Plaquettes : Inflammation et Transfusion

Keywords: Platelet, Innate Immunity, CD40L, Inflammation, TLRs, danger signals, Transfusion

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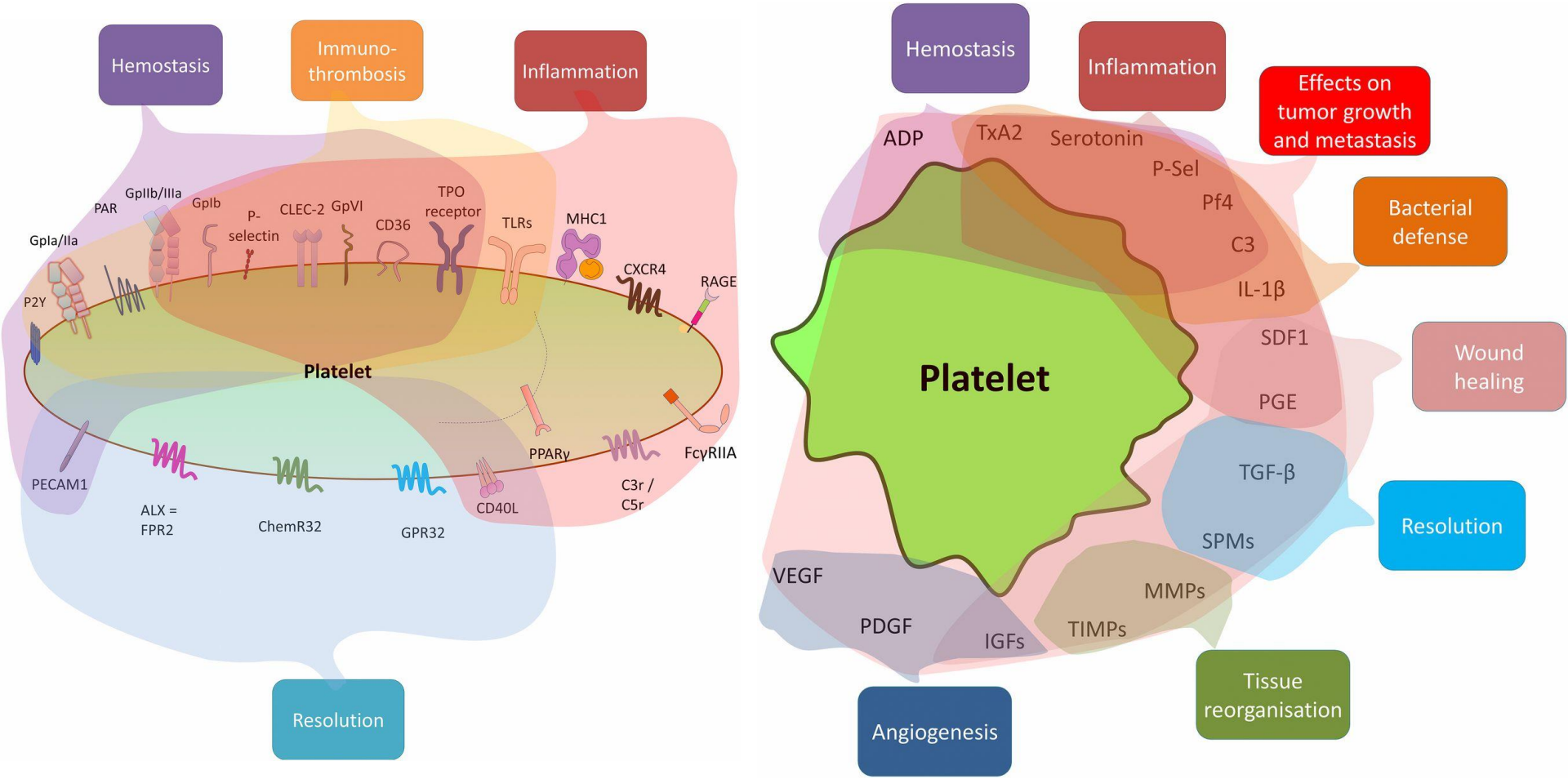
Platelets as immune cells: Introduction

The Journal of Immunology

Platelets in Inflammation and Resolution

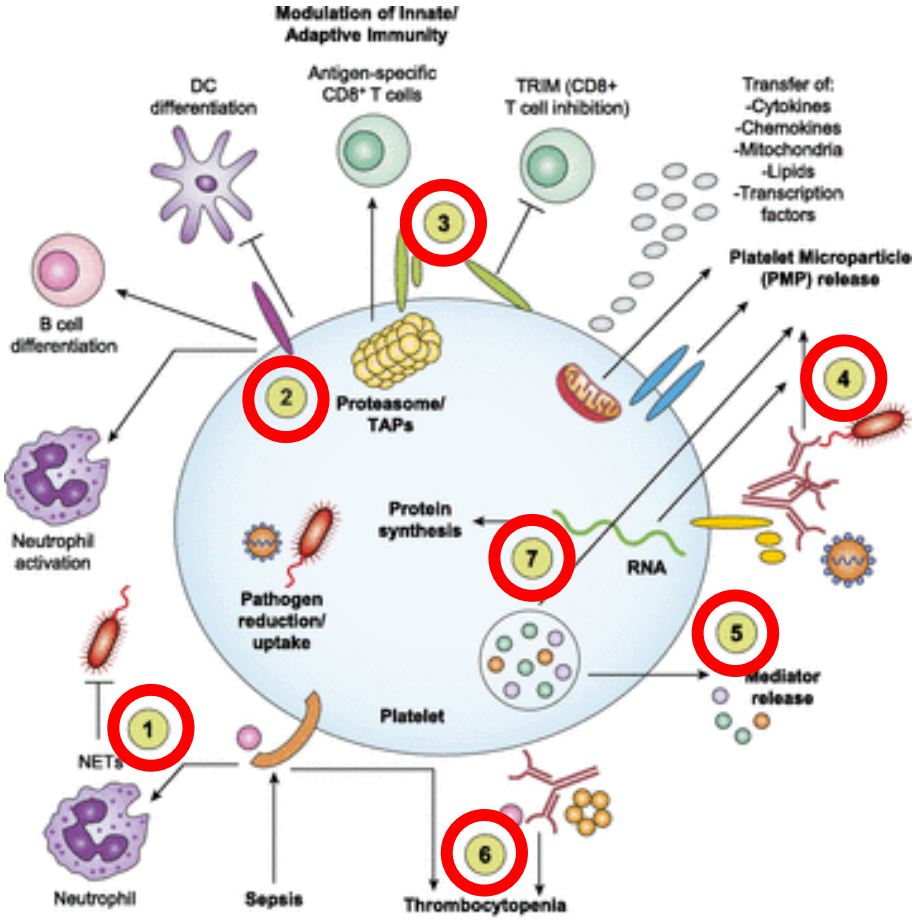
Andreas Margraf and Alexander Zarbock

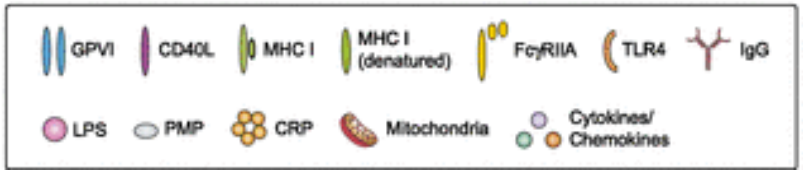
J Immunol 2019; 203:2357-2367; ;
doi: 10.4049/jimmunol.1900899
http://www.jimmunol.org/content/203/9/2357



Platelets contribute to the resolution of inflammation by a multitude of factors

All these events makes platelet a great immunomodulatory cell





Rick Kapur et al J Immunol June 15, 2015

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
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[3]Department of Anesthesiology, Intensive Care, and Pain Medicine, University of Münster, Münster, Germany
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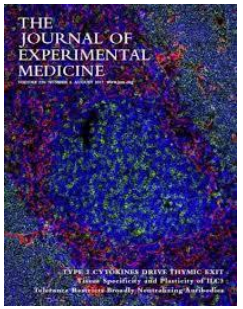
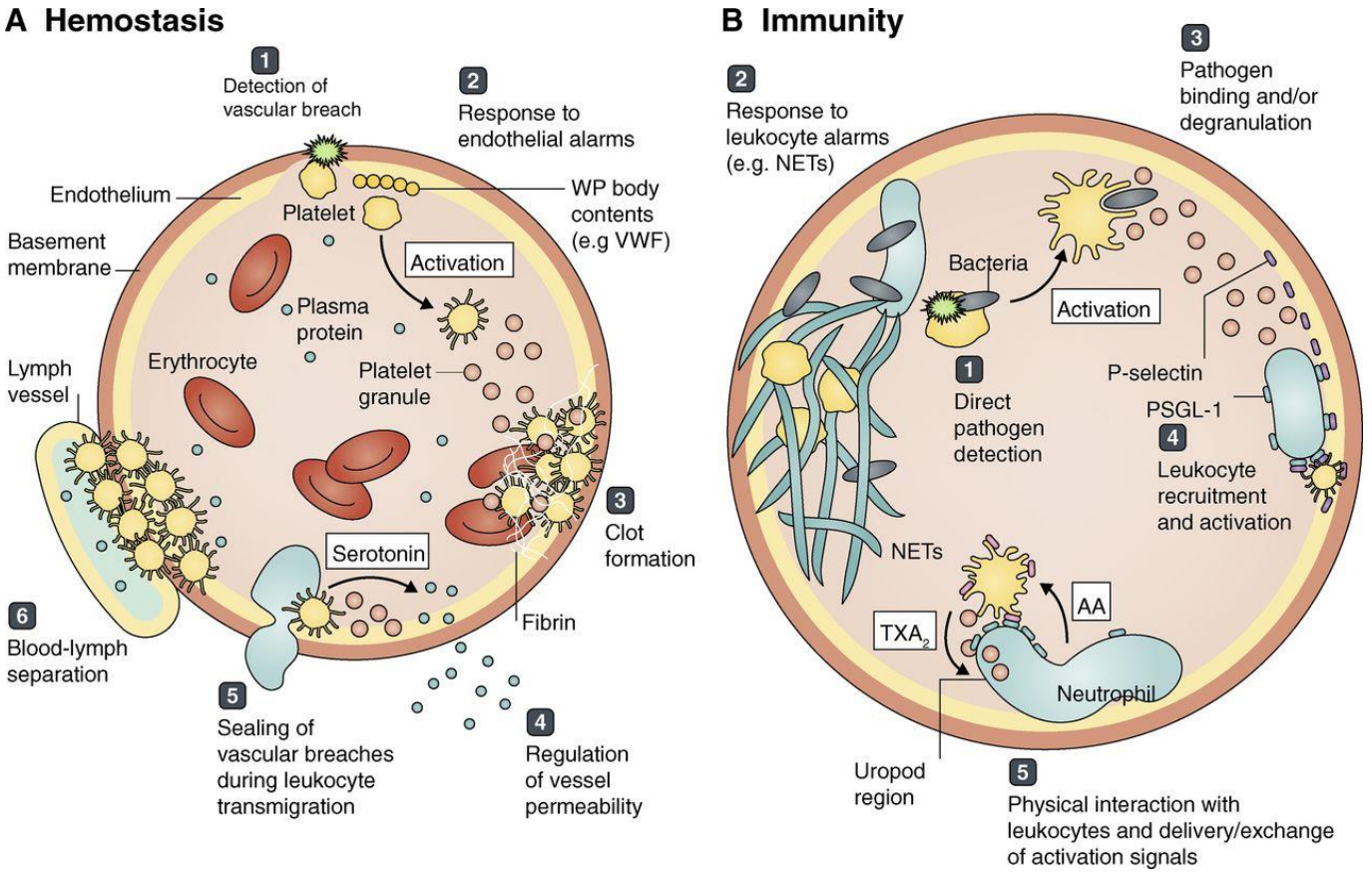


J. Exp. Med. 2017



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

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

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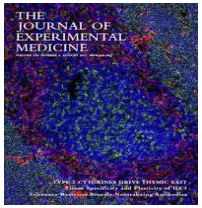
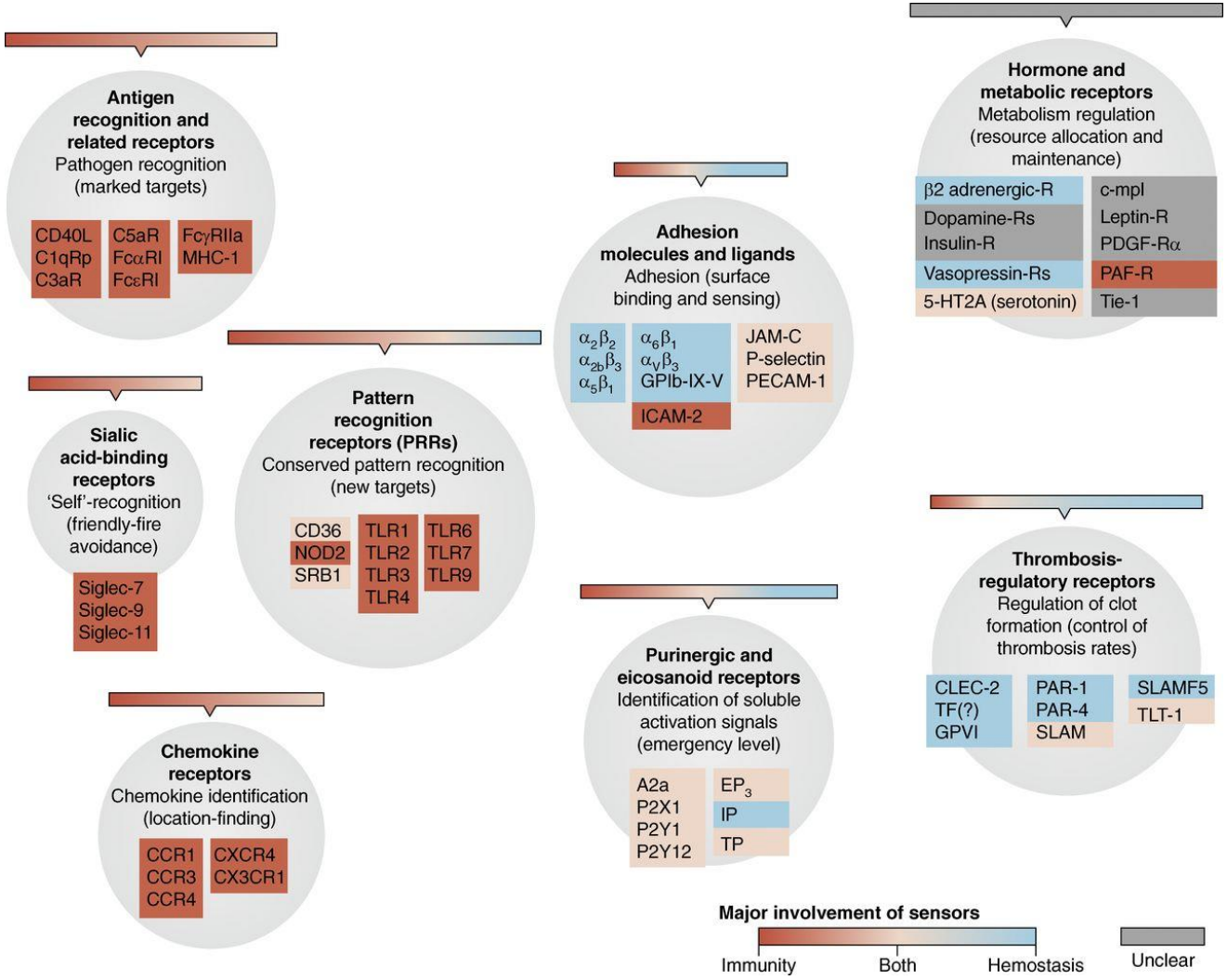


J. Exp. Med. 2017



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

Immunology and Cell Biology (2005) **83**, 196–198 doi:10.1111/j.1440-1711.2005.01314.x

Brief Communication

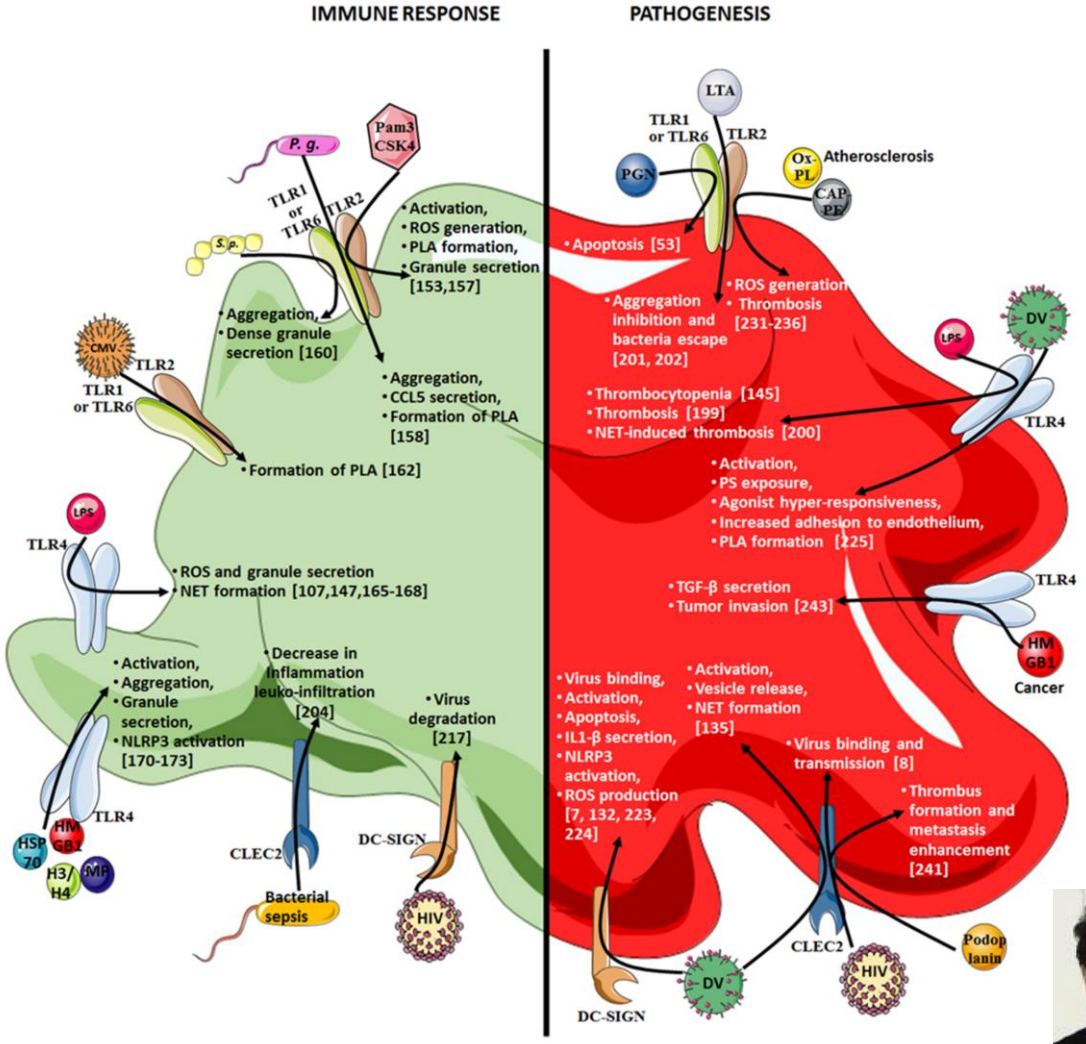
Evidence of Toll-like receptor molecules on human platelets

FABRICE COGNASSE,[1,2] HIND HAMZEH,[2] PATRICIA CHAVARIN,[1] SOPHIE ACQUART,[1] CHRISTIAN GENIN[2] and OLIVIER GARRAUD[1,2]

Review

Platelet Innate Immune Receptors and TLRs: A Double-Edged Sword

Théo Ebermeyer [1], Fabrice Cognasse [1,2], Philippe Berthelot [3,4], Patrick Mismetti [1,5], Olivier Garraud [1] and Hind Hamzeh-Cognasse [1,*]



Platelet membrane innate immunity and toll-like receptors involved in the immune response and pathogenesis

TLRs can recognize both broad microbe-specific pathogen-associated molecular patterns **(PAMPs)** and host-derived damage-associated molecular patterns **(DAMPs)**, and these receptors are **crucial for orchestrating and sustaining the inflammatory response to both types of danger signals**.

@ Hind Hamzeh-Cognasse

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
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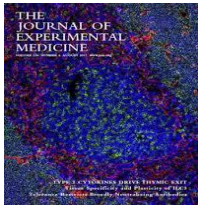


J. Exp. Med. 2017

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)

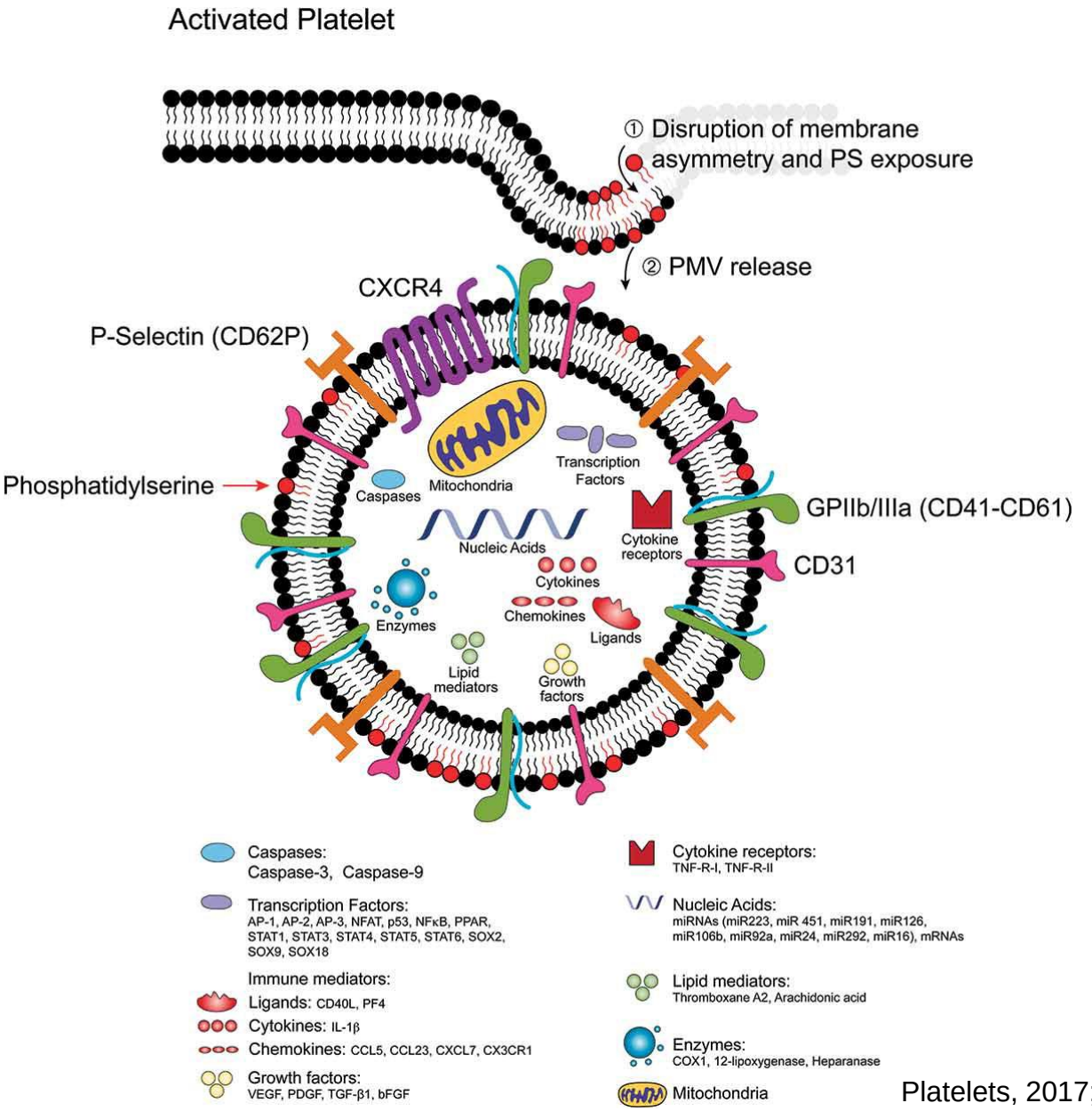
- Angiopoietin-1
- BDNF
- bFGF
- BMP-2,4 and 6
- CTGF
- Thrombospondin
- EGF
- Endostatin
- HGF
- IGF-1
- PDGF
- VEGF
- n-acetylglucosaminidase
- α-arabinosidase
- β-galactosidase
- β-glucuronidase
- RNA (mRNA, miRNA etc.)

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.

The role of microparticles in inflammation and transfusion



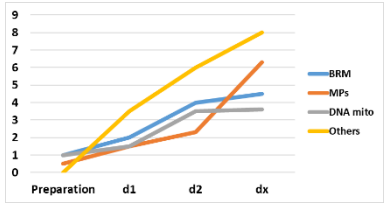
Platelets, 2017; 28(3): 214–221. DOI: 10.1080/09537104.2016.1265924

Platelets as immune cells:

Transfusion context

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

Biological response modifiers (BRMs)



Process and Storage time
« storage lesion »

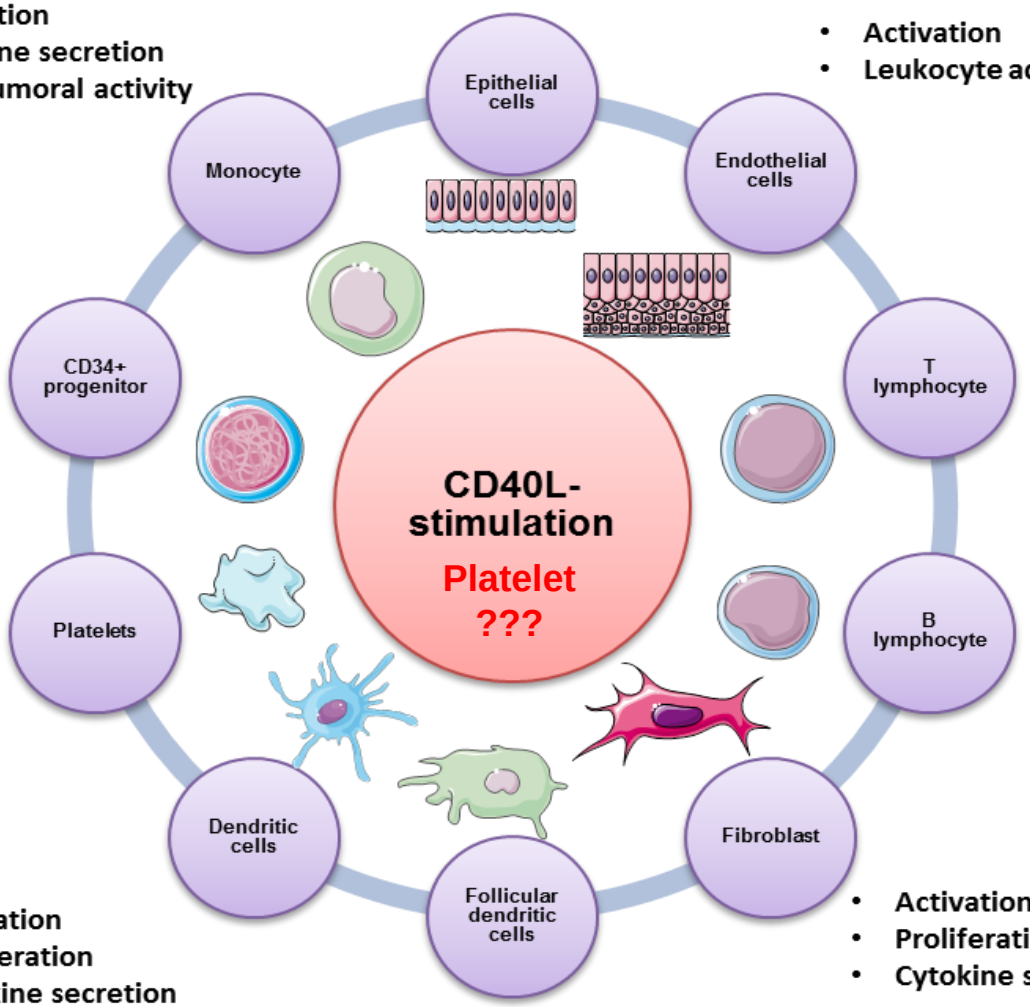
TRANSFUSION

Platelet concentrate

- Epithelial cells
- Endothelial cells
- T lymphocyte
- B lymphocyte
- Fibroblast
- Follicular dendritic cells
- Dendritic cells
- Platelets
- CD34+ progenitor
- Monocyte

All patients receiving a platelet transfusion receive platelets, along with high levels of platelet-derived mediators accumulated in the platelet component.

Platelets - Other Cells Interactions : sCD40L (CD154) – CD40



- Activation
- Cytokine secretion

- Activation
- Cytokine secretion
- Anti-tumoral activity

- Activation
- Leukocyte adhesion

- Proliferation
- Differentiation in to Dendritic cells

- Proliferation

- Isotypic commutation
- Cytokine secretion
- Proliferation/cell survival
- Activation

- Activation
- BRM secretion

- Activation
- Proliferation
- Cytokine secretion

- Activation
- Proliferation
- Cytokine secretion

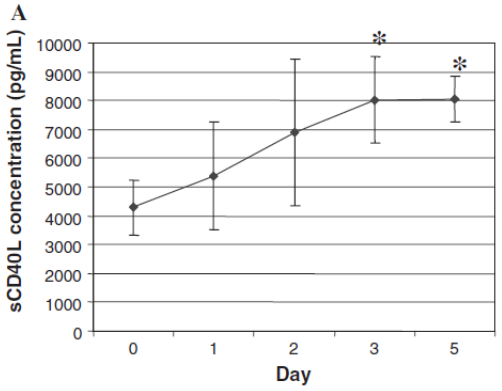
- Proliferation

CD40 Ligand/Platelet: storage

Release of potential immunomodulatory factors during platelet storage

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

TRANSFUSION Volume 46, July 2006



Impact of the platelet washing process on in vitro platelet properties, and the levels of soluble CD40 ligand and platelet-derived microparticles in the storage media

TRANSFUSION 2019;59;1080–1089

Shinji Oikawa,[1,2] Masayoshi Minegishi,[3] Kimika Endo,[1,4] Wataru Kawashima,[1,5] Satoshi Kosunago,[1] Masanori Oyama,[1] Ko Suzuki,[4] and Hiroshi Shimizu[1]

Platelet granule release is associated with reactive oxygen species generation during platelet storage: A direct link between platelet pro-inflammatory and oxidation states

Mehran Ghasemzadeh [a,b], Ehteramolsadat Hosseini [a,*]

[a] Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran
[b] Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria 3004, Australia

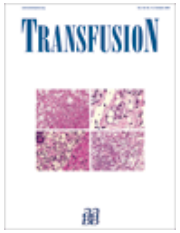
Thrombosis Research 156 (2017) 101–104

CD40 Ligand/Platelet: Clinical Correlates

An association of soluble CD40 ligand (CD154) with adverse reactions to platelet transfusions

Volume 46, October 2006 **TRANSFUSION 1813**

Neil Blumberg, Kelly F. Gettings, Chantal Turner, Joanna M. Heal, and Richard P. Phipps



blood

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

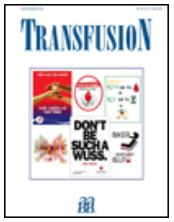
Platelet components associated with acute transfusion reactions: the role of platelet-derived soluble CD40 ligand

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

Platelet transfusion alters CD40L blood level and release capacity in patients suffering from thrombocytopenia

Volume 52, June 2012 **TRANSFUSION 1213**

Folker Wenzel, Wiebke Günther, Anja Baertl, Wolfgang Gruber, Rüdiger Volker Sorg, Rainer Haas, and Günther Giers



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

blood

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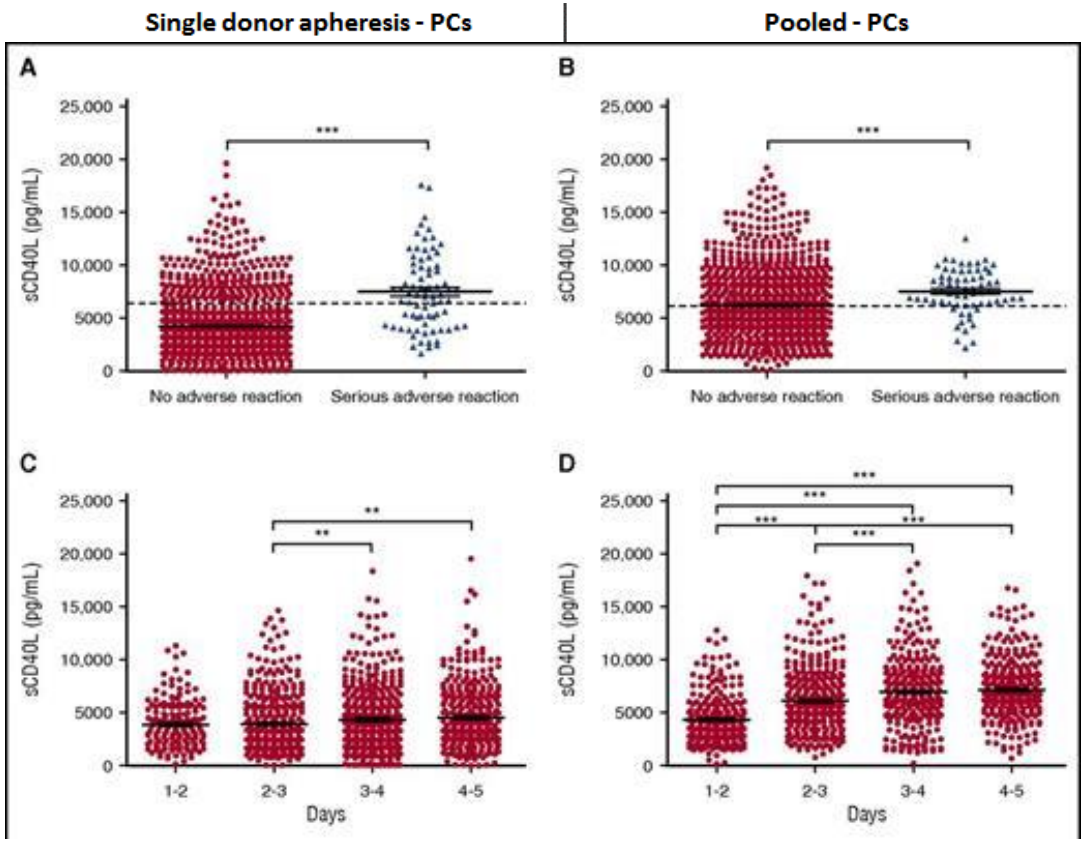
Days	No adverse reaction** (n=2710)		Serious adverse reaction*** (n=140)	
	Single donor apheresis-PCs°	Pooled-PCs°°	Single donor apheresis-PCs°	Pooled-PCs°°
[1-2[*	162	269	6	13
[2-3[	402	395	15	12
[3-4[	491	279	25	20
[4-5]	377	335	29	20
Total (n=2850)	**1432**	**1278**	**75**	**65**



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

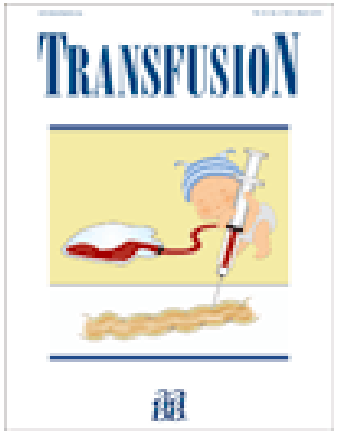
- **The comorbities of the recipient,**
- **Genetic susceptibility (high affinity binding of sCD40L by off target receptors),**
- **Or a causal disease condition,**

Or all three.

Not only sCD40L …

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

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]



Volume 54, March 2014 **TRANSFUSION**

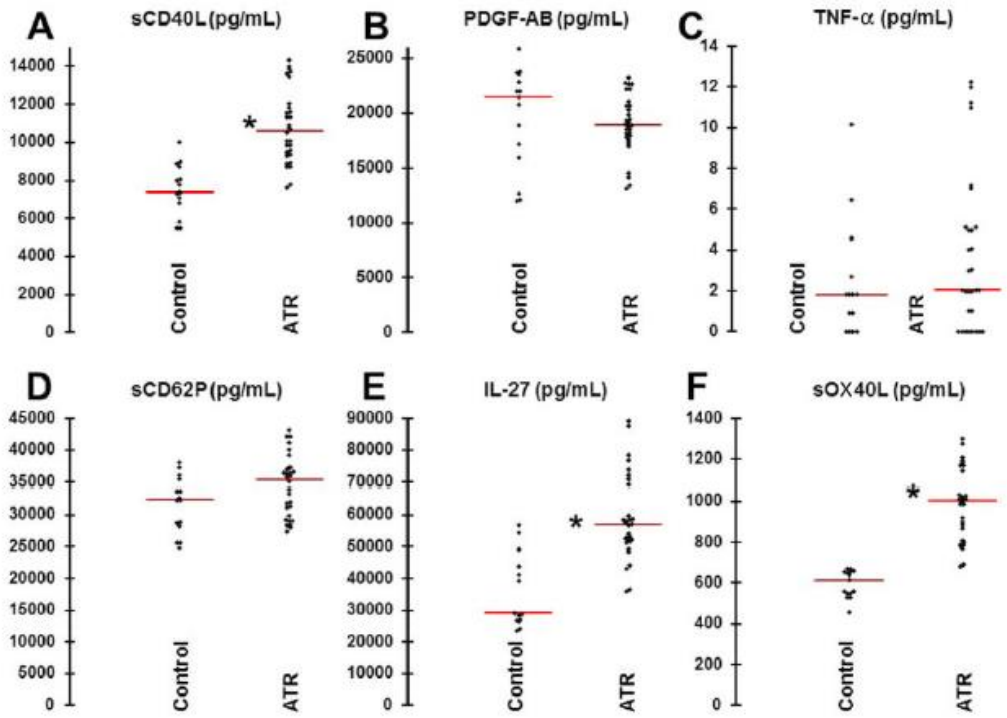


Fig. 1. Assessment of immunomodulatory factors in ATR-associated and control PCs.

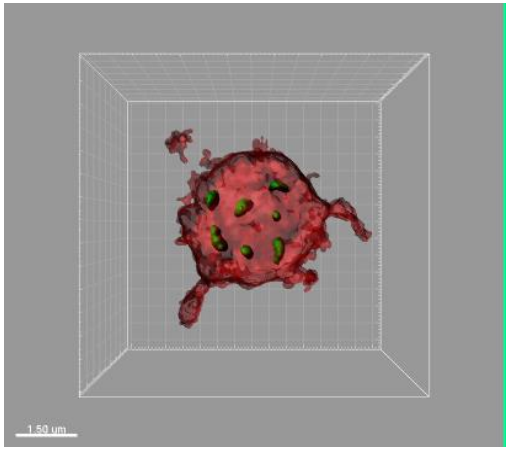
PLATELETS AND THROMBOPOIESIS

blood®

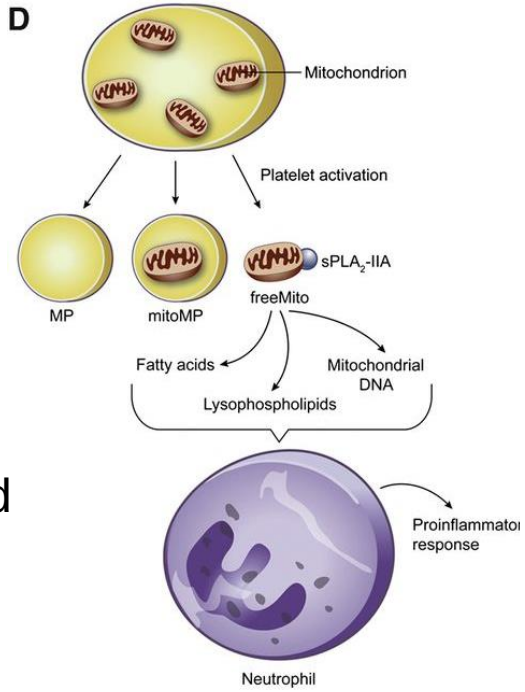
Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A_2 to promote inflammation

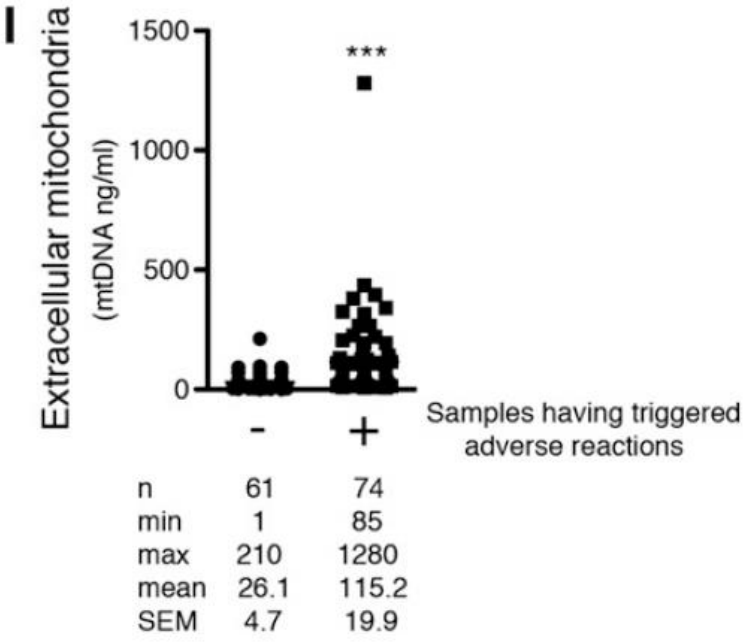
Luc H. Boudreau,[1] Anne-Claire Duchez,[1] Nathalie Cloutier,[1] Denis Soulet,[2] Nicolas Martin,[3] James Bollinger,[4] Alexandre Paré,[2] Matthieu Rousseau,[1] Gajendra S. Naika,[4] Tania Lévesque,[1] Cynthia Laflamme,[1] Geneviève Marcoux,[1] Gérard Lambeau,[5] Richard W. Farndale,[6] Marc Pouliot,[1] 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]

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



Using fluorescence and transmission electron microscopy (TEM), we found that unactivated platelets contain an average of ~4 mitochondria.





Platelet concentrates that had been associated with adverse transfusion reactions in human recipients contain higher concentrations of extracellular mitochondria.

The Lipid Composition of Platelets concentrates and the Impact of Storage

@ Anne Claire Duchez

Original article — Ahead-of-Print

Lipidomic analysis of differently prepared platelet concentrates in additive solution during storage

Anne-Claire Duchez, Sébastien Fauteux-Daniel, Theo Ebermeyer, Marco Heestermans, Charles-Antoine Arthaud, Marie-Ange Eyraud, Amélie Prier, Estelle Audoux, Jean-Charles Portais, Justine Bertrand-Michel, Olivier Garraud, Hind Hamzeh-Cognasse, Eric Boilard, Fabrice Cognasse

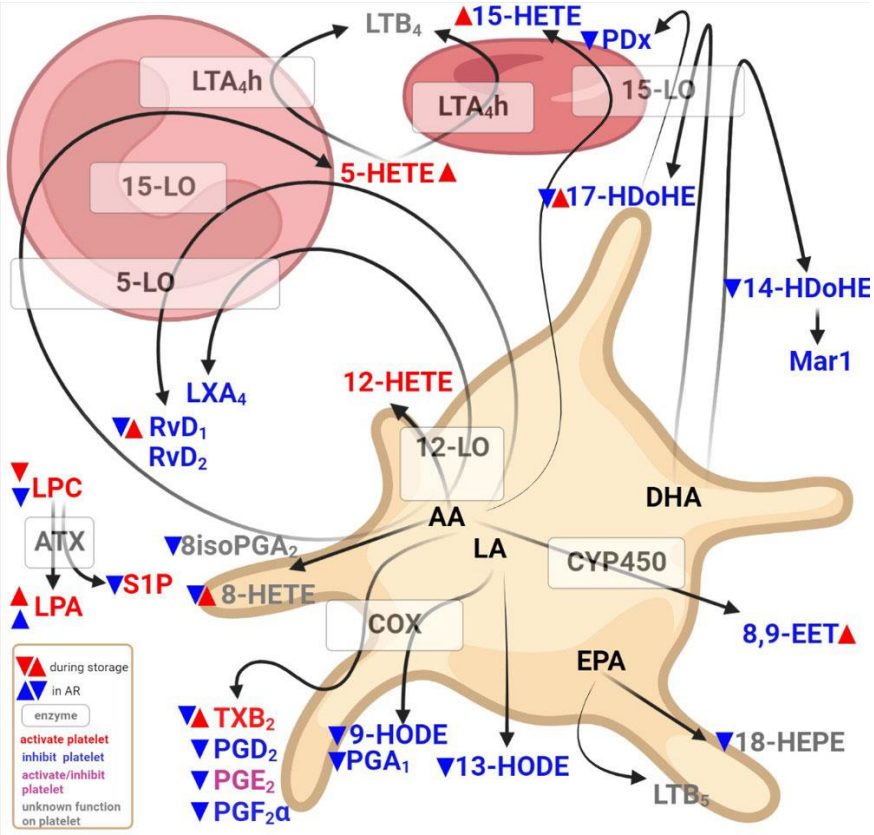
Key words: platelet, lipidomic, transfusion

DOI: 10.2450/2022.0144-22 — Publication Date: 2022-11-04

Bioactive lipids as biomarkers of adverse reactions associated with apheresis platelet concentrate transfusion

Anne-Claire Duchez[1,2*], Sébastien Fauteux-Daniel[1,2], Caroline Sut[1], Theo Ebermeyer[2], Marco Heestermans[1,2], Charles-Antoine Arthaud[1,2], Marie-Ange Eyraud[1,2], Amélie Prier[1,2], Estelle Audoux[1,2], Justine Bertrand-Michel[3,4], Bernard Payrastre[4,5], Olivier Garraud[2], Eric Boilard[6,7], Hind Hamzeh-Cognasse[2] and Fabrice Cognasse[1,2]

TYPE Original Research
PUBLISHED 17 April 2023
DOI 10.3389/fimmu.2023.1031968



Our study highlights bioactive lipids in SDA-PC during storage and some lipids that could shed light on the onset of adverse reaction in recipients.

- Indeed, in the case of an AR, LPA species expressions are increased in SDA-PC whereas other lipid mediator expressions are decreased.
- It is interesting to note that during SDA-PC storage, lipid concentrations rise for the LPA species, TXB2, 5-HETE, 8-HETE, 15-HETE, RvD1, RvD2, 17-HDoHE and 8,9-EET compared to LPC expressions, which decrease during storage.

Platelet-derived HMGB1: critical mediator of SARs related to transfusion

Fabrice Cognasse[1,2], Caroline Sut[1,2], Hind Hamzeh-Cognasse[2], Olivier Garraud[2]

[1]Etablissement Français du Sang Auvergne-Rhône-Alpes, Saint-Etienne, France; [2]GIMAP-EA3064, Université de Lyon, Saint-Étienne, France

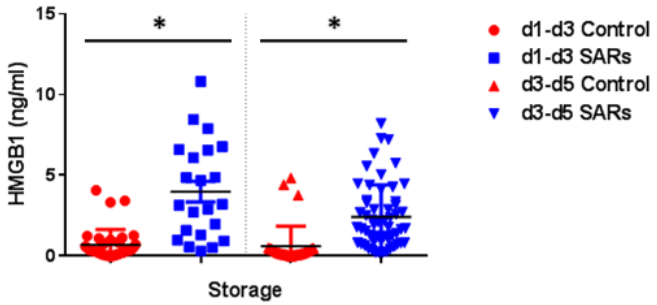
Correspondence to: Dr. Fabrice Cognasse, PhD. Etablissement Français du Sang Auvergne-Rhône-Alpes and GIMAP-EA 3064, Université de Saint-Etienne, Etablissement Français du Sang Rhône-Alpes-Auvergne, 25 Boulevard Pasteur, 42100 Saint-Etienne, France.

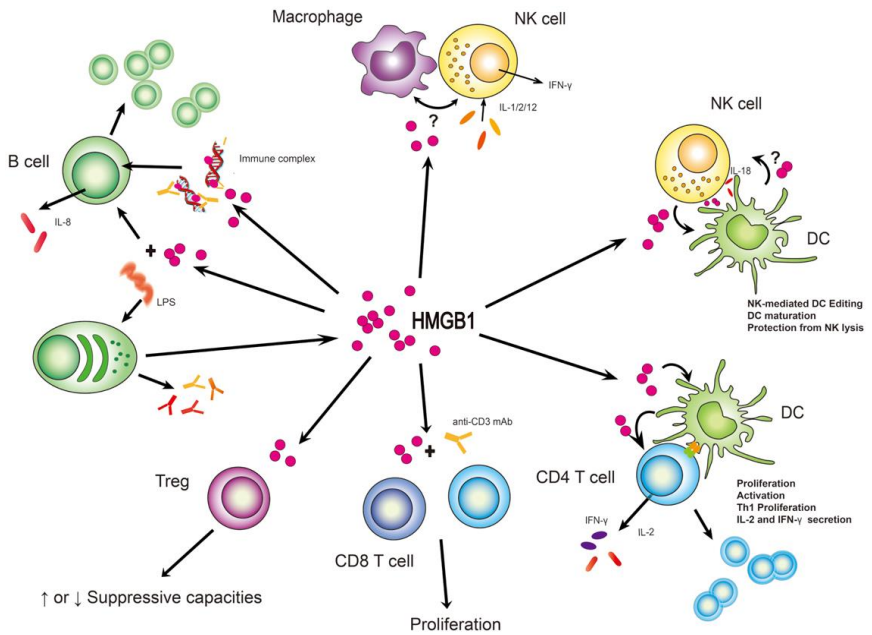
Email: fabrice.cognasse@efs.sante.fr.

Ann Transl Med. 2020 Feb;8(4):140.

- Recently, we investigated, the HMGB1 release through single donor apheresis-Platelet Concentrates - associated or not with SARs - process and during their storage.

- We provide first evidence that levels of soluble HMGB1 are also strongly associated with SARs.





HMGB1 stimulates effector function from immune cells.

Front. Immunol., 20 March 2013.
https://doi.org/10.3389/fimmu.2013.00068

Received: 21 April 2022 | Revised: 22 July 2022 | Accepted: 24 October 2022
DOI: 10.1111/trf.17200

BLOOD COMPONENTS

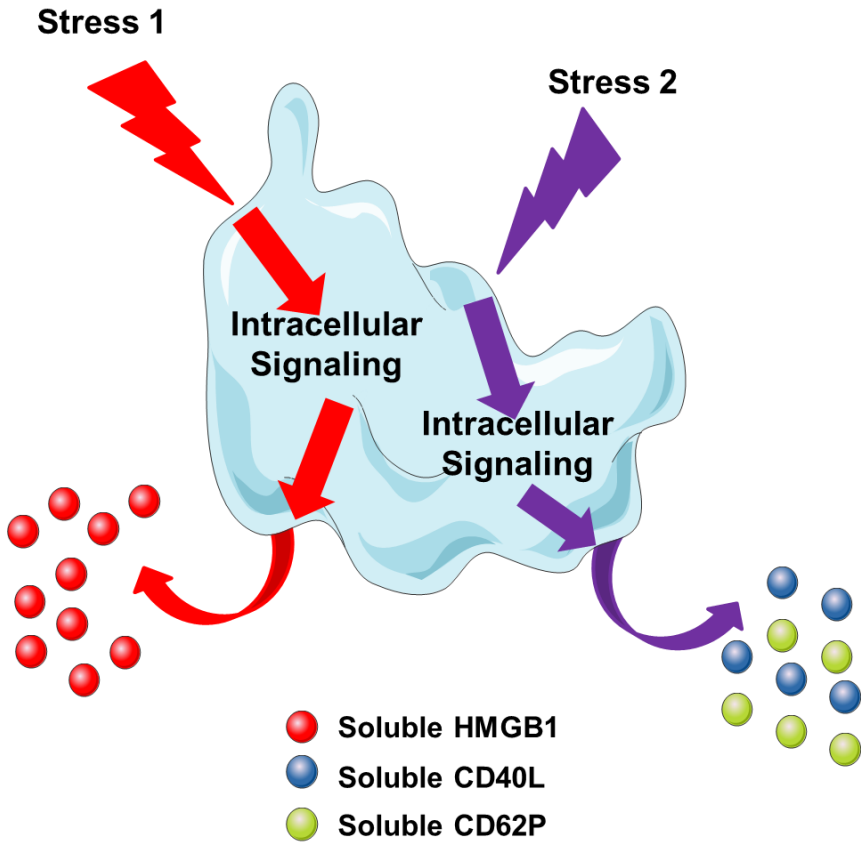
TRANSFUSION

Assessment of the soluble proteins HMGB1, CD40L and CD62P during various platelet preparation processes and the storage of platelet concentrates: The BEST collaborative study

Fabrice Cognasse[1,2] | Hind Hamzeh Cognasse[2] | Marie Ange Eyraud[1,2] | Amélie Prier[1,2] | Charles Antoine Arthaud[1,2] | Pierre Tiberghien[3,4] | Stephane Begue[3] | Dirk de Korte[5] | Eric Gouwerok[5,6] | Andreas Greinacher[7] | Konstanze Aurich[7] | Femke Noorman[8] | Larry Dumont[9,10] | Kathleen Kelly[9,10] | Marc Cloutier[11] | Renée Bazin[11] | Rebecca Cardigan[12] | Sian Huish[12] | Peter Smethurst[12] | Dana Devine[13] | Peter Schubert[13] | Lacey Johnson[14] | Denese C. Marks[14] | Biomedical Excellence for Safer Transfusion (BEST) Collaborative

TABLE 1 Study protocol, samples, and tests

Platelet concentrate processing ($n = 3748$ assays)	HMGB1		sCD40L		sCD62P	
	D1–D3	D4–D7	D1–D3	D4–D7	D1–D3	D4–D7
Apheresis platelet concentrates (plasma/RT)	28	54	35	63	37	63
Apheresis platelet concentrates (plasma/PAS-C/RT)	89	90	142	164	181	177
Apheresis platelet concentrates (plasma/PAS-E/RT)	58	34	118	151	115	144
Buffy coat-derived platelet concentrates (plasma/RT)	58	46	47	48	47	49
Buffy coat-derived platelet concentrates (plasma/PAS-C/RT)	68	95	65	88	67	99
Buffy coat-derived platelet concentrates (plasma/PAS-E/RT)	64	53	124	157	157	140
	D1–D5	D7–10	D1–D5	D7–10	D1–D5	D7–10
Cold-temperature Buffy coat-derived platelet concentrates (plasma)	14	11	14	11	14	11
Cold-temperature Buffy coat-derived platelet concentrates (plasma/PAS-E)	48	59	54	46	55	47
PRP derived from filtered WB	30	20	30	20	29	20



As evidenced in this study, there is a difference in terms of release (sCD40L and sCD62P vs. HMGB1) depending on the stress associated with preparation of the PC and storage lesions

Various stress can cause different platelet responses.

BEST Collaborative

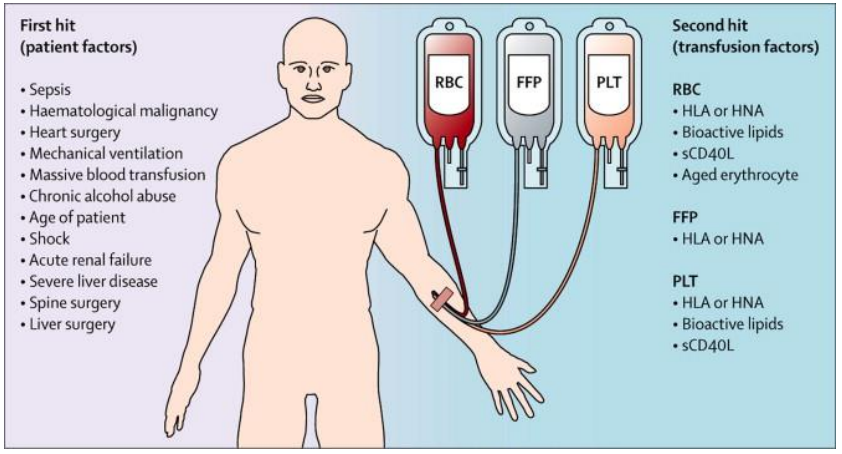
Blood transfusion and inflammation: Platelet components associated with acute transfusion reactions

- **Blood transfusions are associated with adverse reactions during or after the transfusion (190 acute transfusion reactions for 100 000 Transfused blood products).**

The blood transfusion reactions are classified as follows:

- ✓ **Mild (Category 1)** – Urticarial reaction.
- ✓ **Moderate (Category 2)** – Severe hypersensitivity reaction, Febrile non-hemolytic reactions, Bacterial contamination, Pyrogens.
- ✓ **Severe (Category 3)** – Acute intravascular haemolysis, Septic, shock, Fluid Overload, Anaphylactic shock, TRALI (Transfusion-related acute lung injury).

- **TRALI is the leading cause of transfusion-related mortality, with an estimated mortality rate of 5% to 8% of transfusion-related deaths.**



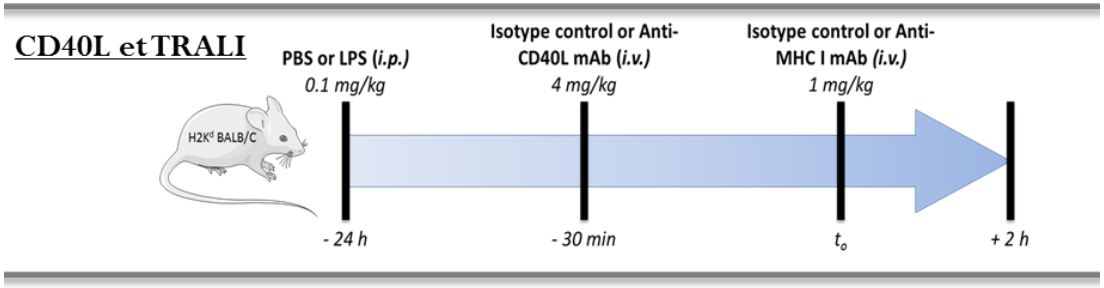
Alexander PJ Vlaar,et al The Lancet, 2013

Evidence of CD40L/CD40 pathway involvement in experimental transfusion-related acute lung injury

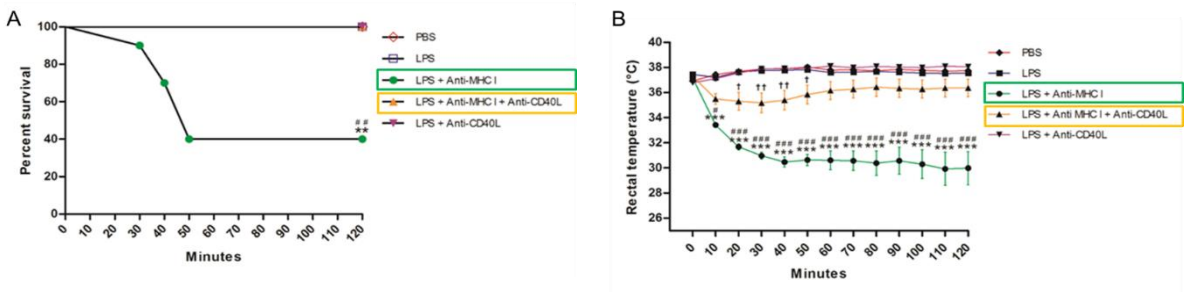
Sofiane Tariket[1,2], Hind Hamzeh-Cognasse[1], Sandrine Laradi[1,2], Charles-Antoine Arthaud[2], Marie-Ange Eyraud[2], Thomas Bourlet[1], Philippe Berthelot[1], Olivier Garraud[1,3] & Fabrice Cognasse[1,2]

SCIENTIFIC REPORTS
nature research

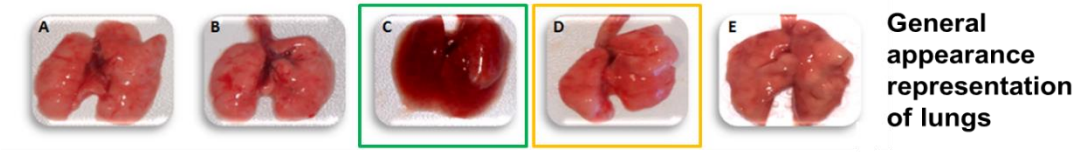
Scientific Reports | (2019) 9:12536



We developed a mouse model of immune TRALI, to investigate the participation of platelets, and particularly the specific function of the CD40/CD40L (sCD40L) complex, to its pathophysiology.



PBS mice | LPS mice | mice experiencing TRALI | anti-CD40L mAb treated-mice | LPS + anti-CD40L mAb mice



General appearance representation of lungs

Inhibition of the CD40/CD40L immunomodulator interaction significantly reduced communication between immune and/or endothelial cells and the development of pulmonary edema.

Hence, our results indicate that targeting of the CD40/CD40L interaction could be an important method to prevent TRALI.

Platelet-derived immune-modulatory mediators and transfusion: time to consider their effects?

Fabrice Cognasse[1,2], Hind Hamzeh-Cognasse[2]

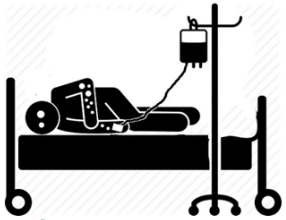
BLOOD TRANSFUSION

Blood Transfus. 2022 May;20(3):177-179.

Production, storage delivering of platelet concentrates (PC)

BRM accumulation throughout storage of PC (Ceramides, sCD40L, DNA mitochondria, lipid mediators microparticles, DAMPS, …)

Increased risk of SAR upon transfusion



Inflammatory characterization of PC (OMICs)

+

Strategies to counterbalance the inflammatory potential of PC (washing procedures, inhibitors, …)

+

In silico modeling to predict the occurrrence of SAR according to PC content and the recipient's pathology (data mining)

Minimize SAR occurrence
Personalized transfusion medicine

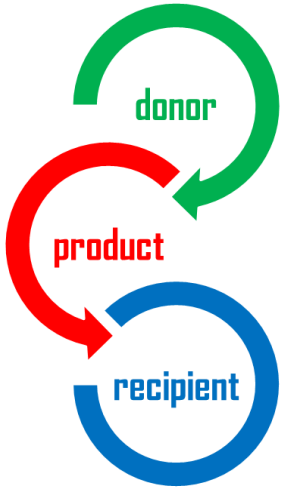
Transfusing the right platelet concentrate to the right patient in terms of inflammation

CONCLUSION : *Key messages*

- ✓ The various data found in the literature consolidate the hypothesis that activation of the platelets in **PCs may directly play a role in an inflammatory response** within the recipient post-transfusion.

- ✓ **In order to minimize the risk of transfusion reactions**, consideration should be given to reducing the concentration of sCD40L and other BRMs accumulate in storage

- ✓ A transfusion of labile blood products involves elements related to the **donor**, the **product** and the **recipient**.



- ✓ By taking into account the characteristics of the three “factors” in transfusion (**donors**, **products** and **patients**) and analyzing databases – with inflammatory factors - using machine-learning type biomathematics tools,

  - ➢ **We will be able to optimize the delivery of the best product to treat each patient in a precise and personalized manner**

Platelet Inflammation Response to Stress : INSERM 1059 SAINBIOSE - DVH

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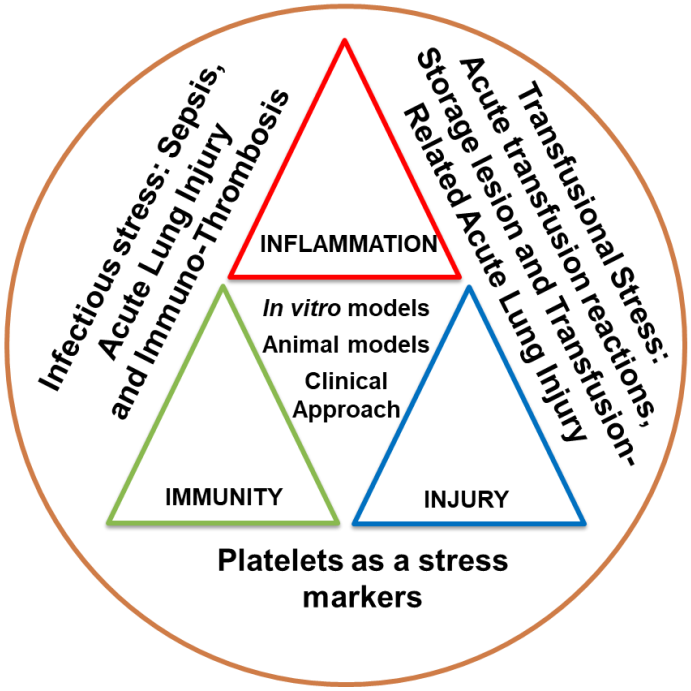

"Because of your generosity, lives will be saved. Thank you for your blood donation."

Dominique Legrand (Director EFS Auvergne-Rhone-Alpes) 

Laurence Vico (Director U1059) 

Stéphane Avril (Director U1059 - DVH) 

Inserm

Les amis de Rémi combattre la leucémie

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