



Cellules stromales mésenchymateuses et sepsis grave

Juliette Peltzer

Institut de Recherche Biomédicale des Armées (IRBA)
Centre de Transfusion Sanguine des Armées (CTSA)-Hôpital Percy

Le Sepsis

Des définitions techniques

- Sepsis: présence (probable ou documentée) d'une infection + manifestations systémiques de l'infection
- Sepsis sévère: sepsis + dysfonction d'organe induite par sepsis:
≈19 millions de cas estimés par an
- Choc septique: sepsis sévère + hypotension résistante à un remplissage vasculaire

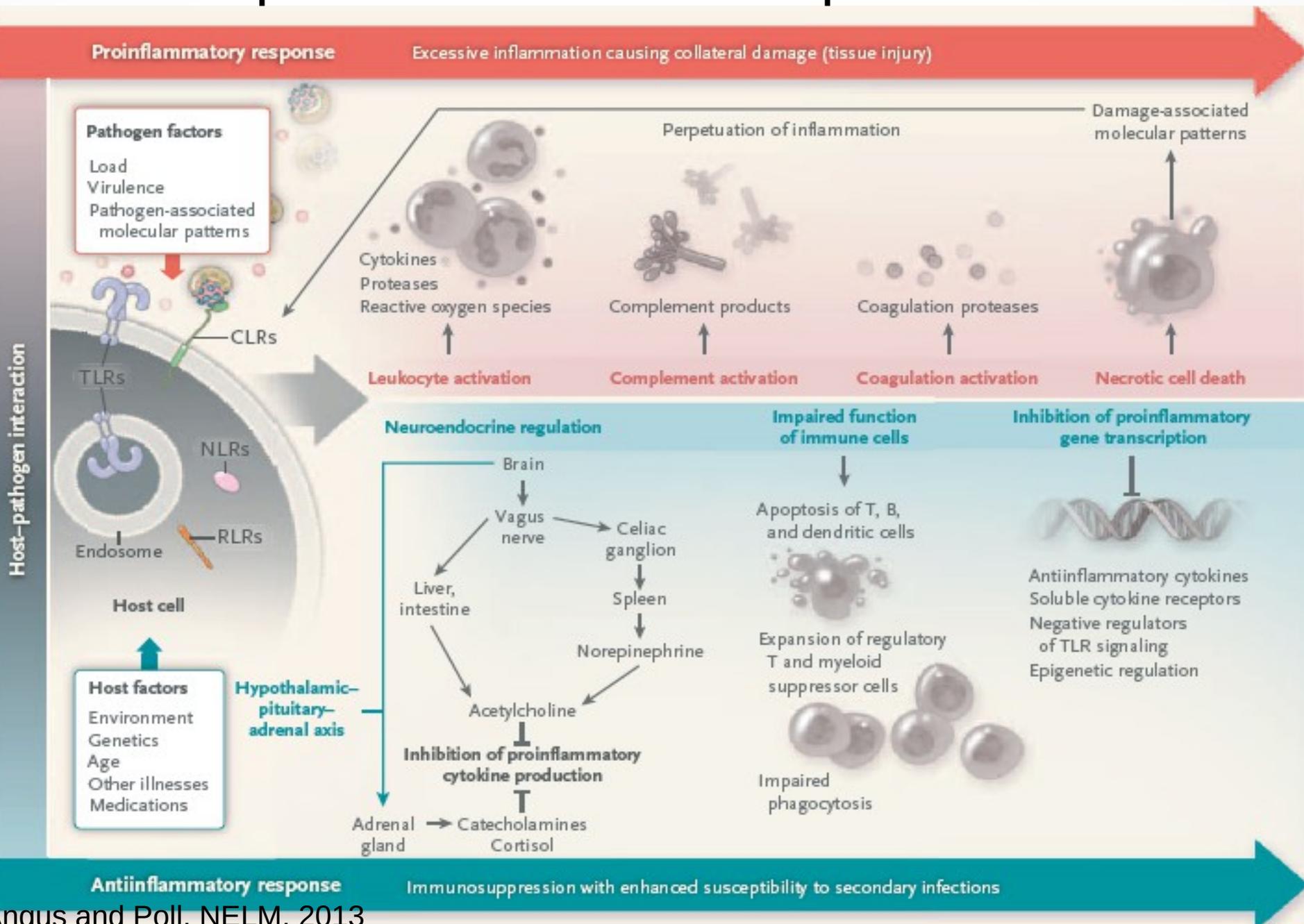
Vision actuelle

Condition potentiellement létale dans laquelle la réponse de l'organisme à un pathogène lèse ses propres tissus et organes

→ Axes de recherche et de thérapie:

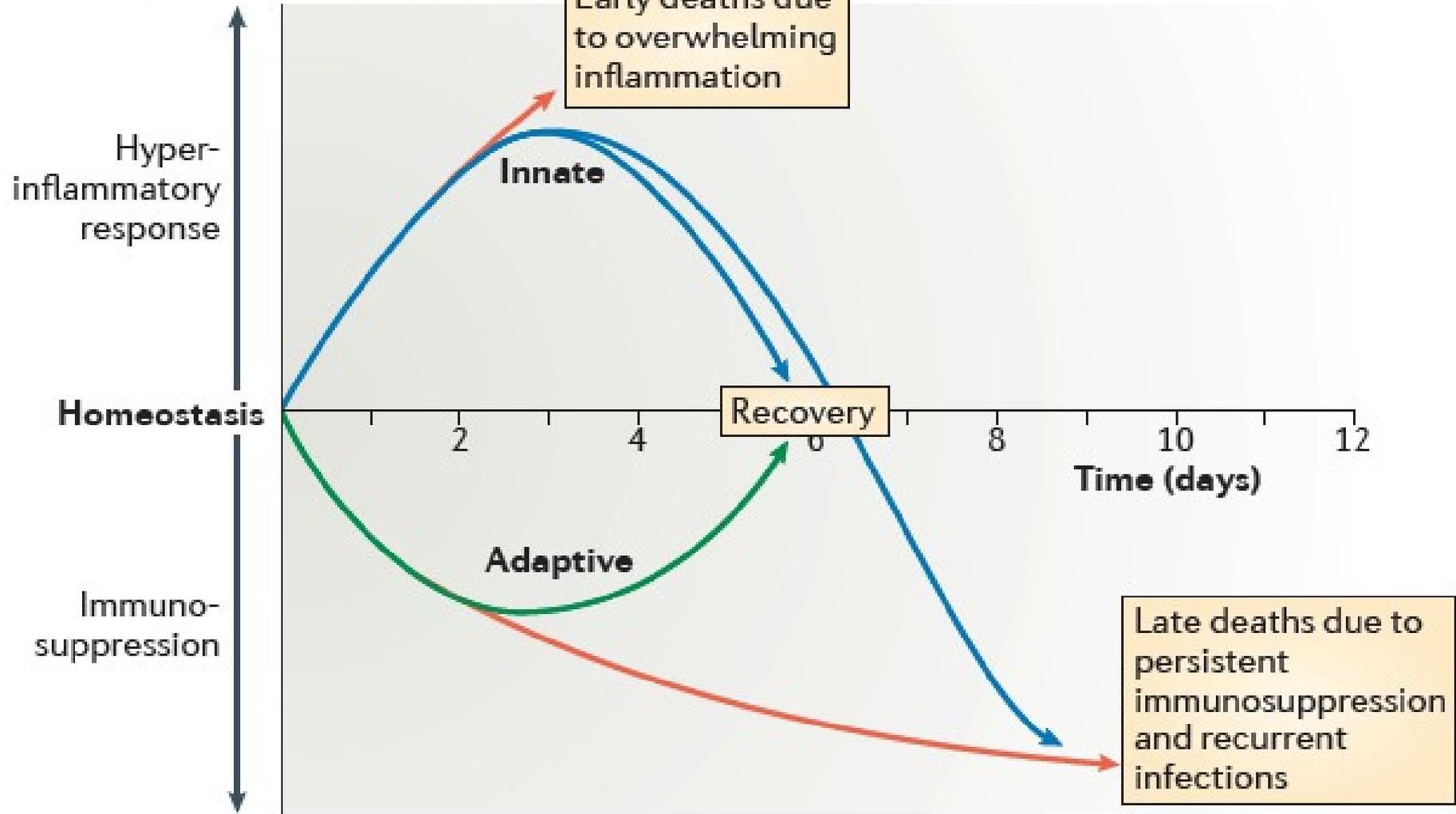
- traitements anti-infectieux
- Contrôle de la réaction de l'organisme

Réponse de l'hôte au sepsis sévère

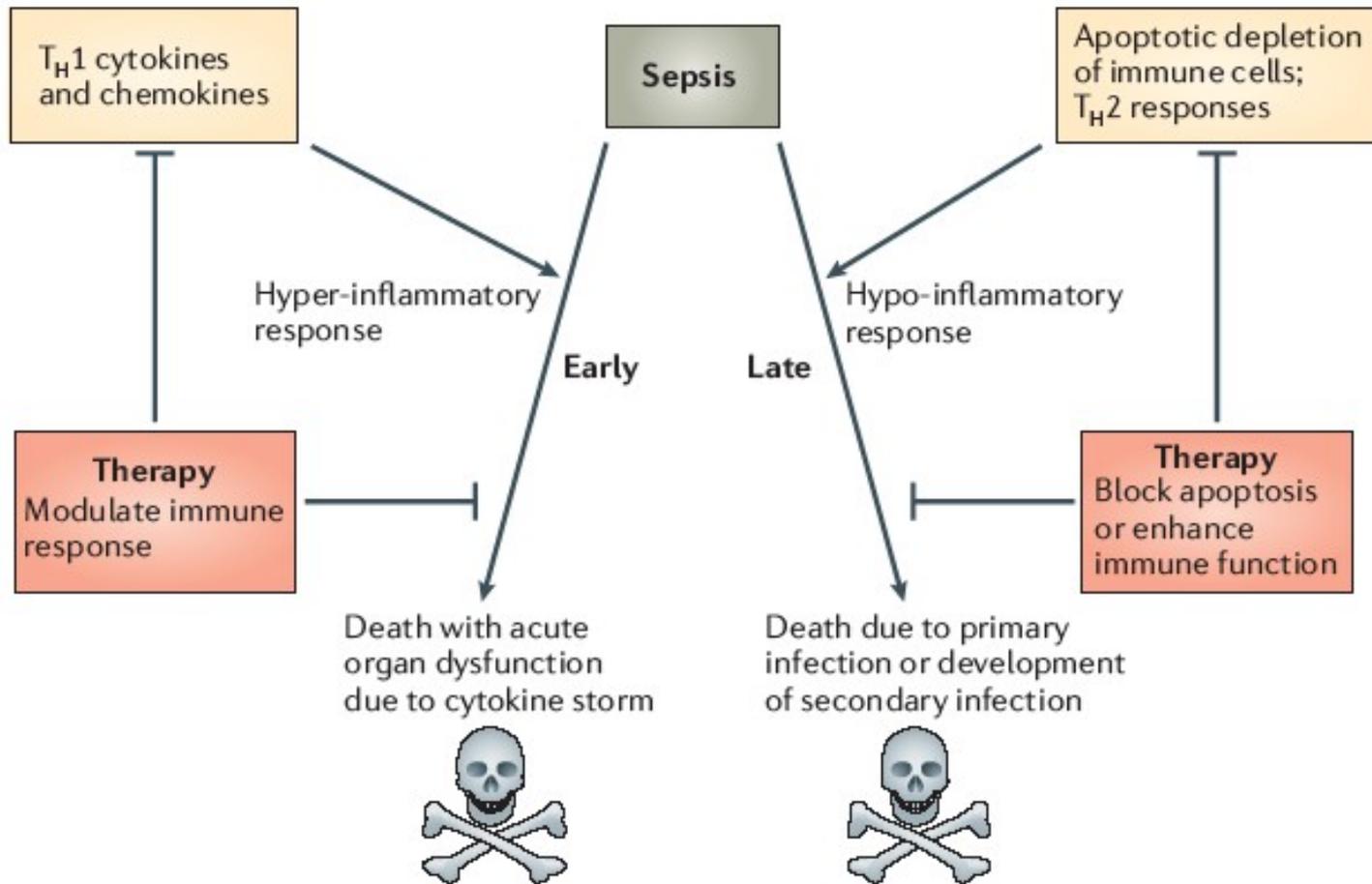


Séquences de la réponse immunitaire dans le sepsis

a Theory 1



Axes thérapeutiques du sepsis



- **Diminution de la bioactivité du LPS bactérien:**

Eritoran tetrasodium

Anti-CD14 mAb...

- **Inhibition des cascades du complément:**

Complement component 1 esterase inhibitor...

- **Inhibition de la coagulation:**

Heparin

Nematode anticoagulant protein c2

Tissue factor pathway inhibitor...

- **Immunosuppresseurs:**

TNF mAb

Chimeric TNF mAb

Humanized TNF mAb

TNF-antigen binding fragment of immunoglobulin

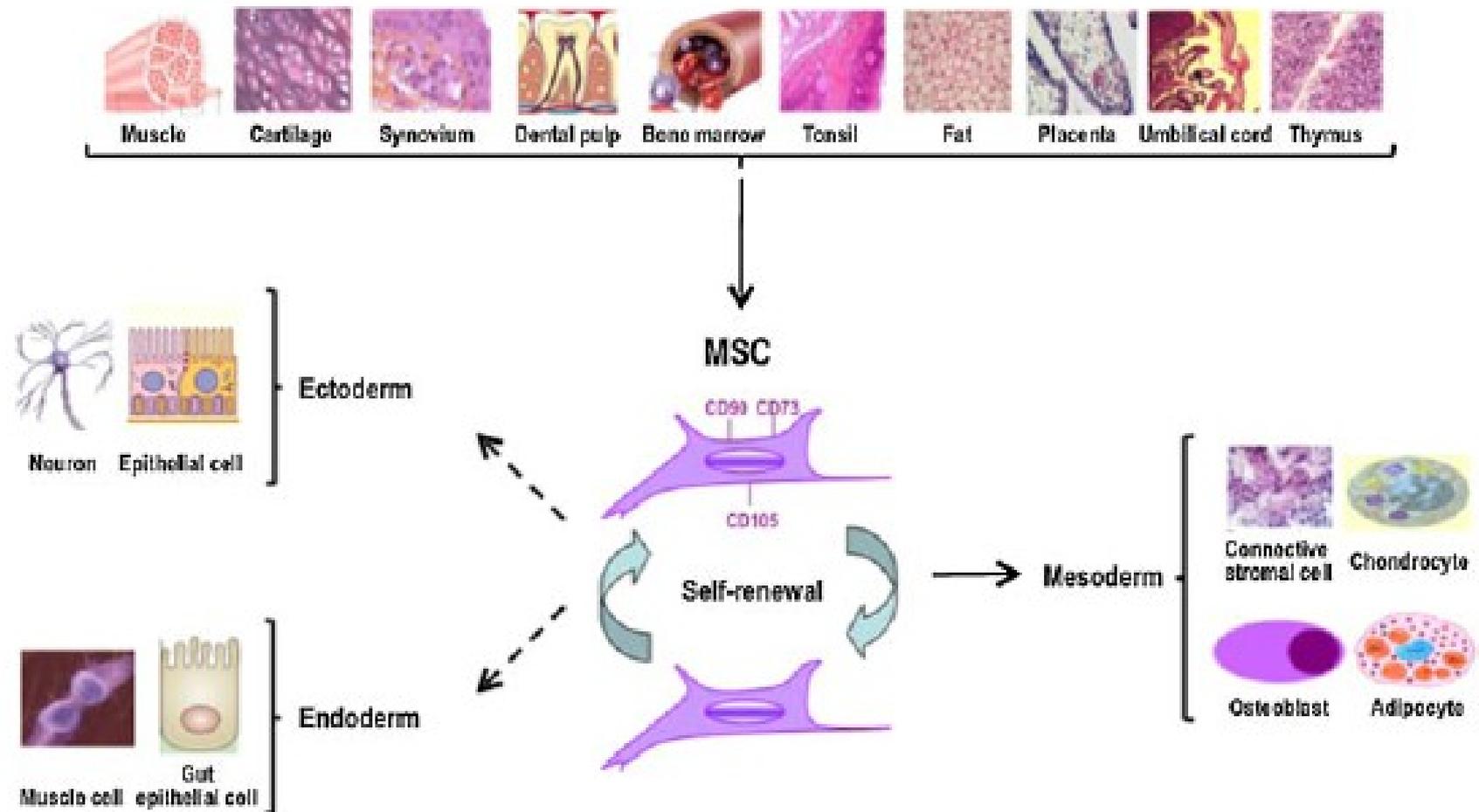
sTNFR1:Fc

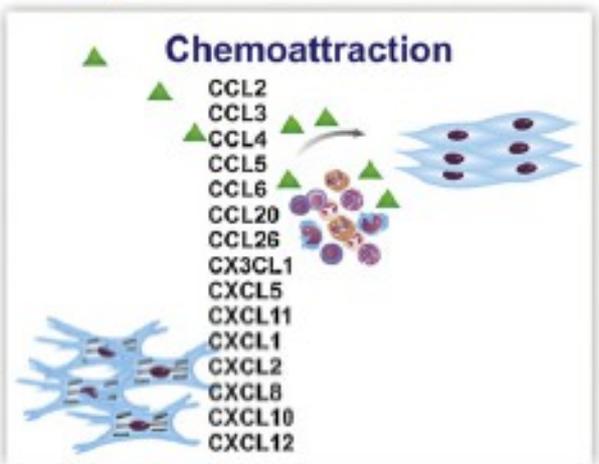
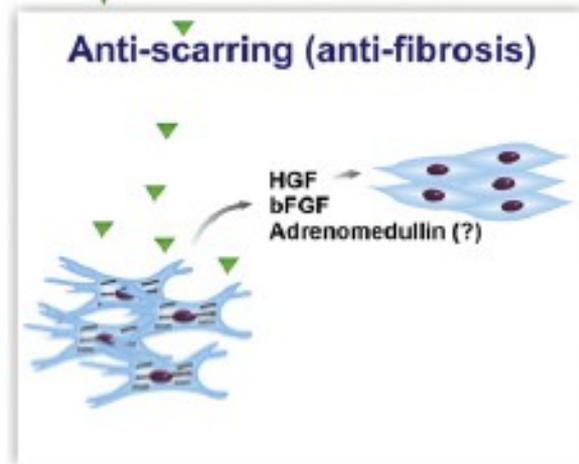
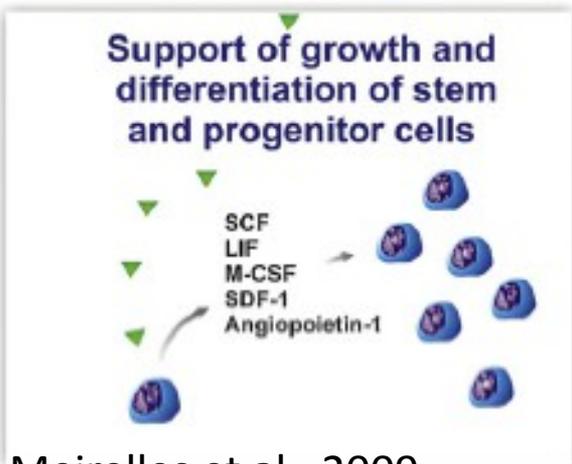
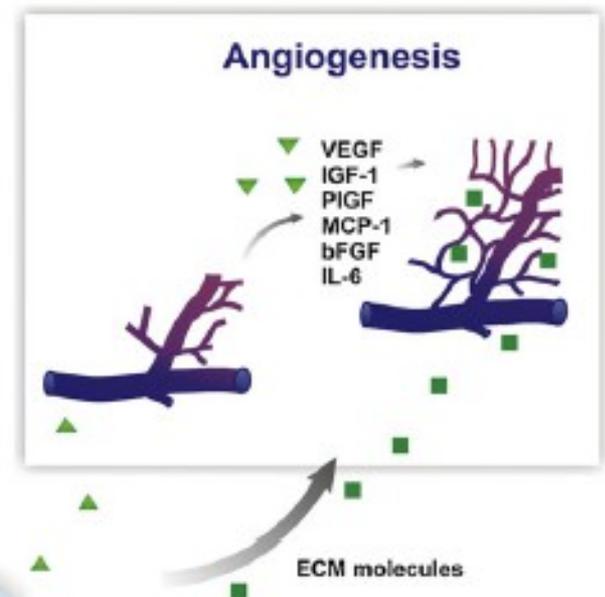
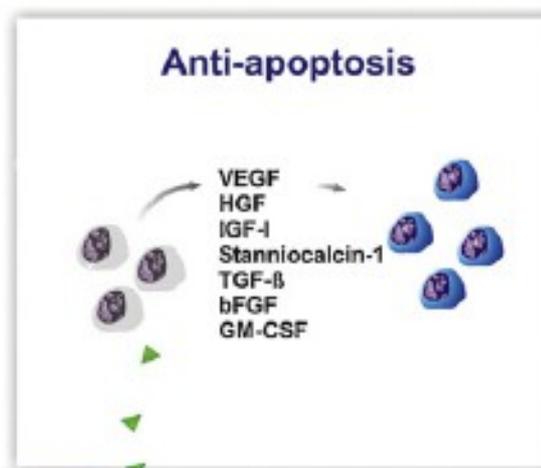
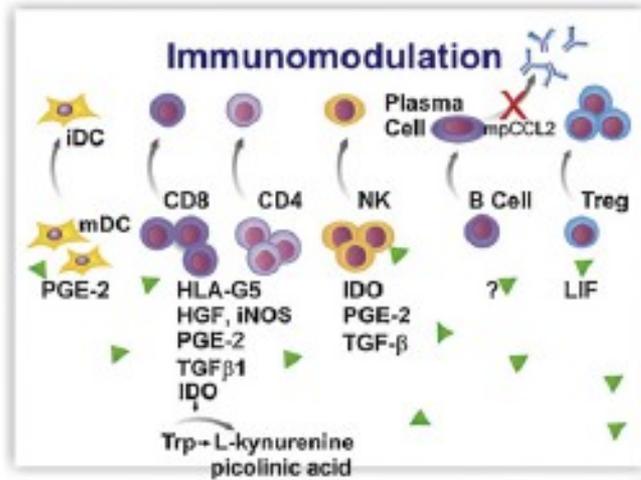
sTNFR2:Fc

High-dose steroids...

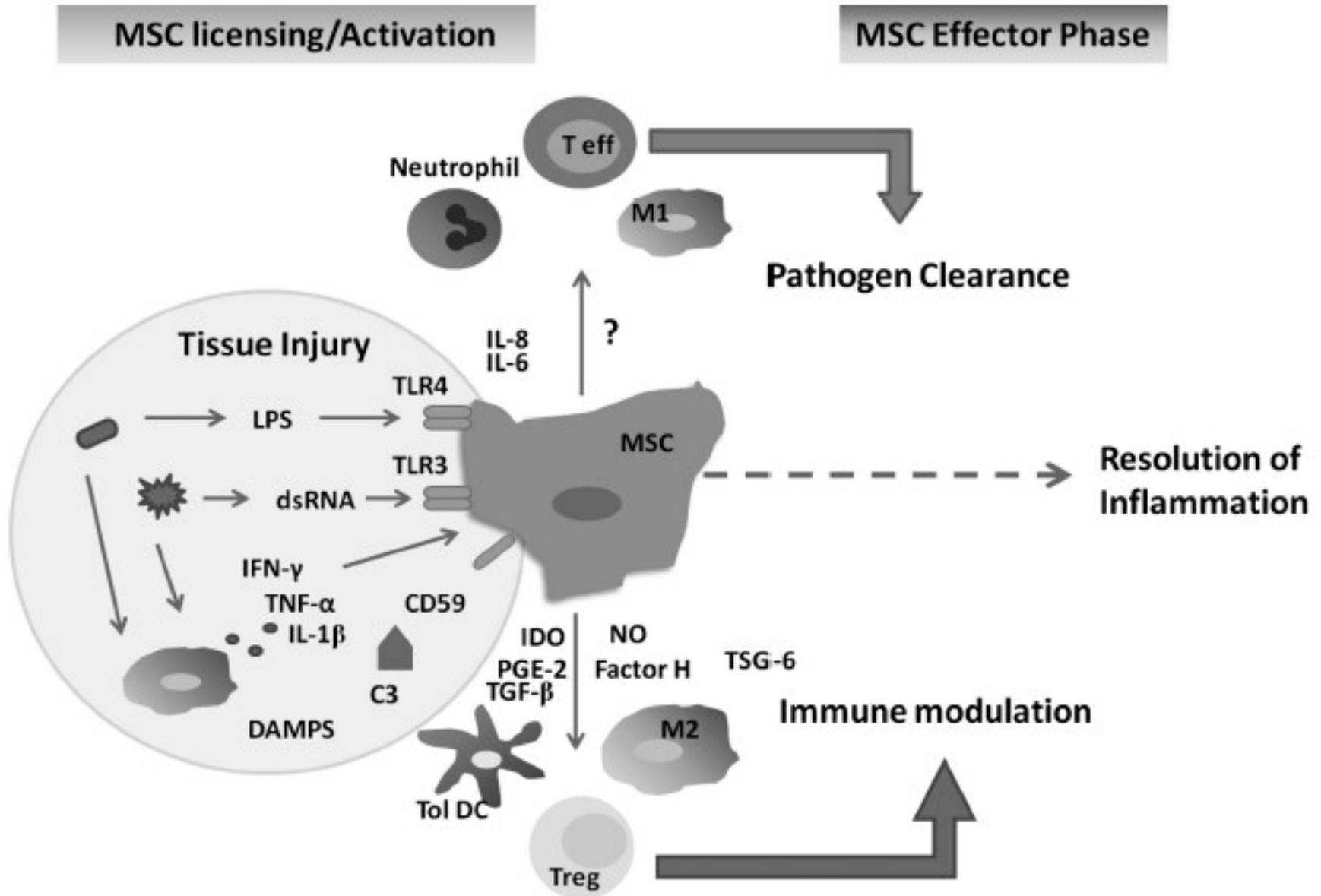
Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement

M Dominici¹, K Le Blanc², I Mueller³, I Slaper-Cortenbach⁴, FC Marini⁵,
DS Krause⁶, RJ Deans⁷, A Keating⁸, DJ Prockop⁹ and EM Horwitz¹⁰ *Cytotherapy*, 2006





Potentialisation fonctionnelle des CSM



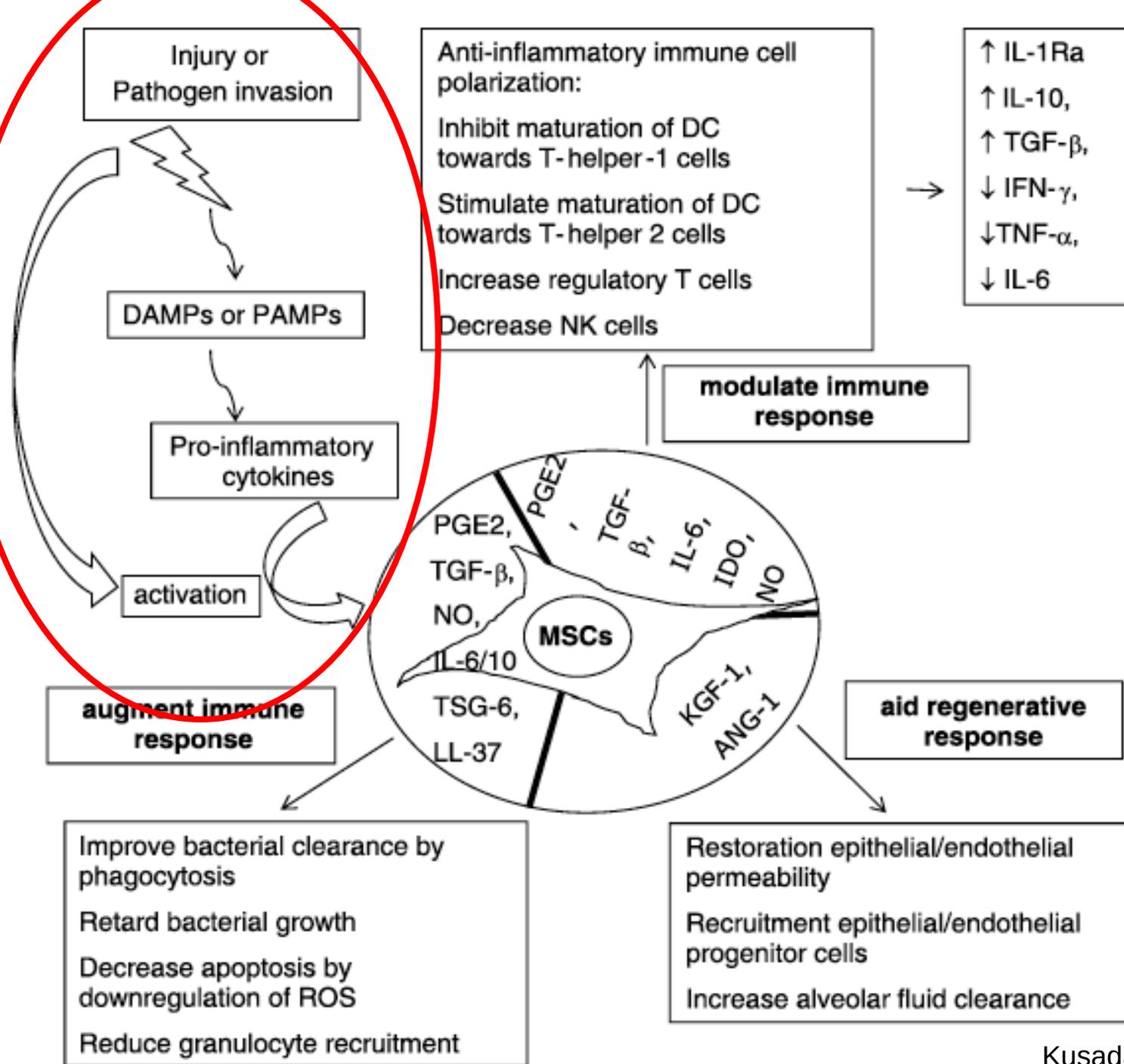
Mesenchymal stem or stromal cells: a review of clinical applications and manufacturing practices

Ratti Ram Sharma,¹ Kathryn Pollock,² Allison Hubel,³ and David McKenna⁴

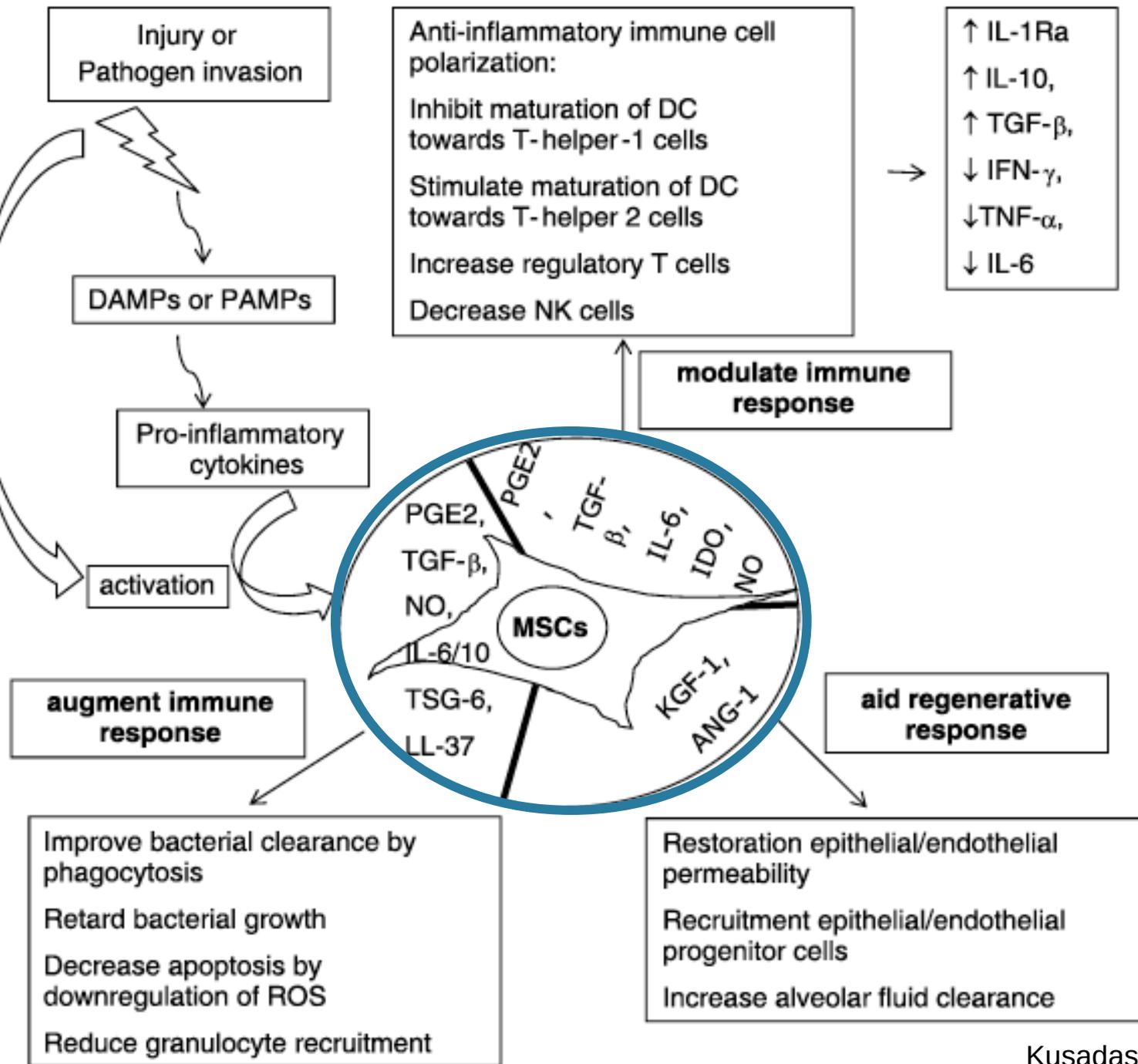
Targeted condition	Phases, number of studies [targeted enrollment]				
	I	II	III	II/III	III
Bone/cartilage disorders					
Bone cysts	1 [6]	1 [10]			
Bone neoplasms				1 [50]	
Cartilage defect	1 [50]	2 [38]	1 [100]		
Degenerative osteoarthritis		2 [30]		1 [25]	
Distraction osteogenesis	1 [6]				
Fractures	2 [16]	1 [24]	1 [40]		
Ligament injury		1 [24]	1 [10]		
Meniscectomy		2 [110]			
Osteoarthritis	5 [42]	2 [45]	4 [222]		1 [104]
Osteodysplasia	1 [8]				
Osteogenesis imperfecta	1 [9]				
Osteonecrosis	1 [21]	2 [39]	1 [10]		
Osteoporosis			1 [290]		
Pseudoarthrosis			1 [50]		
Spinal fusion		1 [52]			
Hematologic disorders					
Aplastic anemia		2 [50]	1 [30]		
BMT	1 [125]	3 [40]	3 [125]		
GVHD	2 [59]	6 [130]	6 [296]	1 [100]	1 [240]
Myelodysplastic syndrome			1 [30]		
Diabetes					
Type 1	1 [24]	5 [168]	1 [60]	1 [80]	
Type 2	1 [24]	3 [170]			
Liver diseases					
Autoimmune hepatitis		1 [100]			
Cirrhosis	3 [29]	7 [715]	5 [266]		
Hypercholesterolemia	1 [1]				
Liver failure		2 [228]	1 [120]		
Liver transplant		1 [40]	1 [60]		
Primary biliary cirrhosis		1 [100]			
Cardiovascular diseases					
Dilated cardiomyopathy		2 [56]	2 [80]		
Heart failure		3 [172]	4 [160]		
Myocardial infarction	1 [53]	2 [45]	2 [380]	1 [80]	2 [165]
Myocardial ischemia	2 [144]	3 [98]	1 [60]		
Gastrointestinal diseases					
Crohn's disease		3 [56]	1 [10]		4 [596]
		1 [10]	1 [40]		
		1 [50]			

etc...

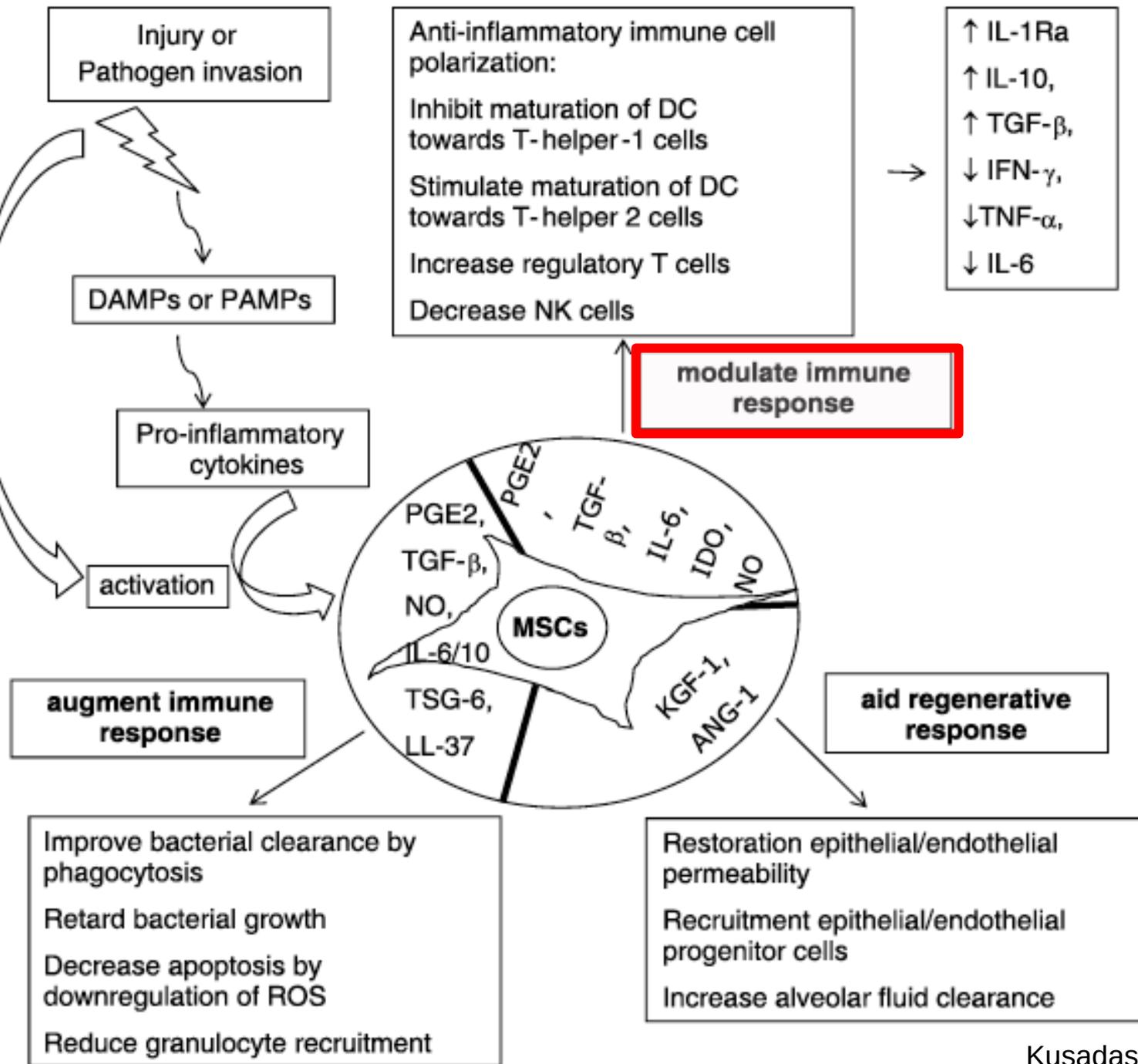
Pourquoi la CSM ?



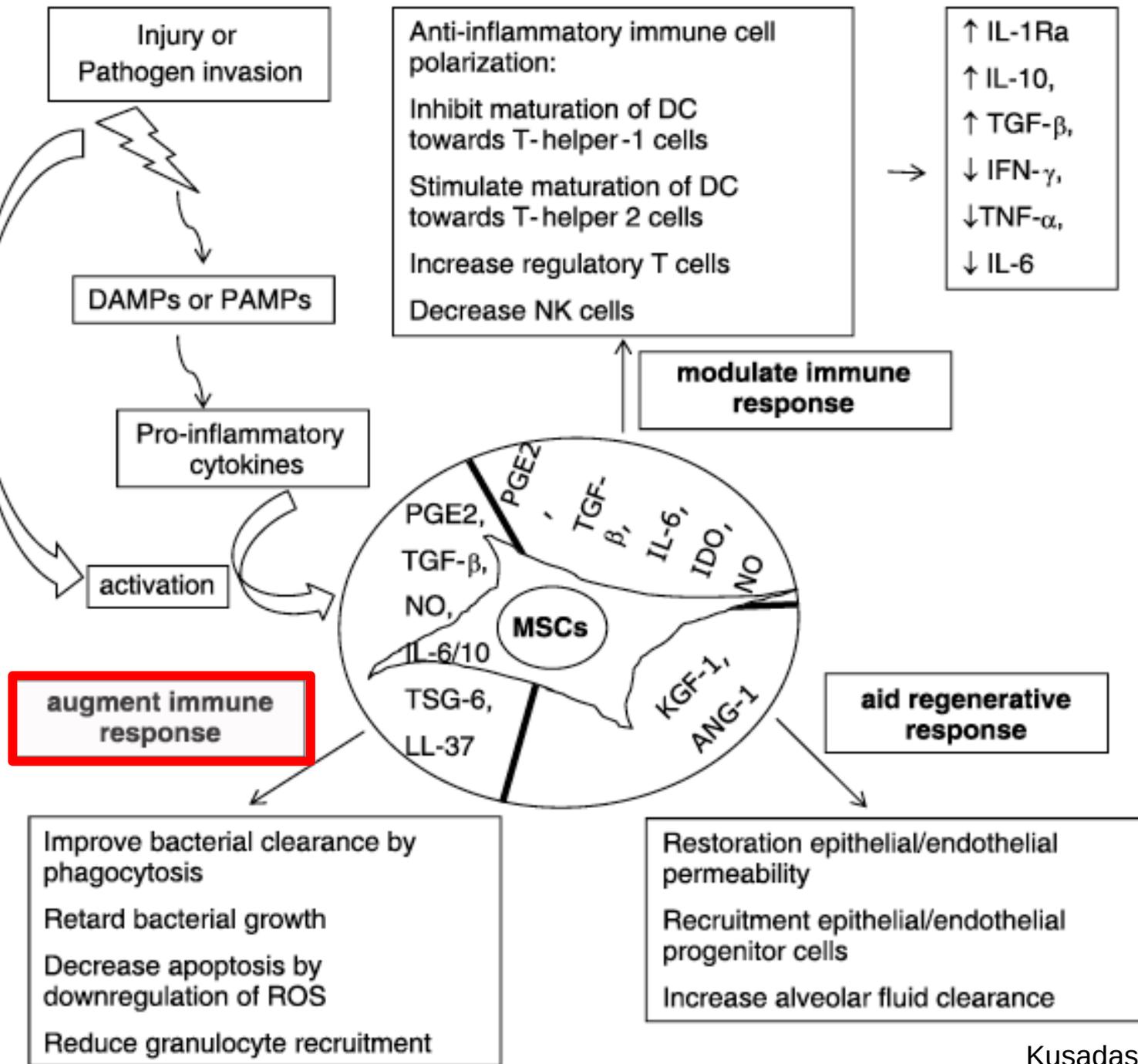
Pourquoi la CSM ?



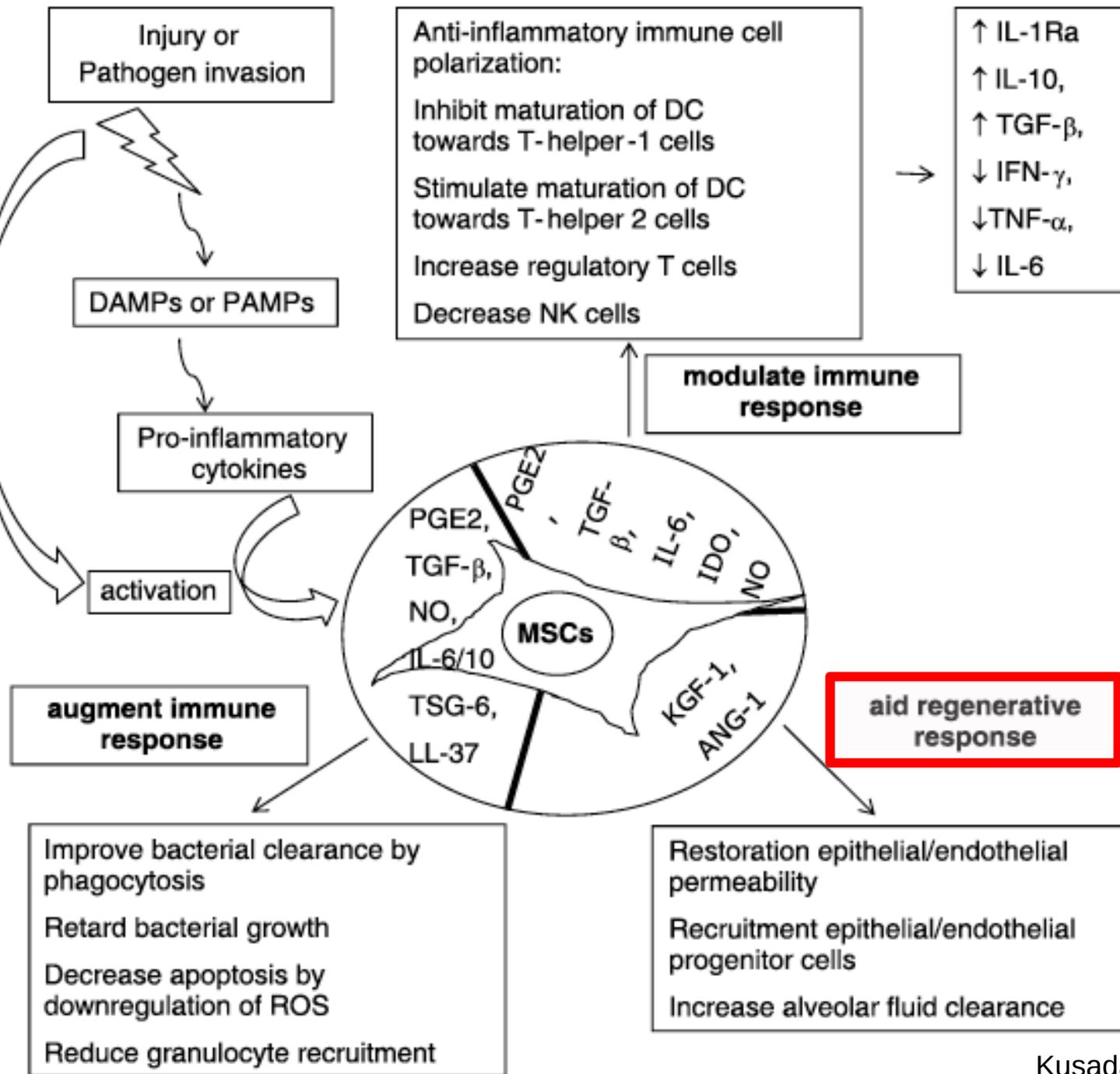
Pourquoi la CSM ?



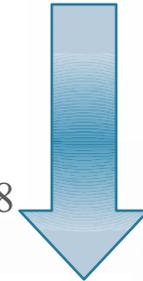
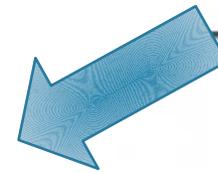
Pourquoi la CSM ?



Pourquoi la CSM ?



Therapy
Block apoptosis
or enhance
immune function



Human Mesenchymal Stem Cells Inhibit Neutrophil Apoptosis: A Model for Neutrophil Preservation in the Bone Marrow Niche

LIZZIA RAFFAGHELLO,^a GIORDANO BIANCHI,^b MARIA BERTOLOTTI,^b FABRIZIO MONTECUCCO,^b
ALESSANDRO BUSCA,^c FRANCO DALLEGRI,^b LUCIANO OTTONELLO,^b VITO PISTOIA^a STEM CELLS 2008

Interleukin 7 Plays a Role in T Lymphocyte Apoptosis Inhibition Driven by Mesenchymal Stem Cell without Favoring Proliferation and Cytokines Secretion

Marilia Normanton^{1,5}, Heliene Alvarenga^{1,5}, Nelson Hamerschlag², Al
Luiz Vicente Rizzo¹, Luciana Cavaleiro Marti^{1,5*}  **PLOS** | ONE 2014

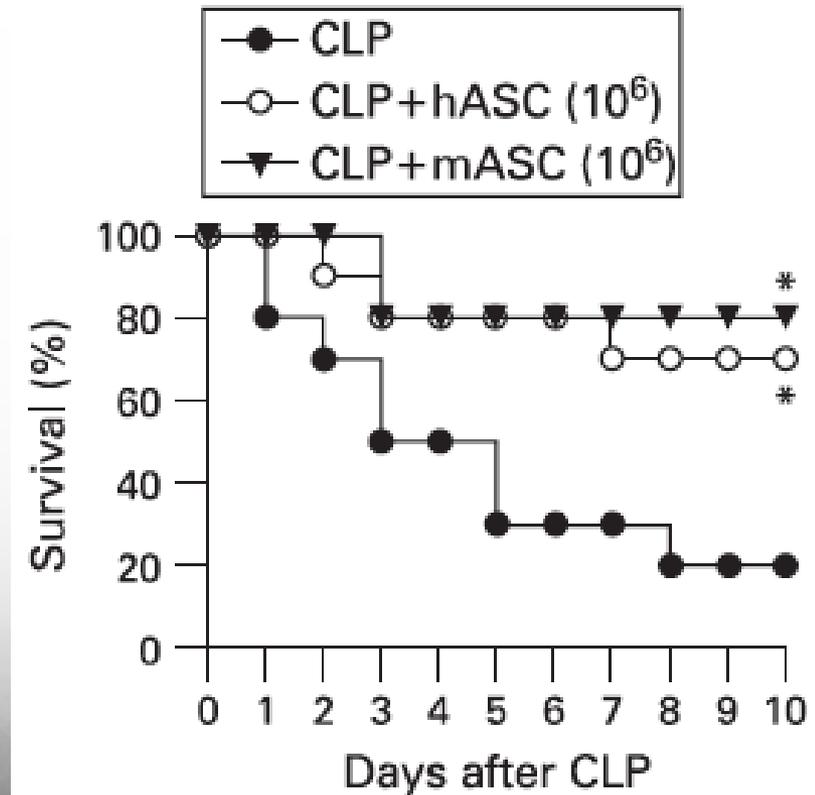
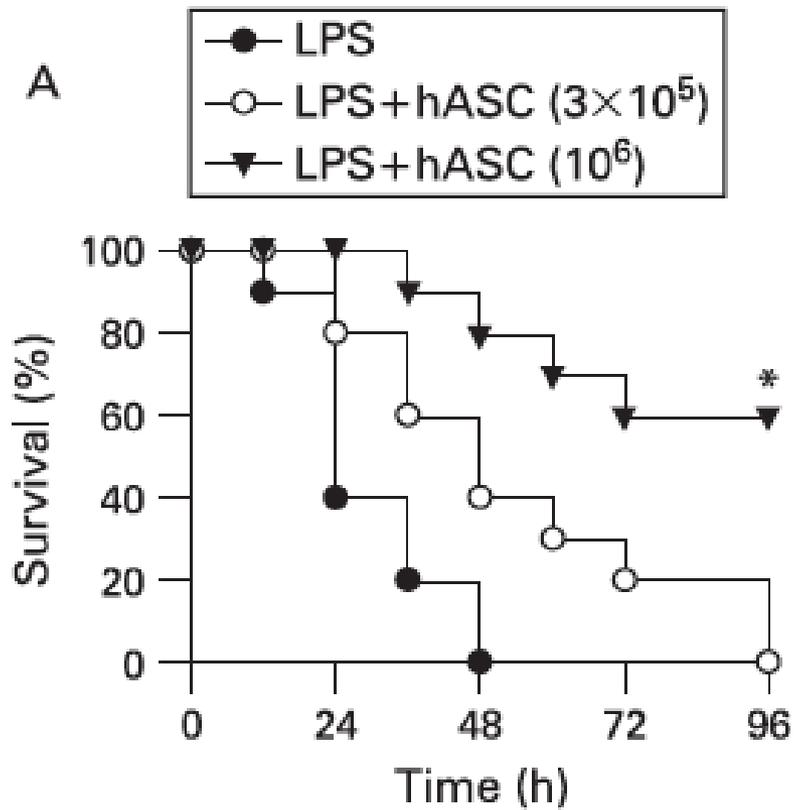
Bone marrow mesenchymal stem cells protect alveolar macrophages from lipopolysaccharide-induced apoptosis partially by inhibiting the Wnt/ β -catenin pathway

Bin Li¹, Hongwu Zhang², Mian Zeng^{1*}, Wanmei He¹, Ming Li³, Xubin Huang¹, David Y. B. Deng²
and Jianfeng Wu⁴ Cell Biol Int 9999 (2014)

Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis

E Gonzalez-Rey,¹ P Anderson,² M A González,³ L Rico,⁴ D Büscher,⁴ M Delgado²

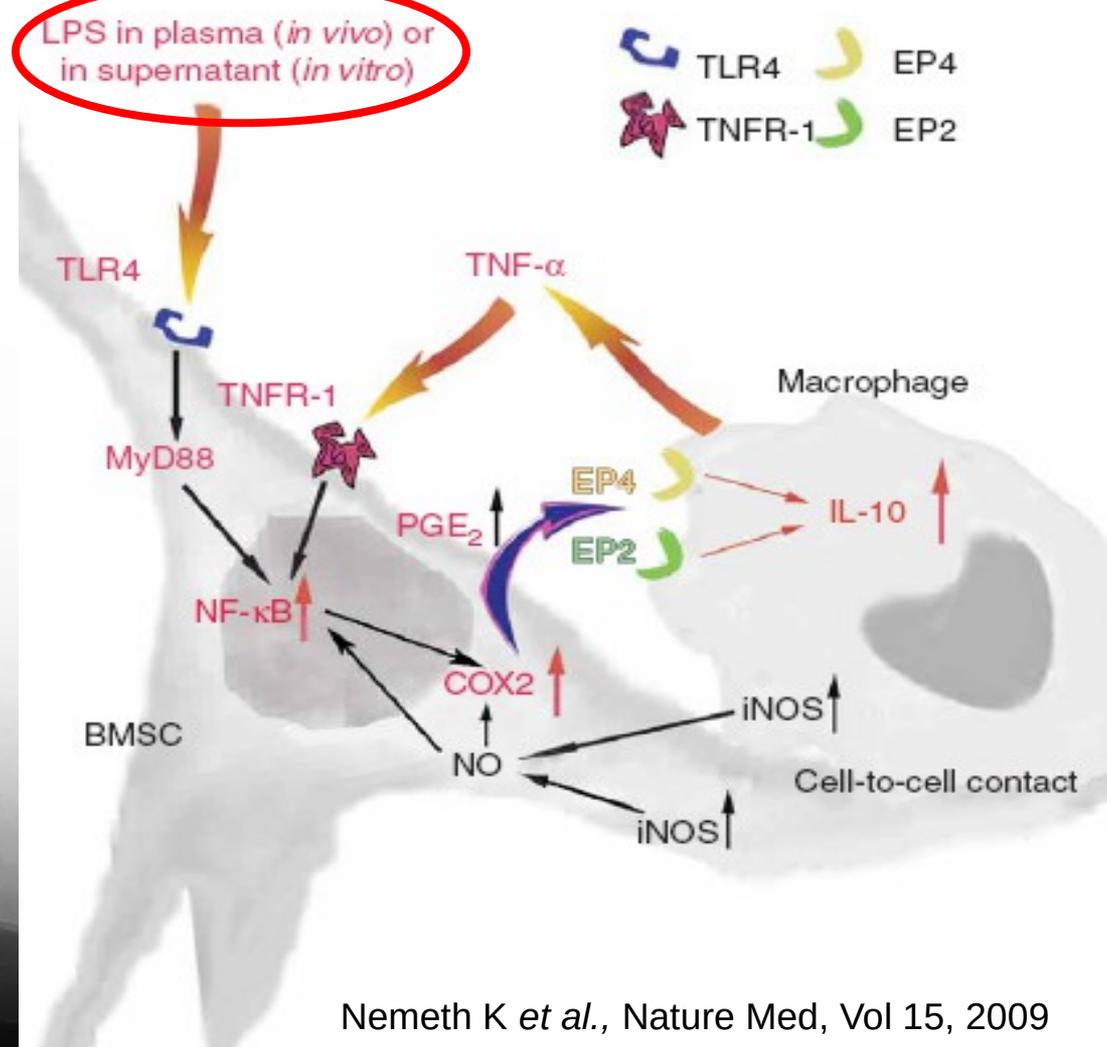
Gut 2009



CSM et sepsis: phase pro-inflammatoire

Bone marrow stromal cells attenuate sepsis via prostaglandin E₂-dependent reprogramming of host macrophages to increase their interleukin-10 production

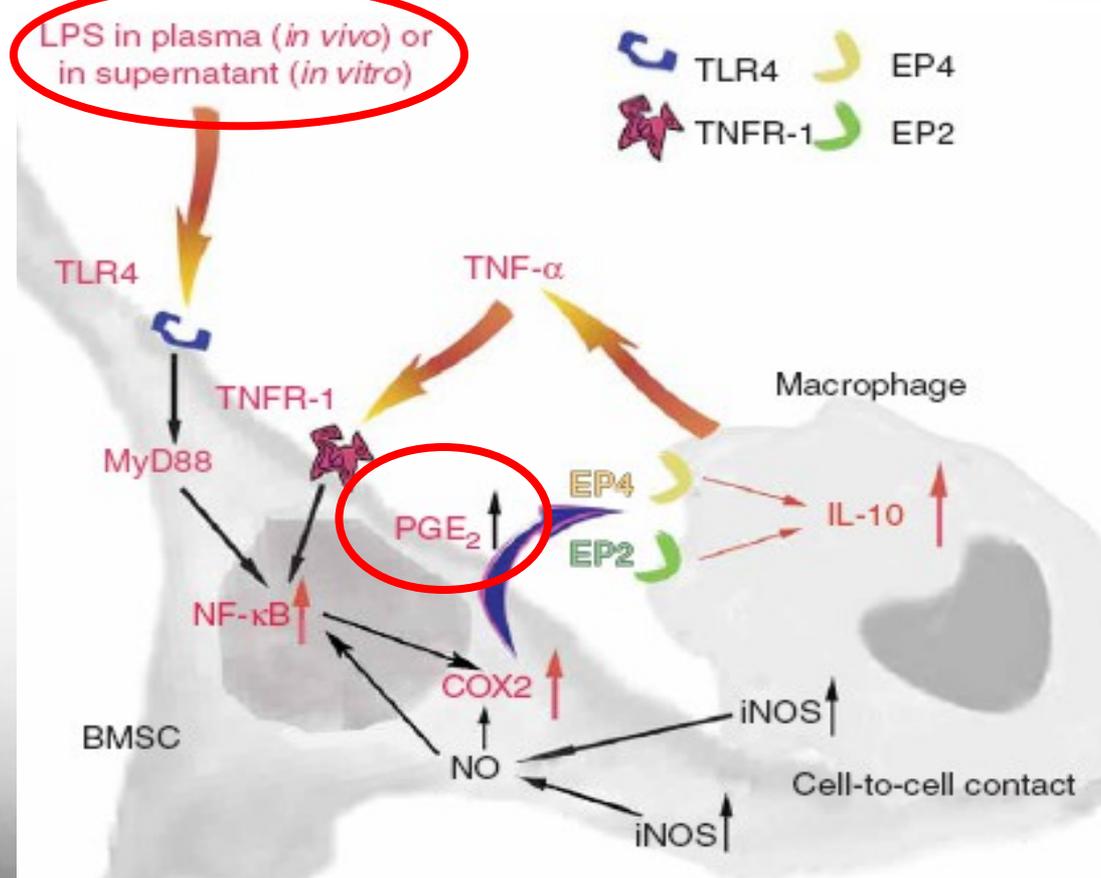
Krisztián Németh^{1,6}, Asada Leelabayanichkul^{2,6}, Peter S T Yuen², Balázs Mayer¹, Alissa Parmelee¹, Kent Doi²,



CSM et sepsis: phase pro-inflammatoire

Bone marrow stromal cells attenuate sepsis via prostaglandin E₂-dependent reprogramming of host macrophages to increase their interleukin-10 production

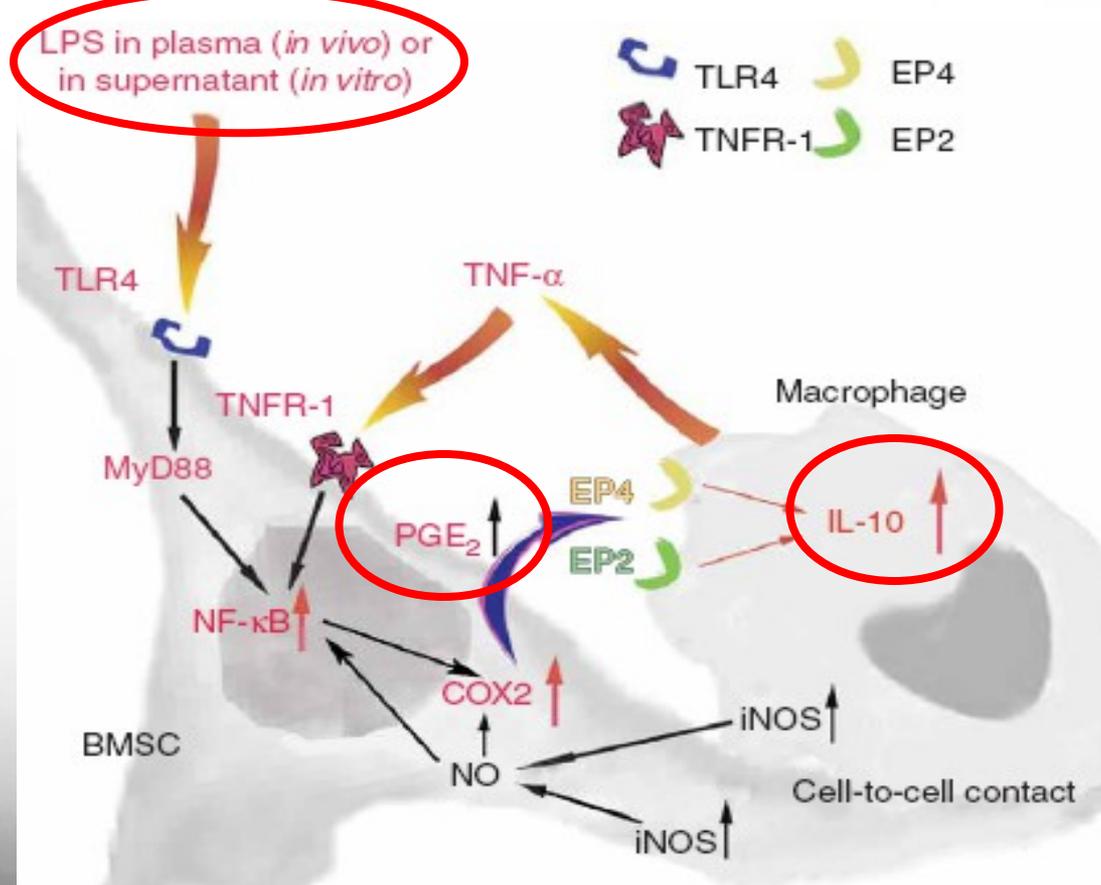
Krisztián Németh^{1,6}, Asada Leelabayanichkul^{2,6}, Peter S T Yuen², Balázs Mayer¹, Alissa Parmelee¹, Kent Doi²,



CSM et sepsis: phase pro-inflammatoire

Bone marrow stromal cells attenuate sepsis via prostaglandin E₂-dependent reprogramming of host macrophages to increase their interleukin-10 production

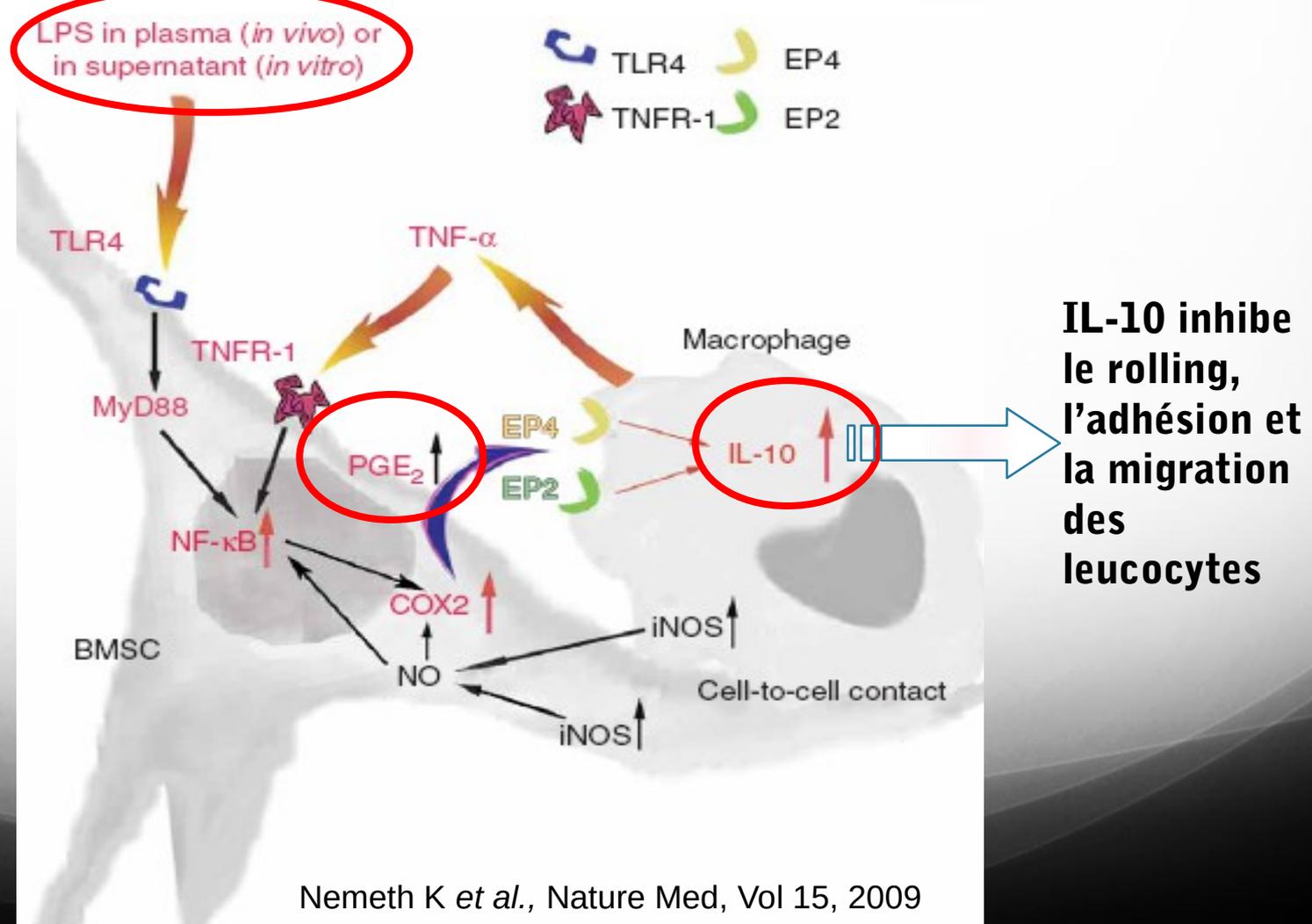
Krisztián Németh^{1,6}, Asada Leelabayanichkul^{2,6}, Peter S T Yuen², Balázs Mayer¹, Alissa Parmelee¹, Kent Doi²,



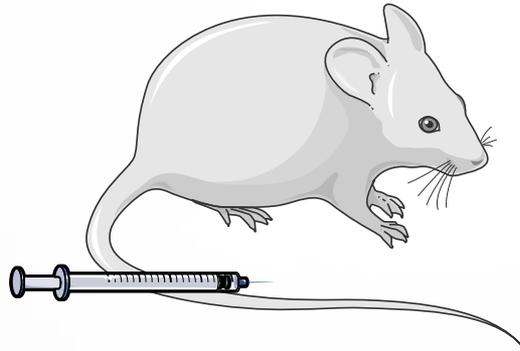
CSM et sepsis: phase pro-inflammatoire

Bone marrow stromal cells attenuate sepsis via prostaglandin E₂-dependent reprogramming of host macrophages to increase their interleukin-10 production

Krisztián Németh^{1,6}, Asada Leelabayanichkul^{2,6}, Peter S T Yuen², Balázs Mayer¹, Alissa Parmelee¹, Kent Doi²,



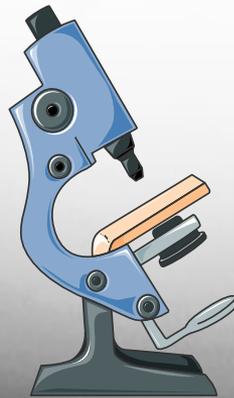
Modele de sepsis murin: analyse de la microcirculation



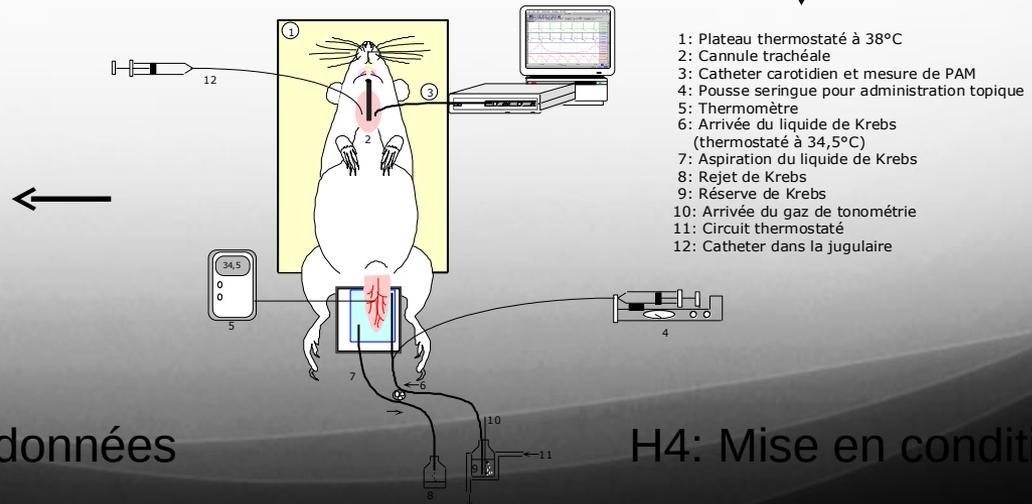
HO : Injection
IP de fécès



H1 : Injection dans la veine de
la queue : CSM naïve ou NaCl



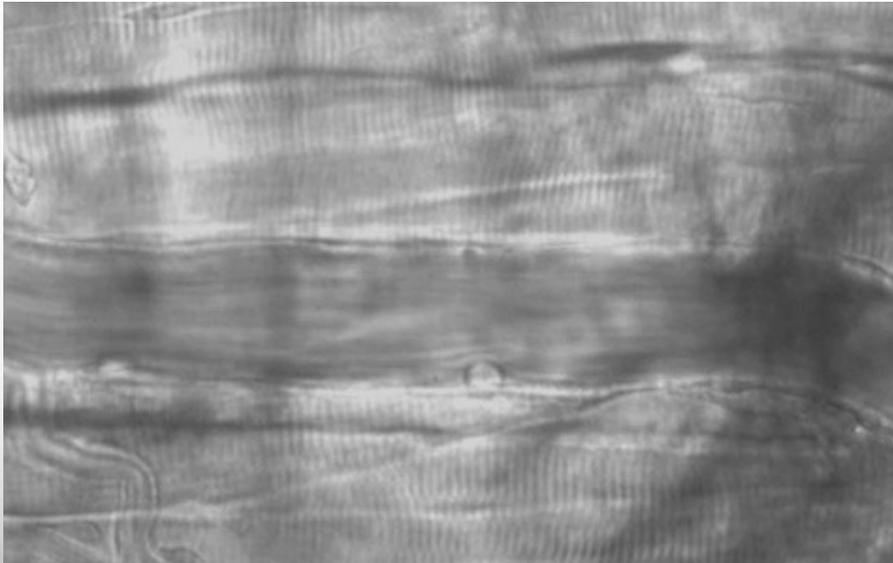
H6: Enregistrement des données



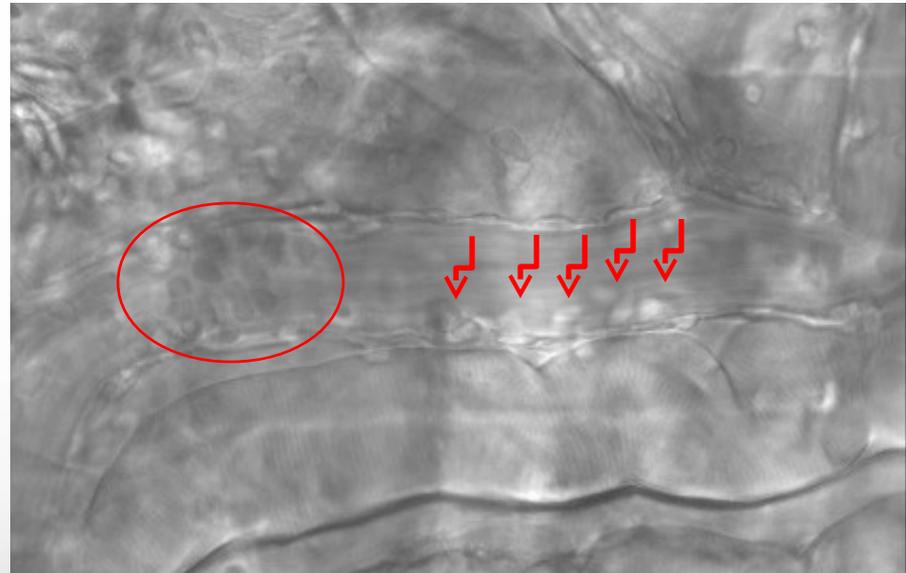
H4: Mise en condition

Mobilité des leucocytes dans les veinules du crémaster

En microscopie optique x50



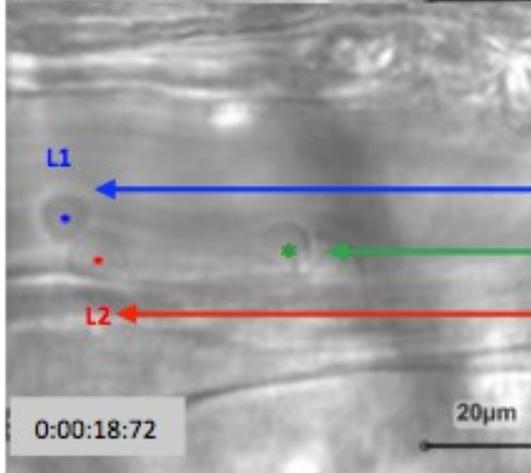
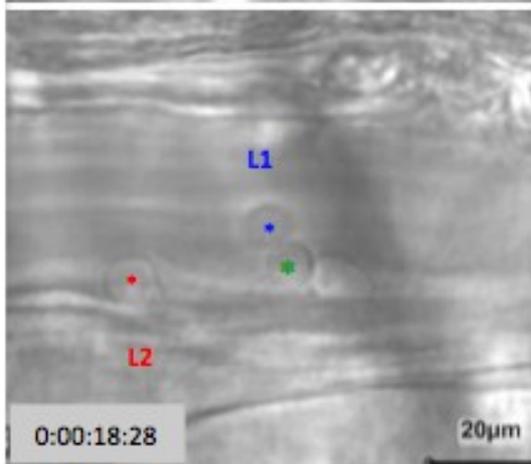
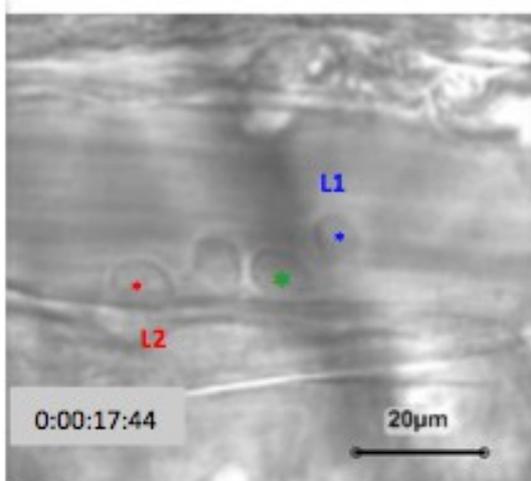
Souris saine



Souris septique

Mobilité des leucocytes dans les veinules du crémaster

Enregistrement par caméra



Leucocyte Roulant

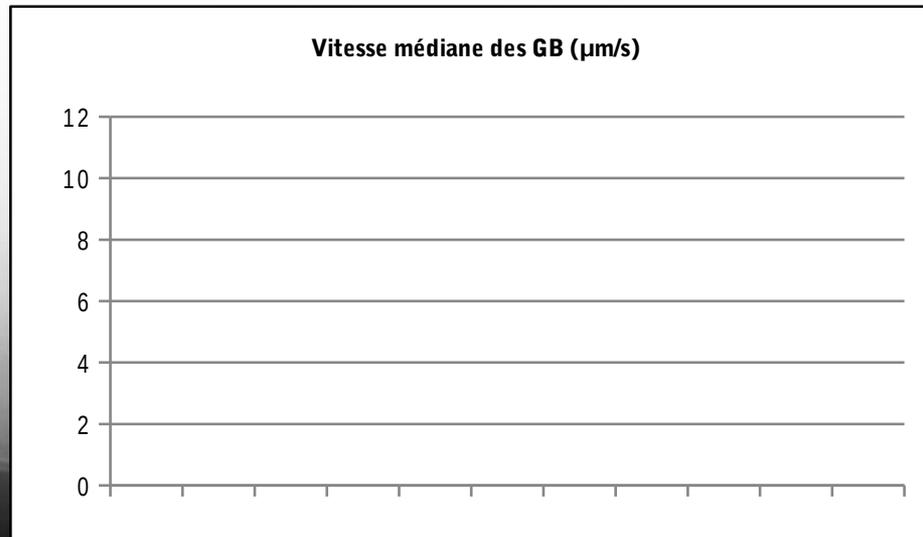
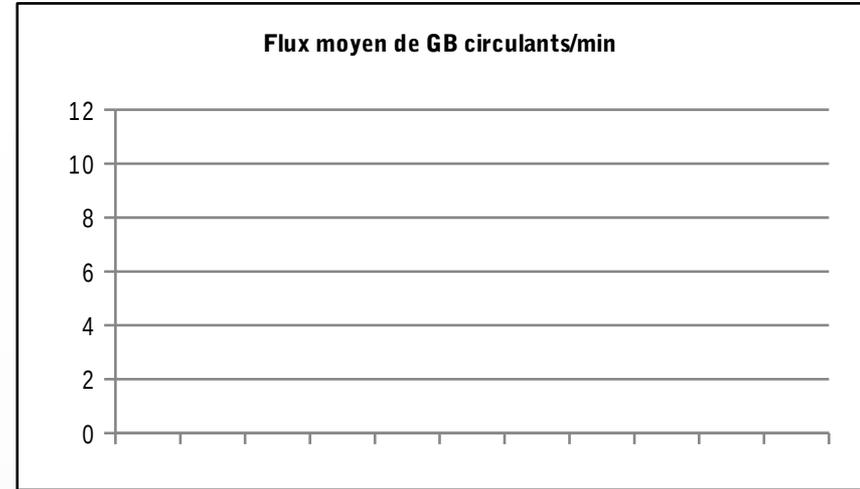
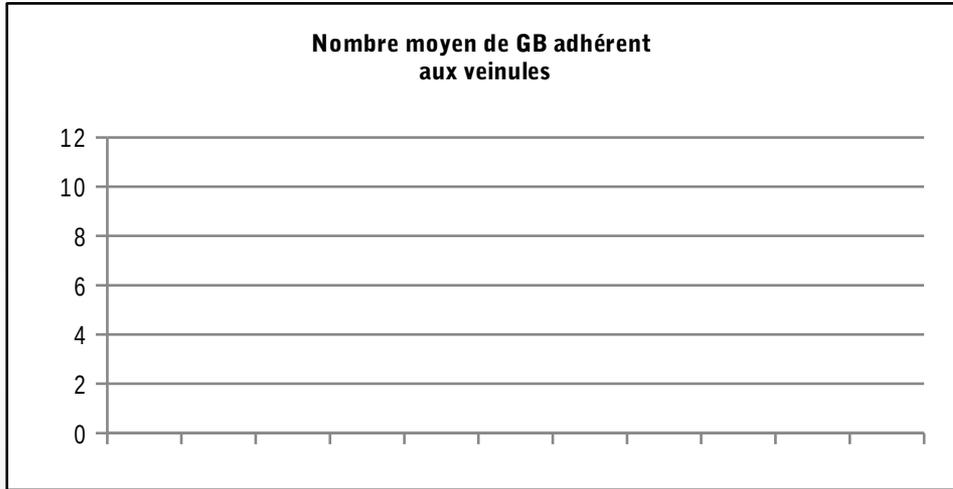
Leucocyte Adhérent

Leucocyte Roulant

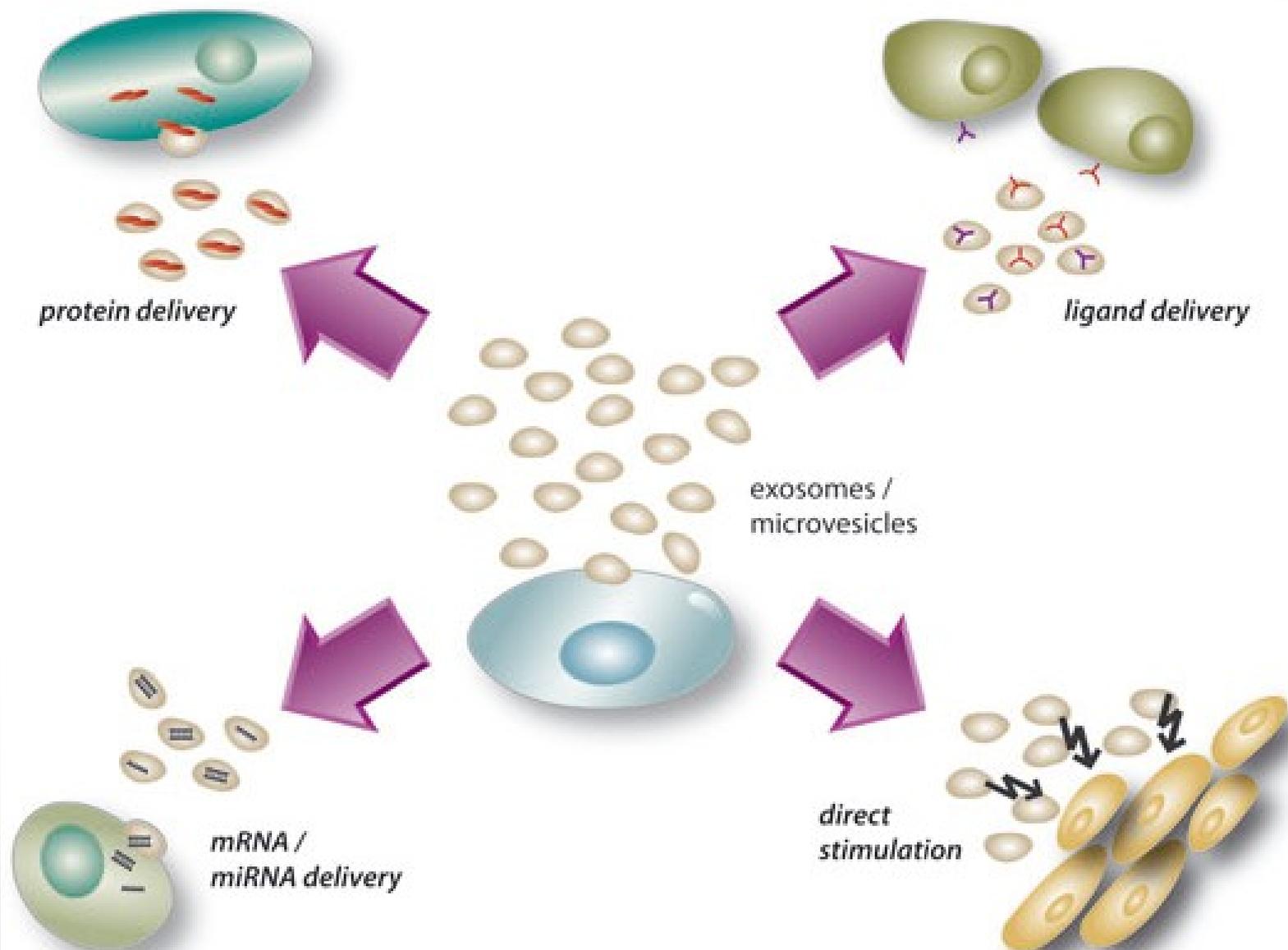
Les CSM diminuent l'adhérence des Leucocytes

(Résultats préliminaires)

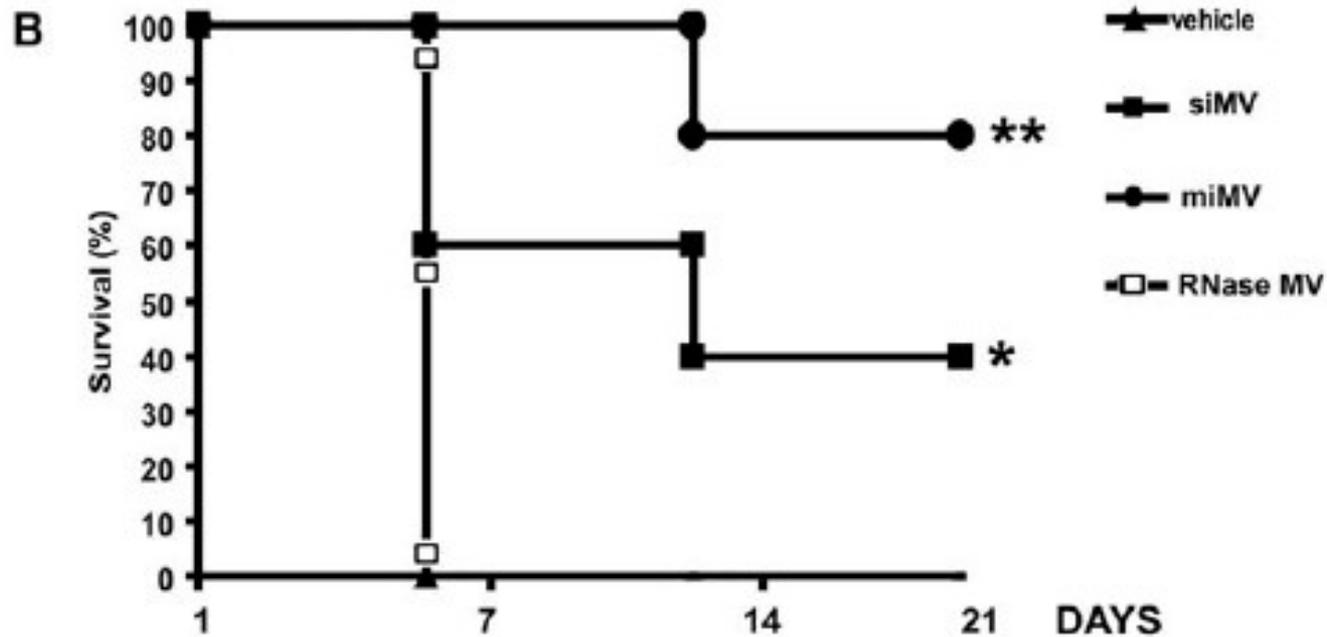
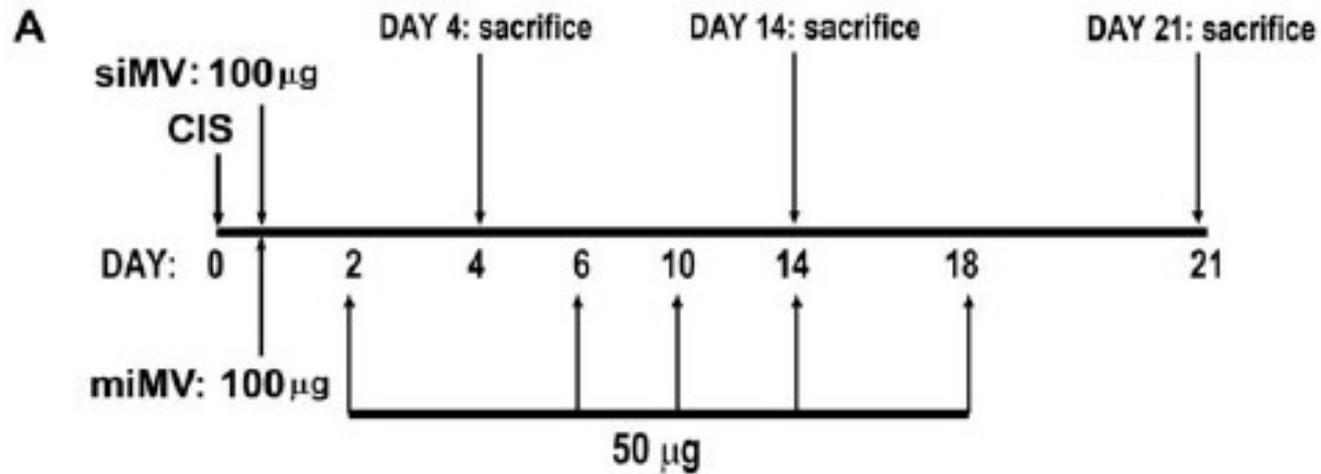
Etude à partir de 7 à 10 veinules pour chaque souris



Perspectives: utilisation des produits dérivés des CSM dans le traitement du sepsis



Microvésicules: exemple d'efficacité sur une lésion d'organe



Merci de votre attention!

CTSA/ IRBA

J.J. Lataillade

F. Montespan

C. Thepenier

K. Lund

M. Trouillas

M. Alexaline

M. Gourven

J. Boyer

F. Tissedre

L. Boutin

S. Banzet

A. Trignol

B. Coulomb



**Laboratoire d'étude de la microcirculation-
INSERM UMR-S942-Université Paris-Diderot**

E. Vicaut

N. Baudry

**Service d'Anesthésie-Réanimation Chirurgicale,
Centre Hospitalier Universitaire de Bicêtre**

J. Duranteau

Autre thérapeutique potentielle du sepsis: les CSH

- Une inflammation chronique ou LPS peut induire une dysfonction des CSH:

Inflammatory modulation of hematopoietic stem cells: viewing the hematopoietic stem cell as a foundation for the immune response

Katherine Y. King¹ and Margaret A. Goodell^{2,*} *Nat Rev Immunol.* ; 11(10): 685–692.

- Modèle murin avec greffe CSH aide survie sepsis:

Hematopoietic Stem-Progenitor Cells Restore Immunoreactivity and Improve Survival in Late Sepsis

Laura Brudecki,^a Donald A. Ferguson,^b Dellng Yin,^a Gene D. Lesage,^a Charles E. McCall,^c and Mohamed El Gazzar^a