

Fonctions inattendues des HDL : neutralisation de microparticules proinflammatoires

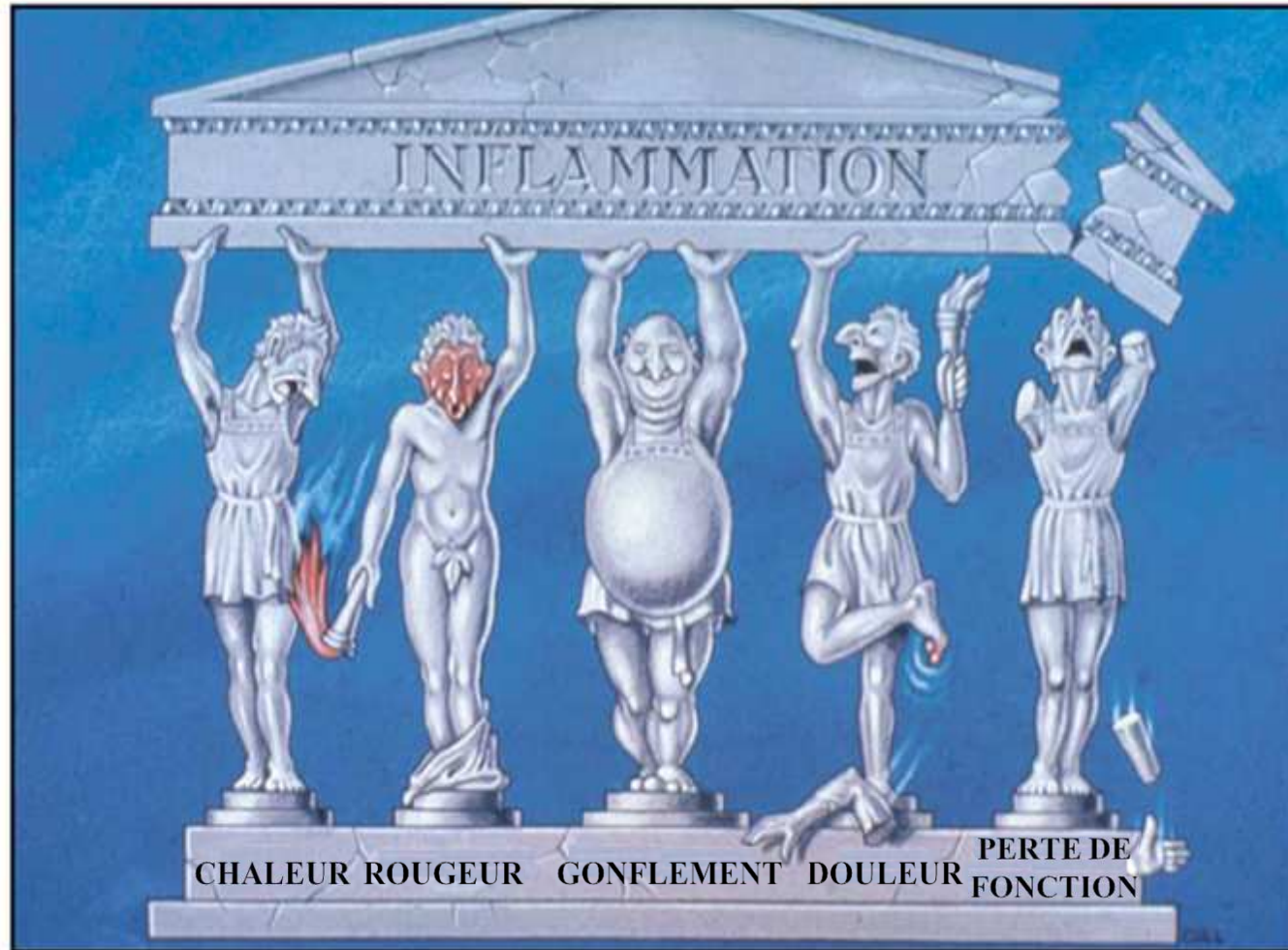
Danielle Burger

JFN, Bruxelles, le 12 décembre 2014

*Fonctions anti-inflammatoires des HDL
dans l'inflammation chronique/stérile*

- Aucun conflit d'intérêt

Signes de l'inflammation



Celsus 1^{er} siècle avant JC

R. Virchow
2^{ème} moitié du XIX siècle

Sclérose en
plaques

Arthrite
rhumatoïde

Diabète de type 1

Athérosclérose

Etc...

Diabète de type 2

Goutte,
Pseudogoutte

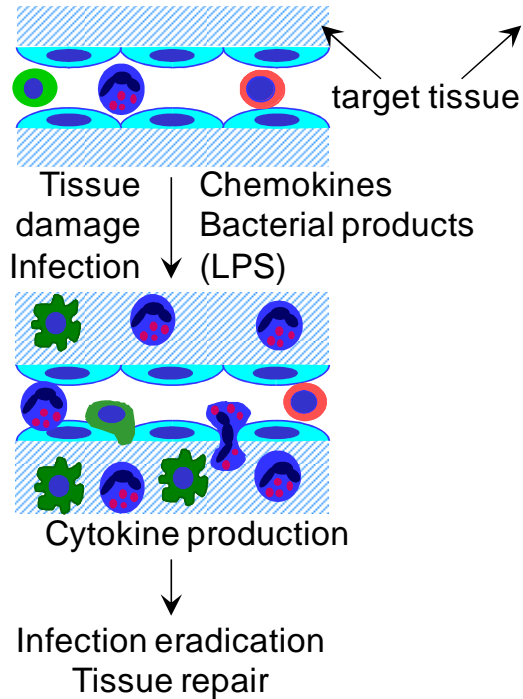
Cancers

Etc...

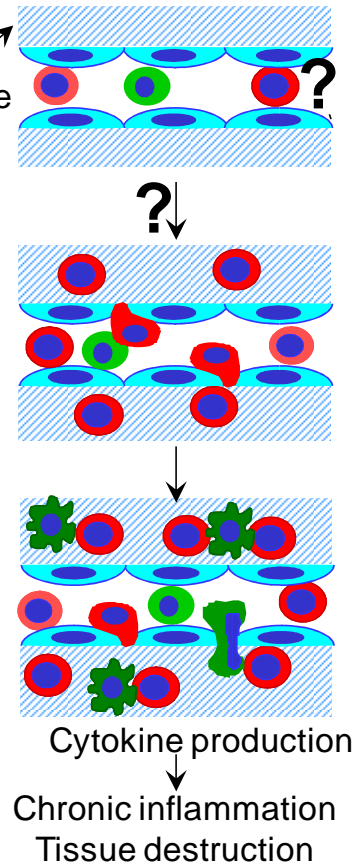
D'après Lawrence et al. Nat. Rev. Immunol. (2002)

Cellules et cytokines dans l'inflammation

ACUTE/INFECTIOUS INFLAMMATION



CHRONIC/STERILE INFLAMMATION



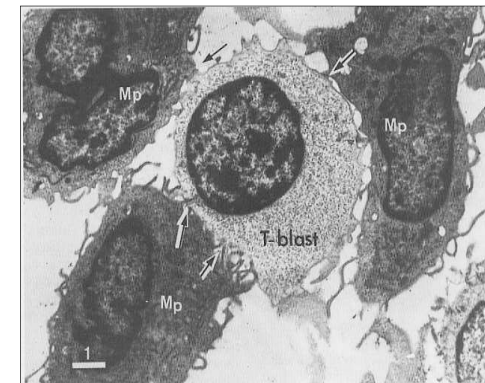
Capillary endothelial cells

neutrophil

T lymphocytes
ns s

Monocyte

macrophage

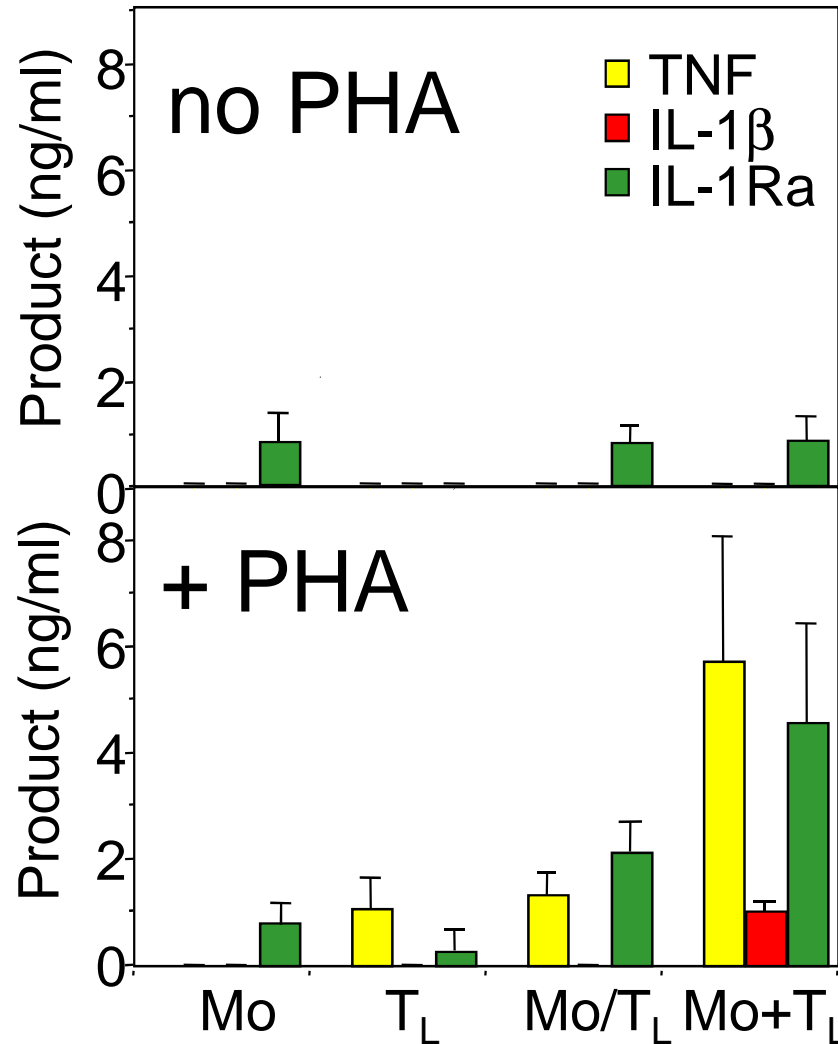
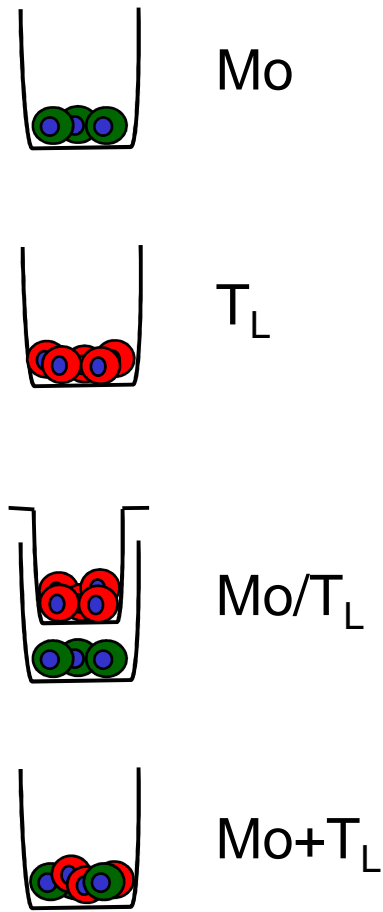


Cellules T et macrophages dans le tissu synovial de PR

Harris E.D., 1997

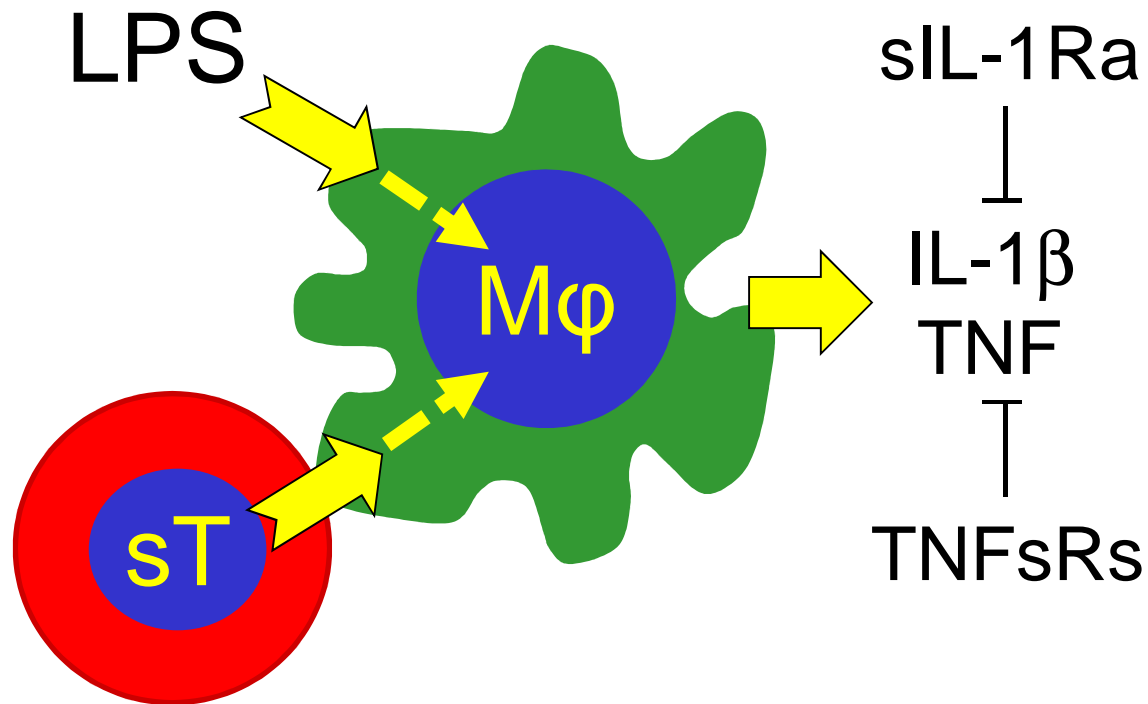
Adapté de Burger, Eur.Cytokine Netw. (2000)

Le contact cellulaire direct avec les lymphocytes T activés est nécessaire à l'induction de la production des cytokines par les monocytes



Induction des cytokines dans l'inflammation

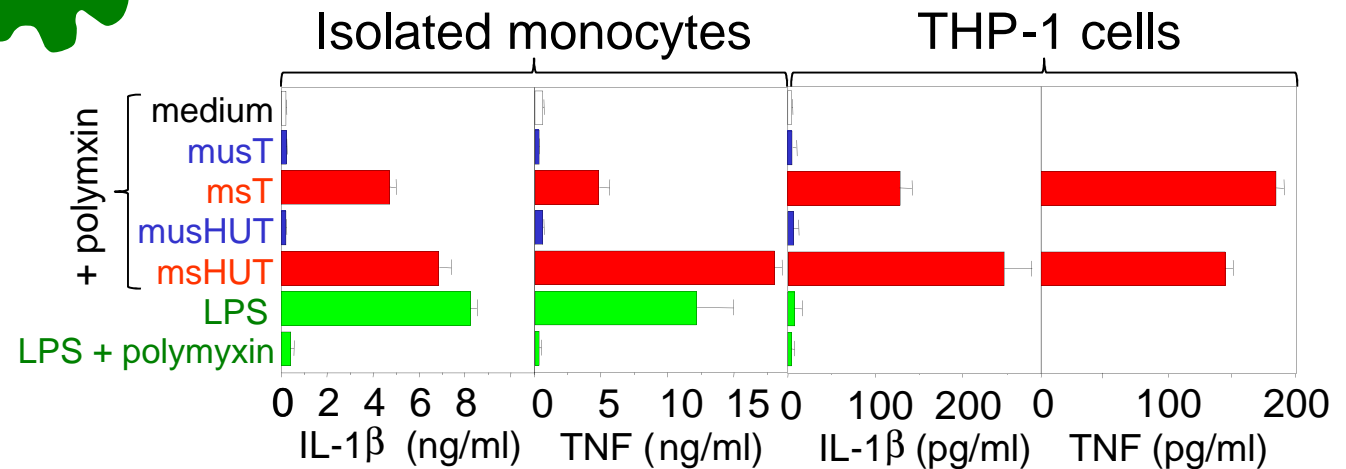
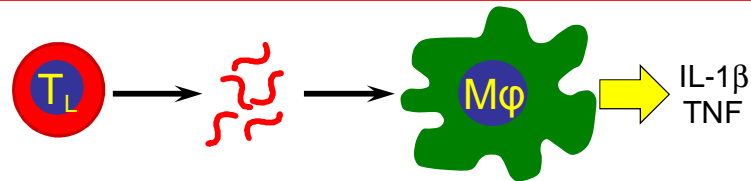
Aigüe/infectieuse



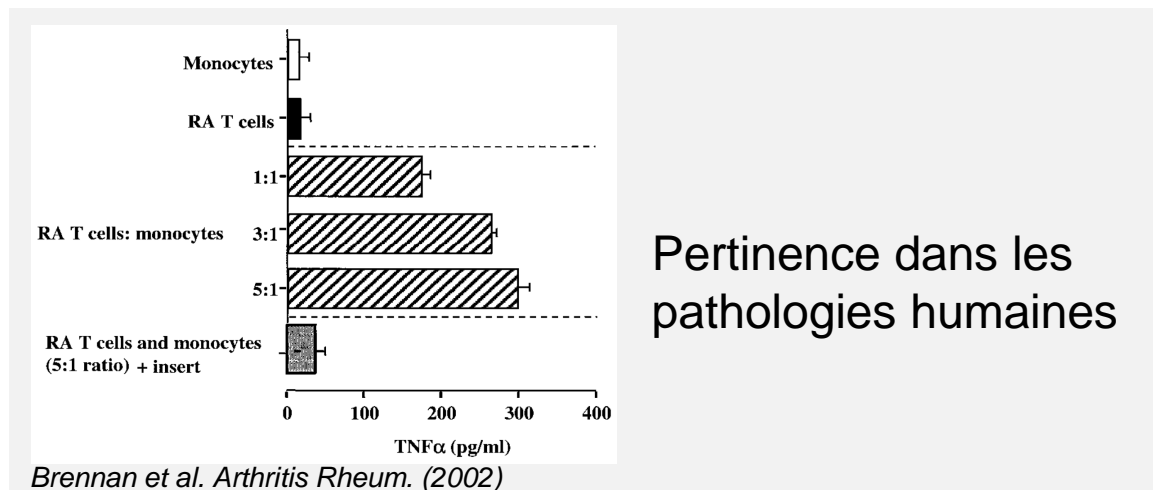
chronique/stérile

Identification de cibles thérapeutiques spécifiques de l'inflammation chronique

Production similaire de cytokines par les monocytes activés par le contact avec des cellules T ou du LPS



Burger Eur.Cytokine Netw. (2000)



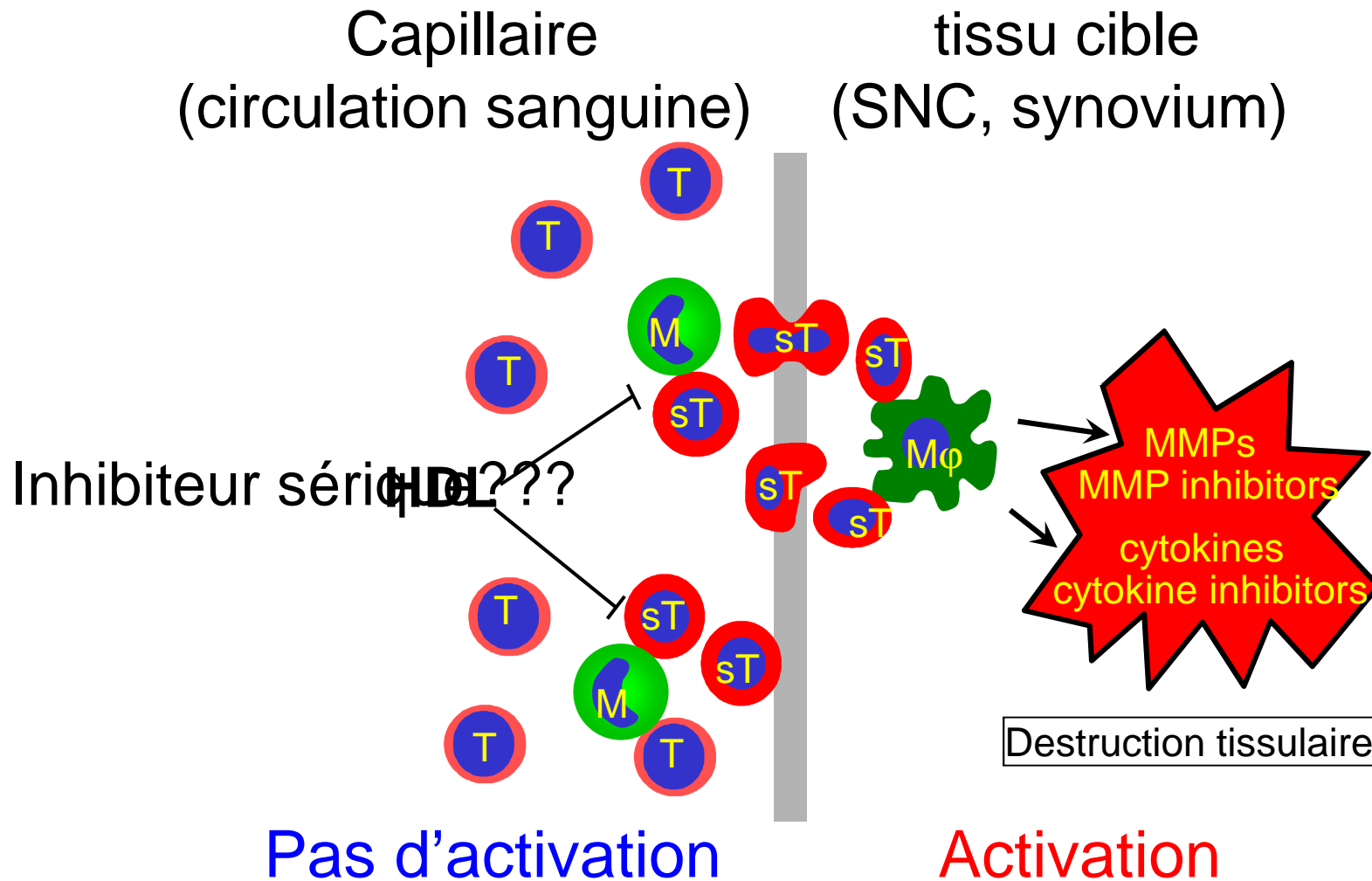
Toute sorte de cellules T induisent l'activation des monocytes et/ou des cellules monocytaires

Stimulus	Type of T cells	Type of monocytes	Products	Refs.
PHA/PMA	PBT _L , HUT-78, Jurkat, synovial and PB T cell clones, CD4 ⁺ , CD8 ⁺ , Th1 and Th2	PB monocytes, THP-1 cells	TNF, IL-1 β , IL-1 α , IL-1Ra, IL-6, IL-8, TNFRs, MMP-1, MMP-9, TIMP-1	Vey et al. 1992, 1996, 1997; Isler et al. 1993; Lacraz et al. 1994; Li et al. 1995.
Anti-CD3	PBT _L , synovial T cells	PB monocytes, THP-1 cells	TNF, IL-10, IL-1 β , MMP-1	Parry et al. 1997; Wagner et al. 1994; Brennan et al. 2002
Anti-CD3	PBT _L	PMA/IFN γ -treated U937 cells	TNF, IL-1 β , IL-12, and IL-4	Chabot et al. 2001.
Anti-CD3 and anti-CD28 or specific Ag	Th1 cell clones	THP-1 cells	IL-1 β , low IL-1Ra	Chizzolini et al. 1997.
Anti-CD3 and anti-CD28 or specific Ag	Th2 cell clones	THP-1 cells	IL-1Ra, low IL-1 β	Chizzolini et al. 1997.
Cytokines ^{a)}	PBT _L , Th1 and Th2 cell clones	PB monocytes	TNF, IL-1 β	McInnes et al. 1997; Sebbag et al. 1997; Avice et al. 1998, 1999; Ribbens et al. 2000; Brennan et al. 2002.
None	RA synovial T cells	PB monocytes	TNF	Brennan et al. 2002.

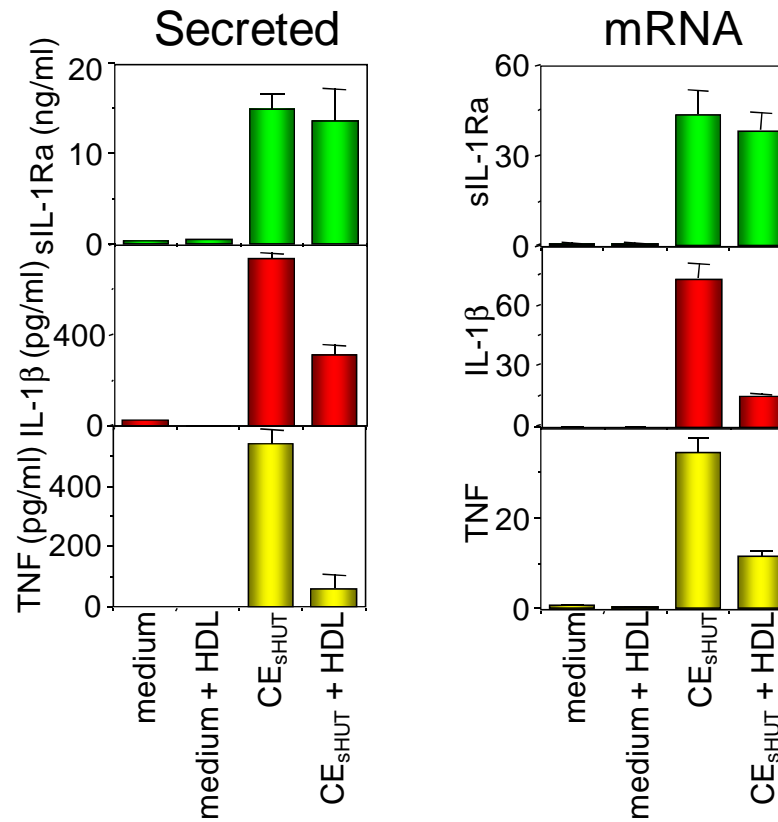
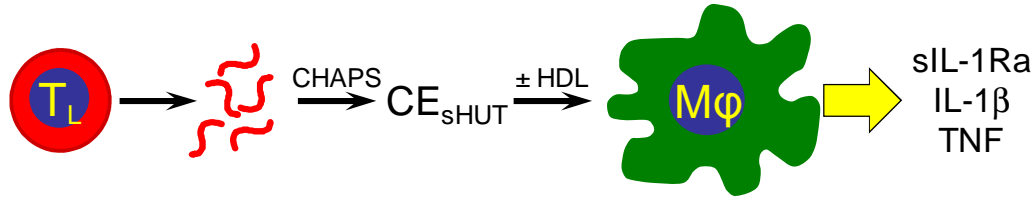
^{a)}IL-2 or IL-15 alone or in combination with IL-6 and TNF

Adapté de Burger, *Eur.Cytokine Netw.* (2000)

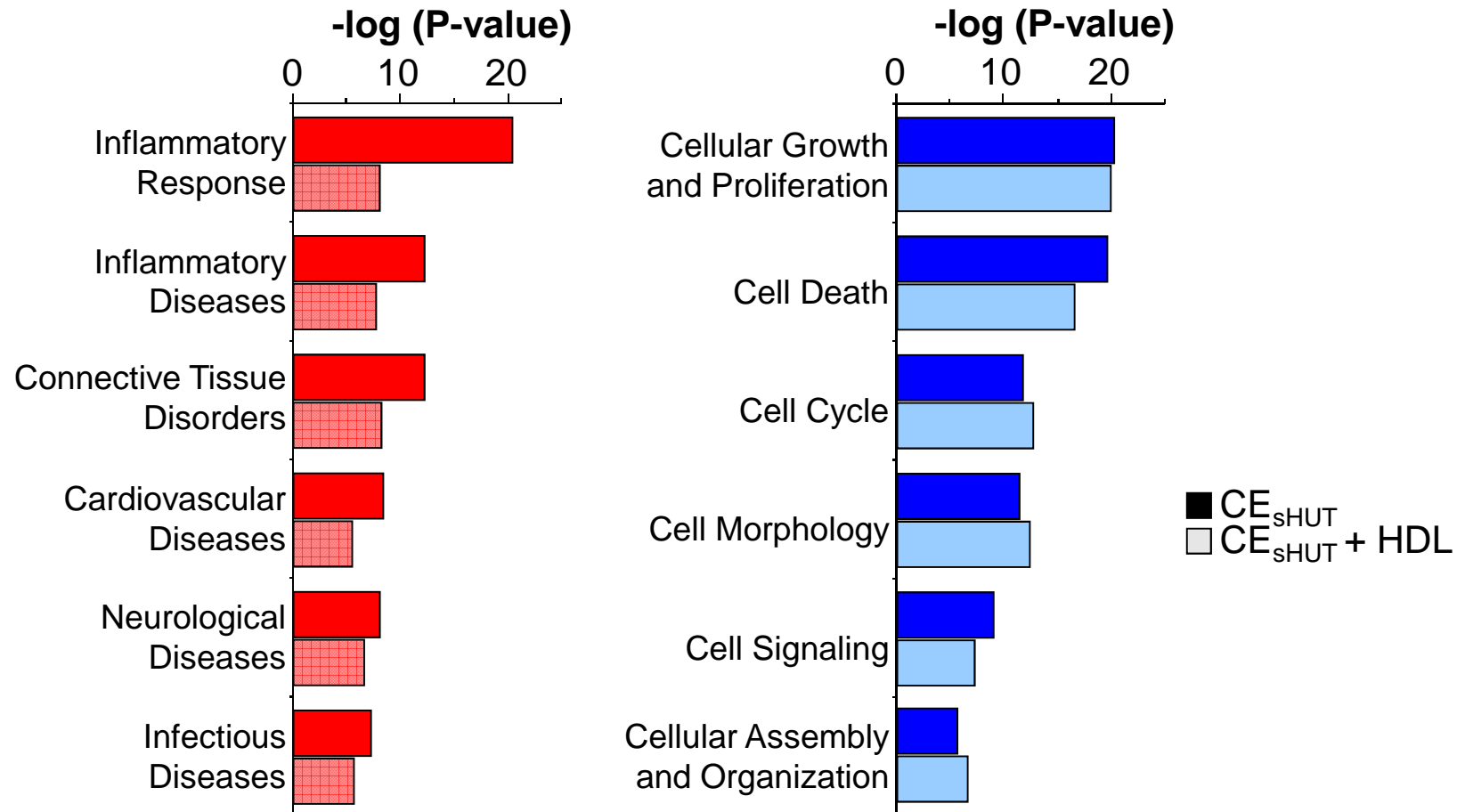
Dans le sang les monocytes ne sont pas activés par le contact avec les lymphocytes T autoreactifs



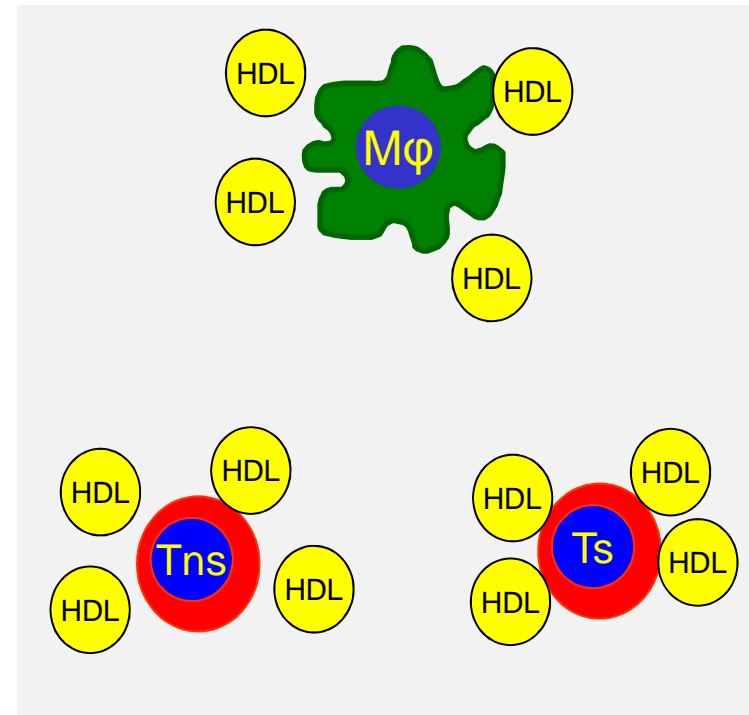
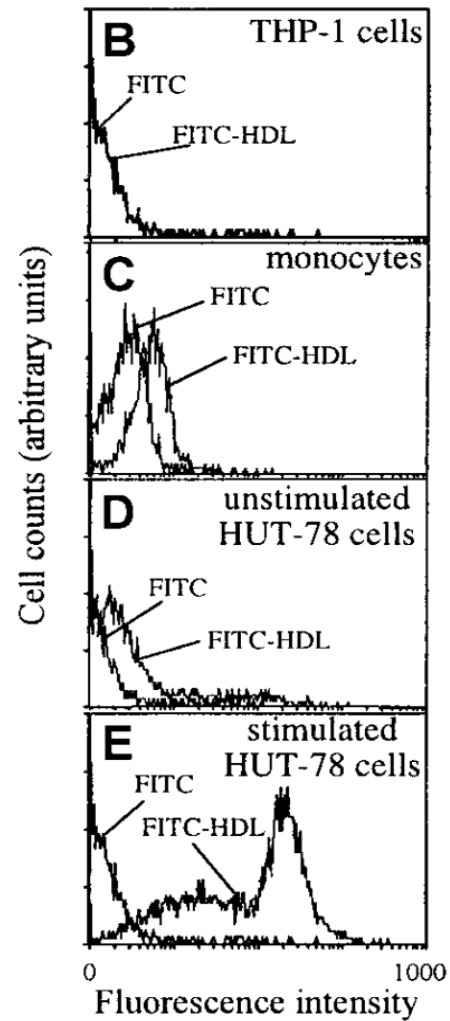
Les HDL n'inhibent que les cytokines pro-inflammatoires



Les HDL inhibent principalement l'expression de gènes impliqués dans l'inflammation



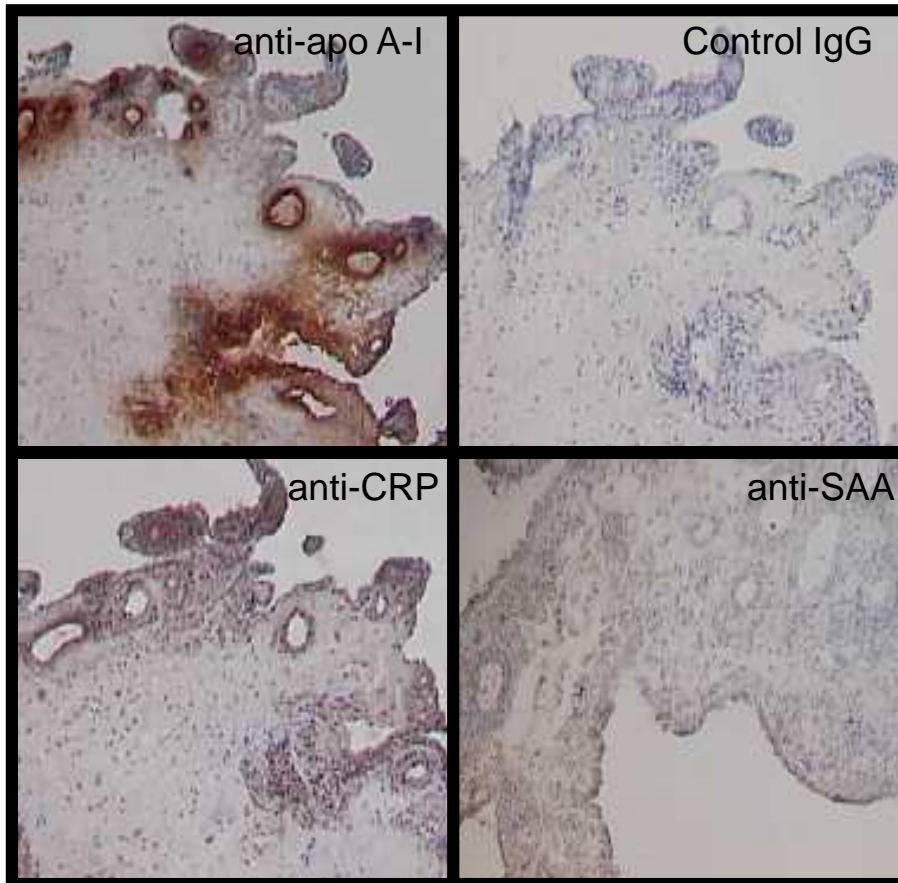
Les HDL se lient préférentiellement aux cellules T stimulées



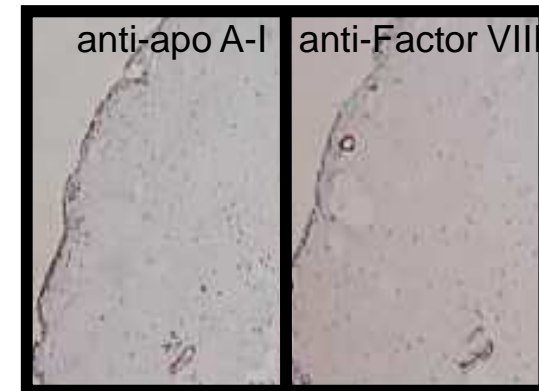
Hyka et al. Blood (2001)

L'Apo A-I infiltre la synoviale inflammatoire dans les régions périvasculaires

PR active



Synoviale normale

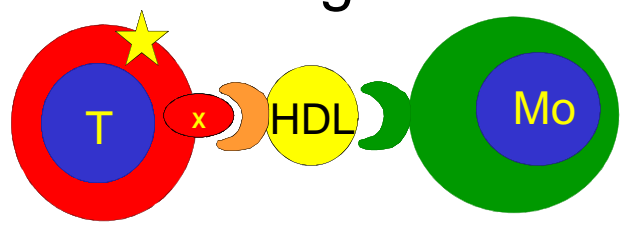


PR en remission



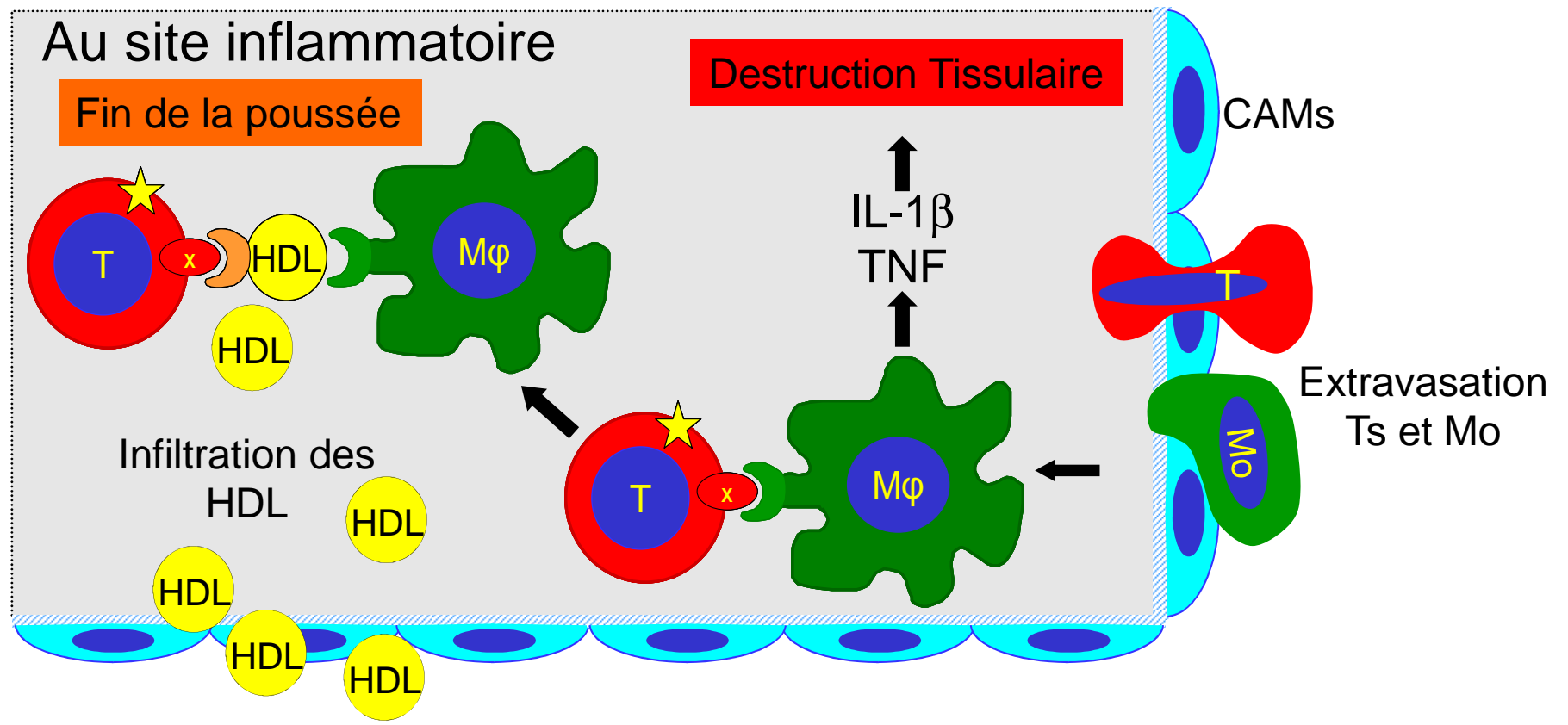
Un rôle pour les HDL dans les maladies inflammatoires de type poussée-remission?

Dans le sang



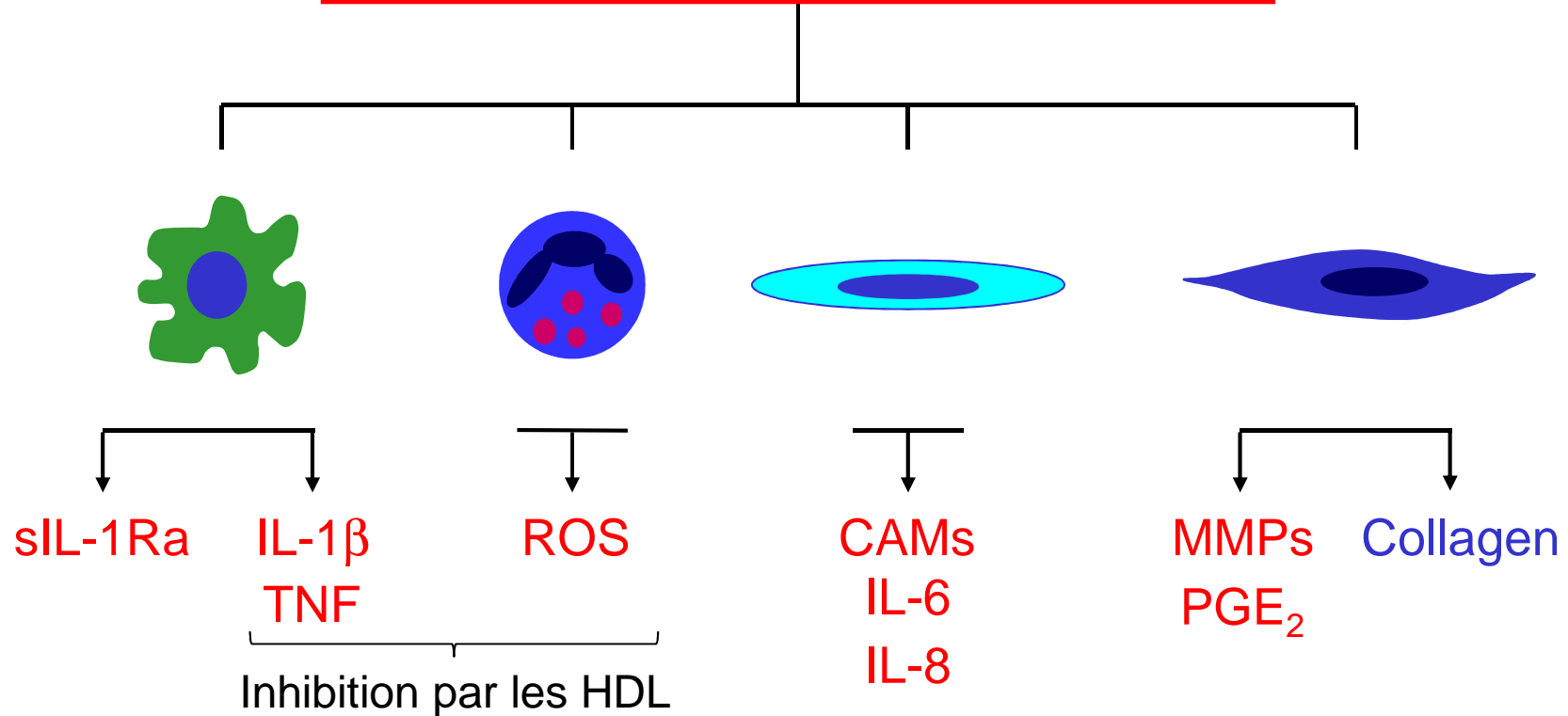
Au site inflammatoire

Fin de la poussée

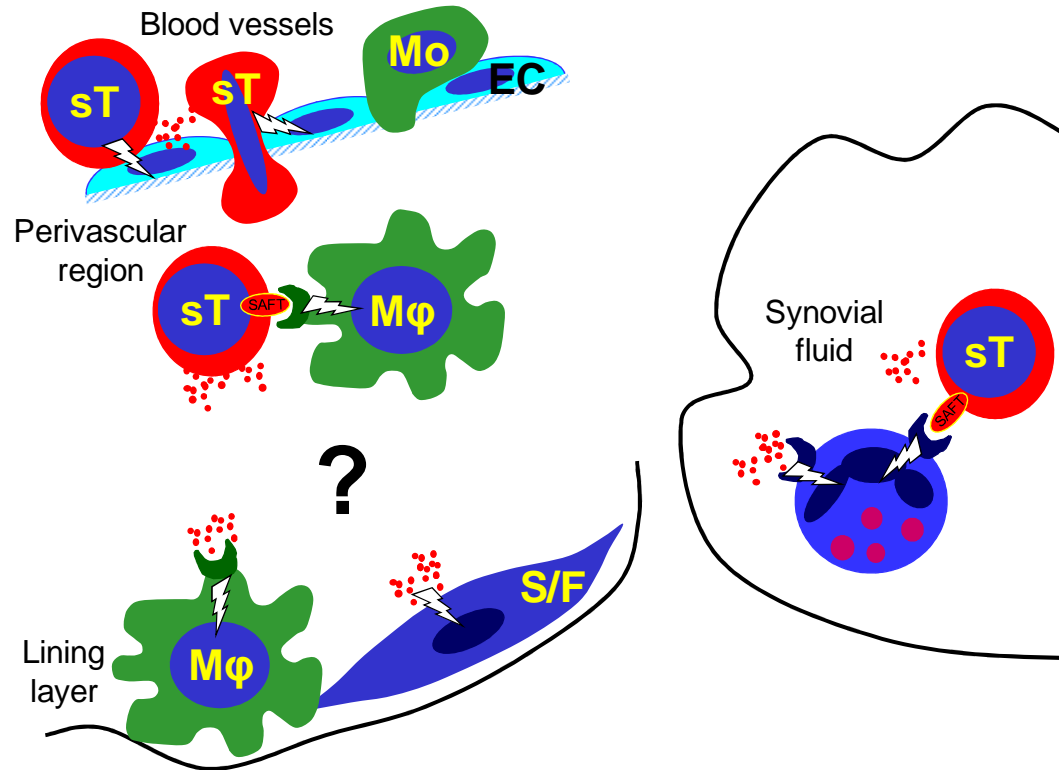


Les cellules T stimulées ont des effets différents selon la cellule qu'elles contactent

Contact cellulaire avec des cellules T



Evénements inflammatoires dépendant du contact avec les cellules T

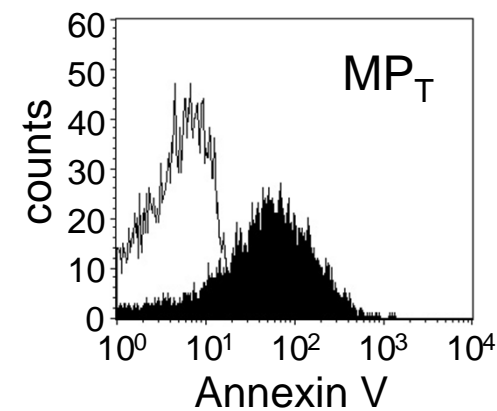
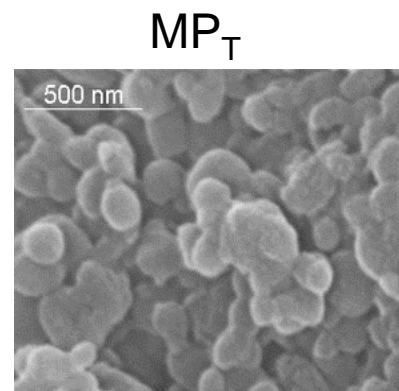
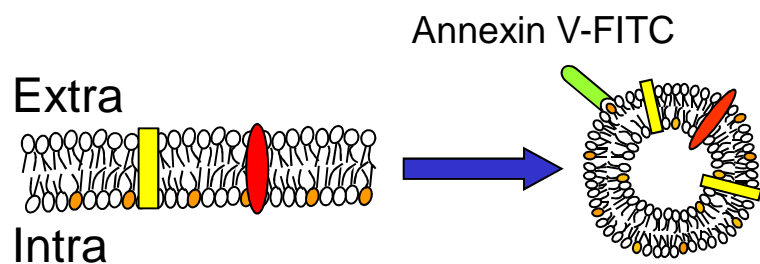
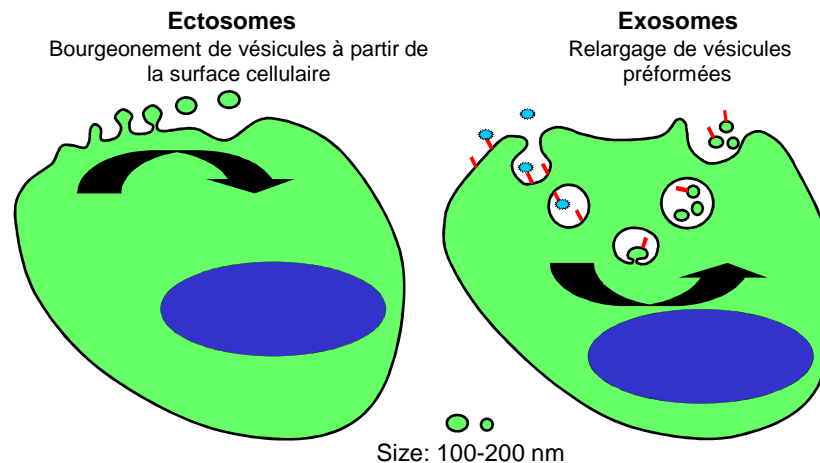
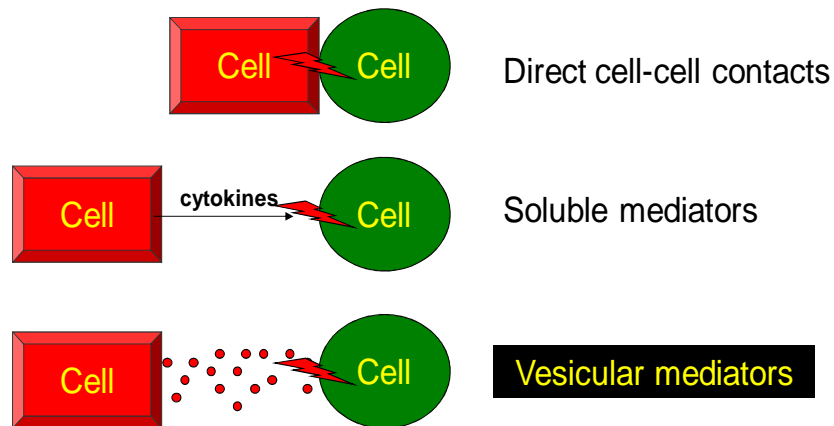


Adapted from Burger et al. *Contemporary Targeted Therapies in Rheumatology* (2007)

RA pat.	cells/ μ l	Cell type (%)			MP (μ g prot/ml)	CD expression by MP linked to beads					
		N	M	L		CD45	CD11b	CD66b	CD14	CD4	CD8
1	2'200	22	67	11	1.8	83.94	50.58	3.46	45.5	3.57	3.84
2	2'900	47	34	19	1.3	86.31	47.6	14.73	5.35	2.84	3.61

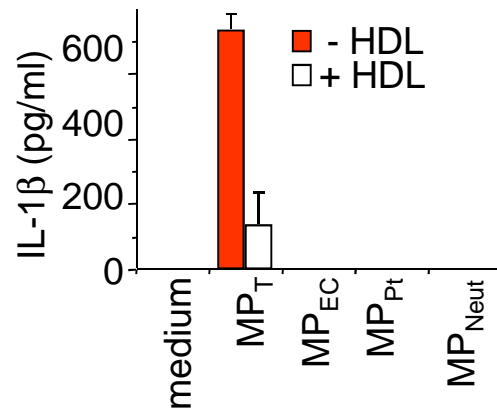
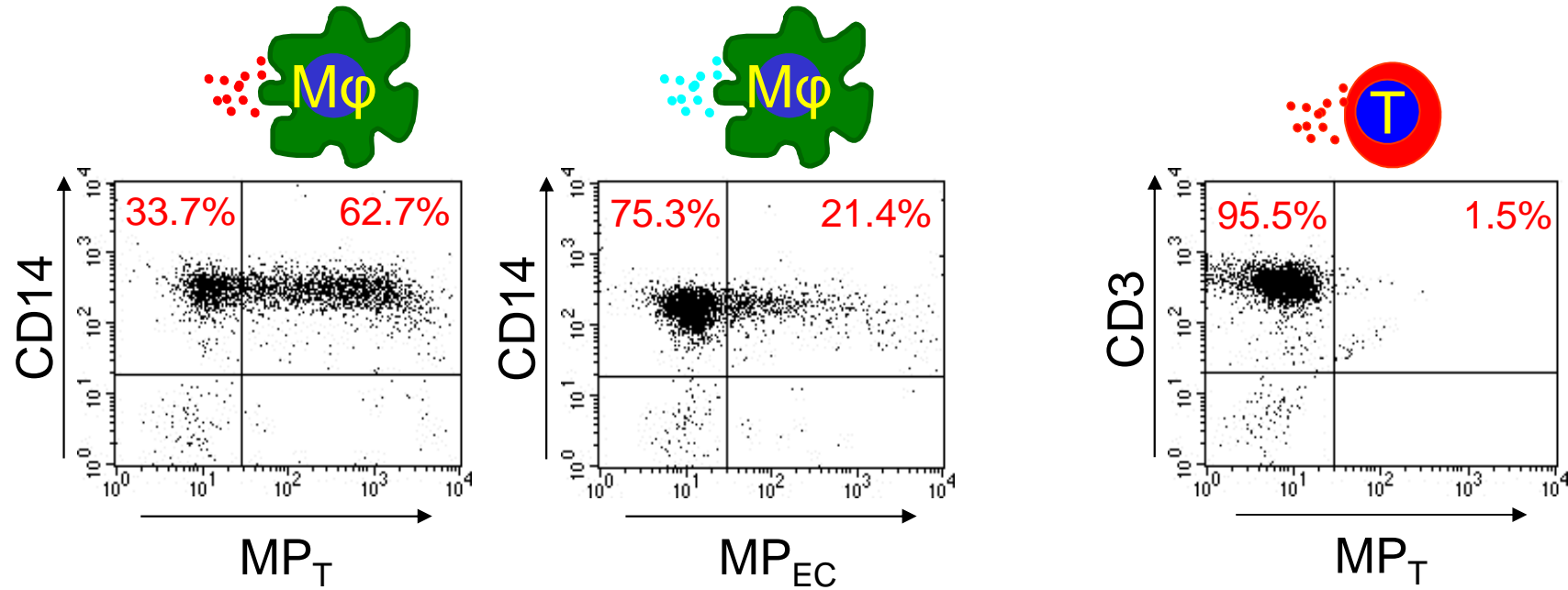
Scanu and Burger. Unpublished

Communication intercellulaire



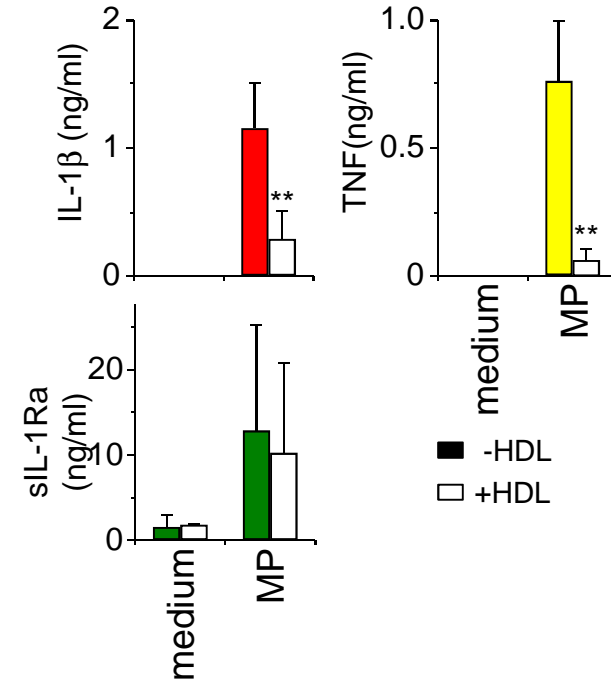
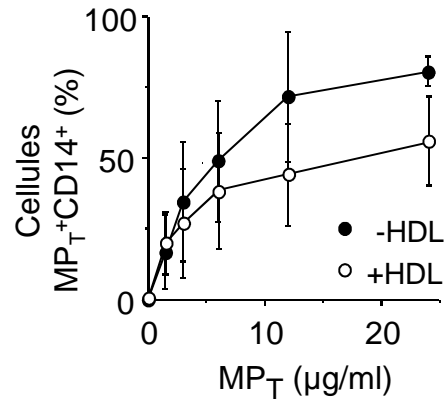
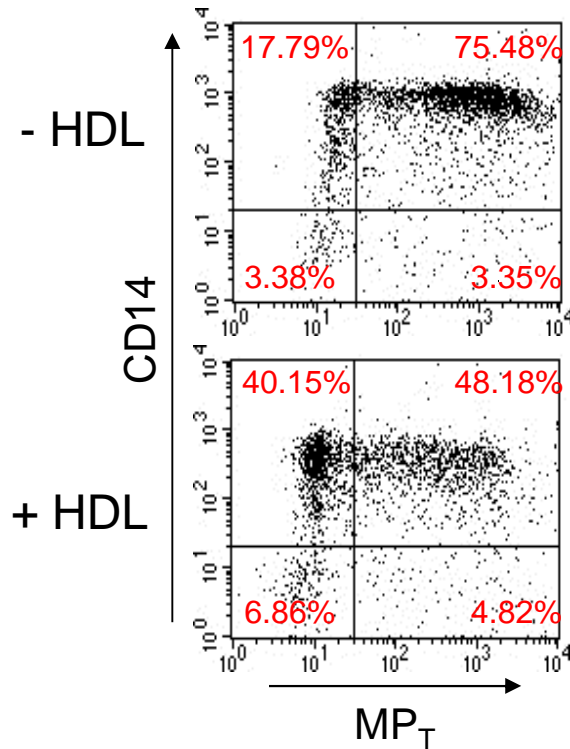
Carpintero et al. PLoS ONE (2010)

Les MP_T se lient aux monocytes et les activent spécifiquement

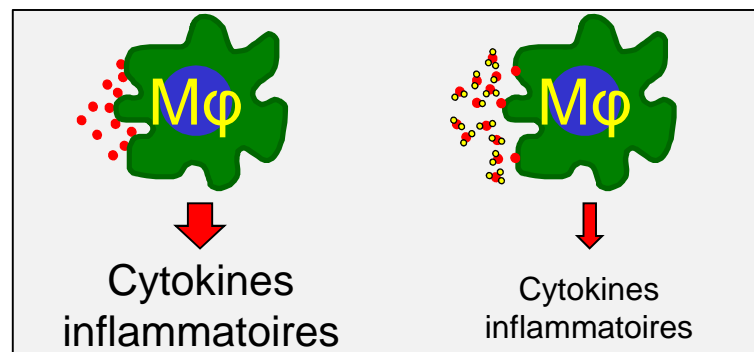


Carpintero et al. PLoS ONE (2010)

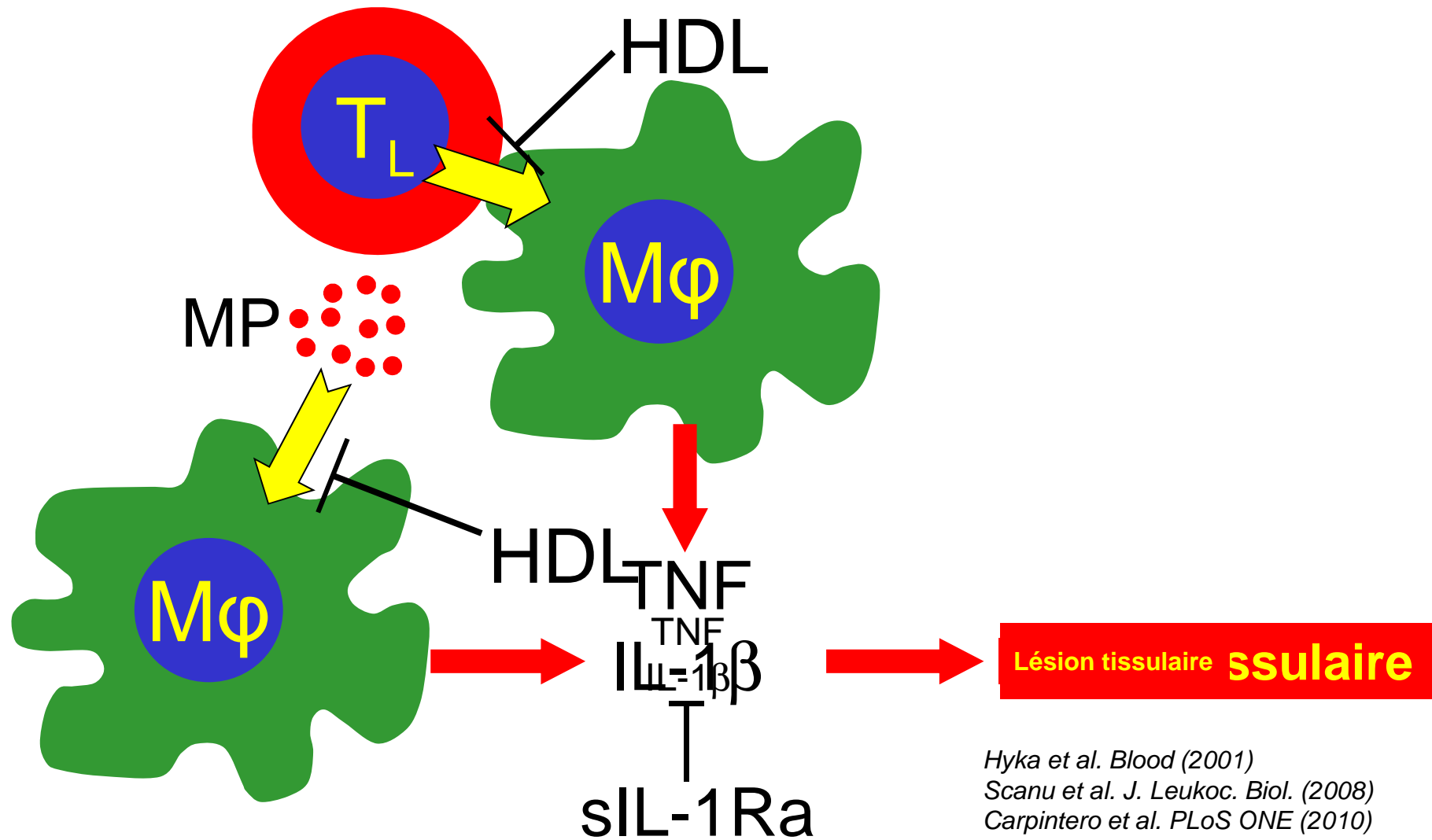
Les HDL inhibent la liaison des MP_T aux monocytes humains et la production de cytokines pro-inflammatoires



Carpintero et al. PLoS One (2010)

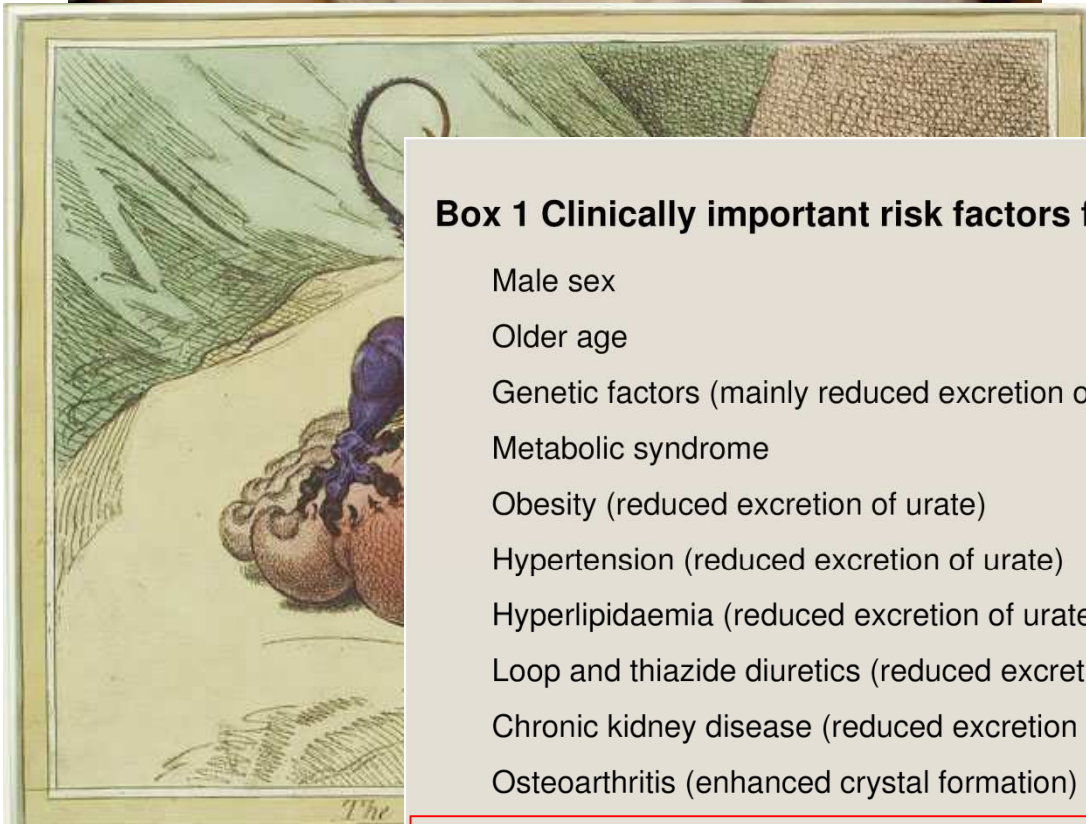


Effets des HDL dans les maladies inflammatoires chroniques d'étiologie autoimmune



Hyka et al. Blood (2001)
Scanu et al. J. Leukoc. Biol. (2008)
Carpintero et al. PLoS ONE (2010)

Goutte

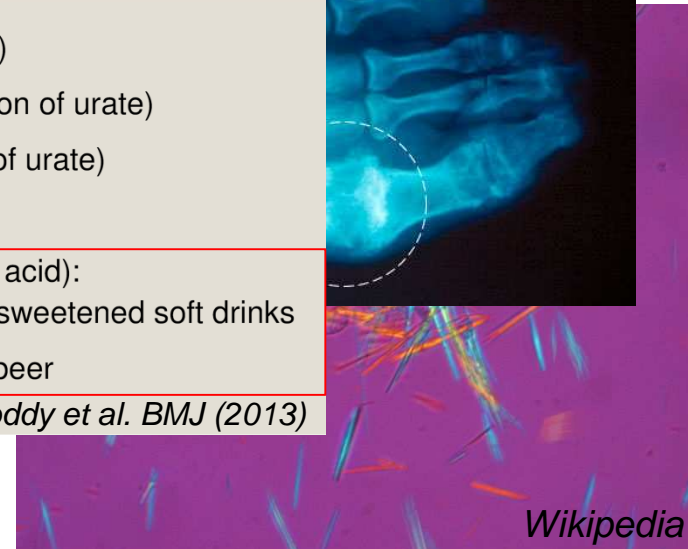
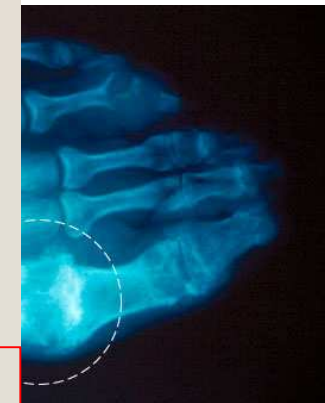


The Gout, cartoon by James Gillray

Box 1 Clinically important risk factors for gout

- Male sex
- Older age
- Genetic factors (mainly reduced excretion of urate)
- Metabolic syndrome
- Obesity (reduced excretion of urate)
- Hypertension (reduced excretion of urate)
- Hyperlipidaemia (reduced excretion of urate)
- Loop and thiazide diuretics (reduced excretion of urate)
- Chronic kidney disease (reduced excretion of urate)
- Osteoarthritis (enhanced crystal formation)
- Dietary factors (increased production of uric acid):
 - Excess purine-rich foods, fructose, sugar sweetened soft drinks
 - Excess alcohol consumption, particularly beer

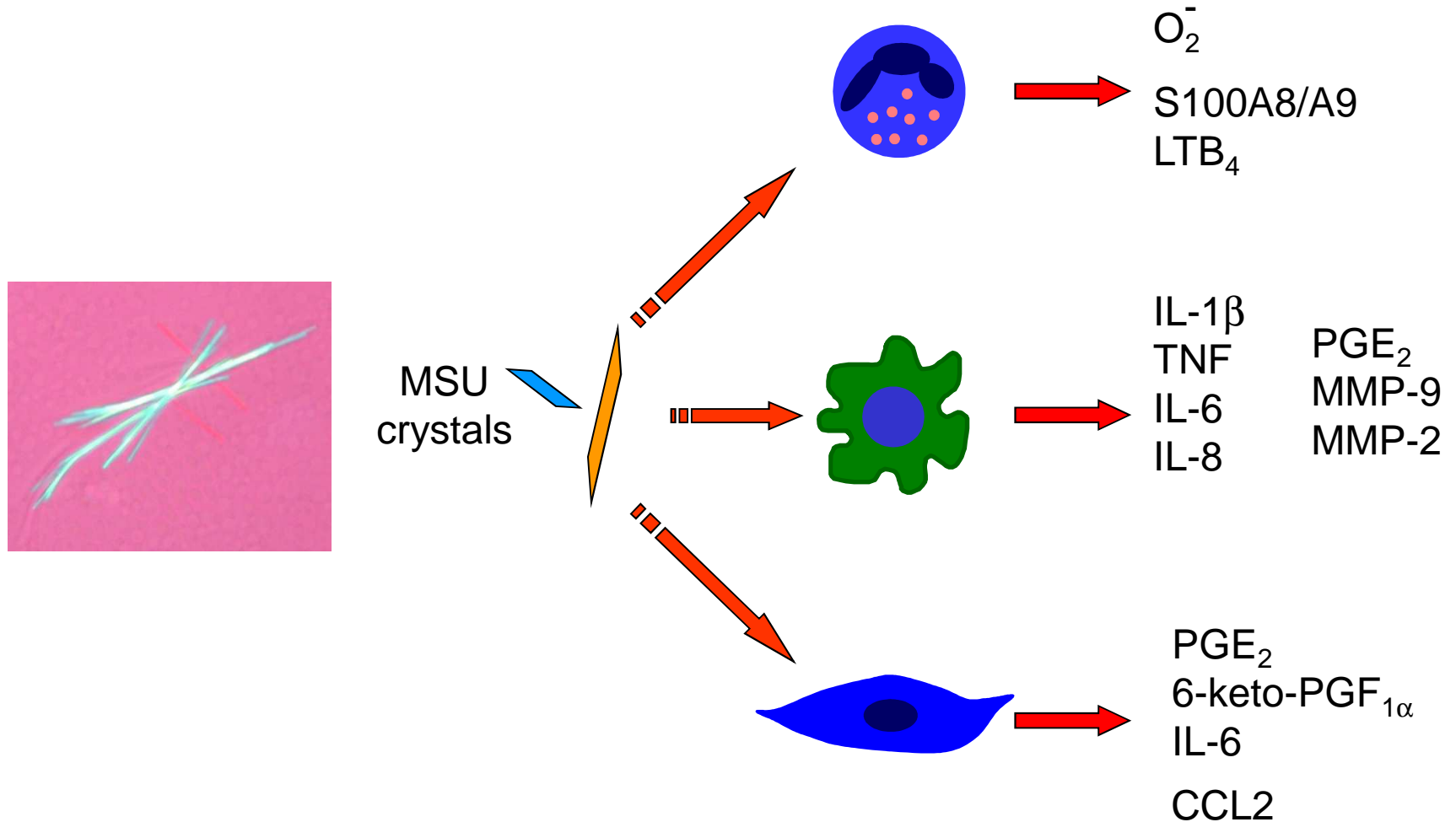
Roddy et al. BMJ (2013)



Wikipedia

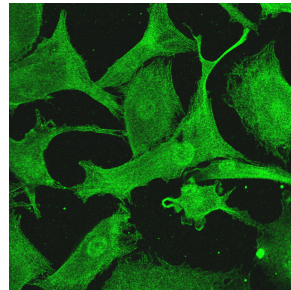
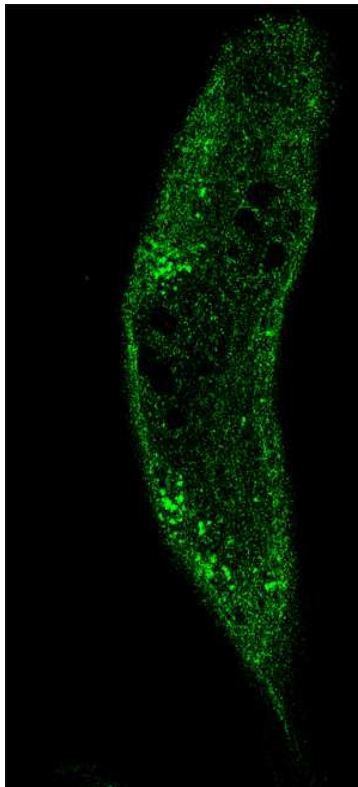
La goutte peut être traitée par des anti-IL-1 β

Inflammation aigüe induite par les cristaux MSU

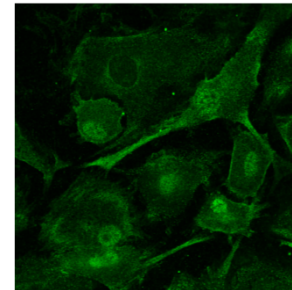


Les HDL inhibent la production de CCL2 par les FLS activés

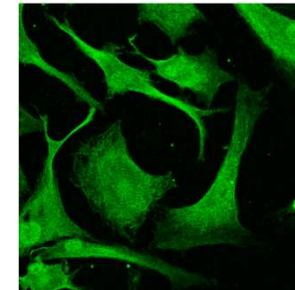
CCL2 est contenu dans des granules intracellulaires



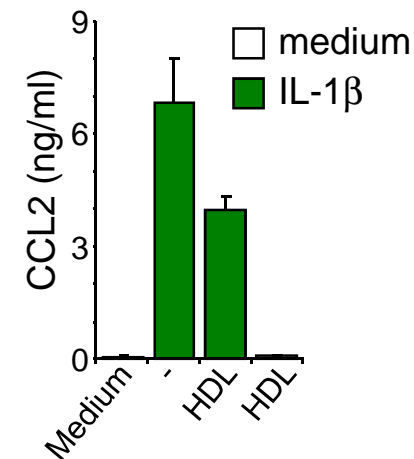
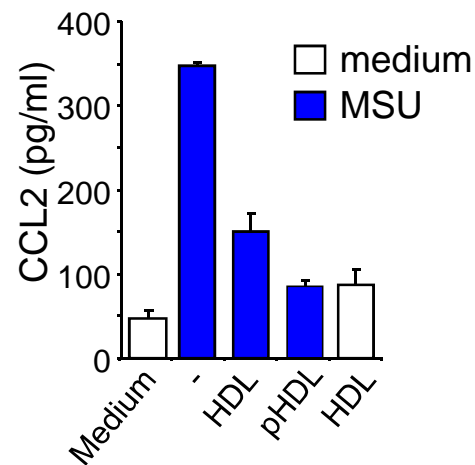
Resting FLS



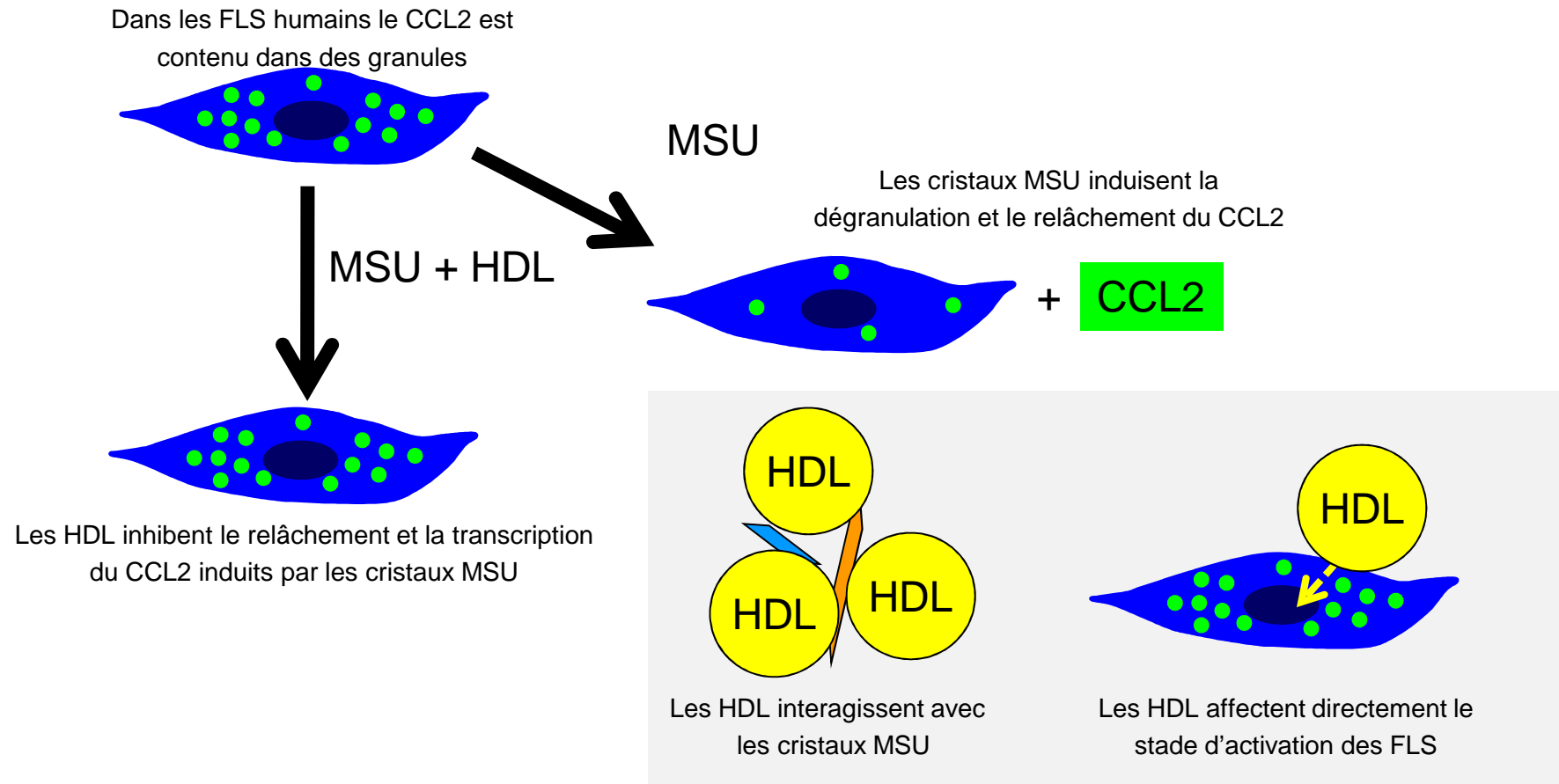
MSU crystals



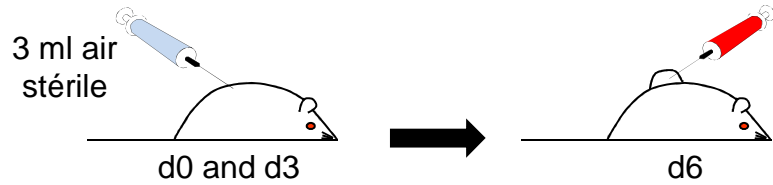
MSU crystals + HDL



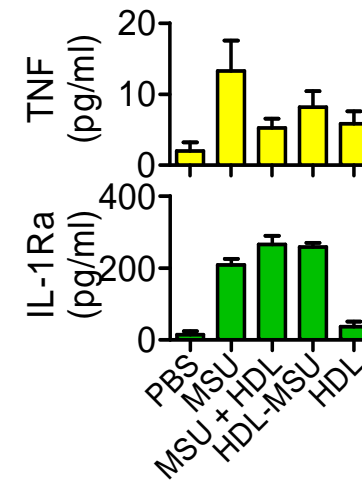
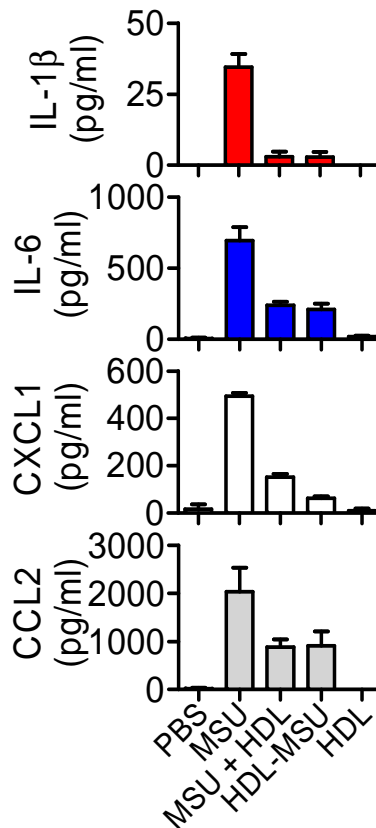
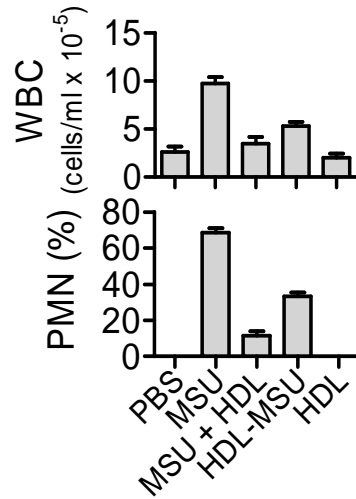
Les HDL inhibent la production de CCL2 en complexant les cristaux MSU et diminuent l'état d'activation des FLS



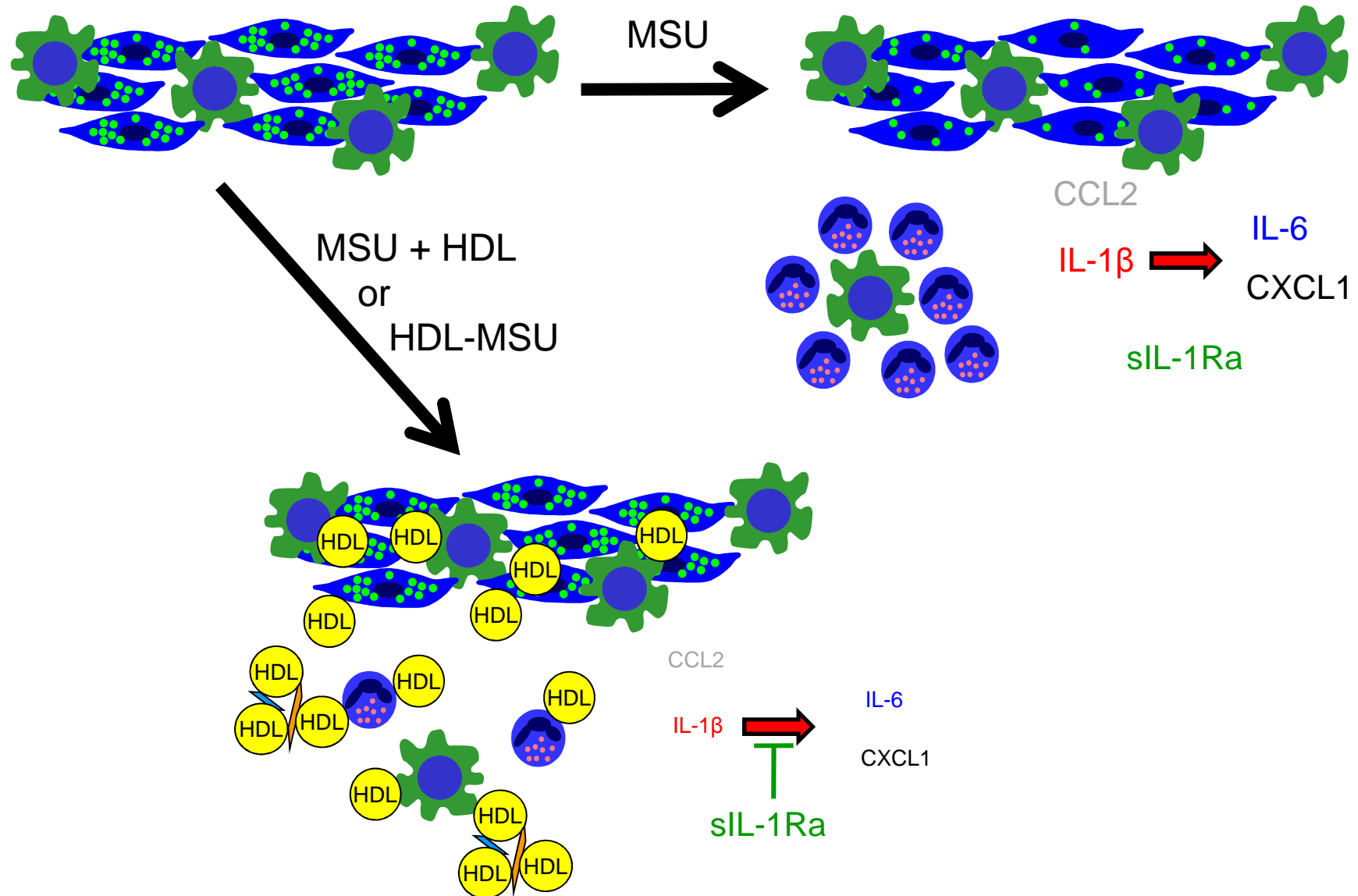
Les HDL modulent l'infiltration cellulaire et la production de cytokines induites par les cristaux de MSU *in vivo*



- MSU dans 1 ml of PBS ± HDL
- MSU prétraités avec HDL dans 1 ml PBS (HDL-MSU)



Les HDL modulent l'inflammation dans un modèle animal de goutte



Conclusions : les HDL ont des fonctions anti-inflammatoires dans les maladies inflammatoires chroniques

Maladies dues aux cellules T

- Les HDL interagissent avec le facteur activateur des cellules T sur les cellules T elles-mêmes et sur leur microparticules, et inhibent la production de cytokines et autres facteurs pro-inflammatoires

Goutte

- Les HDL exercent une activité anti-inflammatoire en interagissant avec les cristaux MSU.
- Les HDL représentent un important modulateur de l'inflammation goutteuse en agissant à la fois sur les cellules résidentes du tissu et sur les cellules infiltrantes.

Collaborators

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