PROADI–SUS

# Seminário Internacional Sobre o Uso e a Regulação do Plasma Rico em Plaquetas

HOSPITAL SÍRIO-LIBANÊS

PROADI-SUS

Agência Nacional de Vigilância Sanitária

SUS MINISTÉRIO DA SAÚDE

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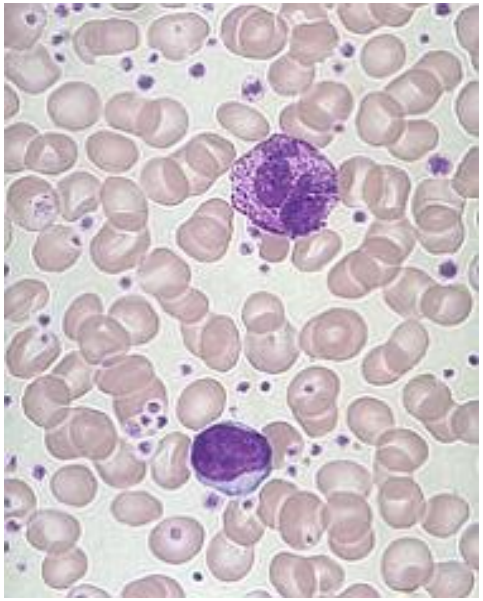
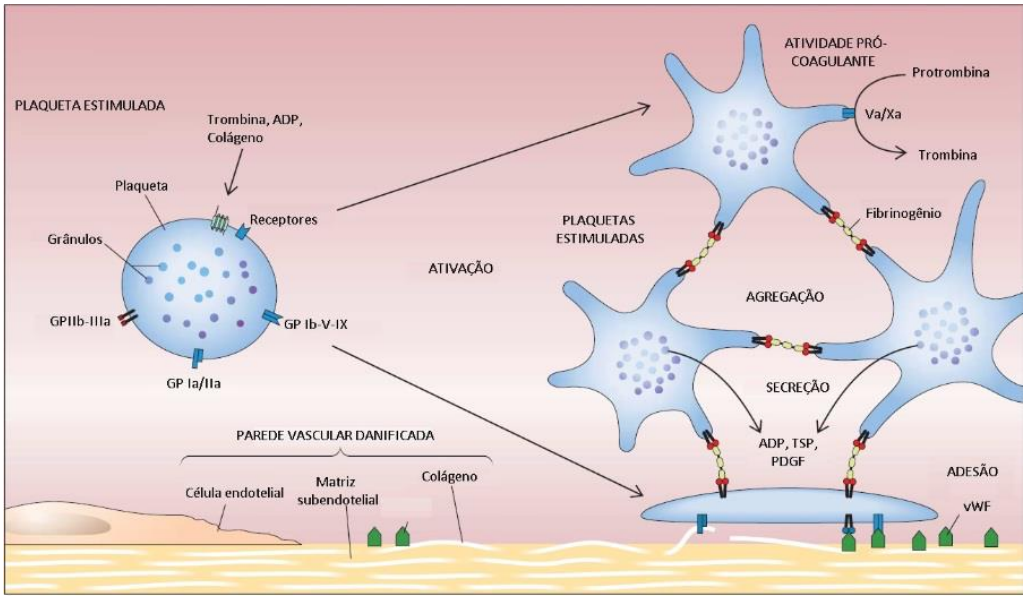
# CONTEXTUALIZAÇÃO

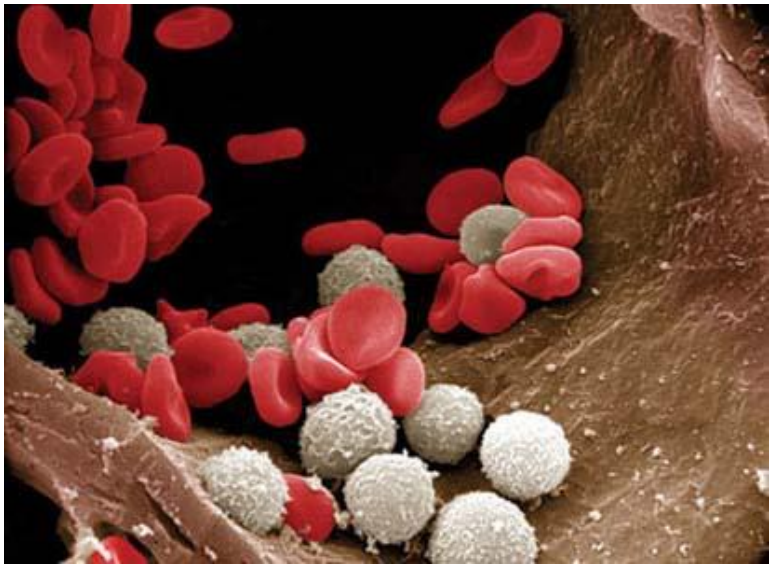
## Derivados de plaquetas humanas em medicina regenerativa e bioengenharia

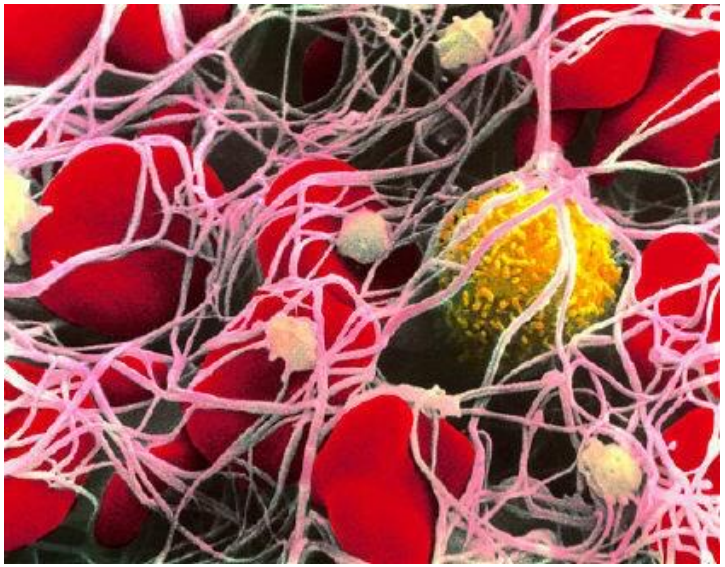
## DEFINIÇÕES
## FUNÇÕES

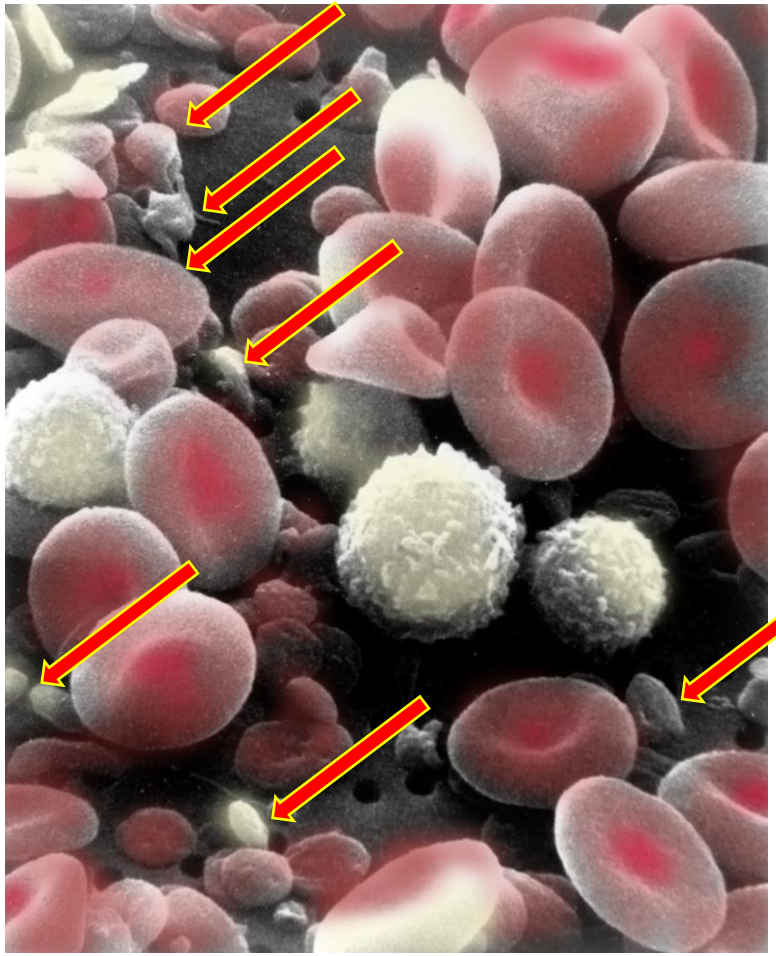
# Trombócitos

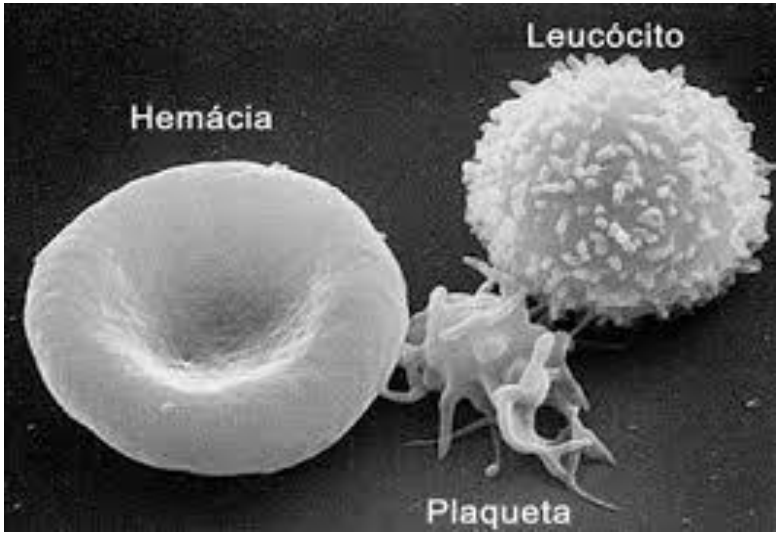


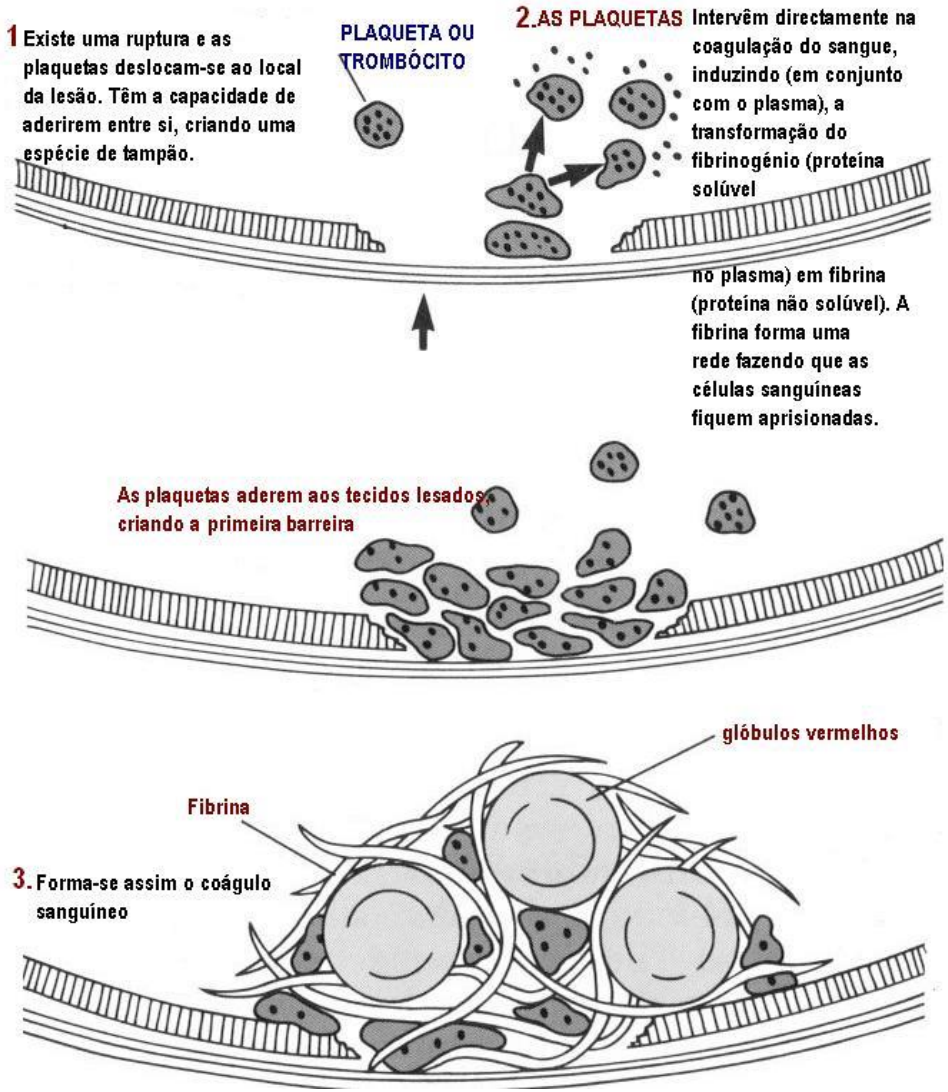


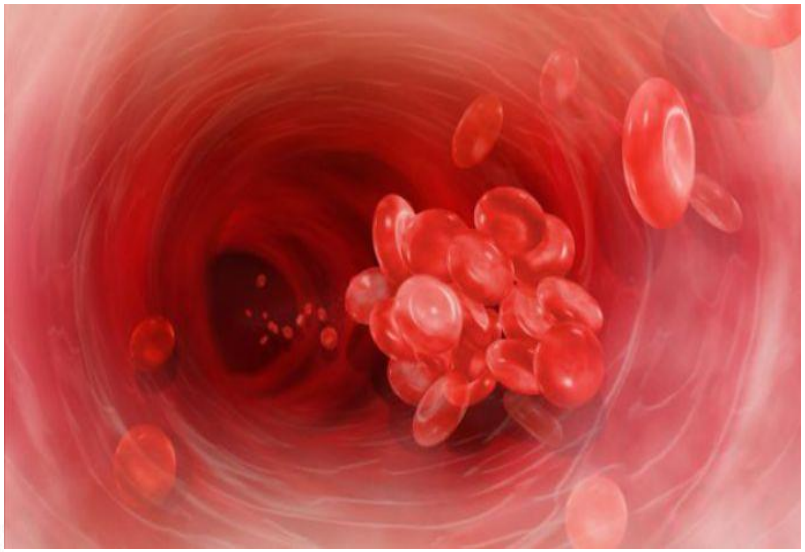



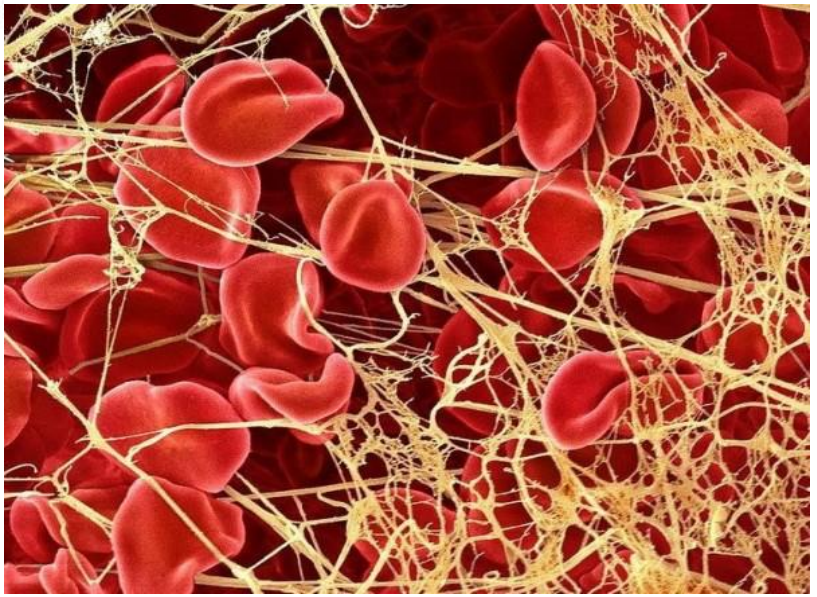





Leucócito
Hemácia
Plaqueta


1 Existe uma ruptura e as plaquetas deslocam-se ao local da lesão. Têm a capacidade de aderirem entre si, criando uma espécie de tampão.
PLAQUETA OU TROMBÓCITO
2.AS PLAQUETAS Intervêm directamente na coagulação do sangue, induzindo (em conjunto com o plasma), a transformação do fibrinogénio (proteína solúvel no plasma) em fibrina (proteína não solúvel). A fibrina forma uma rede fazendo que as células sanguíneas fiquem aprisionadas.
As plaquetas aderem aos tecidos lesados, criando a primeira barreira
glóbulos vermelhos
Fibrina
3. Forma-se assim o coágulo sanguíneo





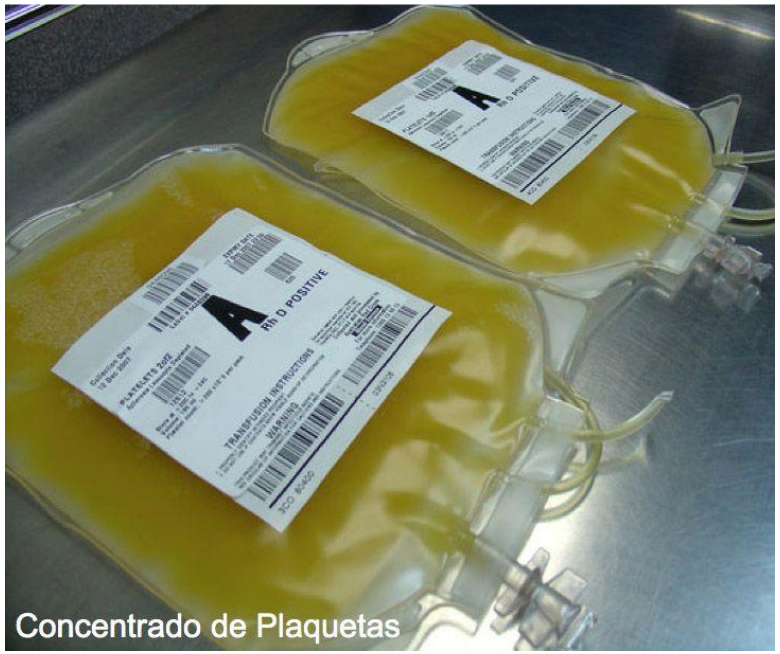
Localizam-se e circulam sempre nos vasos sanguíneos, em contato com o endotélio, e a sua função é essencialmente ligada ao controle da processo de coagulação.
A lesão endotelial permite o contato das plaquetas com a matriz extracelular, em particular com o colágeno, que causa a sua ativação imediata, adesão nas superfícies vasculares desnudadas, agregação de outras plaquetas, formação do ”plug plaquetário”, com a liberação de mediadores inflamatórios, ativação da cascata de coagulação e depósito de fibrina.

No contexto do controle de hemostasia e coagulação a
INTERVENÇÃO TERAPÉUTICA envolve o
CONCENTRADO DE PLAQUETAS

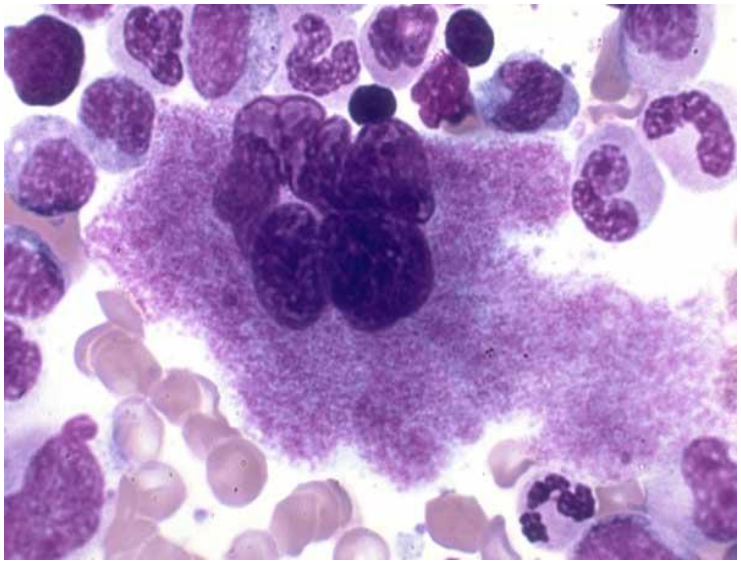
O **CONCENTRADO DE PLAQUETAS** é o hemocomponente obtido do fracionamento do sangue total ou por aférese.

- O seu uso terapêutico se aplica aos pacientes com plaquetopenia ou com anormalidades da função plaquetária, como pacientes cirúrgicos com sangramento ativo, transfusões maciças, circulação extra-corpórea, trombocitopenias, coagulação intravascular disseminada.
- O uso profilático se aplica aos pacientes com aplasias medulares, submetidos a quimio- ou radioterapia, pacientes entrando em procedimentos cirúrgicos críticos.

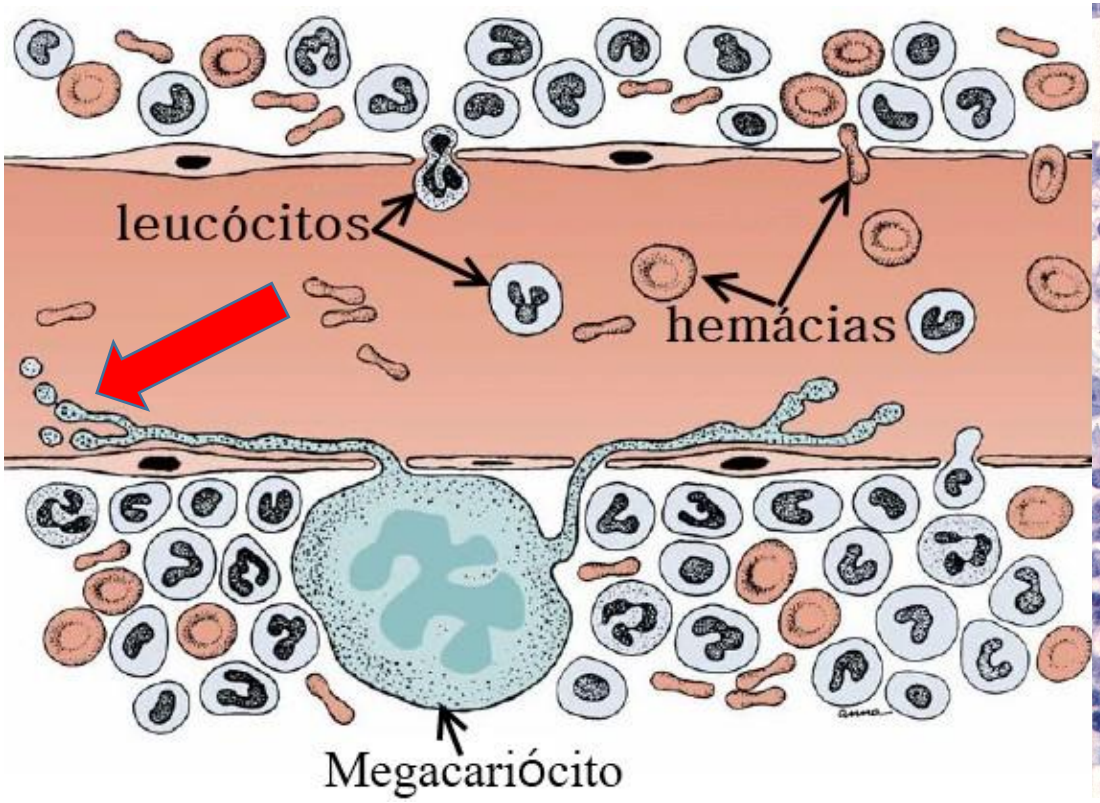
O uso do concentrado de plaquetas por infusão vascular, e a sua função como suplemento da quantidade e/ou qualidade das plaquetas já existentes, caracterizam a terapia como ortóloga e convencional, sob responsabilidade dos centros de hemoterapia, submetida aos controles de qualidade desses produtos.

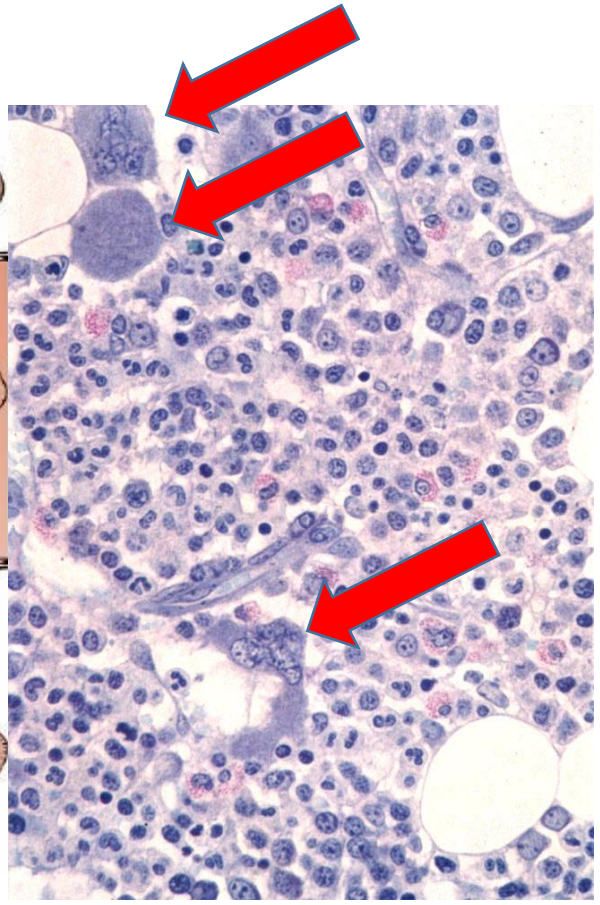


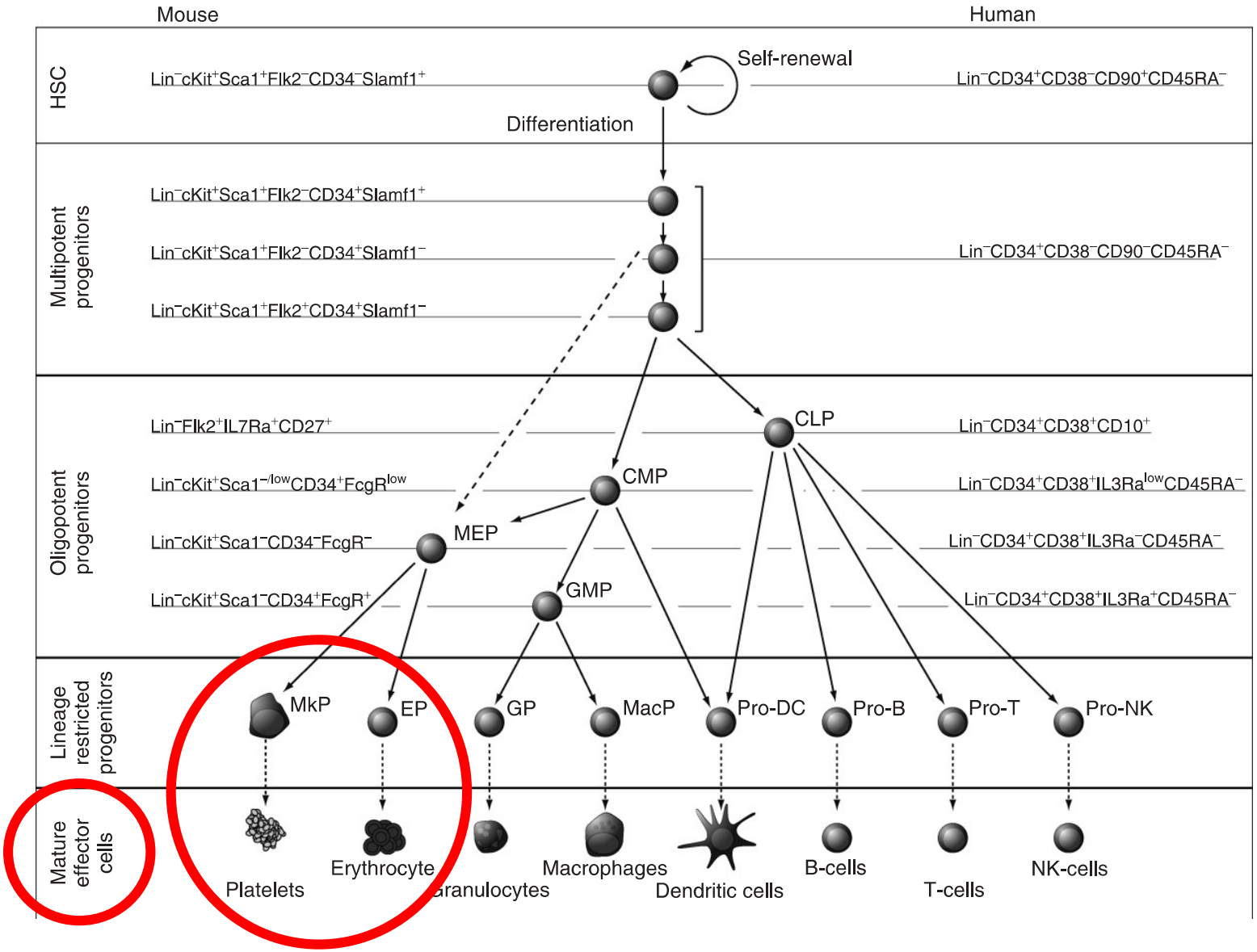
Concentrado de Plaquetas

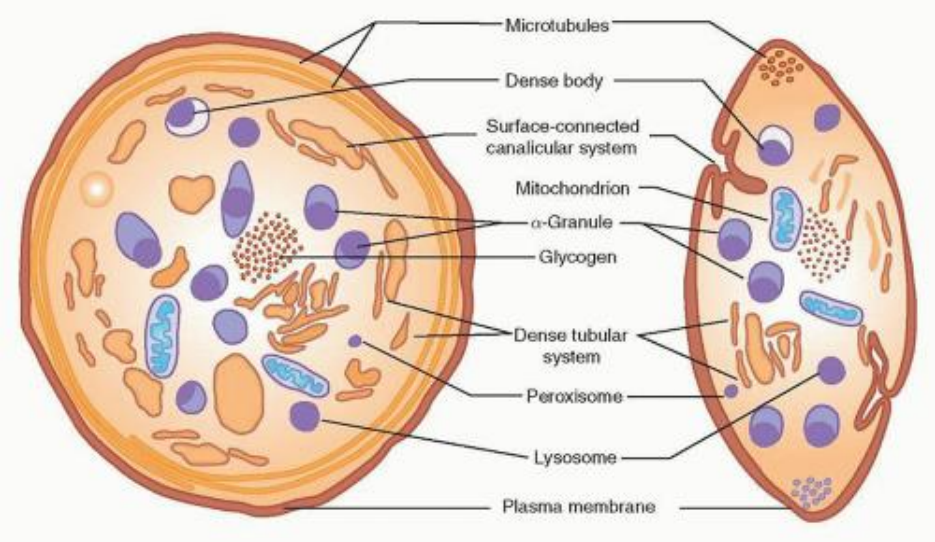


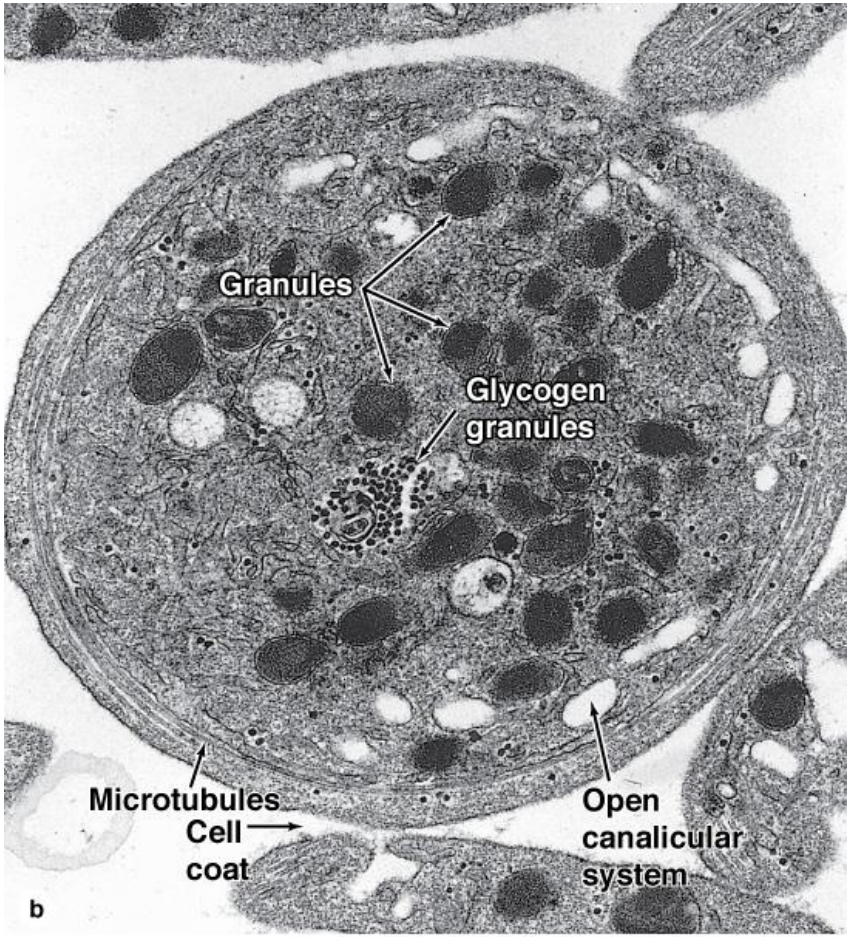
**Plaquetas são formadas na medula óssea, pela fragmentação do citoplasma de megacariócitos maduros, sendo liberadas diretamente na circulação sanguínea.**



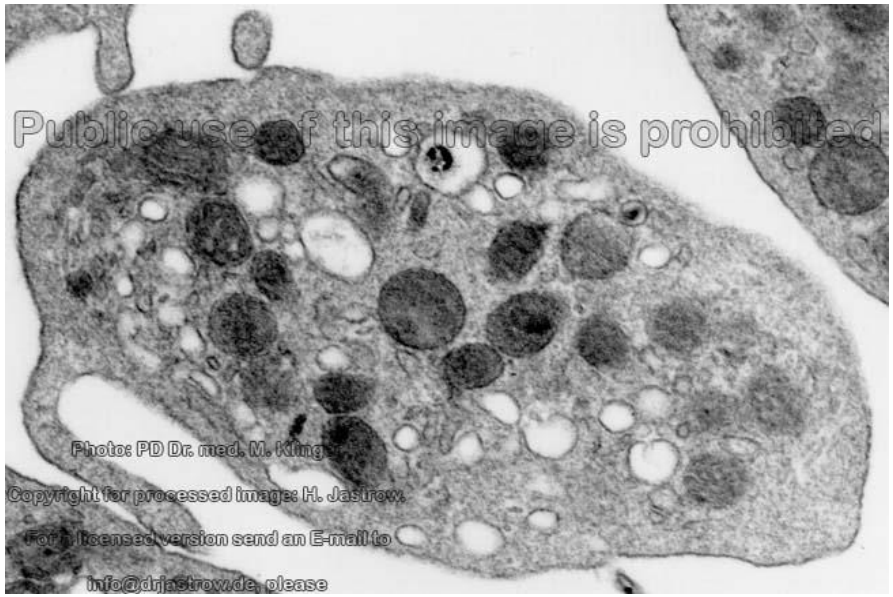

Mouse
Human
HSC
Self-renewal
Lin⁻cKit⁺Sca1⁺Flk2⁻CD34⁻Slamf1⁺
Lin⁻CD34⁺CD38⁻CD90⁺CD45RA⁻
Differentiation
Multipotent progenitors
Lin⁻cKit⁺Sca1⁺Flk2⁻CD34⁺Slamf1⁺
Lin⁻cKit⁺Sca1⁺Flk2⁻CD34⁺Slamf1⁻
Lin⁻cKit⁺Sca1⁺Flk2⁺CD34⁺Slamf1⁻
Lin⁻CD34⁺CD38⁻CD90⁻CD45RA⁻
Oligopotent progenitors
Lin⁻Flk2⁺IL7Ra⁺CD27⁺
CLP
Lin⁻CD34⁺CD38⁺CD10⁺
Lin⁻cKit⁺Sca1⁻/lowCD34⁺FcgRlow
CMP
Lin⁻CD34⁺CD38⁺IL3RalowCD45RA⁻
Lin⁻cKit⁺Sca1⁻CD34⁻FcgR⁻
MEP
Lin⁻CD34⁺CD38⁺IL3Ra⁻CD45RA⁻
Lin⁻cKit⁺Sca1⁻CD34⁺FcgR⁺
GMP
Lin⁻CD34⁺CD38⁺IL3Ra⁺CD45RA⁻
Lineage restricted progenitors
MkP
EP
GP
MacP
Pro-DC
Pro-B
Pro-T
Pro-NK
Mature effector cells
Platelets
Erythrocyte
Granulocytes
Macrophages
Dendritic cells
B-cells
T-cells
NK-cells

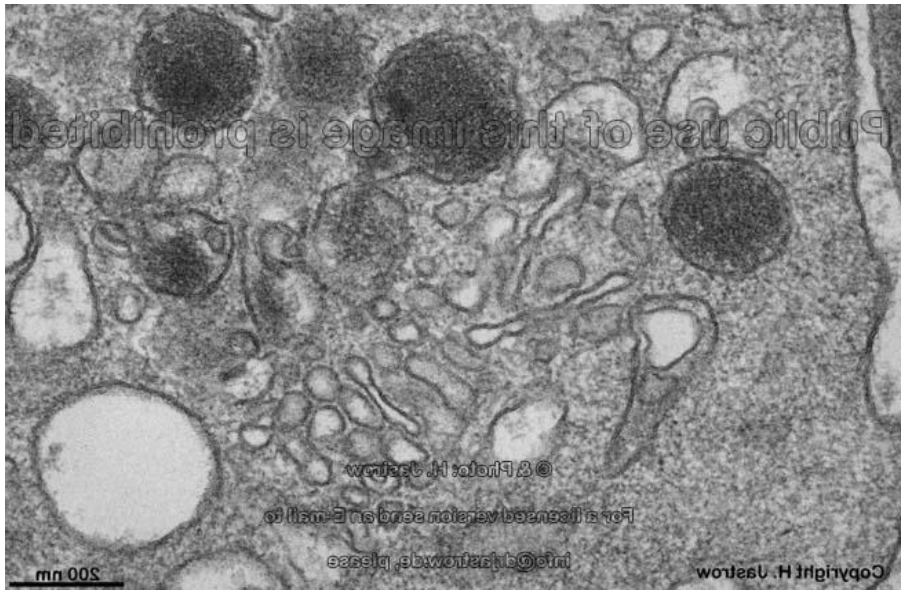


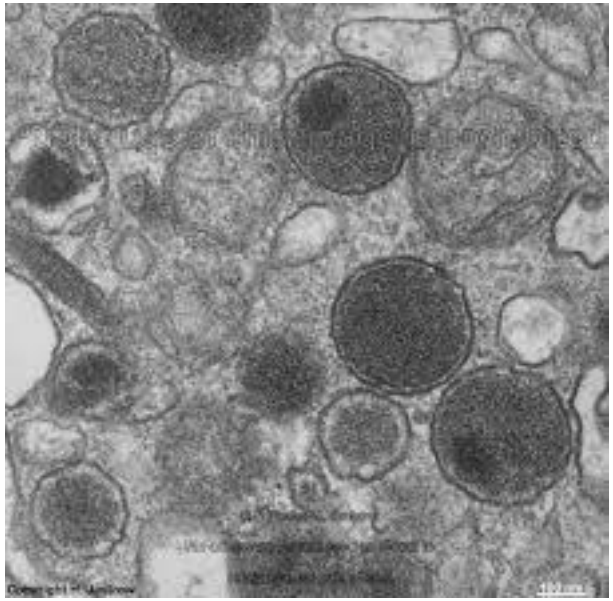



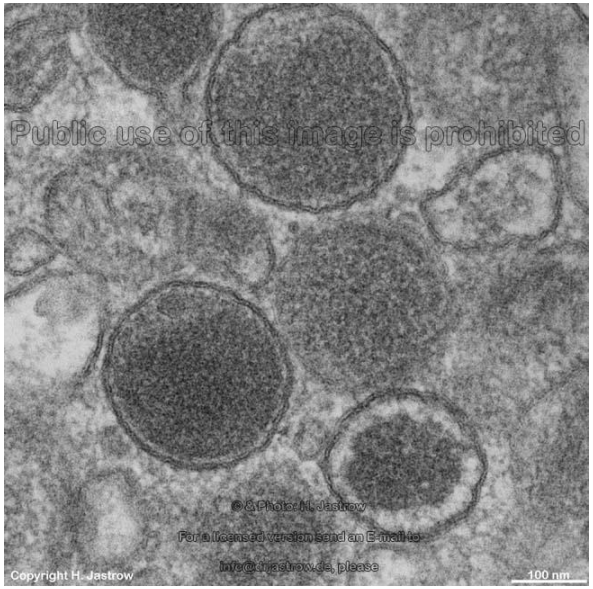

Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

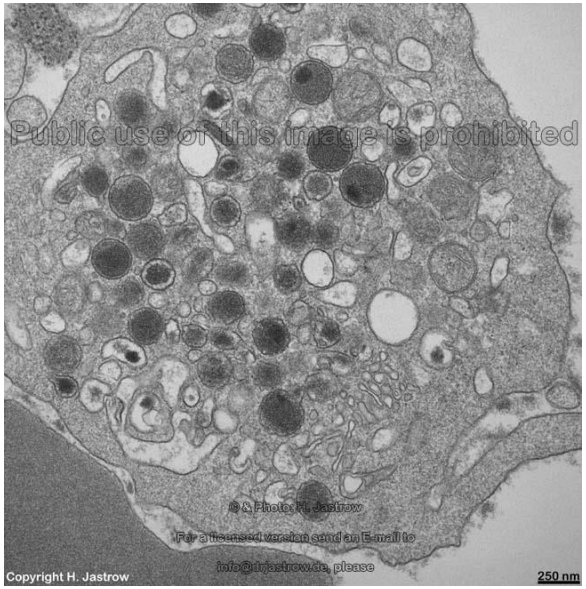
# Seminário Internacional Sobre o Uso e a Regulação do Plasma Rico em Plaquetas





# PRODUTOS:
# PLASMA RICO EM PLAQUETAS - PRP

Vol. 85 No. 6 June 1998

ORAL SURGERY,
ORAL MEDICINE,
ORAL PATHOLOGY,

ORAL AND MAXILLOFACIAL SURGERY Editor: Larry J. Peterson

## Platelet-rich plasma

### Growth factor enhancement for bone grafts

Robert E. Marx, DDS,[a] Eric R. Carlson, DMD,[b] Ralph M. Eichstaedt, DDS,[c] Steven R. Schimmele, DDS,[d] James E. Strauss, DMD,[e] and Karen R. Georgeff, RN,[f] Miami, Fla.
UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

- Marx (2001): "at least 1.10 million platelets/mL in 5 mL of plasma"
- Marx (2004): "Studies suggesting that there is no benefit from PRP can often be traced to poor-quality PRP produced by inadequate devices"

# Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors

Vigil. sanit. debate 2018;6(1):125-136 |

**Tabela 1.** Fatores presentes no PRP.

| Fator de crescimento | Efeitos |
|---|---|
| Fator de crescimento tumoral (TGF-ß 1 e 2) | Regula o efeito mitogênico de outros fatores de crescimento; estimula a proliferação de células mesenquimais indiferenciadas; fibroblastos e osteoblasto. Estabilizador vascular e regulador da síntese de colágeno e secreção de colagenase. Estimula angiogênese e quimiotaxia endotelial, inibe a proliferação de macrófagos e linfócitos. |
| Fator de crescimento de fibroblastos (FGF) | Efeito mitogênico para células mesenquimais, condrócitos e osteoblastos. Estimula o crescimento e diferenciação de cartilagem e osso. |
| Fator de crescimento derivado de plaquetas (PDGF) | Estimula a quimiotaxia e a mitose de fibroblastos, células musculares lisas e células da glia. Regula a secreção de colagenase e síntese de colágeno, mitogênico para células mesenquimais e osteoblastos. Estimula a quimiotaxia de macrófagos e neutrófilos. |
| Fator de crescimento epidérmico (EGF) | Estimula a mitose das células mesenquimais. Regula a secreção de colagenase. Estimula a quimiotaxia e a angiogênese das células endoteliais. |
| Fator de crescimento vaso-endotelial (VEGF) | Estimula a mitose das células endoteliais. Aumenta a angiogênese e a permeabilidade do vaso. |
| Fator de crescimento tipo insulina (IGF) | Estimula a diferenciação e mitogênese de células mesenquimais e de células de revestimento. Estimula a proliferação de osteoblastos e a produção de colágeno tipo I, osteocalcina e fosfatase alcalina. |

# Sistemas abertos

Amable et al. Stem Cell Research & Therapy 2013, 4:67

## Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors

Conclusions: Our study resulted in a consistent PRP preparation method that yielded a cytokine and growth factor pool from different donors with high reproducibility. These findings support the use of PRP in therapies aiming for tissue regeneration, and its content characterization will allow us to understand and improve the clinical outcomes

- Produto de qualidade reprodutível, passível de padronização, economicamente vantajoso, podendo atender um número considerável de pacientes. PRP pode ser preparado antecipadamente e transportado para ser entregue no local de uso.

- A quantidade de mediadores intercelulares no PRP se mantém inalterado por até 6 h na temperatura ambiente. Preservado em 2-4$^{o}$C mantém a sua atividade biológica acima de 95% por 24 h, 90% por 48 h e 90% por 96 h. Não pode ser congelado.

Quantificação citocinas e fatores de crescimento obtidos no sistema aberto, seguindo Amable et al 2013.

**Table 5 Statistical comparison (q-values) of cytokine concentration between plasma and activated PRP2**

| Cytokine | PRP2-Ca | PRP2-Thr | Result |
|---|---|---|---|
| PDGF-AA | **6.674** | **5.931** | **Platelet-secreted factor** |
| PDGF-AB | **9.352** | **9.556** | **Platelet-secreted factor** |
| PDGF-BB | **8.072** | **7.886** | **Platelet-secreted factor** |
| IGF-1 | 0.038 | 0.302 | Plasmatic factor |
| TGF-β1 | **5.912** | **4.143** | **Platelet-secreted factor** |
| TGF-β2 | **5.574** | **3.850** | **Platelet-secreted factor** |
| TGF-β3 | | | Not detected |
| EGF | **9.243** | **8.386** | **Platelet-secreted factor** |
| IL-5 | 2.568 | 2.539 | Plasmatic factor |
| IL-6 | 0.303 | 0.388 | Plasmatic factor |
| Eotaxin | 5.829 | 6.169 | [a] |
| bFGF | 0.101 | 1.173 | Plasmatic factor |
| G-CSF | 0.081 | 0.097 | Plasmatic factor |
| GM-CSF | 0.711 | 0.716 | Plasmatic factor |
| HGF | 2.657 | 2.469 | Plasmatic factor |
| IFNα | **4.188** | **2.514** | **Platelet-secreted factor** |
| IL-1β | 0.480 | 0.590 | Plasmatic factor |
| IL-2 | 0.869 | 0.882 | Plasmatic factor |
| IL-2R | 0.604 | 0.256 | Plasmatic factor |
| IL-4 | **4.894** | **4.003** | **Platelet-secreted factor** |
| IL-7 | 1.881 | 1.739 | Plasmatic factor |
| IL-1RA | 1.216 | 0.856 | Plasmatic factor |
| IL-8 | **10.590** | **9.597** | **Platelet-secreted factor** |
| IL-10 | 1.433 | 1.357 | Plasmatic factor |
| IL-12 | 2.079 | 1.070 | Plasmatic factor |
| IL-13 | **3.884** | **3.901** | **Platelet-secreted factor** |
| IL-15 | 0.001 | 0.337 | Plasmatic factor |
| IL-17 | **3.911** | **3.902** | **Platelet-secreted factor** |
| VEGF | | | not detected |
| IFNγ | | | not detected |
| IP-10 | 3.131 | 3.288 | Plasmatic factor |
| MCP-1 | 4.247 | 4.392 | [a] |
| MIG | 1.462 | 1.136 | Plasmatic factor |
| MIP-1α | 0.750 | 1.046 | Plasmatic factor |
| MIP-1β | 3.341 | 2.442 | Plasmatic factor |
| RANTES | 0.463 | 0.839 | Plasmatic factor |
| TNFα | **6.752** | **4.584** | **Platelet-secreted factor** |

Determination of platelet-secreted cytokines using the Tukey *post-hoc* test. *q*-value = 3.68 ($k = 3$, $n = 6$, $\alpha = 0.05$). *bFGF* basic fibroblast growth factor, *EGF* endothelial growth factor, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *HGF* hepatocyte growth factor, *IGF-1* insulin-like growth factor-1, *IP-10* IFNγ-induced protein 10, *MCP-1* monocyte chemoattractant protein-1, *MIG* IFNγ-induced monokine, *MIP* macrophage inflammatory protein, *PDGF* platelet-derived growth factor, *PRP2* platelet-rich plasma after the second centrifugation step, *PRP2-Ca* calcium-activated PRP2, *PRP2-Thr*, calcium plus human thrombin-activated PRP2, *TGF* transforming growth factor, *VEGF* vascular endothelial growth factor. [a]Eotaxin and MCP-1 showed statistically significant differences due to concentration reduction but they cannot be classified as platelet-secreted factors because their concentration was reduced, probably due to degradation by other products secreted following degranulation, or because they were associated with secreted molecules.

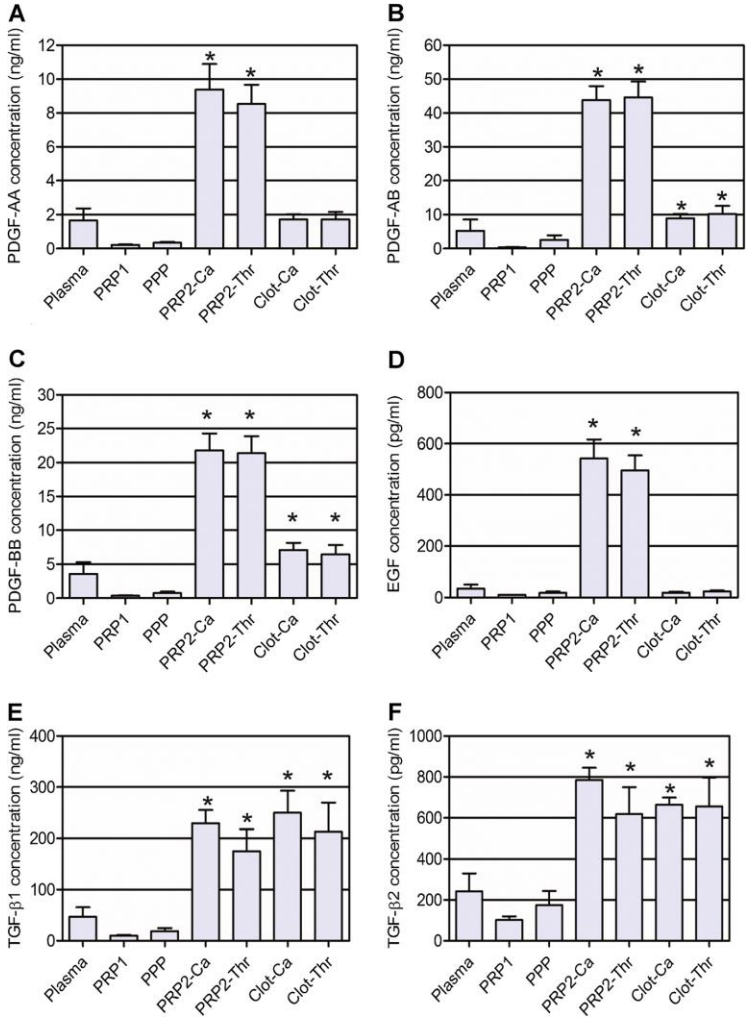



**Figure 4 Growth factor concentrations secreted after platelet activation. (A)** Platelet-derived growth factor (PDGF)-AA, **(B)** PDGF-AB, **(C)** PDGF-BB, **(D)** endothelial growth factor (EGF), **(E)** transforming growth factor (TGF)-β1, and **(F)** TGF-β2. *Statistically significant differences from the plasmatic concentration (analysis of variance followed by Dunnett's multiple comparison test, $n = 6$, $\alpha = 0.05$). PPP, platelet-poor plasma; PRP1, platelet-rich plasma after the first blood centrifugation step; PRP2, platelet-rich plasma after the second centrifugation step; PRP2-Ca, calcium-activated PRP2; PRP2-Thr, calcium plus human thrombin-activated PRP2.

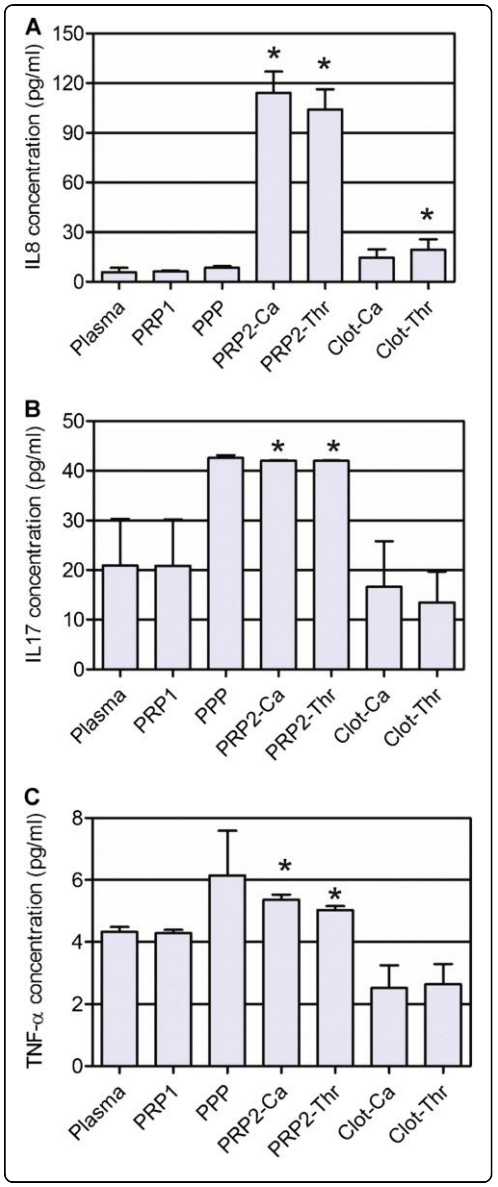
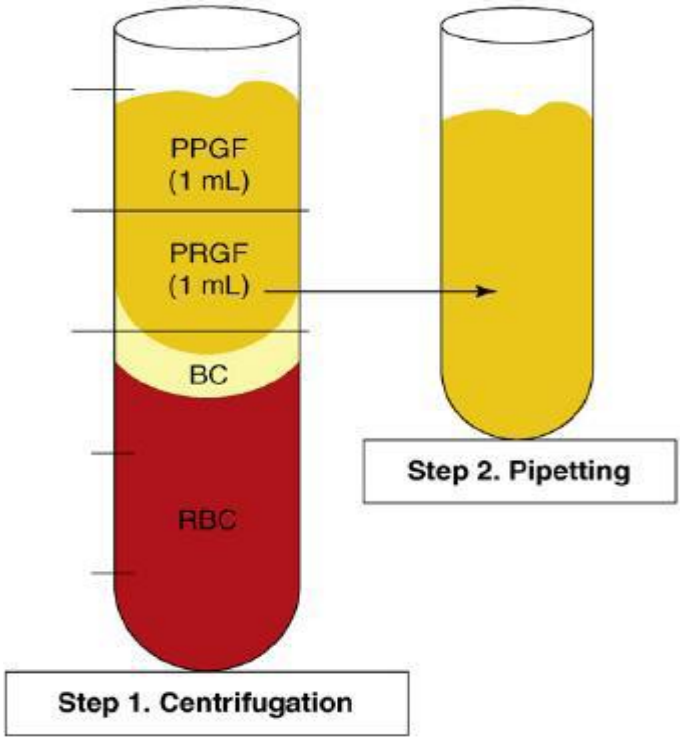
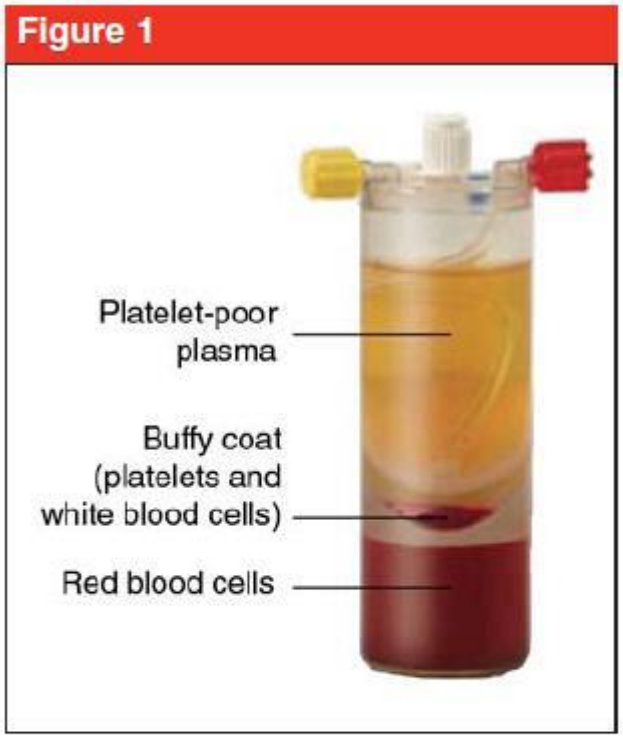



**Figure 6 Proinflammatory cytokine concentration.** Concentrations of **(A)** IL-8, **(B)** IL-17, and **(C)** TNFα. *Statistically significant differences from the plasmatic concentration (analysis of variance followed by Dunnett's multiple comparison test, $n = 6$, $\alpha = 0.05$). PPP, platelet-poor plasma; PRP1, platelet-rich plasma after the first blood centrifugation step; PRP2, platelet-rich plasma after the second centrifugation step; PRP2-Ca, calcium-activated PRP2; PRP2-Thr, calcium plus human thrombin-activated PRP2.

# Sistemas fechados

**1ª geração**




Example of a platelet-rich plasma preparation device (GPS III, Biomet, Warsaw, IN). The buffy coat is platelet-rich plasma. (Adapted with permission from Biomet.)

Uso extemporâneo
Padronização e confiabilidade baixa
Podem ser usados em ambientes não protegidos (ambulaltórios, clínicas particulares)

**Table 2**

**Common Platelet-rich Therapy Preparation Systems***

| System | Volume of Blood (mL) | Centrifuge Time/Speed | Final PRP Volume (mL) | Final Platelet Concentration (compared with average) | Activator | Level of Growth Factors (compared with average) |
|---|---|---|---|---|---|---|
| Autologous Conditioned Plasma (Arthrex, Naples, FL)† | 9 | 5 min/1,500 rpm | 3-5 | 2-3× | None | PDGF (25×)<br>EGF (5×)<br>VEGF (11×)<br>TGF-β1 (4×)<br>IGF-1 (1×) |
| Cascade (Musculoskeletal Tissue Foundation, Edison, NJ)‡ | 9 or 18 | First: 6 min/1,100*g*; Second: 15 min/1,450*g* | 2 or 4 | N/A | Calcium (forms a suturabl clot for intraope a-tive use | PDGF (N/A)<br>EGF (5-10×)<br>VEGF (5-10×)<br>TGF-β1 (5-10×)<br>IGF-1 (5-10×) |
| GPS III (Biomet, Warsaw, IN)§ | 27 or 54 | 15 min/1,900*g* | 3 or 6 | 4-8× | Calcium chloride/ thrombin | PDGF (N/A)<br>EGF (3.9×)<br>VEGF (6.2×)<br>TGF-β1 (3.6×)<br>IGF-1 (1×) |
| SmartPReP (Harvest Technologies, Plymouth, MA)‖ | 20 or 60 | 14 min/1,000*g* | 3 or 7 | 4.4-7.6× | Thrombin | PDGF (4.4×)<br>EGF (4.4×)<br>VEGF (4.4×)<br>TGF-β1 (4.4×)<br>IGF-1 (N/A) |

* Information obtained from product manufacturers (platelet and growth factor concentration obtained from unpublishe company data for all products listed except for Biomet GPS III [Eppley et al[1]])
† Arthrex: https://www.arthrex.com/innovations/index.cfm?adid=28&CFID=2168033&CFTOKEN=63754575
‡ Musculoskeletal Tissue Foundation: http://platelettherapy.com/
§ Biomet: http://www.biomet.com/biologics/information/pdf/BBI0003.0.pdf
‖ Harvest Technologies: http://www.harvesttech.com/products/smartprepmain.html
EGF = epidermal growth factor, IGF-1 = insulin-like growth factor-1, N/A = not available, PDGF = platelet-derived growth factor, PRP = platelet-rich plasma, TGF-β1 = transforming growth factor-β1, VEGF = vascular endothelial growth factor

Confiabilidade limitada

Menos de 1 milhão / mL

TABLE 2
Mean Platelet, Red Blood Cell, White Blood Cell, and Fibrinogen Concentration in Whole Blood, Platelet-Rich Plasma, and Platelet-Poor Plasma

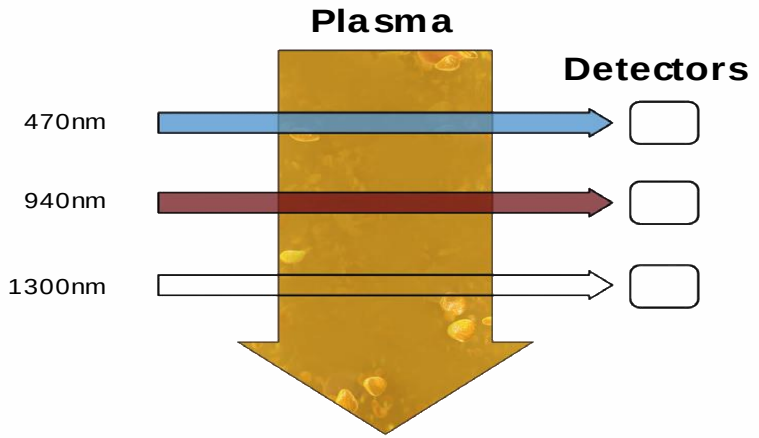
| | Platelet Concentration ($\times 10^3/\mu L$) | Factor Increase in Platelet Concentration | Platelet Capture Efficiency (%) | White Blood Cells ($\times 10^3/\mu L$) | Red Blood Cells ($\times 10^6/\mu L$) | Fibrinogen (mg/dL) |
|---|---|---|---|---|---|---|
| Blood Product | | | | | | |
| Whole blood | 273.8 ± 7.4 | — | — | 6.4 ± 2.3 | 4.35 ± 0.4 | 239.2 ± 69.0 |
| Platelet-rich plasma | 596.7 ± 250.4 | × 2.2 ± 0.9 | 51.9 ± 24.8 | 15.5 ± 16.8 | 0.7 ± 1.1 | 282.4 ± 33.7 |
| Platelet-poor plasma | 45.2 ± 6.5 | — | — | 0.2 ± 0.1 | 0.01 ± 0.02 | 287.1 ± 53.4 |
| *P*[a] | < .0001 | — | — | .09 | < .0001 | .18 |
| Platelet-rich plasma by separation system, company | | | | | | |
| Cascade, MTF | 443.8 ± 24.7 | × 1.62 ± 0.1 | 67.6 ± 4.1 | 1.1 ± 0.2 | 0.1 ± 0.1 | 283.8 ± 34.2 |
| GPS III, Biomet | 566.2 ± 292.6 | × 2.07 ± 1.1 | 22.6 ± 11.8 | 34.4 ± 13.6 | 1.5 ± 1.7 | 286.0 ± 42.7 |
| Magellan, Arteriocyte | 780.2 ± 246.5 | × 2.8 ± 0.8 | 65.5 ±19.6 | 11.0 ± 8.2 | 0.5 ± 0.3 | 277.4 ± 30.5 |
| *P*[b] | .09 | .09 | < .0001 | < .0001 | .10 | .93 |

[a]From analysis of variance comparison of means among whole blood, platelet-rich plasma, and platelet-poor plasma.
[b]From analysis of variance comparison of means among platelet-rich plasma separation systems.

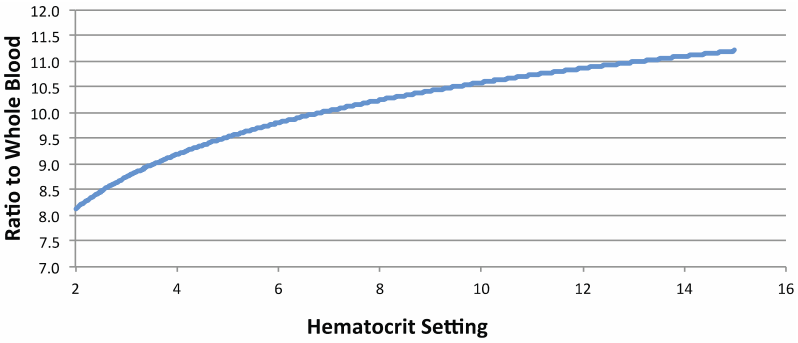
# Sistemas fechados

**2ª geração**

Totalmente automatizados,
Leitura por sensores com comandos extemporâneos integrados
Rendimento reprodutível




Os sistemas de ambas as gerações se enquadram em conceito de "manipulação limitada"



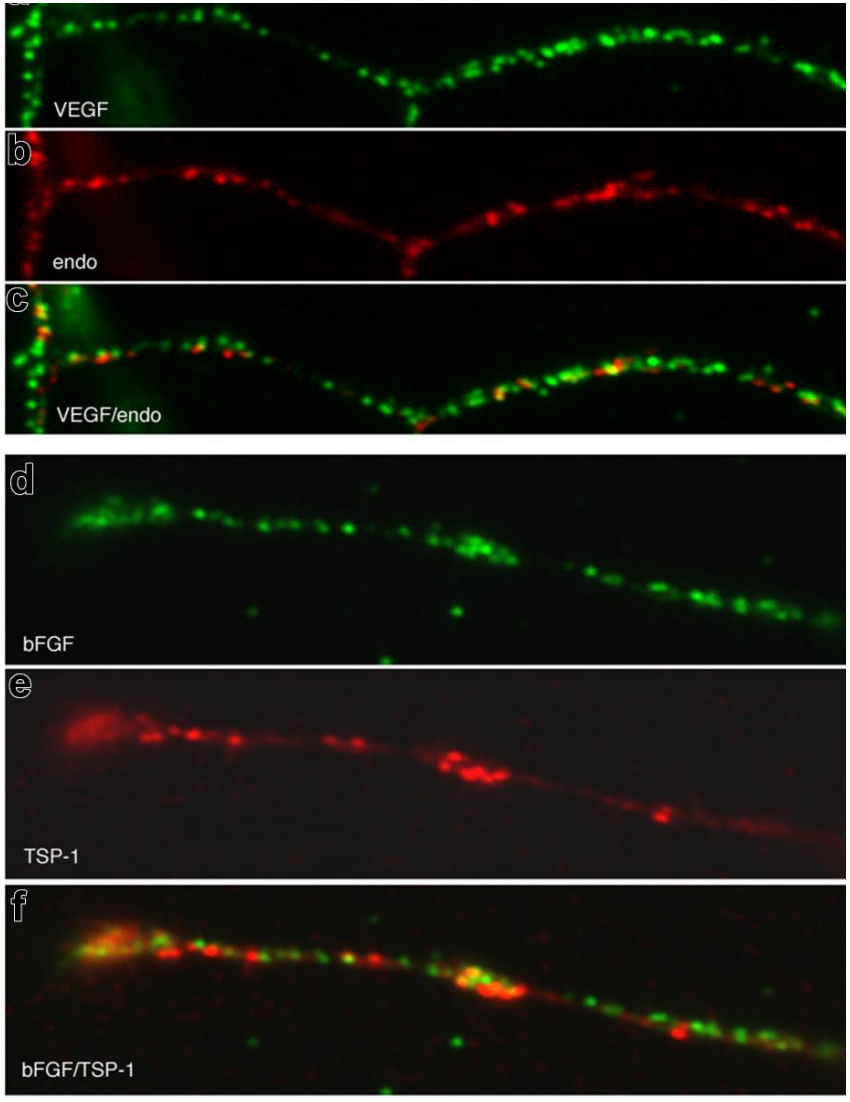

ANVISA RDC 09-2011 = CTC-1

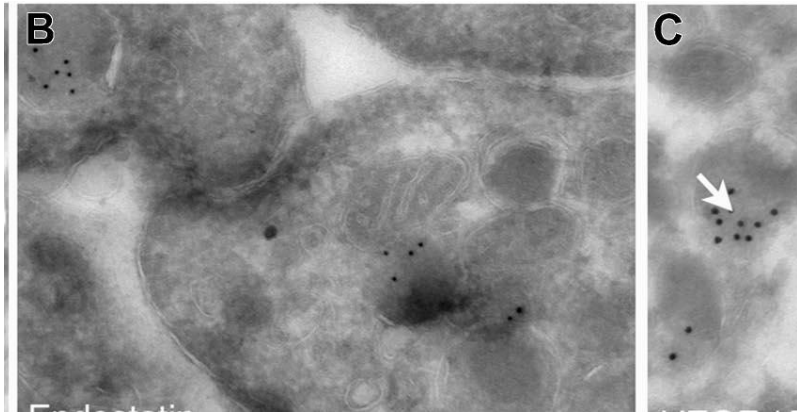
FDA – USA: "Minimally manipulated" '361' HCT/Os - uso livre
ATMP – EUR: Uso autólogo no ato cirúrgico, homólogo – uso livre

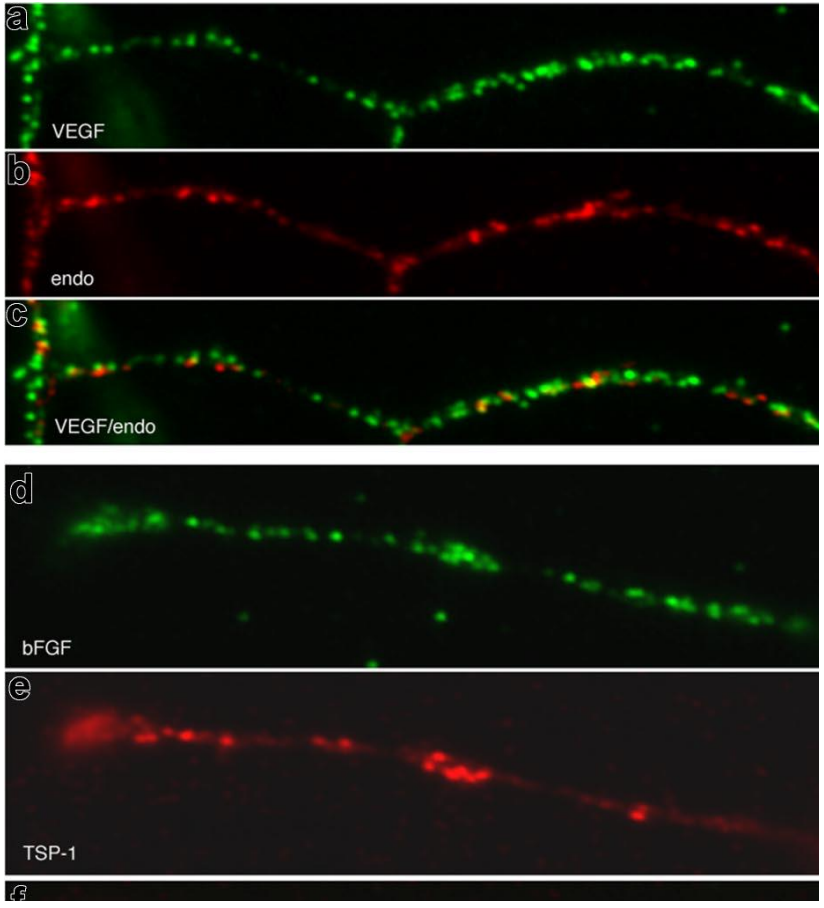
# Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet α granules and differentially released

Joseph E. Italiano Jr,[1,2] Jennifer L. Richardson,[1] Sunita Patel-Hett,[1,2] Elisabeth Battinelli,[1,3] Alexander Zaslavsky,[2] Sarah Short,[2] Sandra Ryeom,[2] Judah Folkman,[2] and Giannoula L. Klement[2,4]

BLOOD, 1 FEBRUARY 2008 • VOLUME 111, NUMBER 3



Cellular and Molecular Life Sciences
https://doi.org/10.1007/s00018-018-2771-6
Published online: 09 February 2018

# Dissecting the biochemical architecture and morphological release pathways of the human platelet extracellular vesiculome

Silvia H. De Paoli[1] · Tseday Z. Tegegn[1] · Oumsalama K. Elhelu[1] · Michael B. Strader[2] · Mehulkumar Patel[1] · Lukas L. Diduch[3] · Ivan D. Tarandovskiy[1] · Yong Wu[4] · Jiwen Zheng[4] · Mikhail V. Ovanesov[5] · Abdu Alayash[2] · Jan Simak[1]

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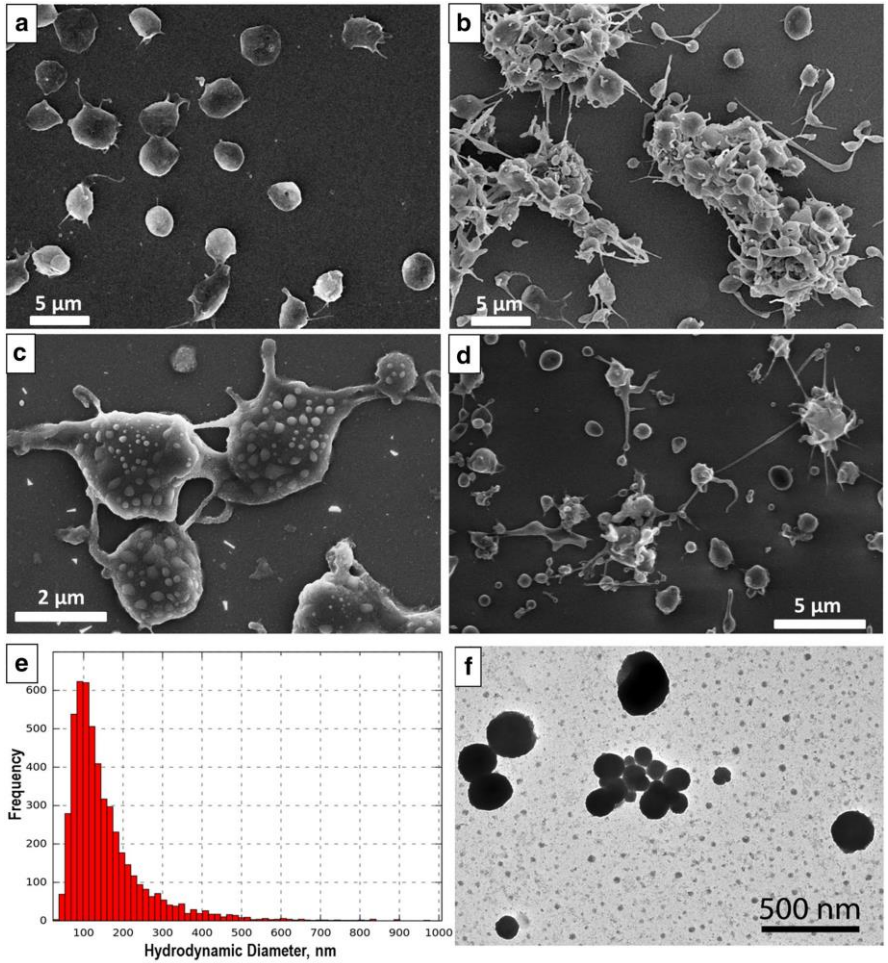
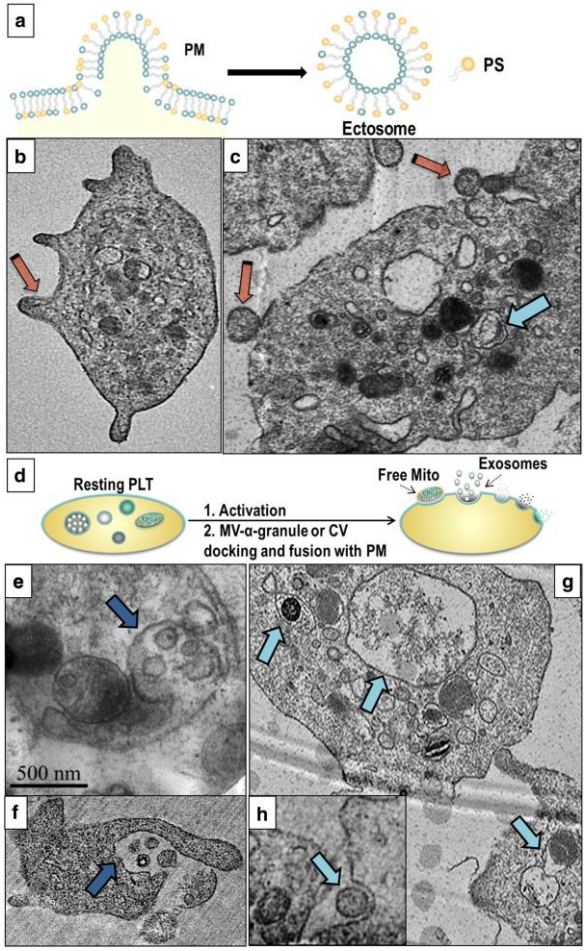
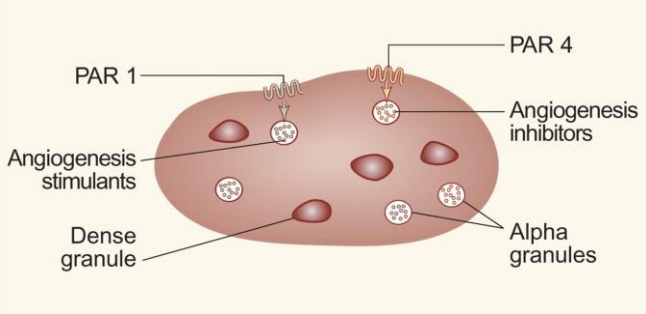
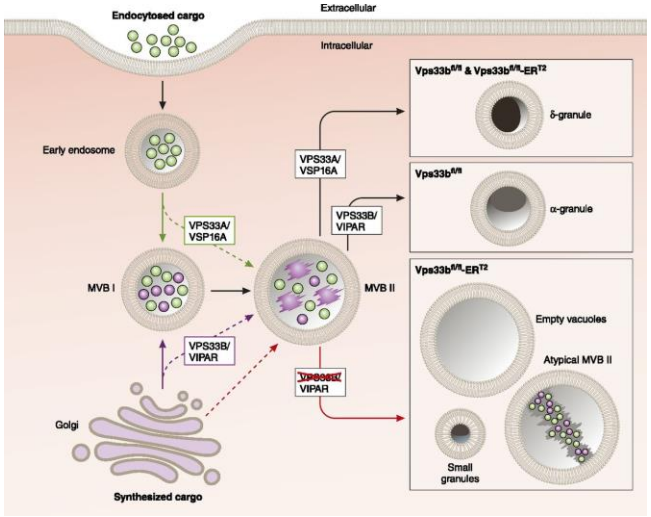
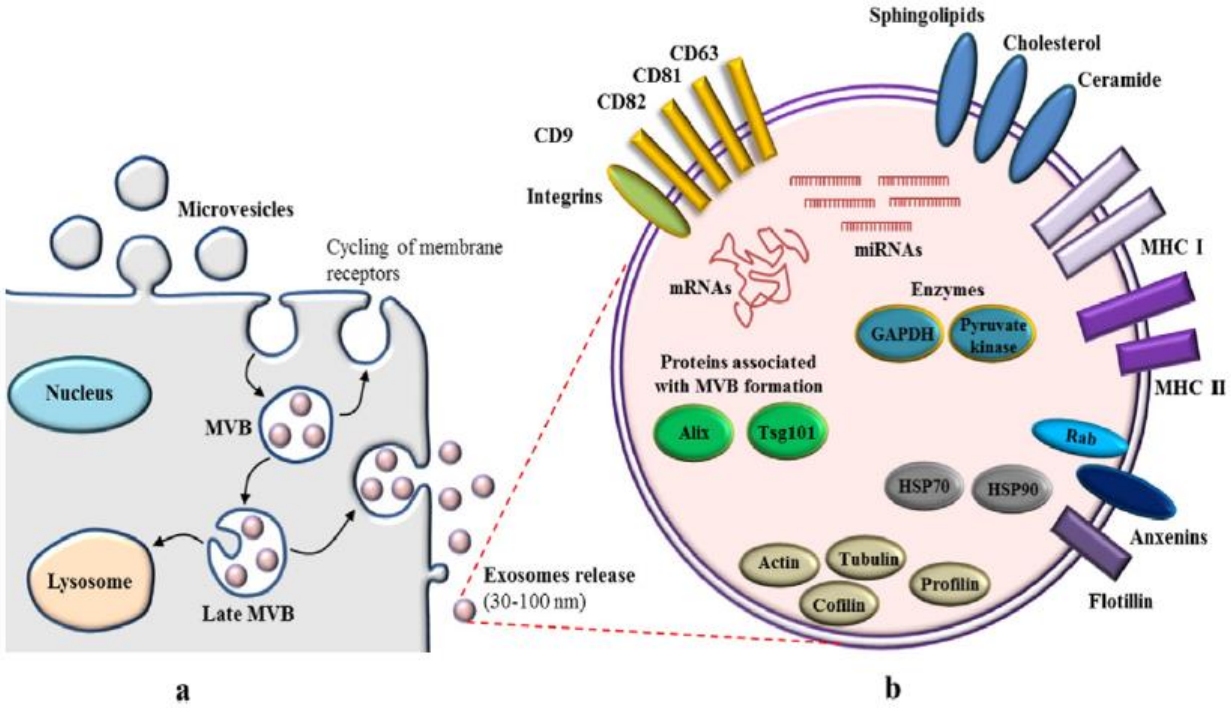
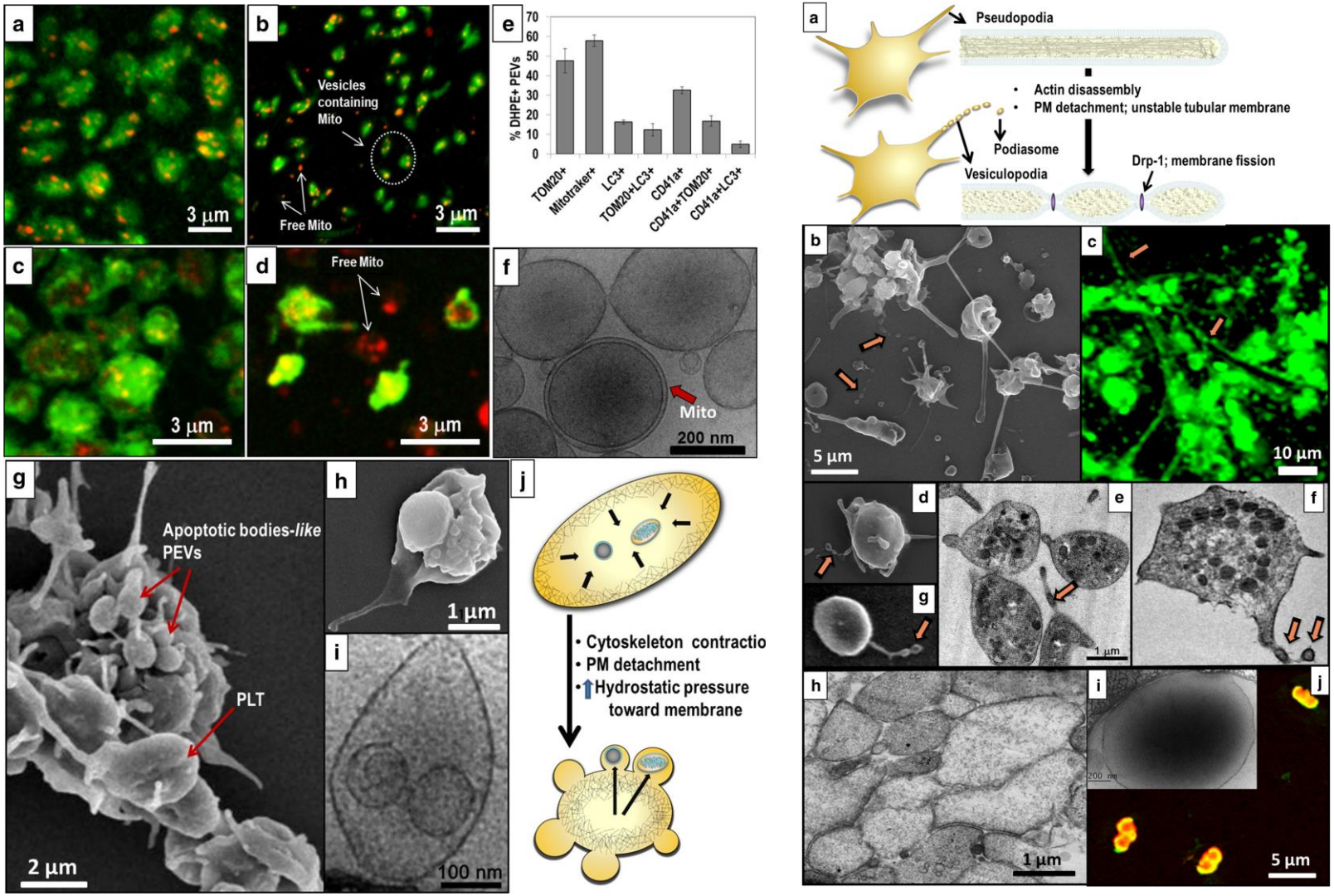


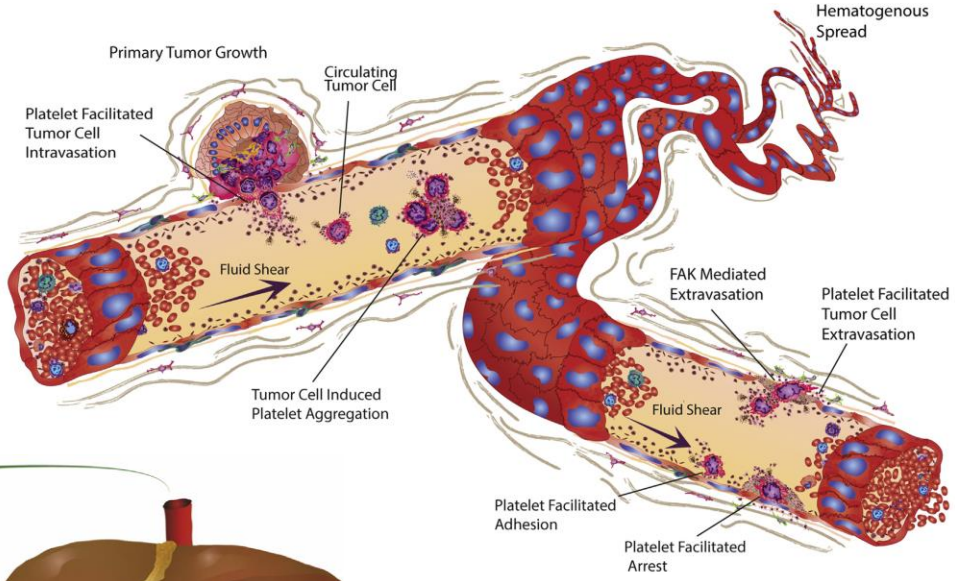

PAR 1
PAR 4
Angiogenesis inhibitors
Angiogenesis stimulants
Dense granule
Alpha granules

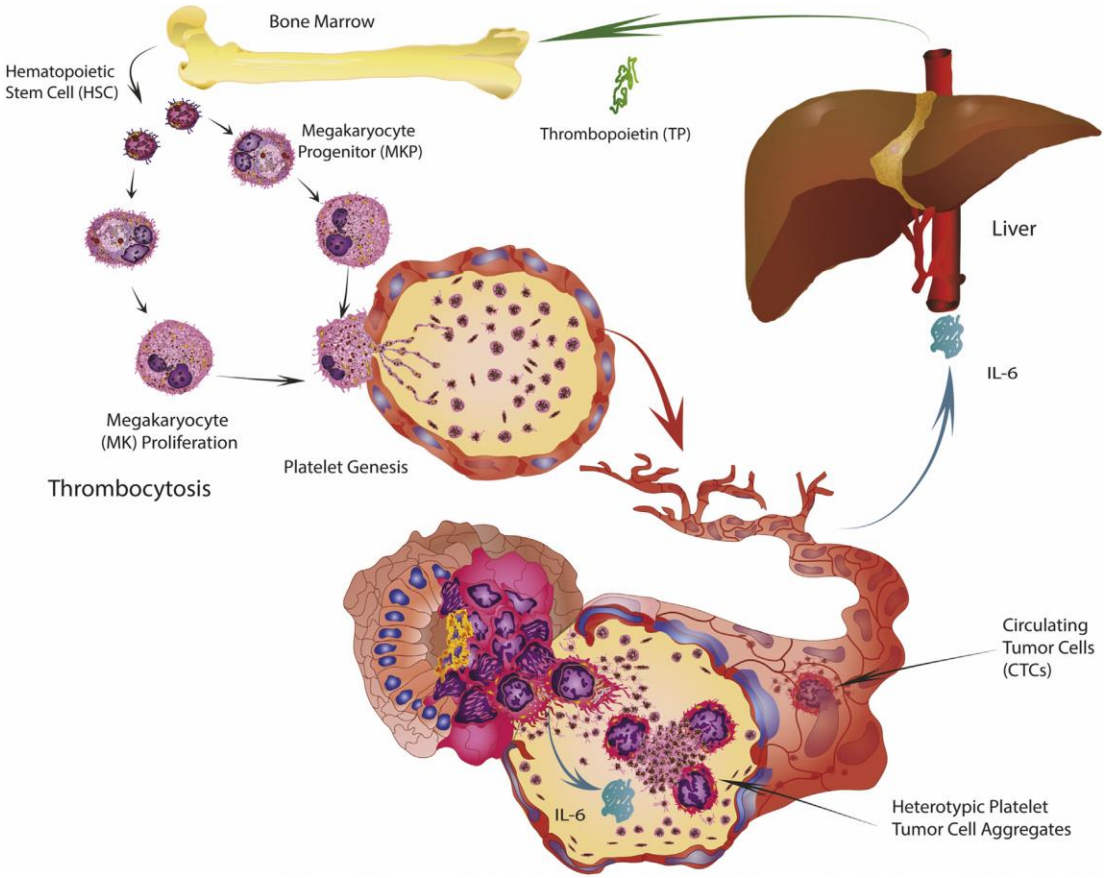

Endocytosed cargo
Extracellular
Intracellular
Early endosome
VPS33A/ VSP16A
VPS33B/ VIPAR
MVB I
MVB II
Golgi
Synthesized cargo
δ-granule
α-granule
Empty vacuoles
Atypical MVB II
Small granules


Microvesicles
Cycling of membrane receptors
Nucleus
MVB
Lysosome
Late MVB
Exosomes release (30-100 nm)
a
Sphingolipids
Cholesterol
Ceramide
CD63
CD81
CD82
CD9
Integrins
miRNAs
mRNAs
MHC I
Enzymes
GAPDH
Pyruvate kinase
Proteins associated with MVB formation
Alix
Tsg101
MHC II
Rab
HSP70
HSP90
Anxenins
Actin
Tubulin
Profilin
Cofilin
Flotillin
b


a
3 µm
b
Vesicles containing Mito
Free Mito
3 µm
c
3 µm
d
Free Mito
3 µm
e
% DHPE+ PEVs
70
60
50
40
30
20
10
0
TOM20+
Mitotraker+
LC3+
TOM20+LC3+
CD41a+
CD41a+TOM20+
CD41a+LC3+
f
Mito
200 nm
g
Apoptotic bodies-*like* PEVs
PLT
2 µm
h
1 µm
i
100 nm
j
• Cytoskeleton contractio
• PM detachment
• ⇧Hydrostatic pressure toward membrane
a
Pseudopodia
• Actin disassembly
• PM detachment; unstable tubular membrane
Podiasome
Vesiculopodia
Drp-1; membrane fission
b
5 µm
c
10 µm
d
g
e
1 µm
f
h
1 µm
i
200 nm
j
5 µm

# SIDETRACKS 1

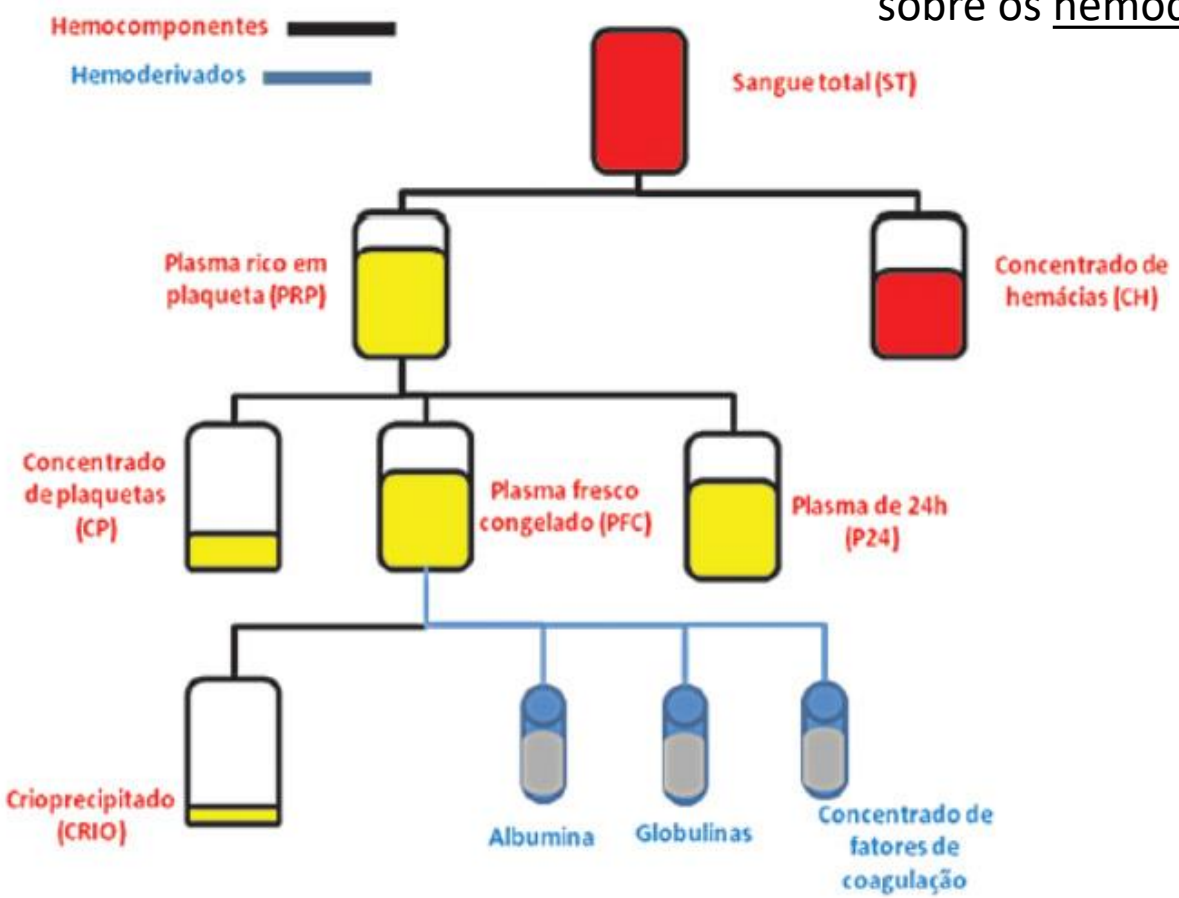



Haemmerle et al.,
**The Platelet Lifeline to Cancer: Challenges and Opportunities**
Cancer Cell *33*, June 11, 2018 © 2018

# SIDETRACKS 2

A questão do uso eventual de material fora do prazo, que não foi destinado a procedimentos hemoterapêuticos, enquadra-se na legislação sobre os hemoderivados, aplicados nesse caso especificamente aos derivados das plaquetas.



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Seminário Internacional Sobre o Uso e a Regulação do Plasma Rico em Plaquetas

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