

Selected topics in Clinical Immunology

Psoriasis

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Immunology and Pathogenesis

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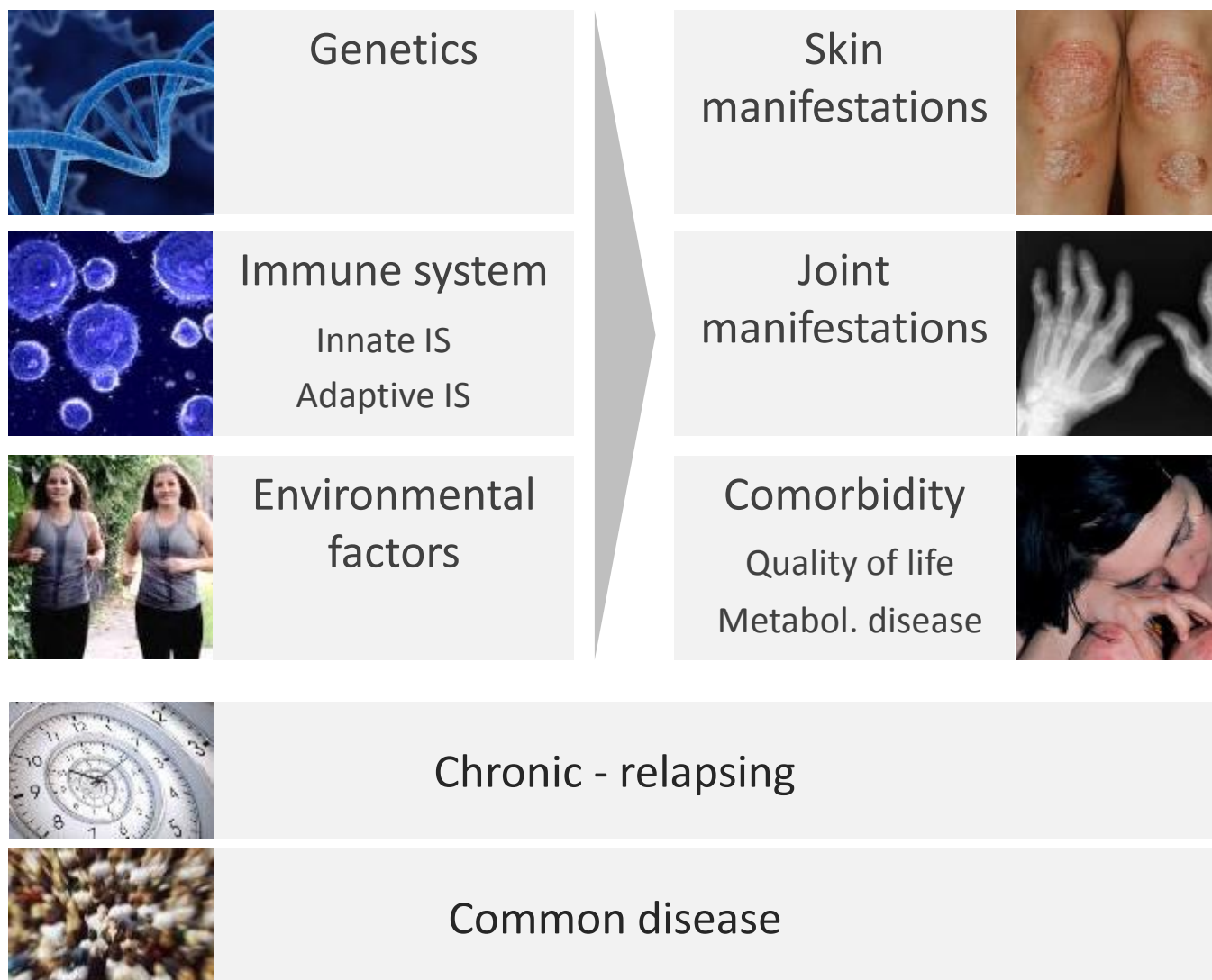
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Definition of Psoriasis



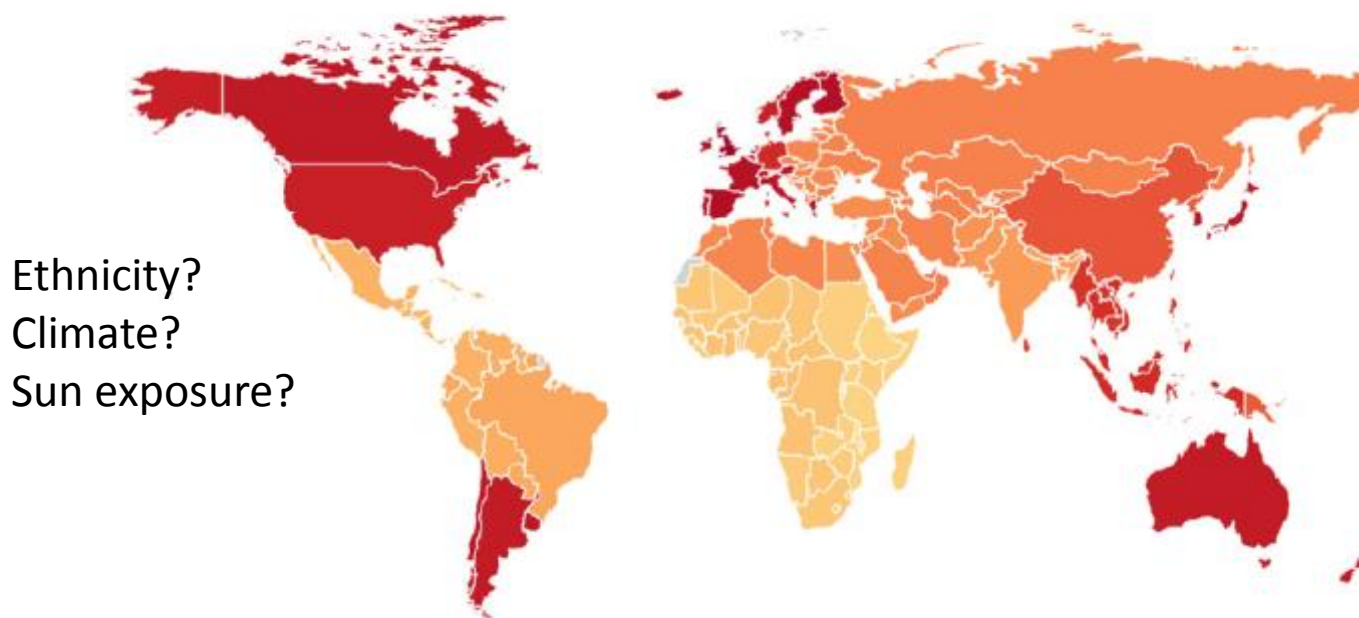


Prevalence

Prevalence world wide: 2%

North America / Europe: up to 4%

Lapps/Africa/Asia: 0.4 – 0.7%



Prevalence **Asthma** world wide: 4.5% - 14%

Prevalence **Rheumatoid Arthritis** world wide: 0.4 – 1.3%

Epidemiology: Good and bad news



80% mild psoriasis
(topical treatment only)

5 - 20% psoriasis arthritis



75% onset before 40 years of age

80% psoriasis of the scalp (most frequent localisation)

nail changes: 50% at diagnosis, 70% life time

Clinical face of psoriasis



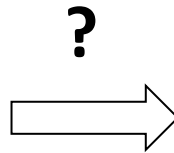
Clinical face of psoriasis



Clinical face of psoriasis



Clinical face of psoriasis



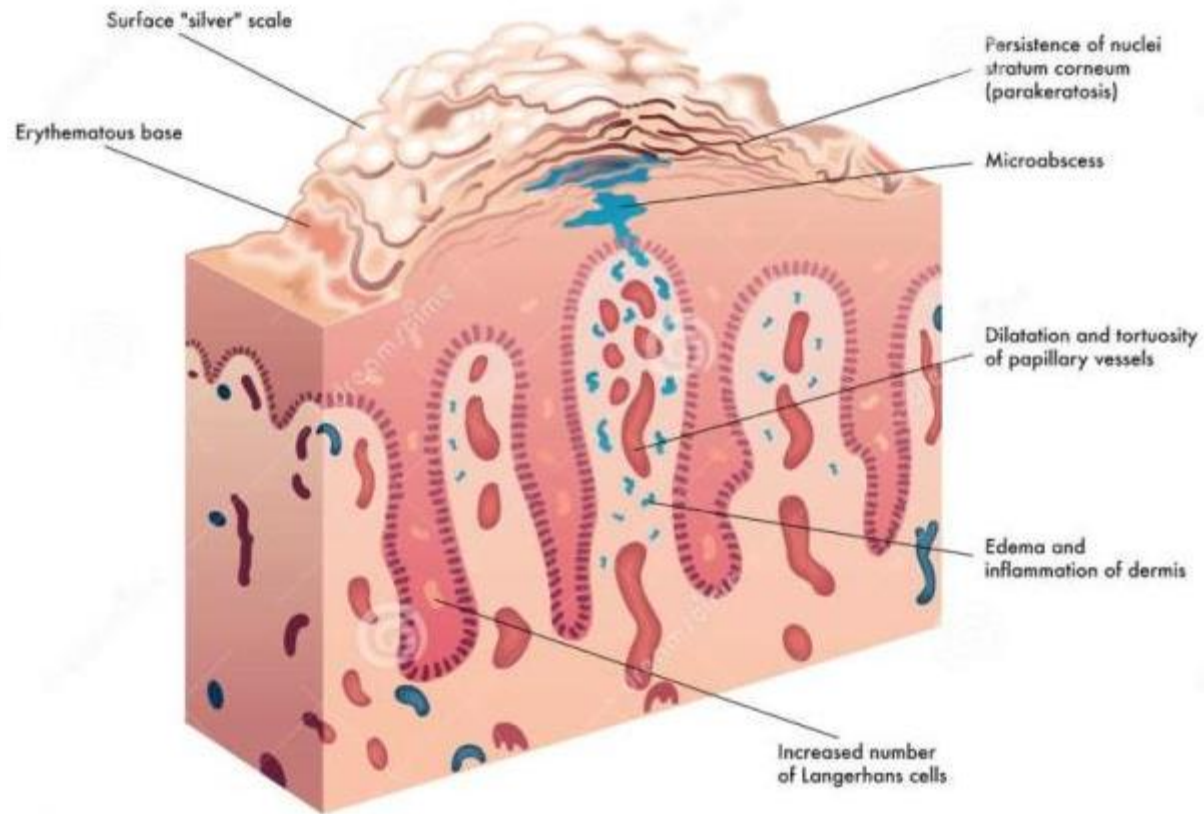
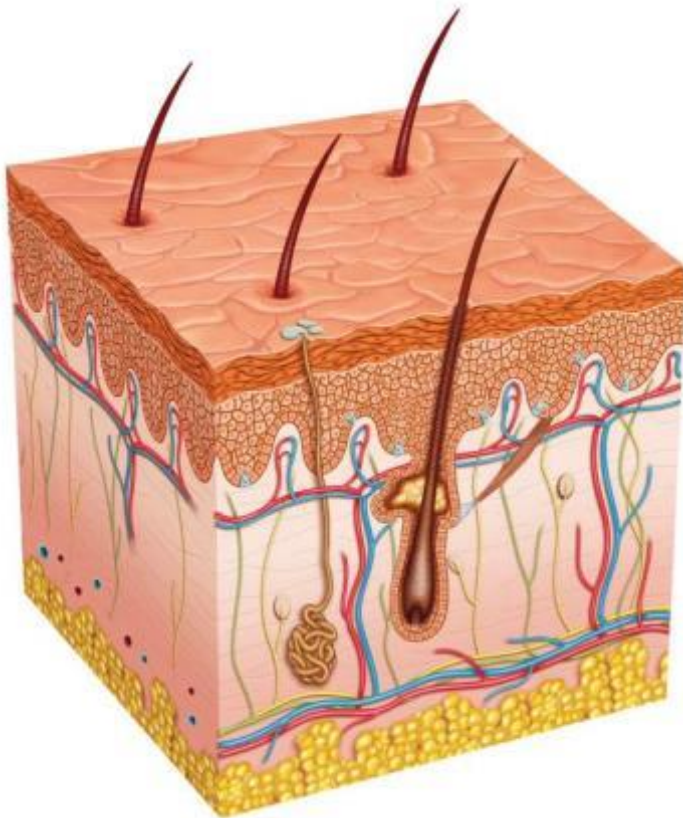
Pathological hallmarks of psoriasis

Abnormal differentiation and hyperproliferation of keratinocytes

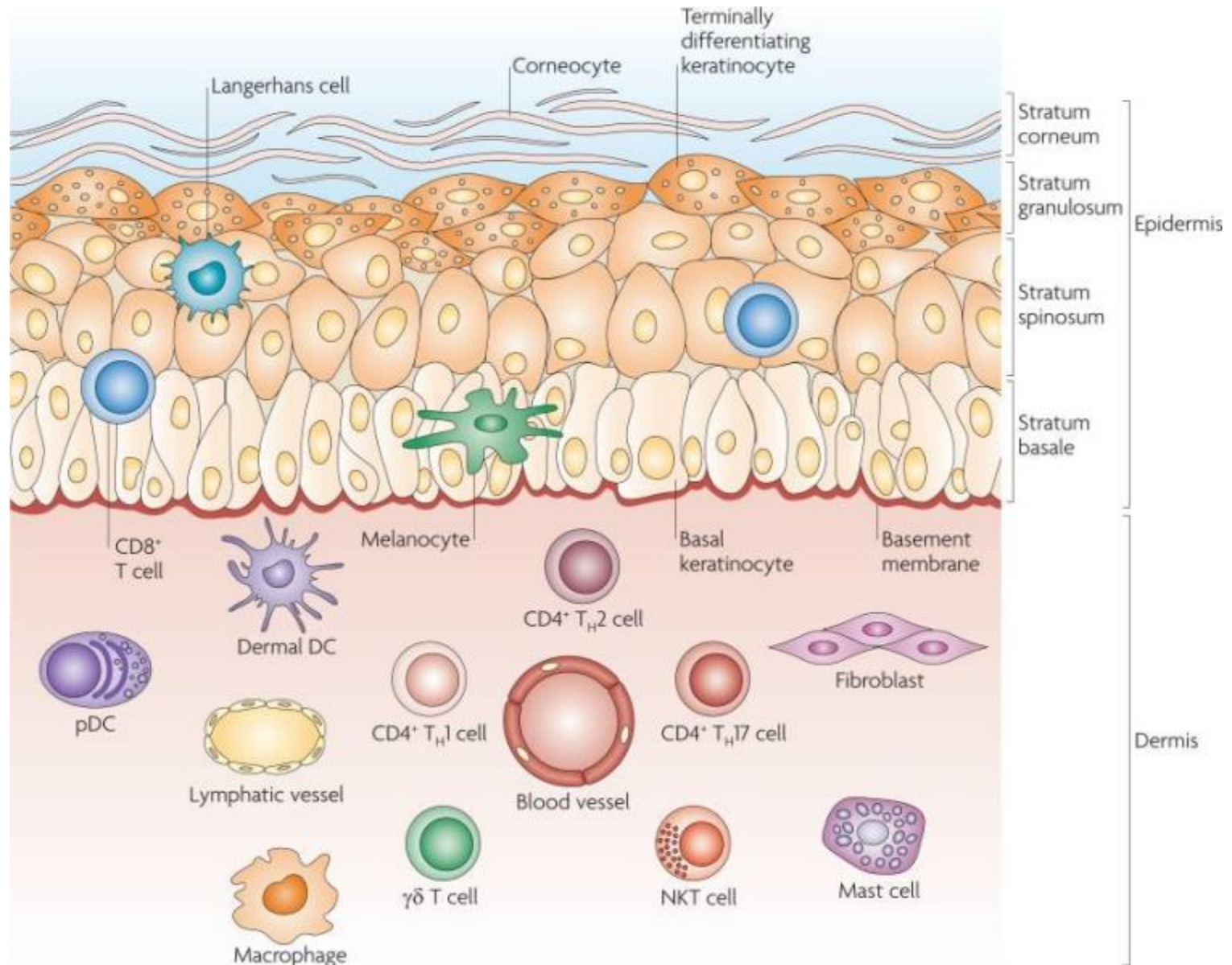


Infiltration of inflammatory cells
Increased dermal blood vessels

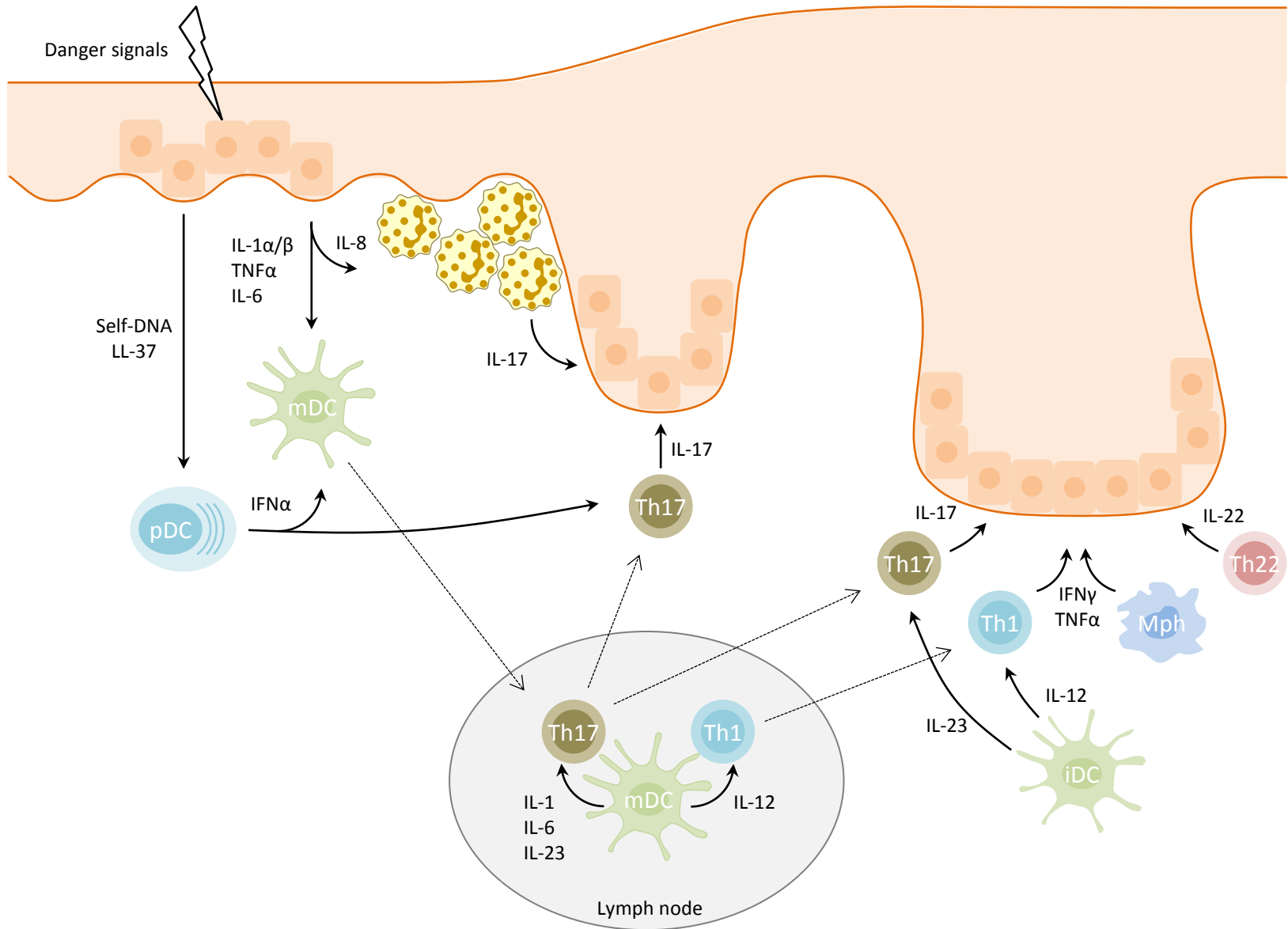
Normal & psoriatic skin



The skin immune system



Immuno-pathogenesis of psoriasis



Trigger factors

Trauma

Koebner phenomenon



Infections

Streptococci
HIV



Drugs



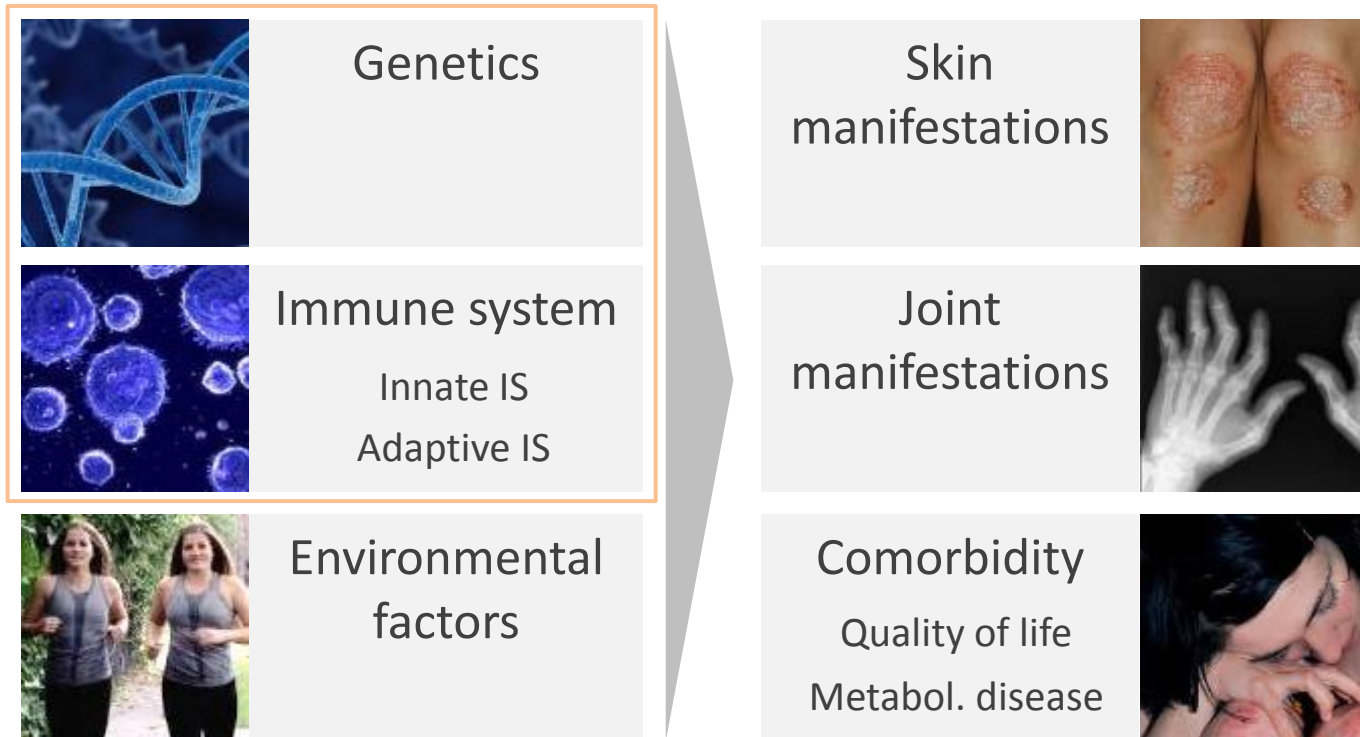
Behavioural factors



Occupational factors



Genetics & Pathogenesis



Genetics of psoriasis



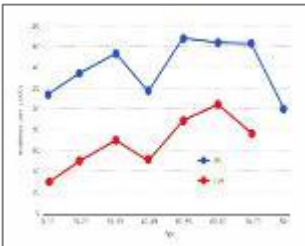
Population studies



1st/2nd degree relatives: Higher incidence of psoriasis



Concordance rate in monozygotic twins =
3-times higher than in discordant twins



Type I: positive family history – more severe course

Type II: negative family history – milder course

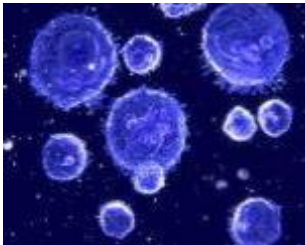
Genetics of psoriasis



Genetic studies



>40 susceptibility loci are associated with psoriasis

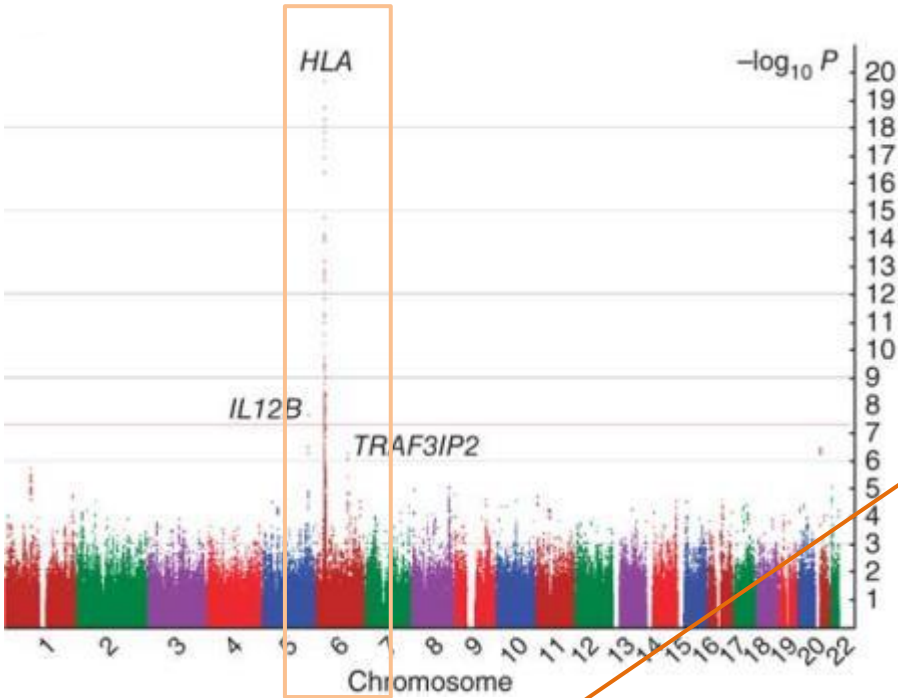


Candidate genes suggest key role for

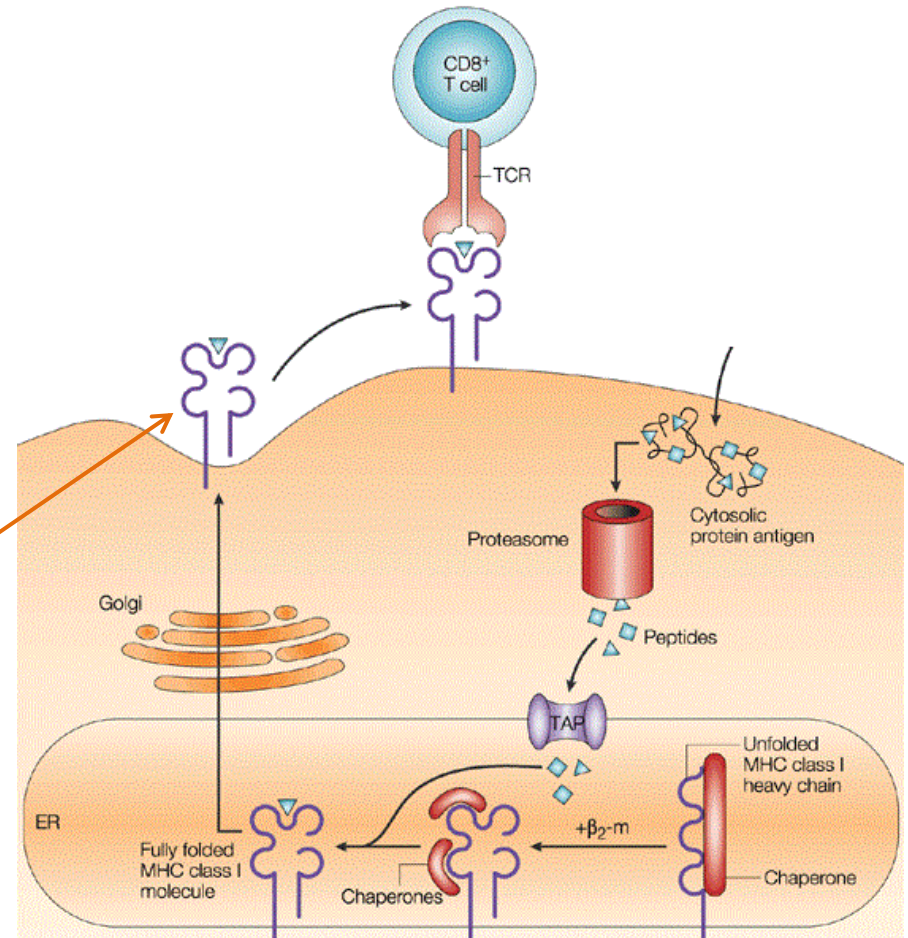
- adaptive immunity
- innate immunity
- skin barrier functions

Genetics of psoriasis

PSORS1



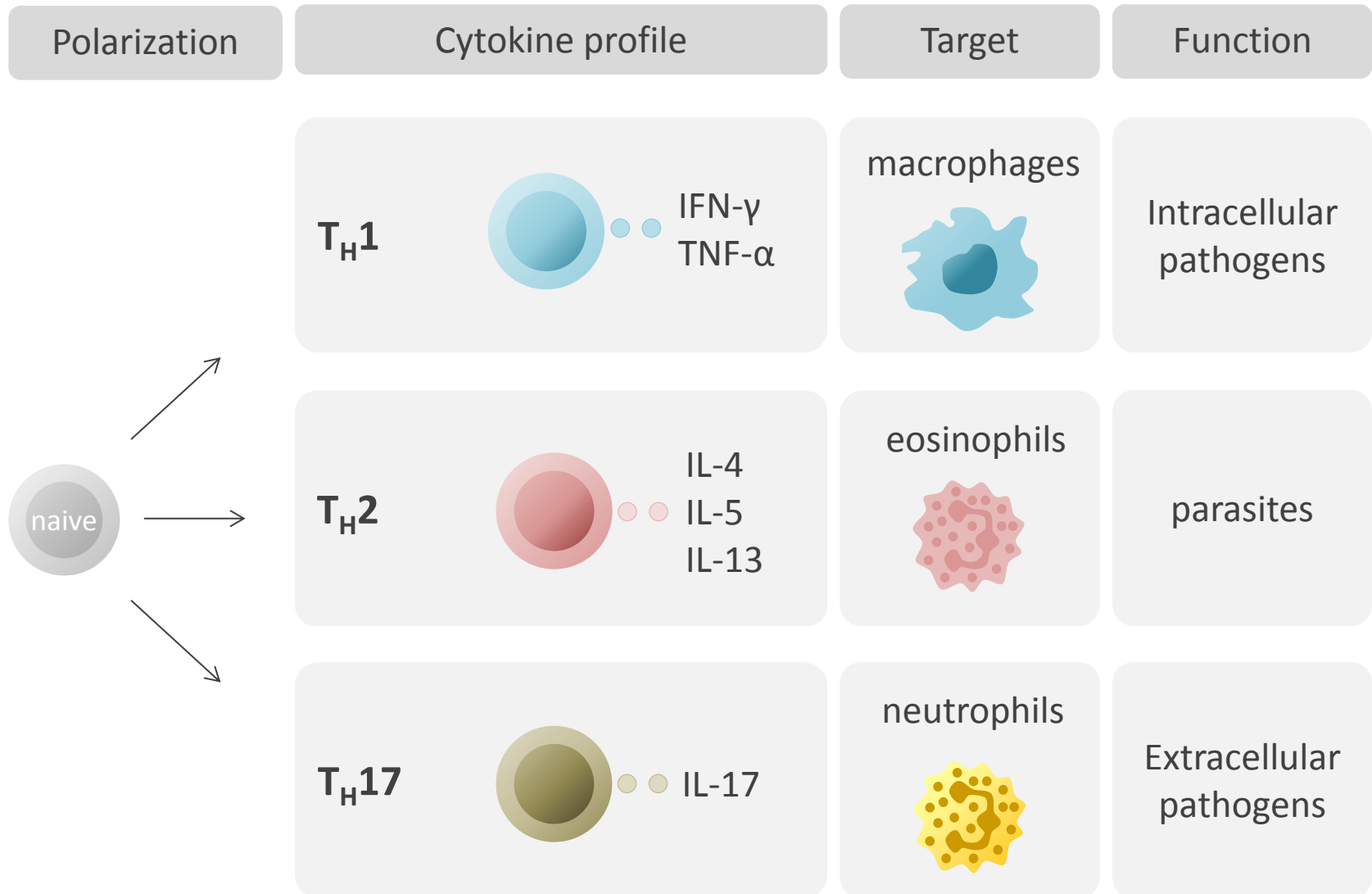
HLA-Cw6



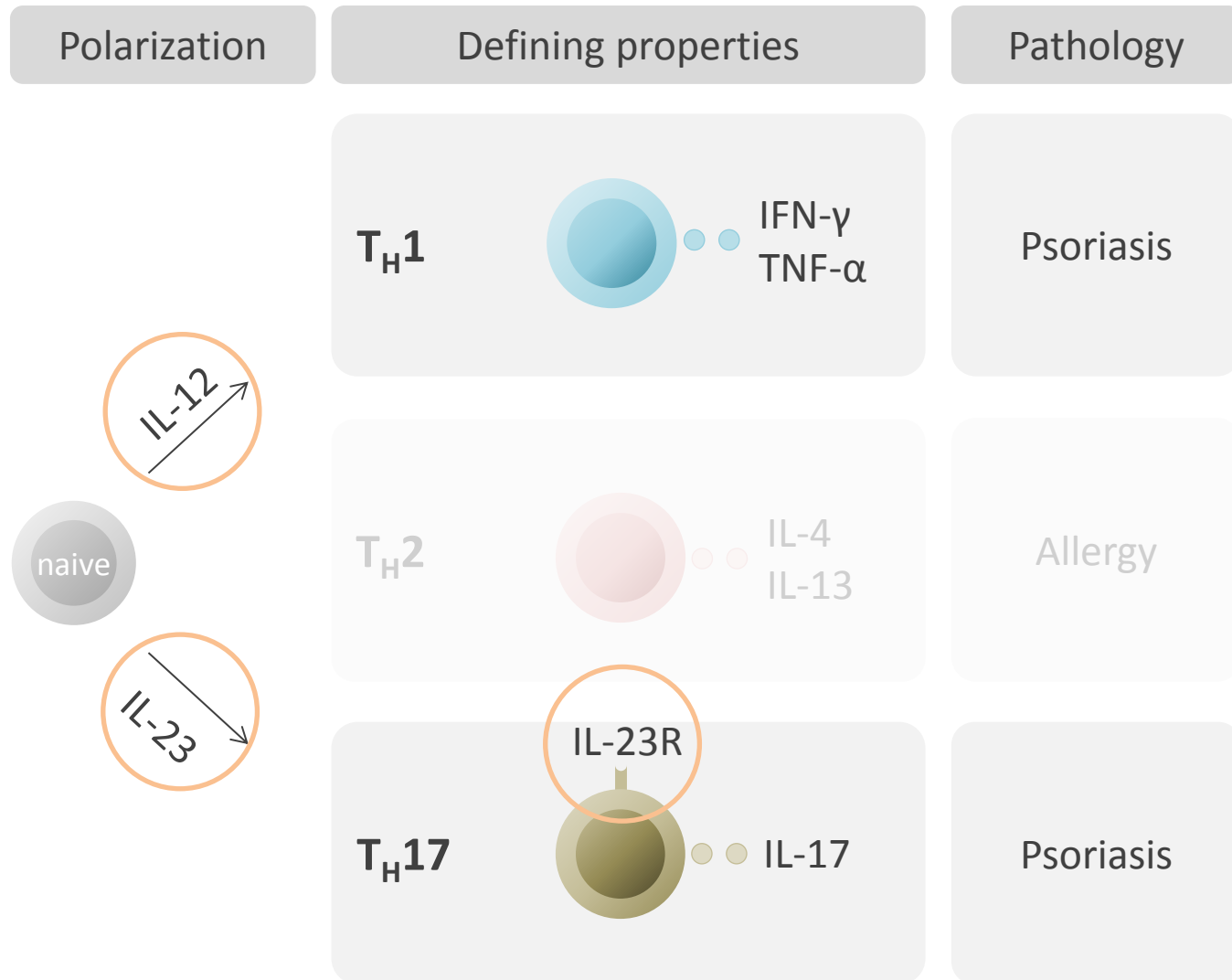
Genetics of psoriasis

Gene / locus	Chromosomal location	Odds ratio
PSORS1	6p	6.4
PSORS2	17q	–
IL12B	5q	1.4
IL23R	1p	2.0

T helper (T_H) cells



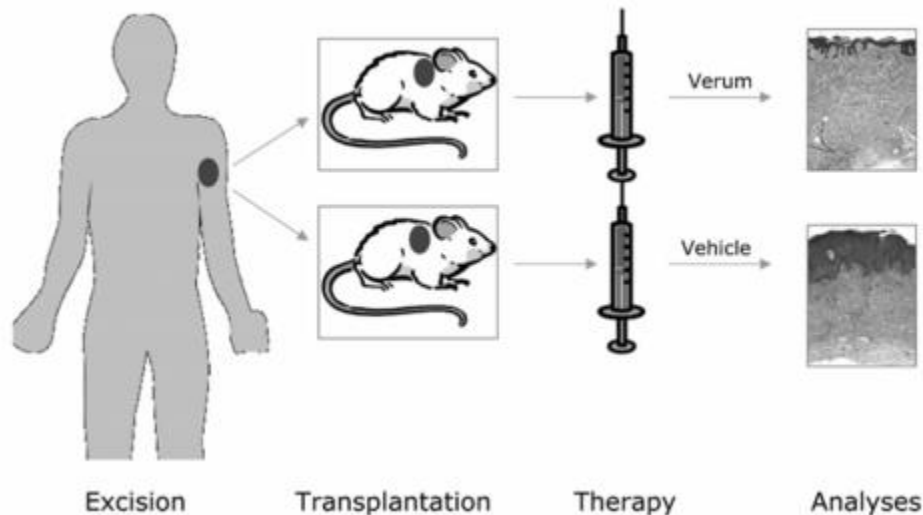
T helper cell subsets



Role of T cells in psoriasis

Xenotransplantation models

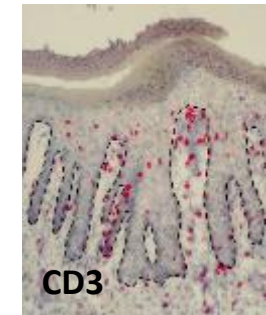
1. Non-lesional human skin from healthy or psoriasis donor
2. Engrafted onto immuno-compromised mice
3. Spontaneous development of psoriatic phenotype (psoriasis donors but not healthy donors)
4. Blocking of T cells lead to inhibition of psoriasis development



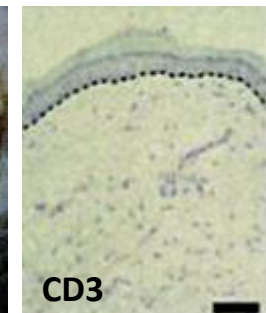
Day 0



Day 56



anti-human CD3 mAb



Role of T cells in psoriasis

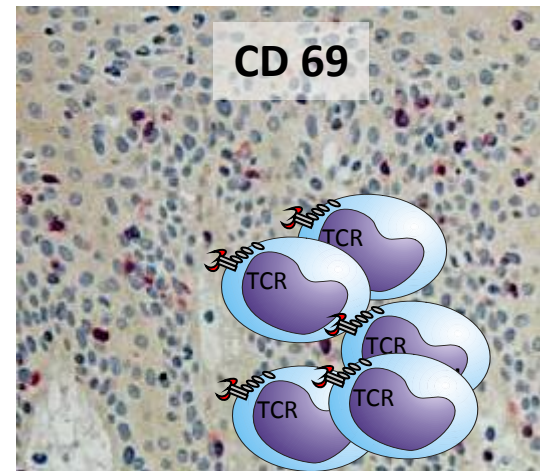
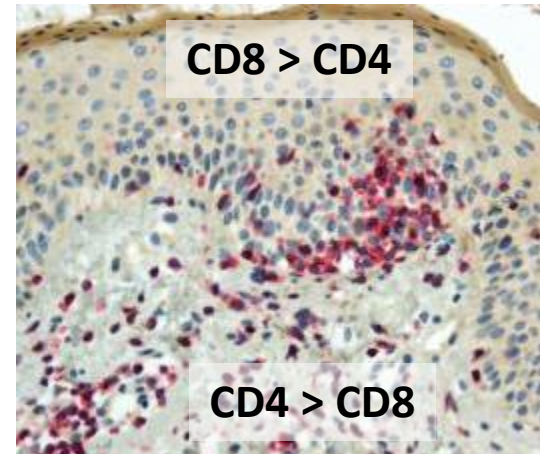
Infiltrate:

- memory-effector T cells

CD4 ↔ DC, macrophages

CD8 ↔ keratinocytes

- T cells are activated
 - CD69, CD25, HLA-DR
- clonal T cell expansions
 - antigen-specific stimulation



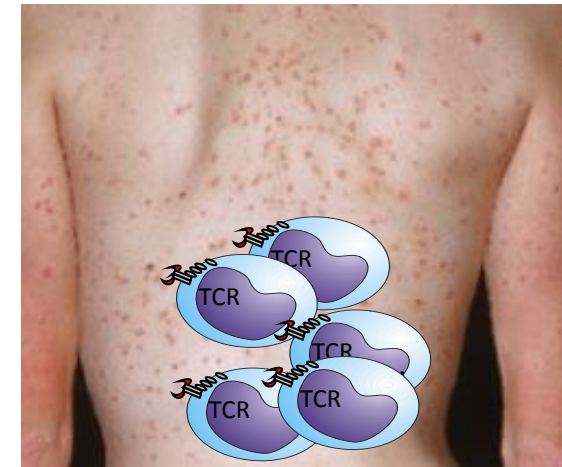
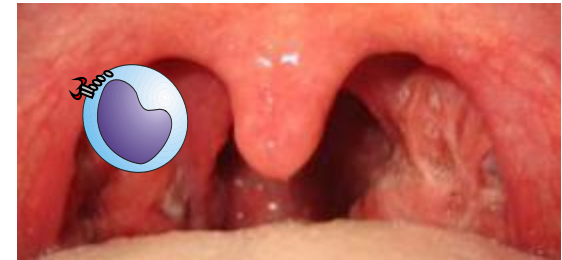
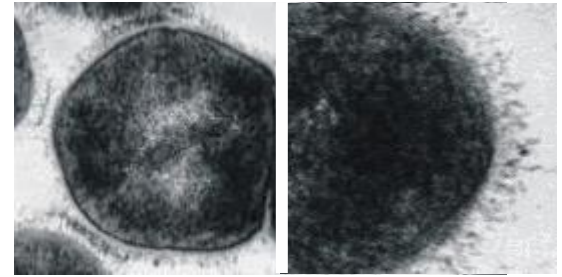
The 1 million dollar question in psoriasis



What is the antigen ?

Putative antigen(s)?

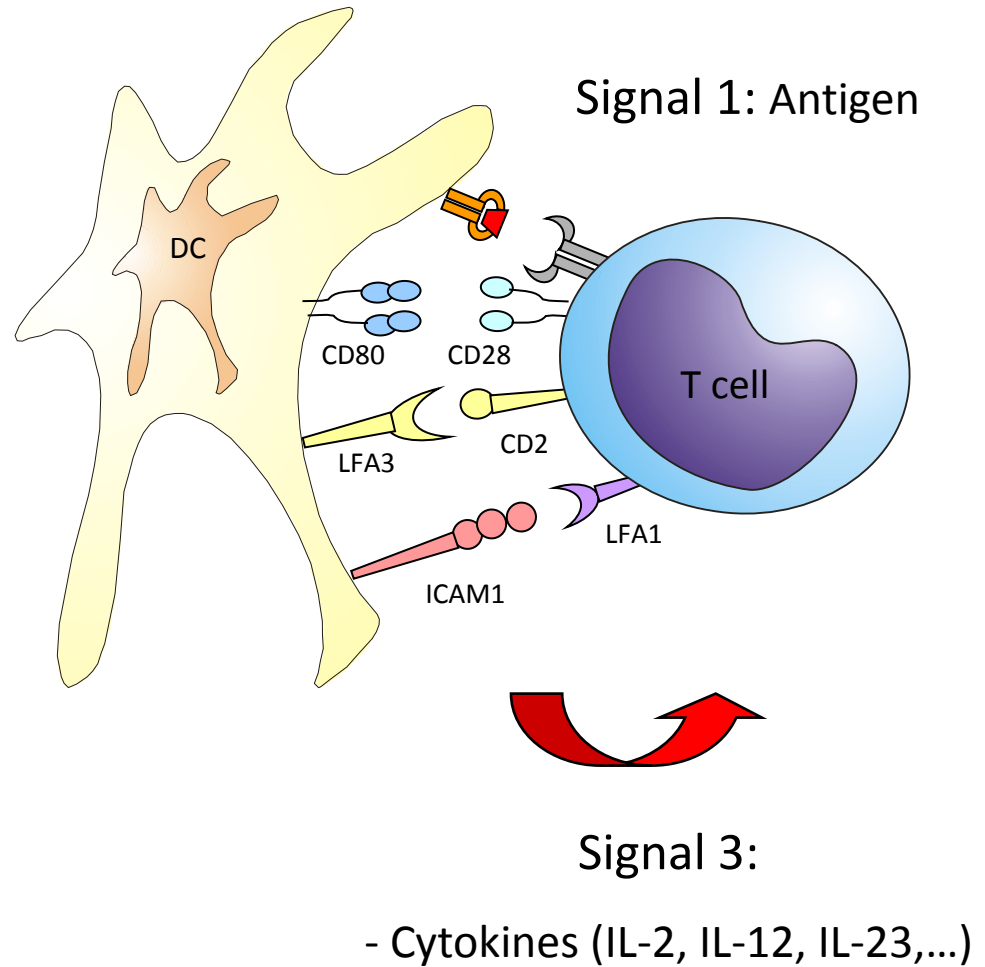
- β -haemolytic streptococci can trigger psoriasis
- T cells cross-react with epitops which are common to streptococcal M protein and keratins



Innate immunity is critical for T cell activation

Signal 2:

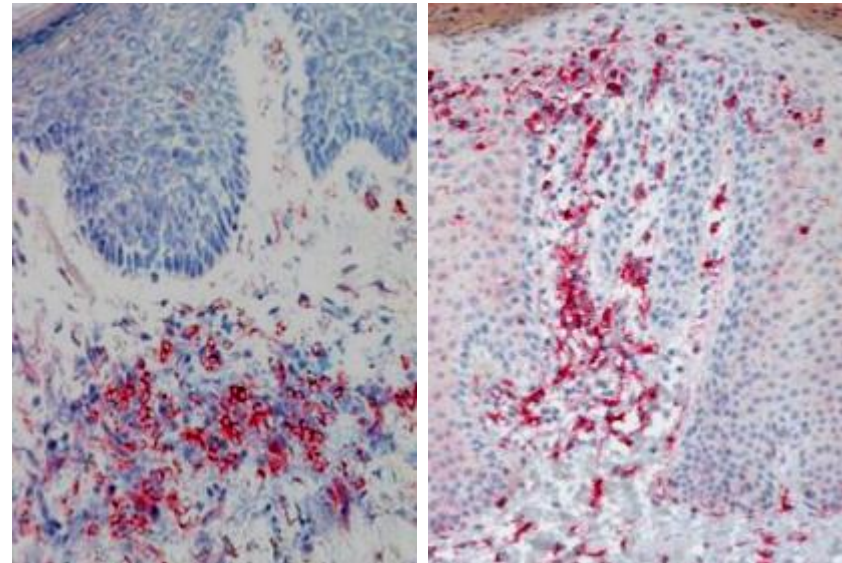
- Co-stimulatory molecules
- Adhesion molecules



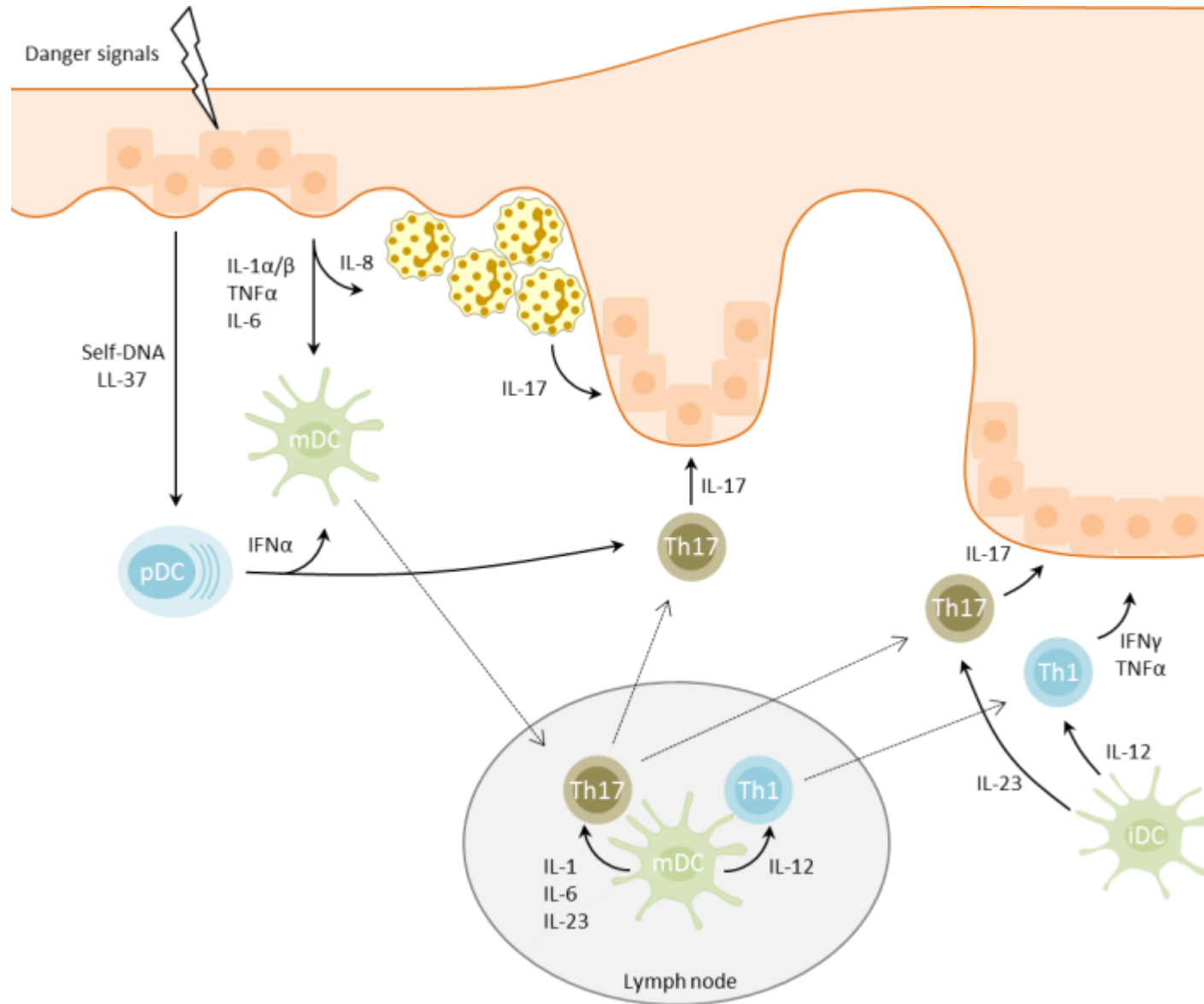
Innate immunity in psoriasis

Psoriatic skin is highly infiltrated by dendritic cells (DC)

- plasmacytoid DC (BDCA-2)
- myeloid DC (CD11c, BDCA-1⁺)



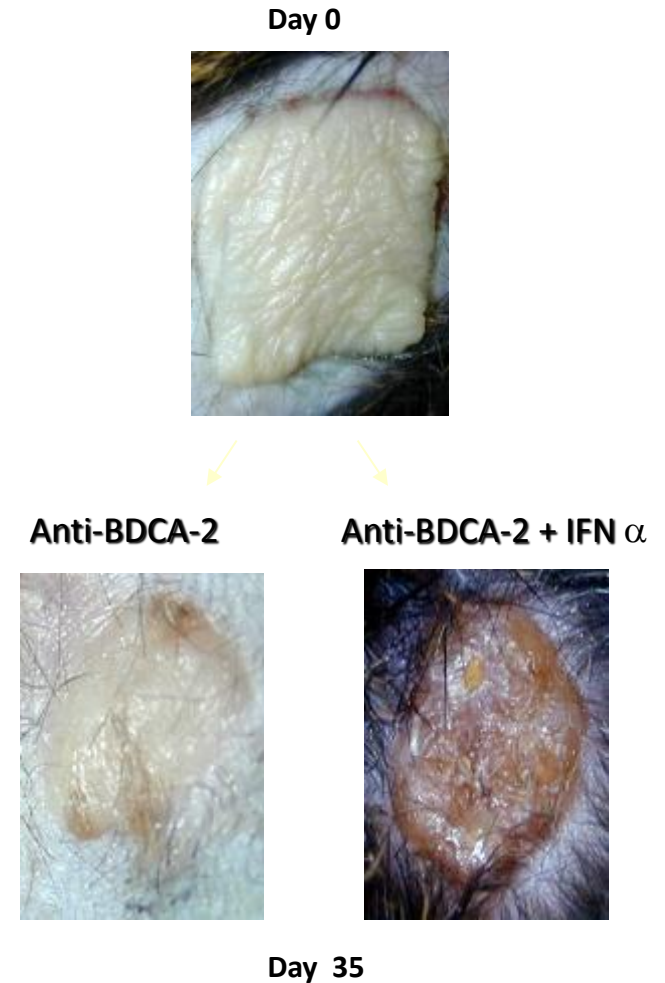
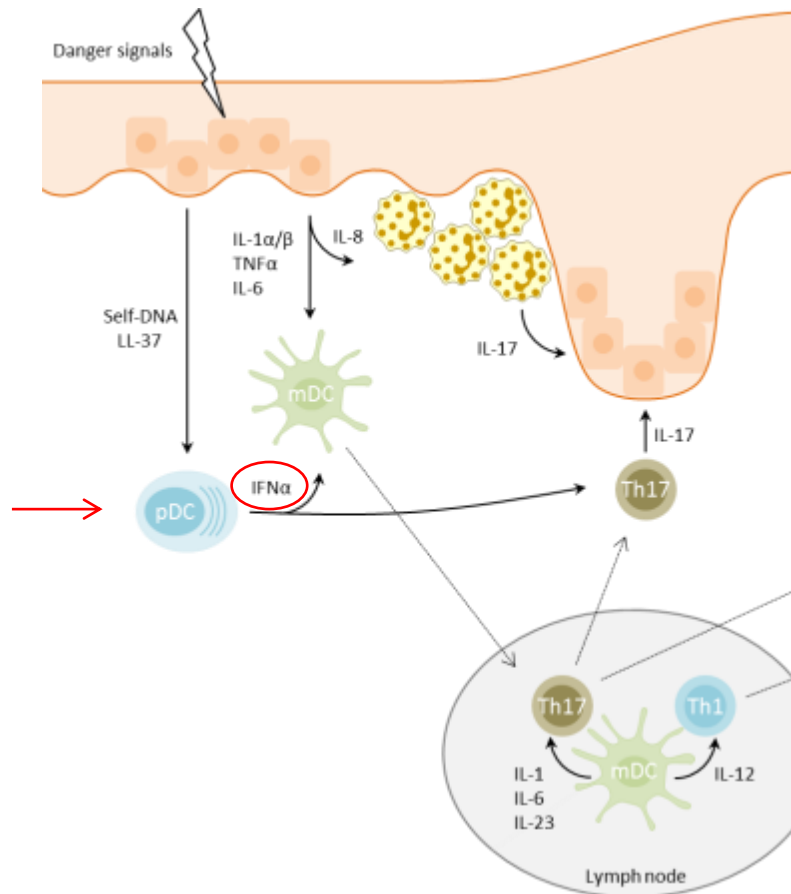
Activation of DC and production of cytokines



Key cytokines in psoriasis: IFN- α

Xenotransplantation models:

- Psoriasis is inhibited by anti-BDCA-2
- fully restored by addition of human IFN- α

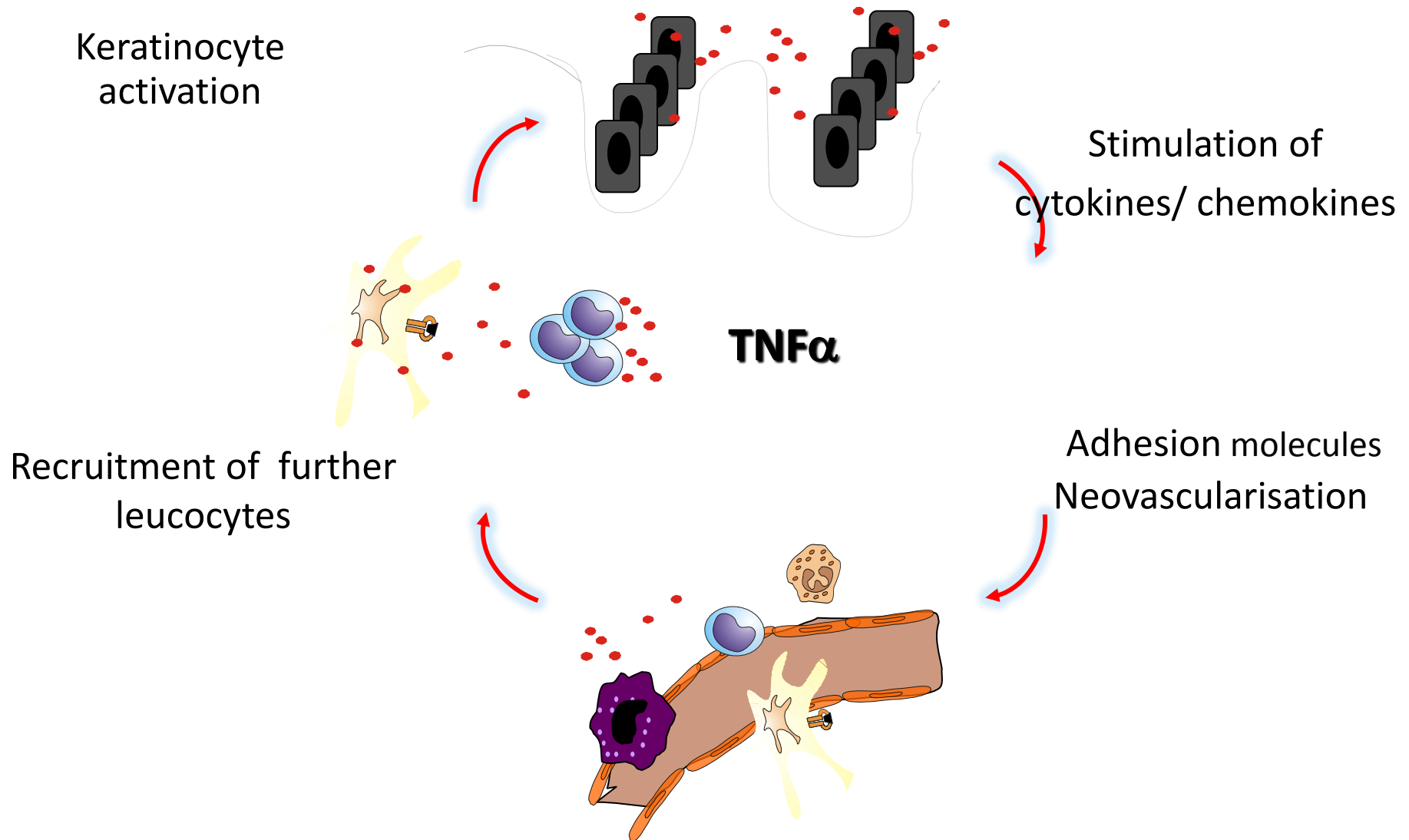


Key cytokines in psoriasis: TNF- α

- Enhanced expression in
 - skin
 - joints
 - serum (correlates with activity)
- Produced by multiple cells
 - DC, macrophages
 - T cells
 - mast cells
 - keratinocytes, endothelial cells



Key cytokines in psoriasis: TNF- α



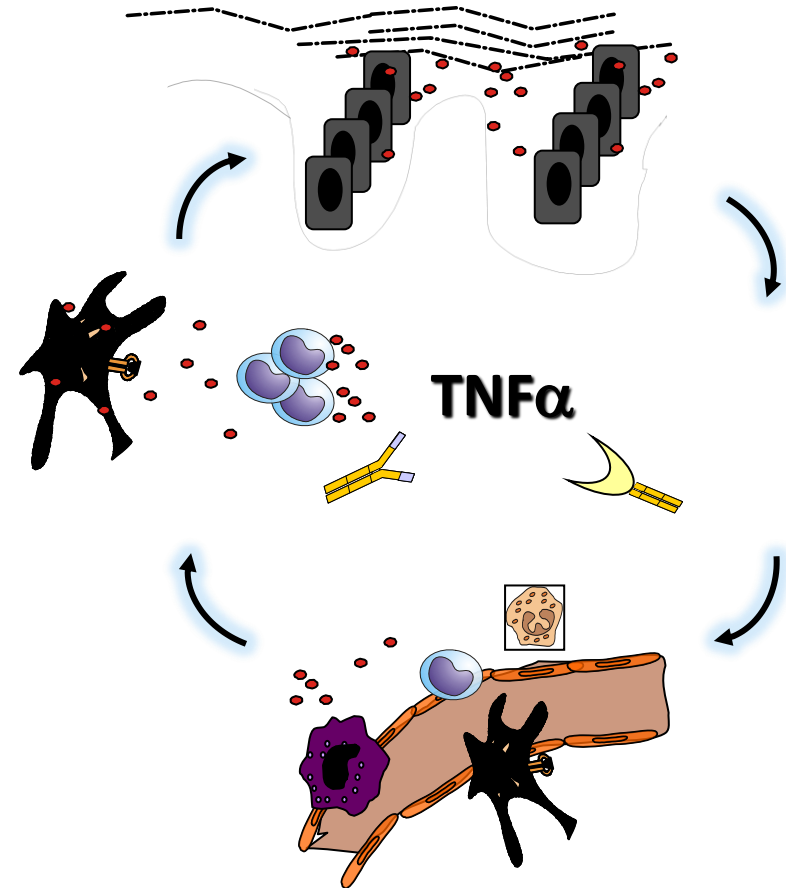
Modulation of key cytokines

TNF Antagonists

Etanercept

Adalimumab

Infliximab



Infliximab (anti-TNF- α Antibody)



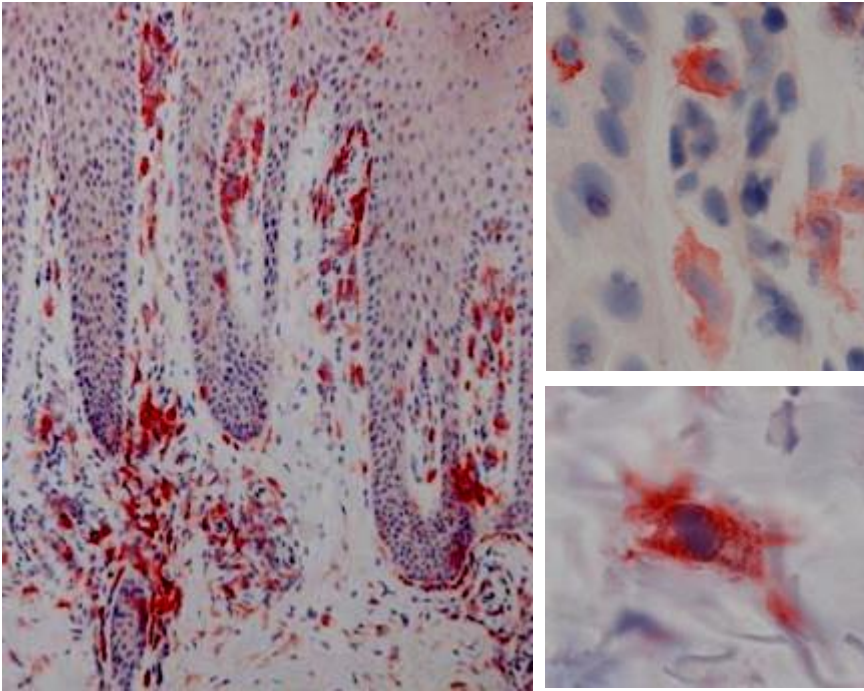
before Infliximab



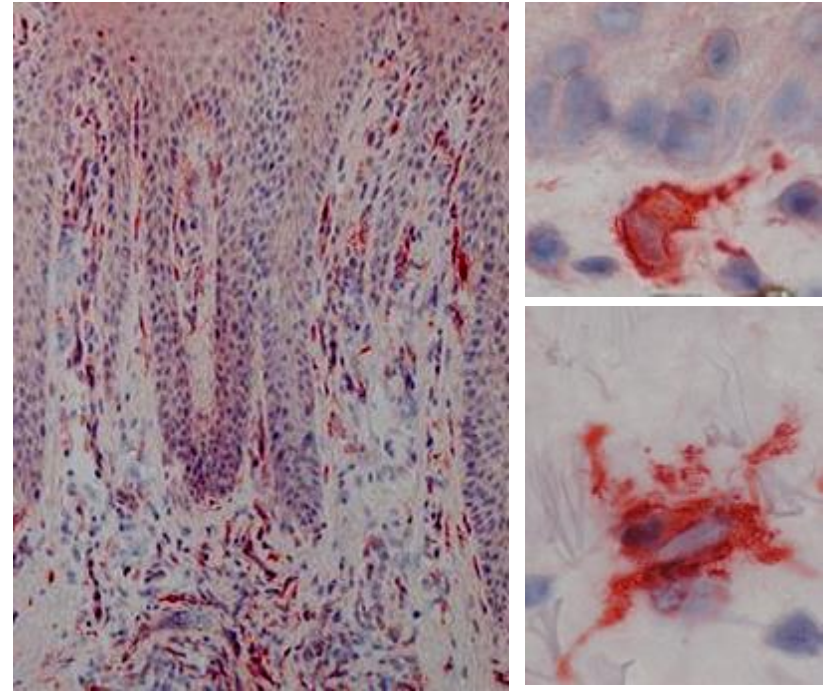
on Infliximab since 3 years

Key cytokines in psoriasis: IL-12 and IL-23

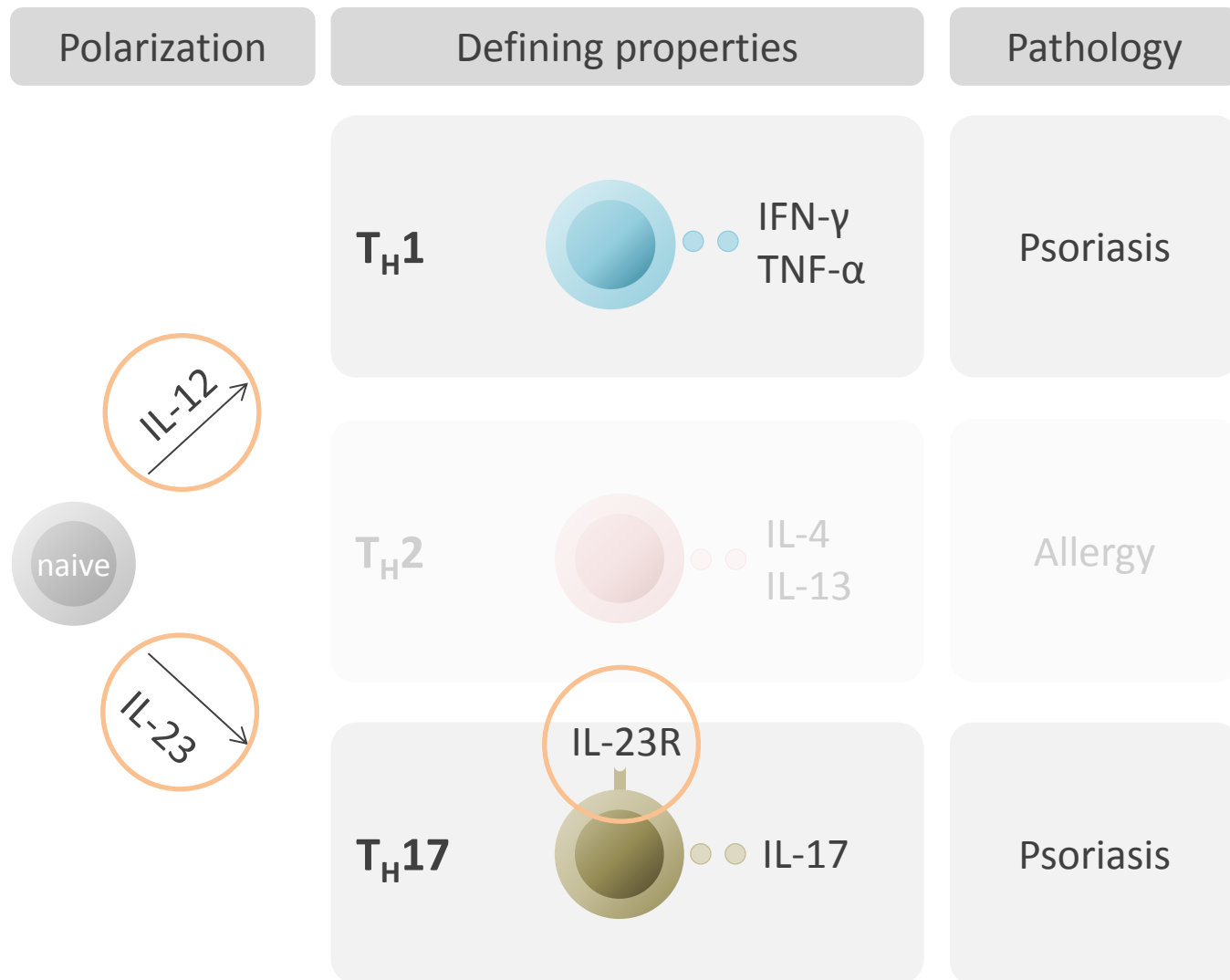
IL-12



IL-23

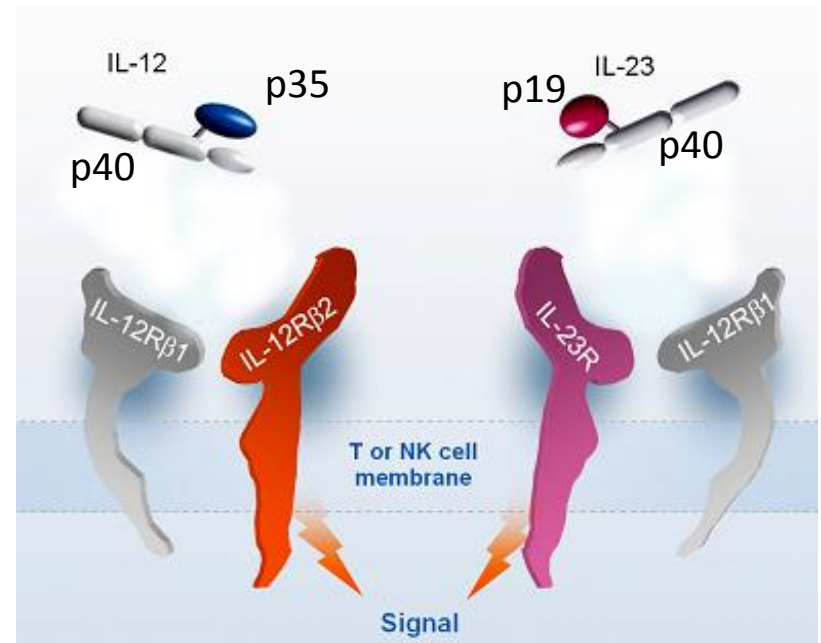


T helper cell subsets

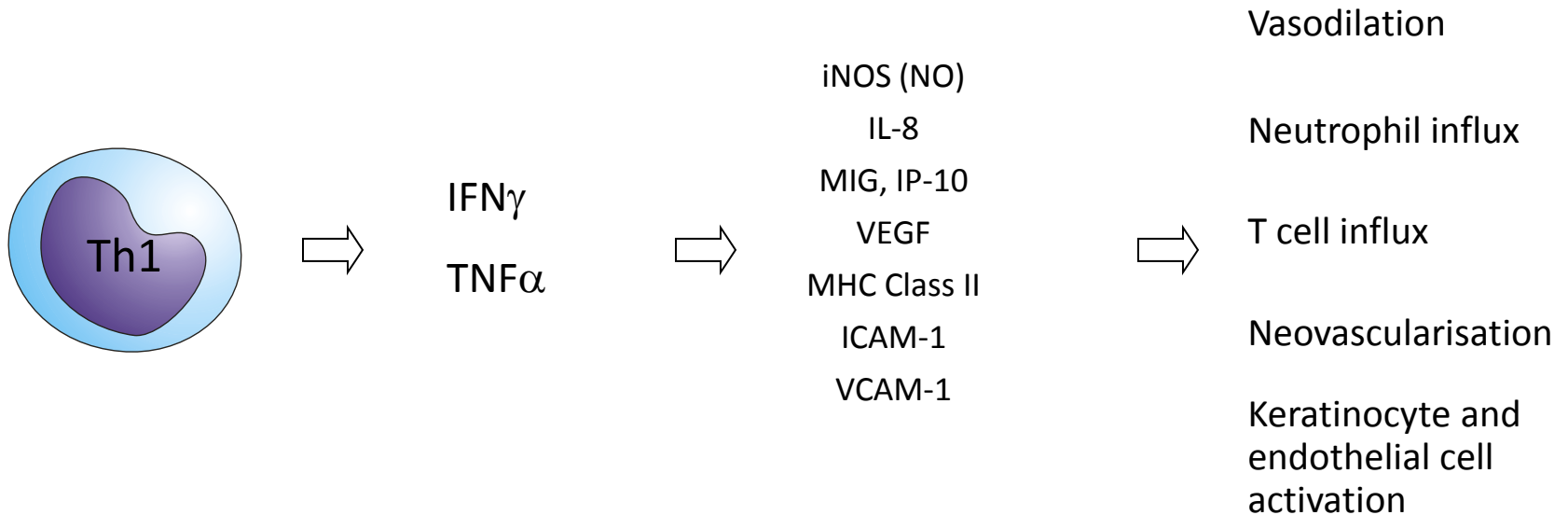


IL-12 & IL-23: heterodimers with common p40 subunit

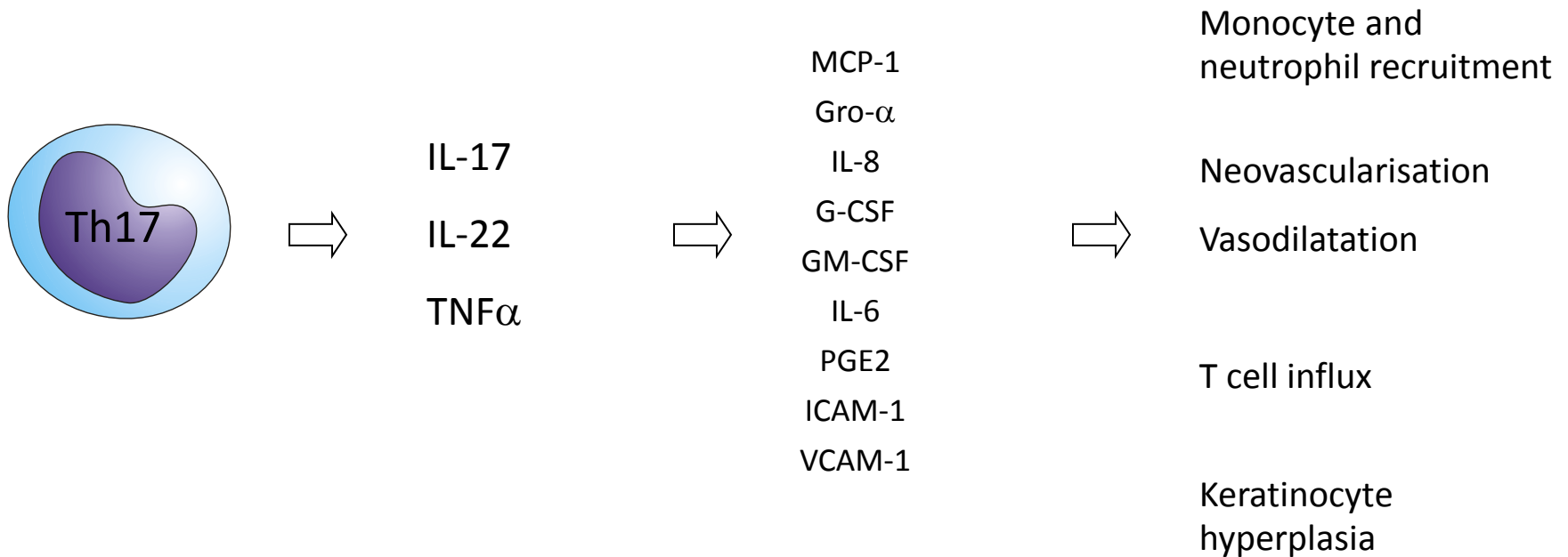
- IL-12 and IL-23 bind to specific receptors on T cells and natural killer cells
- Strongly influence T cell differentiation and activation



Th1 cytokines: inflammatory processes in psoriasis



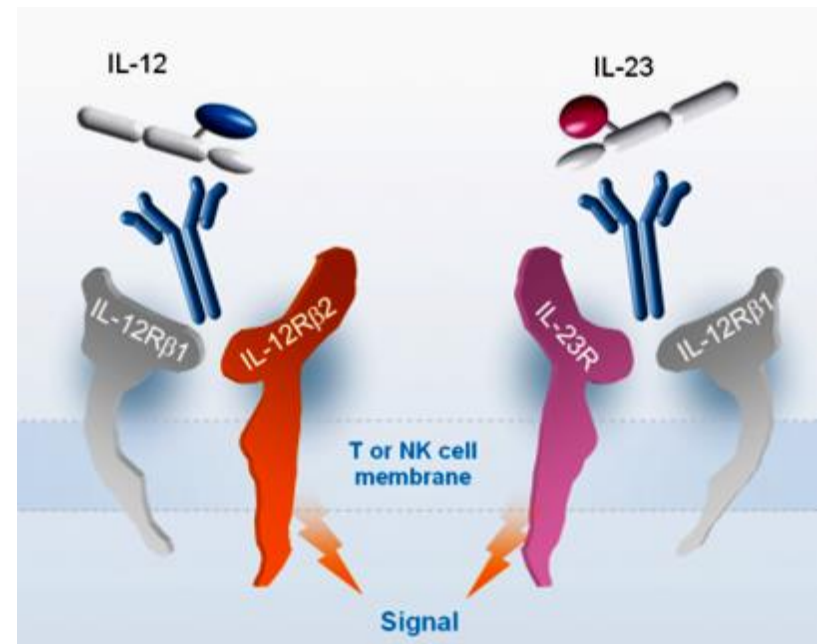
Th17 cytokines: inflammation and keratinocyte hyperplasia



Modulation of key cytokines

- **Anti-IL-12/IL-23 p40**

Ustekinumab



Ustekinumab (anti-p40-Ab)



Before Ustekinumab



week 12



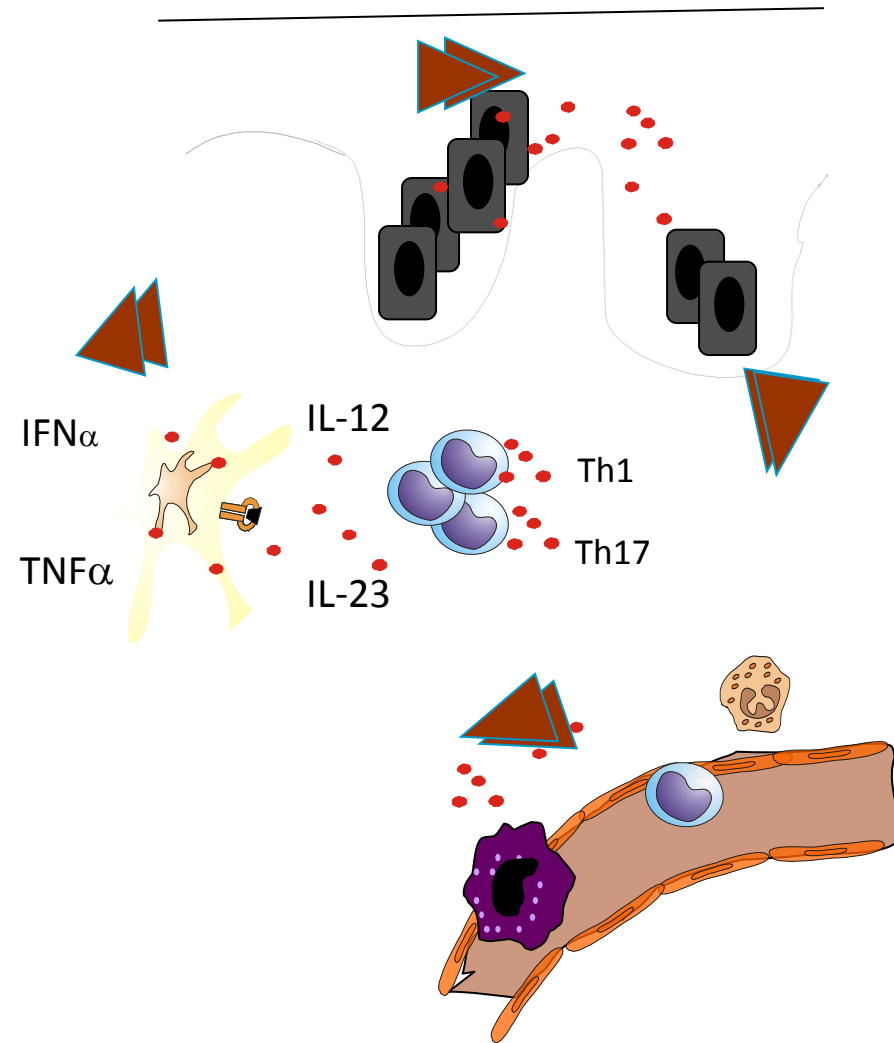
week 52

Summary: Key steps in the immunopathogenesis

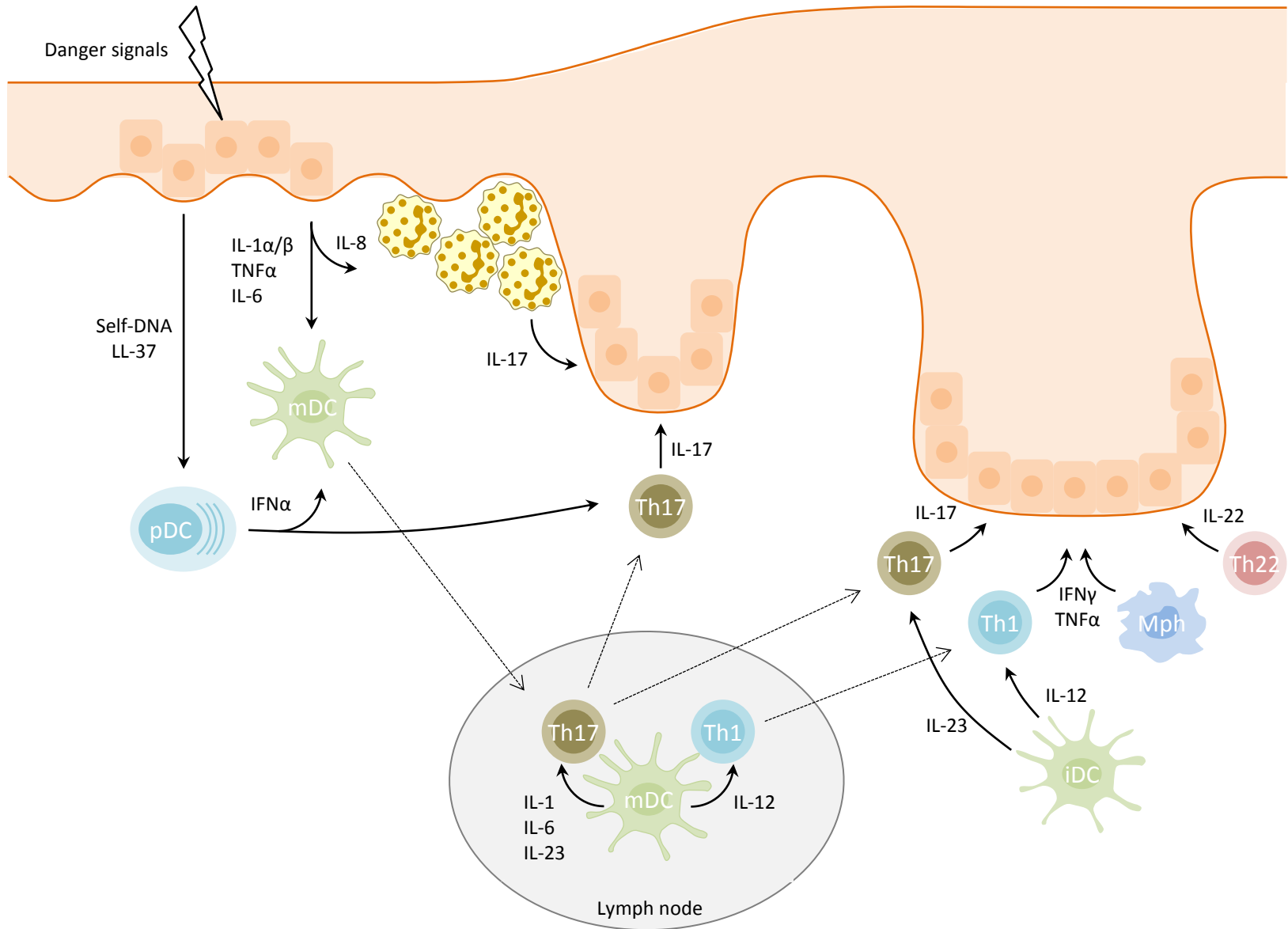
Activation of DC and T cells

- Stimulation of keratinocytes
- Neovascularisation
- Recruitment of further leucocytes

Perpetuation of inflammation



Immunogenetics of psoriasis



Thank you for your attention

