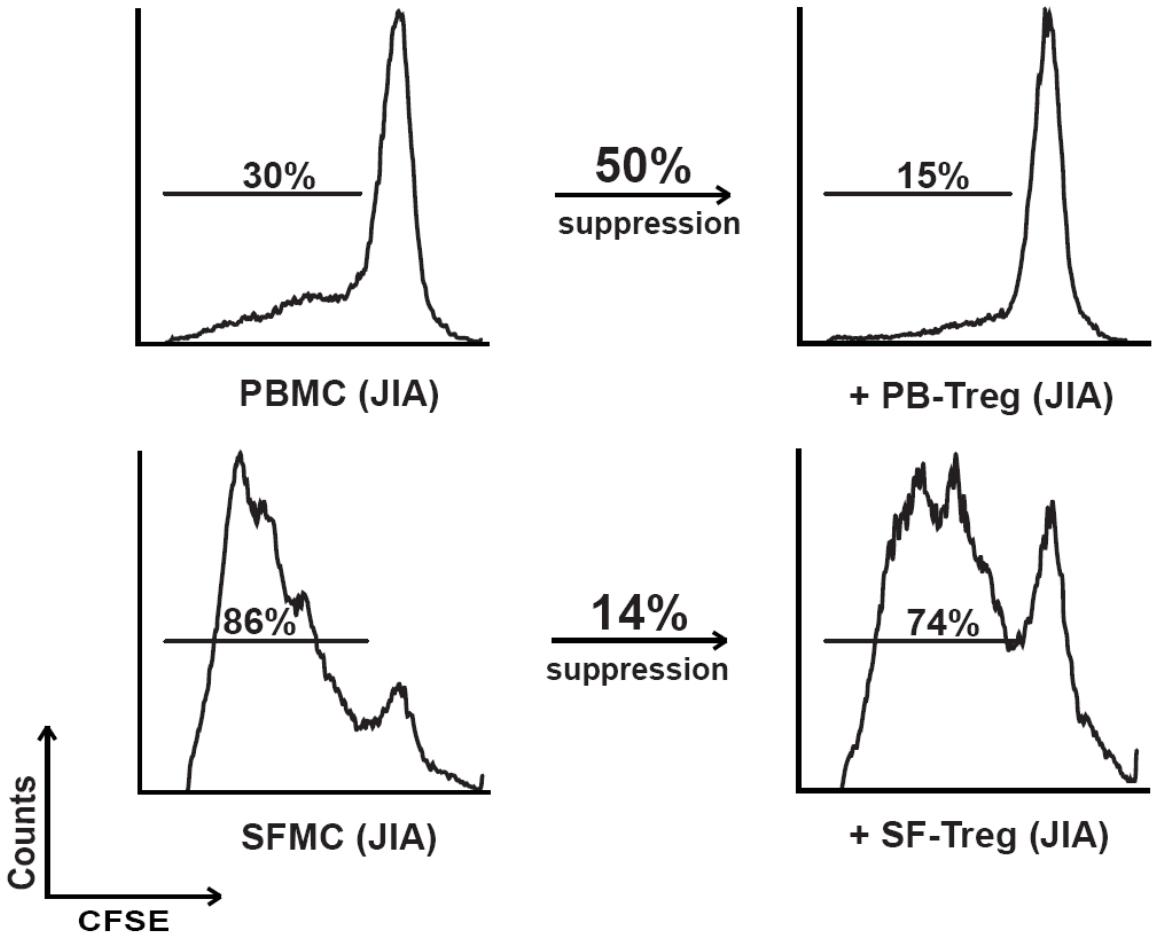
- **Hsp60-specific T cells** (De Kleer et al *Arthr Rheum 2003*, Kamphuis et al *Lancet 2005*, van Eden & Prakken *Nature Rev Immunol 2005* J Immunol 2011)

Tregs are enriched at the site of inflammation



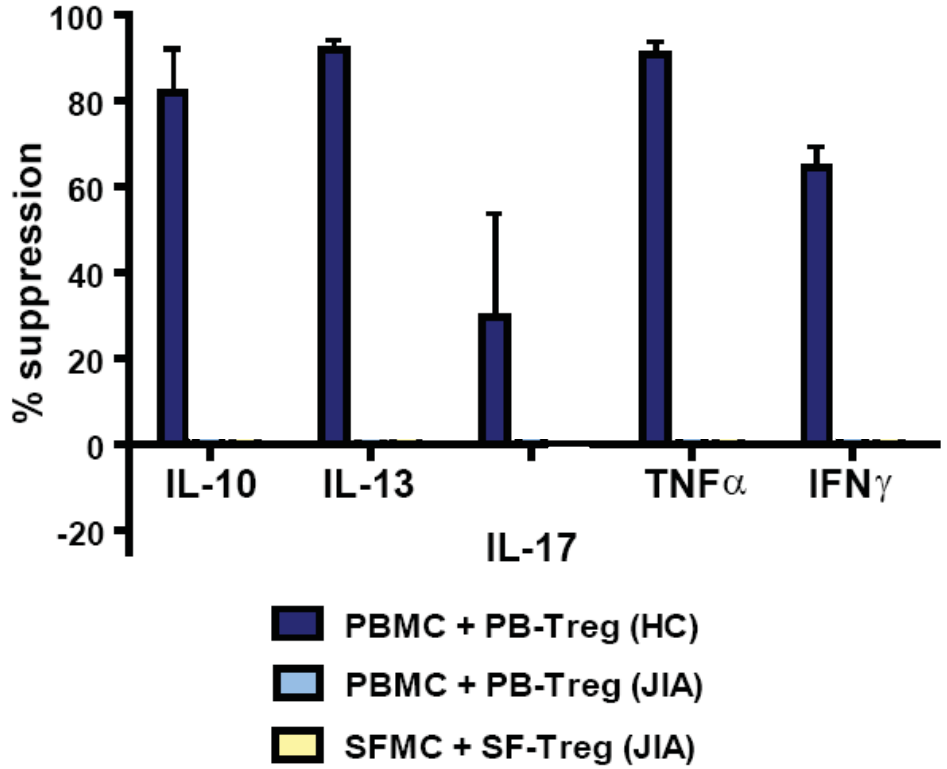
* $p < 0.05$

Reduced suppression of proliferation in synovial fluid



Wehrens et al, Blood 2011

Suppression of cytokine production impaired at the site of inflammation



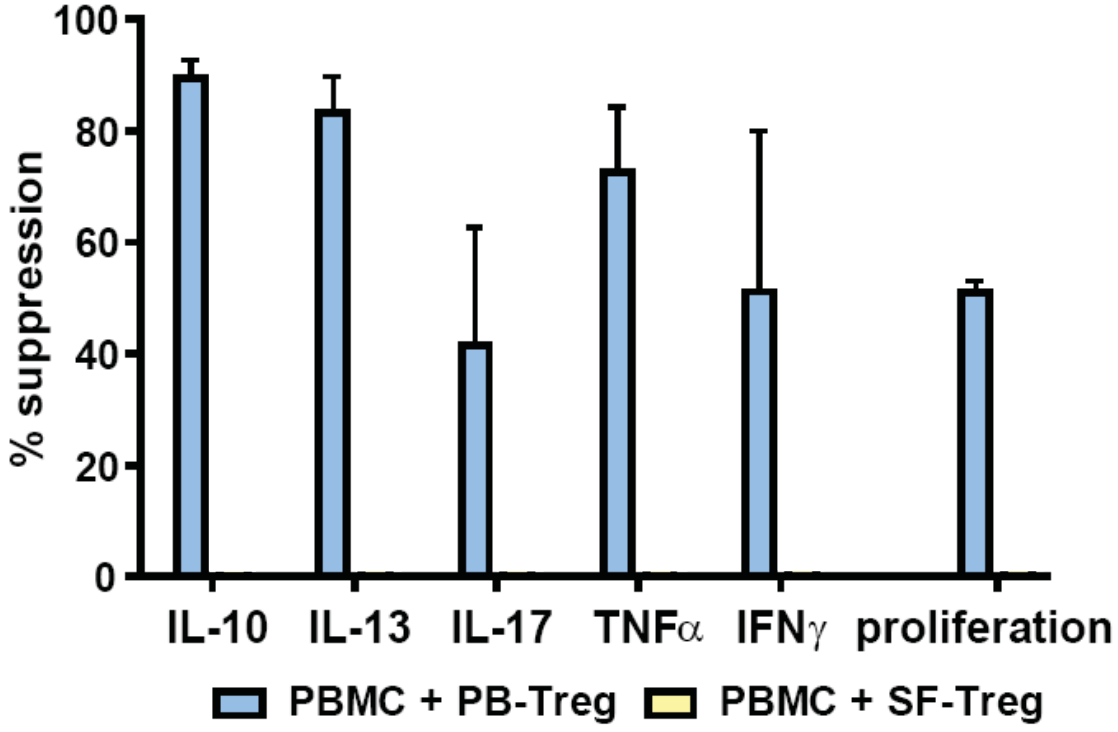
Defects in the suppressive function of Treg

or

Are effector cells resistant to suppression?

Ellen Wehrens

Cross-over experiments: No functional defect in SF-Treg! (but SFMC are resistant!)



And what about TH17?

The balance of inflammation and tolerance

- TH17: Pro-inflammatory (IL17)
- Inverse relationship Tregs-TH17
- Derived from same precursor T cell?
- Th17 cells may convert to Th17/1 and Th1 cells in human arthritis

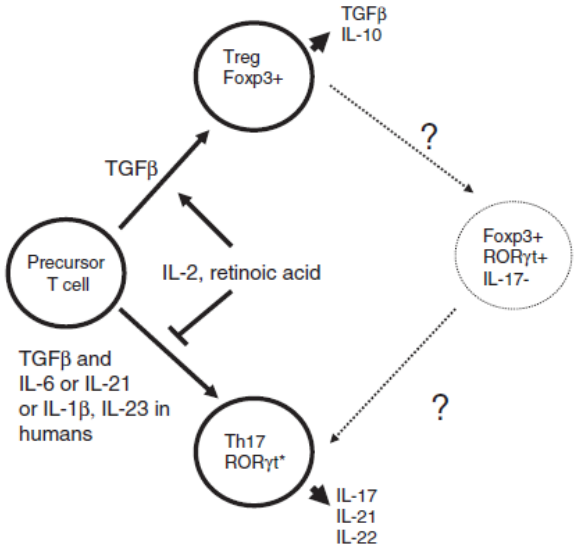


FIG. 1. Schematic diagram to show proposed relationships between Th17 cells and Tregs. Both Th17 cells and Tregs (most likely induced Tregs or so-called iTregs) may arise from a common precursor. In experimental systems this precursor has been sorted naive T cells. Cytokines thought to be involved in the generation of Tregs or Th17 cells are shown adjacent to thin arrows, while cytokines produced by the two cell types are shown with heavy arrows. A putative 'mixed' cell expressing Foxp3 and RORγt has been demonstrated in mice, and is shown here with dashed lines. Although its origin and exact relationship to other cell types is still controversial. RORγt in mice is equivalent to RORC2 in human cells.

Conclusions

Pathogenesis of chronic inflammation

Interplay between innate and adaptive immune system

Balance of pro- and anti-inflammatory signals, such as the Inverse relation Th17-Th1

MRP (DAMP proteins) are upregulated in systemic inflammation, esp SJIA

Tregs in SF are not deficient, but T effector cells are resistant to suppression

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Collaboration with PRES

- Educational courses
- Fellow exchange
- Research
- PRINTO drug trials
- Patient information

Basic & advanced course Mumbai 2012

Methods: suppression assay

isolate mononuclear cells
from peripheral blood (PBMC) and synovial fluid (SFMC)

FACS sort

total SFMC / PBMC

$CD4^{+}CD25^{+}CD127^{low}$
regulatory T-cells

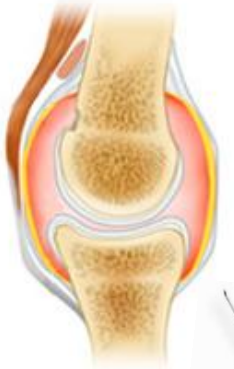
label with CFSE

culture with αCD3

day 4

Luminex: cytokine production

CFSE: proliferation



Are Tregs in poly articular JIA functionally impaired?

Ellen
Wehrens

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