SFVTT

GIMAP EA 3064
Groupe Immunité des Muqueuses et Agents Pathogènes
SAINT-ETIENNE

FACULTÉ DE MÉDECINE
JACQUES LISFRANC I SAINT-ÉTIENNE

UNIVERSITÉ DE LYON

UNIVERSITÉ JEAN MONNET SAINT-ÉTIENNE

Cytokines / molécules apparentées et évènements indésirables receveurs liés aux transfusions de concentrés plaquettaires

EFS
ÉTABLISSEMENT FRANÇAIS DU SANG
Du donneur aux patients

22/11/2018 - Auditorium Chateaubriand

11:00-12:30 : Session 13 - SFVTT/SFTS - Du produit au malade (2)

Fabrice Cognasse

Platelet Inflammation Response to Stress: PIRS team – St Etienne / France
Senior Scientist, Director for Scientific Affairs French National Blood System EFS / Rhône-Alpes-Auvergne Regional Branch & GIMAP EA3064 Lyon Univeristé, Health Innovation Campus of Saint-Etienne
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Journal of Thrombosis and Haemostasis, **14**: 794–796 DOI: 10.1111/jth.13262

COMMENTARY

How can non-nucleated platelets be so smart?

F. COGNASSE,*† O. GARRAUD,†‡ B. POZZETTO,†§ S. LARADI*† and H. HAMZEH-COGNASSE†
*Etablissement Français du Sang Auvergne-Loire; †Groupe Immunité des Muqueuses et Agents Pathogènes, EA 3064, Université de Lyon, Saint-Etienne; ‡Institut National de la Transfusion Sanguine, Paris; and §Laboratoire des Agents Infectieux et d'Hygiène, University Hospital of Saint-Etienne, Saint-Etienne, France

- **Platelet a great immunomodulatory cell**
  - Brief Overview of Platelet Functions
- **The Non-Hemostatic Aspects of Transfused Platelets**
  - Blood platelets are important reservoirs of soluble mediators
  - Machine learning and inflammatory aspects of transfused platelets
  - Interaction between transfused platelets and endothelial cells
- **CONCLUSION : Getting the right product to the right patient !**

Platelets as autonomous drones for hemostatic and immune surveillance

Jackson LiangYao Li,[1,2] Alexander Zarbock,[3] and Andrés Hidalgo[1,4]

[1]Area of Developmental and Cell Biology, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain
[2]Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore
[3]Department of Anesthesiology, Intensive Care, and Pain Medicine, University of Münster, Münster, Germany
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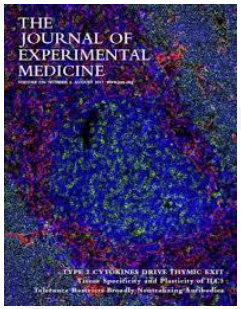
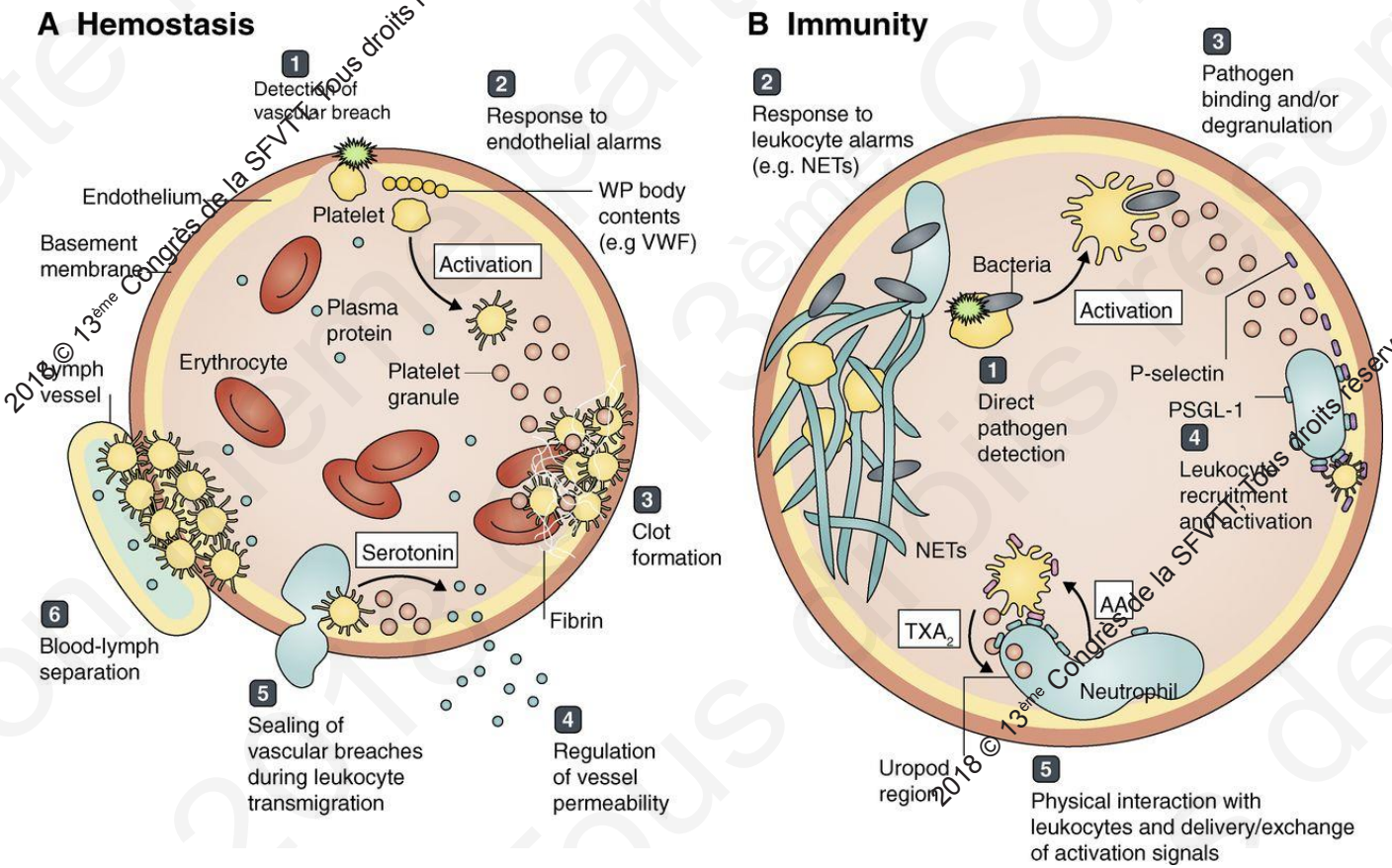


J. Exp. Med. 2017



Major platelet tasks in hemostasis and immunity.

Platelets circulate in blood, surveying the vasculature for

(A) hemostatic and
(B) immune stress

Platelets as autonomous drones for hemostatic and immune surveillance

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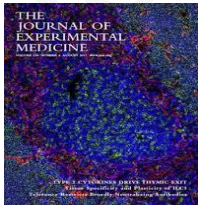

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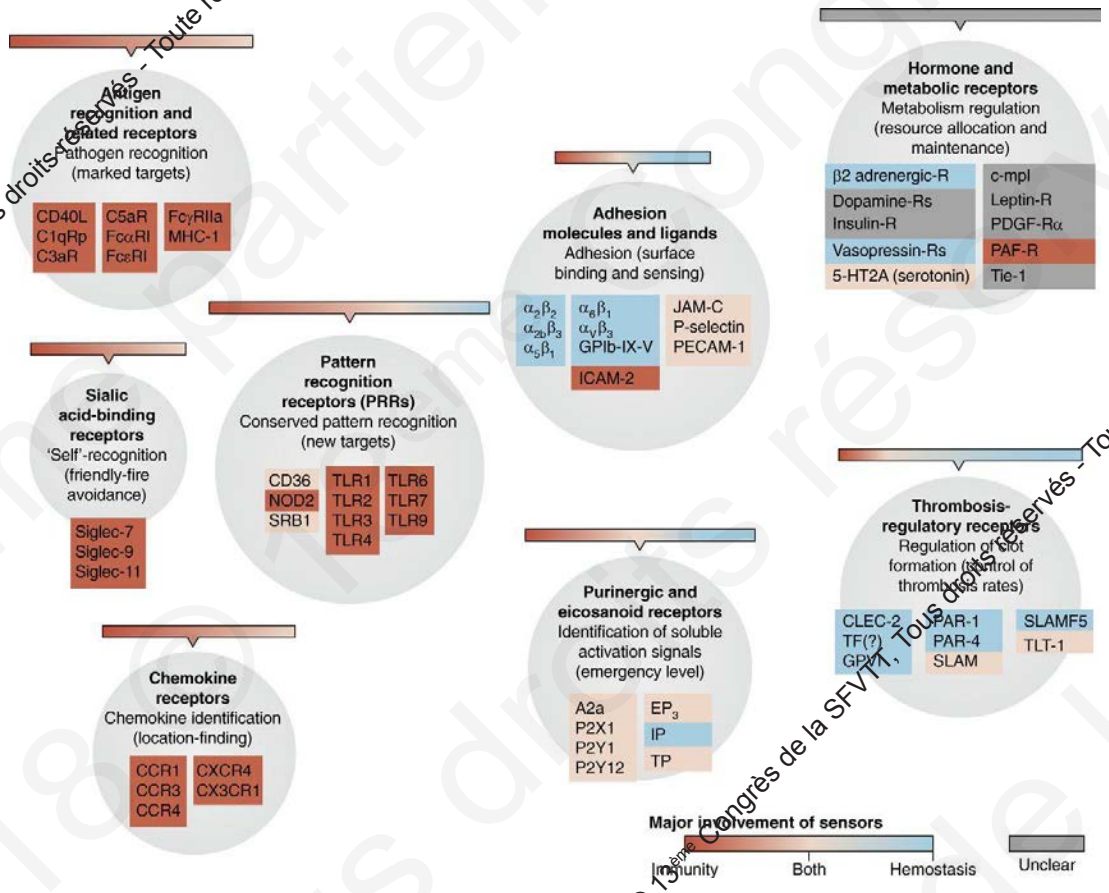

Platelet receptors. List of receptors in human platelets categorized by their major functional types.

Platelets as autonomous drones for hemostatic and immune surveillance

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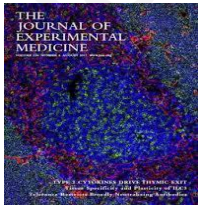


J. Exp. Med. 2017

Microbicidal effectors (Immune payload)
- C3 precursor
- C4 precursor
- Complement factor D
- CXCL7-derived peptides (PBP, TAP-III, thrombocidin-1 and 2, β-thromboglobulin)
- IgG
- MMP-1, 2 and 9
- Thymosin-β4
- Cathepsin D and E

Coagulation factors (Thrombotic payload)
- α2-antiplasmin
- Factor II/prothrombin
- Factor V
- Factor XI
- Factor XIII
- Fibrinogen
- Fibronectin
- HMW kininogens
- PAI-1
- Vitronectin
- VWF
- Glutamate

Signaling factors (communication)
- P-selectin (CD62P)
- TGF-β
- ADP
- ATP
- Calcium
- Epinephrine
- Histamine
- Polyphosphate
- Pyrophosphate
- Serotonin
- Acid phosphatase
- IL-1β
- Thromboxane A2

Chemokines (calling reinforcements)
- CCL2
- CCL3
- CCL5
- CXCL1
- CXCL12
- CXCL4/PF4
- CXCL5
- CXCL8
- NAP2 (CXCL7)

Anti-microbicidal factors (Immune regulation)
- C1 inhibitor
- Complement factor H
- TIMP-1 and 4

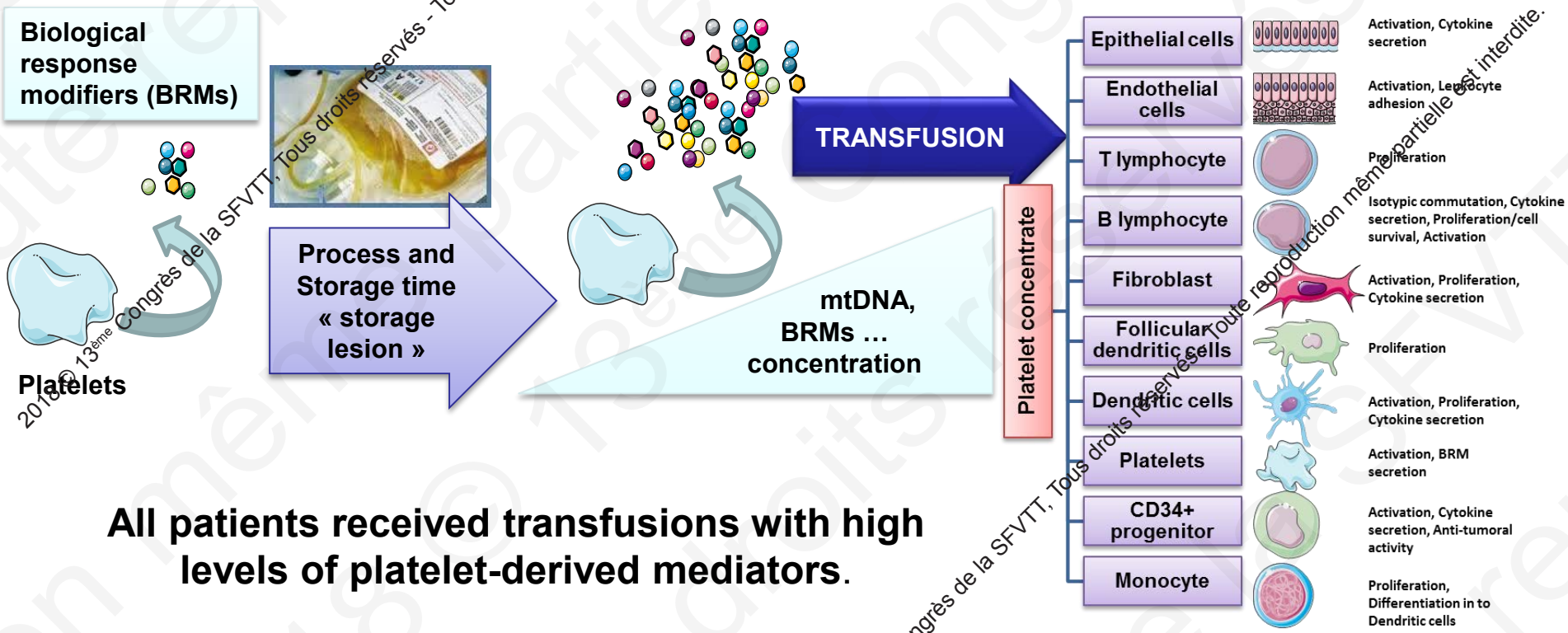
Anti-coagulative factors (Thrombotic regulation)
- α2-macroglobulin
- Antithrombin
- Plasmin
- Plasminogen
- Protein S
- TFPI

Growth/angiogenic regulators (support and delivery)
- Angiopoietin-1
- BDNF
- bFGF
- BMP-2,4 and 6
- CTGF
- Thrombospondin
- EGF
- Endostatin
- HGF
- IGF-1
- PDGF
- VEGF
- n-acetylglucosaminidase
- α-arabinosidase
- β-galactosidase
- β-glucuronidase
- RNA (mRNA, miRNA etc.)

Secretory package
- α granules
- Dense granules
- Lysosomes
- Microparticles or other

Platelet payloads. List of bioactive mediators released by human platelets categorized by their major functional roles.

Blood transfusion and inflammation: Platelet components associated with acute transfusion reactions



All patients received transfusions with high levels of platelet-derived mediators.

Blood transfusion and inflammation: Platelet components associated with acute transfusion reactions

Storage lesion

Main product transformation:

- Automated cell separation
- Centrifugation
- Leucoreduction
- Platelet additive solutions
- Occasionally pathogen or Reduction or inactivation technology
- Irradiation
- Deplasmatisation/washing
- Cryopreservation
- Volume reduction

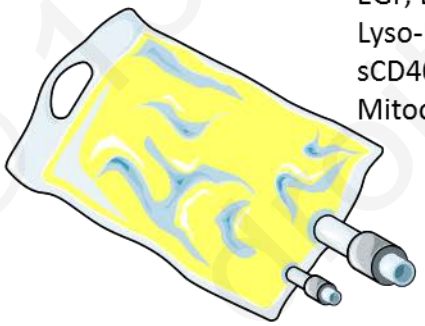
Increase:

- Activation (release of granular contents)
- Proteolysis
- Platelet aggregates
- Volume and density heterogeneity
- Procoagulant activity
- Platelet apoptosis
- pCO2
- Lactate production
- Glucose consumption

Decrease:

- pH,
- pO2
- glucose
- mean platelet volume
- Calcium ion flux
- Mitochondrial oxidative respiration
- Fibrinogen binding

Released/increased factor:
EGF, ENA-78, Gro-α, IL-1β, IL-6, IL-7, IL-8, IL-27, Lyso-PCs, sOX40L, PAI-1, PDGF-AA, PF4, RANTES, sCD40L, TGF-β, TNF-α, VEGF, β-TG, Microvesicles, Mitochondrial DNA



Storage lesion:

- Shape changes from discoid to spheroid
- Altered platelet surface receptor expression
- ATP/ADP ratio change

Typical storage duration for platelets is 5-7 days

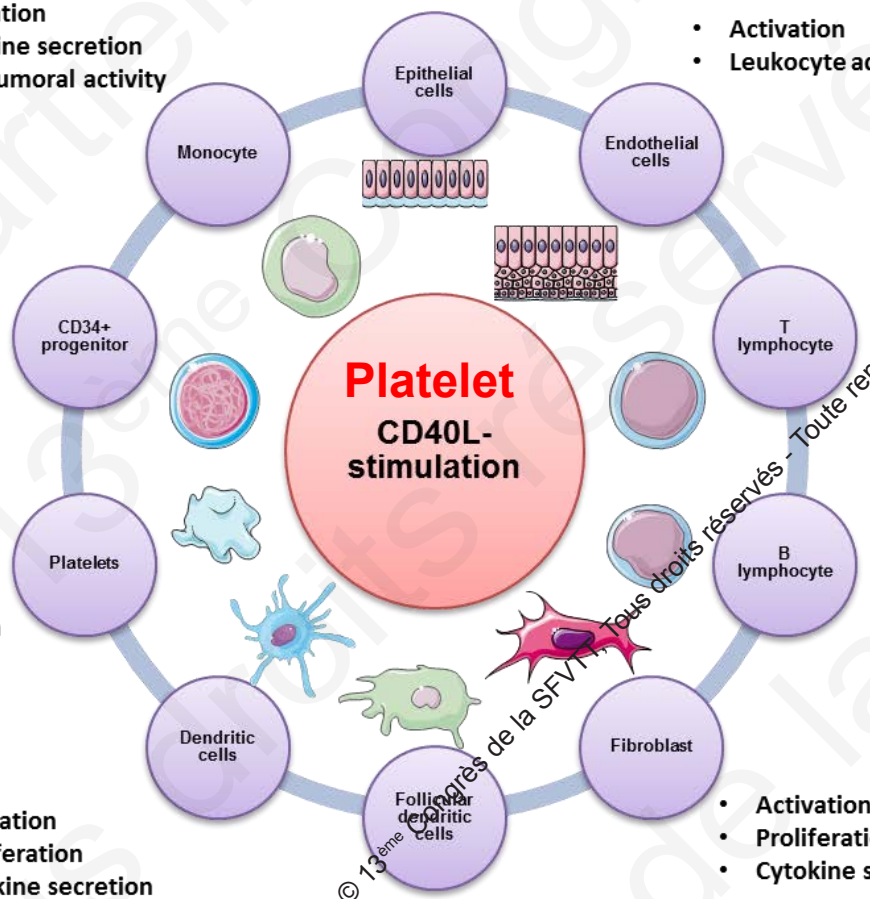
Platelet concentrates storage and biological response modifier release. *(Front Med (Lausanne). 2018 Feb 27;5:42)*

CD40/CD40L, is well known for its roles of bridging between innate and adaptive immunity

- **Hypothetical mechanisms by which platelet membrane CD40/CD40L and soluble CD40L might regulate interactions between immune cells.**

Platelets can interact with numerous immune cells such as

- **B cells,**
- **T cells,**
- **Neutrophils,**
- **Macrophages,**
- **Endothelial cells,**
- **Natural killer (NK) cells**
- **Dendritic cells (DC)**



[(1)] *Garraud et al, Crit Care 2013,* [(2)] *Cognasse et al, Front Imunol 2015*

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COMMENTARY

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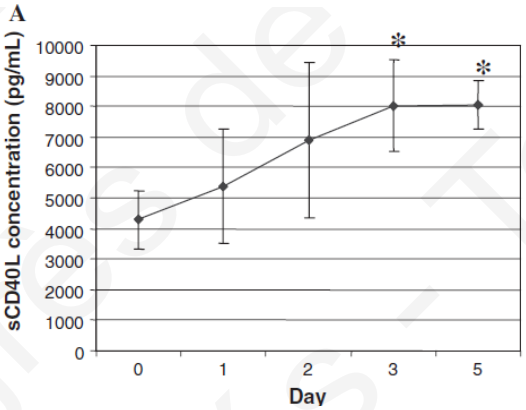
- **CONCLUSION : Getting the right product to the right patient !**

BLOOD COMPONENTS

TRANSFUSION Volume 46, July 2006

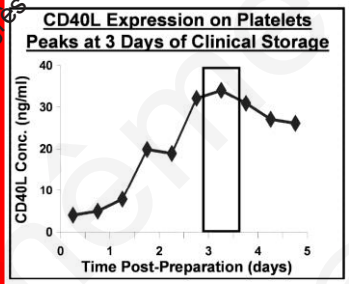
Release of potential immunomodulatory factors during platelet storage

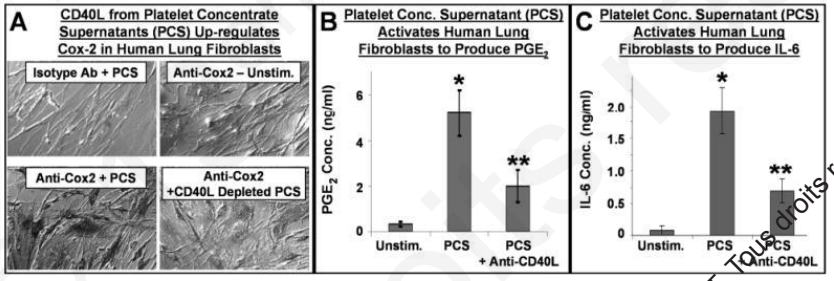
Fabrice Cognasse, Françoise Boussoulade, Patrick Chavarin, Sophie Acquart, Patrick Fabrigli, Bernard Lamy, and Olivier Garraud

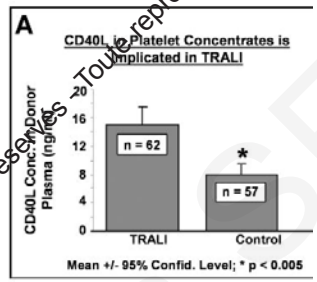


The platelet as an immune cell--CD40 ligand and transfusion immunomodulation

Neil Blumberg, MD[1], Sherry L. Spinelli, PhD[1], Charles W. Francis, MD[2], Mark B. Taubman, MD,PhD[2], and Richard P. Phipps, PhD[1,3,4]







blood

2008 112: 4779-4780
doi:10.1182/blood-2008-05-157578

Platelet components associated with acute transfusion reactions: the role of platelet-derived soluble CD40 ligand

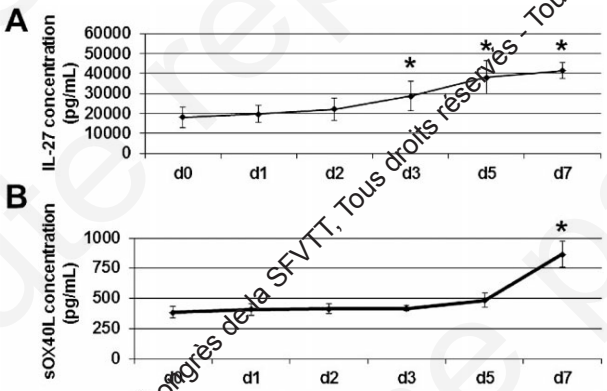
Fabrice Cognasse, Jean Marc Payrat, Larry Corash, Jean Claude Osselaer and Olivier Garraud

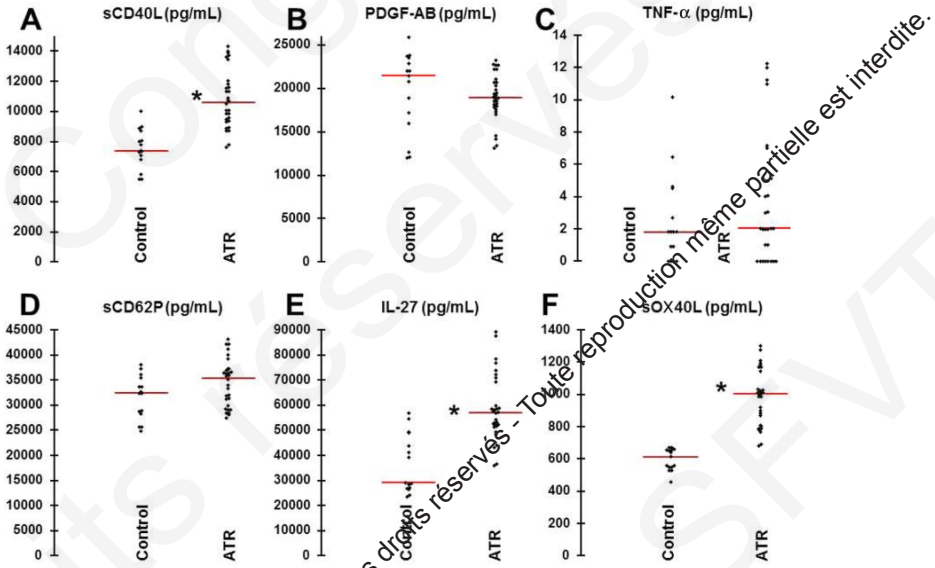
Increased levels of sCD40L in transfused blood are associated with transfusion-related Adverse Events (AEs)

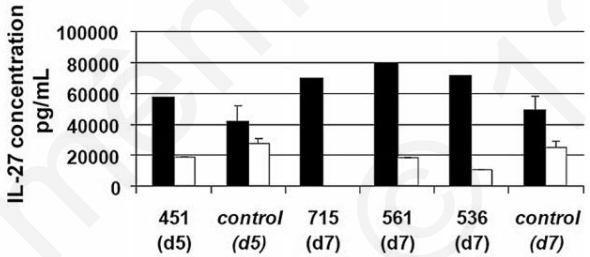
Immune-reactive soluble OX40 ligand, soluble CD40 ligand, and interleukin-27 are simultaneously oversecreted in platelet components associated with acute transfusion reactions

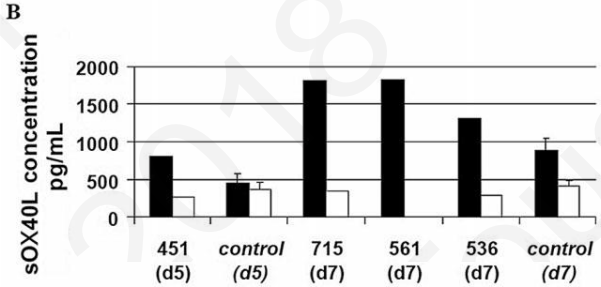
Volume 54, March 2014 TRANSFUSION

Hind Hamzeh-Cognasse,[1] Pauline Damien,[1] Kim Anh Nguyen,[1] Charles-Antoine Arthaud,[2] Marie-Ange Eyraud,[2] Patricia Chavarin,[2] Léna Absi,[2] Jean-Claude Osselaer,[3] Bruno Pozzetto,[1] Fabrice Cognasse,[1,2] and Olivier Garraud[1,2]



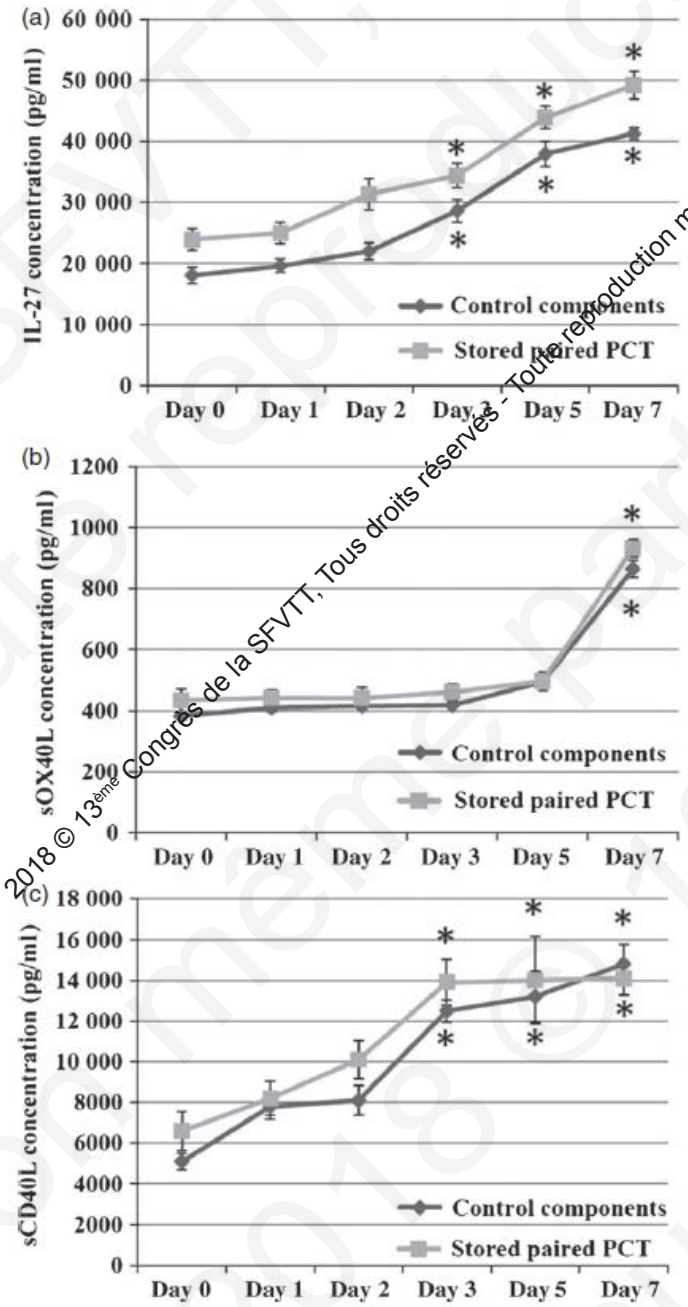






Bioactivity of IL-27- and sOX40L-rich pathologic PLT supernatant

- IL-27 bioactivity was tested on isolated, purified blood B lymphocytes
- sOX40L bioactivity was tested on isolated, purified, activated blood T lymphocyte



Amotosalen-HCl-UVA pathogen reduction does not alter poststorage metabolism of soluble CD40 ligand, Ox40 ligand and interkeukin-27, the cytokines that generally associate with serious adverse events

H. Hamzeh-Cognasse,[1] S. Laradi,[1,2] J. C. Oseliere,[3] F. Cognasse[1,2] & O. Garraud[1,4]
[1]Université de Lyon, GIMAP-EA3064, Saint Etienne, France
[2]EFS Auvergne-Loire, Saint Etienne, France
[3]Service régional vaudois de transfusion sanguine, Epalinges, Switzerland
[4]Institut National de Transfusion Sanguine (INTS), Paris, France

Vox Sang. 2015

- Levels of such cytokine-like factors increased significantly during storage,
- but no significant difference was detected between PRT- and control PCs.

blood

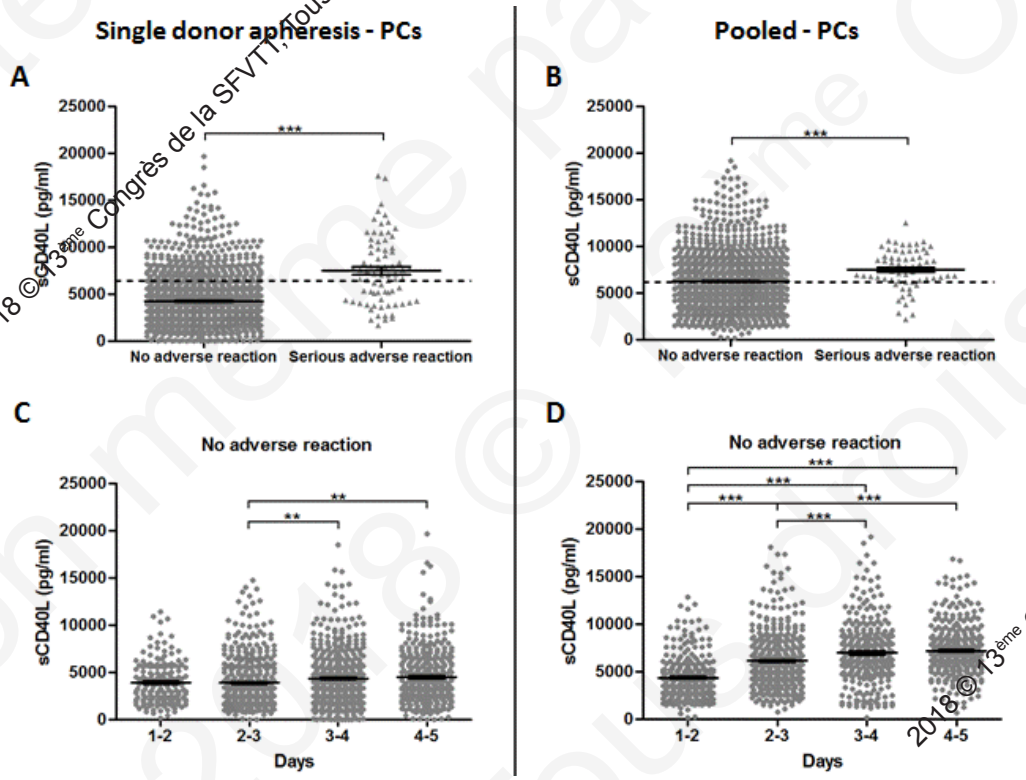
BLOOD, 14 SEPTEMBER 2017 • VOLUME 130, NUMBER 11

Platelet soluble CD40-ligand level is associated with transfusion adverse reactions in a mixed threshold-and-hit model

Fabrice Cognasse,[1,2] Caroline Sut,[1,2] Elisa Fromont,[3] Sandrine Laradi,[1,2] Hind Hamzeh-Cognasse,[2] and Olivier Garraud[2,4]

[1]Etablissement Français du Sang Auvergne-Rhône-Alpes, Saint-Etienne, France; [2]Université de Lyon, GIMAP-EA3064, Saint Etienne, France; [3]Laboratoire Hubert Curien - UMR CNRS 5516, Saint Etienne, France; and [4]Institut National de Transfusion Sanguine, Paris, France

Days	No adverse reaction** (n=2710)		Serious adverse reaction*** (n=140)	
	Single donor apheresis-PCs°	Pooled-PCs°°	Single donor apheresis-PCs°	Pooled-PCs°°
[1-2[*	162	269	6	13
[2-3[	402	395	15	12
[3-4[	491	279	25	20
[4-5]	377	335	29	20
Total (n=2850)	**1432**	**1278**	**75**	**65**

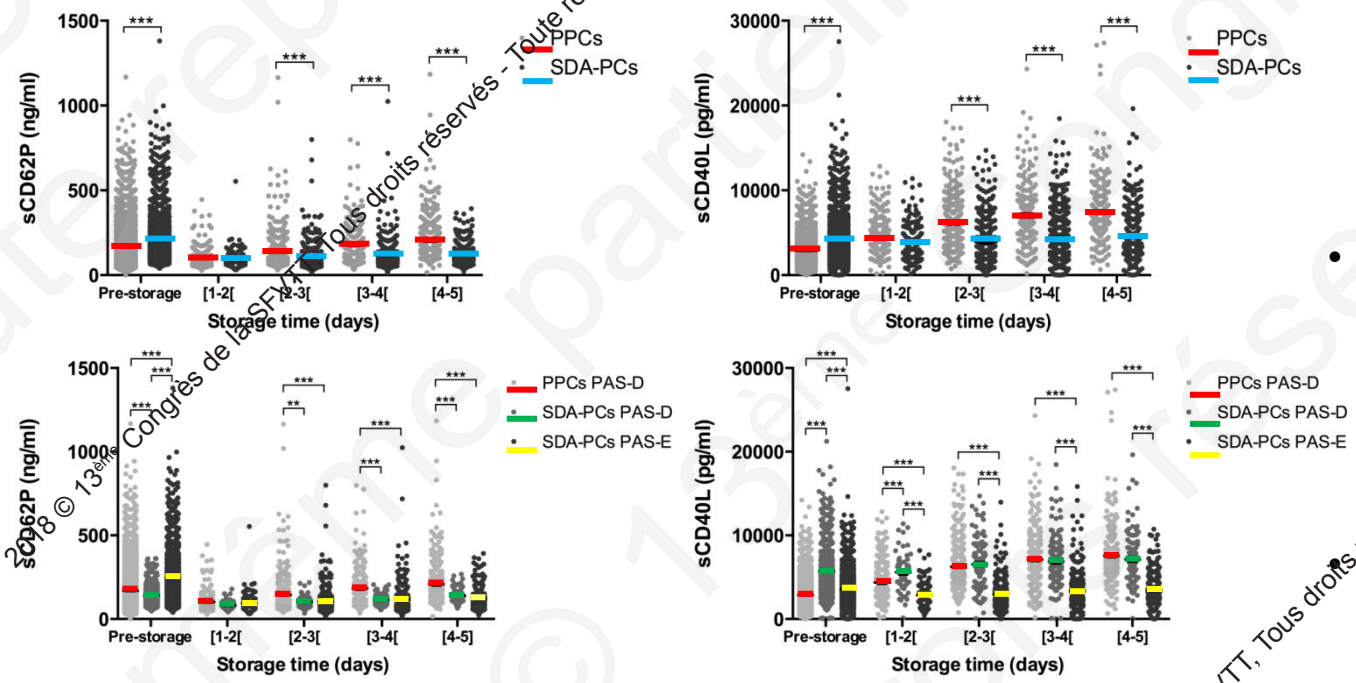


This study clearly showed that sCD40L levels are not fully predictive of SARs, but leaves open the possibility of

- **The comorbities of the recipient,**
- **Genetic susceptibility (high affinity binding of sCD40L by off target receptors),**
- **Or a causal disease condition,**

Or all three.

Soluble CD40L and CD62P levels differ in single donor apheresis platelet concentrates and Buffy-coat-derived pooled platelet concentrates – *Transfusion in press – Sut et al.*



- SDA-PCs appeared more activated than PPCs at the end of the production step (i.e. prior to storage);
- However, pro-inflammatory soluble factors increases in PPCs than in SDA-PCs during storage.
- In SDA-PCs, PAS-D (65%) led to reduced secretion of sCD62P, but favored secretion of sCD40L, compared with the alternative PAS-E.

Conclusion: These data stress the importance of the production (processing) steps of PC manufacture, and of storage.

blood®

PLATELETS AND THROMBOPOIESIS

Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A_2 to promote inflammation

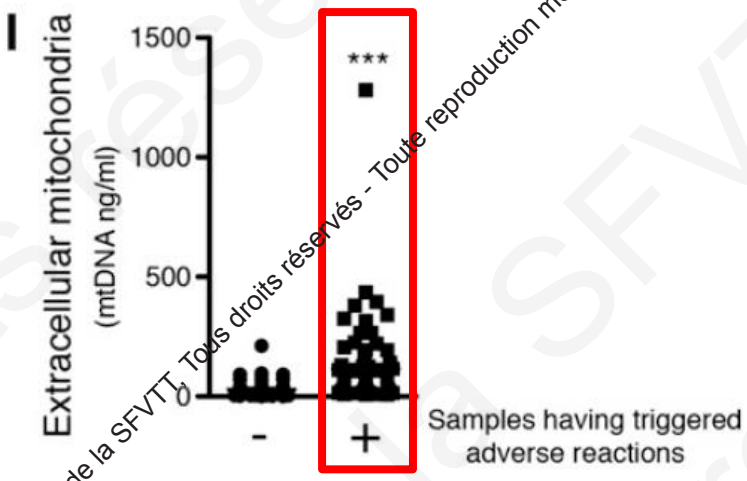
Luc H. Boudreau,[1] Anne-Claire Duchez,[1] Nathalie Cloutier,[1] Denis Soulet,[2] Nicolas Martin,[3] James Bollinger,[4] Alexandre Paré,[2] Matthieu Rousseau,[1] Gajendra S. Naika,[4] Tania Lévesque,[1] Cynthia Laflamme,[1] Geneviève Marcoux,[1] Gérard Lambeau,[5] Richard W. Farndale,[6] Marc Pouliot,[1] Hind Hamzeh-Cognasse,[7] Fabrice Cognasse,[7] Olivier Garraud,[7] Peter A. Nigrovic,[8] Helga Guderley,[3] Steve Lacroix,[2] Louis Thibault,[9] John W. Semple,[10] Michael H. Gelb,[4] and Eric Boilard[1]

Extracellular mitochondria, produced by platelets, at the midpoint of a potent mechanism leading to inflammatory responses

Dr Boilard: Centre de Recherche du Centre Hospitalier Universitaire de Québec, Faculté de Médecine de l'Université Laval, Quebec, QC, Canada

Extracellular mitochondria are present in various situations where platelets are known to be activated

(I) Extracellular mitochondria (as detected by mtDNA quantification) are found at higher concentration in PFP of platelet storage bags that have cause adverse transfusion reaction to the recipient (no adverse reaction group [n = 61] *vs* adverse reaction group [n = 74] matched in term of storage duration).



	-	+
n	61	74
min	1	85
max	210	1280
mean	26.1	115.2
SEM	4.7	19.9

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- **CONCLUSION : Getting the right product to the right patient !**

The machine learning base models could be used for predicting the probability of adverse reactions, with a goal towards better informing the clinician prior to a transfusion decision.

A Computerized Prediction Model of Hazardous Inflammatory Platelet Transfusion Outcomes

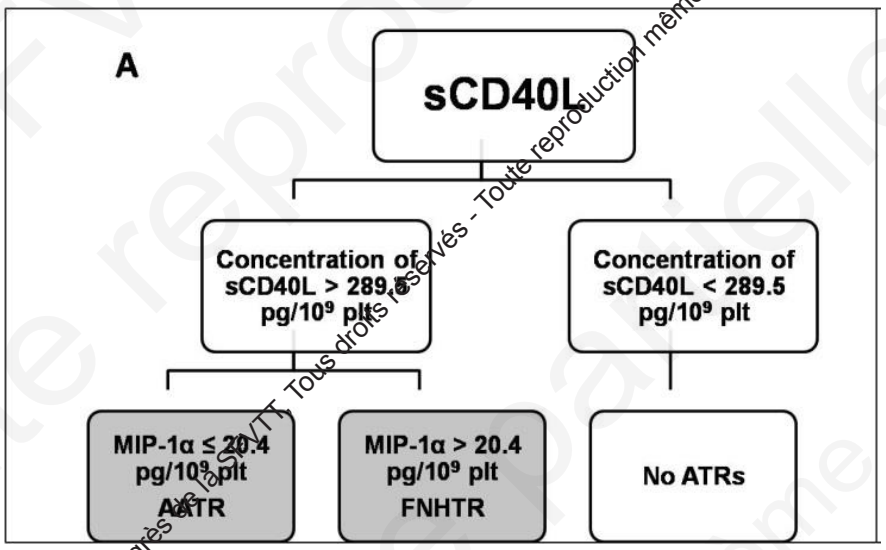
PLOS ONE
A peer-reviewed, open access journal
May 2014 | Volume 9 | Issue 5 | e97082

Kim Anh Nguyen[1], Hind Hamzeh-Cognasse[1], Marc Sebban[2], Elisa Fromont[2], Patricia Chavarin[3], Lena Absi[3], Bruno Pozzetto[1], Fabrice Cognasse[1,3], Olivier Garraud[1,3]*

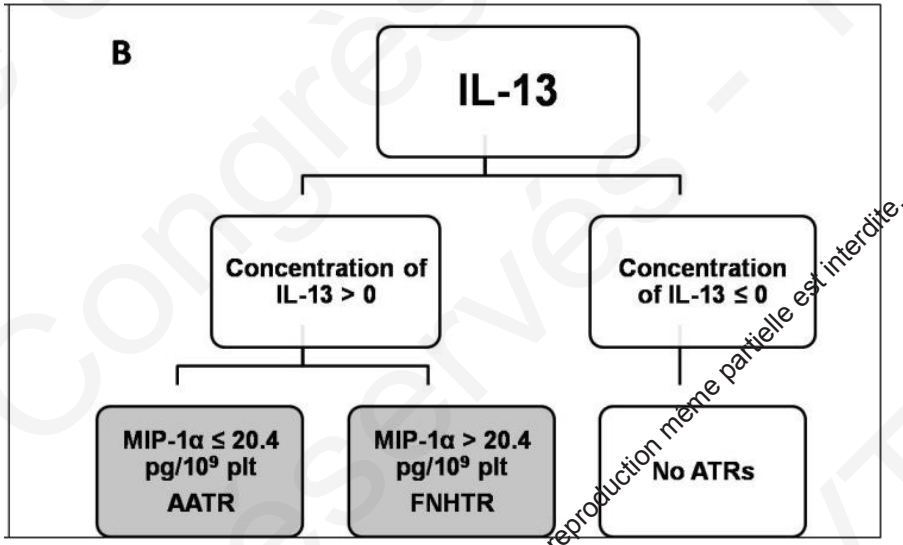
1 GIMAP-EA3064, Université de Lyon, Saint-Étienne, France, **2** Laboratoire Hubert Curien - UMR CNRS 5516, Saint-Etienne, France, **3** EFS Auvergne-Loire, Saint-Etienne, France

- **We investigated a large series of AEs after platelet component transfusions reported.**
- We used a combination of **clinical observations, *ex vivo* and *in vitro* investigations, and mathematical modeling systems.**
- **We calculated the statistical association of a large variety (n = 17) of cytokines, chemokines with acute inflammatory potential in patients presenting with transfusion-related Adverse Events .**

Decision-tree learning: febrile non-hemolytic transfusion reactions (**FNHTRs**), atypical allergic transfusion reactions (**AATRs**), Acute transfusions reaction (**ATRs**)



A. Assays without IL13 (among 16 assays, the success rate of the sCD40L model was the highest, 78%)



B. Assays with IL13 (among 17 assays, the success rate of the IL13 model was the highest, 82%).

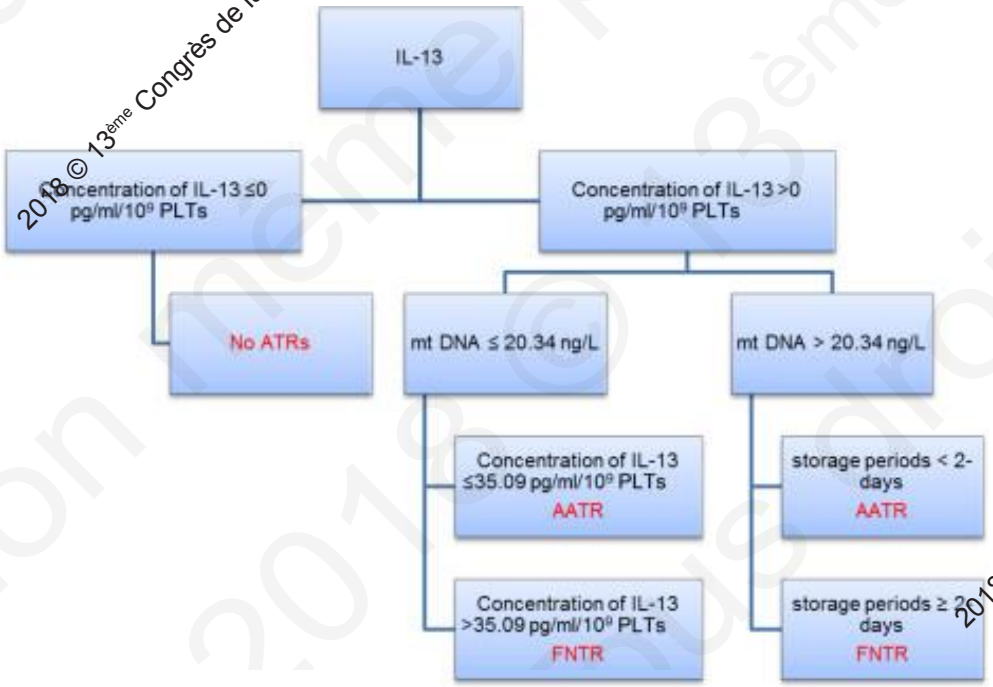
- **Decision-tree learning :** that proved Acute transfusions reaction (ATRs) are dependent on the level (amount) of a given cytokine-like platelet product.
- We further modelled the risk of the patient presenting either a FNHTRs or an AATRs, **depending on the amount of the chemokine MIP-1α.**

TRANSFUSION

TRANSFUSION COMPLICATIONS

Platelet components associated with adverse reactions: predictive value of mitochondrial DNA relative to biological response modifiers

Fabrice Cognasse,[1,2] Chaker Aloui,[2] Kim Anh Nguyen,[2] Hind Hamzeh-Cognasse,[2] Jocelyne Fagan,[1] Charles-Antoine Arthaud,[1] Marie-Ange Eyraud,[1] Marc Sebban,[3] Elisa Fromont,[3] Bruno Pozzetto,[2] Sandrine Laradi,[1,2] and Olivier Garraud[2,4]



Decision tree. Assays from a set **of 101 training samples with 18 attributes** (age of the blood sample; age of the donor; PLT count; and levels of Gro-a, sCD40L, 6-Ckine, CXCL9, IL-23, MIP-1a,IL-13,IFN-c, IL-15, MDC, IL-33, CCL19, CD62P, RANTES, and mtDNA).

The success rate of the IL-13 model was the highest: 83%

Journal of Thrombosis and Haemostasis, **14**: 794–796 DOI: 10.1111/jth.13262

COMMENTARY

How can non-nucleated platelets be so smart?

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- **Platelet a great immunomodulatory cell**
  - Brief Overview of Platelet Functions
- **The Non-Hemostatic Aspects of Transfused Platelets**
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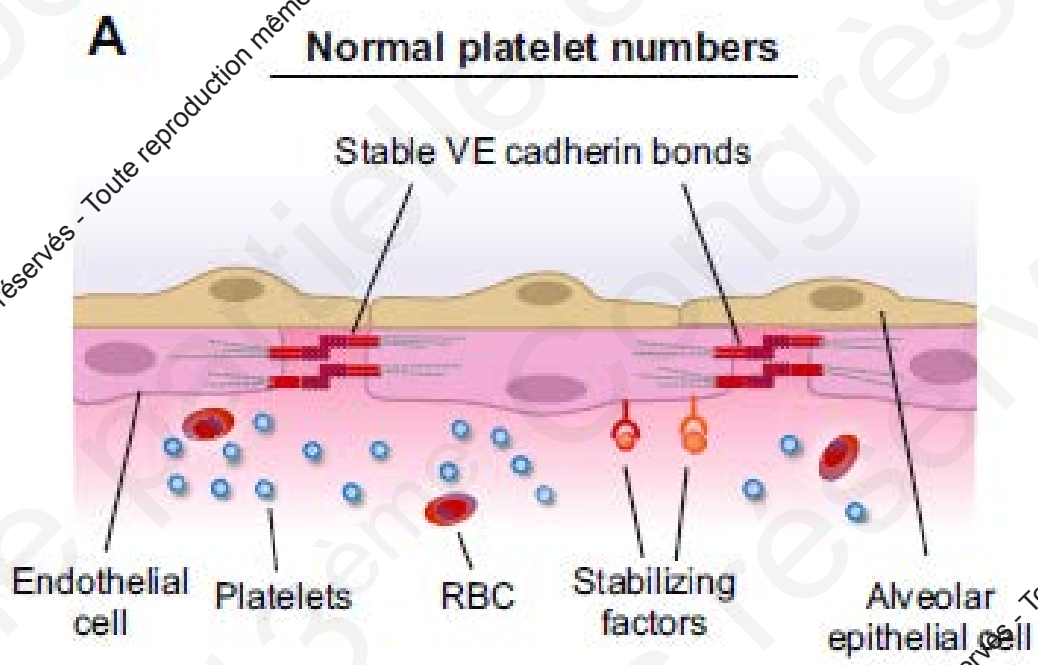
Platelets *(and Transfused Platelets)* are critical in maintenance of endothelial barrier function

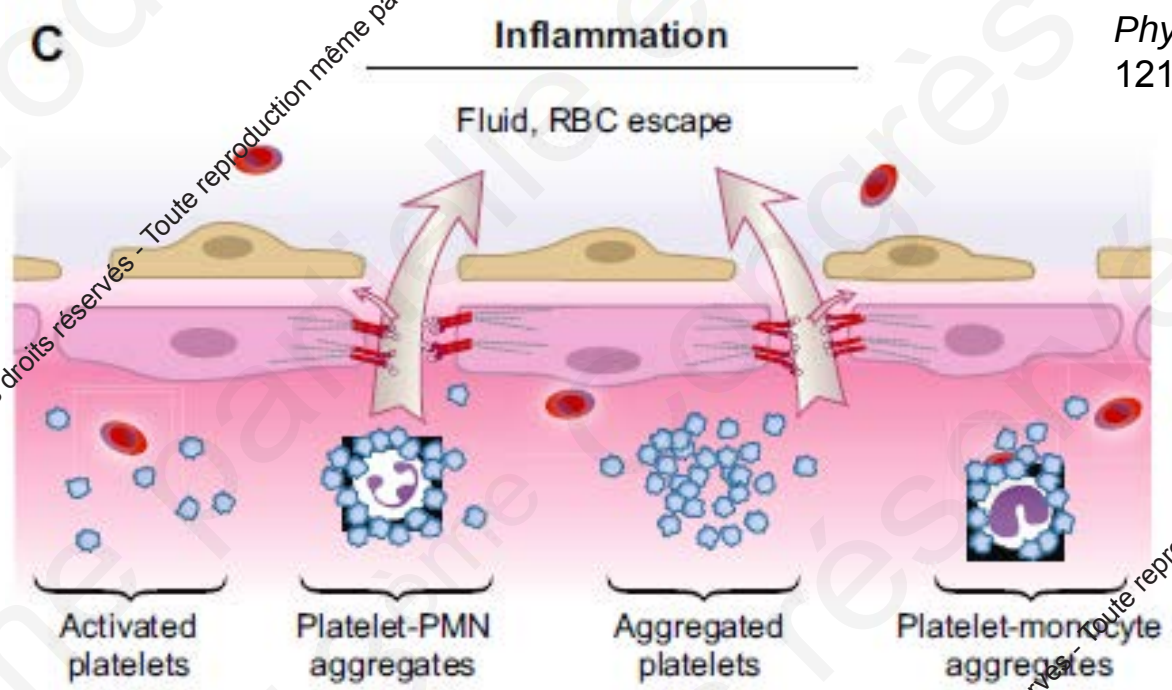
Physiol Rev 96: 1211–1259, 2016



- ✓ *A*: **when platelet numbers are sufficient, semipermeable endothelial barriers** that restrict transfer of water and proteins out of systemic and alveolar capillaries **are maintained and protected**.
- ✓ **Release of stabilizing factors by platelets is one mechanism for endothelial barrier maintenance**.

Platelets *(and Transfused Platelets)* are critical in maintenance of endothelial barrier function but also induce increased endothelial permeability in inflammation.

Physiol Rev 96: 1211–1259, 2016



Transfused Platelets ?

- ✓ ***C*: activated platelets can induce or amplify increased permeability of alveolar and systemic endothelial barriers in inflammation.**
- ✓ Several mechanisms have been proposed or demonstrated in experimental models, including **release of platelet factors that disrupt endothelial barriers, signaling of endothelial cells, and interaction with PMNs and monocytes, leading to disruption of endothelial bonds and leak of fluid, proteins, and RBC.**

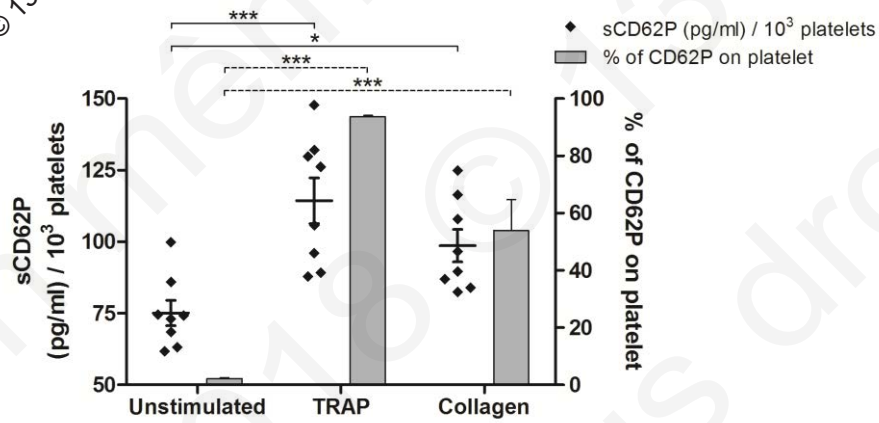
Modeling the effect of platelet concentrate supernatants on endothelial cells: focus on endocan/ESM-1

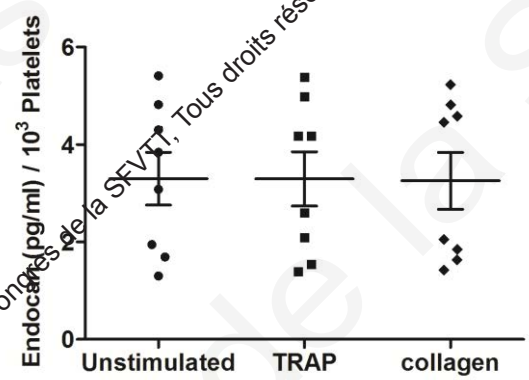
Transfusion. 2018 Feb;58(2):439-445.

Sofiane Tariket,[1,2] Caroline Sut,[1,2] Charles-Antoine Arthaud,[1] Marie-Ange Eyraud,[1] Astrid Meneveaux,[1] Sandrine Laradi,[1,2] Hind Hamzeh-Cognasse,[2] Olivier Garraud,[2,3] and Fabrice Cognasse[1,2]

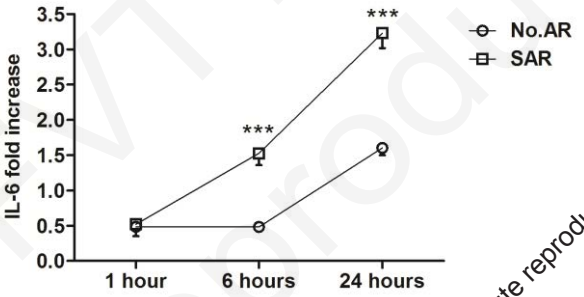
Endocan/ESM-1 is a proteoglycan secreted by endothelial cells under the control of proinflammatory cytokines.

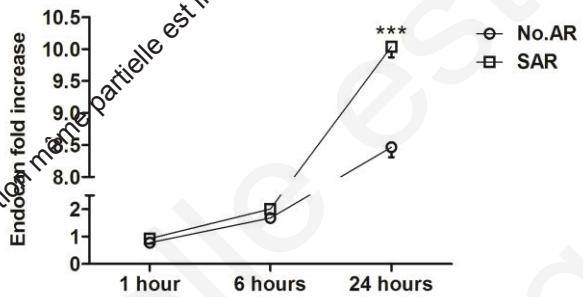
We aimed to measure endocan activity (EA.hy926 endothelial cells) in supernatants of PLT components (PCs), implicated in serious adverse reactions (SARs) or not (no.AR), sampled at different stages during storage.

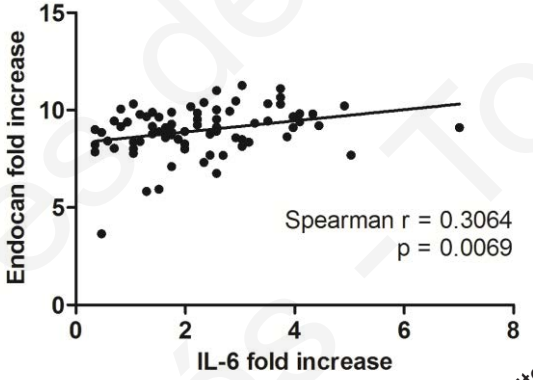


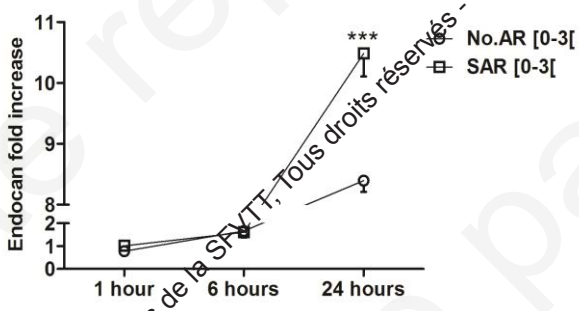


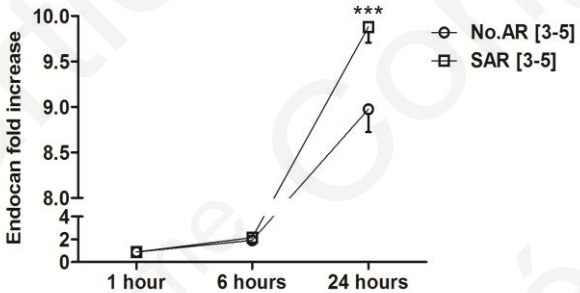
PLT activation does not induce endocan release











We next investigated the bioactivity of the no.AR and SAR PC supernatants aged 0 to 3 or 3 to 5 days on EA.hy926 cells by measuring IL-6 and endocan secretion after 6- or 24-hour exposure to the supernatant.

IL-6 and endocan secretion were significantly higher for cells stimulated with SAR than those stimulated with the no.AR PC supernatants, regardless of the time in storage.

There was a significant correlation between IL-6 and endocan secretion after of EA.hy926 cell activation.

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COMMENTARY

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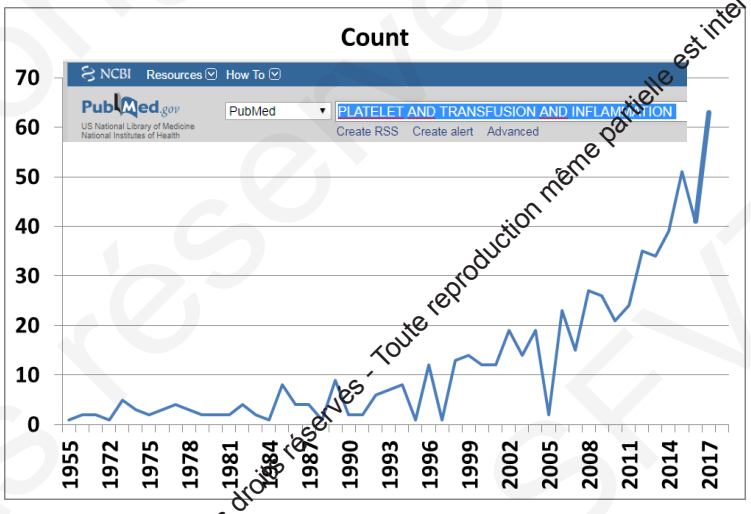
CONCLUSION : *Getting the right product to the right patient !*

- ✓ Transfusion of platelets is generally safe and largely beneficial to patients.
- ✓ On rare occasions, SARs, occur with clinical presentation of acute inflammation.
- ✓ In all cases investigated to date, either based on clinical observations or tested experimentally, Biological response modifiers (BRMs) (such as sCD40L) are found to be in close association.

Since 20 years: A growing interest from the scientific community !!!

Main reviews:

- Aubron C et al Critical Care (London, England). 2018
- Koupenova M et al Circ Res. 2018 ***
- Sut C et al Front Med (Lausanne). 2018
- Kapur R et al J Immunol 2015 ***
- Jenne CN et al Platelets. 2015
- Morrell CN et al Blood. 2014 ***
- Vlaar AP et al Lancet. 2013 ***
- Refaai MA et al Thromb Res. 2011
- Hod E et al Br J Haematol. 2008



- ✓ Transfusion-linked inflammation is likely the result of a combination of factors related to the **Donor**, the **BC**, and the **Recipient**.
- ✓ Unfortunately the main factor that can be targeted at present is the **BC**
- ✓ Transfusion medicine may become one of the first medical specialties where personalized medicine comes into effect: **"How can a given patient be given the BC most suited to his or her condition"?**

Platelet Inflammation Response to Stress : Team PIRS / GIMAP EA3064

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Olivier Garraud (MD, PhD, HDR) / UJM-INTS

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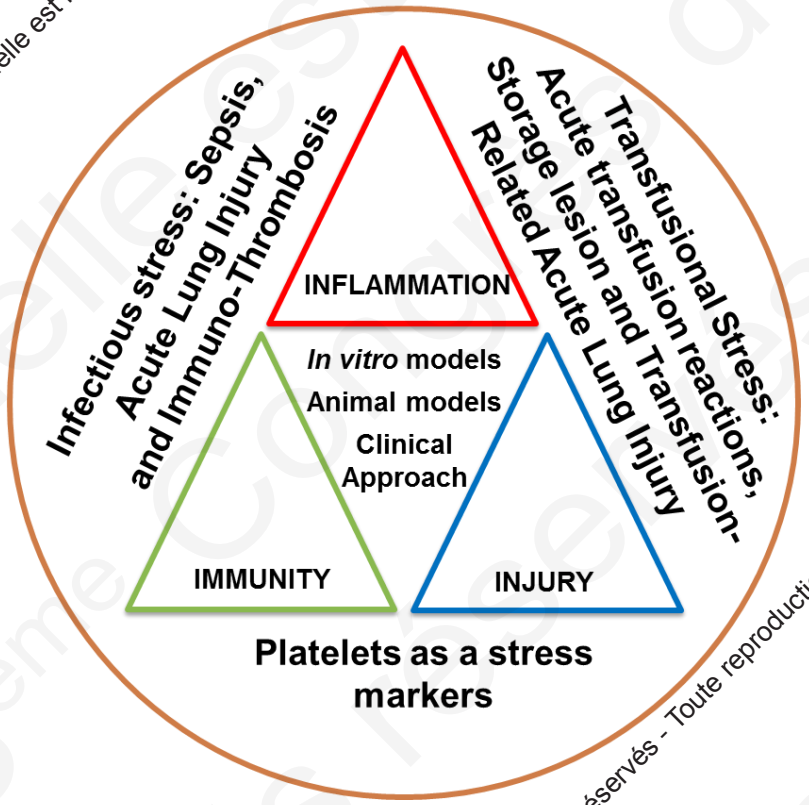
Charles Antoine Arthaud Technician) / EFS

Jocelyne Fagan (Technician) / EFS

Maelle Detoc (CRA) / CHU



Thomas Bourlet (Director)

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