PHYSIOPATHOLOGIE DE LA MALADIE DE BEHCET MALADIES AUTO-INFLAMMATOIRES

G. KAPLANSKI

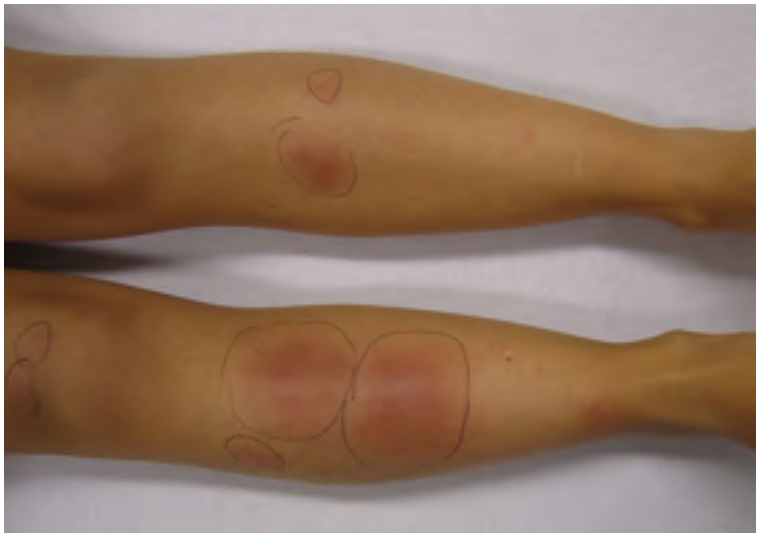
Service de Médecine Interne, CH Conception, Marseille

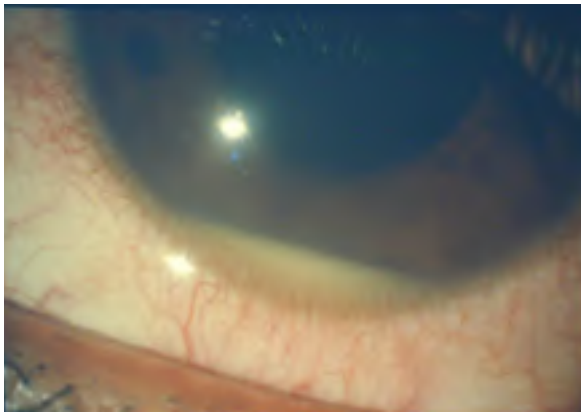
INSERM UMR_S1076

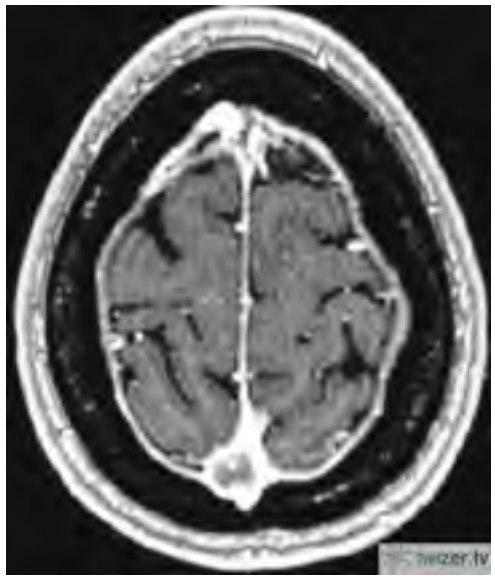
Vascular Research Center Marseille

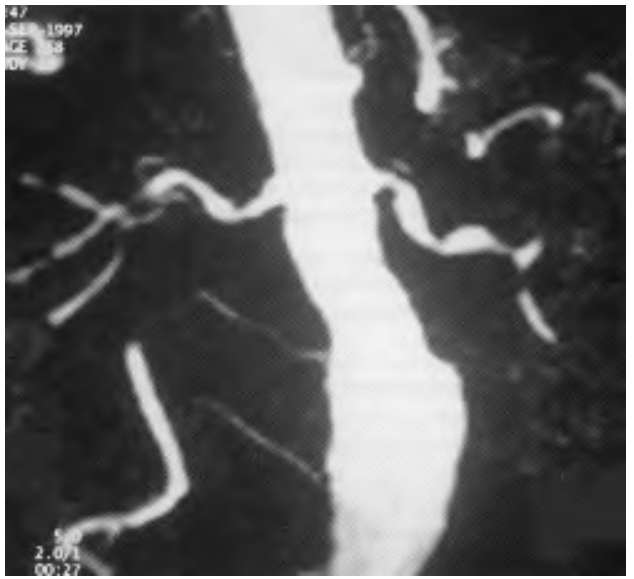
84e Journée de Médecine, Société Médicale des Hôpitaux de Paris

BEHCET DISEASE (BD)
A Systemic Chronic Inflammatory Disorder









BD: A COMPLEX PATHOGENESIS

Microbial Infections
Streptococcus sanguis, salivarius..

Impaired Microbial Clearance

Complex Genetic Background
HLA B51, MICA
IL-10, IL-23R, CCR1, TLR2/4
MEFV

Heat shock proteins
Hsp60/65

Exuberant Host Response
Excess Th1, Th17
Decreased Th2
Excess Innate immune response

Vasculitis
Neutrophilic infiltrates
Lympho/monocytes

ROLE DE L'INFECTION MICROBIENNE

➢ **Rôle du *Streptocoque sanguis* (Mumcu et al , Clin Exp Rheumatol 2009)**

-Présence d'infections fréquentes et d' *Ac anti-S.sanguis* au cours de BD
-Efficacité des TRT antibiotiques sur les lésions muqueuses et articulaires

➢ **Lien avec l'hygiène bucco-dentaire**

(Mumcu et al, Rheumatology 2004/Karacayli et al, J Oral Pathol Med 2009)

	Oral ulcers (+) (n= 92) Mean ± SD	Oral ulcers (−) (n= 28) Mean ± SD	p	Severe (n =34) Mean ± SD	Moderate (n=42) Mean ± SD	Mild (n= 44) Mean ± SD	p
Plaque index	2.2 ± 0.9	1.2 ± 0.9	0.000*	2.4 ± 0.7	2.1 ± 0.9	1.5 ± 1.01	0.000*
Gingival index	2.4 ± 0.9	1.5 ± 1.0	0.000*	2.6 ± 0.6	2.3 ± 1.1	1.7 ± 1.1	0.001*
Sulcus bleeding index	2.2 ± 0.9	1.4 ± 1.1	0.001*	2.6 ± 0.7	2.1 ± 0.9	1.6 ± 1.04	0.000*
Probing depth (mm)	3.1 ± 0.8	2.1 ± 0.8	0.000*	3.4 ± 0.7	2.9 ± 1.01	2.4 ± 0.9	0.000*
DMFT	6.9 ± 5.02	7.3 ± 7.1	0.566	6.5 ± 4.1	7.6 ± 6.09	6.9 ± 6.04	0.536
Number of extracted teeth	3.7 ± 4.9	3.2 ± 4.9	0.246	4.1 ± 4.4	4.1 ± 5.7	2.9 ± 4.6	0.423
Number of carious teeth	2.6 ± 2.3	1.9 ± 2.1	0.178	2.09 ± 2.1	2.3 ± 2.3	2.6 ± 2.1	0.540
Oral ulcers (number/month)	6.3 ± 6.7	—	—	8.7 ± 5.1	8.4 ± 8.1	6.1 ± 6.1	0.004
Healing time of oral ulcers (days)	8.7 ± 3.5	–	–	8.6 ± 3.1	9.3 ± 4.1	8.8 ± 3.8	0.637
Disease duration (yr)	9.1 ± 7.3	8.1 ± 8.1	0.991	6.9 ± 5.4	10.5 ± 8.6	9.02 ± 7.9	0.171
Tooth brushing/day	1.1 ± 0.8	1.1 ± 0.7	0.877	0.8 ± 0.8	1.2 ± 1.01	1.2 ± 0.7	0.186
Cigarette consumption/day	2.1 ± 7.6	1.6 ± 4.7	0.013*	7.3 ± 8.5	2.1 ± 4.7	2.7 ± 6.3	0.013*

Lésions gingivales et parodontales chez les BD avec lésions buccales. Corrélation avec sévérité

ROLE DE L'INFECTION MICROBIENNE

➢ **Rôle de l'Antigène KTH-1 du *S. sanguis* dans l'induction de prolifération des Lymphocytes γδ (Mochizuki et al , Eur J Immunol 1994/Hirohata et al Cell Immunol 1992)**

-Production de cytokines Th-1 et d'IL-6

➢ **Mais pas toujours spécifique (Staph aureus, E. Coli, Mycobactéries, Hélicobacter)**

➢ **Pas de rôle de HSV-1 ou autres virus**

ROLE DES SUPERANTIGENES

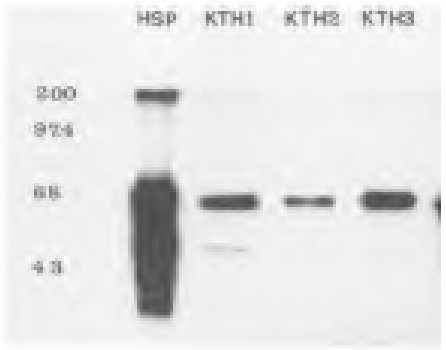
(Heat Shock Proteins, Ag-S retinal)

HSP: rôle protecteur des protéines intra-cellulaires contre le stress (chaleur, infection, trauma..)

Fortes Homologies de séquences entre HSP microbienne et humaine: HSP65 (*S. Sanguis*) et HSP60 humaine ont 50% d'homologies autorisant des Réactions Croisées de mimétisme moléculaire

- **HSP65 est très présente dans les lésions muco-cutanées de BD (Direskeneli, Ann Rheum Dis 2001)**

- **Réactivité croisée des anti-HSP65 avec des homogénats de muqueuse orale ou des streptos oraux (Lehner, Infect Immunity 1991)**



ROLE DES SUPERANTIGENES

➢ **Augmentation des réponses lymphocytaires T aux peptides de HSP65 et HSP60 chez les BD (Direskeneli, J Rheumatol 2000)**

Surtout au peptide 425-41 de HSP60

Surtout les lymphocytes T γδ

➢ **Augmentation des anticorps anti-strepto et anti-HSP dans le serum des BD avec uvéite (Tanaka, Ocular Immunology and Inflammation 1999)**

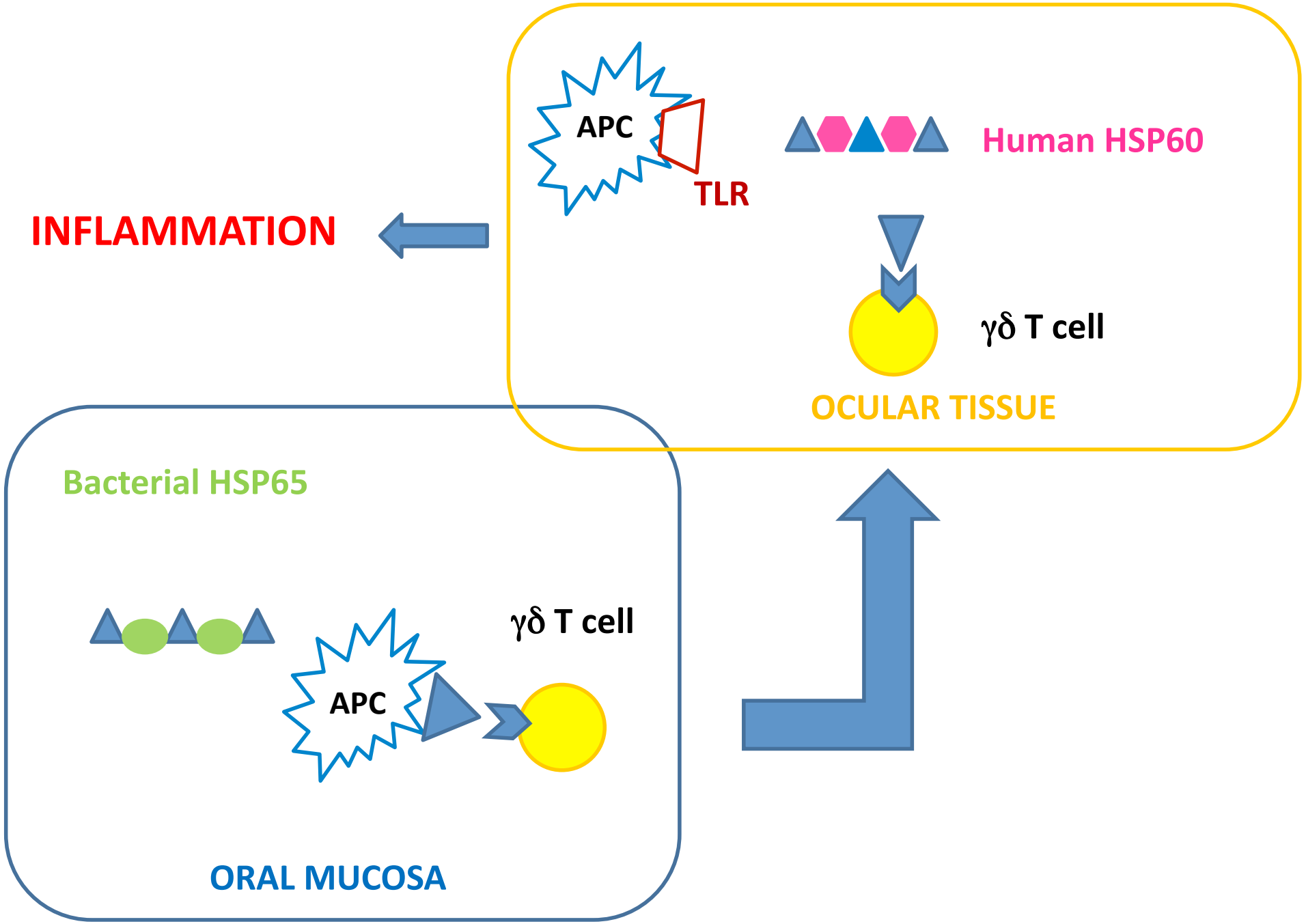
ROLE DES SUPERANTIGENES

➢**Injection de HSP SC induit une uvéite expérimentale chez le rat**
(Stanford et al, Clin Exp Immunol 1994)

➢**Choc thermique de la muqueuse orale augmente la colonisation buccale par *S.sanguis* et inflammation oculaire chez la souris (Isogai et al 2000)**

Chambre antérieure
Synéchies postérieures

Chambre postérieure
Lésion rétinienne


APC
TLR
Human HSP60
INFLAMMATION
γδ T cell
OCULAR TISSUE
Bacterial HSP65
γδ T cell
APC
ORAL MUCOSA

PREDISPOSITION GENETIQUE
GENES DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢ **Association avec HLAB5-B51, en particulier B5101 est la plus reconnue (Ohno et al, Arch Ophtalmol 1982/de Menthon et al, A&R 2009)**

-Risque relatif de développer BD est de 5,78%

-Dans la population turque, fréquence du HLAB51 est de 59% chez les BD vs 29% chez contrôles

-Associé au sexe masculin, aphtes génitaux, atteintes cutanées et oculaires

-Ne représente que 20% des BD

-Lien physiopathologique est obscur

-Hyperactivation des polynucléaires neutrophiles chez les patients et dans la souris transgénique HLAB51 (Takeno, A&R 1995)

PREDISPOSITION GENETIQUE
GENES DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢Association avec MICA -A6

-MICA se lie à NKG2D à la surface des NK et des T Cytotoxiques et les activent

-Non confirmé sur des études plus importantes

➢ Association à HLA-A26 (Kang, Arthritis Res Ther 2011)

-Association aux lésions cutanées, arthrites, uvéites, atteinte vasculaires

➢Promoteur du gène du TNFα (Zhang Mol Vis 2013 meta-analysis)

Discuté+++. Allèles -308G, -857C sont associé à BD chez les Asiatiques,
-238A, -1031C sont associés à BD chez les Caucasiens

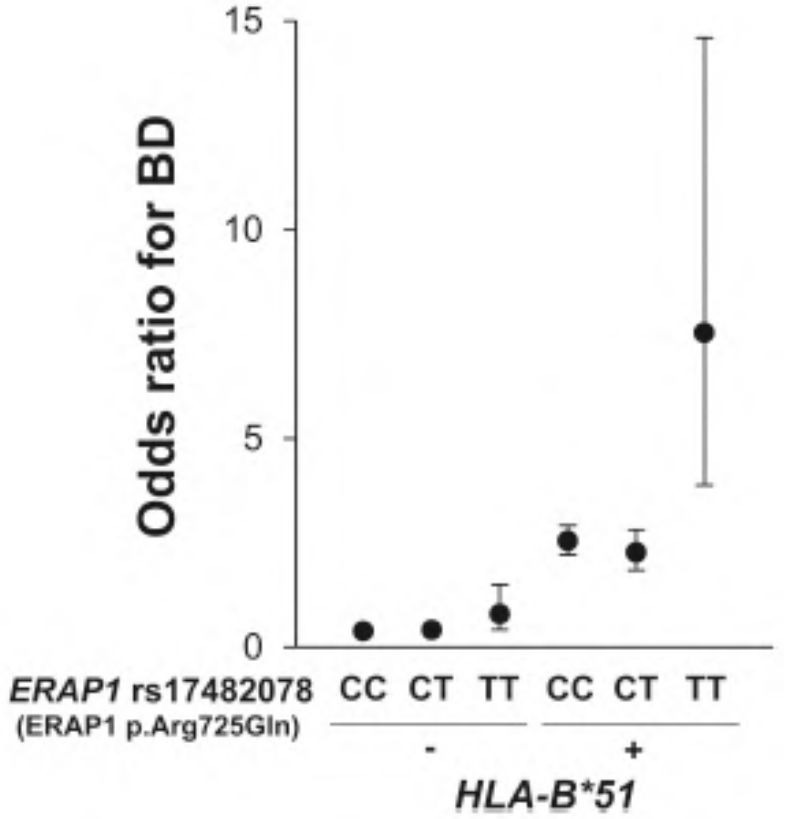
Augmentation des concentrations de TNF dans le serum et humeur aqueuse

Efficacité des anti-TNF dans le TRT des formes oculaires, digestives

PREDISPOSITION GENETIQUE
GENES EN DEHORS DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢ **Genome-Wide Association study** ***(Kirino Nat Genet 2013) confirme les associations avec HLA B51 ou MICA***

❖ **Snp de ERAP-1: aminopeptidase du reticulum endoplasmique qui est impliquée dans l'association des peptides avec HLA classe I**
Association surtout si BD HLAB51+ avec uvéite



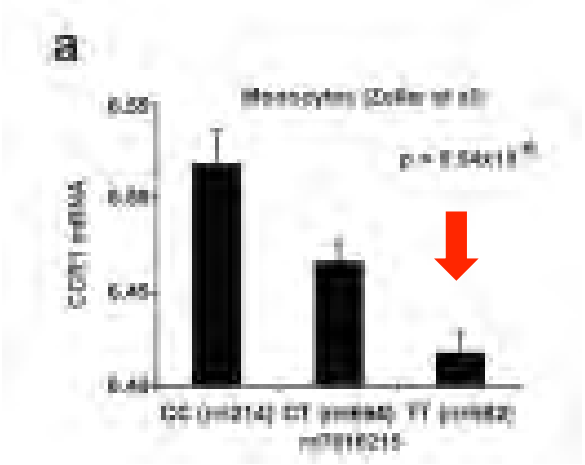
NB: Liens de snp ERAP-1 avec SPA HLAB27+: plutôt protecteur

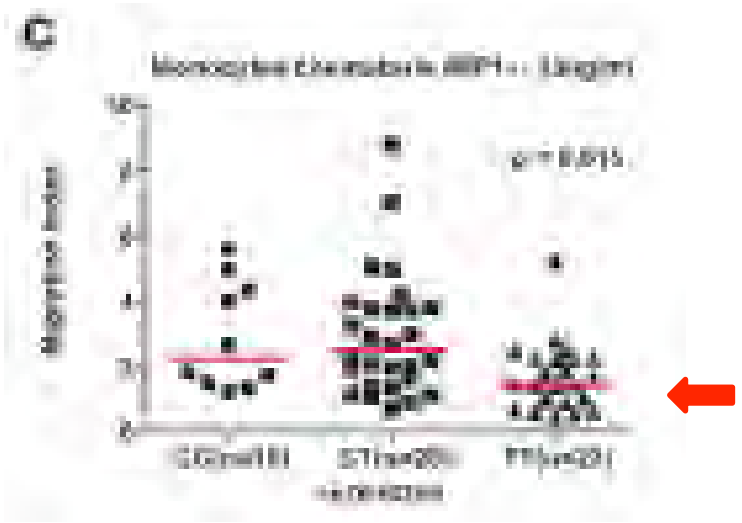
PREDISPOSITION GENETIQUE
GENES EN DEHORS DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢ **Genome-Wide Association study** ***(Kirino Nat Genet 2013) confirme les associations avec HLA B51 ou MICA***

❖ **Snp de KLRC4: NKG2F impliqué dans la cytotoxicité NK. Défaut de cytotoxicité?**

❖ **Snp de CCR1: Rec pour les chimiokines. Défaut d'expression du Rec sur mono. Défaut d'élimination des microbes?**





❖ **Snp de STAT-4**

PREDISPOSITION GENETIQUE
GENES EN DEHORS DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢ **TH-1 cytokine Gene Polymorphisms in BD (Alayi, Clin Rheumatol 2007): Liens avec l'immunité adaptative**

80 BD patients vs 105 healthy controls from Turkey

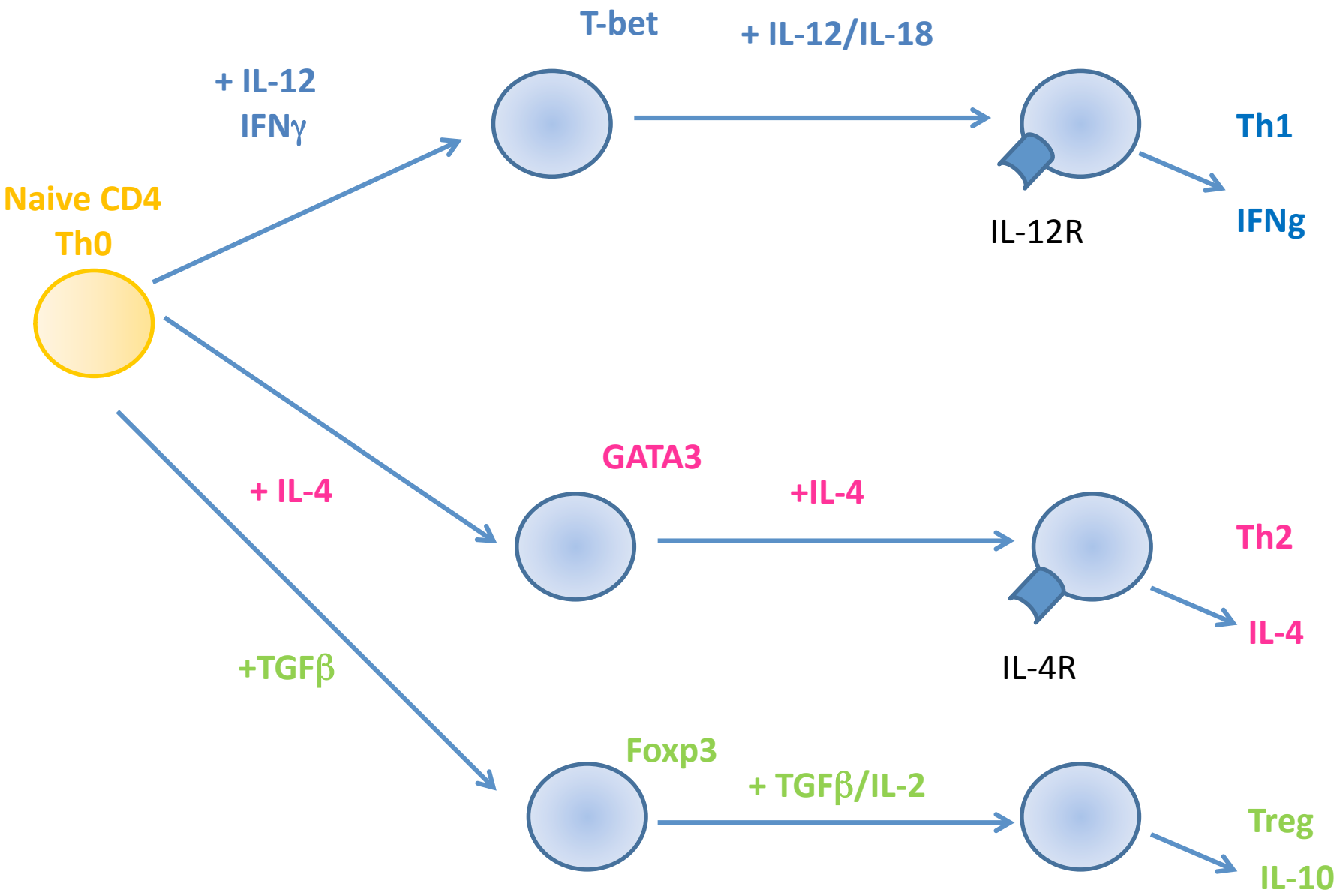
Genotype distribution showed significant differences for

-IL-12 (C/A -1188)

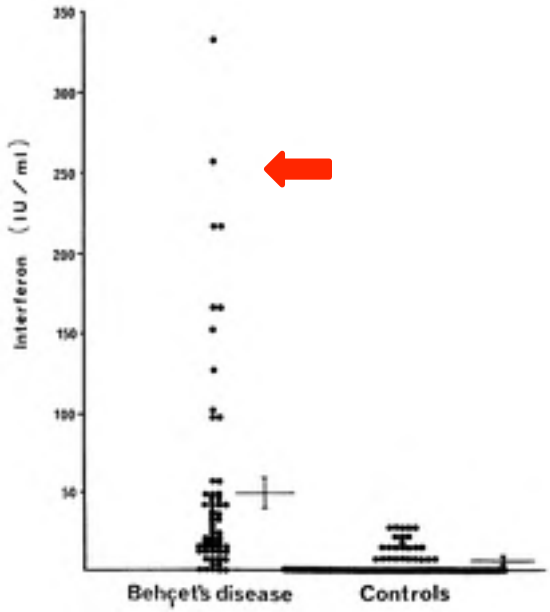
-IFNγ (A/T UTR 5644)

-TNFα (G/A -238)

Th-1/Th2 DIFFERENTIATION PATHWAYS AND BD



Th1/Th2 Imbalance in BD



Increased IFNγ levels/low IL-4
in serum and circulating CD4 and CD8 T cells
from active BD patients
(Ohno Infect Immun 1982, Hamzaoui Scand J Rheumatol 2002, Bacon Clin Exp Immunol 1984, Frassanito A&R 1999)

Table 1. Th1/Th2 cytokine production by CD3+ lymphocytes*

Group	CD3+ lymphocytes producing		
	IL-2	IFNγ	IL-4
Behçet's disease (n = 31)	37.4 ± 21.3†	23.6 ± 16.7†	2.7 ± 2.5
Inflammatory arthritis (n = 11)	19.5 ± 7.6	10.6 ± 3.2	18.7 ± 4.5‡
Normal donors (n = 10)	13.7 ± 5.2	5.4 ± 0.8	4.8 ± 4.3

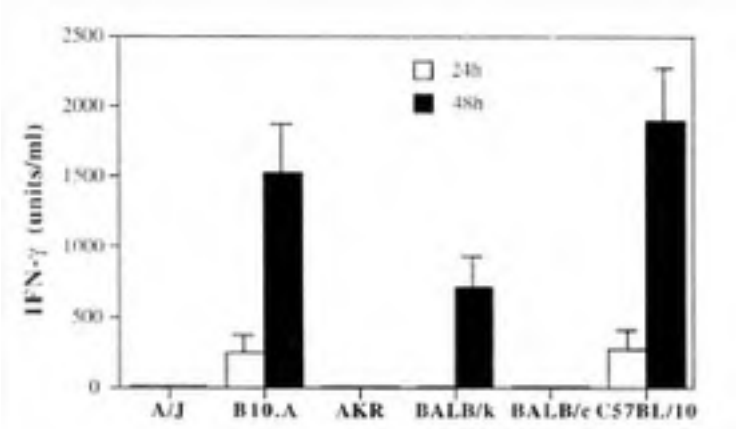
Group	IFNγ producing	
	CD4+ cells	CD8+ cells
Active Behçet's disease (n = 14)	25.7 ± 5.7†	14.3 ± 7.6†
Behçet's disease in complete remission (n = 17)	1.1 ± 1.6	0.9 ± 0.6
Normal donors (n = 10)	1.8 ± 0.6	0.6 ± 0.5

Th1/Th2 Imbalance in BD uveitis

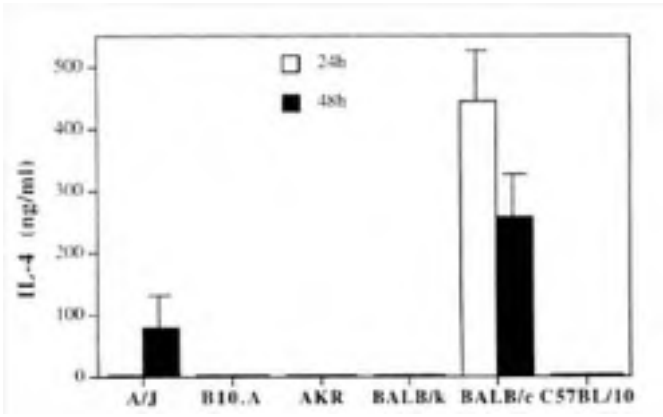
Cytokines	Controls (n = 10)	Non-Behçet Uveitis (n = 16)	Behçet Uveitis (n = 12)
Aqueous			
IFN-γ (pg/ml)	4 ± 3	49 ± 23*	108 ± 30†
IL-4 (pg/ml)	5 ± 4	120 ± 44*	54 ± 19†
IFN-γ/IL-4 ratio	1.09 ± 0.63	0.37 ± 0.29*	2.31 ± 0.88†

Increased IFNγ/IL-4 ratio in acqueous humor
(Ahn, Am J Ophtalmol 2006)

Experimental autoimmune uveitis



Th1 profile in EAU sensitive mice



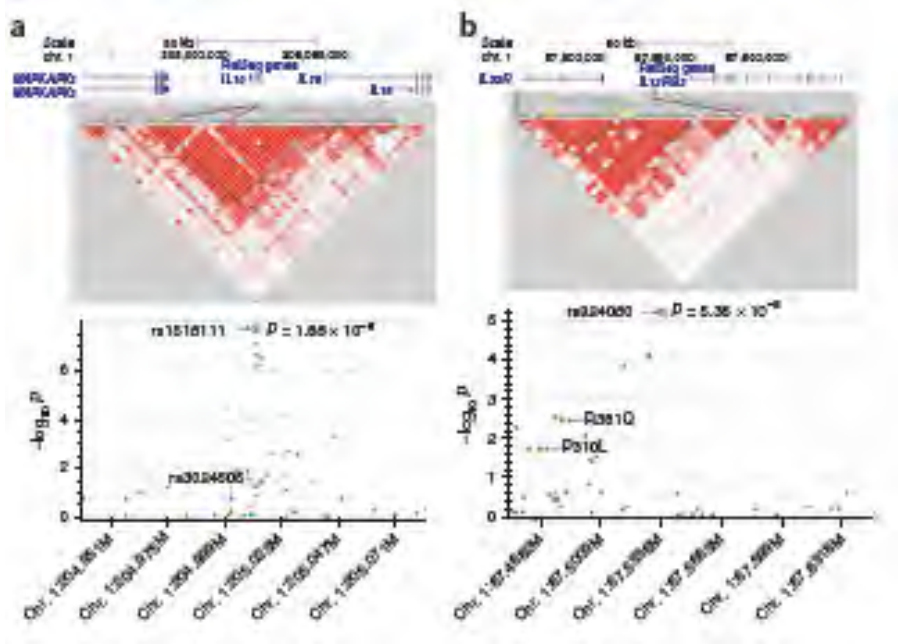
Th2 profile in EAU resistant mice

Sun, J Immunol 1997

PREDISPOSITION GENETIQUE
GENES EN DEHORS DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

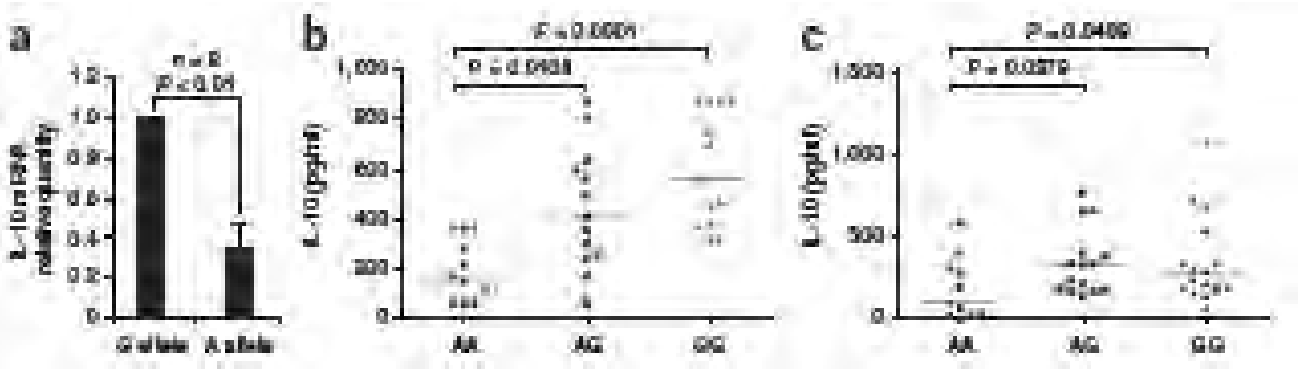
➢ **Genome-Wide Association study** ***(Remmers, Nat Genet 2010, Mizuki, Nat Genet 2010, Xavier A&R 2012)***

Common variants in IL-10 (rs1518111, OR: 1.45) and IL-23R/IL12RB2 loci (rs924080, OR: 1.28) are associated with BD in 2000 BD patients from Turkey, Japan, Middle-East, Europe and Asia



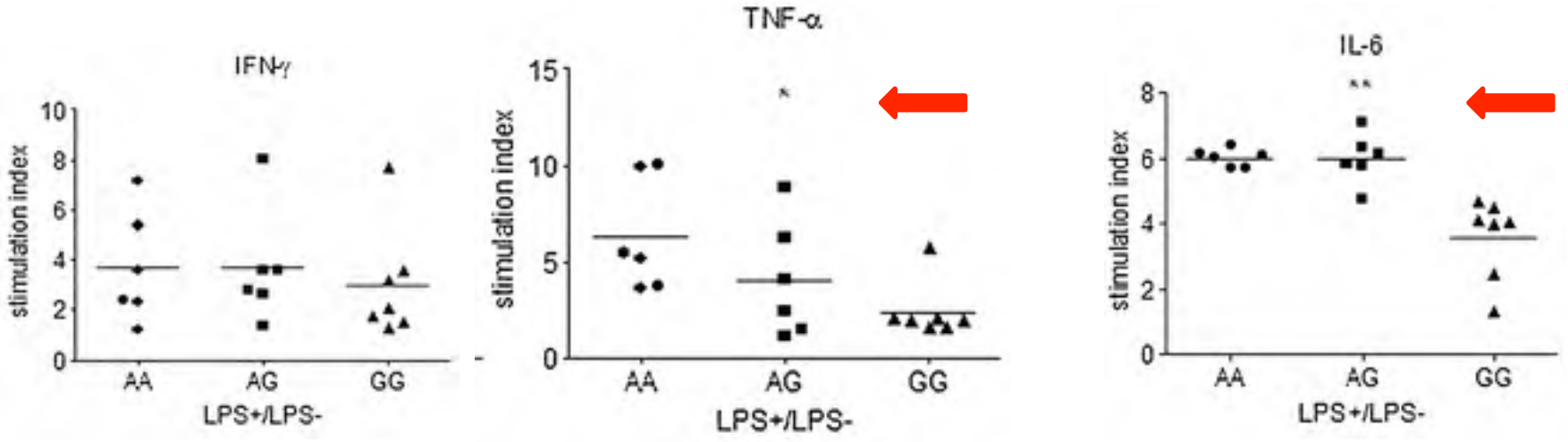
ALLELIC VARIANTS ASSOCIATED WITH BD ARE PRO-INFLAMMATORY

IL-10 variants are associated with lower IL-10 production



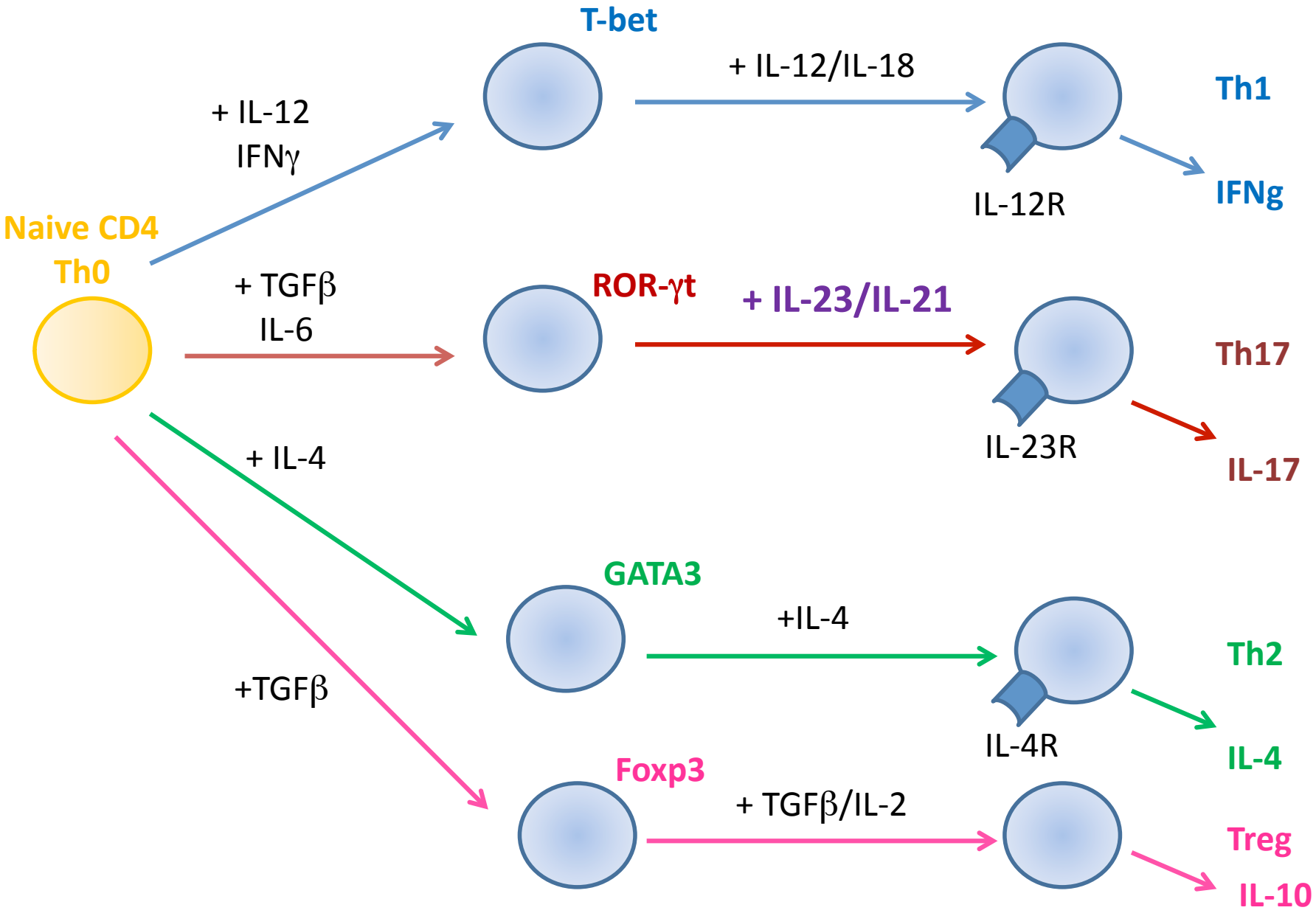
Remmers, Nat Genet 2010

IL-23R-IL-12RB2 variants are associated with higher IL-23R but not with IL-12R stimulation index

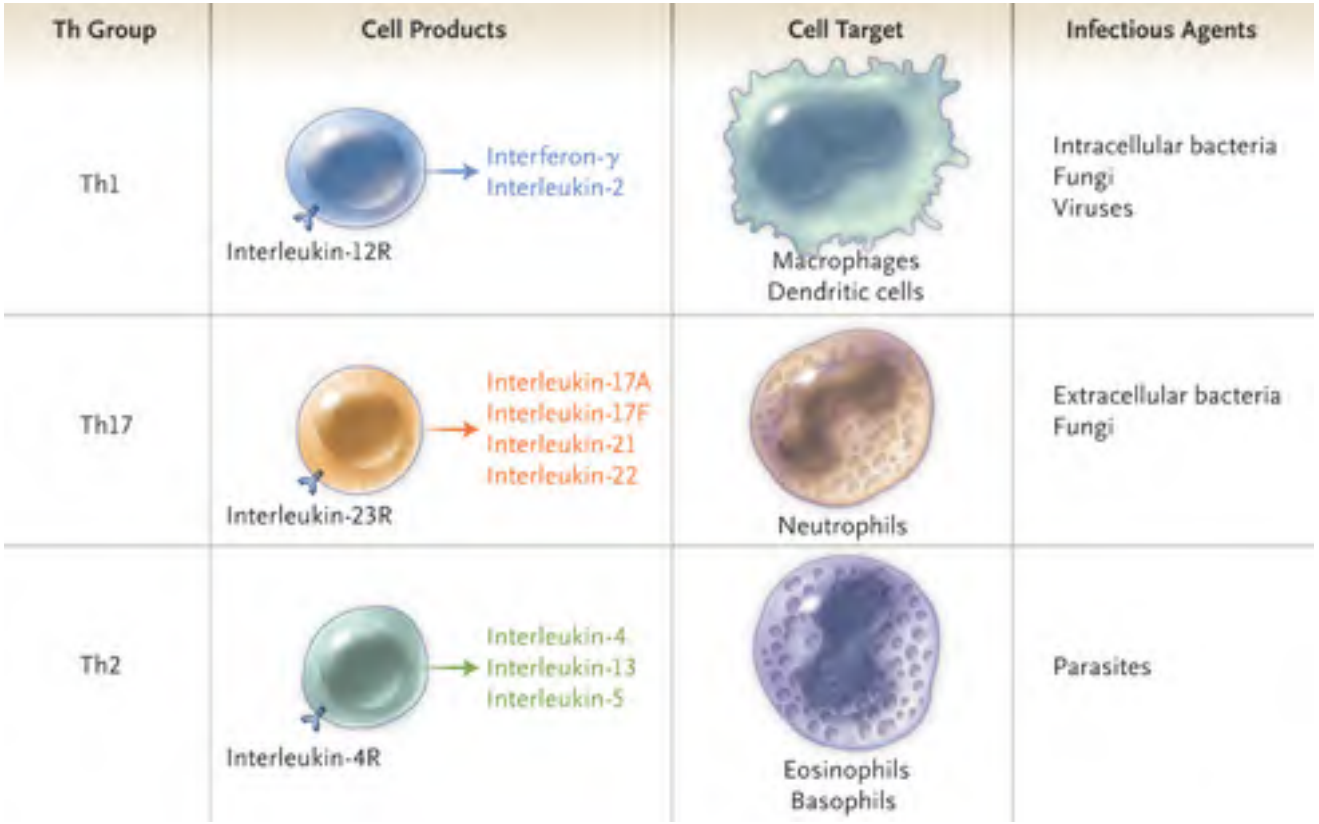


Cavus, Immunol Lett 2014

GWAS studies links BD to an IL-10 vs IL-23/IL-17 axis imbalance



The IL-23/IL-17 axis is linked to neutrophilic inflammation against extra-cellular bacteria

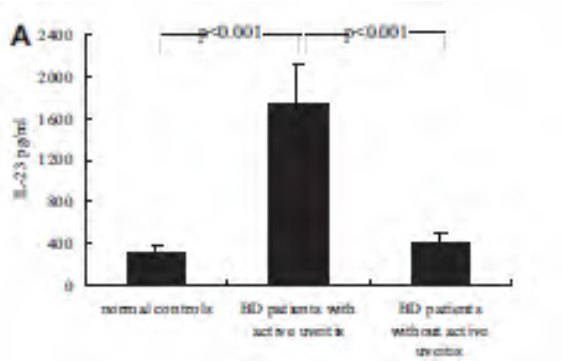


and is involved in various chronic inflammatory diseases (Rheumatoid arthritis, Spondylarthropathy, Multiple sclerosis….)

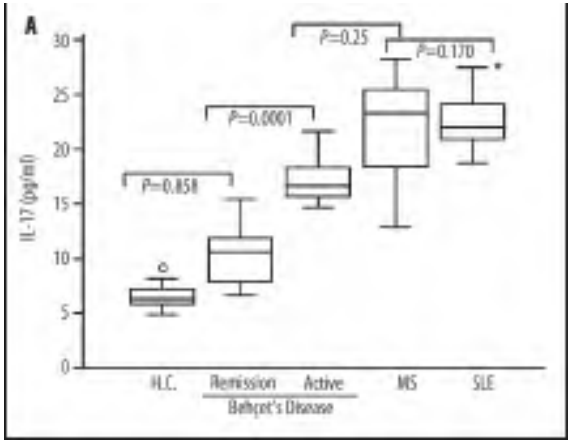
Miossec N Engl J Med 2009

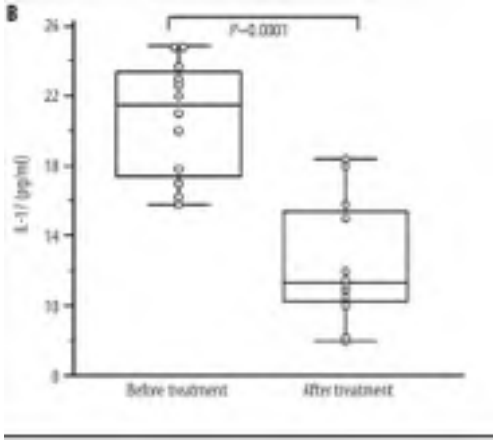
Evidence of IL-17/23 axis involvement in BD

Active Inactive



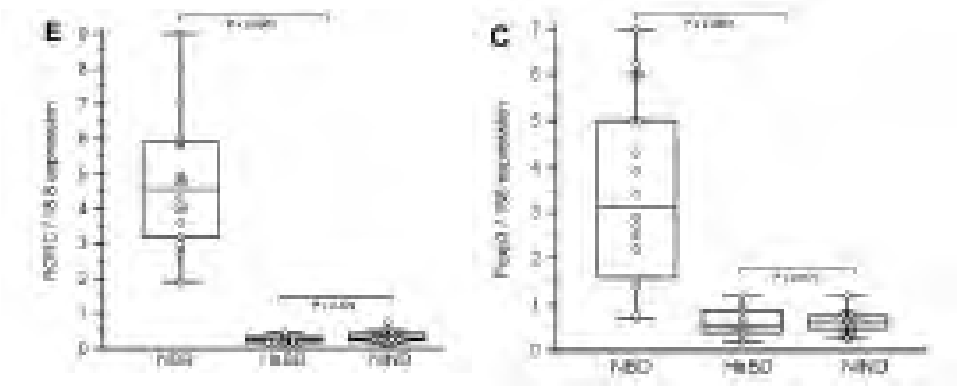
Increased IL-23p19 mRNA in PBMC and serum IL-23 in BD with active uveitis (33 BD, *Chi IOVS 2008*)





Increased IL-17 in active BD ***(45 BD, Hamzaoui Med Sci Monit 2011, Na J Rheumatol 2013)***

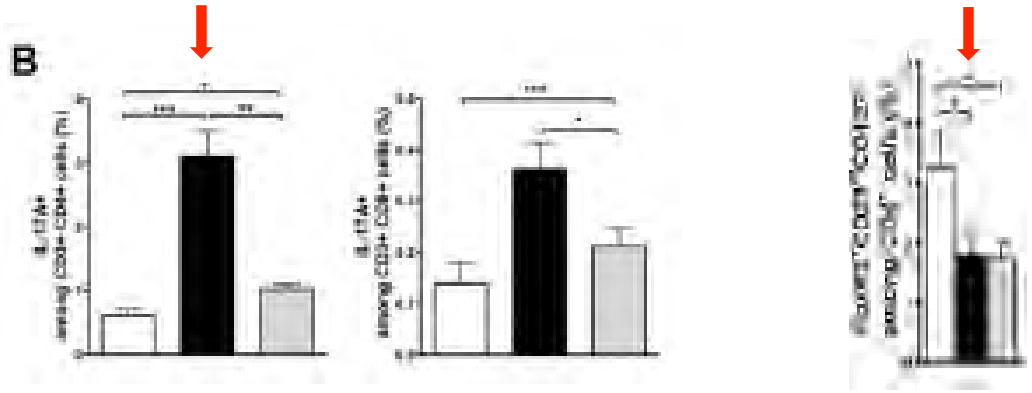
Evidence for IL-17/IL-10 imbalance in BD



Increased ROR-gT and Foxp3 positive CD4 T cells in 18 neuro-BD

Increased ROR-gt/FoxP3 ratio in neuro BD

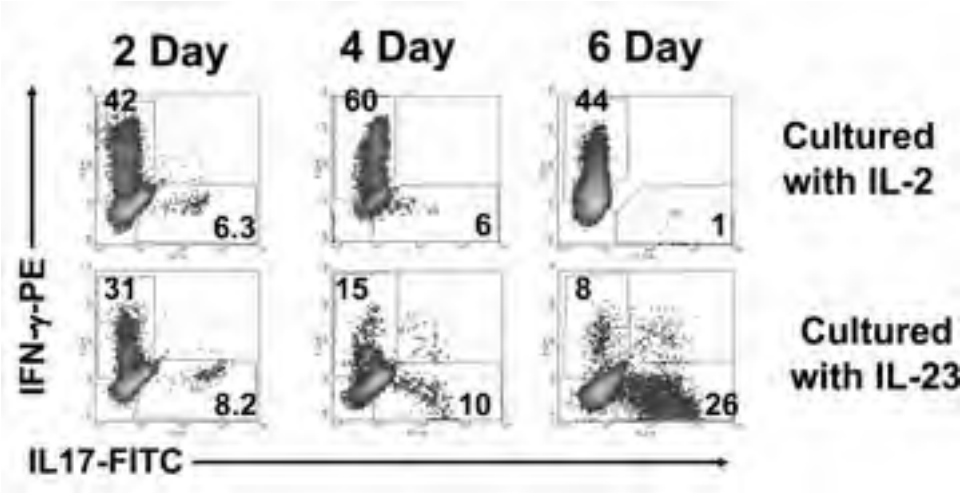
(Hamzaoui, J Neuroimmunol 2011)

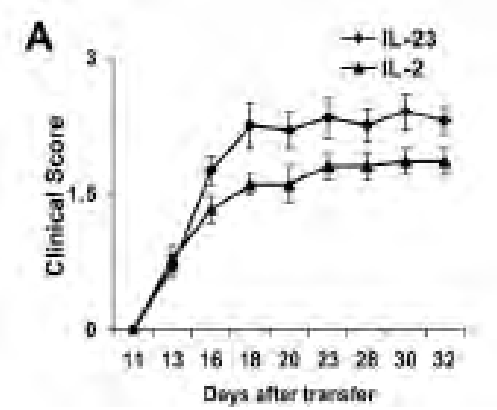


Increased Th17 and decreased FoxP3 CD4 T cells in 45 active BD

(Geri, J All Clin Immunol 2011)

Role of Th1/Th17 in Experimental Auto-immune Uveitis (EAU): Immunization with Interphotoreceptor retinoid-binding protein (IRBP)



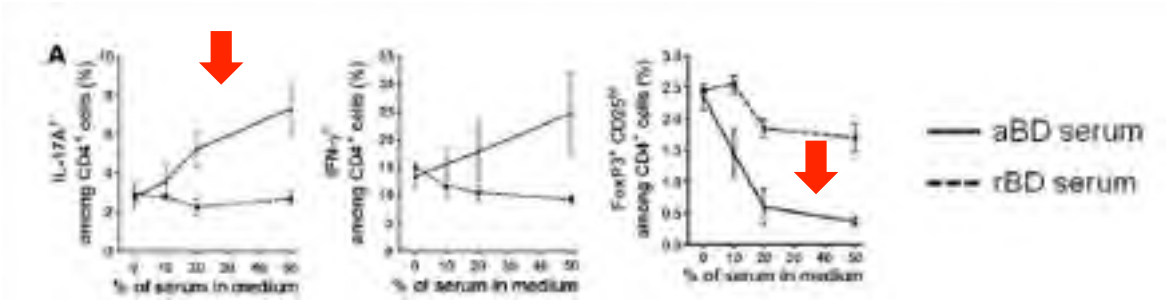


Expansion of Th17 and Th1 cells which are both uveitogenic

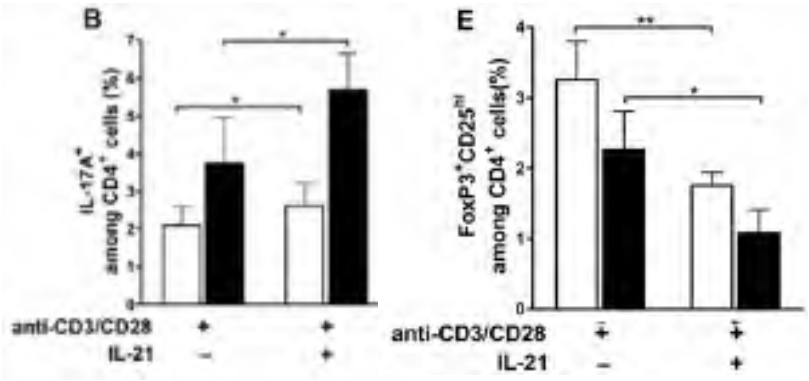
Anti-IL-17 treatment is protective

Peng, IOVS 2007

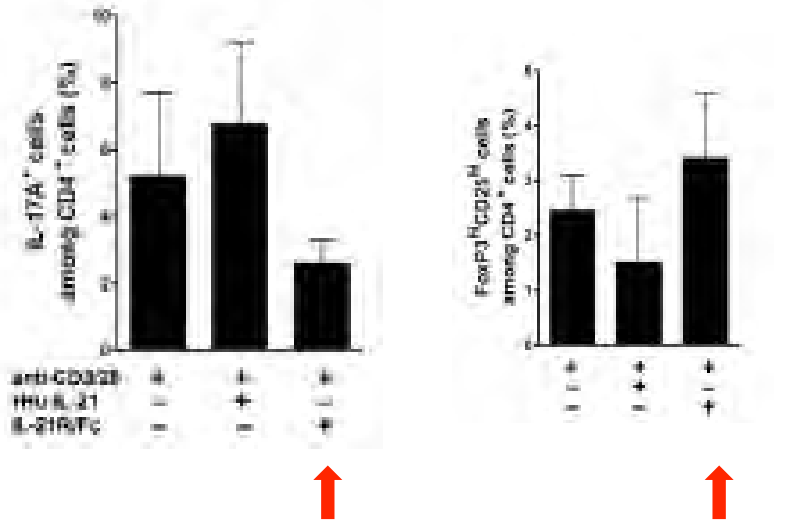
IL-21 modulates IL-17-IFNg/IL-10 imbalance in BD



Serum of active BD increased Th17/Th1 and decreased Treg differentiation in vitro



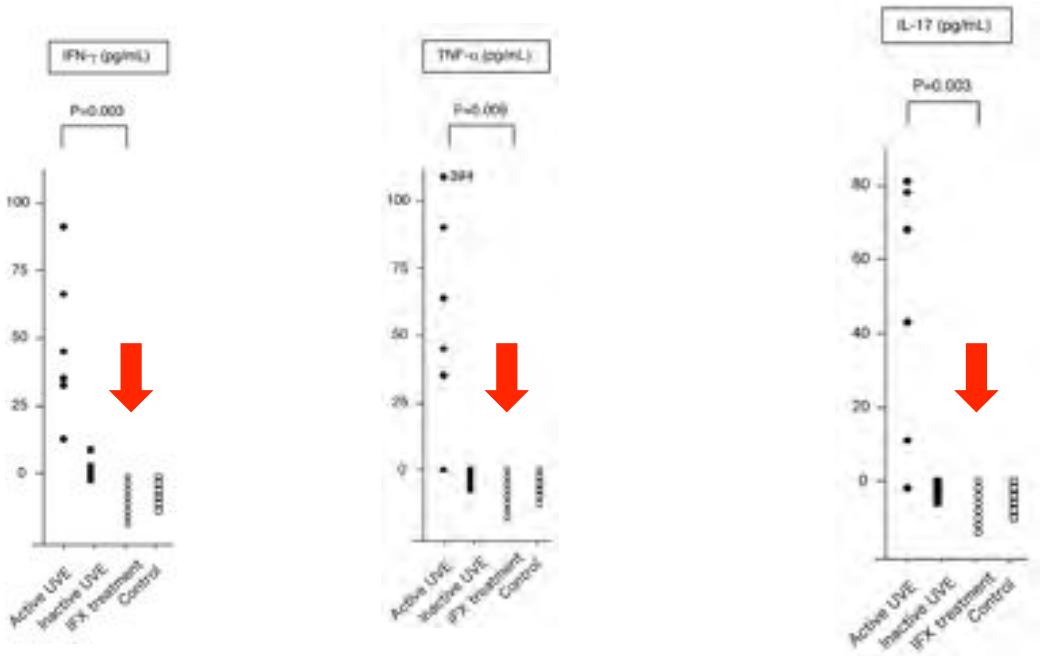
Due to IL-21



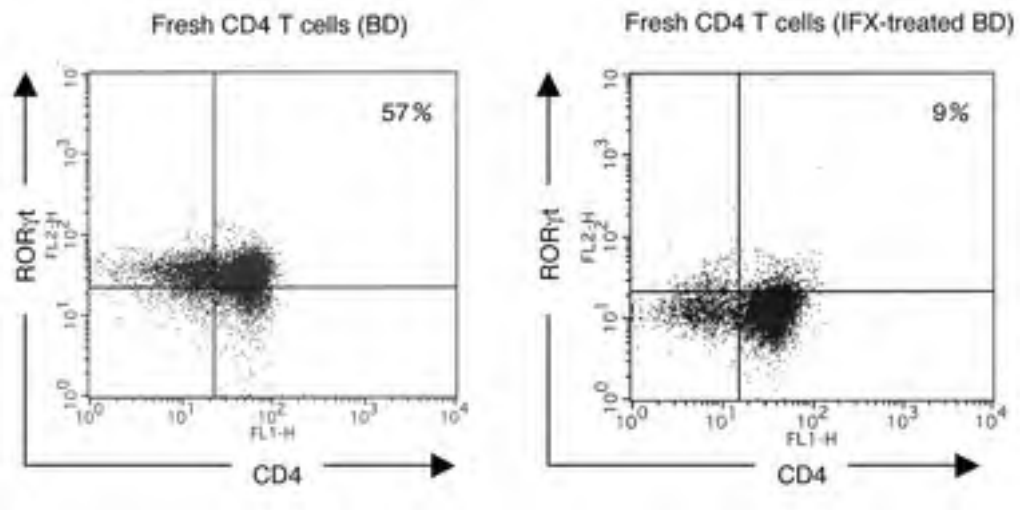
Reversed by anti-IL-21R

(Geri, J All Clin Immunol 2011)

Infliximab therapy inhibits Th1/Th-17 differentiation in BD

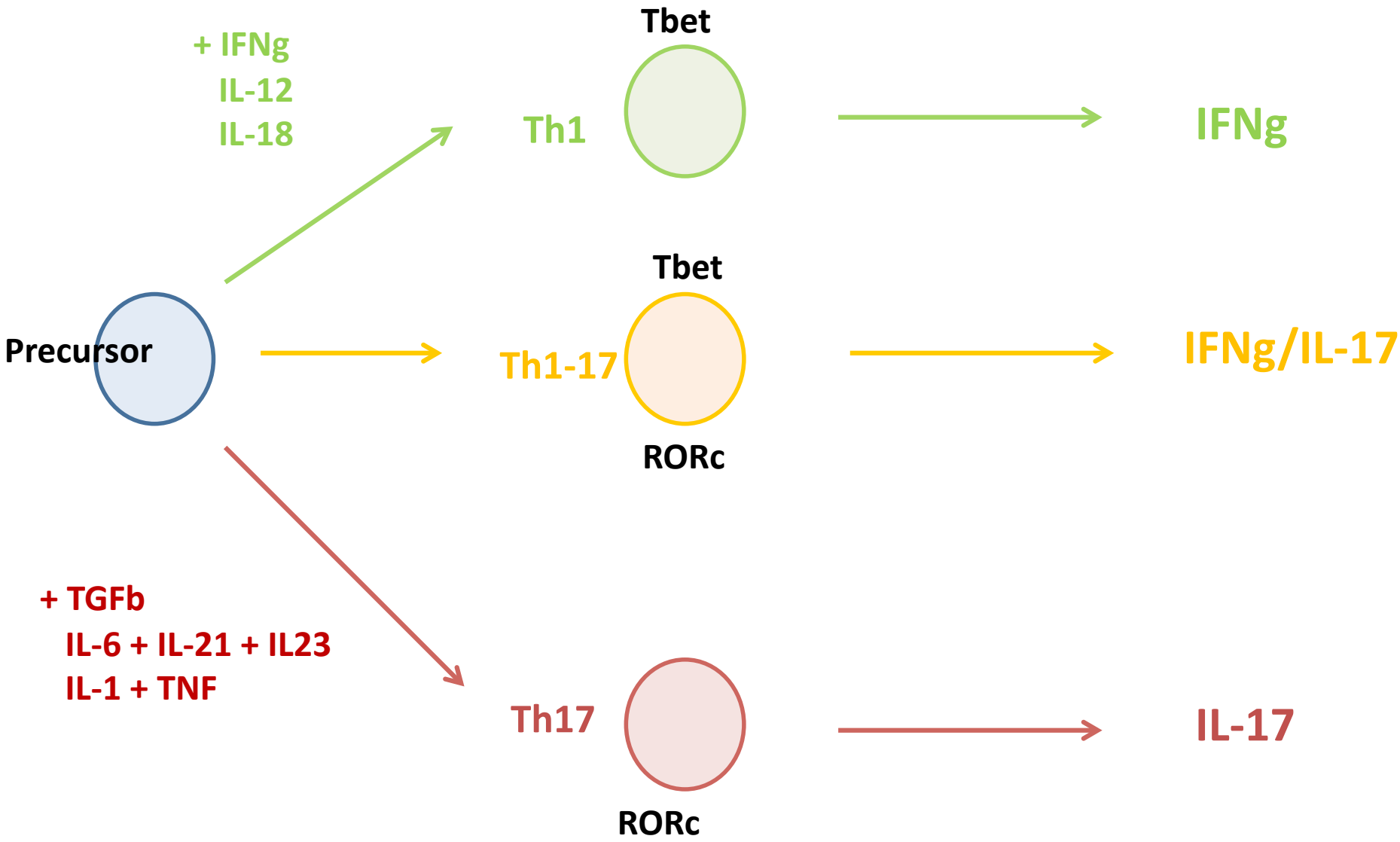


Cytokine concentrations
in ocular fluids from BD uveitis
decreased after infliximab

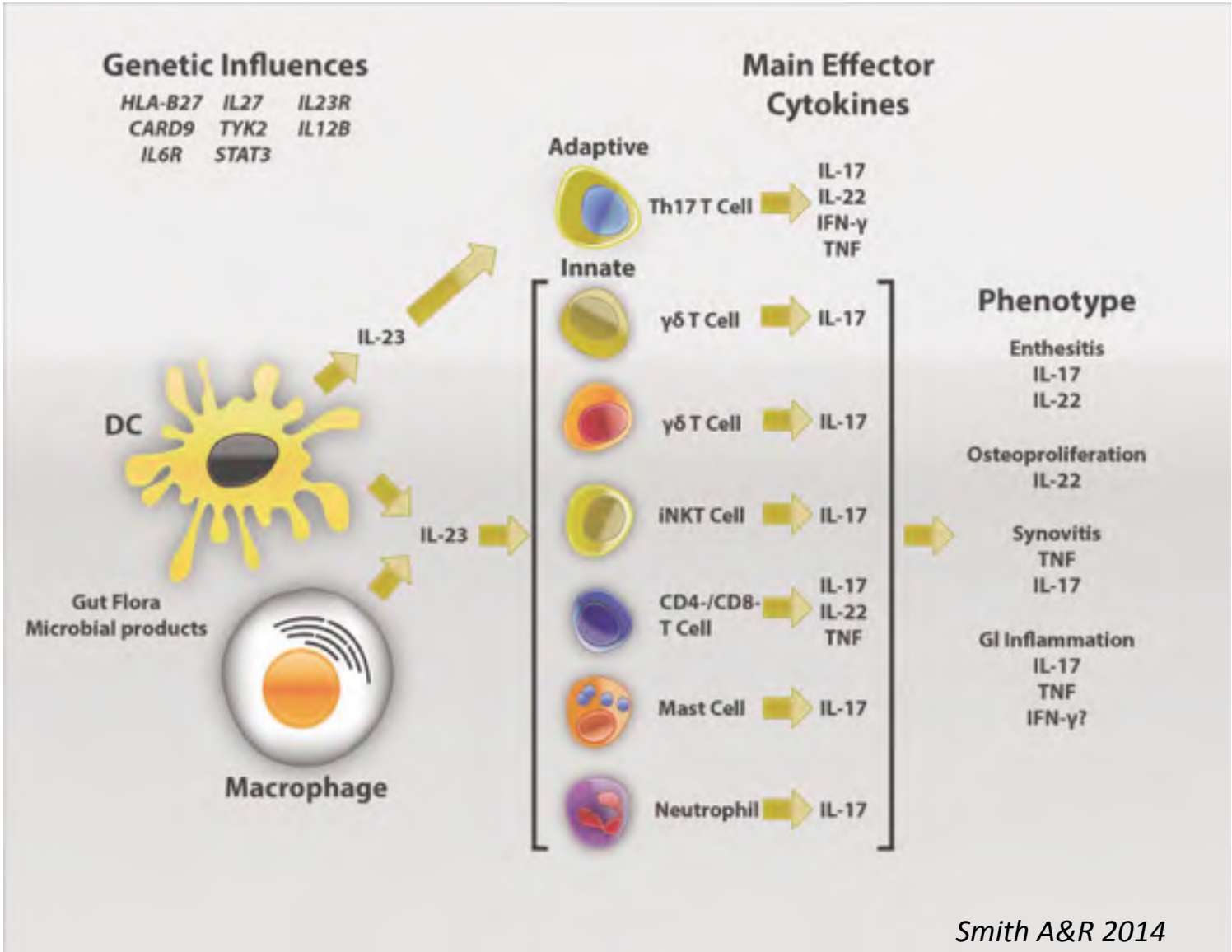


Decreased Th-17 in
BD treated with infliximab

A new population of T cells re-conciliates Th-1 and Th17 paradigms



IL-17 is produced by Innate Immune Cells: gamma/delta T lymphocytes



Smith A&R 2014

ROLE of gamma/delta LYMPHOCYTES in BD
LINK WITH INNATE IMMUNITY

- **γδ T cells are non conventional T cells derived from CD4-CD8- thymocytes, play a role in anti-infectious or stress-induced defenses , in mucosae**

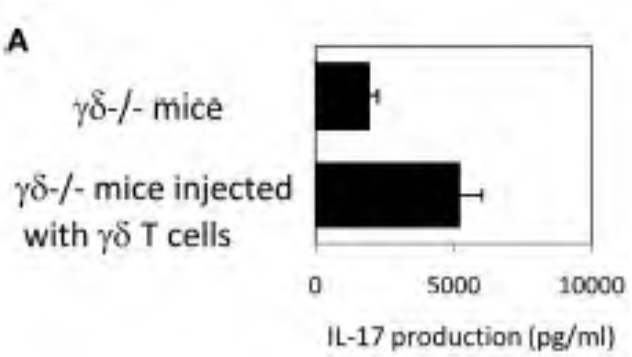
- **γδ T cells express IL-17, CD44+, IL-23R+, IL-21R+, Dectin 1, TLR1 and TLR2**

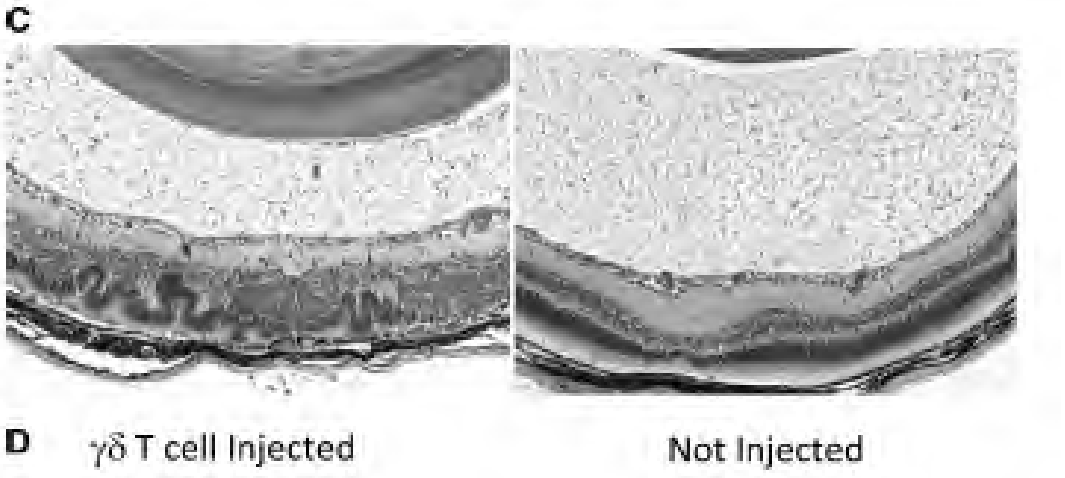
- **Increased γδ T cells in BD** ***(Fortune Clin Exp Immunol 1990; Hamazoui J Rheumatol 1992; Suzuki J Rheumatol 1992)***

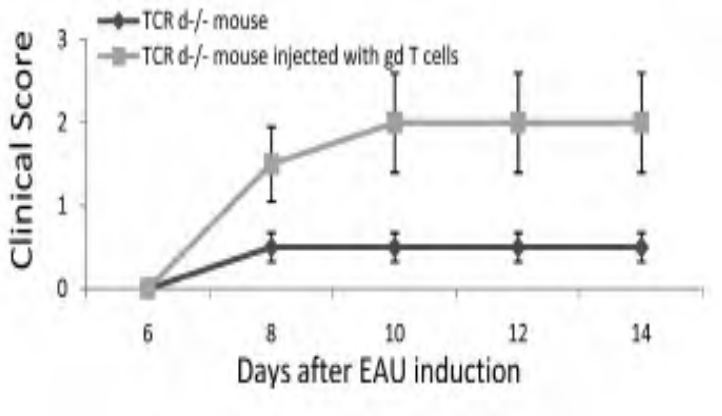
- **γδ T cells in BD expressed an activated phenotype (CD69+), produced TNFα and IFNγ** ***(Freysdottir Clin Exp Immunol 1999)***

- **Increased γδ T cells paralleled disease activity and proliferated with addition of oral ulcer sterile liquid** ***(Bank J Lab Clin Med 2003)***

ROLE OF γδ T CELLS IN BD UVEITIS







-γδ T cell KO mice are resistant to EAU
Successful transfer with γδ T cells expanded from EAU mice

Cui J Immunol 2009

-Vγ9δ2 T cells in ocular fluid of 50% of BD patients with uveitis, are CD69+, recognized non peptide pyrophosphate antigens and produced IFNγ

(Verjans J Neuroimmunol 2002; Triolo Arthr Res Ther 2002)

ROLE OF IL-1 in BD-LINK WITH INNATE IMMUNITY

➢ **XOMA 052 (anti-IL-1β mAb) in resistant uveitis of BD: open-label pilot study** ***(Gül Ann Rheum Dis 2012)***

7 Patients with acute posterior or panuveitis and/or retinal vasculitis resistant to immunosuppressive drugs received a single IV XOMA 0.3 mg/kg injection + Pred 10mg/j

-Good tolerance

-Rapid improvement in visual acuity (start at day 1), intra-ocular inflammation (4-21 days) Fluorescein angiogram improvement (40-75%)

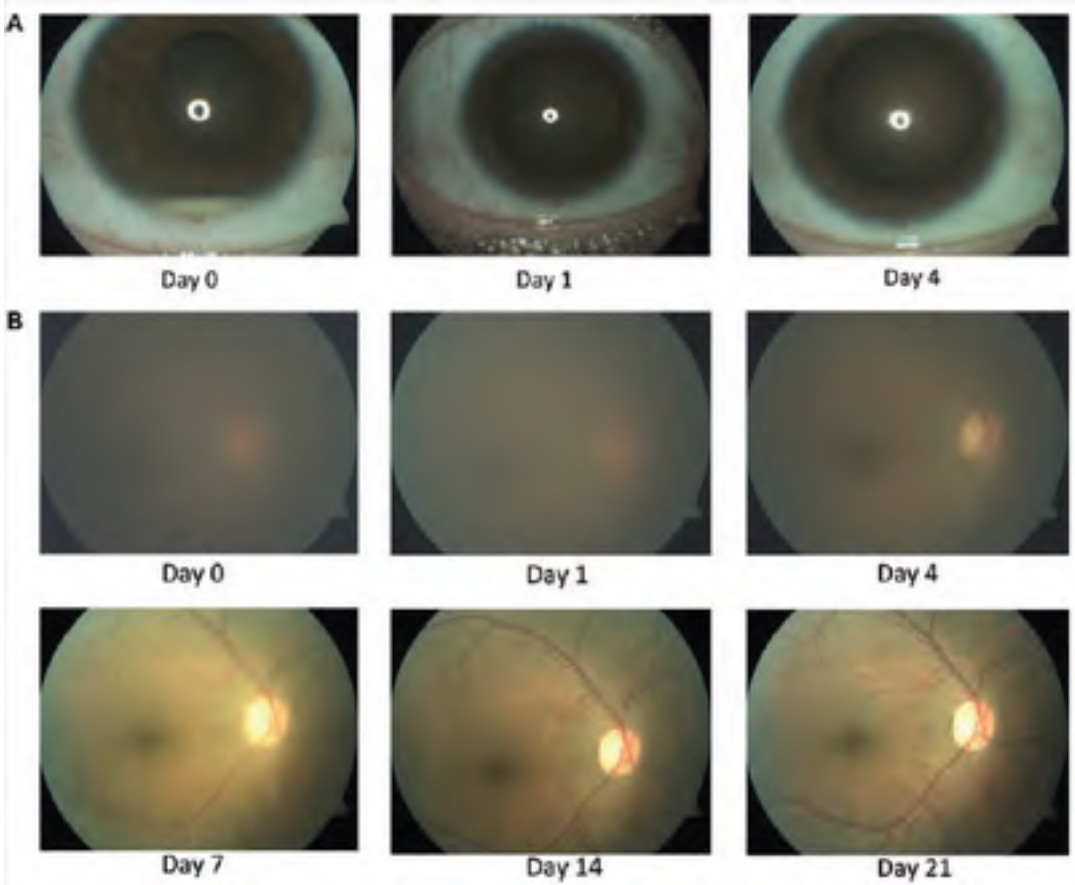
-Response duration after a single injection (mean: 49 days)

-100% responders to a 2nd infusion for a median of 115 days

-100% discontinuation of Immunosuppressive drugs and decrease corticosteroids

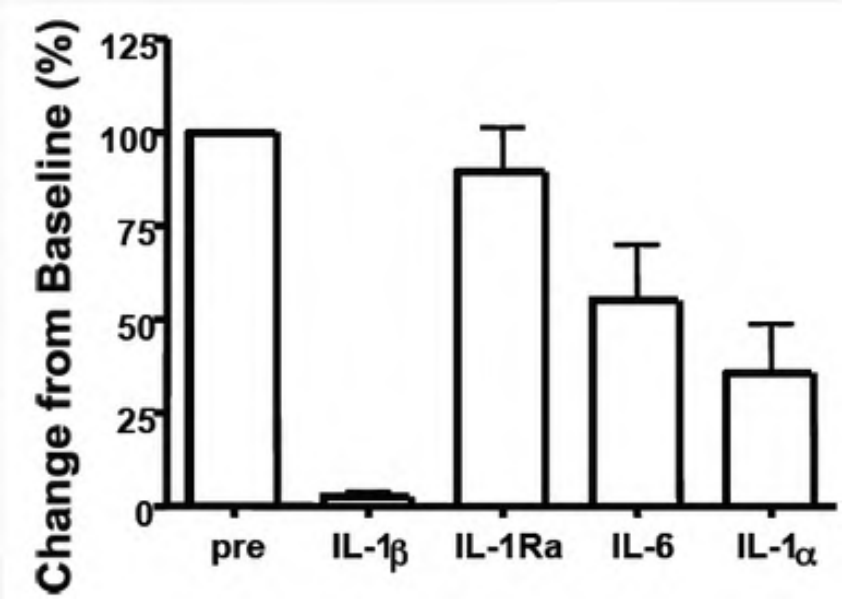
-Decreased IL-1α/β, IL-6 production by PBMC ex vivo

➢XOMA 052 in resistant uveitis of BD: open-label pilot study *(Gül Ann Rheum Dis 2012)*



Anterior eye

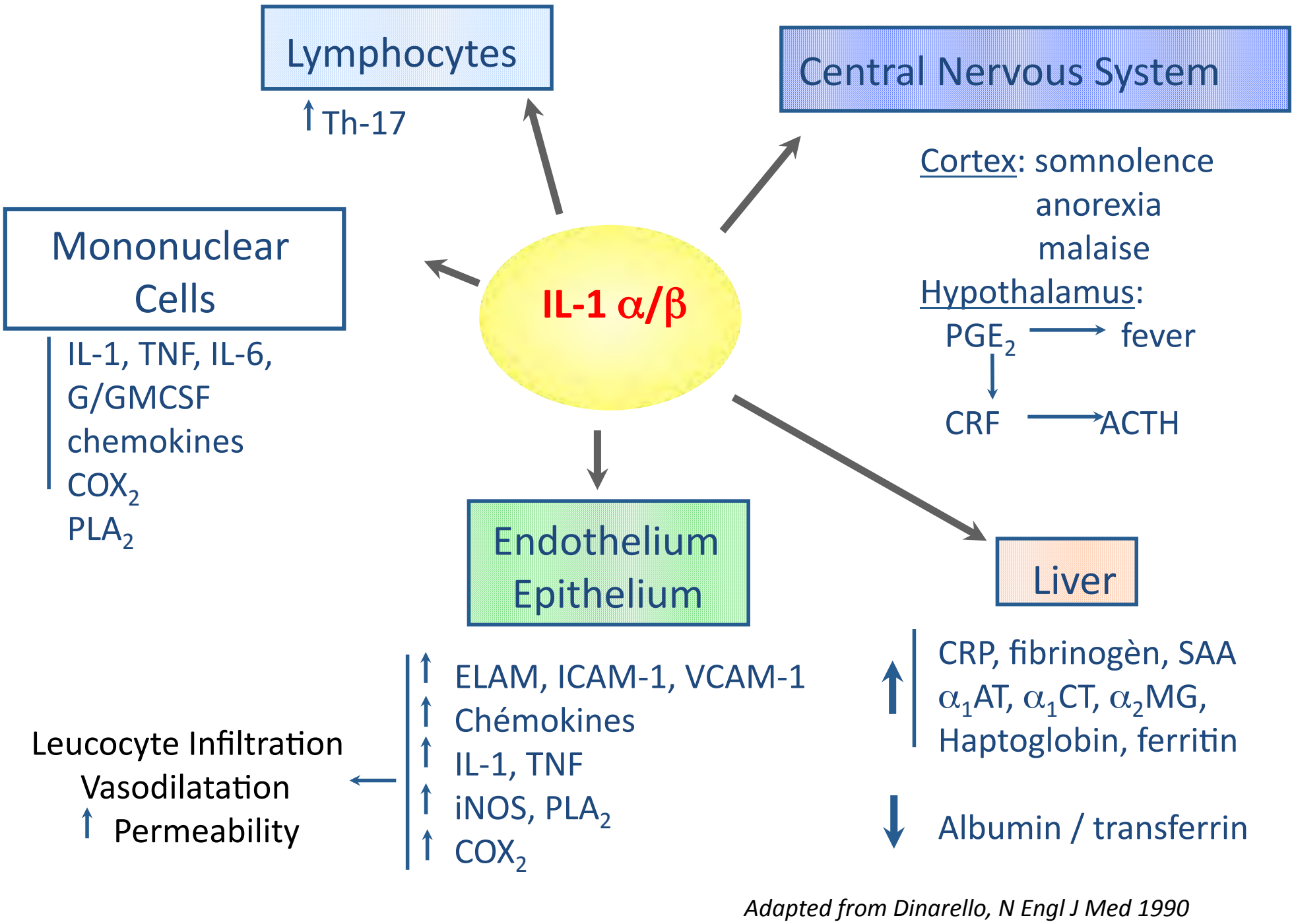
Retinal



IL-1 FAMILY

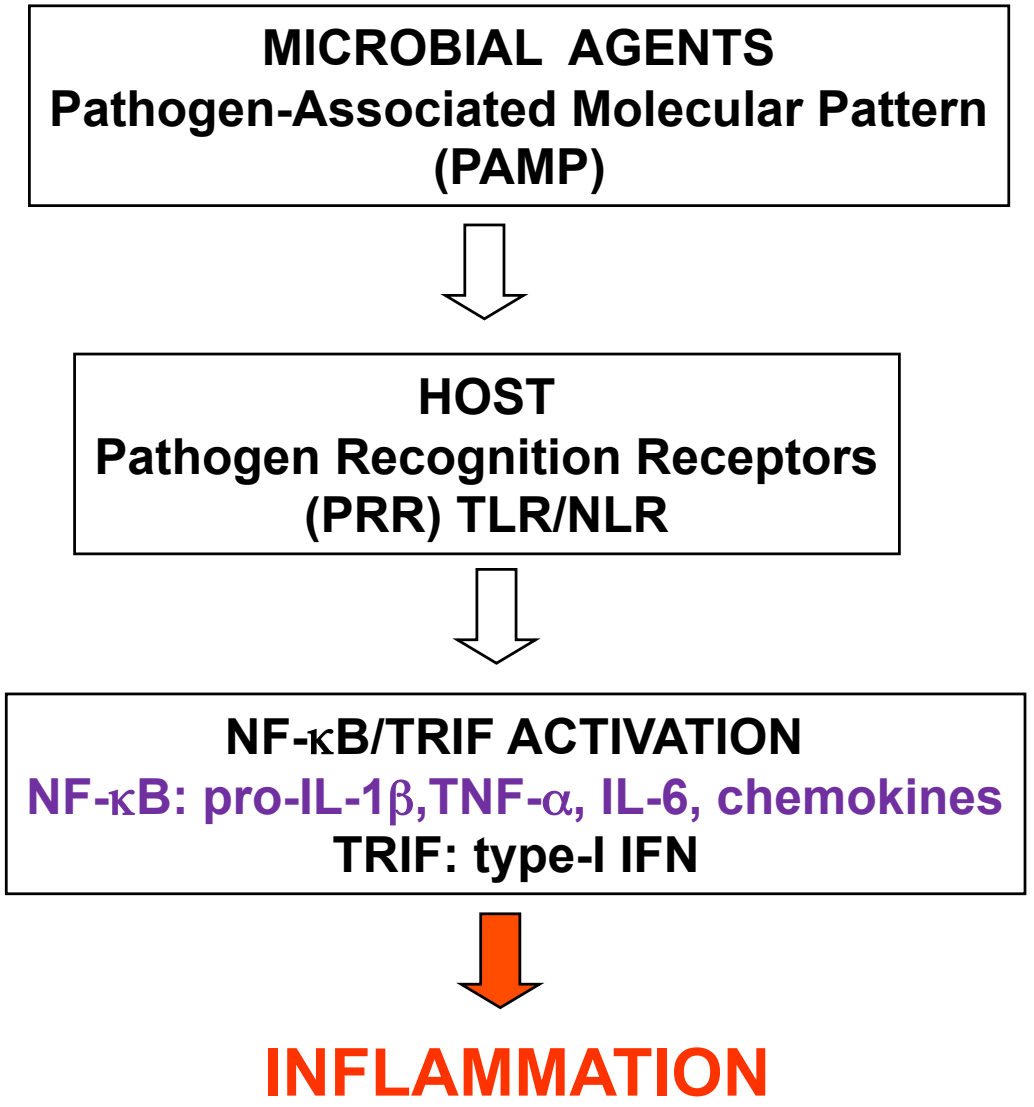
New name	Other name	Receptor	Co-receptor	Property
IL-1F1	IL-1α	IL-1RI	IL-1RAcP	Pro-inflammatory
IL-1F2	IL-1β	IL-1RI	IL-1RAcP	Pro-inflammatory
IL-1F3	IL-1Ra	IL-1RI	n.a.	Receptor antagonist (IL-1α; IL-1β)
IL-1F4	IL-18	IL-18Rα	IL-18Rβ	Pro-inflammatory
IL-1F5	FIL1δ	IL-1Rrp2	n.a.	Receptor antagonist (IL-1F6, 8, 9)
IL-1F6	FIL-1ε	IL-1Rrp2	IL-1RAcP	Pro-inflammatory
IL-1F7	IL-1H4	IL-18Rα	Unknown	Anti-inflammatory
IL-1F8	IL-1H2	IL-1Rrp2	IL-1RAcP	Pro-inflammatory
IL-1F9	IL-1ε	IL-1Rrp2	IL-1RAcP	Pro-inflammatory
IL-1F10	IL-1Hy2	Unknown	Unknown	Receptor antagonist (?)
IL-1F11	IL-33	ST2	IL-1RAcP	Th2 responses

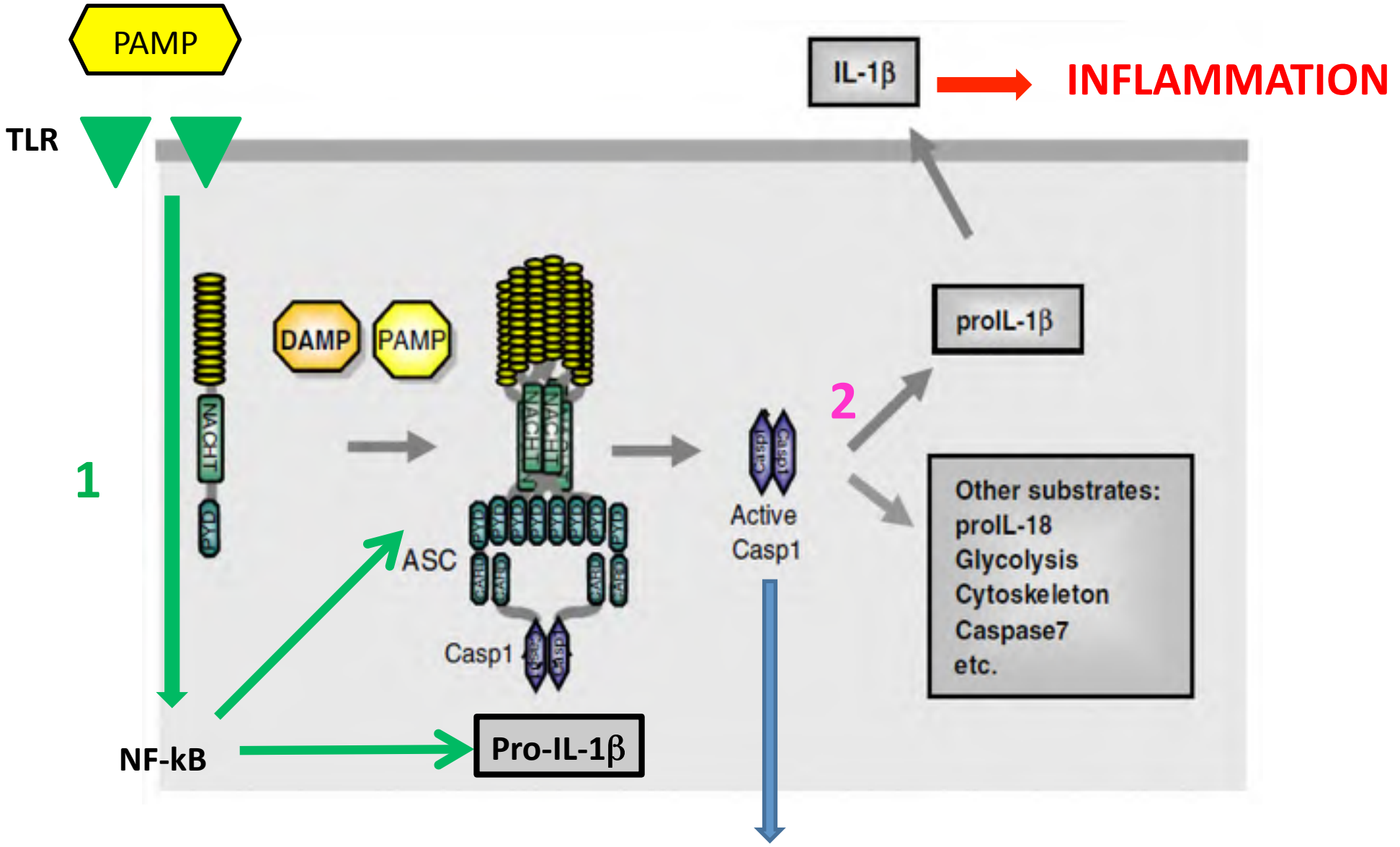
Dinarello , A&R 1990



Adapted from Dinarello, N Engl J Med 1990

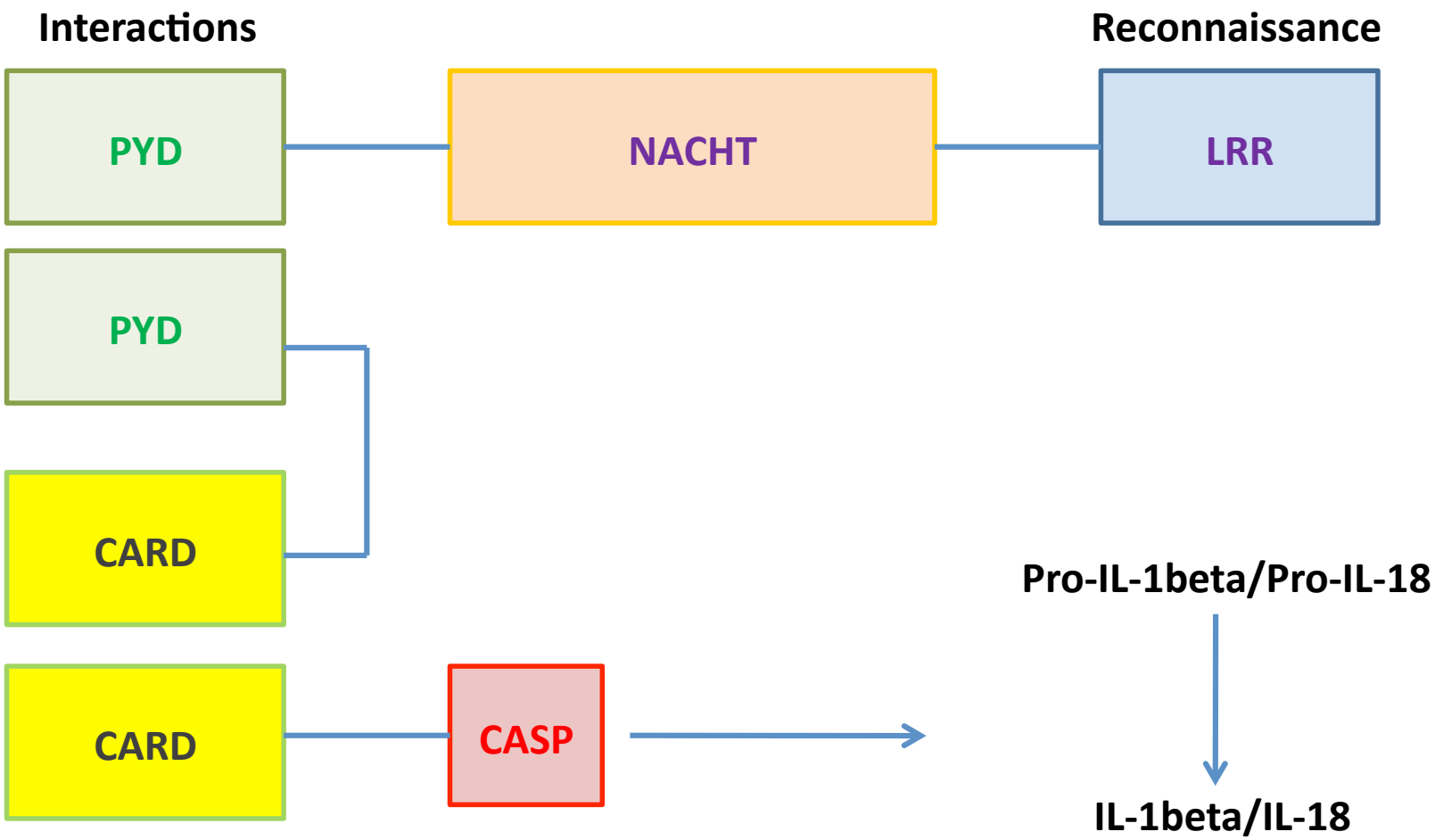
INFECTION-INDUCED INFLAMMATION





INFLAMMASOME NLRP-3
2 step activation
(Tschopp, Eur J Immunol 2010)

NLRP3 INFLAMMASOME



➢IL-1 in BD

❖Increased IL-1β concentrations in serum/ Synovial fluid of BD patients

(Hamzaoui J Rheumatol 1990, Yosipovitch Isr Med Sci 1995, Düzgun Rheumatol Int 2005)

-Low concentrations

-Conflicting data *(Saniyalp, J Rhumatol 1996)*

-No association with disease activity

❖Moderate increased IL-1Ra concentrations in serum or synovial fluid of BD patients

(Düzgun Rheumatol Int 2005, Ertenli Clin Exp Rheumatol 2001)

-No association with disease activity

❖Increased IL-1β production by active BD mononuclear cells after LPS stimulation

(Mege J Rheumatol 1993, Liang IOVS 2013, Castrichini Eur J Immunol 2014)

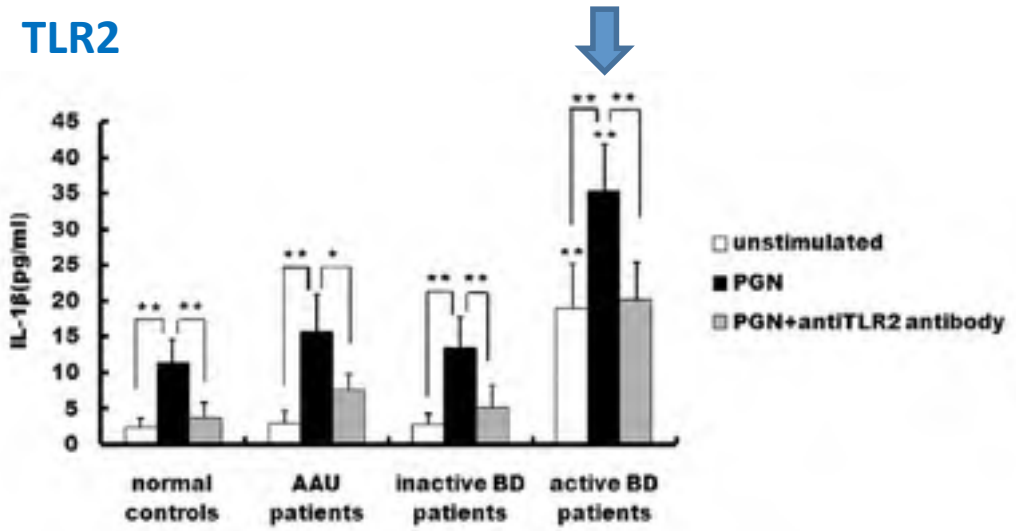
❖Due to IL-1 gene polymorphisms? conflicting data

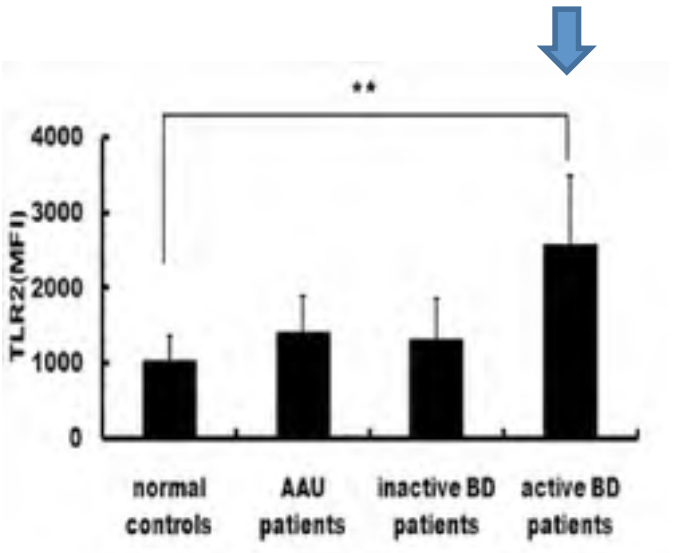
Association of BD with snp: IL-1A -889CT, IL-A -889TT, IL-1B +3962C, T, CC, CT, IL-1RA mspa 1100TT, 1100CT in Turkish population

(Zhou Mol Rheumatol 2014: Meta-analysis)

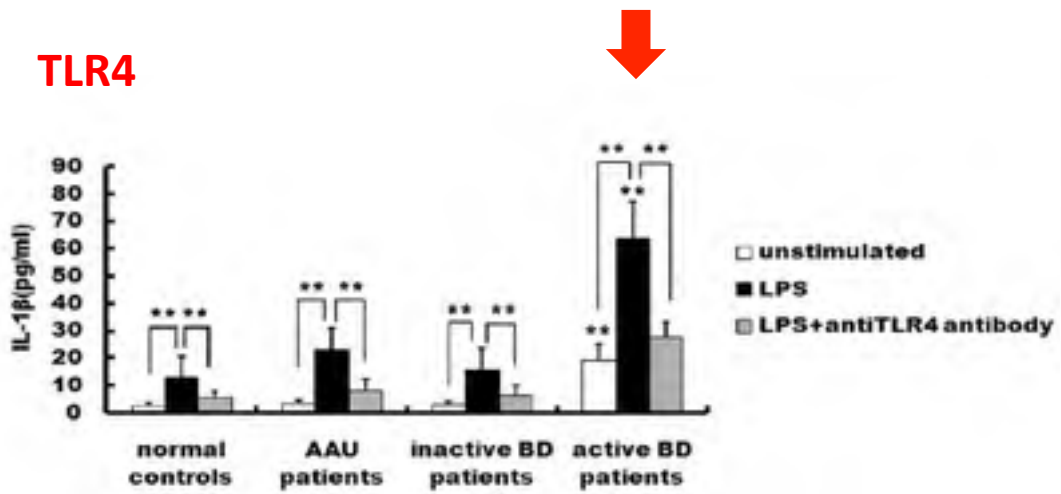
INCREASED IL-1β PRODUCTION BY BD MONOCYTES IS MEDIATED BY INCREASED TLR 2/4 EXPRESSION

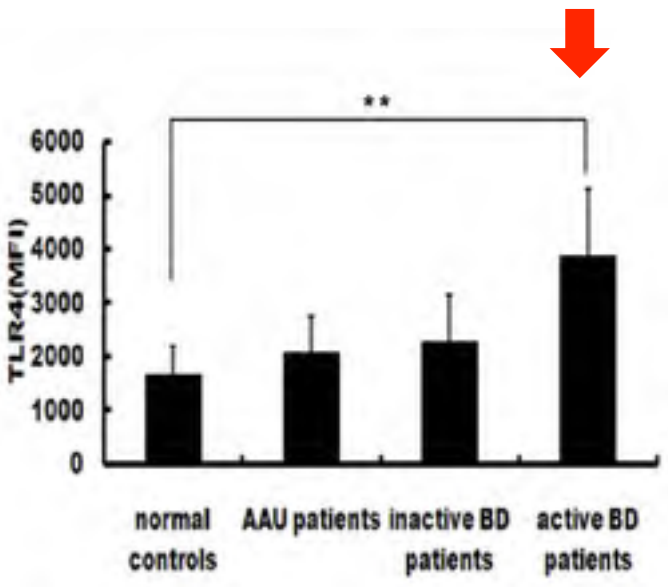
TLR2





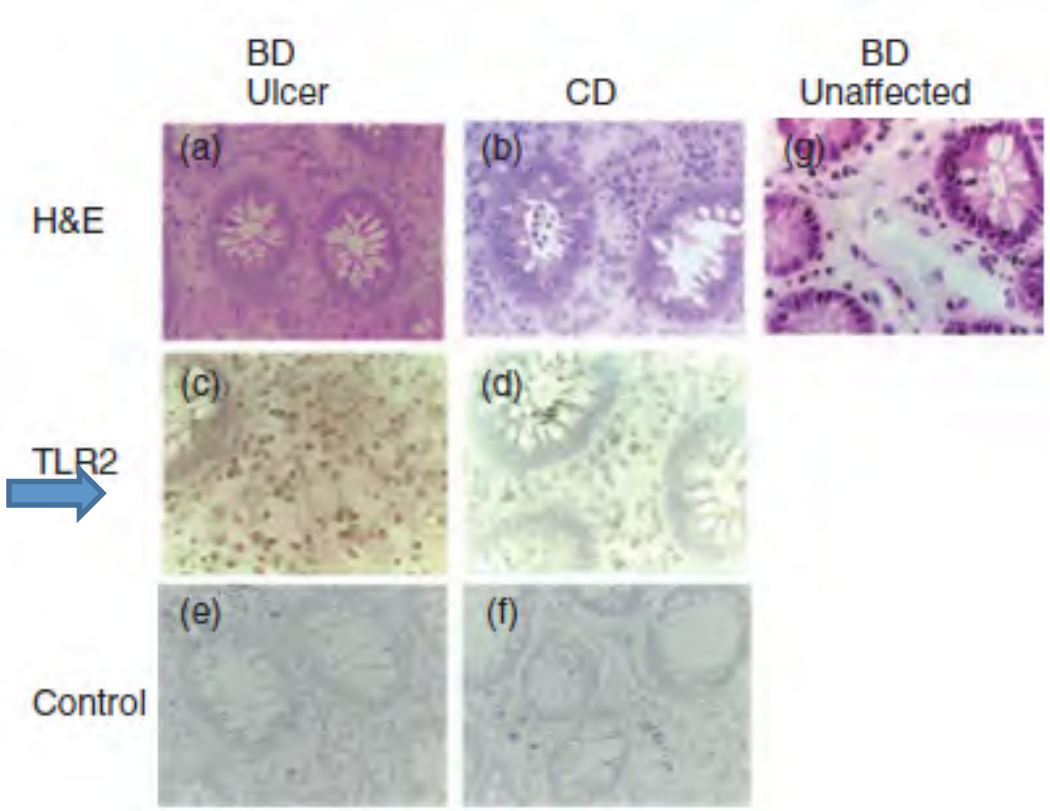
TLR4





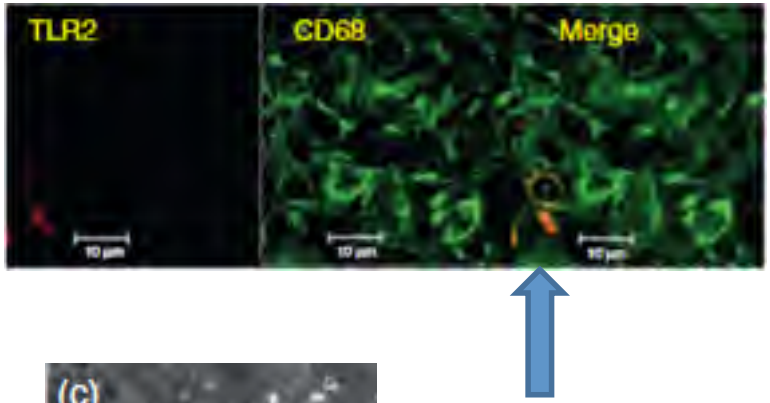
Liang IOVS 2013

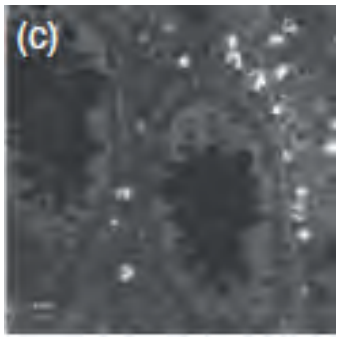
INCREASED MONOCYTE TLR2/4 EXPRESSION IN INFLAMMED TISSUES OF BD



INTESTINAL LESIONS

Nara Clin Exp Immunol 2008

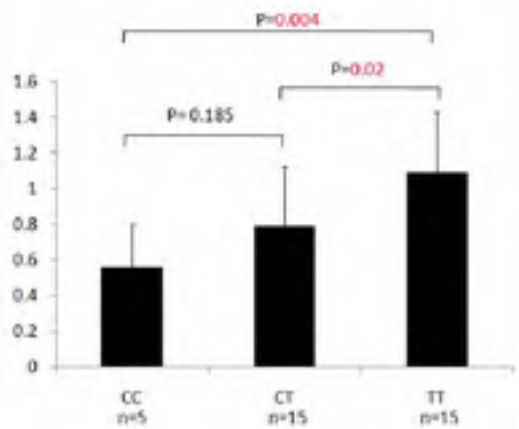




HSP 60

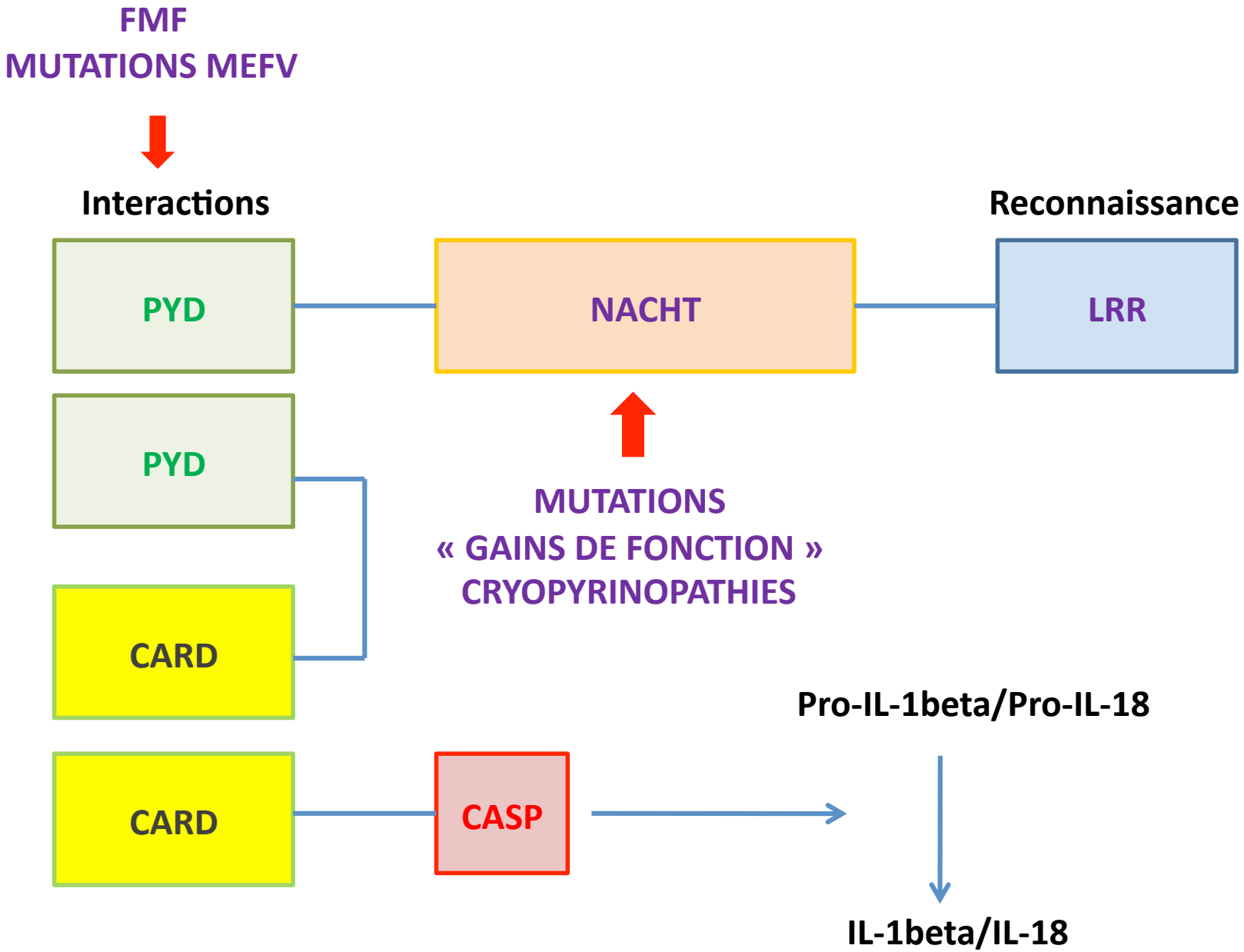
TLR-2/4 POLYMORPHISMS IN BD
LINK WITH INNATE IMMUNITY

➢**Polymorphisme du gène de TLR2, mais pas TLR 4, 8, 9 chez 400 BD chinois avec uvéite (Fang, IOVS 2013):** association à une augmentation de l'expression de TLR2, mais pas de la réponse inflammatoire



➢**Snp du gène de TLR4 (récepteur du LPS) chez BD japonais et turcs (Kirino, PNAS 2014)**

MUTATIONS DE MEFV AU COURS DE BD



MUTATIONS DE MFEV AU COURS DE BD

- **M694V chez 7% des BD, E148Q chez 10% des BD Turcs, arabes, sépharades (Touitou, Hum Mutation 2000)**

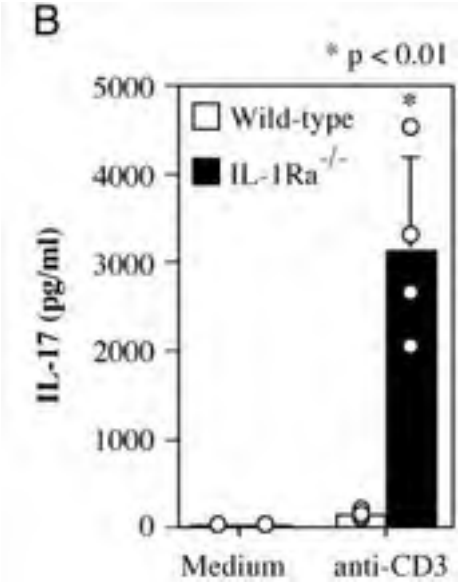
- **M694V chez BD turcs (Kirino, PNAS 2014)**

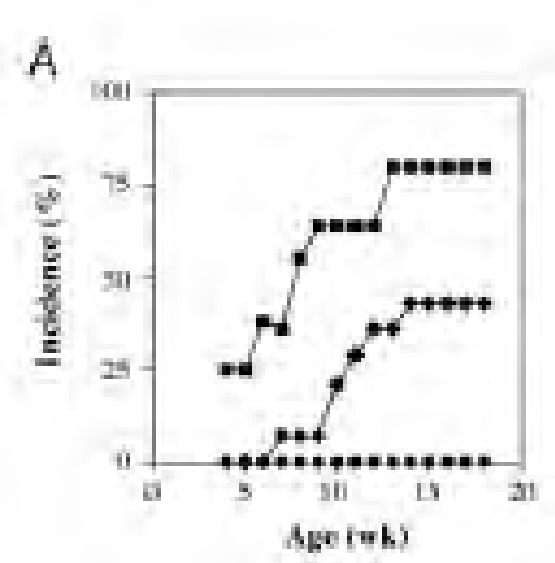
- **Mutations de la PYRINE(MEFV) induisent un état pro-inflammatoire dépendant de l'IL-1β chez l'animal (Chae, Immunity 2011)**

LIENS ENTRE BD ET IMMUNITE INNEE

IL-1 AND THE IL-23/IL-17 axis

IL-17 is required downstream of IL-1 to induce arthritis in IL-1Ra KO mice



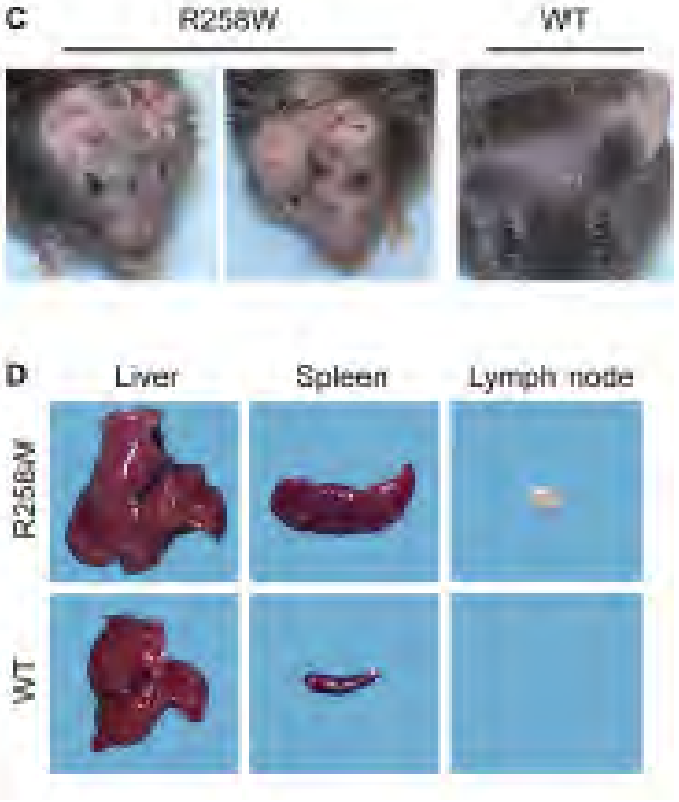


IL-17+/+

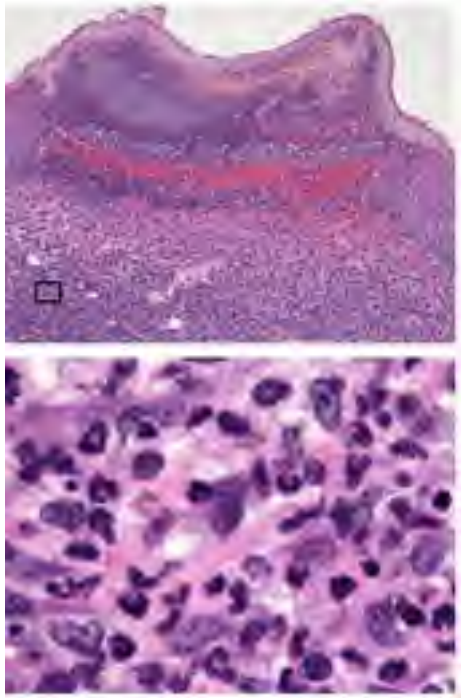
IL-17-/-

Nakae PNAS 2003
Koenders A&R 2008
Lamacchia A&R 2010

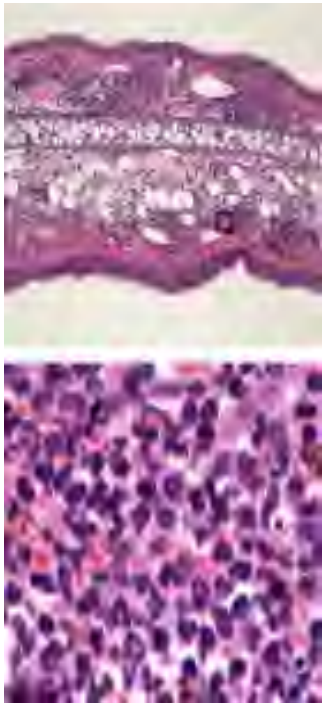
IL-1 AND THE IL-23/IL-17 AXIS

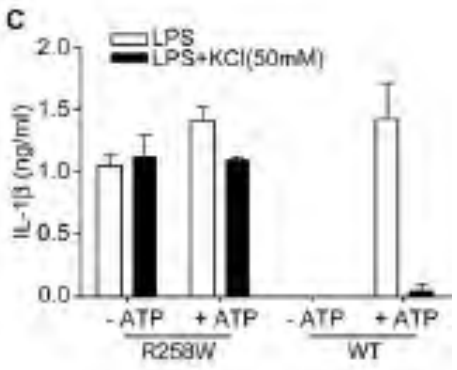


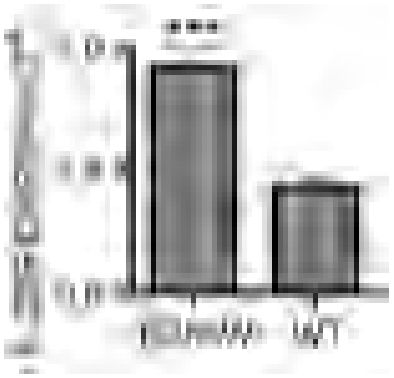
PMN infiltrate

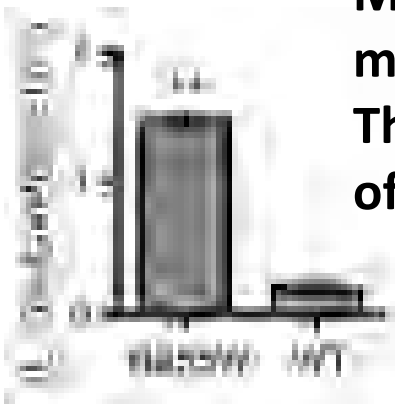


IL-17 labeling



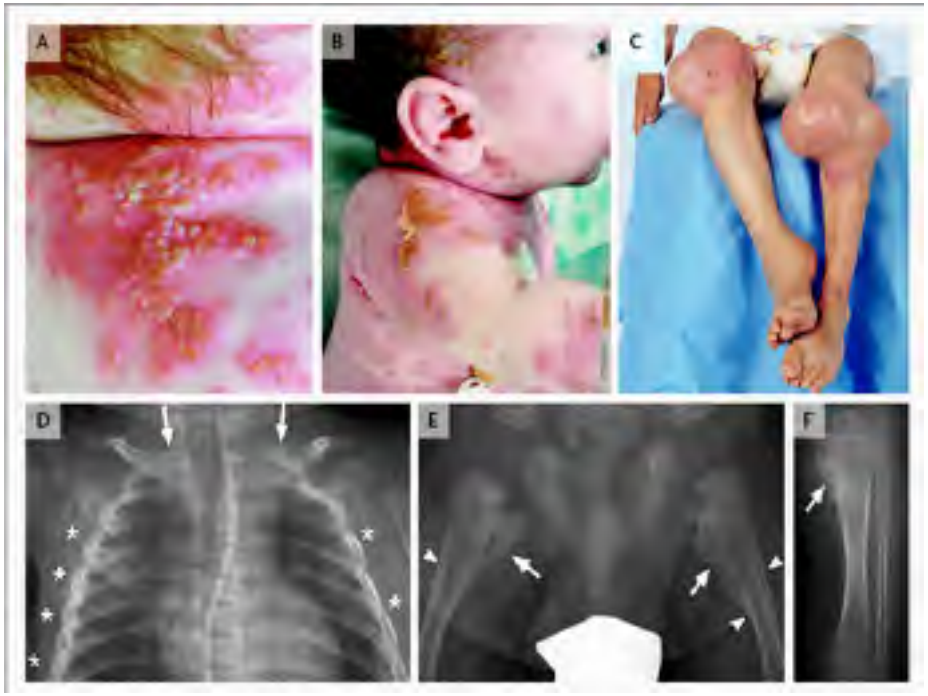






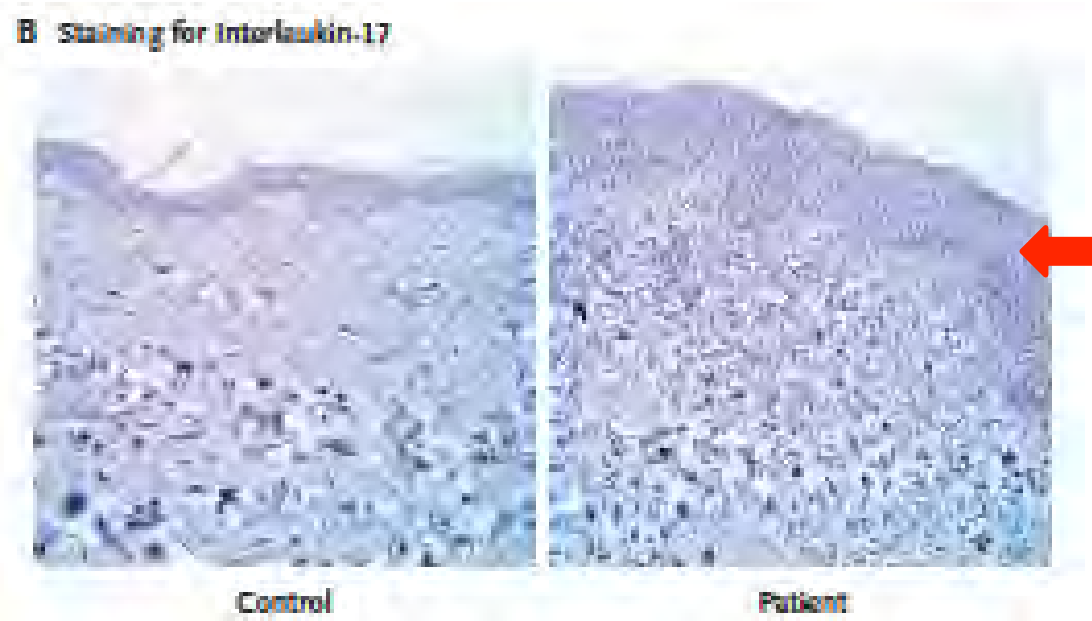
Muckle-Wells animal model reveals excess Th-17 response downstream of IL-1

ROLE OF IL-1 IN THE IL-23/IL-17 AXIS



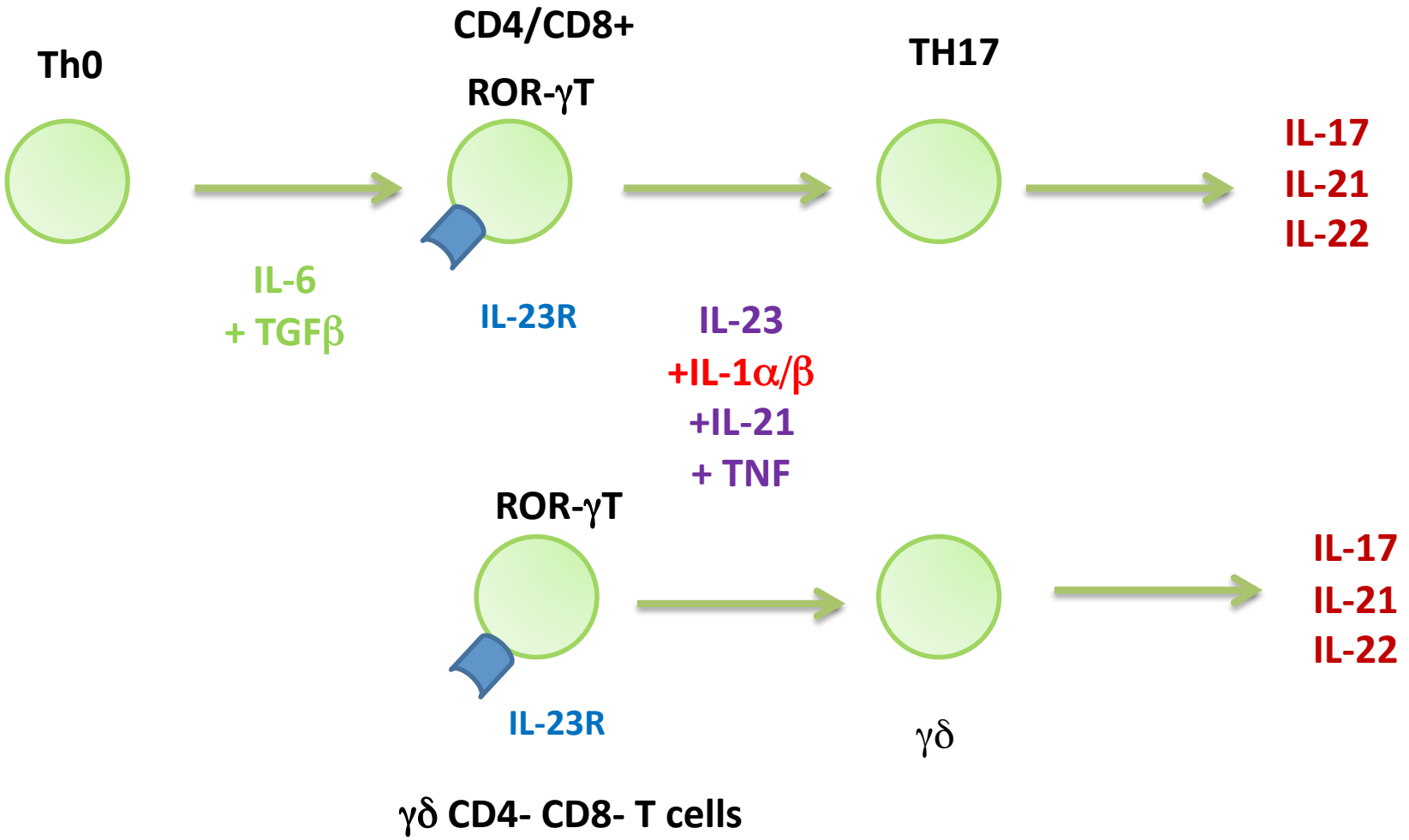
INCREASED IL-17 EXPRESSION IN PATIENTS WITH DEFICIENCY OF IL-1Ra (DIRA)

(Aksentijevich, N Engl J Med 2009)



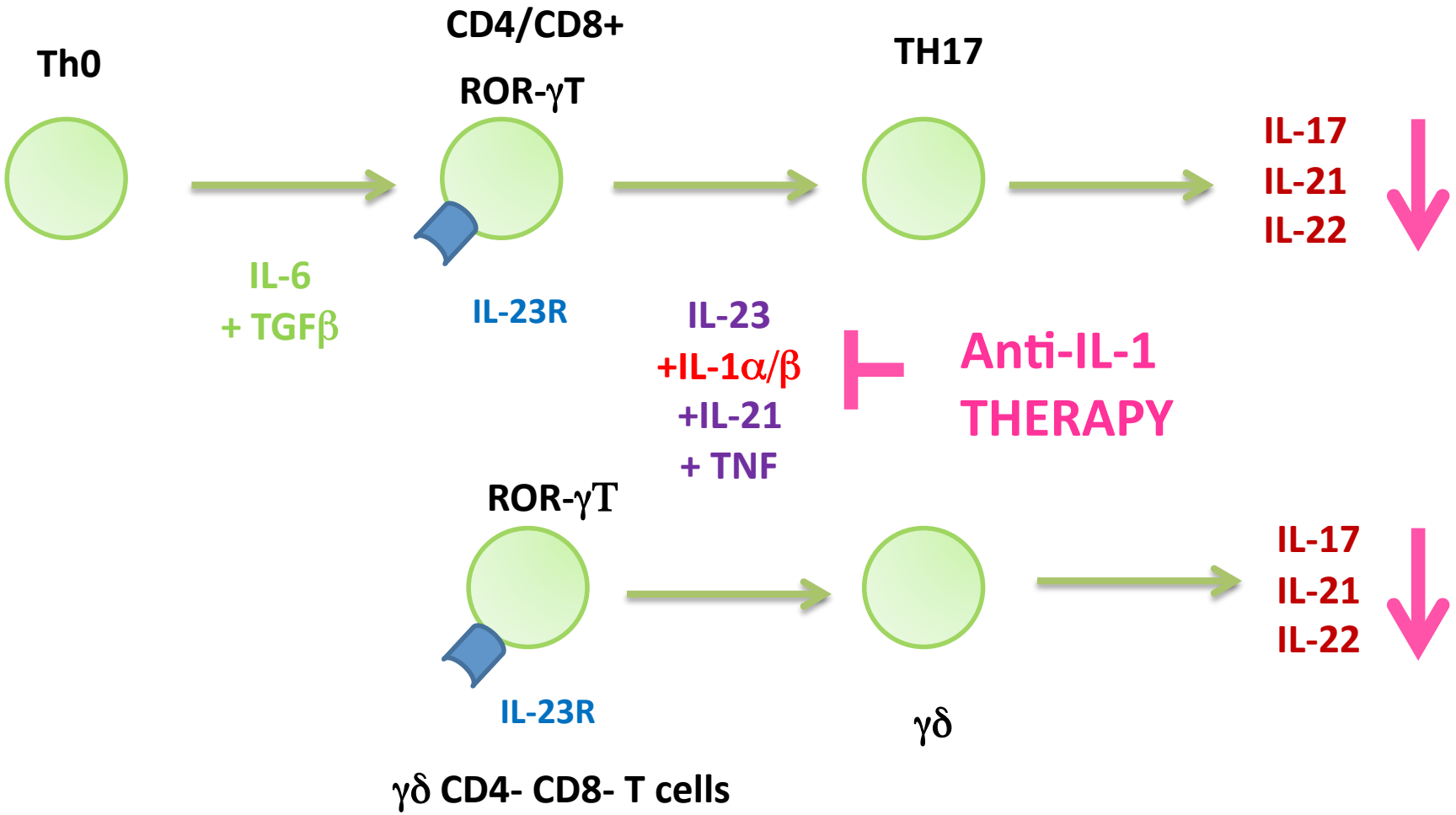
IL-17 in skin biopy

IL-1 synergizes with IL-23 to induce IL-17 secretion by CD4 T cells and γδ T cells

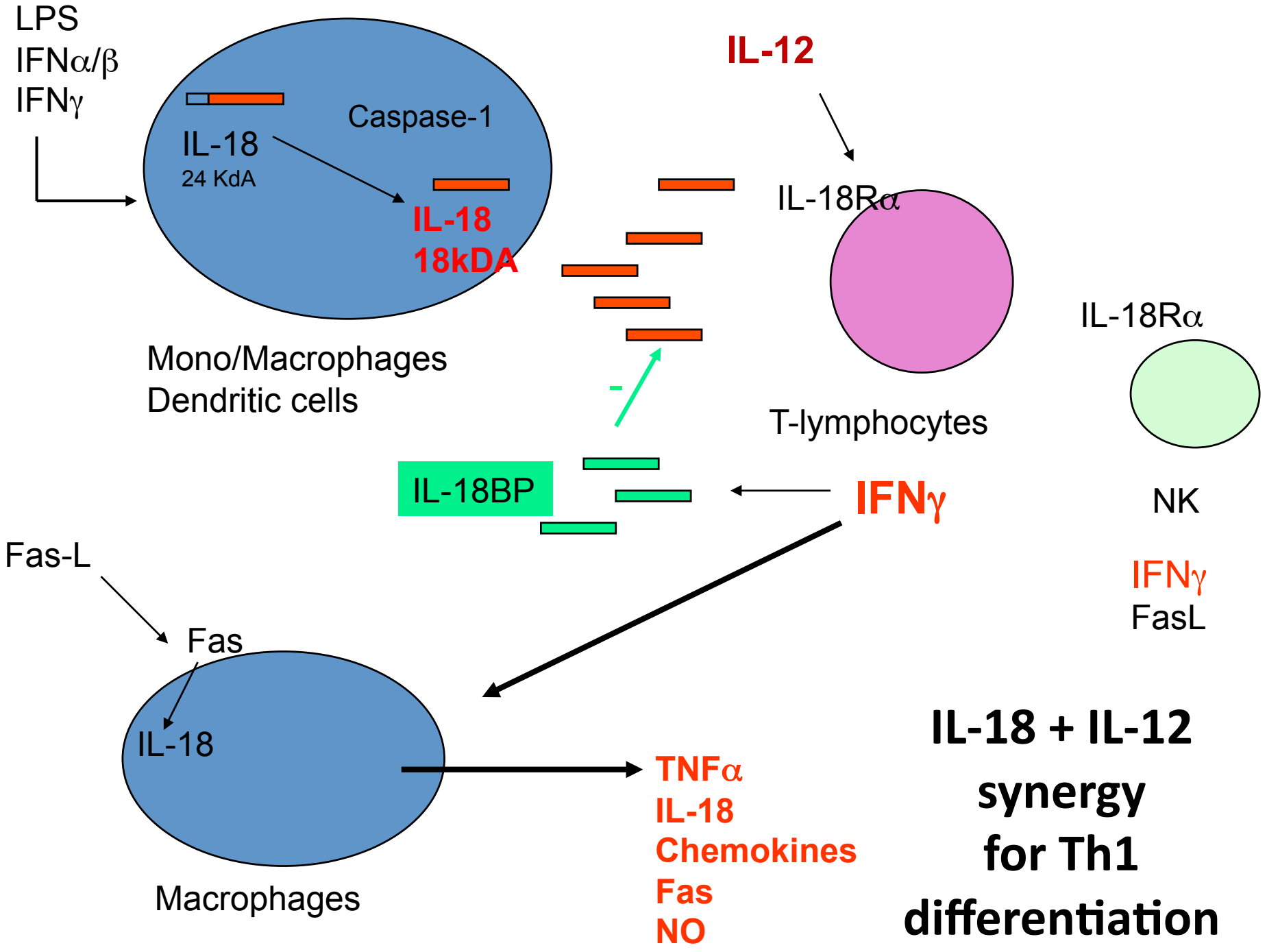


Sutton Immunity 2009; Martin Immunity 2009

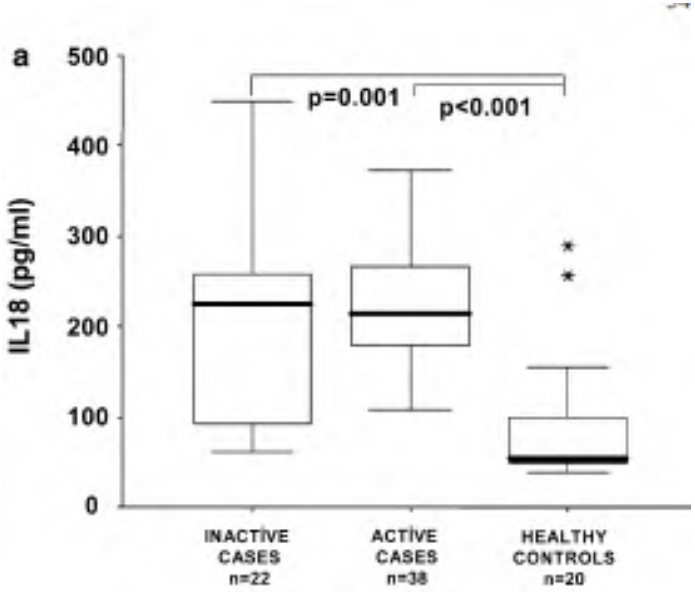
ANTI-IL-1 THERAPY INHIBITS IL-17-MEDIATED EFFECTS

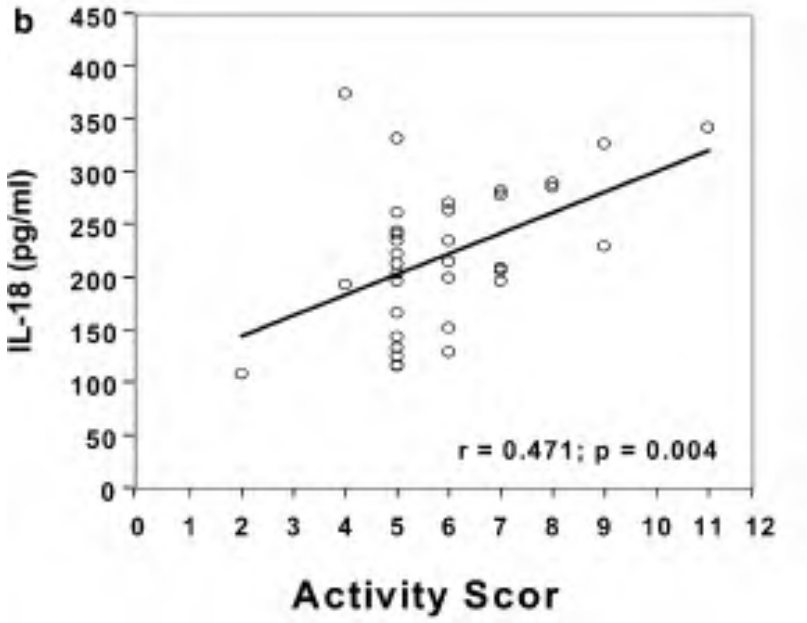


Sutton Immunity 2009; Martin Immnuity 2009

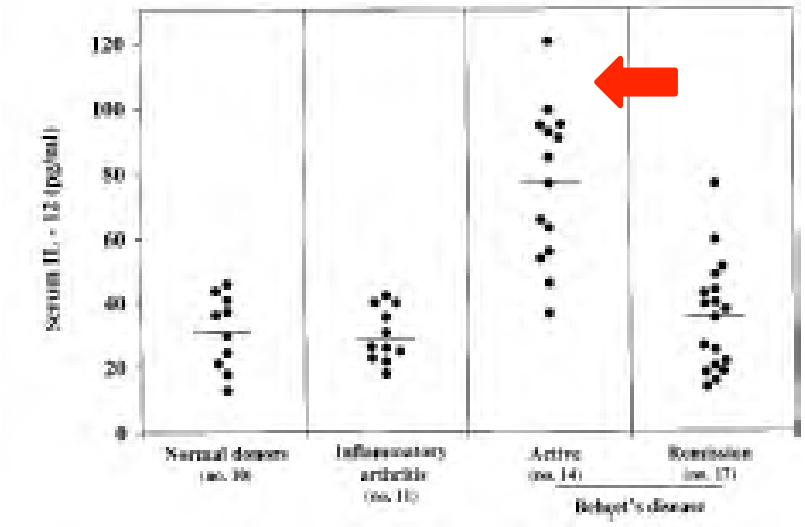

LPS
IFNα/β
IFNγ
IL-18
24 KdA
Caspase-1
IL-18
18kDA
Mono/Macrophages
Dendritic cells
IL-12
IL-18Rα
T-lymphocytes
IL-18Rα
NK
IFNγ
FasL
IL-18BP
IFNγ
Fas-L
Fas
IL-18
Macrophages
TNFα
IL-18
Chemokines
Fas
NO
IL-18 + IL-12
synergy
for Th1
differentiation

IL-18 and IL-12 in BD



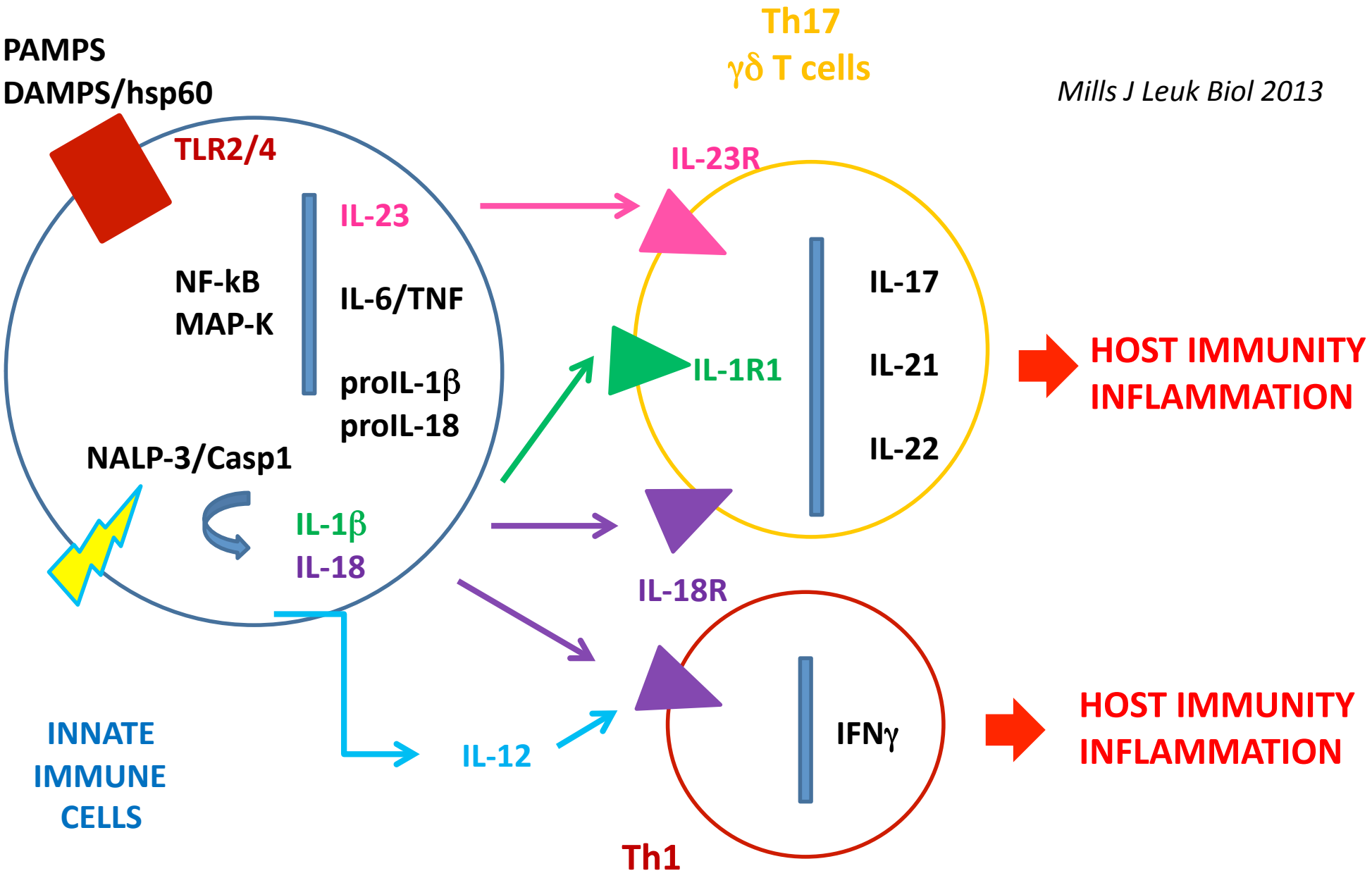


Increased IL-18 concentrations in serum of active and inactive BD patients
(Oztas Exp Dermatol 2005; Musabak Rheumatol Int 2006)



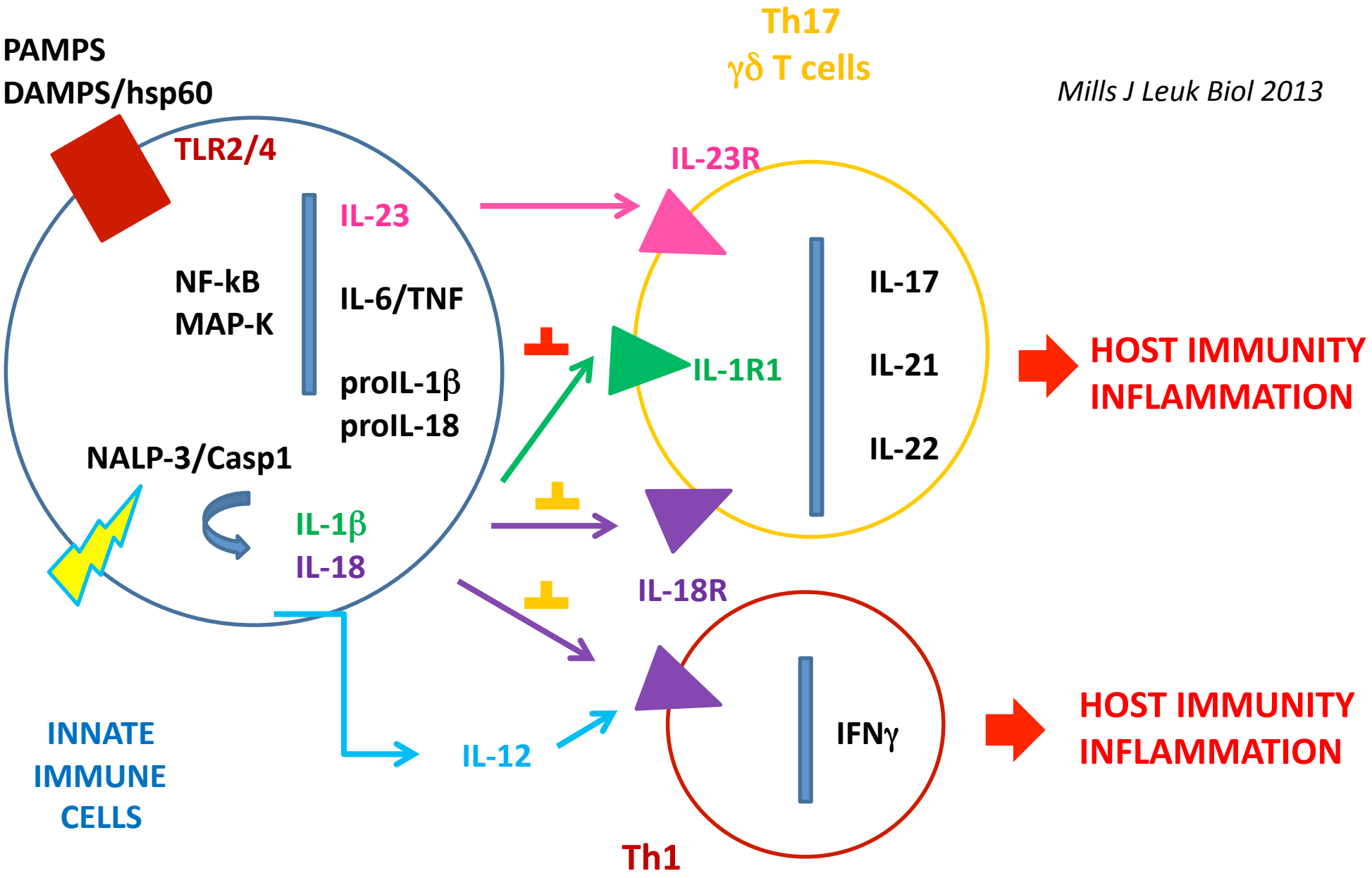
Increased IL-12 concentrations in serum of active BD ***(Frassanito A&R 1999)***

CASPASE-1 PROCESSED CYTOKINES DRIVE Th1 and Th17 RESPONSES



Mills J Leuk Biol 2013

CASPASE-1 PROCESSED CYTOKINES DRIVE Th1 and Th17 RESPONSES



Mills J Leuk Biol 2013

CONCLUSIONS

La physiopathologie de la maladie de BEHCET implique des facteurs environnementaux et génétiques influant sur:

➢ **L'immunité adaptative:**

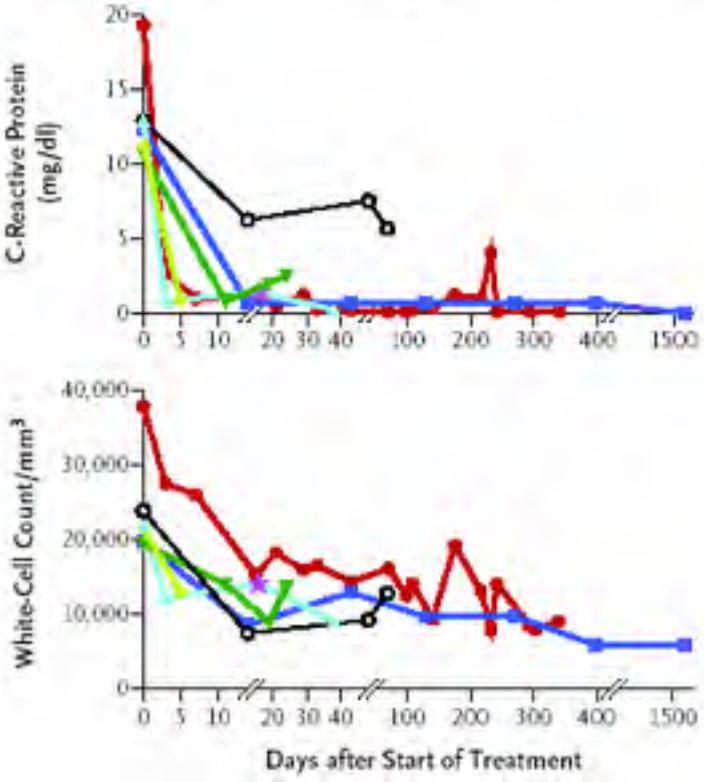
- **Liens avec HLA-B51/ERAP-1**
- **Immunité croisée entre *s. sanguis*, HSP-65 et HSP-60**
- **Excès de réponse TH-1 vs TH-2 et excès de TH-17 vs Treg**

Mais aussi

➢ **L'immunité innée:**

- **Défaut de clearance des agents infectieux**
- **Rôle des lymphocytes T γδ**
- **Sur ou sous-expression expression de TLR2/4**
- **Excès d'activation de la voie caspase-1 (liens avec FMF)**
- **Excès de production d'IL-1, IL-18 qui activent Th-17 et Th-1**

Nouvelles thérapeutiques: anti-TNF, anti-IL-1, caspase1? TLR?…….



DIRA TREATMENT
WITH
KINERET (IL-1ra)

IL-18 promoter polymorphisms in BD

-607 C/A -137G/C **polymorphism which is associated with IL-18 gene promoter activity**

- **No association with these genotypes in Korean BD** ***(Jang Clin Exp Rheumatol 2005)***

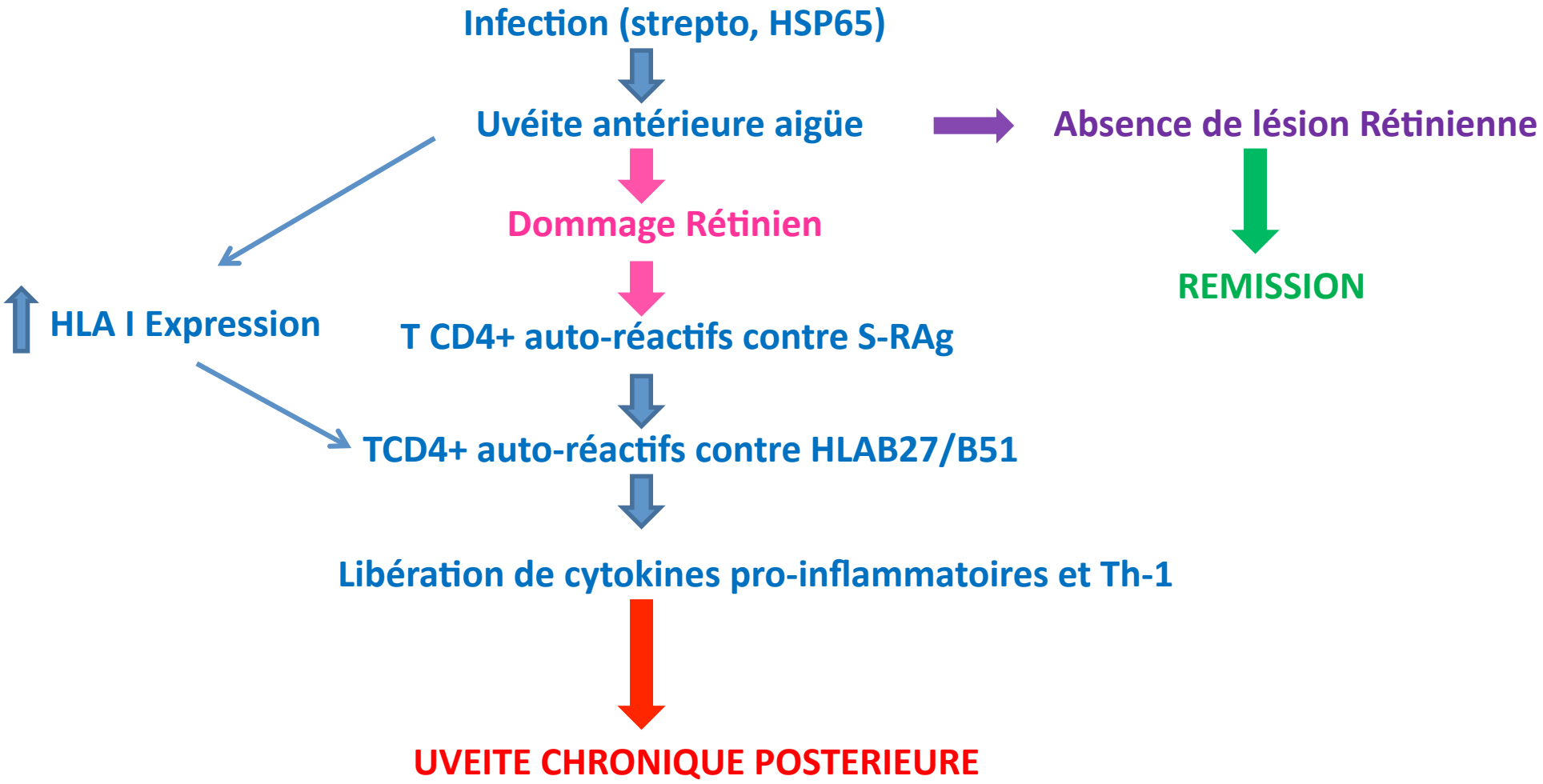
- ***-607 CC*** **genotype and C allele are more frequent in Korean BD**
  -607C/-137G **homozygotes are associated with earlier BD symptoms** ***(Lee, Human Immunol 2006)***

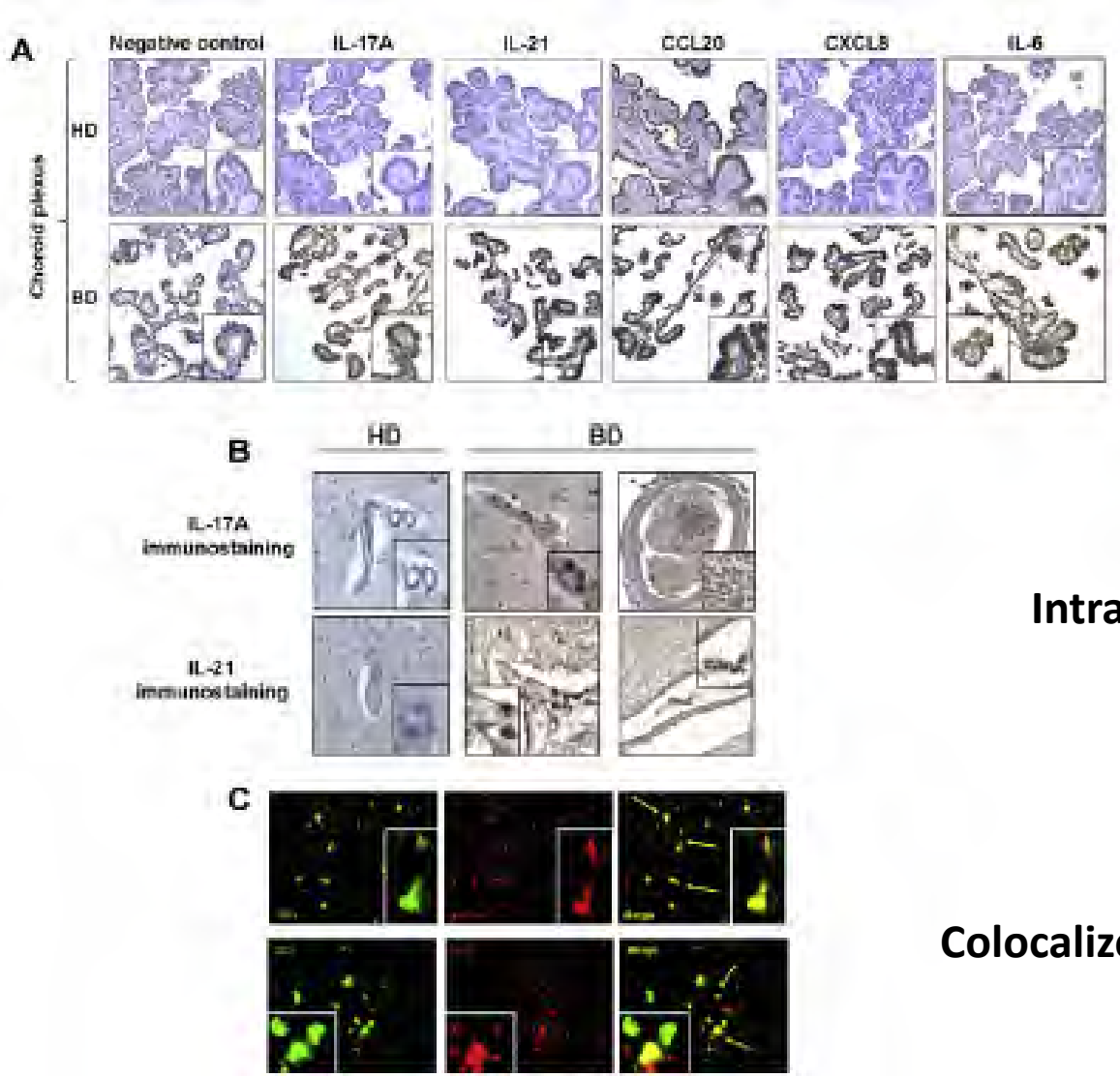
- ***-607 CC*** **genotype and C allele are more frequent in Turkish BD**
  -607 C/-137G **especially in BD with muco-cutaneous symptoms** ***(Keskin Clin Exp Rheumatol 2007)***

- ***-607 A*** **allele is associated with BD in Turkish patients** ***(Htoon J Rheumatol 2011)***

- ***-607*** **genotype and allele distribution are associated with BD in Egyptian patients**
  -137 GG **genotype is associated with more severe ocular symptoms** ***(Hazzaa J Oral Pathol Med 2014)***

PREDISPOSITION GENETIQUE
GENES DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE





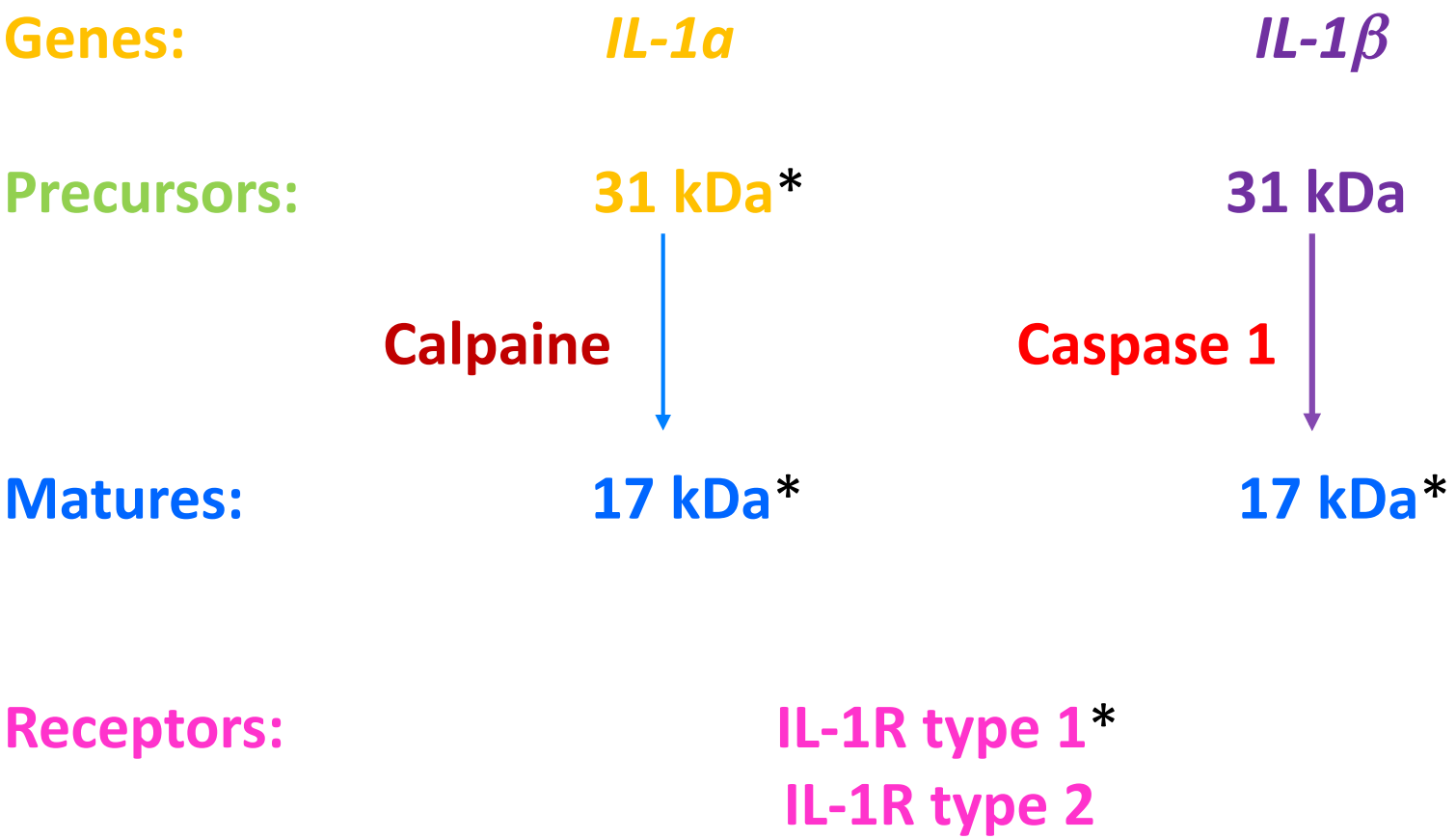
Choroid plexus

Intra-cerebral blood vessels

Colocalize with CD3 in brain lesions

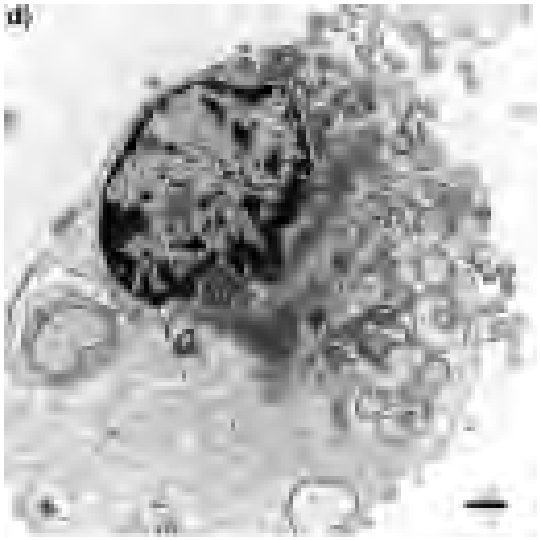
IL-17 and IL-21 expression in the brain of neuro-BD

(Geri, J All Clin Immunol 2011)


Genes:
IL-1α
IL-1β
Precursors:
31 kDa*
31 kDa
Calpaine
Caspase 1
Matures:
17 kDa*
17 kDa*
Receptors:
IL-1R type 1*
IL-1R type 2

NECROSIS/ DAMPS

Plasma membrane rupture+++ DAMPs release out of the cell



Nucleotides: **ATP**

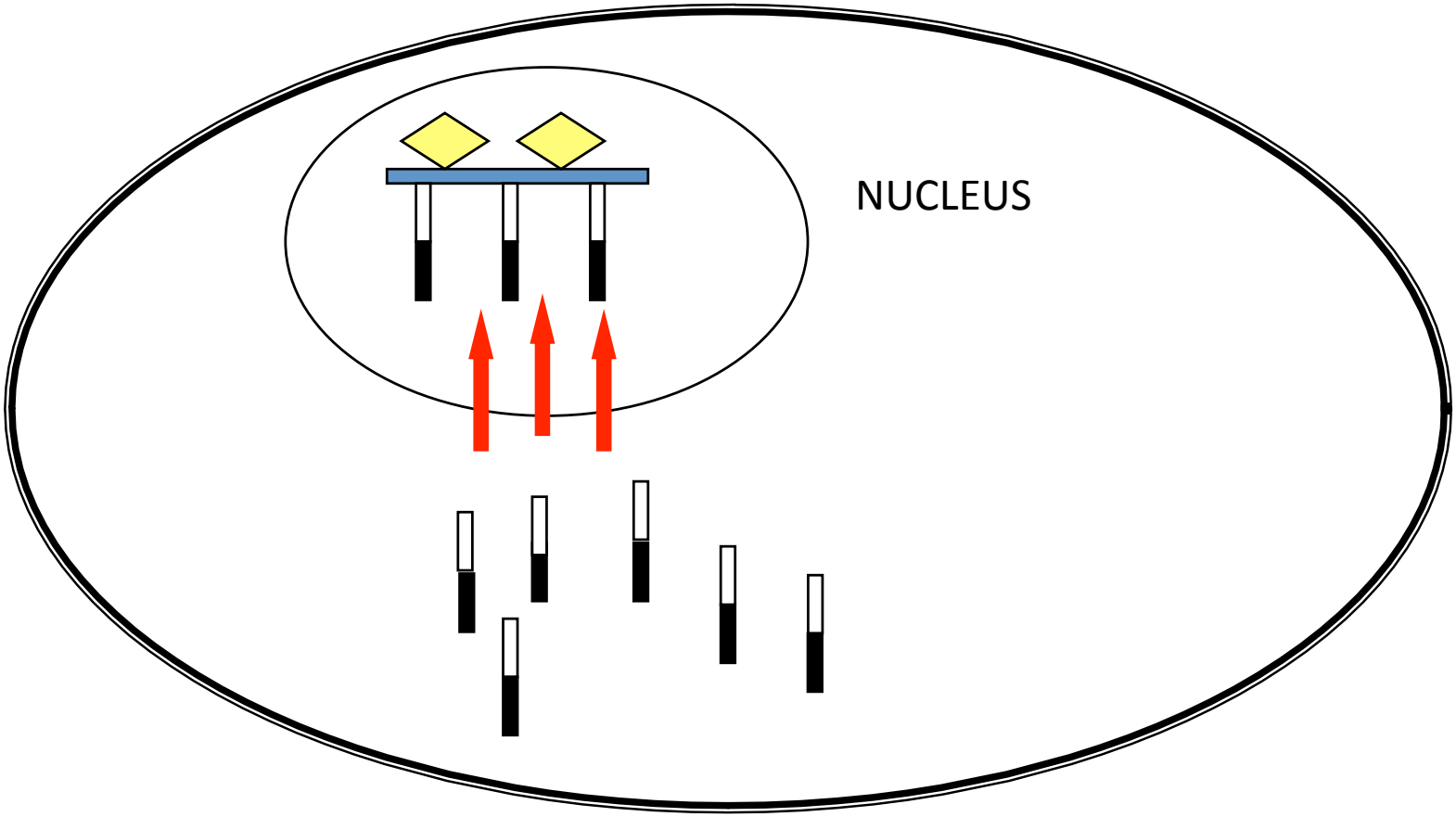
RNA, dsDNA

Heat shock proteins (hsp 70, 90, 96)

Uric acid

« Dual cytokines »:
High-mobility group box 1 (HMGB-1)
IL-1α

NALP-3 ACTIVATION
IL-1β



ACTIVATED
or
APOTOTIC

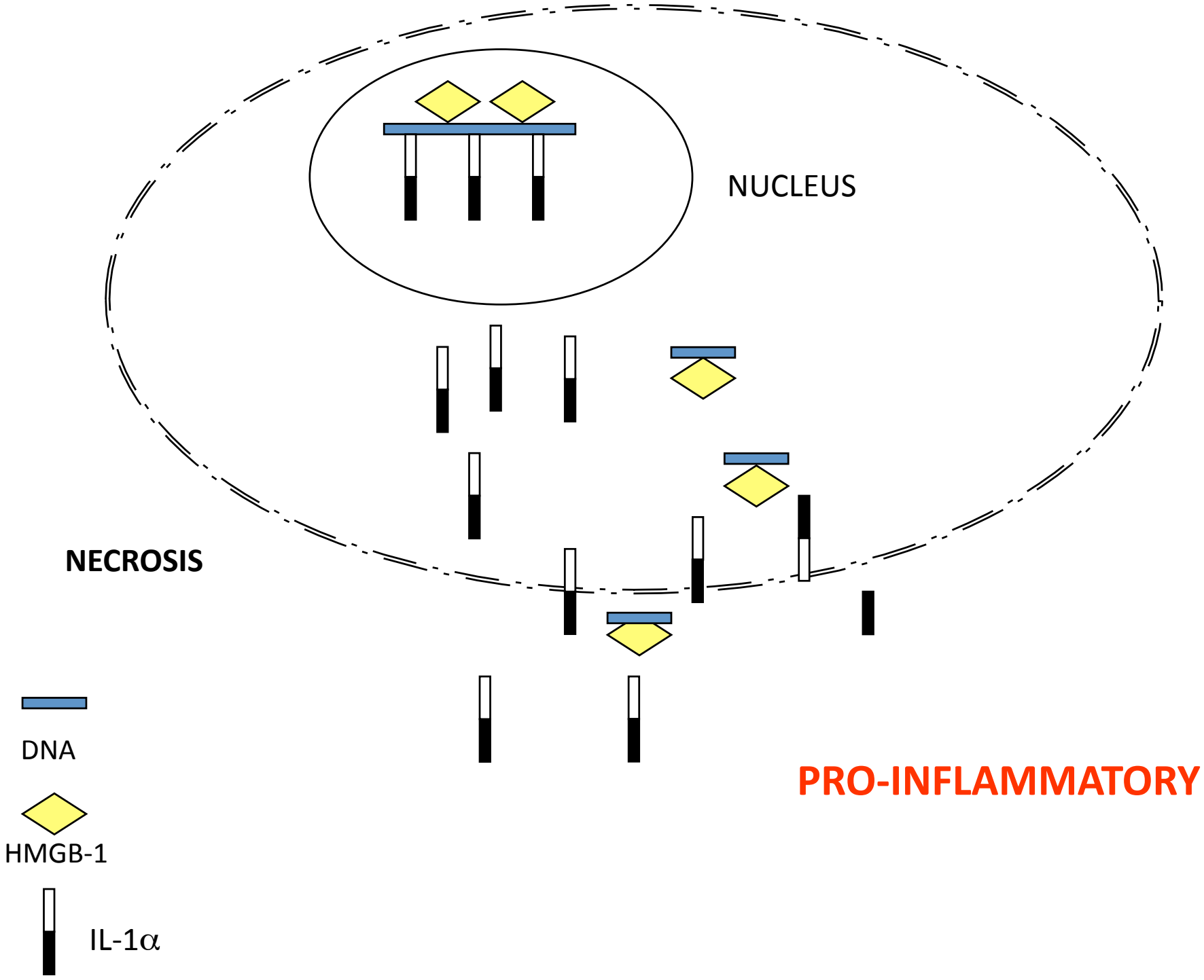
NO INFLAMMATION

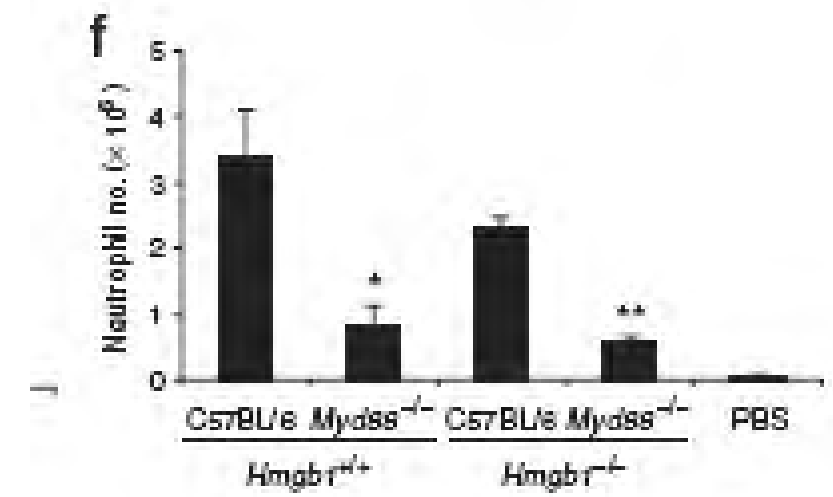
HMGB-1

DNA

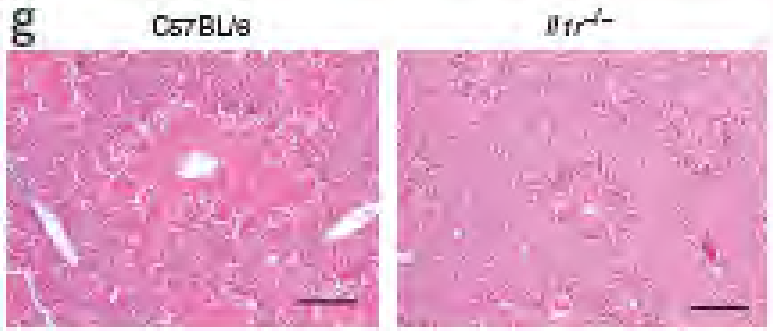
IL-1α

Scaffidi I Nature 2002; Dinarello CA Ann Rev Immunol 2009,
Cohen I et al PNAS 2010

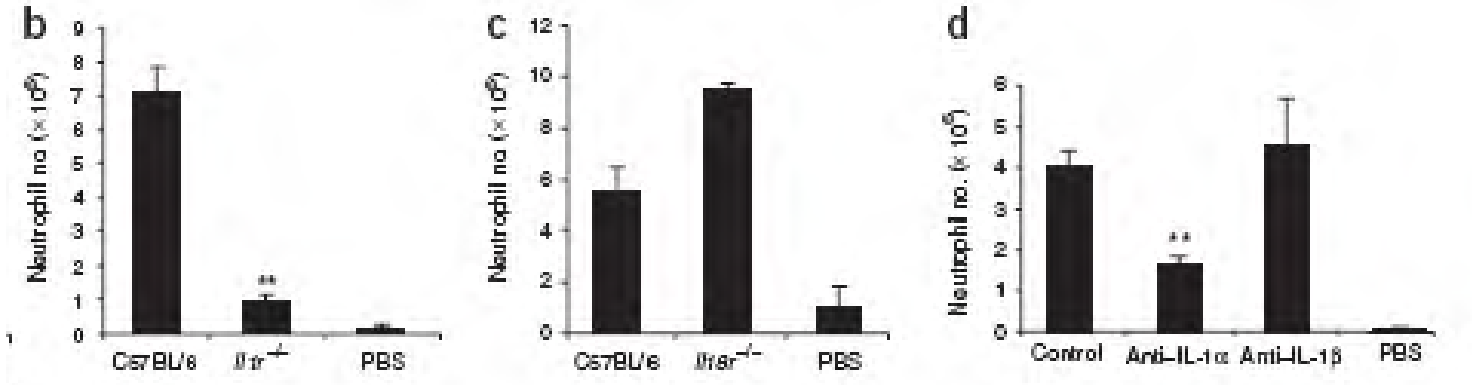

NUCLEUS
NECROSIS
DNA
HMGB-1
IL-1α
PRO-INFLAMMATORY



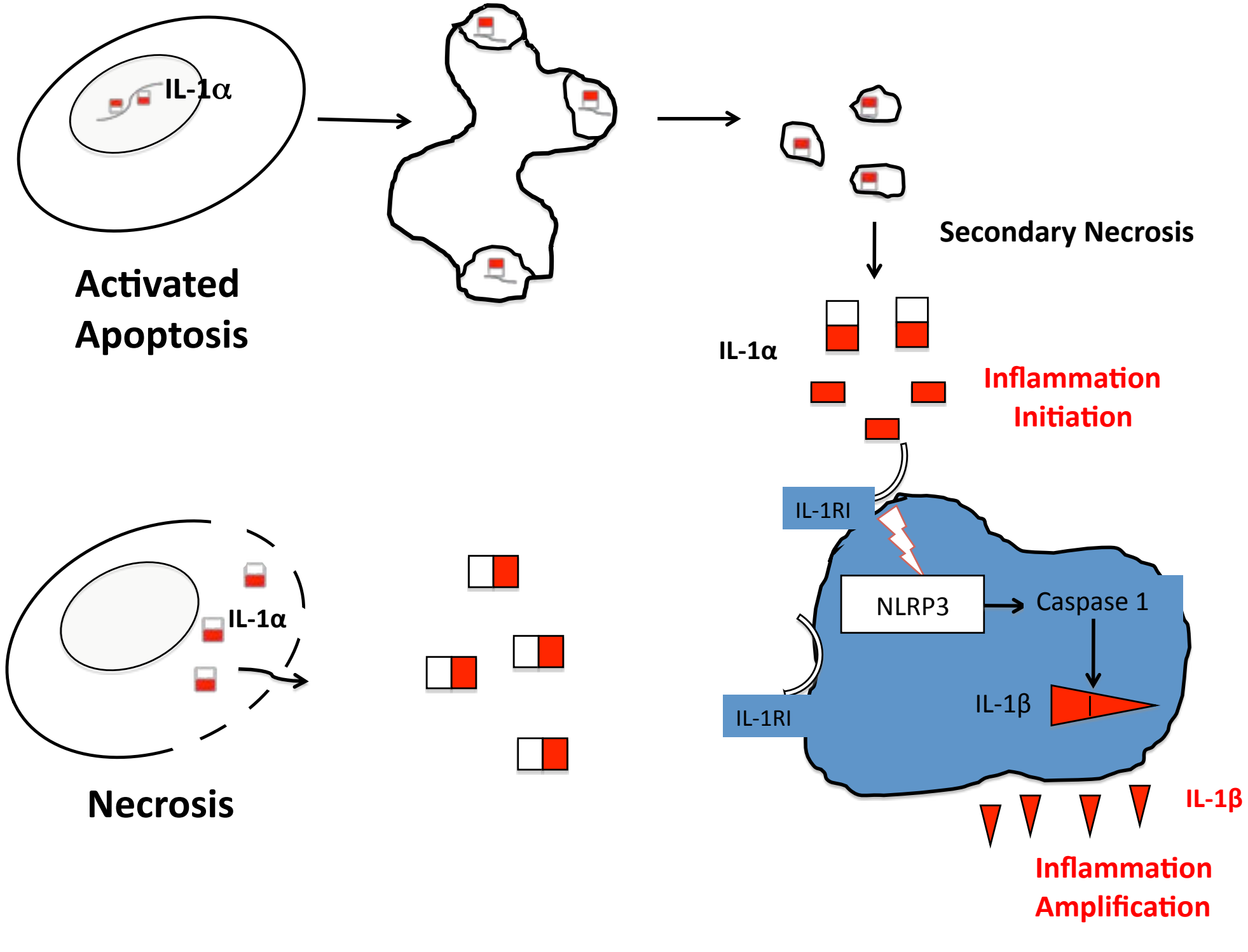
-Completely dependent on MYD88
-HMGB-1-independent
-Not mediated by TLR



STERILE INFLAMMATION
Is
mainly IL-1alpha-mediated



Chen C-J et al, Nature Medicine 2007


IL-1α
Activated
Apoptosis
Secondary Necrosis
IL-1α
Inflammation
Initiation
IL-1RI
NLRP3
Caspase 1
IL-1β
IL-1RI
IL-1α
Necrosis
IL-1β
Inflammation
Amplification

ANTI-IL-1 TREATMENTS IN BD: 24 reported cases!!!!

- **Rapid efficacy on ocular symptoms**

- **Efficacy on joint involvement**

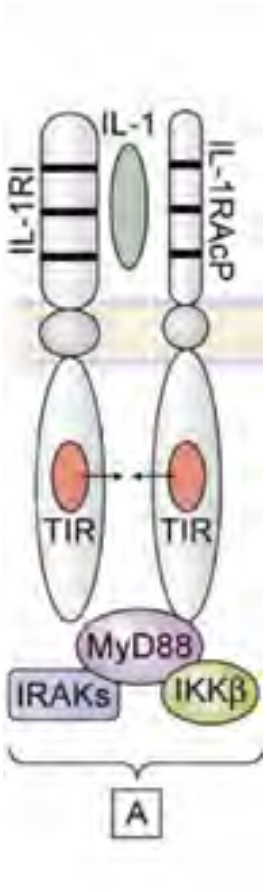
- **No protection against deep venous thrombosis**

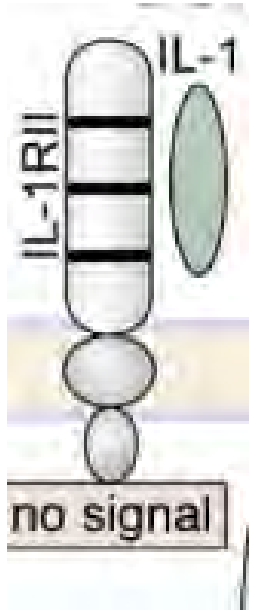
- **Poor efficacy on muco-cutaneous symptoms (colchicine) and digestive tract symptoms (anti-TNF). Neuro-BD?**

- **In case of Anakinra PR, or flare despite anakinra, it may be possible to increase the dose to 150-200 mg/day (ClinicalTrials NCT01441076)**

- **or to shift to an anti-IL-1β mAb (Gevokizumab or Canakinumab)**

IL-1 ACTION MODULATION

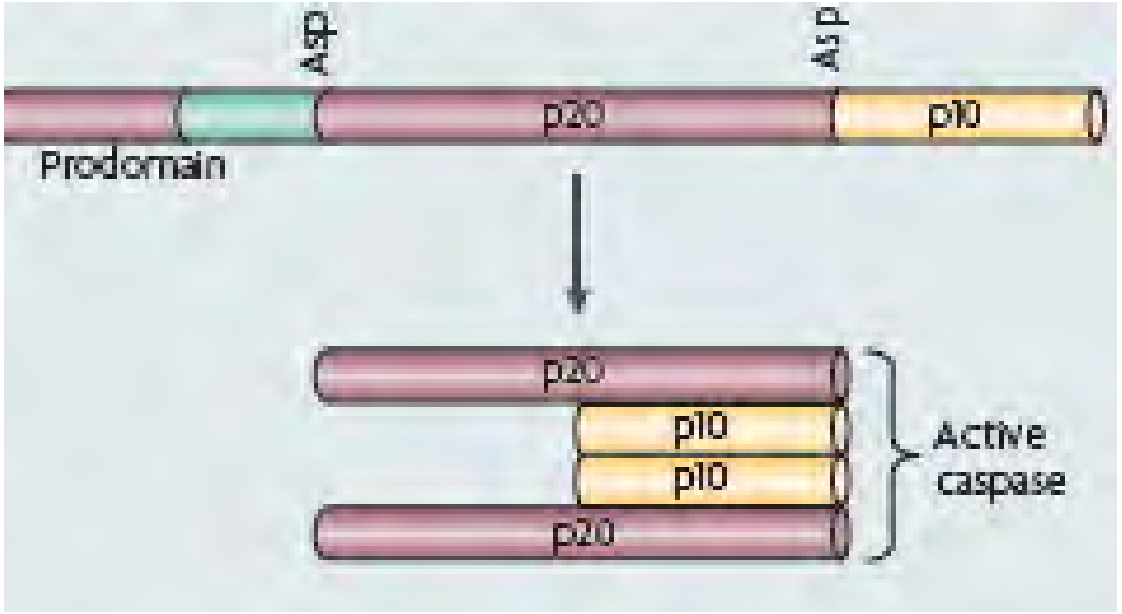




SIGNAL +

SIGNAL -

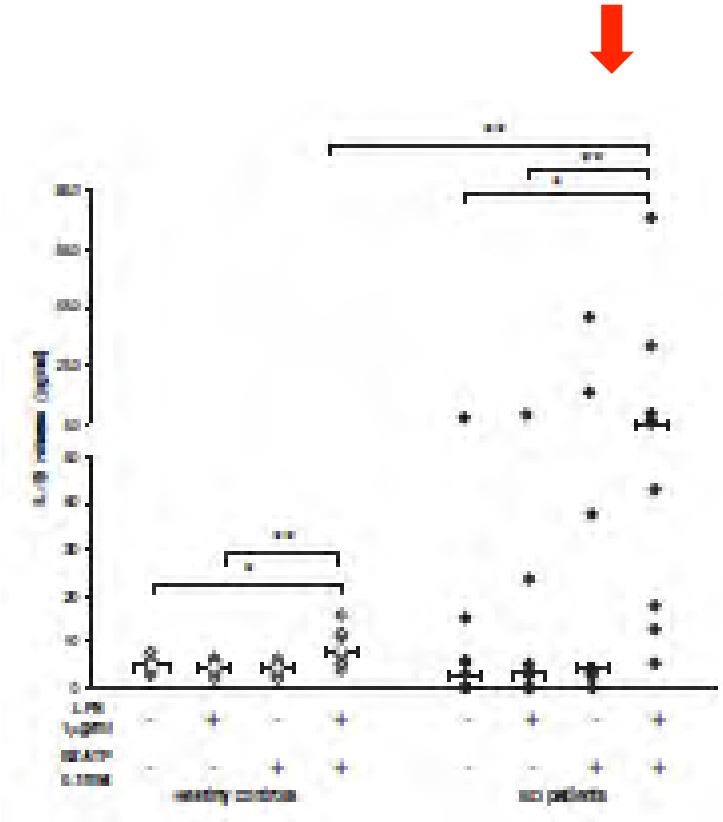
Cysteine-rich Asparagin Protease: CASPASE

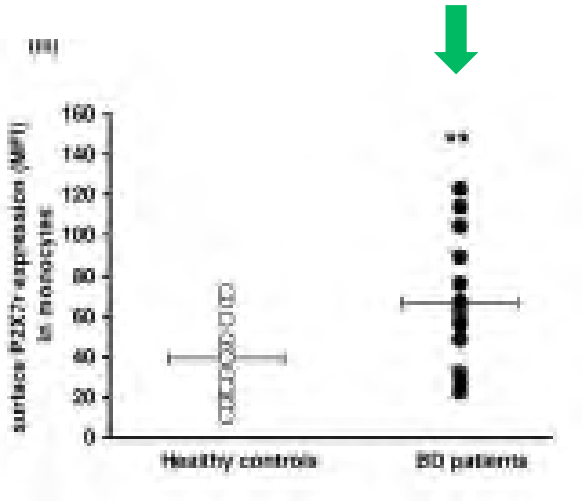


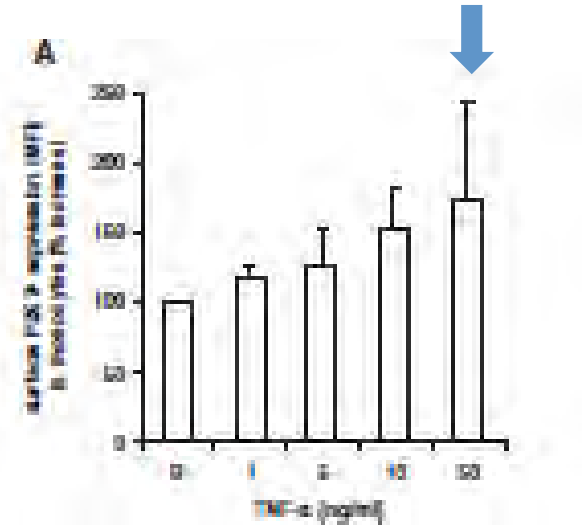
1/ Pro-inflammatory
Caspase-1

2/ Proapoptotic
Caspase-8, 9, 3

INCREASED IL-1β PRODUCTION BY BD MONOCYTES IS MEDIATED BY INCREASED ATP RECEPTORS



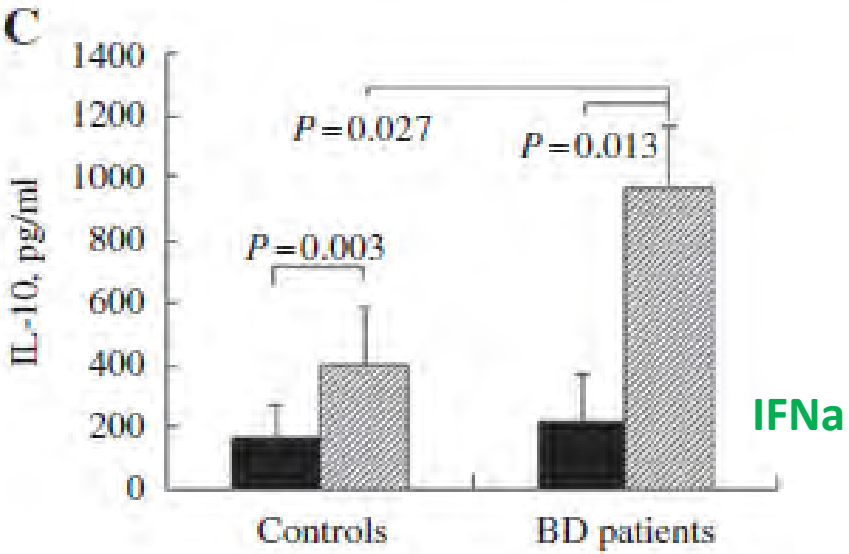




Increased IL-1β secretion with LPS+ATP
Increased P2X7 Rec (ATP Rec) on BD monocytes
TNFα increased P2X7 Rec expression

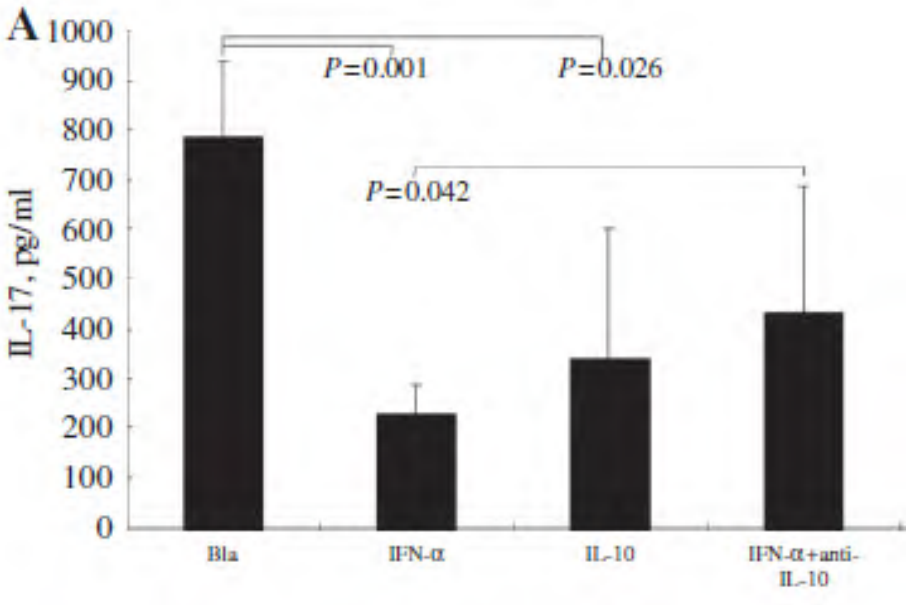
Castrichini , Eur J Immunol 2014

THERAPEUTIC EFFECT OF IFNα in BD IS ONLY IN PART DUE TO IL-10-MEDIATED IL-17 INHIBITION



IFNa

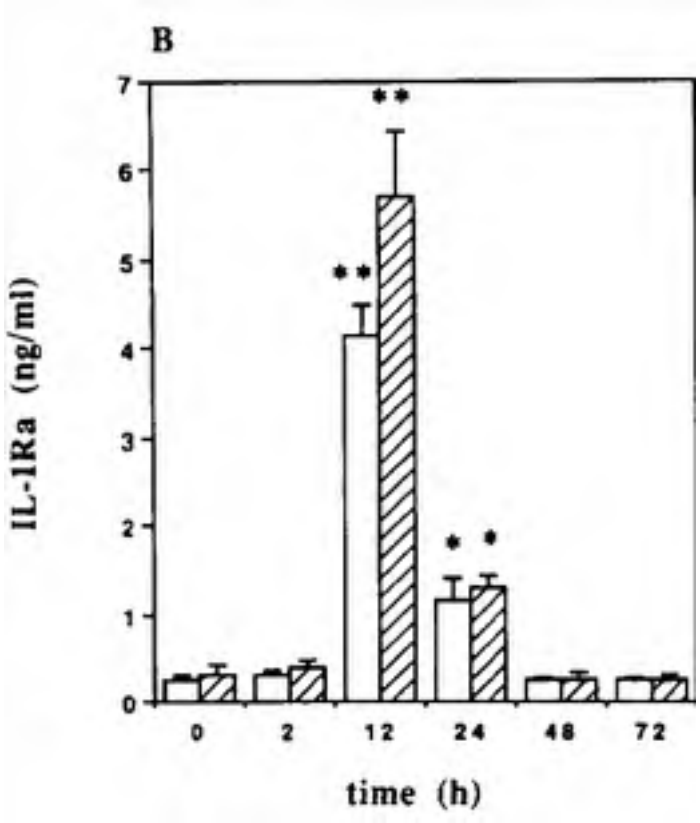
IFNα increases IL-10 production by CD4 T cells in BD



IFNα decreases IL-17 production by CD4T cells via an-IL-10-mediated mechanism. But partially!

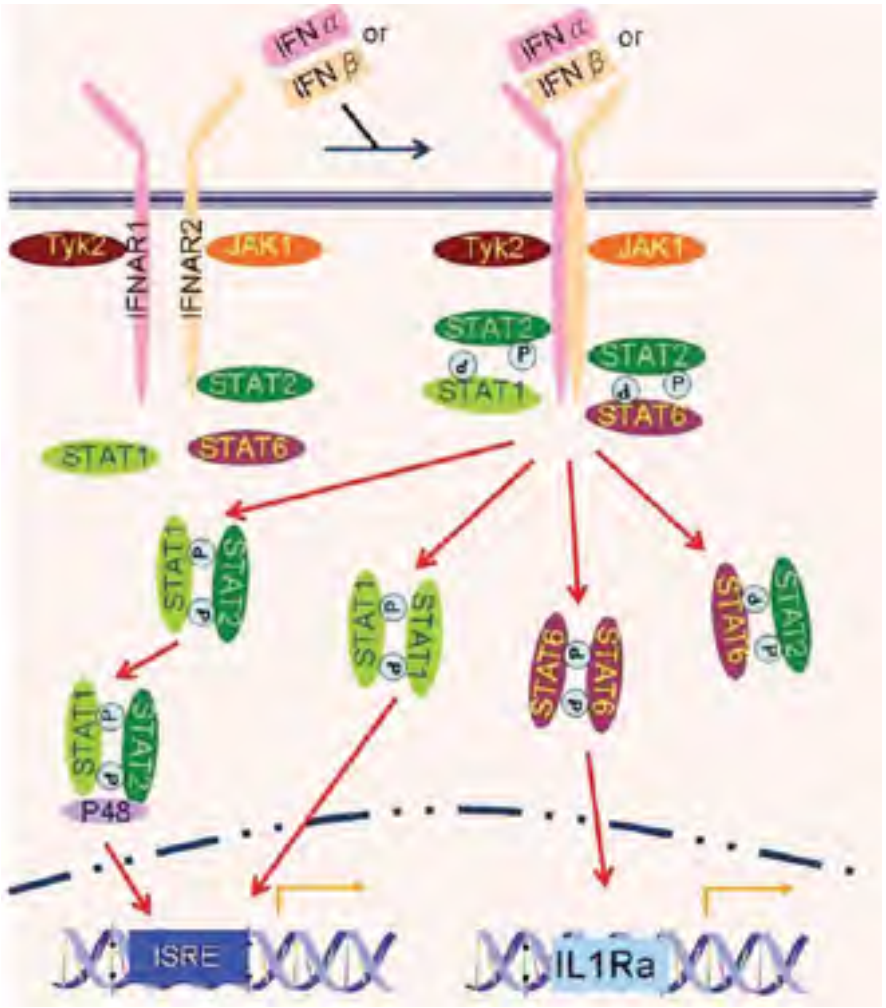
Liu Rheumatology 2011

THERAPEUTIC EFFECT OF INFα in BD
MAY BE DUE TO IL-17 INHIBITION BY IL-1Ra



IFNα treatment in hepatitis C

(Tilg J Immunol 1993)



(Wan J Cell Mol Med 2008)

INCREASED IL-1 PRODUCTION AND IL-1 GENES POLYMORPHISMS

Conflicting results, but some snp of IL-1A:B genes seems associated with BD

- **Association of IL-1A -889 allele and CC genotype/IL-1B+5887T allele and TT genotype with BD** ***(Karanesh Rheumatology 2003, Alayli Clin Rheumatol 2007)***

- **Association with IL-1B +3953T allele and TT genotype with BD, but not IL-1A -889**
(Coskun Exp Dermatol 2005)

- **Association with IL-1B -511TT, but not with IL-1A**
(Oczimen Int J Immunogenetics 2011)

- **No association with IL-1A or IL-1B polymorphisms, only with TNFA -308A/G, IL-10-819C/T**
***(Liang Intl Rev Rheum Dis 2013*: Meta-analysis)**

- **Association of BD with snp: IL-1A -889CT, IL-A -889TT, IL-1B +3962C, T, CC, CT, IL-1RA mspa 1100TT, 1100CT in Turkish population**
***(Zhou Mol Rheumatol 2014*: Meta-analysis)**

EFFICACITE DE l'INHIBITION DE l'IL-1 dans BD

Resistant BD responsive to anakinra , Botsios Ann Intern Med 2008

24 refractory BD patients have been reported to be treated using anti-IL-1 strategy, usually as a 3rd-4th line treatment

- **14 received ANAKINRA. Complete Remission: 9 patients, PR: 3, Inefficacy: 2**
- **3 received Canakinumab. CR: 3**
- **7 received Gevokinumab (XOMA052)**

Cantarini , Autoimmun Rev 2014

PREDISPOSITION GENETIQUE
GENES DU COMPLEXE MAJEUR D'HISTOCOMPATIBILITE

➢ **Association avec HLAB5-B51, en particulier B5101 est la plus reconnue**
(Ohno et al, Arch Ophtalmol 1982/de Menthon A&R 2009)

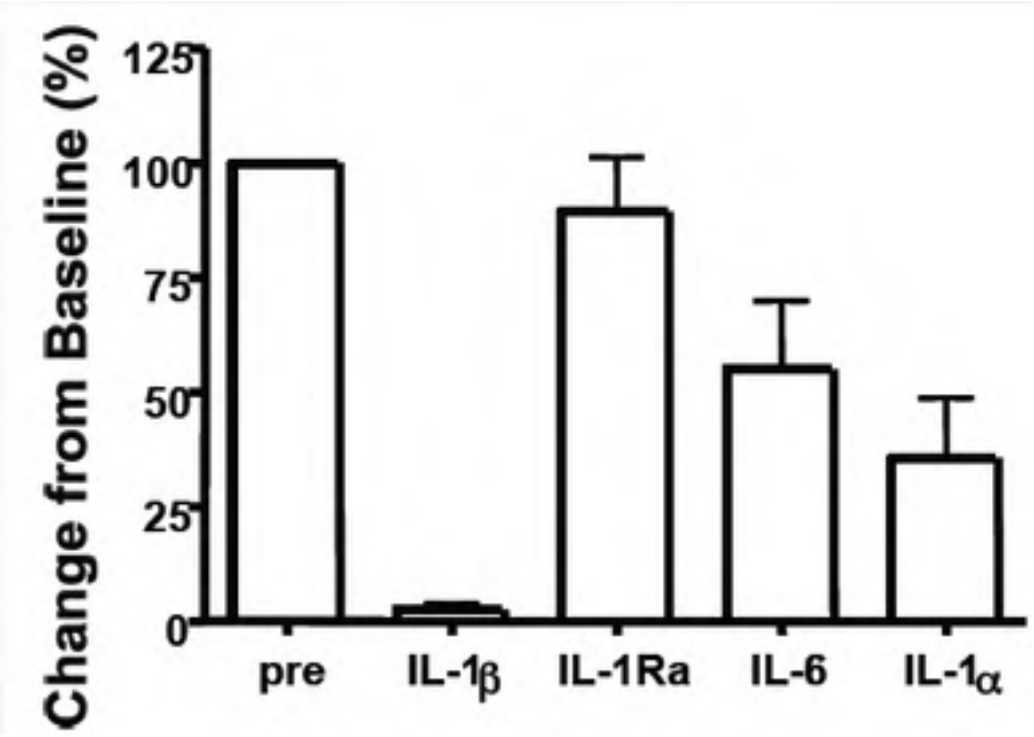
-Liens avec Retinal-S Antigen? Dans la rétine. Perte de tolérance si lésion tissulaire

-1 épitope de R-SAg (342-355) a des homologies de séquence avec HLAB51 et HLAB27

-Les molécules HLA classe I pourraient se comporter en Auto-Ag et être présentées au T CD4 via le HLA II par réaction croisée avec R-SAg après une première uvéite et favoriser une uvéite chronique

-Seuls les patients BD HLA B51+ avec uvéite postérieure ont des réactions immunes vis-à-vis des peptides R-SAg, donc nécessité d'une lésion rétinienne pour qu'apparaisse une réaction croisée vis-à-vis du HLA

➢XOMA 052 in resistant uveitis of BD: open-label pilot study *(Gül Ann Rheum Dis 2012)*



Decreased IL-1α/β, IL-6, but not IL-1Ra production by stimulated PBMC from treated patients