Actualités en recherche translationnelle dans les CAI

Pr Sylvain AUDIA

Service de Médecine Interne et Immunologie Clinique,

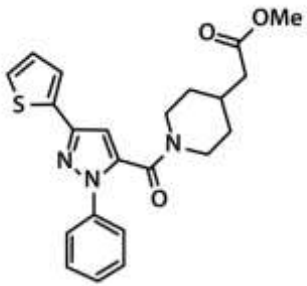
Centre constitutif de références des cytopénies auto-immunes Bourgogne/Franche-Comté

Journée nationale du CERECAI, 10 octobre 2025

A novel small molecule phagocytosis inhibitor, KB-208, ameliorates ITP in mouse models with similar efficacy as IVIG

Melika Loriamini[1,2] | Melissa M. Lewis-Bakker[3] | Beth Binnington[2] | Lakshmi P. Kotra[3,4] | Donald R. Branch[1,2,5]

TRANSFUSION
2024;64:2233–2240.



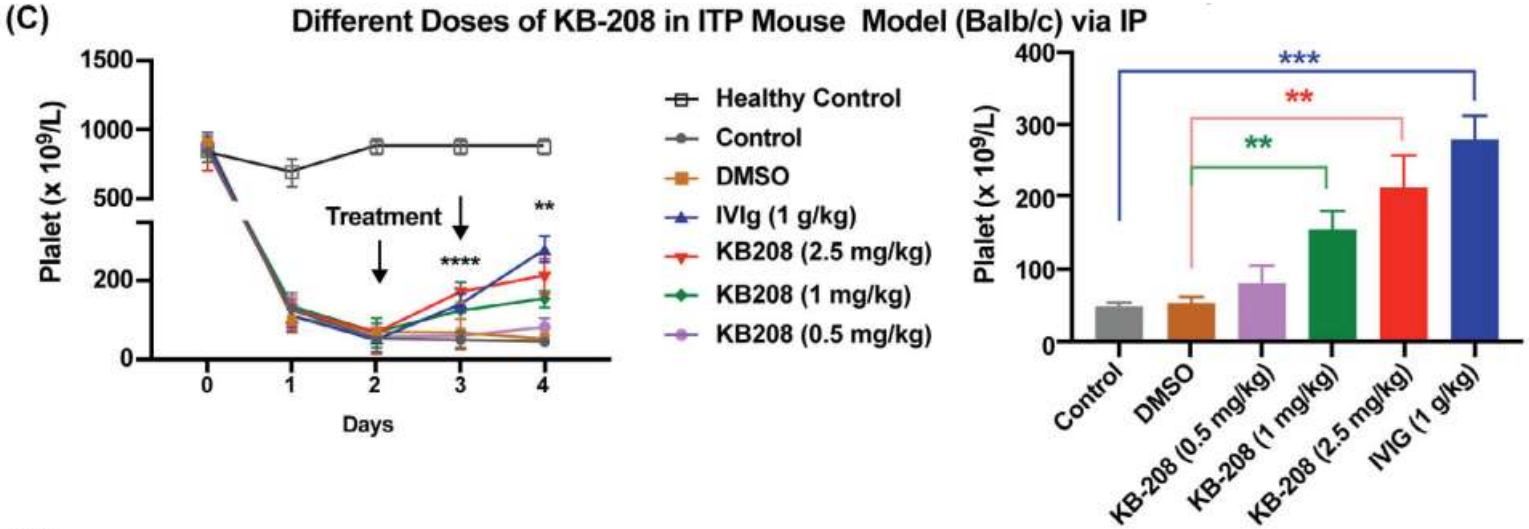
KB-208

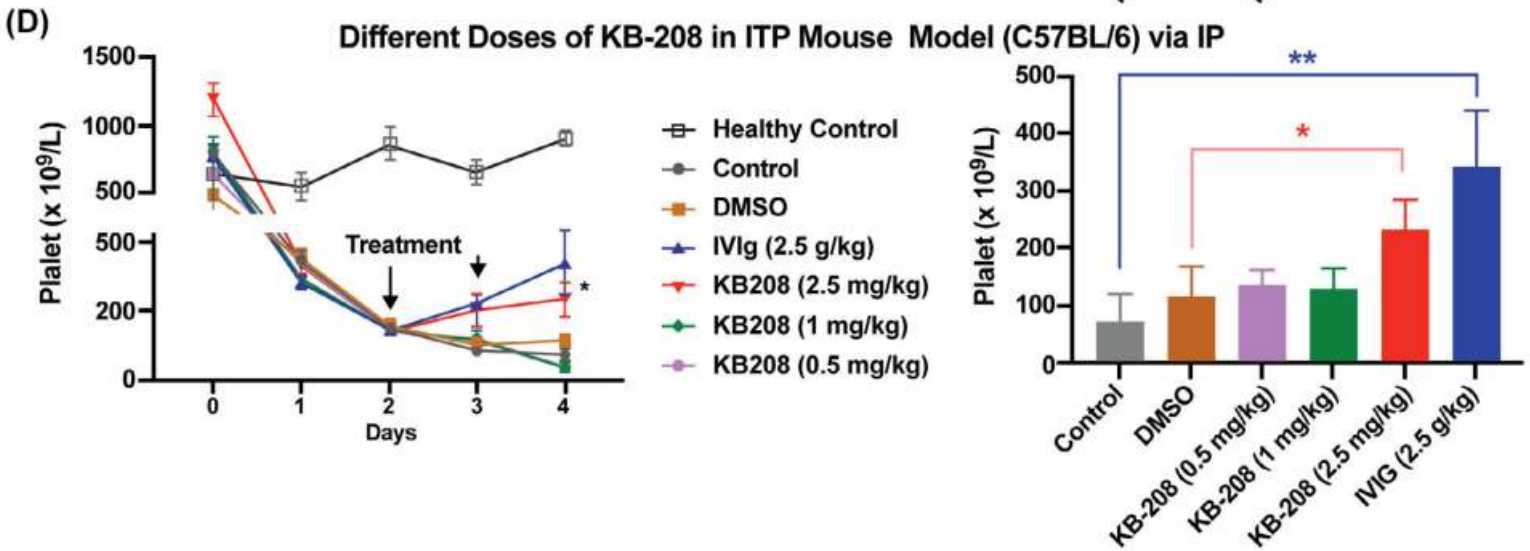
Methyl 2-{1-{1-phenyl-3-{thiophen-2-yl}-1*H*-pyrazole-5-carbonyl}piperidin-4-yl}acetate

Fixation / inhibition des FcγR ?

Study Design and Methods: KB-208, a small molecule drug, previously shown to be efficacious for the in vitro inhibition of phagocytosis was synthesized. A passive antibody mouse model of immune thrombocytopenia (ITP) was used. Three different mouse strains (BALB/c, C57BL/6, CD1) were used to determine the efficacy of KB-208 compared with IVIG to ameliorate the ITP. Toxicity was investigated after 60-day chronic administration of KB-208 by a biochemistry panel, gross necroscopy and histopathology.

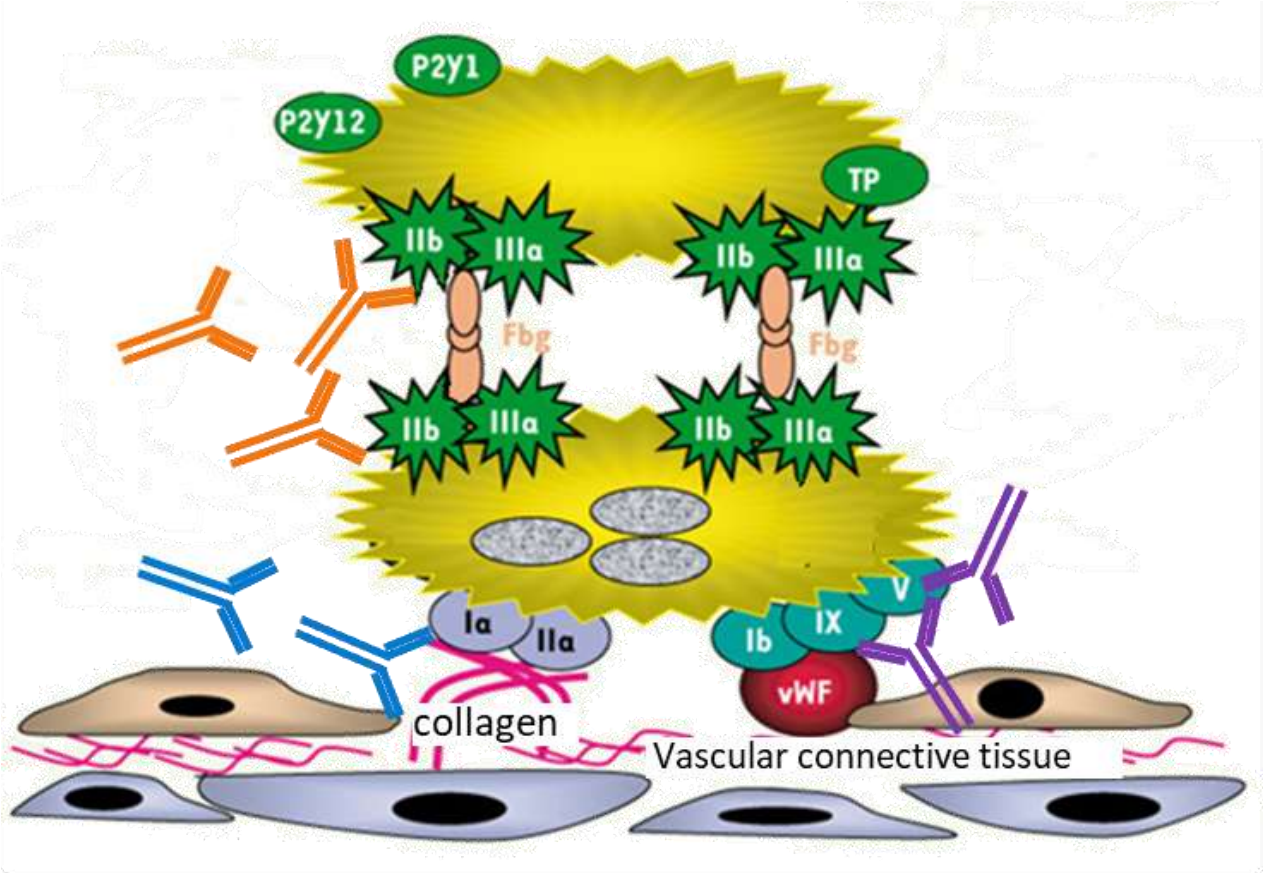
Results: KB-208 showed similar efficacy to ameliorate the thrombocytopenia compared with IVIG in all three mouse strains. This small molecule drug was effective at 1 mg/kg in ameliorating ITP, in comparison with IVIG at 1000–2500 mg/kg. KB-208 did not affect other blood parameters or elevate serum biochemistry markers of toxicity nor were any abnormal histopathological findings found.





Anticorps antiplaquettes et PTI

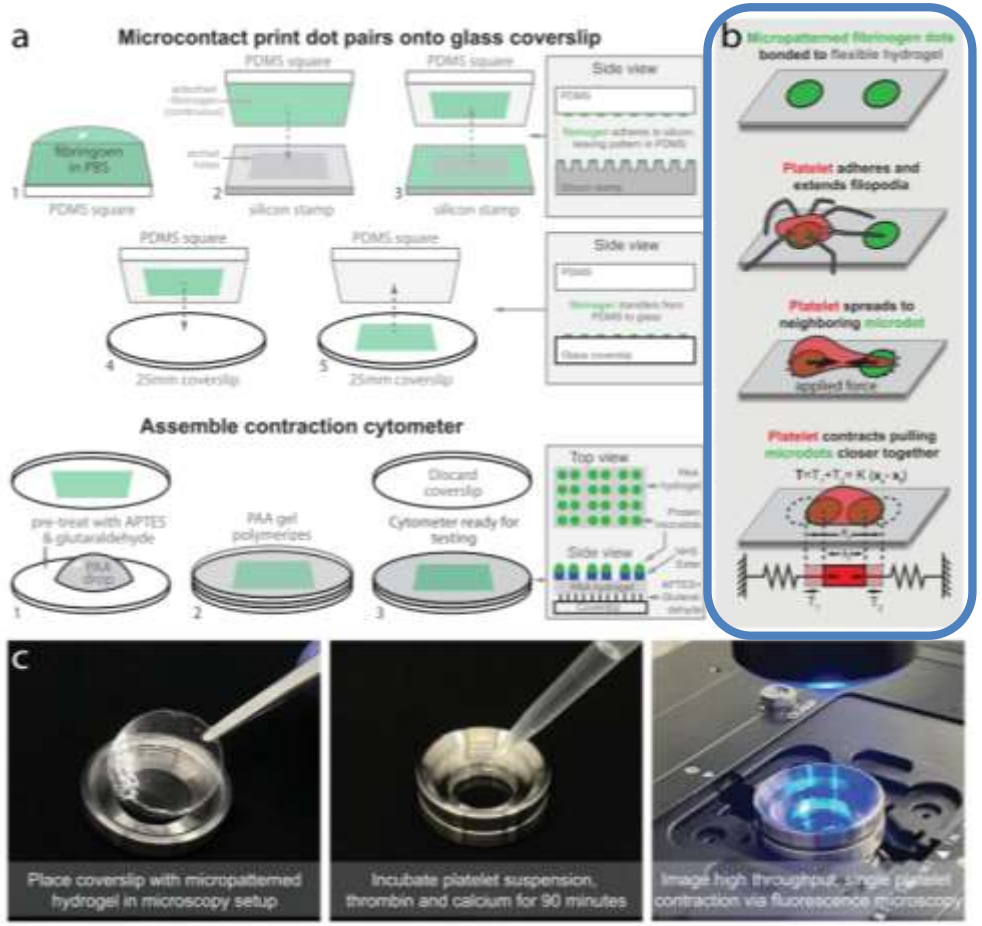
Les anticorps antiplaquettes, par leurs interactions avec les glycoprotéines plaquettaires, peuvent-ils perturber les fonctions plaquettaires ?



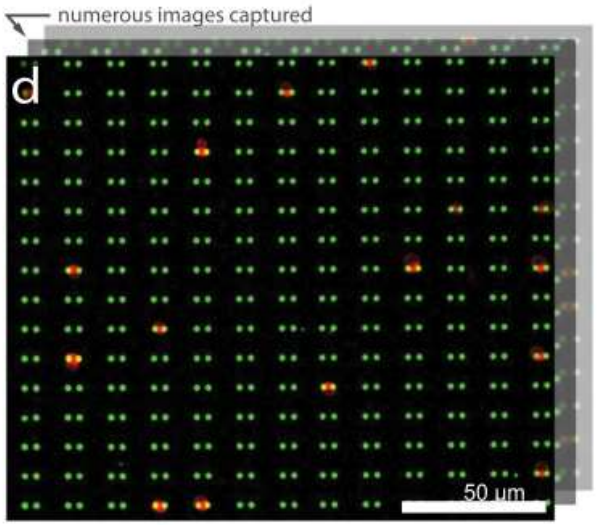
Autoantibodies immuno-mechanically modulate platelet contractile force and bleeding risk

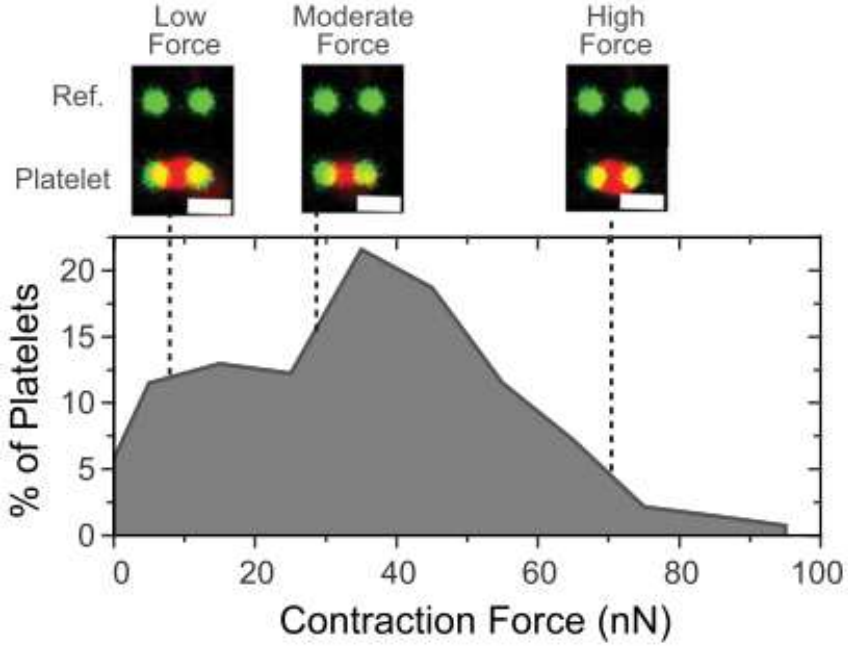
Nature Communications | (2024)15:10201

Oluwamayokun Oshinowo[1,2,3,4,5], Renee Copeland[1,2,3,4,5], Anamika Patel[6], Nina Shaver[1,2,3,4,5], Meredith E. Fay[1,2,3,4,5], Rebecca Jeltuhin[1], Yijin Xiang[7], Christina Caruso[2,3], Adiya E. Otumala[1,2,4], Sarah Hernandez[7], Priscilla Delgado[1,2,4], Gabrielle Dean[8], James M. Kelvin[1], Daniel Chester[9], Ashley C. Brown[9], Erik C. Dreaden[1], Traci Leong[10], Jesse Waggoner[9], Renhao Li[2], Eric Ortlund[6], Carolyn Bennett[2], Wilbur A. Lam[1,2,3,4,5] & David R. Myers[1,2,4]



- Paires de « points » de microcontact sous une lentille
- « Points » contenant du fibrinogène fluorescent
- Incubation de plaquettes, activation => liaison au fibrinogène
- Contraction cellulaire est proportionnelle au rapprochement des points





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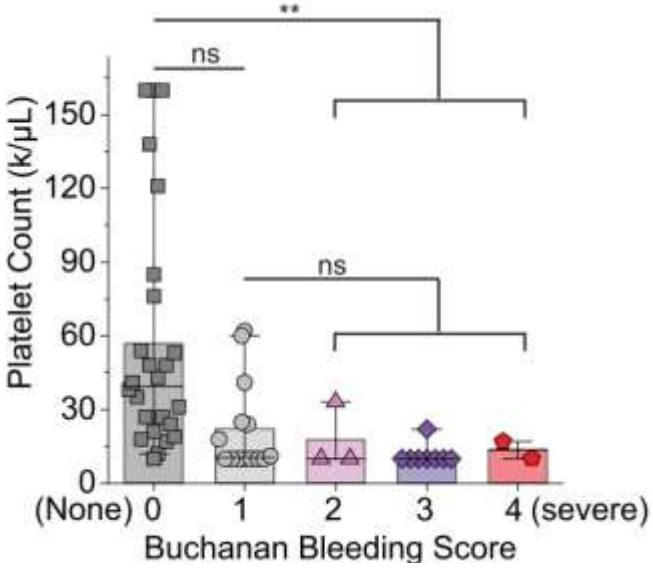
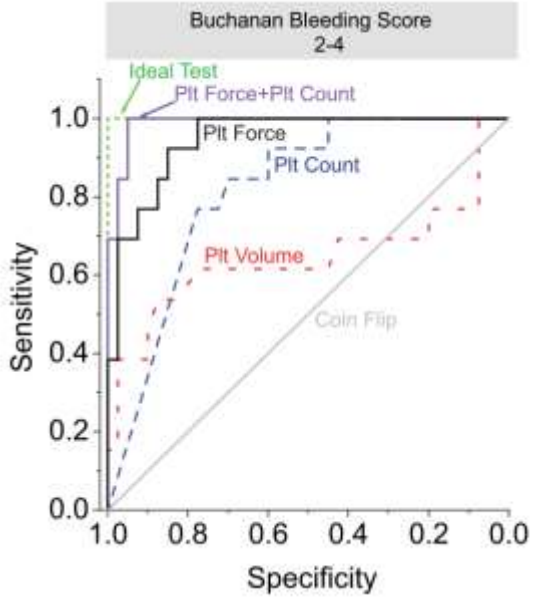
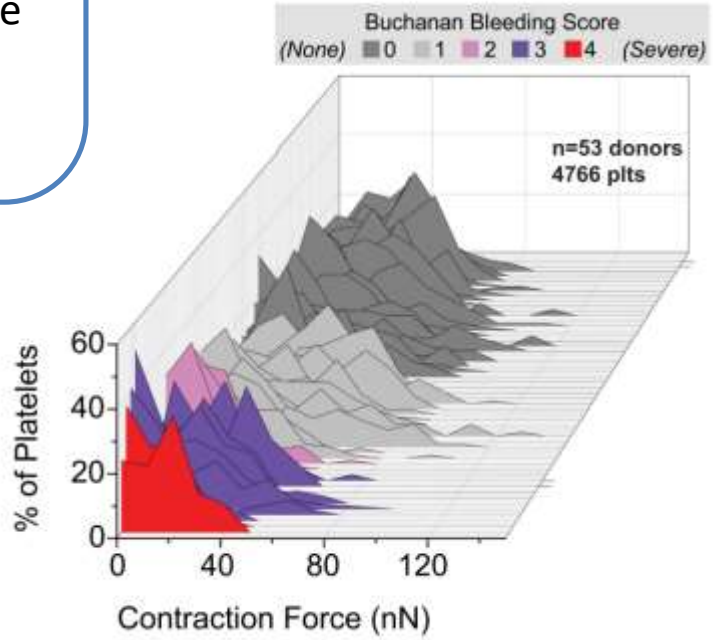
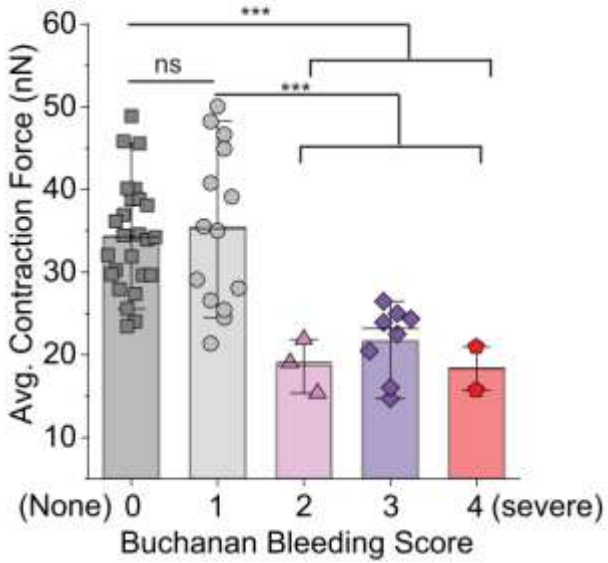
- 53 enfants
- Saignement évalué par le score de Buchanan (0-5)

- Association entre saignement et plaquettes (< 20 G/L)
- Association entre sgt et faible contractilité plaquettaire
- Saignements mieux prédits par l'association chiffre de plaquettes & contractilité plaquettaire









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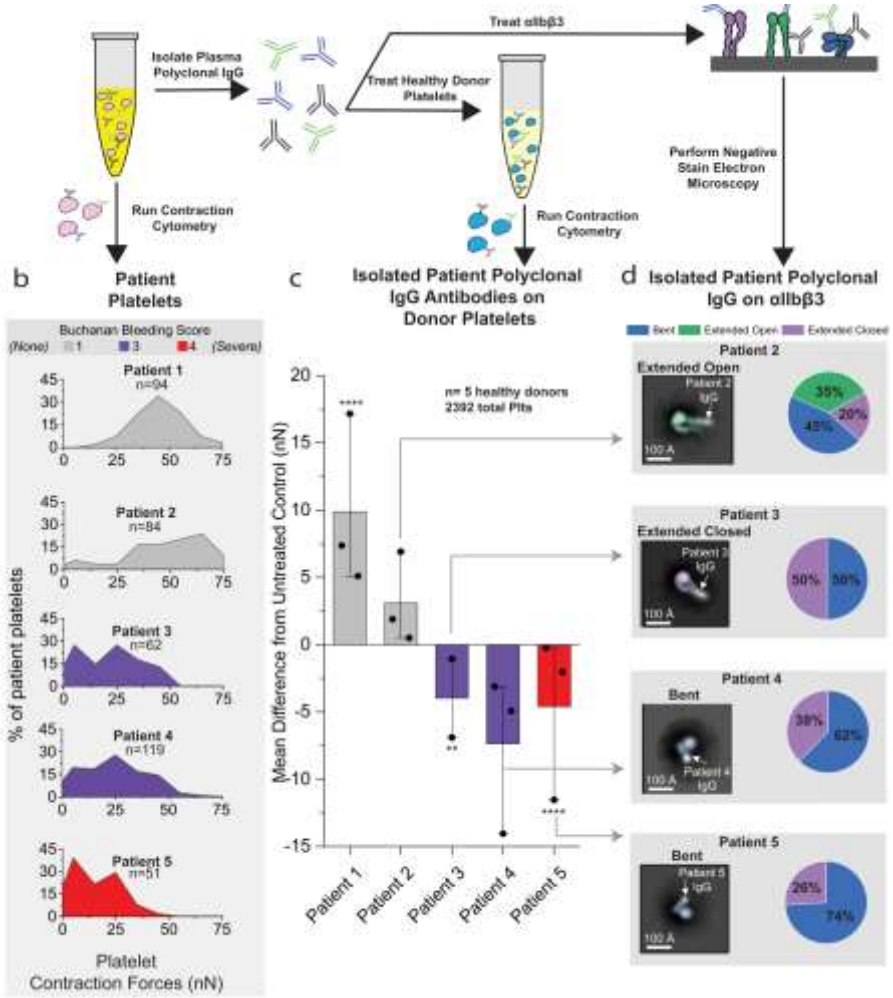
- Contractilité plaquettaire différente d'un patient à l'autre
- Contractilité plaquettaire est modulée par les Ac anti-plaquettes
- Ac anti-GPIIb/IIIa modifient la conformation (d'ouverte à fermée)



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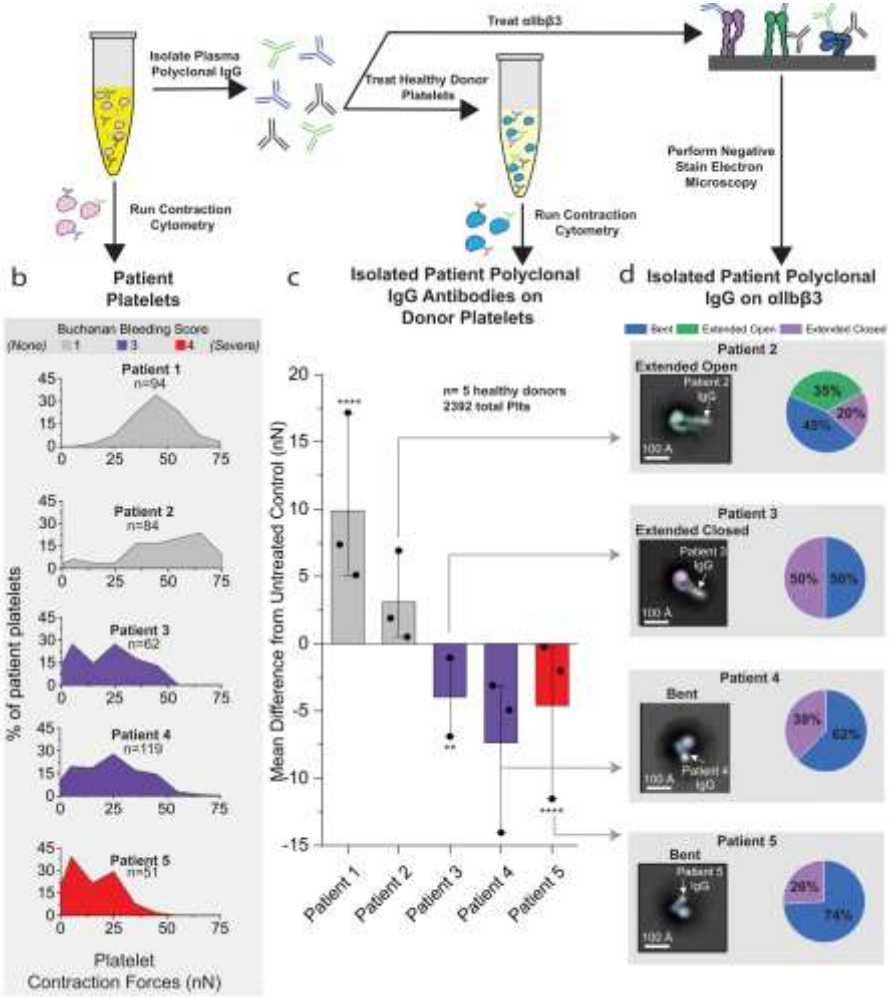
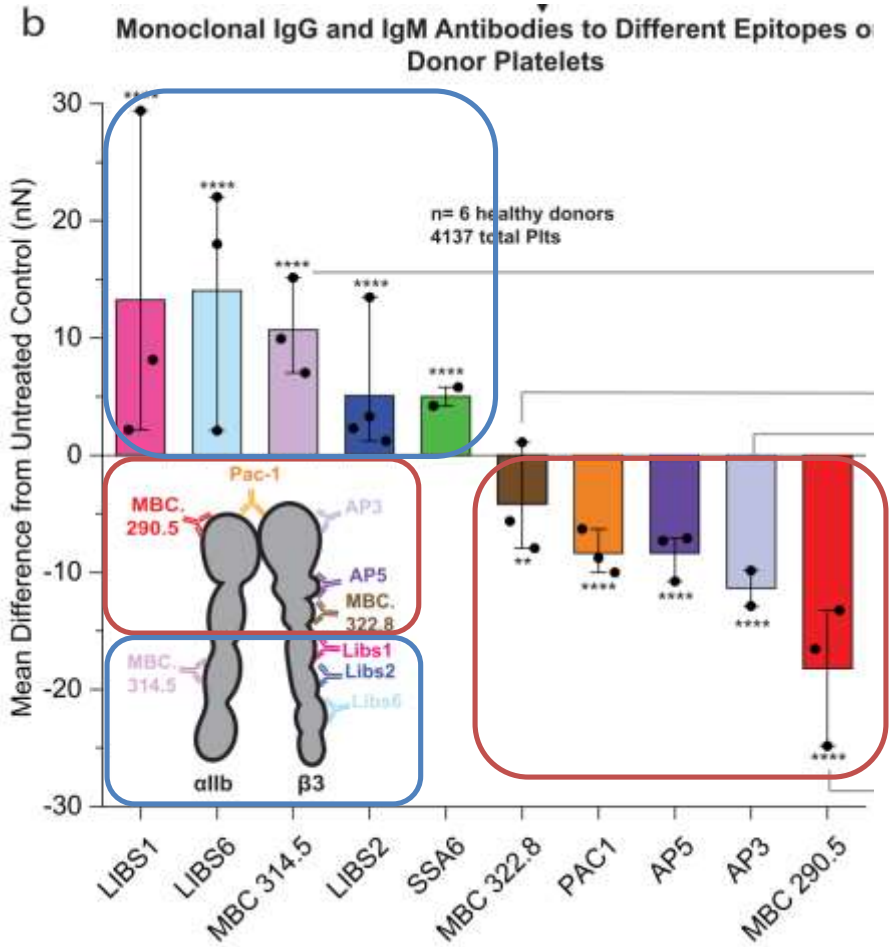
- Cette modification de conformation dépend des épitopes ciblés par les Ac anti-plaquettes





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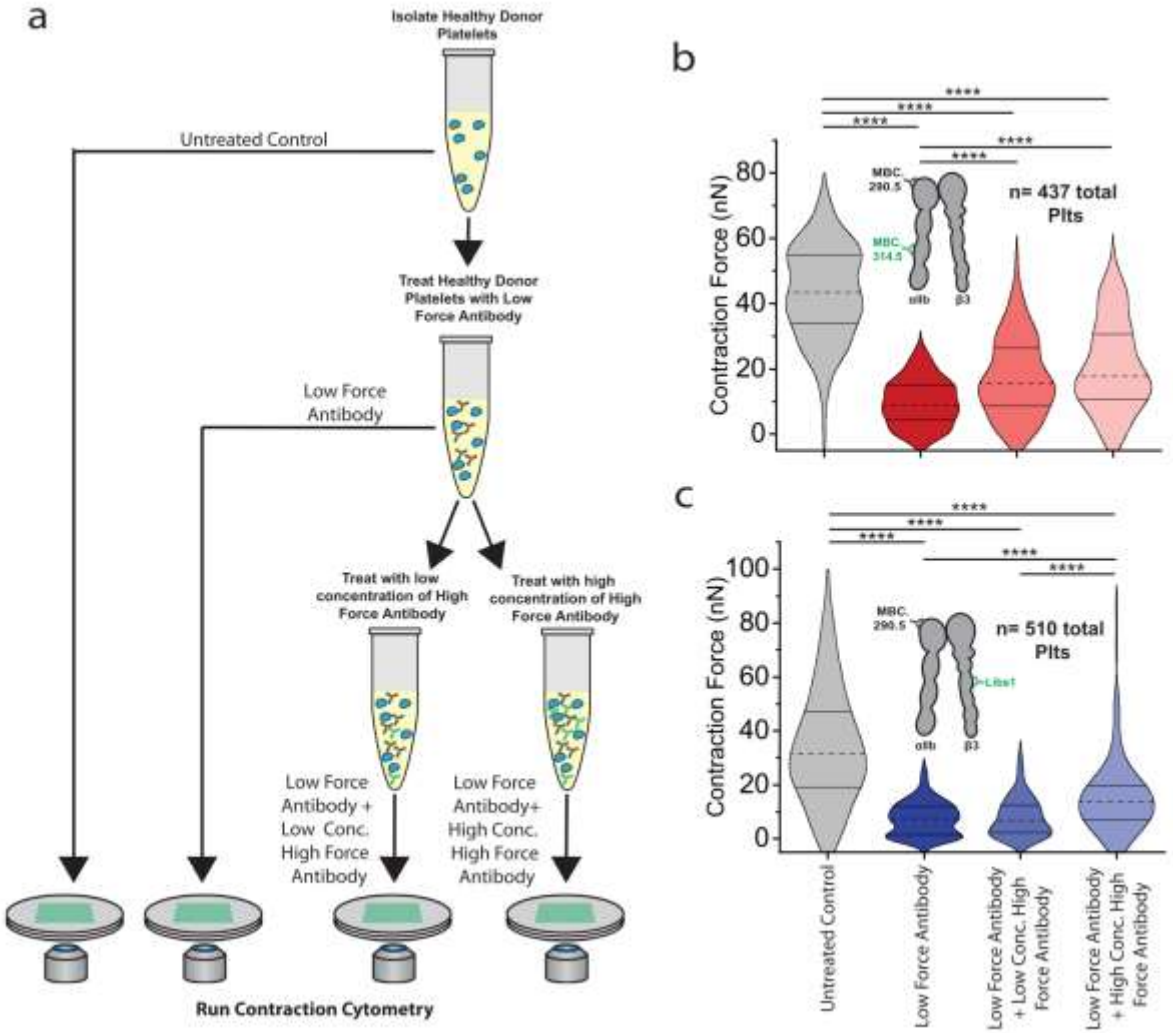
- L'effet des Ac diminuant la contractilité plaquettaire est partiellement réversible par les Ac augmentant la contractilité
- Les Ac anti-plaquettes augmentant la contractilité pourraient avoir un intérêt thérapeutique



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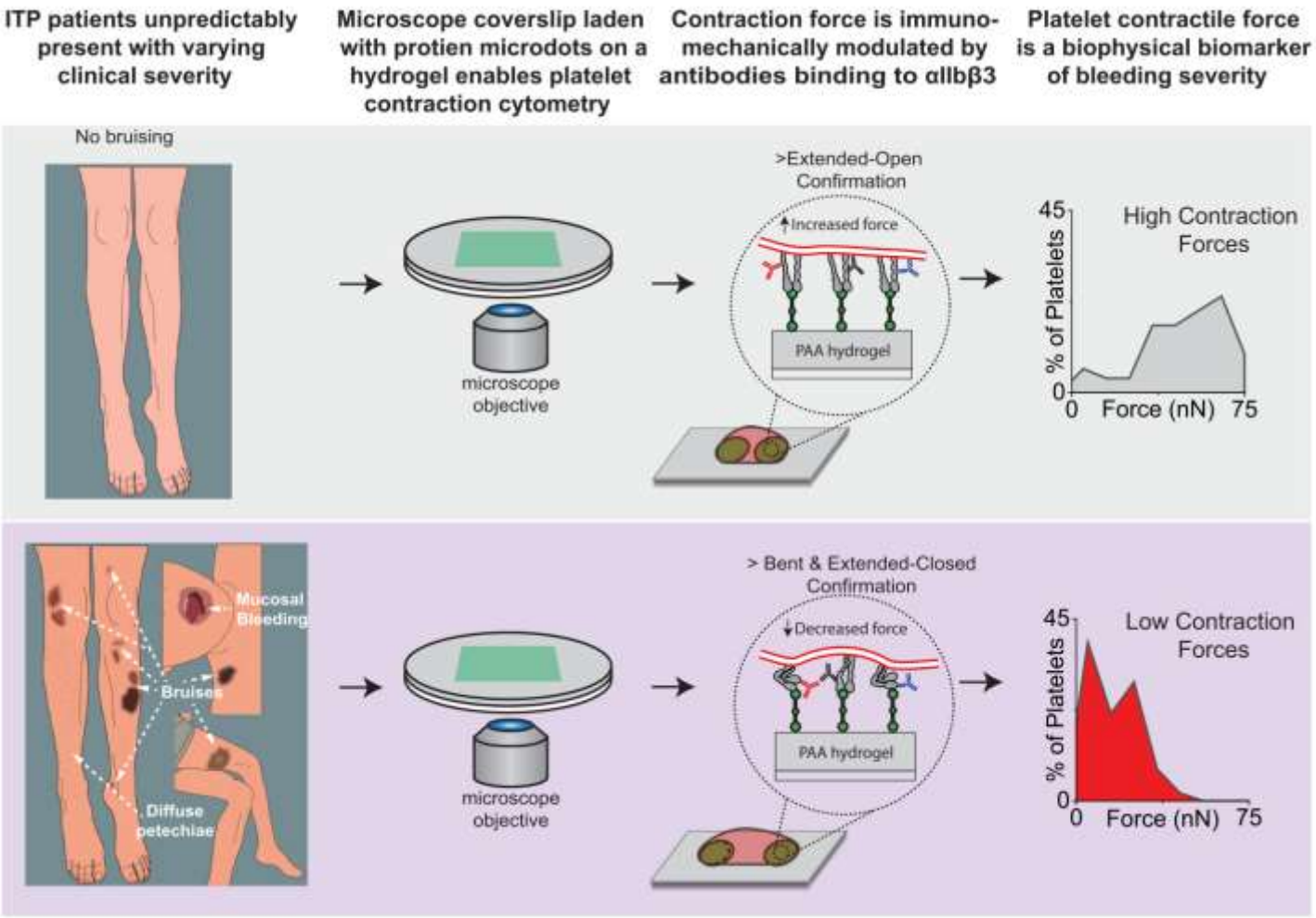


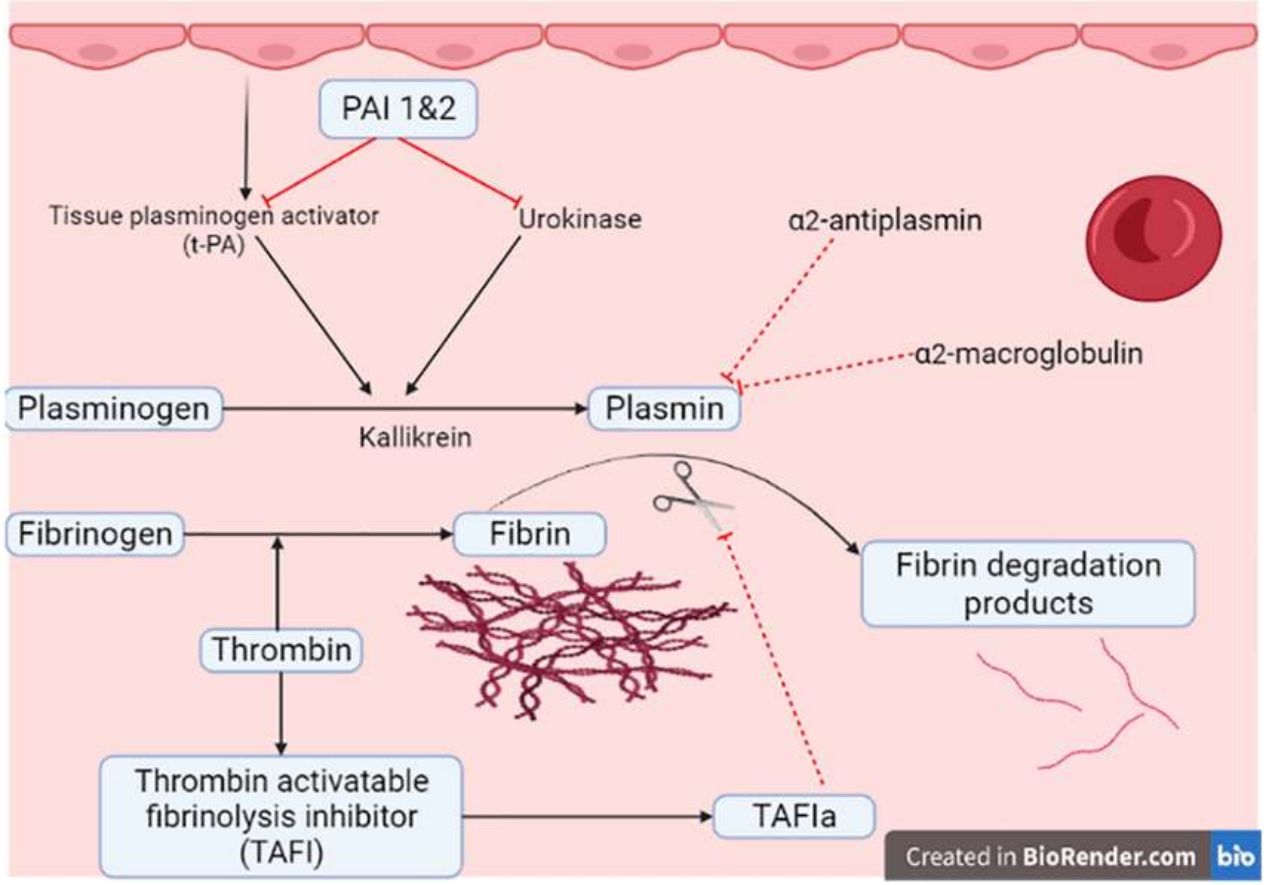
- Au-delà du chiffre de plaquettes, les saignements peuvent être en partie expliqués par les Ac antiplaquettes
- Selon l'épitope ciblé, les Ac anti-plaquettes modifient la conformation de la GPIIb/IIIa et la contractilité plaquettaire
- Rôle des Ac anti-plaquettes dans les thromboses au cours du PTI?

Fibrinolysis is impaired in patients with primary immune thrombocytopenia

J Thromb Haemost. 2024;22:3209–3220

Theresa Schramm[1] | Jasmin Rast[1] | Dino Mehic[1] | Stéphanie E. Reitsma[2] | Claire de Moreuil[3,4] | Michael Fillitz[5] | Peter Quehenberger[6] | Bas de Laat[7,8,9] | Alisa S. Wolberg[2] | Cihan Ay[1] | Ingrid Pabinger[1] | Johanna Gebhart[1]

- 86 adultes, PTI primaire, 43% sous traitement (CS ou TPO-RA), 10% ATCD de ETV ou A
- 78 contrôles
- Mesures :
  - Plasmatiques: tPA, PAI-1, tPA-PAI-1, α2-antiplasmine, TAFI, D-Dimères
  - Fonctionnelle : formation et lyse de caillot / test de génération de plasmine



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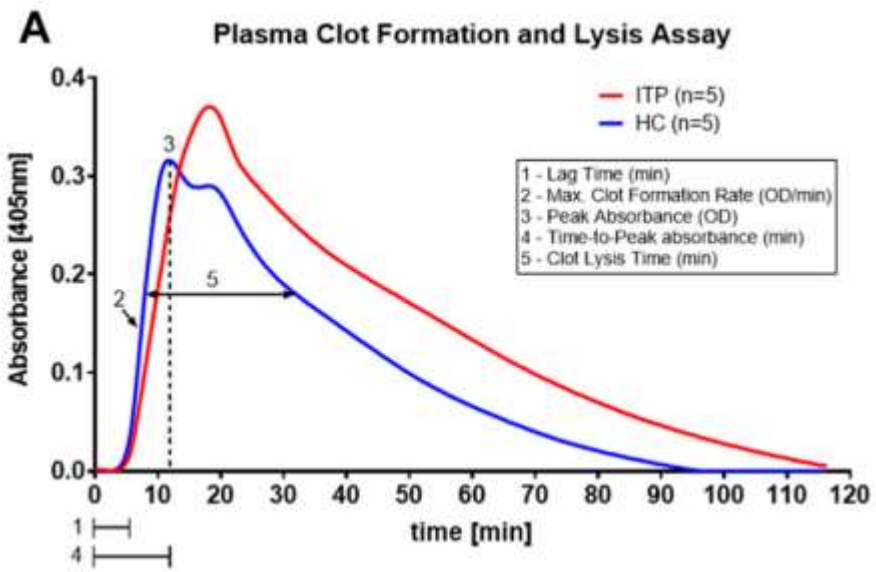
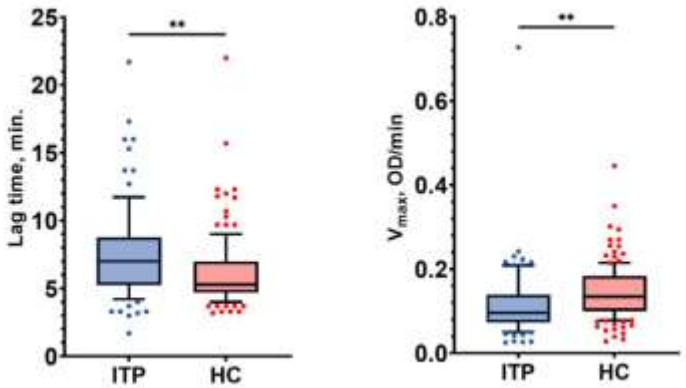
- Tests fonctionnels au cours du PTI
  - ↗ du temps de formation du caillot
  - ↗ densité du caillot
  - ↗ temps de lyse du caillot

- Dosages plasmatiques au cours du PTI
  - ↗ inhibiteur de fibrinolyse PAI-1
  - ↘ fibrinolytique tPA



- Corrélation entre temps de lyse du caillot et complexes tPA-PAI-1
- 6 patients avec TVP: tPA-PAI-1 plus élevés



- ↘ fibrinolyse au cours du PTI
- Pas d'association avec phénotype hémorragique
- Association avec thromboses

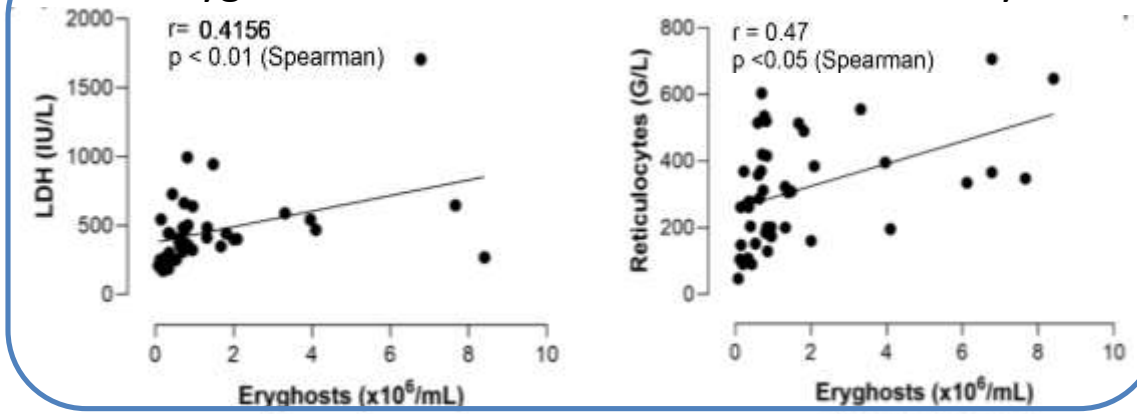
Protein S Enhances the Phagocytosis of Phosphatidylserine-Exposing Erythrocytes: Implications in Sickle Cell Disease.

Claire Auditeau[1,2#], Aurélie Fricot[3,#], Raphaël Gauthier[3], Abdoulaye Sissoko[3] , Zeynep Cacan[3], Céline Gounou[4], Laure Joseph[5], Sandra Manceau[5], Slimane Allali[6], Michael Dussiot M.[7], Mickael Marin[3], Alexis Lavergne[3], Mariem Khamari[1], Sophie Moog[1,8], Elsa Bianchini[1], Laetitia Claer[3], Sandrine Laurence[3], Valentine Brousse[3,9], Sébastien Eymieux[10,11], Philippe Roingeard[10,11], Pascal Amireault[3,7], Thiago Trovati-Maciel[7], Alain Brisson[4] , Pierre Buffet[3,12], François Saller[1], Delphine Borgel[1,2#], Camille Roussel[2,3#]

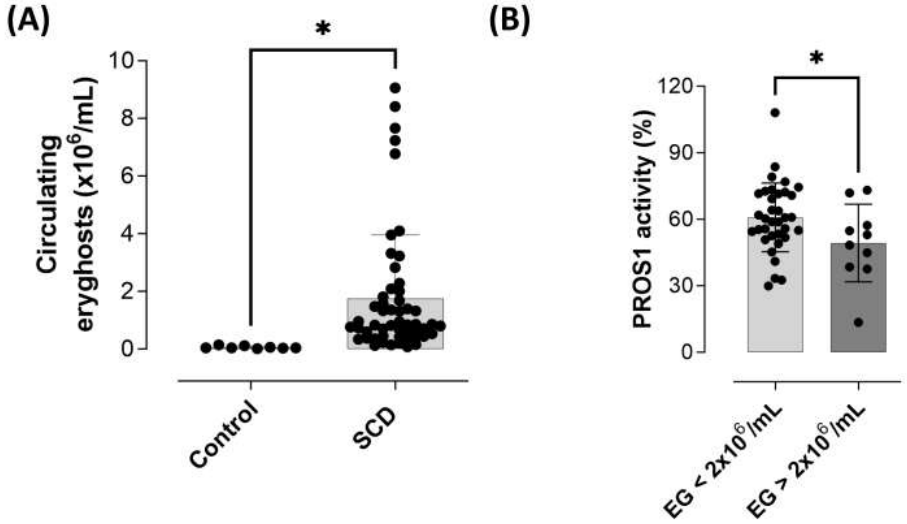
AJH
Sous presse

- Protéine S est anticoagulante
- Protéine S impliquée dans l'efferocytose (élimination de corps/cellules apoptotiques)
  - Pont entre PS des corps apoptotiques
  - Récepteur macrophagique (MerTK)
- GR sénescents hémolysent dans la rate
- Génération d'éryghosts (structure de GR mais sans Hb)

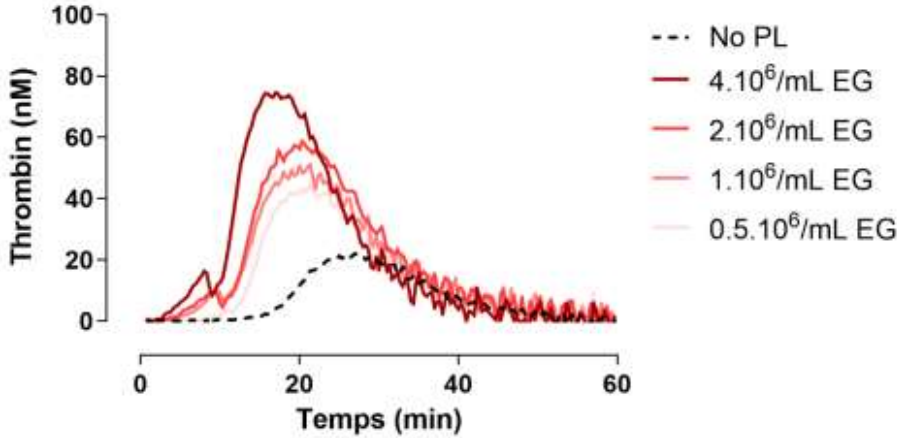
Éryghosts circulants sont corrélés à l'hémolyse



↗ éryghosts circulants au cours de la drépanocytose
↗ éryghosts circulants = ↘ activité de la protéine S sérique



Les éryghosts ont une activité procoagulante (génération de thrombine)



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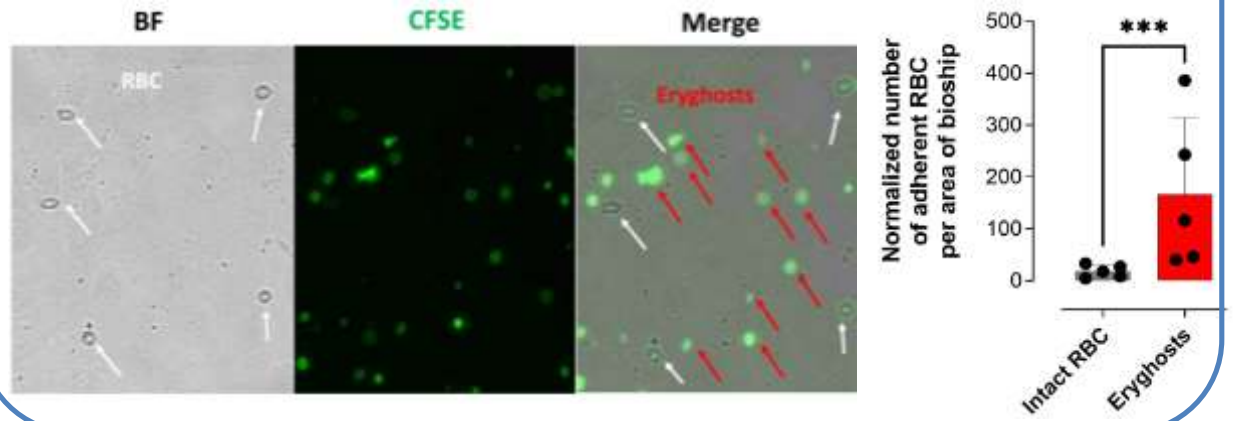
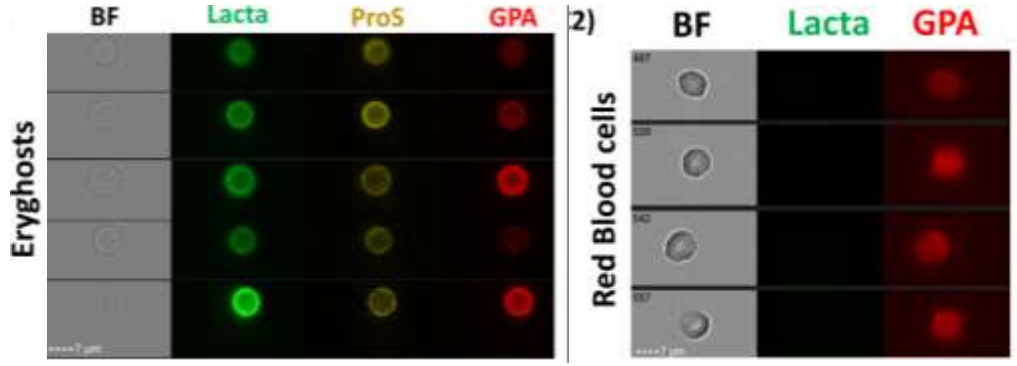
AJH
Sous presse

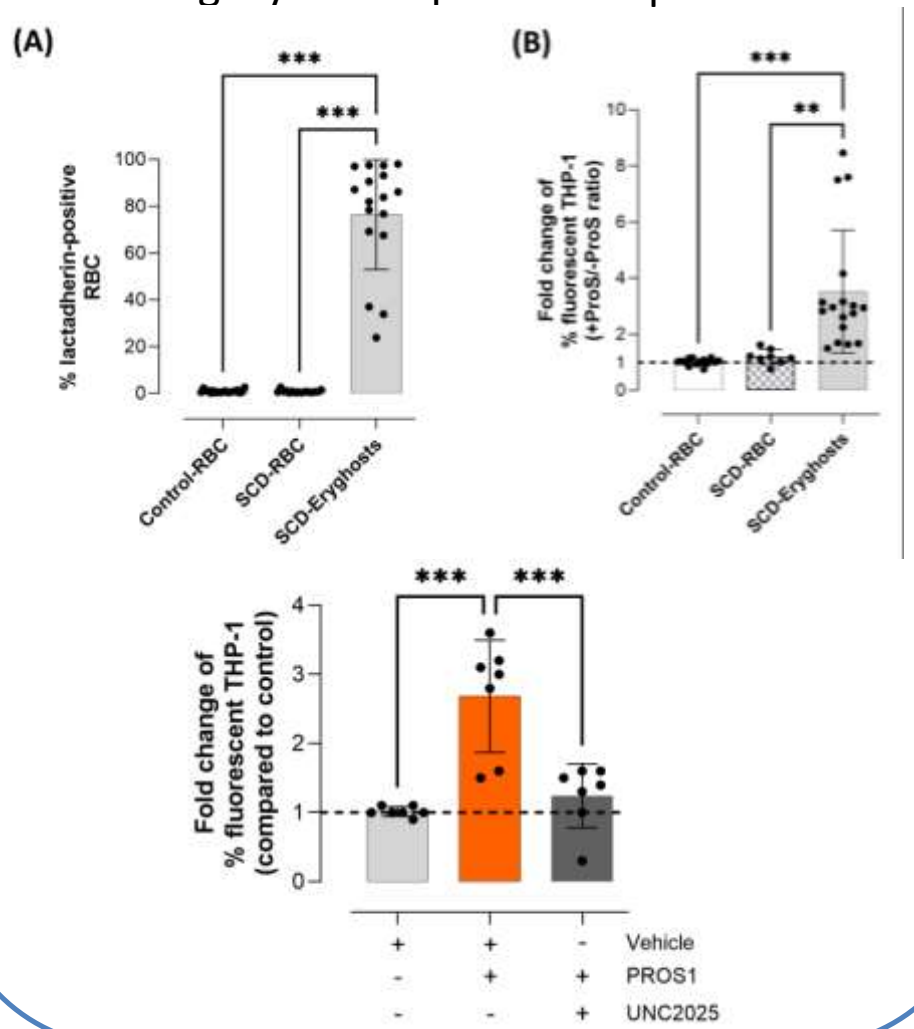
Éryghosts adhèrent plus à la paroi endothéliale que les GR (test d'adhésion en flux, HMEC-1)



Éryghosts expriment PS (marquage lactadhérine)
Éryghosts fixent la protéine S



Éryghosts expriment PS au cours drépa
Éryghosts sont phagocytés
Phagocytose dépend de la protS



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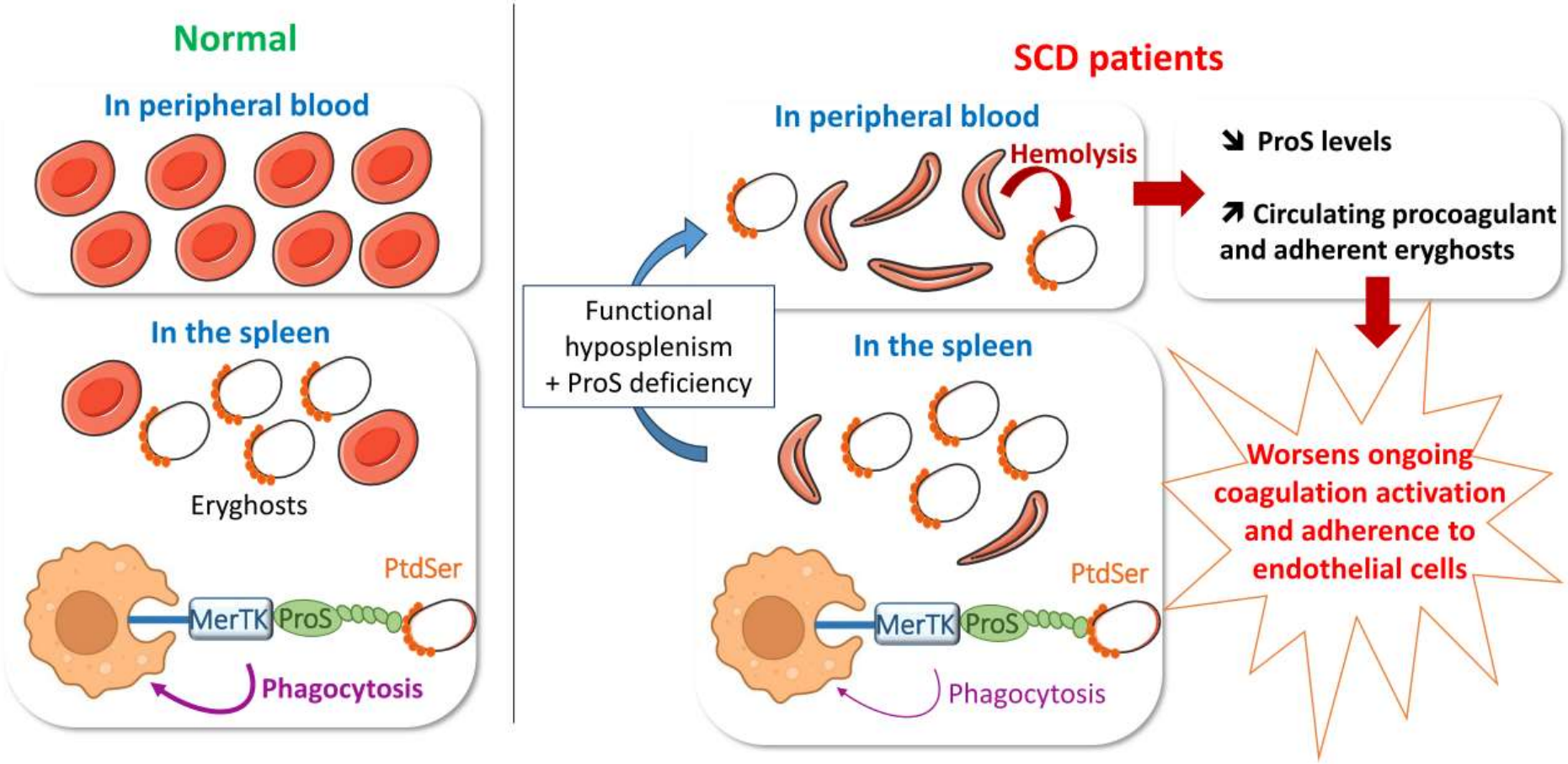


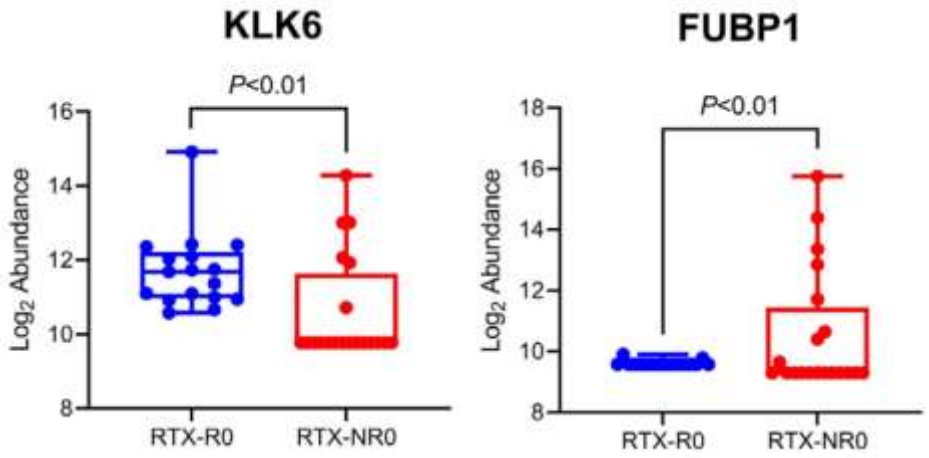
Mécanisme similaire au cours de l'AHAI ?
Collaboration / API-AHAI

Urine proteomics uncovers biomarker candidates for early identifying rituximab beneficiaries in paediatric steroid-resistant immune thrombocytopenia

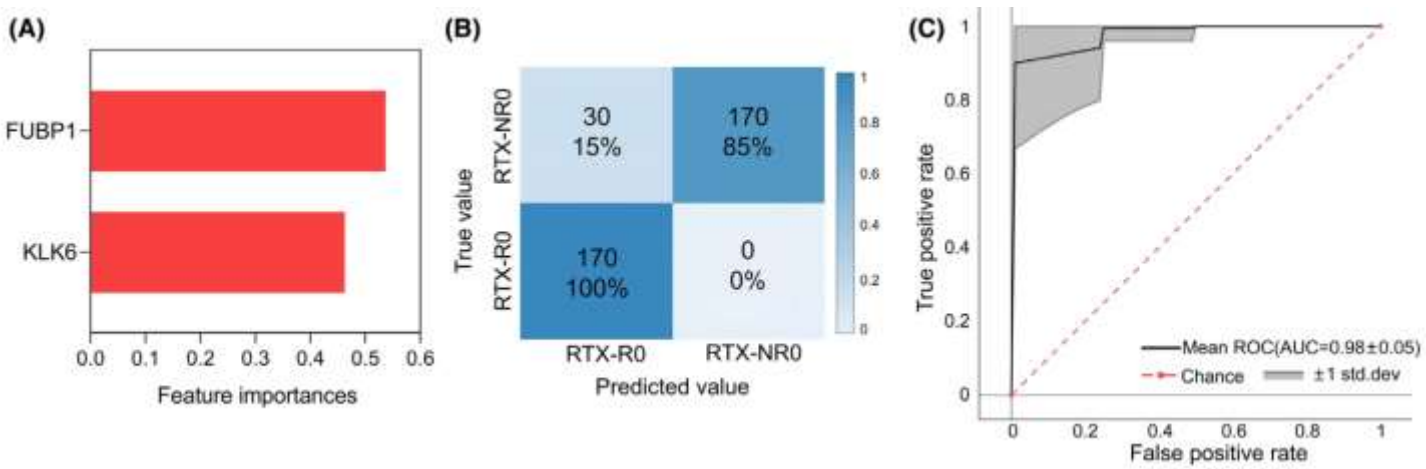
Yuncui Yu[1] | Xingjuan Xie[2,3] | Zhenping Chen[4] | Jing Wei[1] | Juntao Ouyang[2] | Zheyan Lin[2] | Jingyao Ma[2] | Peng Guo[1] | Runhui Wu[2] | Lulu Jia[1] | Jingang Gui[5,6]

Br J Haematol. 2025;00:1–11.

- 37 enfants PTI
- 17 R / 20 NR (à 3 mois)
  (Seulement 11 R à 6 mois…)
- 40 contrôles
- Analyse protéomique urinaire
  - Avant/après RTX
  - Avant RTX, R *vs.* NR



2 protéines candidates avant RTX pour prédire R
- ↘ FUBP1 (régule hématopoïèse, stimule prolif. lymphoblastes via cKit)
- ↗ KLK6
- Modèle « *machine learning* »
  - Sn=100%, Sp=85%
  - AUC= 0,98
- Pas de [c] seuil proposées…
- Pas de cohorte de validation…



PREDICT-IT: identification biomarqueurs prédictifs de réponse au rituximab au cours du PTI

Patients / méthodes

- 20 R à 5 ans *vs*. 18 NR
- 20 H / 18 F, 61 ans
- 74% PTI primaire,
- 58% PTI chronique, 21% persistant
- scRNAseq, bulk RNAseq, CMF, sérum

Praliaud *et al*. unpublished data, ASH 2025

PREDICT-IT: identification biomarqueurs prédictifs de réponse au rituximab au cours du PTI

centre de référence maladies rares

Inserm

Patients / méthodes

- 20 R à 5 ans *vs*. 18 NR
- 20 H / 18 F, 61 ans
- 74% PTI primaire,
- 58% PTI chronique, 21% persistant
- scRNAseq, bulk RNAseq, CMF, sérum

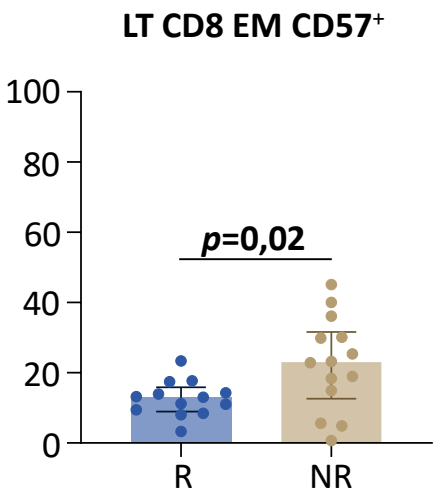
Résultats préliminaires

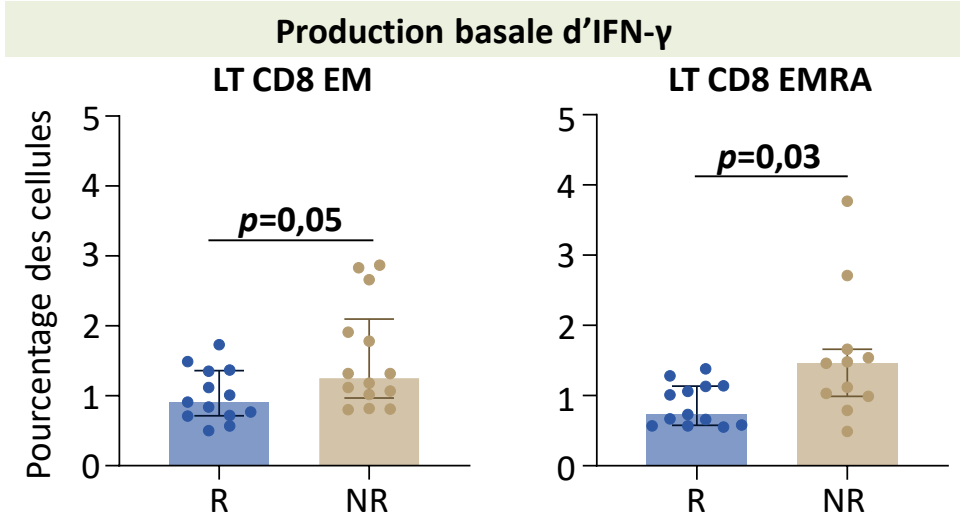
- **CMF**
  - Différenciation accrue LB et LT
  - Seuils à déterminer / score ?
- **Sérum**
  - 2 protéines candidates
- **Signature transcritpomique**
  - *Confirmation PCR en cours*

Perspectives

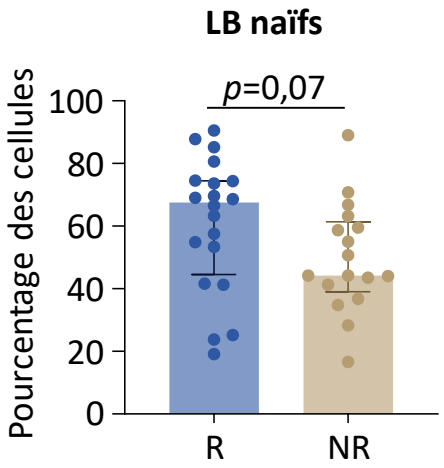
- Validation cohorte extérieure (PHRC)
- Biomarqueurs en routine ?

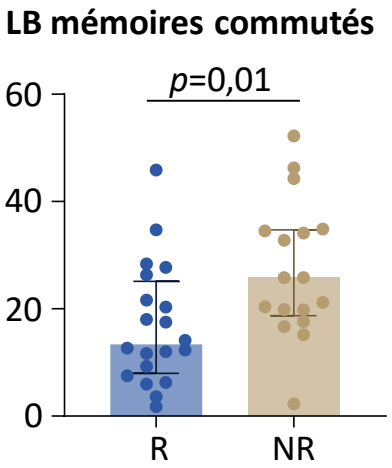
Lymphocytes T CD8

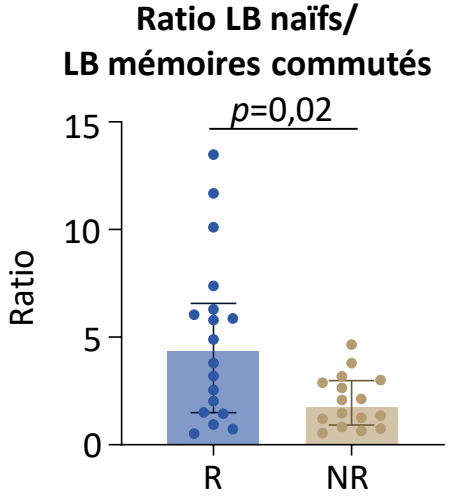




Lymphocytes B



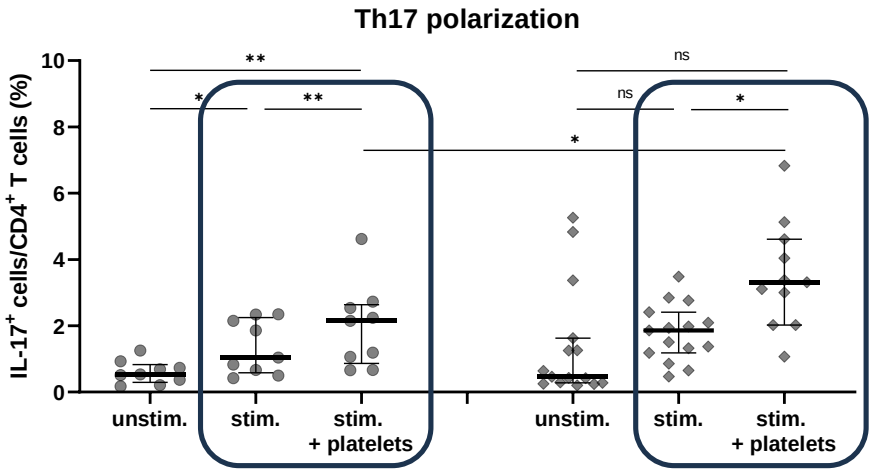


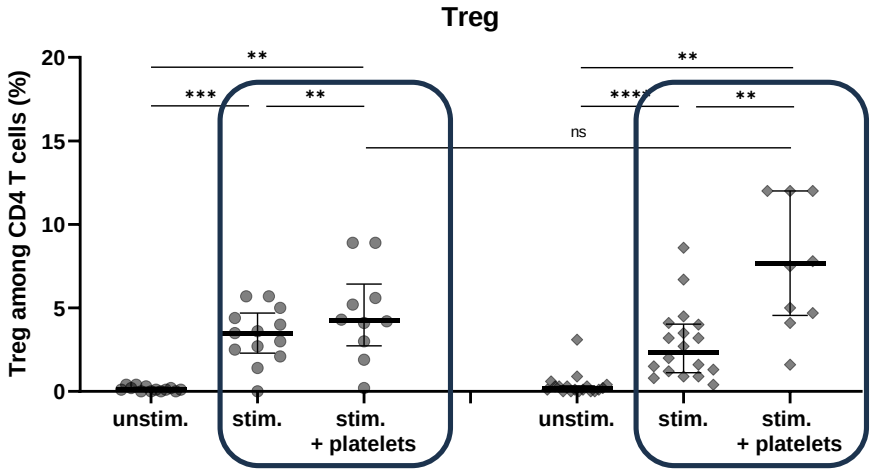


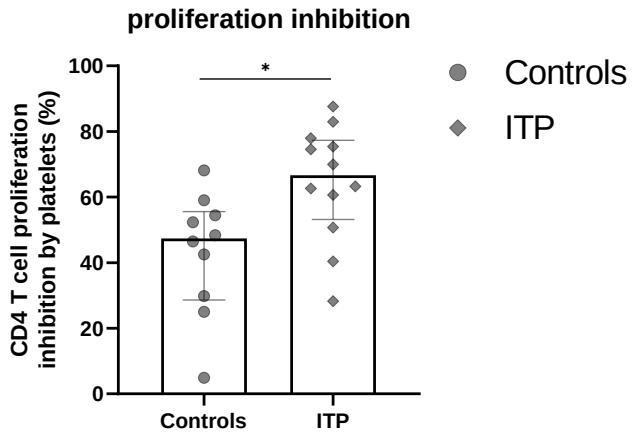
Praliaud *et al*. données non publiées, ASH 2025

Shimon Sakagusi
Prix Nobel Médecine 2025
Lymphocytes T régulateurs

Rôle immunomodulateur des plaquettes sur les LT CD4





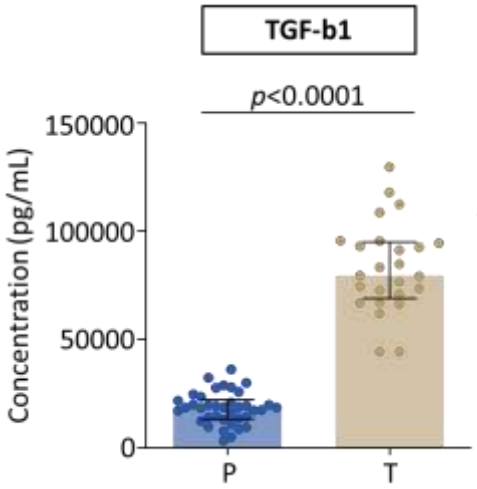


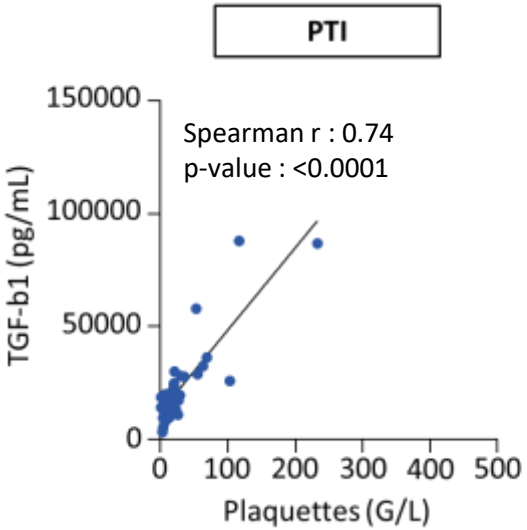
Résultats

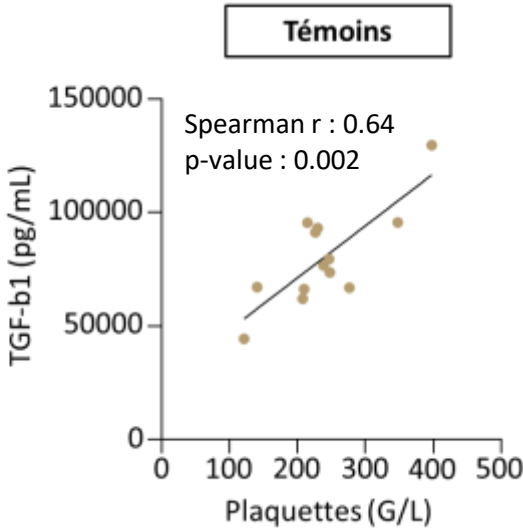
- Culture LT CD4 *in vitro*
- +/- plaquettes autologues (25/1)
- En présence de plaquettes
  - ↗ polarisation Th17
  - ↗ Treg ($CD4^{+}CD25^{Hi}Foxp3^{+}$)
  - Inhibition prolifération
  - Rôle de TGF-β?
    - Corrélation avec chiffre plaquettes

⇒ **Masse plaquettaire / restauration tolérance ?**

⇒ **Intérêt de normaliser le taux de plaquettes ?**







Praliaud *et al*. données non publiées, ASH 2025

Merci de votre attention