



SITUATIONS HÉMOLYTIQUES & LEURS CONSÉQUENCES

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Member of the ERN Eurobloodnet

Clinical Investigation Center 1430

Réseau Erythrocyte Drépanocytose RED



AP-HP.
Hôpitaux universitaires
Henri-Mondor



UNIVERSITÉ
PARIS-EST CRÉTEIL
VAL DE MARNE



Inserm
Institut national
de la santé et de la recherche médicale



INSTITUT MONDOR
DE RECHERCHE
BIOMÉDICALE



European
Reference
Network
for rare or low prevalence
complex diseases

Network
Hematological
Diseases (ERN EuroBloodNet)



RÉSEAU ÉRYTHROCYTE ET DRÉPANOCYTOSE

CONFLITS D'INTÉRÊT

- Consultant for THERAVIA, ROCHE, PFIZER, NOVONORDISK
- Lecture fees for THERAVIA, AGIOS, VERTEX, ROCHE
- Steering committee for ROCHE, THERAVIA, PFIZER
- Research support from THERAVIA, EMMAUS
- Cofounder of INNOVHEM

ANÉMIE

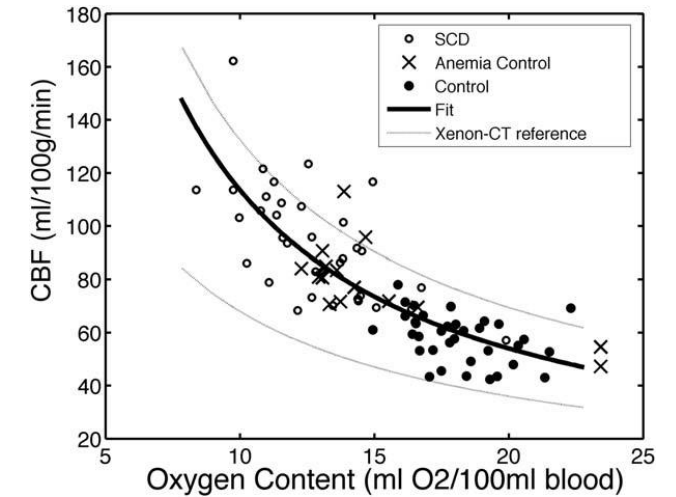
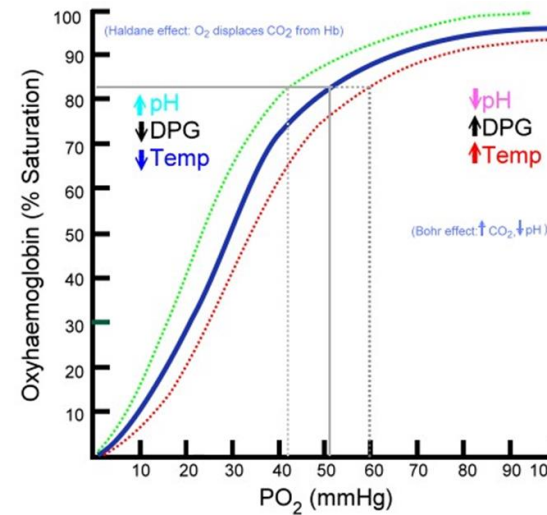


↓ Apport d'oxygène

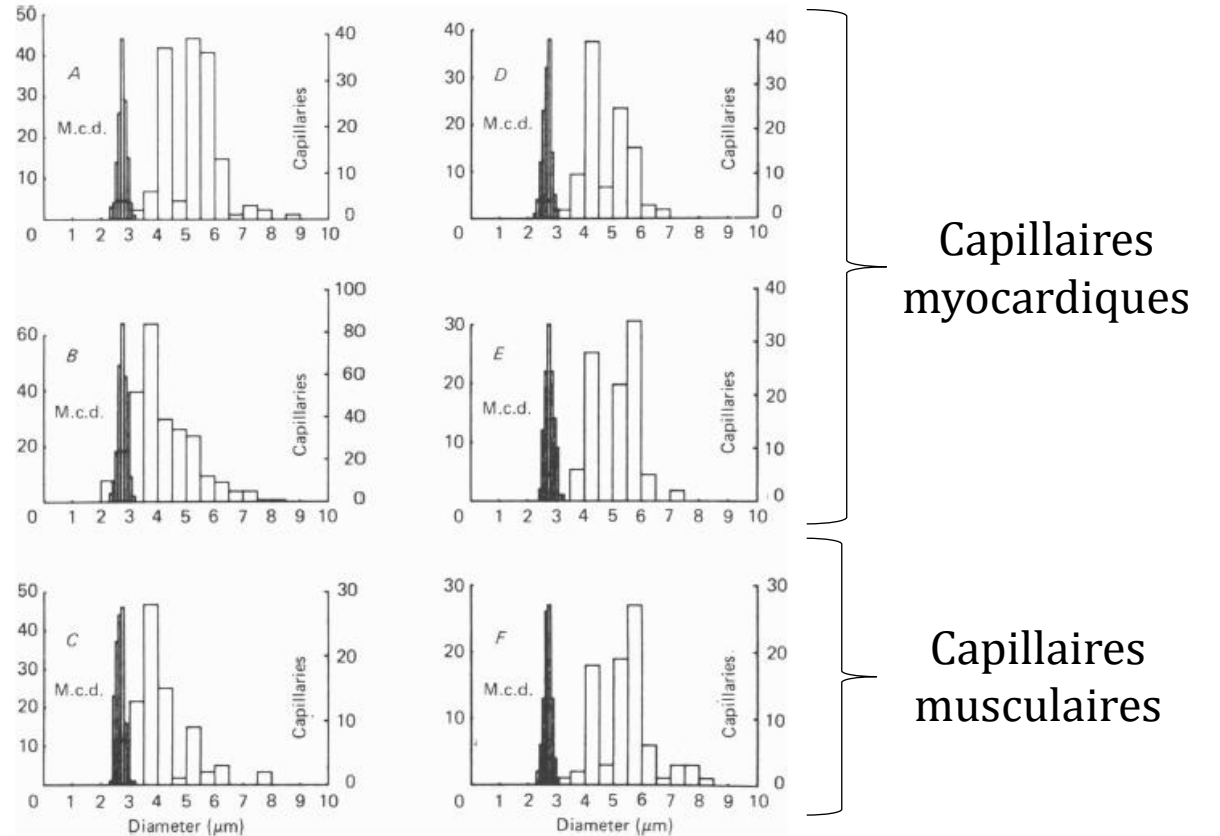
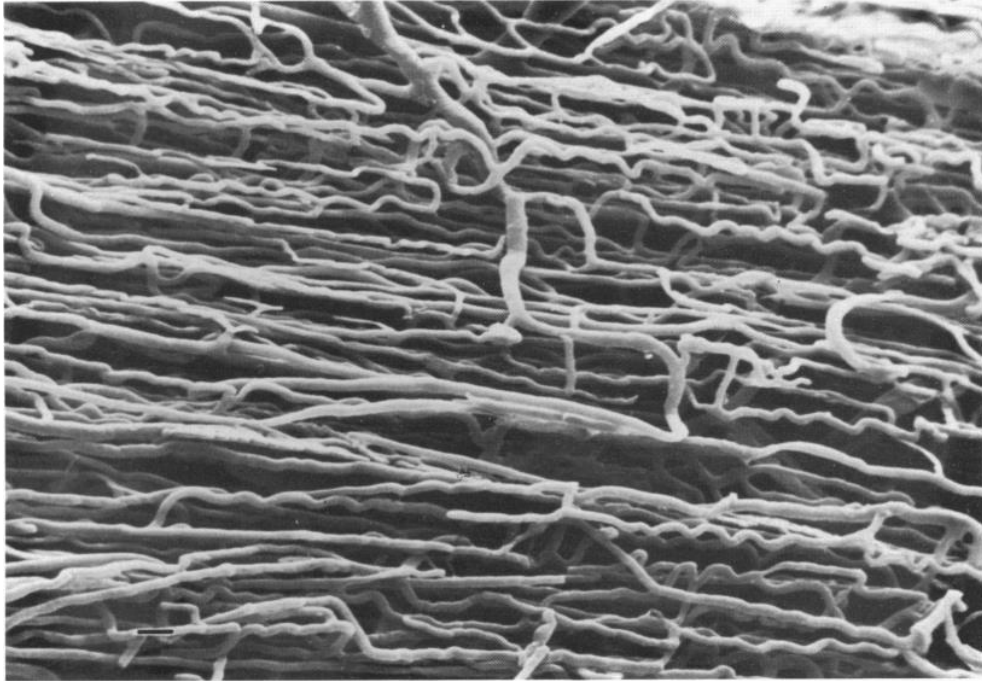
Maintien des apports en oxygène



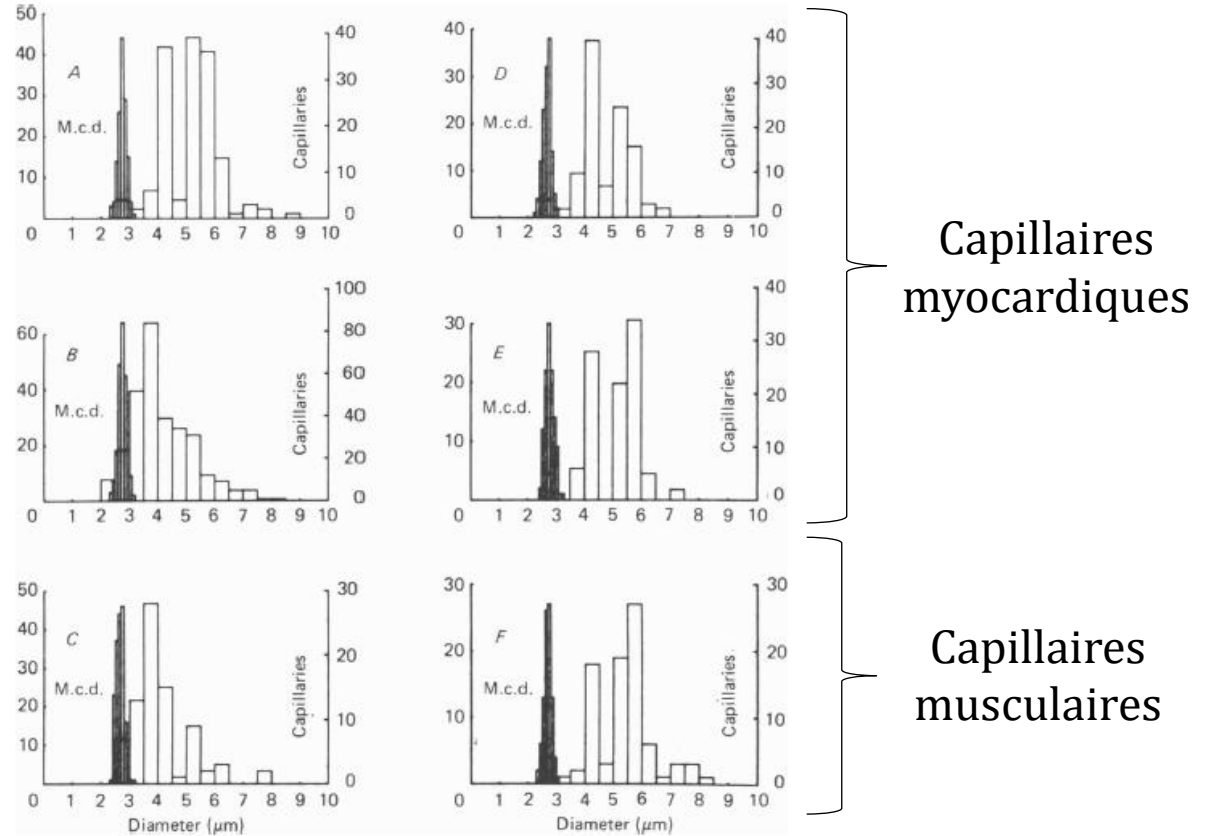
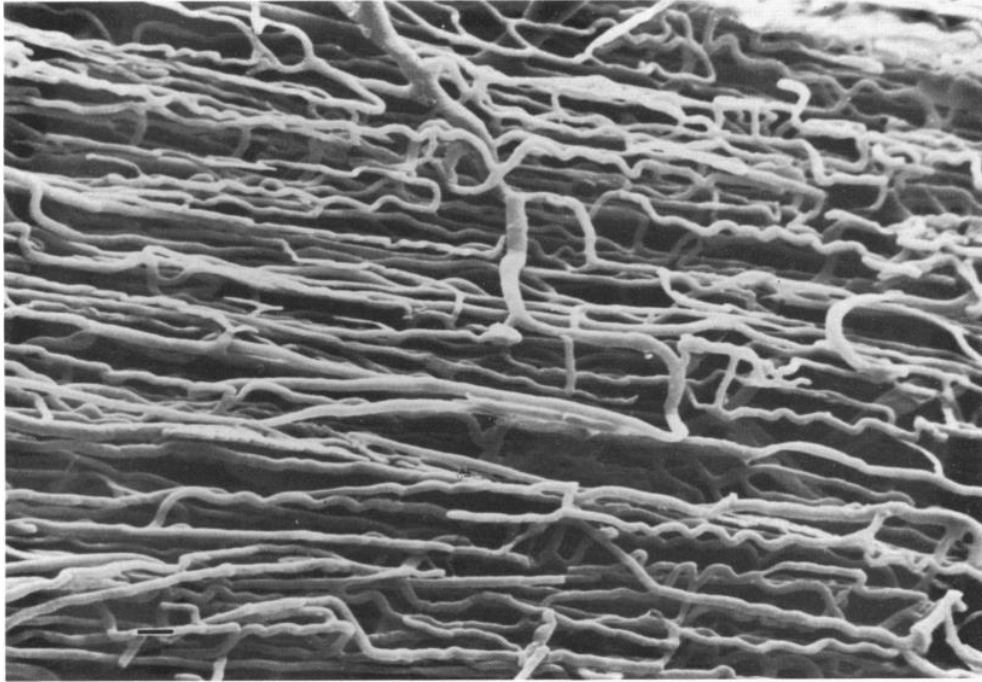
↑ Débits
↑ 2-3 DPG



LES ÉCHANGES GAZEUX AU NIVEAU VASCULAIRE

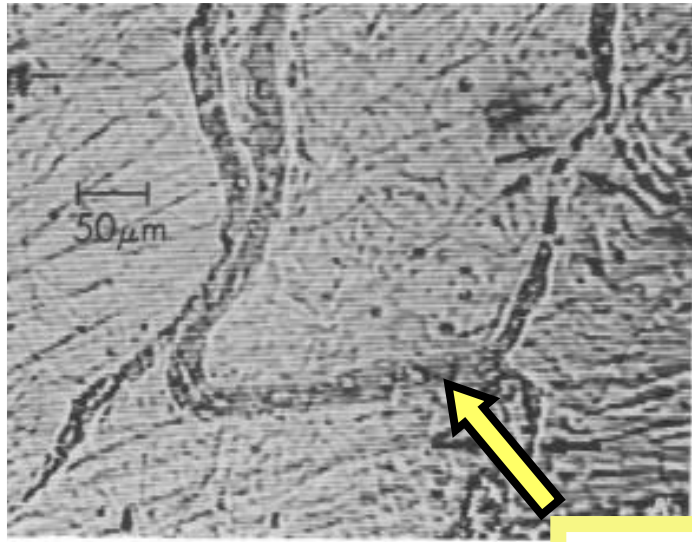


LES ÉCHANGES GAZEUX AU NIVEAU VASCULAIRE

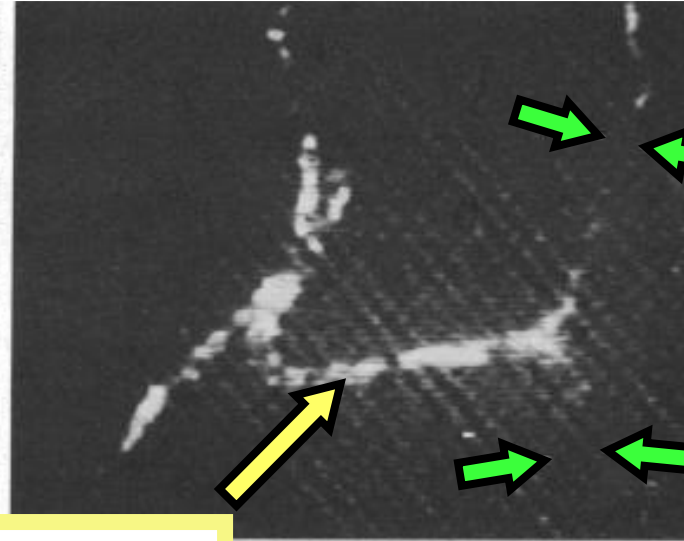


LA VASO-OCCLUSION UN PROCESSUS COMPLEXE

EST-CE EXCLUSIF DE LA DRÉPANOCYTOSE ?



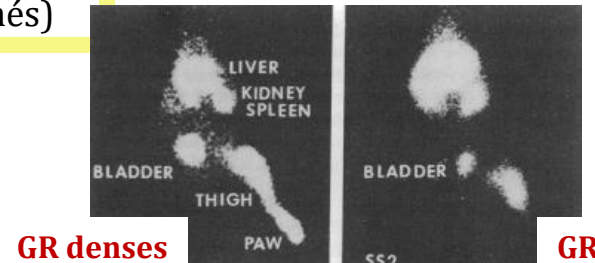
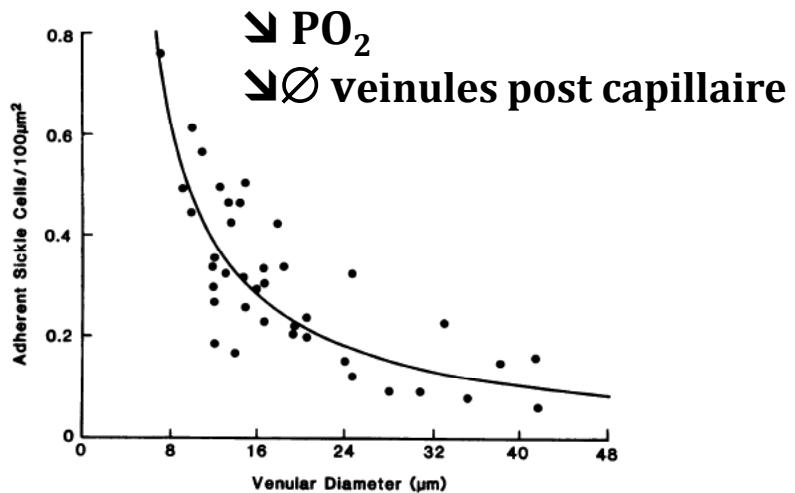
GR denses (FITC)
(GR falciformés)



Kaul et al 1989

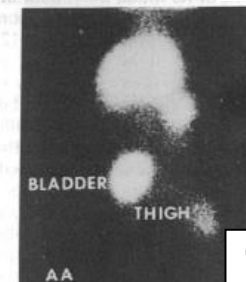
GR non falciformés
(non marqués FITC)

Phénomènes
d'adhérence
non spécifiques
à la drépanocytose



GR denses

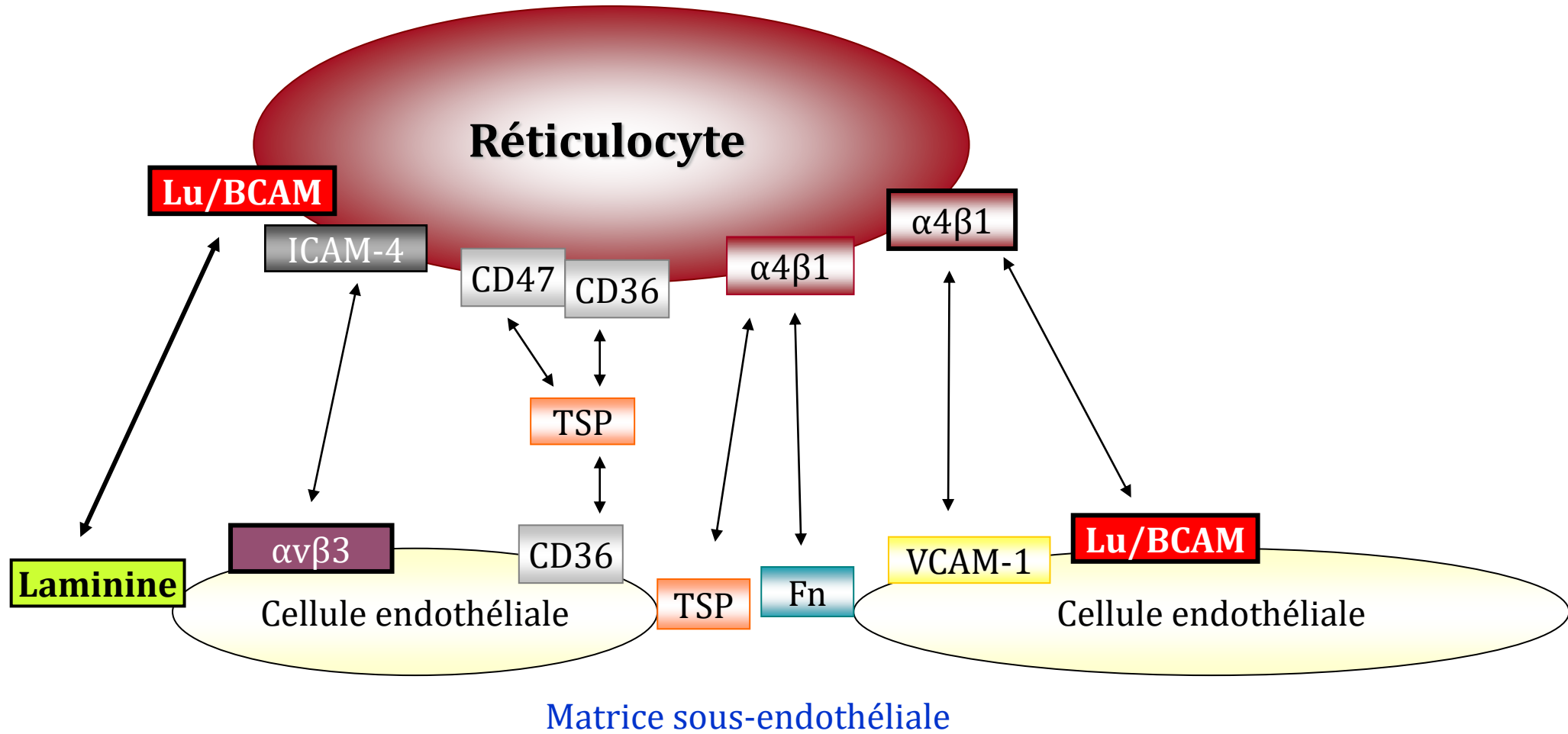
GR



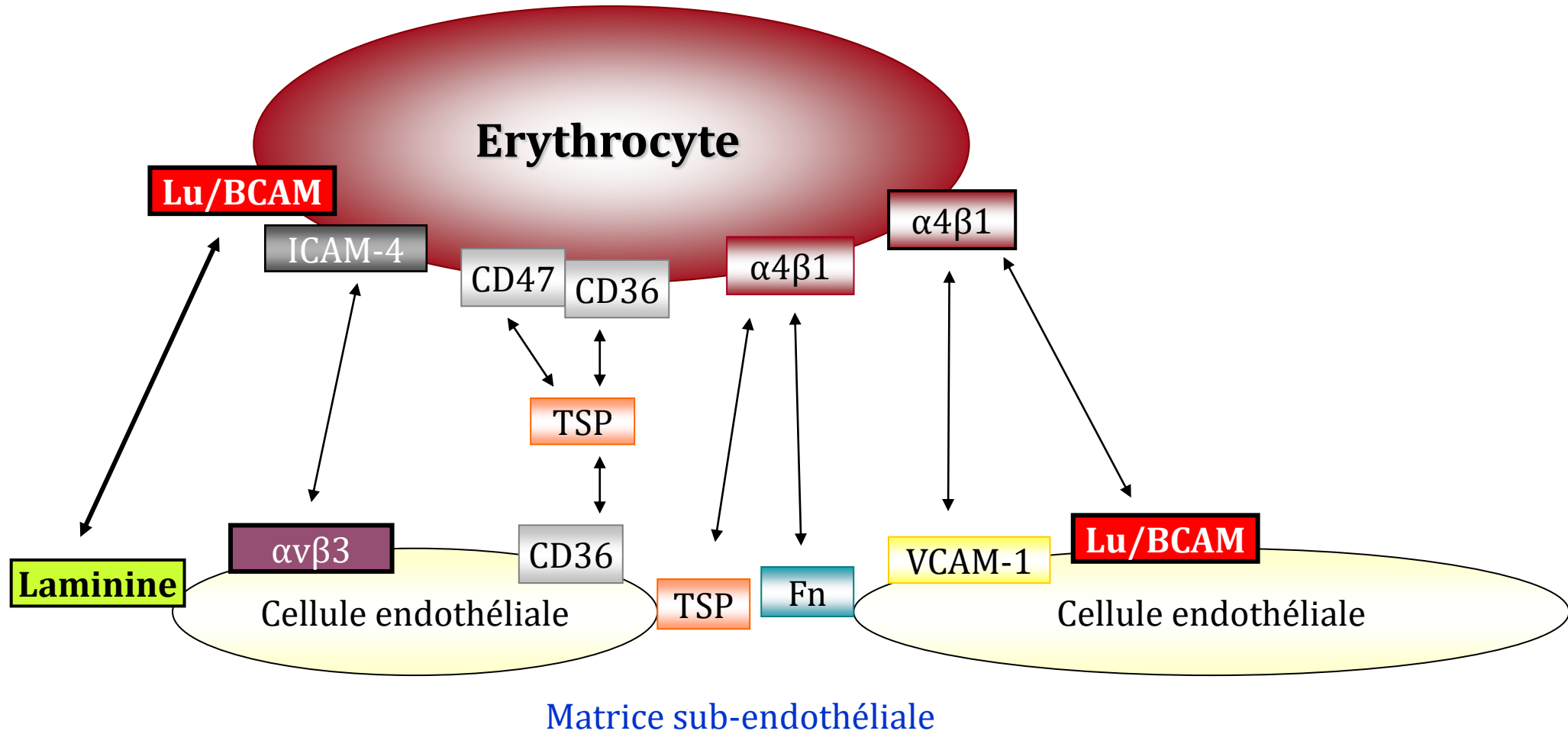
Témoin AA

Fabry et al 1989

INTERACTIONS GR – ENDOTHÉLIUM PAROI VASCULAIRE



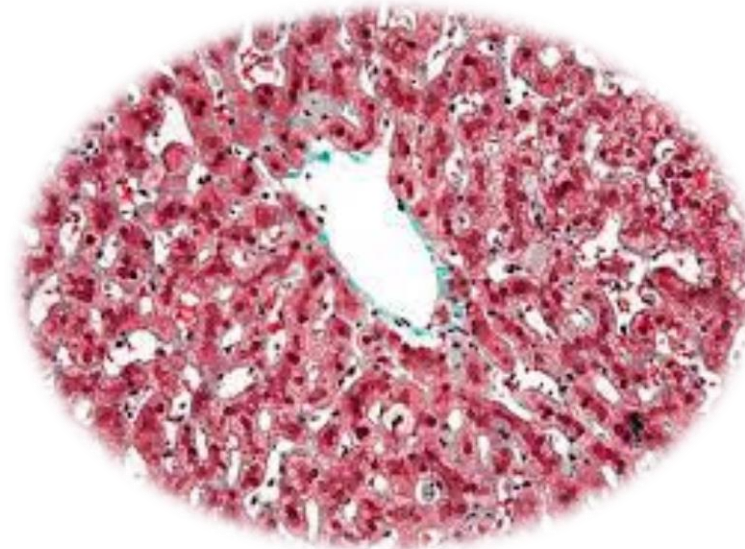
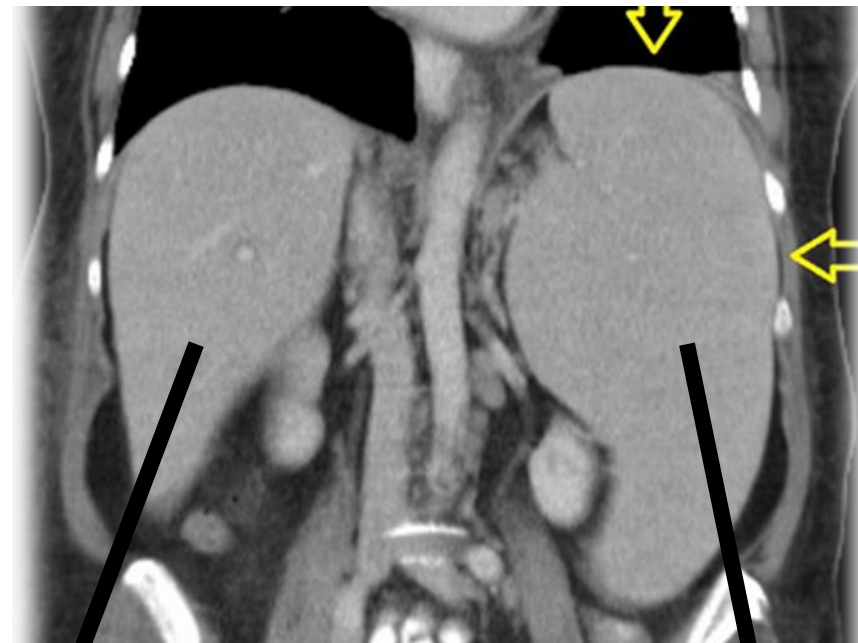
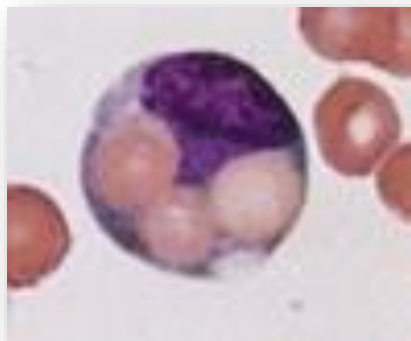
INTERACTIONS GR – ENDOTHÉLIUM PAROI VASCULAIRE



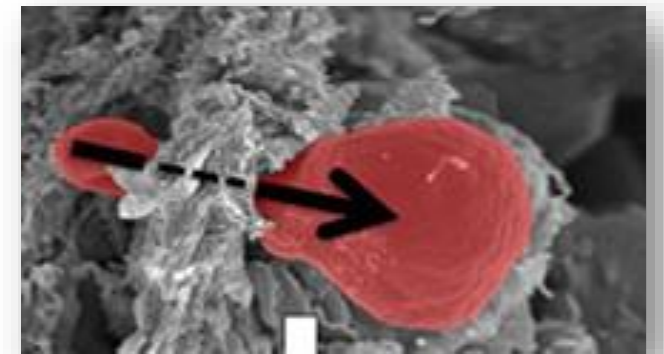
Hémolyse extra vasculaire



Séquestration
Activation macrophagique



Zafrani, données personnelles



Buffet, données personnelles

Drépanocytose

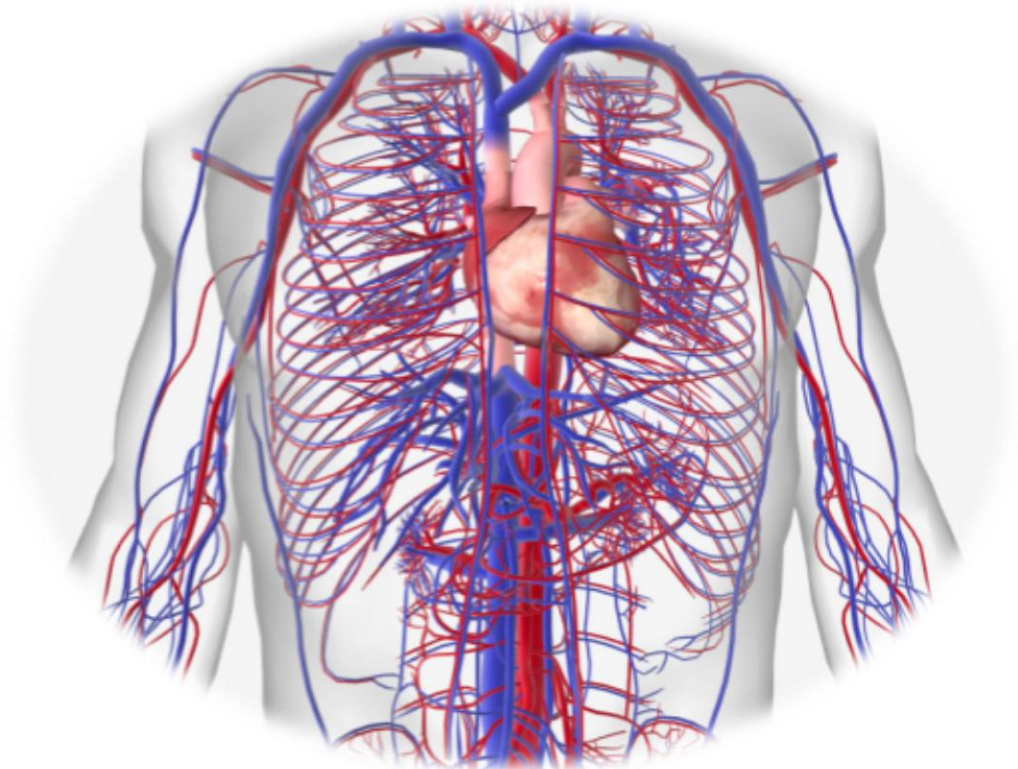
Occlusion de la veine centrale de la rétine

↑ adhérence
GR

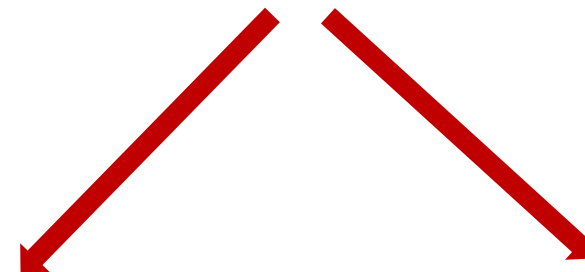
Sphérocytose

Maladie de Gaucher

Paludisme



Hémolyse intra vasculaire



**Vasculopathie
aigüe**

**Vasculopathie
chronique**

Hémoglobinurie paroxystique nocturne

Drépanocytose

b thalassémie

AHAI

Hémoglobinoze H

Hémolyse intra vasculaire

DHTR

Stomatocytose splénectomisé
Pyropoikilocytose

Déficit G6PD

ECMO

Déficit PK

Hémoglobinurie paroxystique nocturne

Drépanocytose

b thalassémie

HémoglobinoH

AHAI

**Hémolyse intra vasculaire
avec discordance
Hème - Hémoglobine plasmatique
(Hème médullaire ou cinétique ?)**

Stomatocytose splénectomisé
Pyropoikilocytose

DHTR

Déficit G6PD

ECMO

Déficit PK

Hémoglobinurie paroxystique nocturne

Drépanocytose

b thalassémie

AHAI

Hémoglobinoze H

**Hémolyse intra vasculaire
avec activation du complément**

Stomatocytose splénectomisé
Pyropoikilocytose

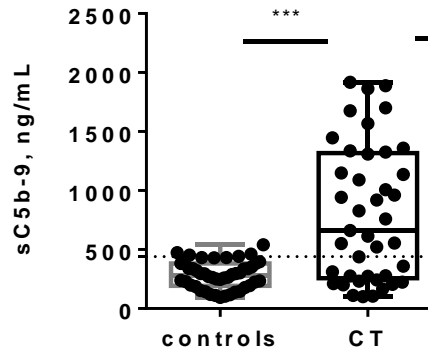
DHTR

Déficit G6PD

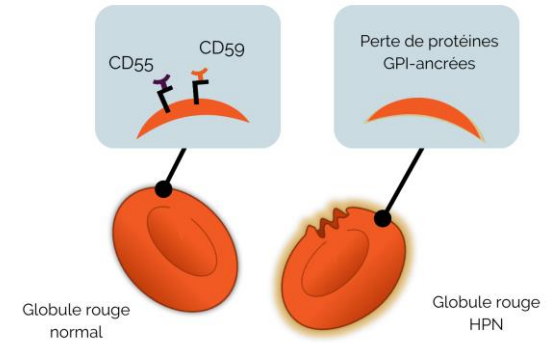
ECMO

Déficit PK

Drépanocytose

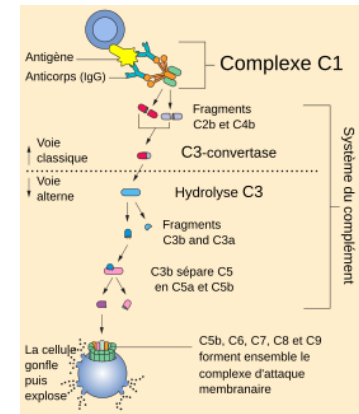


Hémoglobinurie paroxystique nocturne



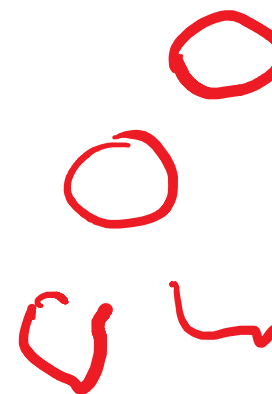
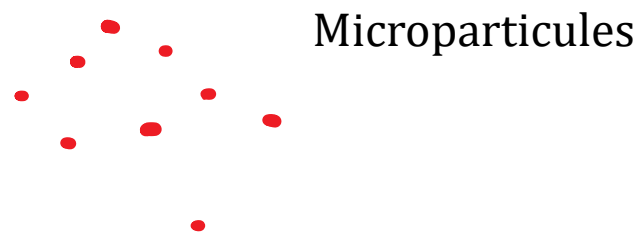
Hémolyse intra vasculaire avec activation du complément

AHAI

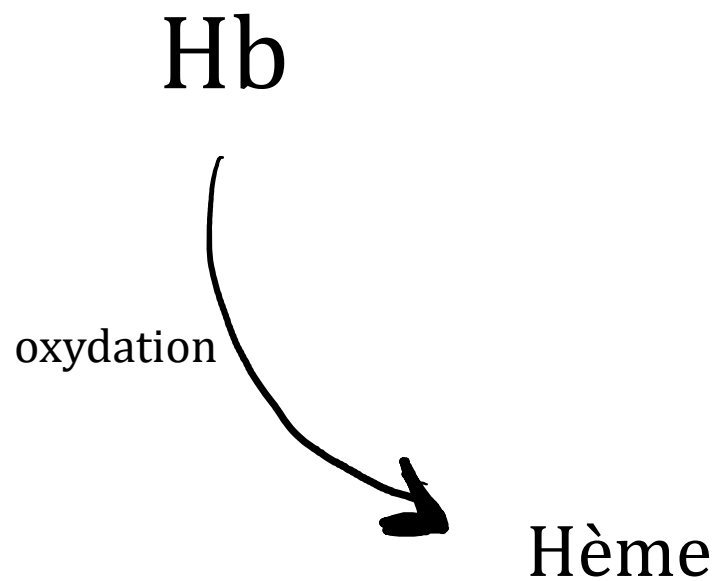


DHTR

	Day*	C3 level (mg/L)	C4 level (mg/L)	sC5B9 level (mg/L)
Patient 1				
Before eculizumab infusion	0	1080	266	856
First follow-up assessment	2	1030	283	1223
Second follow-up assessment	14	1050	248	1406
Patient 2				
Before eculizumab infusion	0	—	—	—
First follow-up assessment	7	1270	257	1797
Patient 3				
Before eculizumab infusion	0	1070	220	1527
First follow-up assessment	4	313	104	296
Second follow-up assessment	6	359	129	224
Third follow-up assessment	9	928	526	355
Fourth follow-up assessment	13	1210	290	509

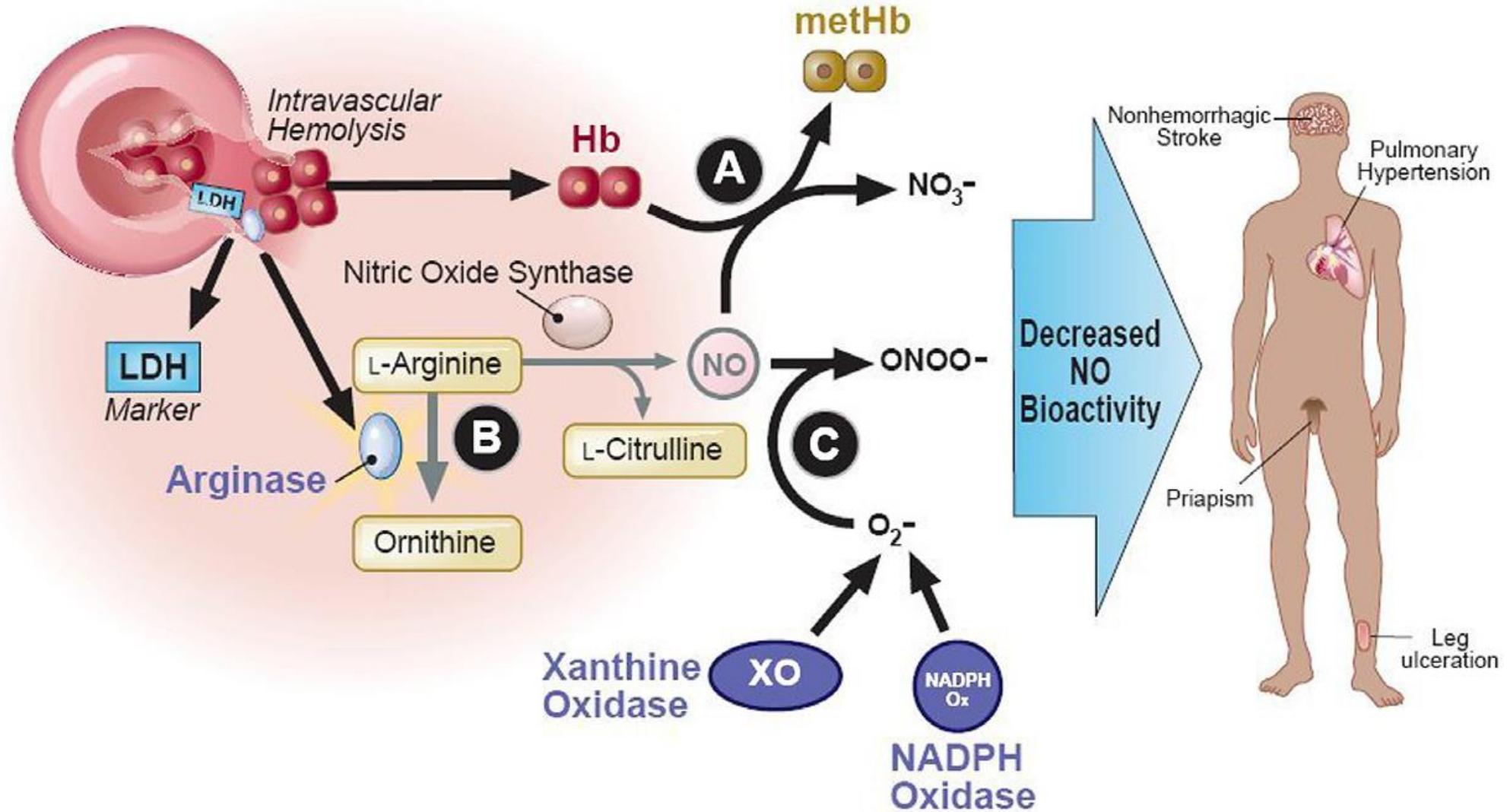


particules > 1 μ m

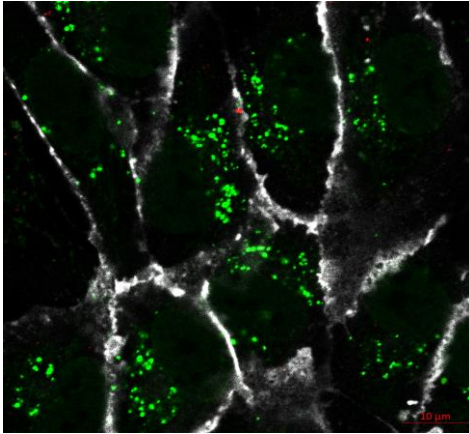


ENZYMES

HÉMOGLOBINE

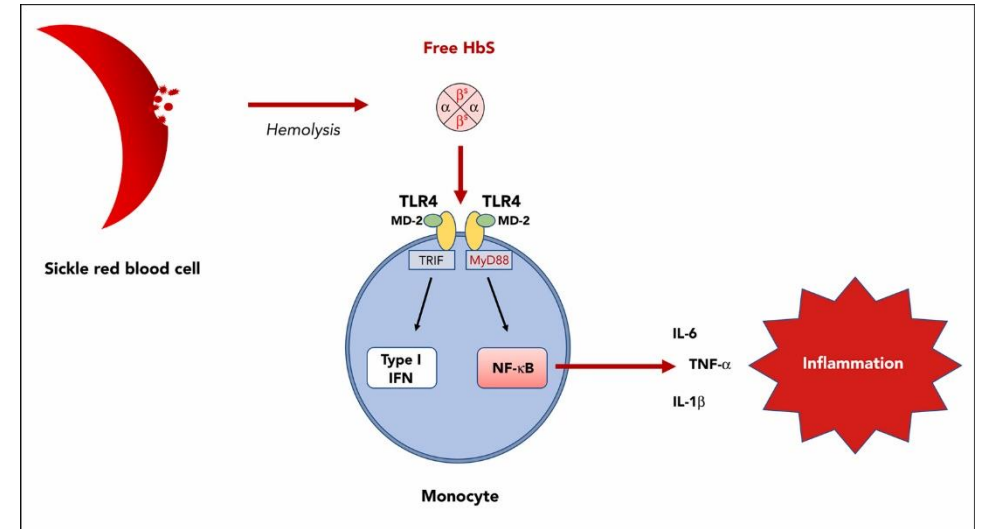


HÉMOGLOBINE



Hb plasma

Pratiquement aucun effet
sur les cellules endothéliales



Allali Blood 2022

HbS → Activation monocyte

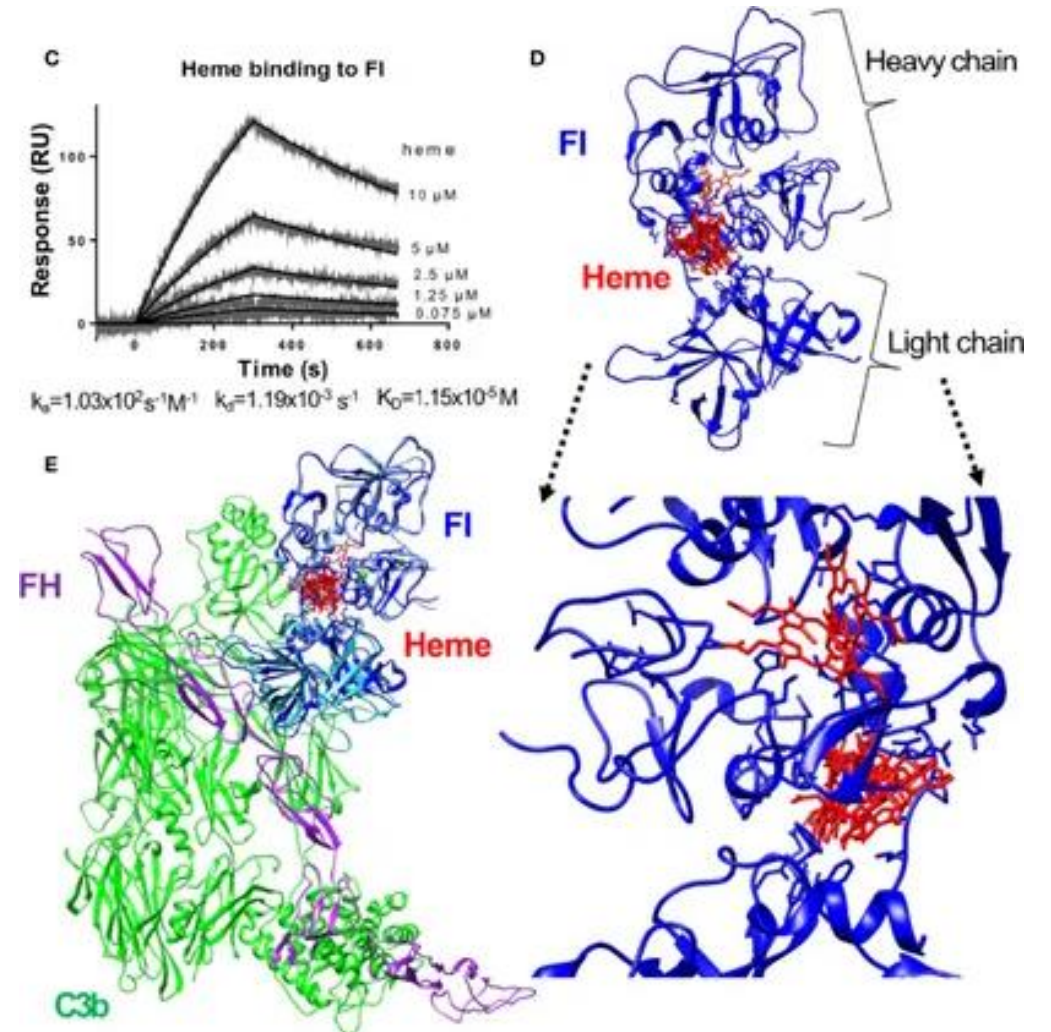
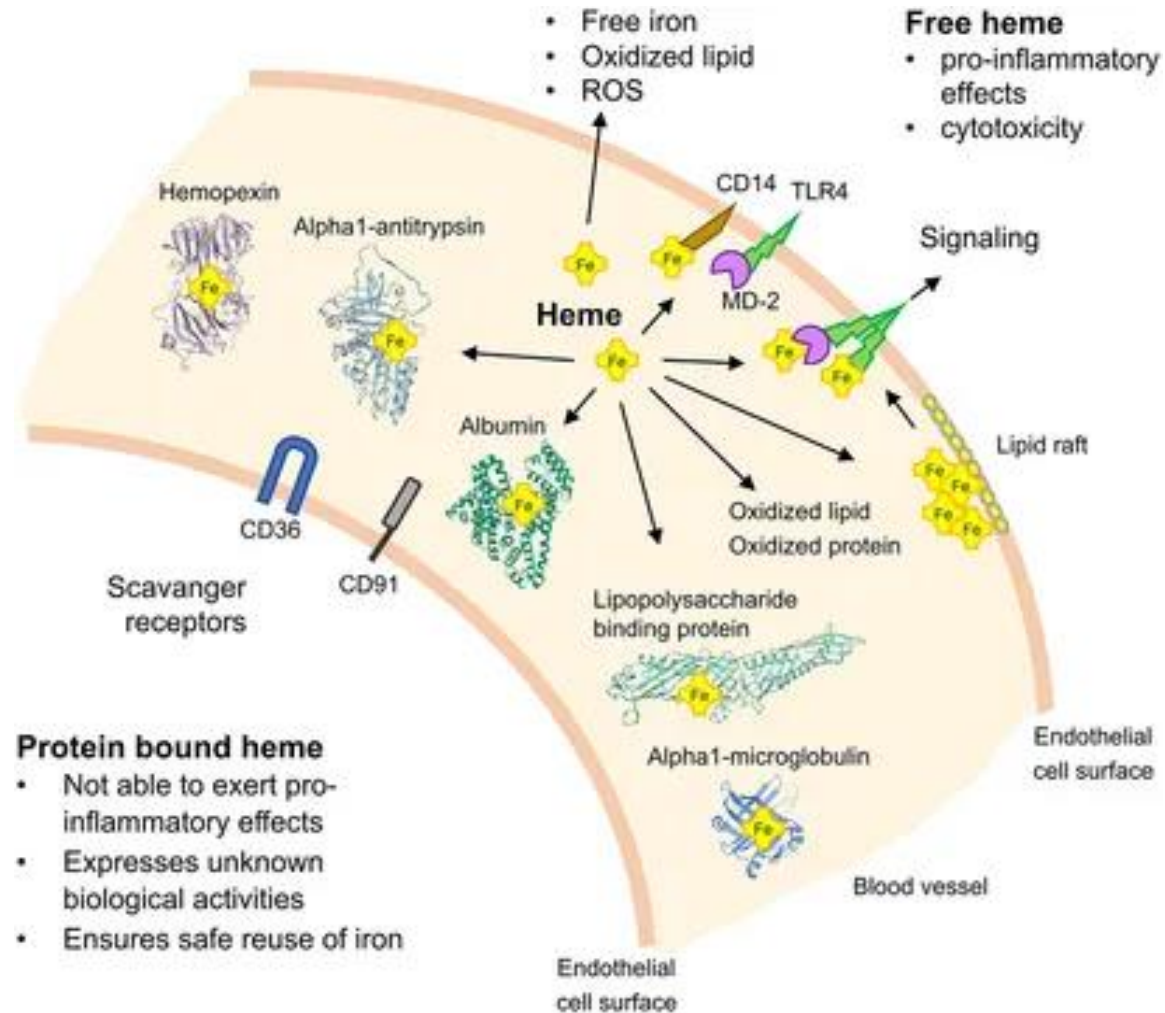
Toxicité tubulaire

Libération Hème
Stress oxydatif

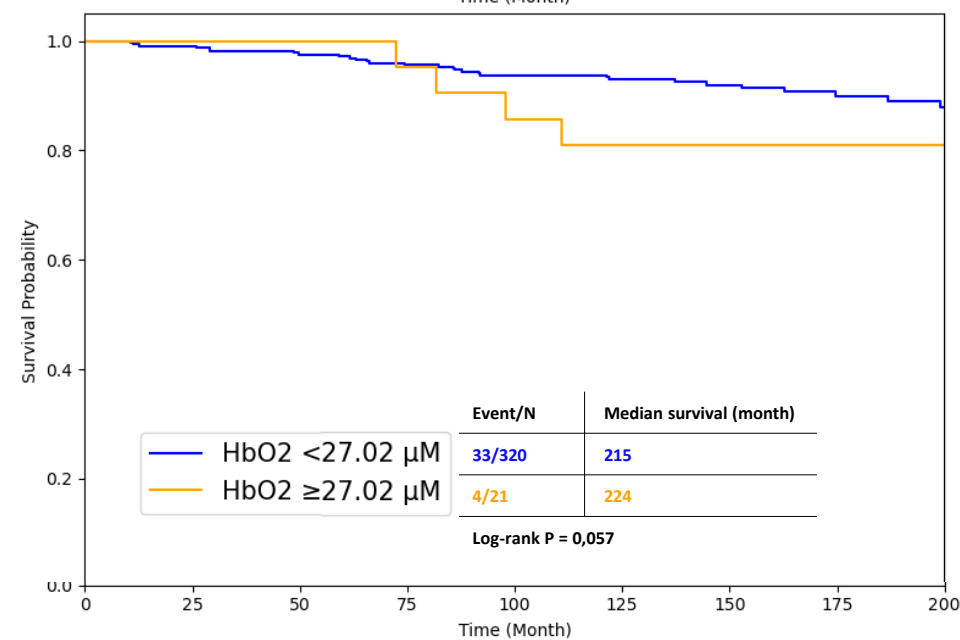
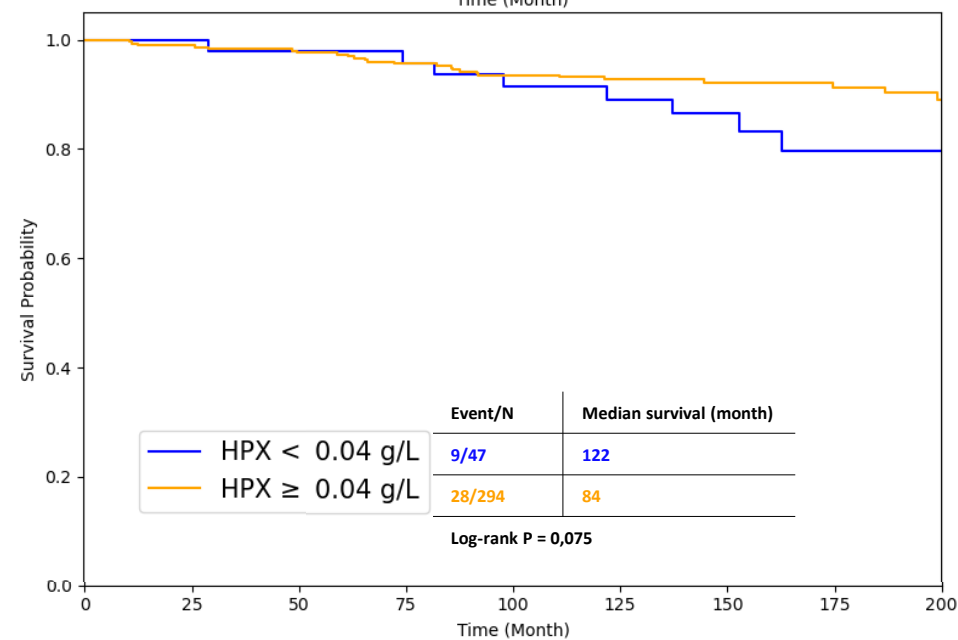
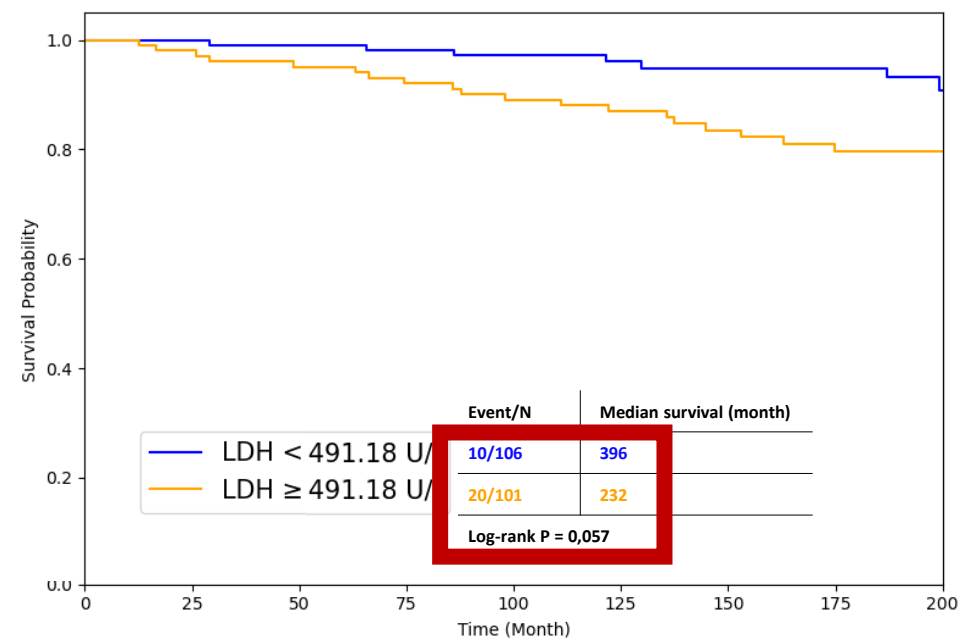
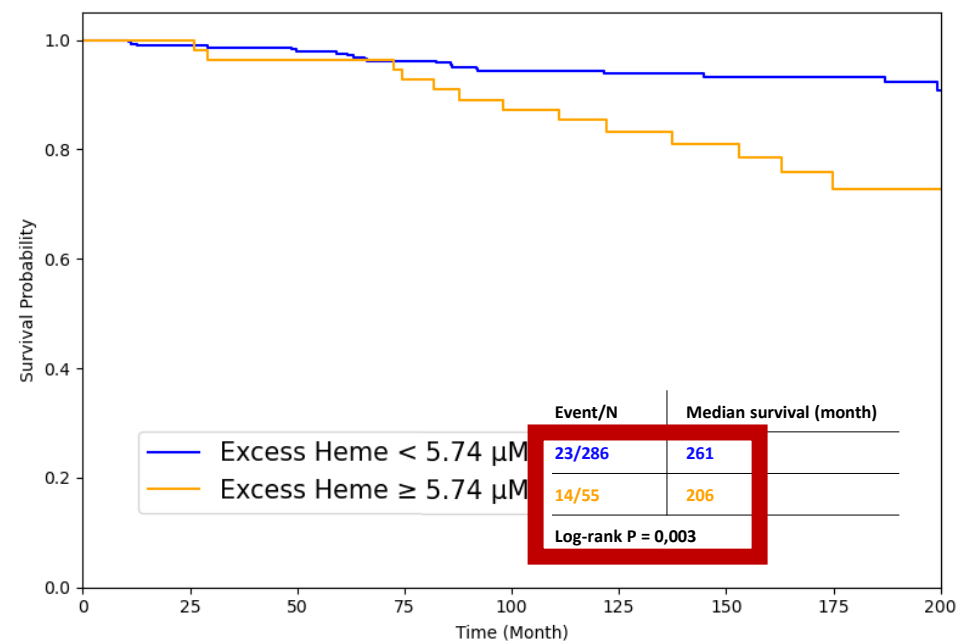
Précipitation
tubulaire

Compétition pour megalin/cubulin
↓ Réabsorption proximale

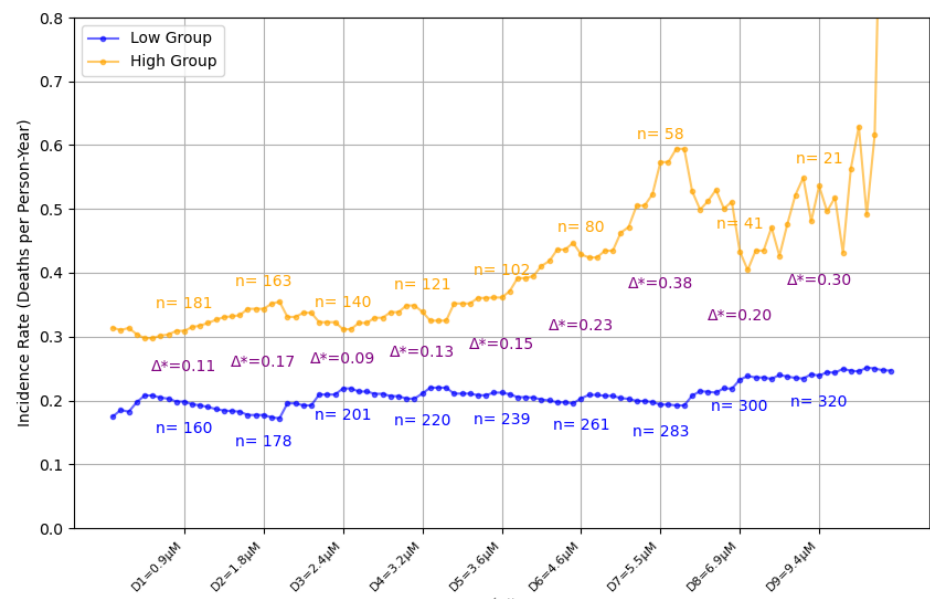
HÈME



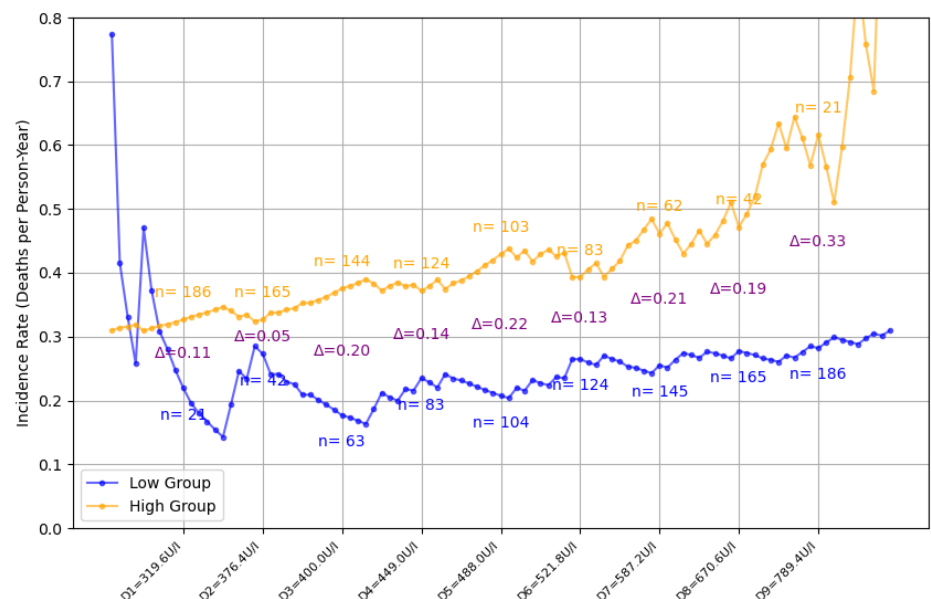
SURVIE À 15 ANS D'UNE COHORTE DE 341 PATIENTS DRÉPANOCYTAIRES (DONNÉES PRÉLIMINAIRES)



SURVIE À 15 ANS D'UNE COHORTE DE 341 PATIENTS DRÉPANOCYTAIRES (DONNÉES PRÉLIMINAIRES)



HEME

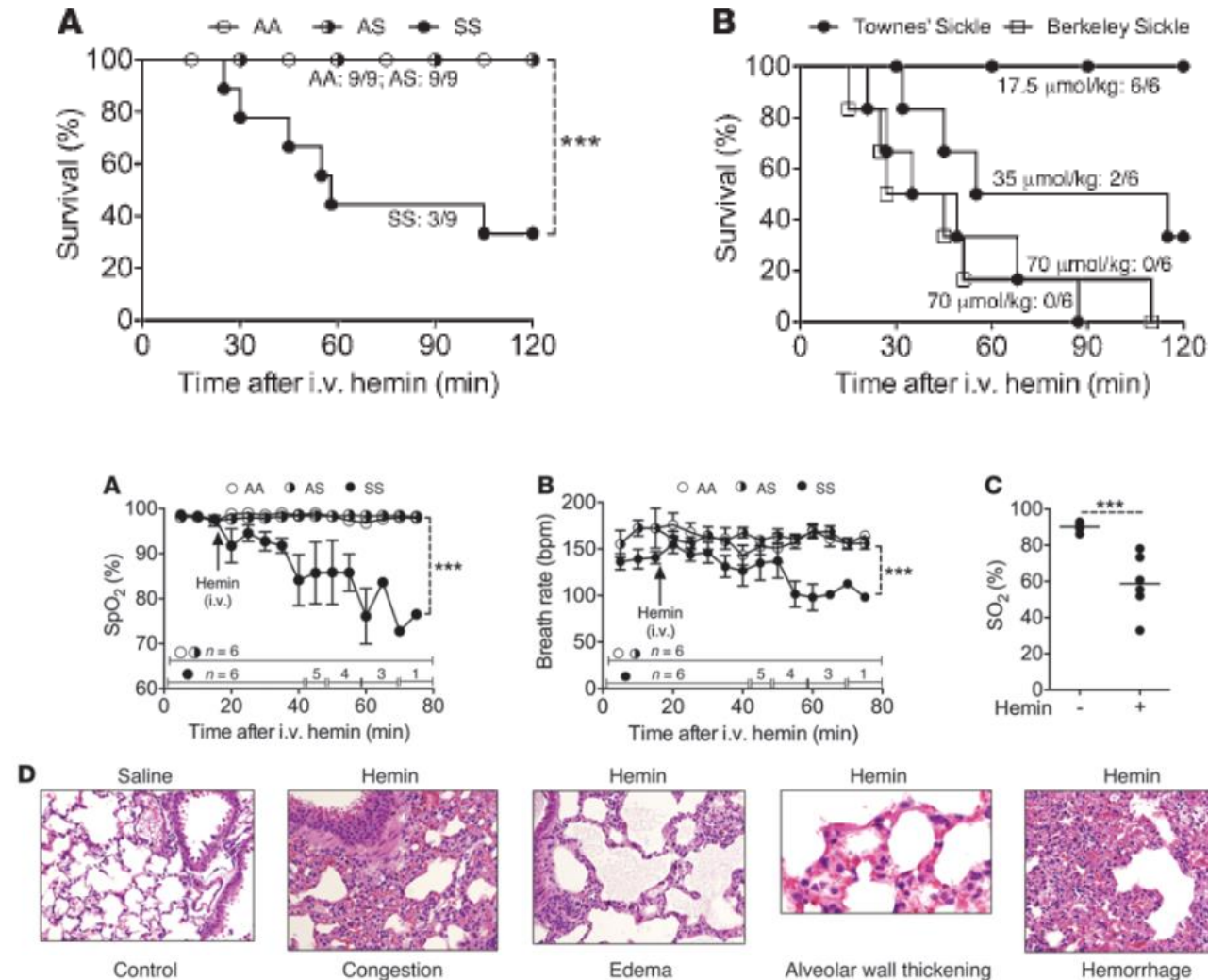


LDH

Cumulative incidence rate trends and differences with statistical significance stratified by hemolytic factor thresholds in sickle cell patients.

L'HÈME PROVOQUE UNE VASO-OCCLUSION SÉVÈRE

MODÈLE MURIN DRÉPANOCYTAIRE



PARTICULES ÉRYTHROCYTAIRES INFLAMMATION



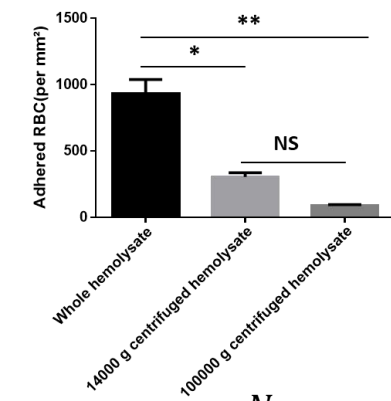
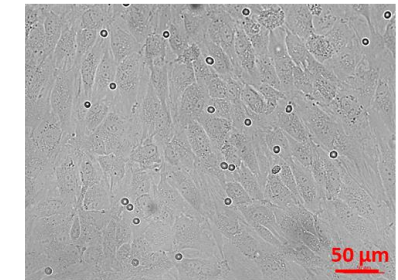
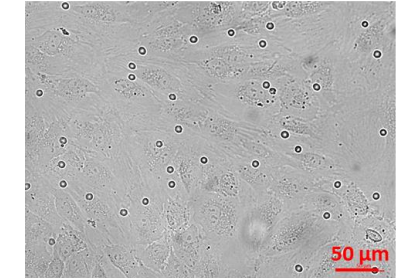
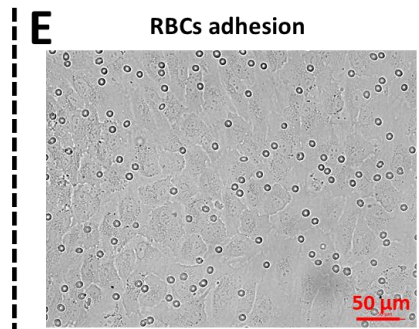
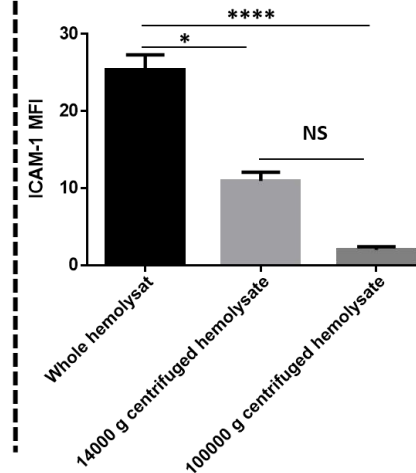
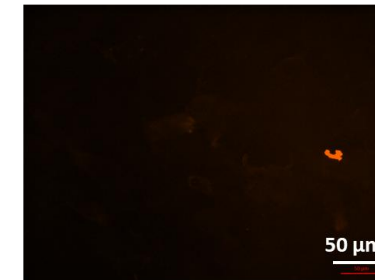
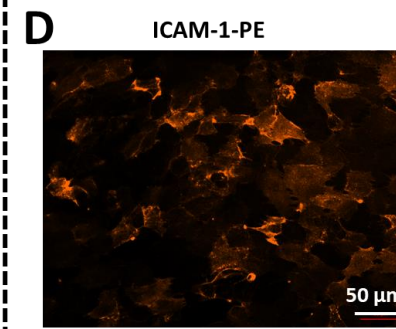
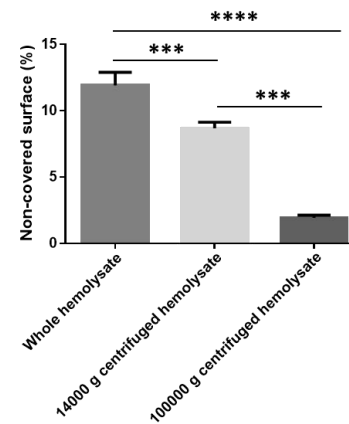
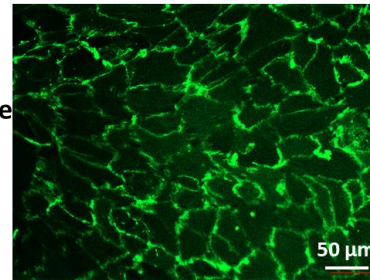
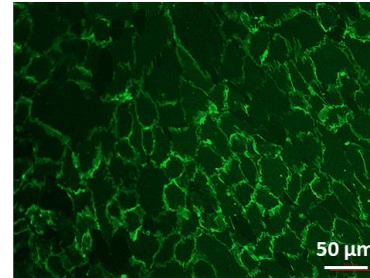
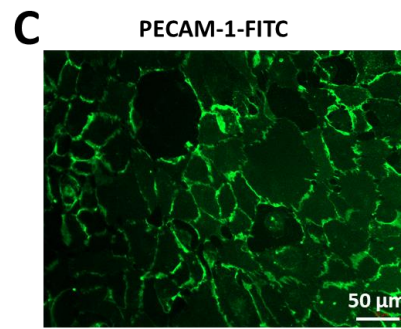
Particules > 1 μ m

Microparticules

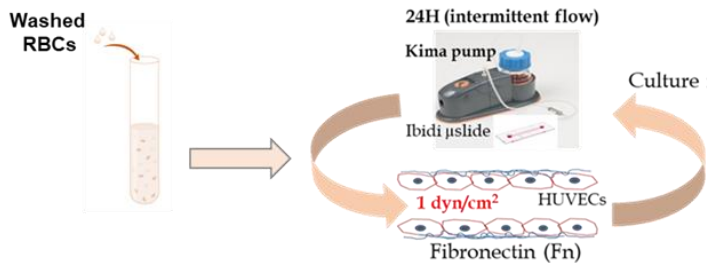
Whole hemolysate

14000 g centrifuged hemolysate

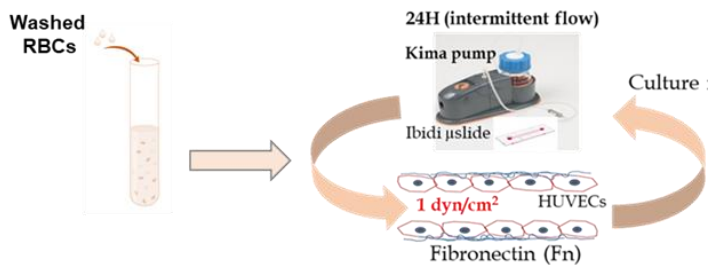
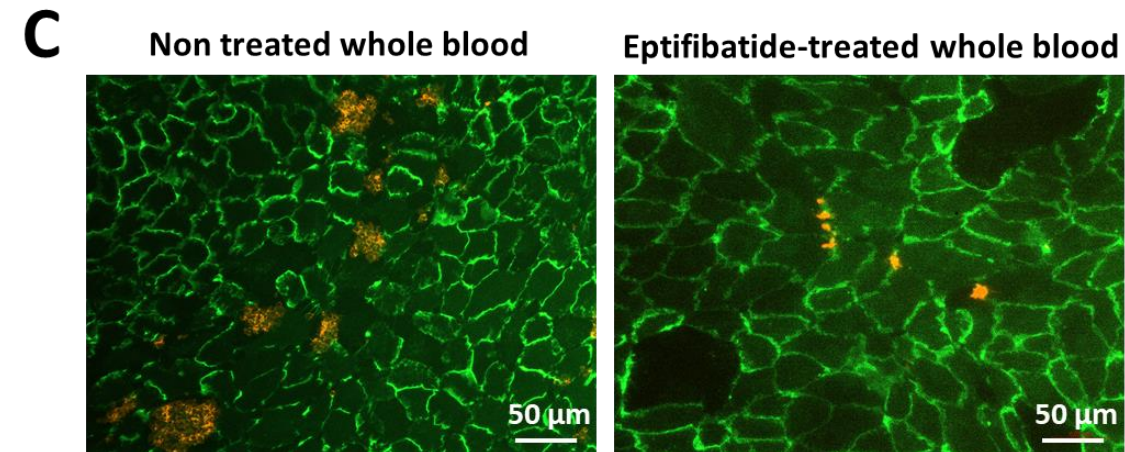
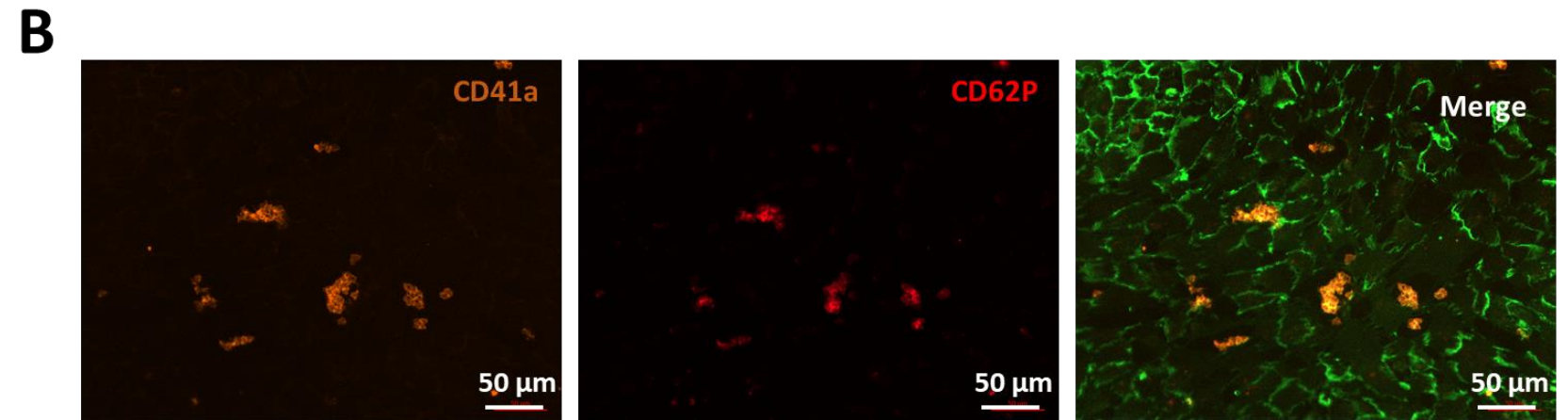
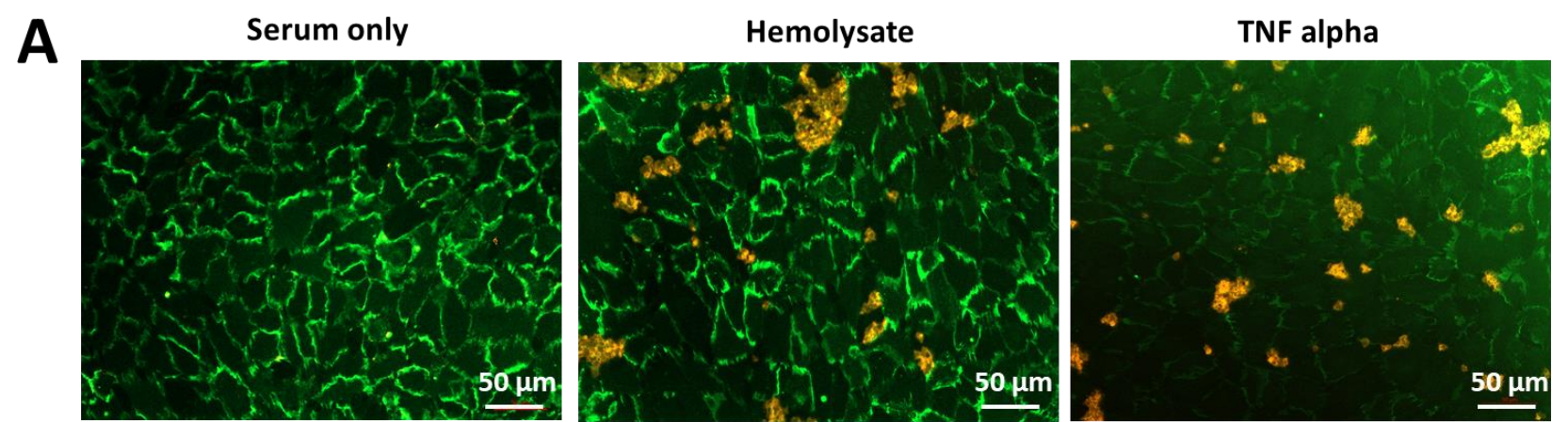
100000 g centrifuged hemolysate



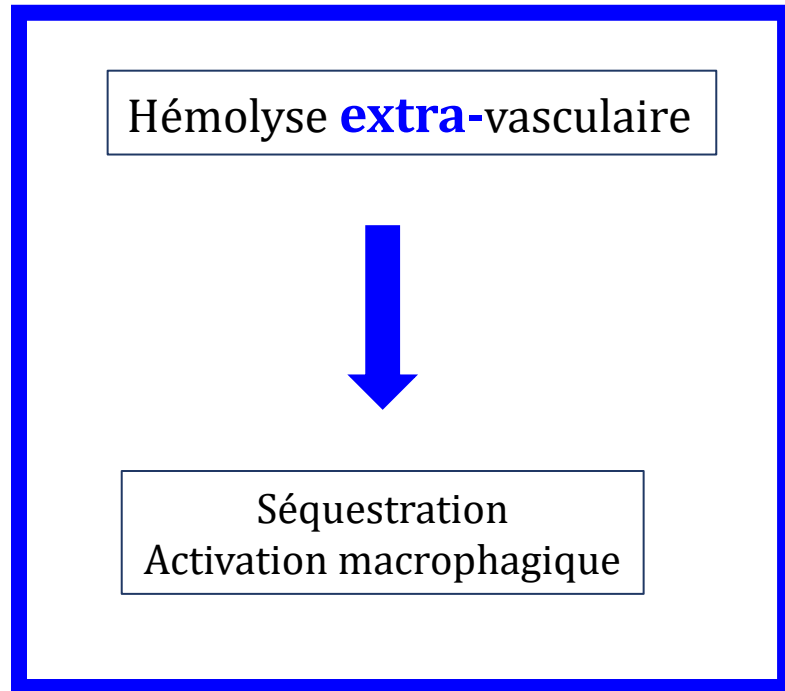
Nguyen, en préparation



PARTICULES ÉRYTHROCYTAIRES COAGULATION



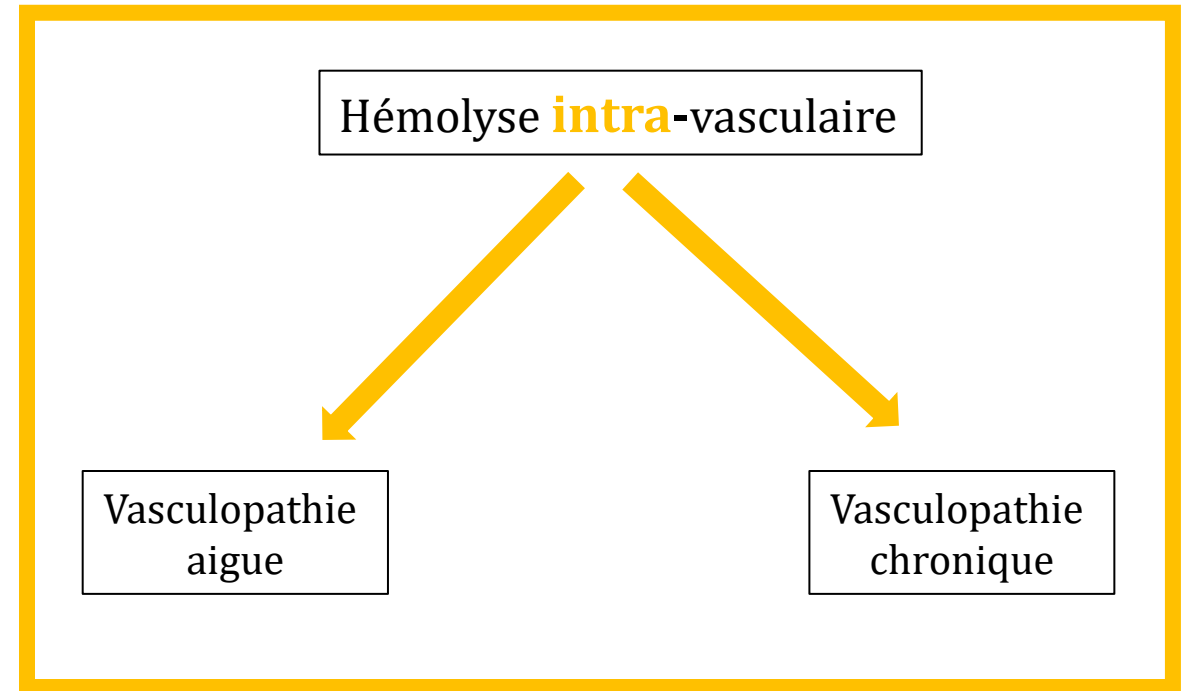
ASPECTS THÉRAPEUTIQUES GÉNÉRAUX



Traitement de la cause

Splénectomie ?

Traitement visant la ↓ activation macrophagique



Traitement de la cause ++

Inhibiteurs du complément

Hémopexine
Echange plasmatique
avec plasma

Nouvelles approches
plus ciblées sur les voies
effectrices

CONCLUSION

- Les hémolyses recoupent des processus très différents et complexes
- Nécessité de déterminer :
 - La cause de l'hémolyse
 - Le caractère extra ou intra vasculaire
- Besoin d'outils biologiques
- Meilleure compréhension des hémolyses pour adapter les traitements

