I TPO MIMETICI

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Meccanismo d'azione dei TPO RA: dalla biologia all'applicazione clinica

Indice

- **La megacariopoiesi**
- **La trombopoietina ed il suo recettore (MPL)**
- **Trombopoietino-mimetici e loro meccanismo d'azione**
  - **Romiplostim**
  - **Eltrombopag**
- **Potenziali effetti indesiderati dei trombopoietino-mimetici**
- **Nuove possibili indicazioni dei trombopoietino-mimetici**

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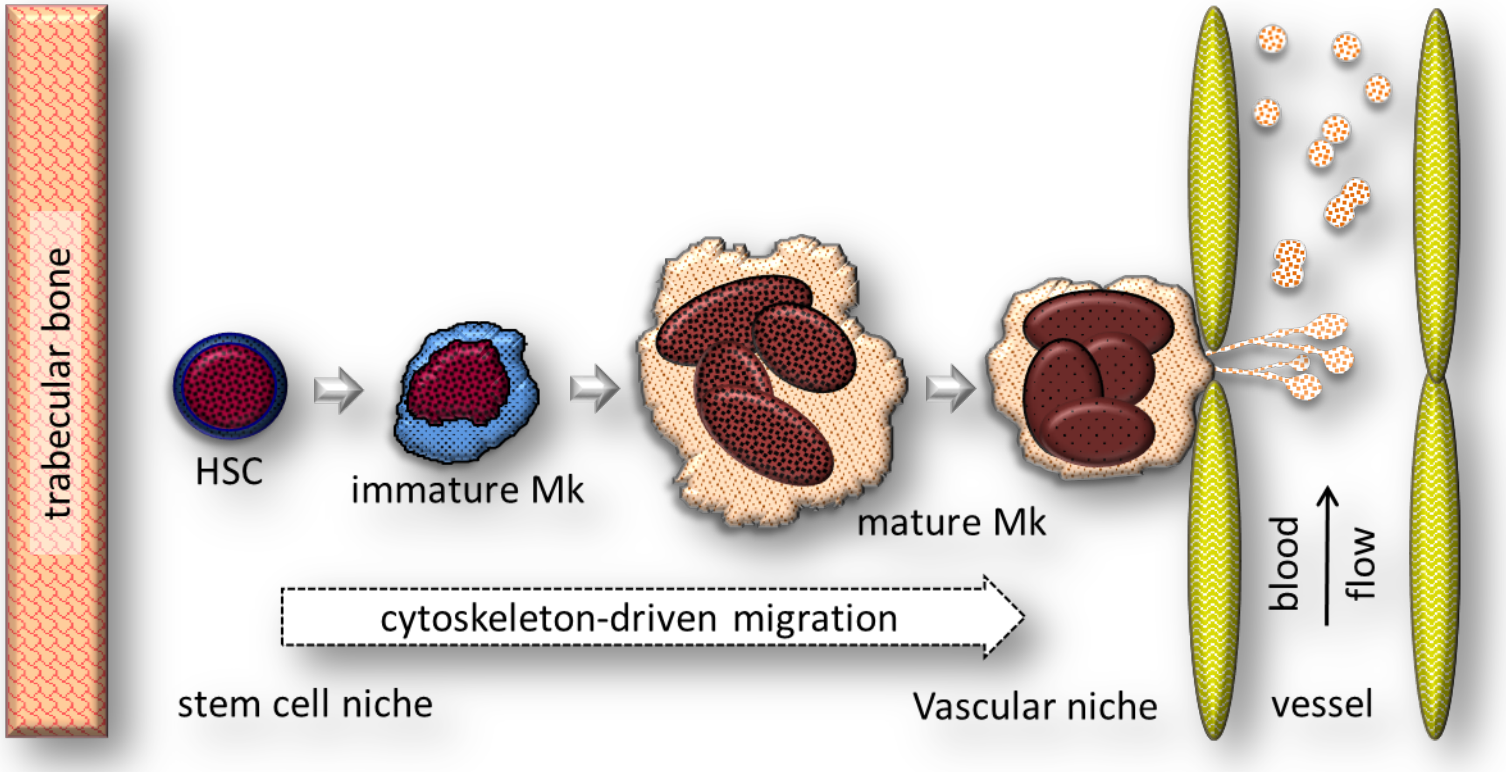
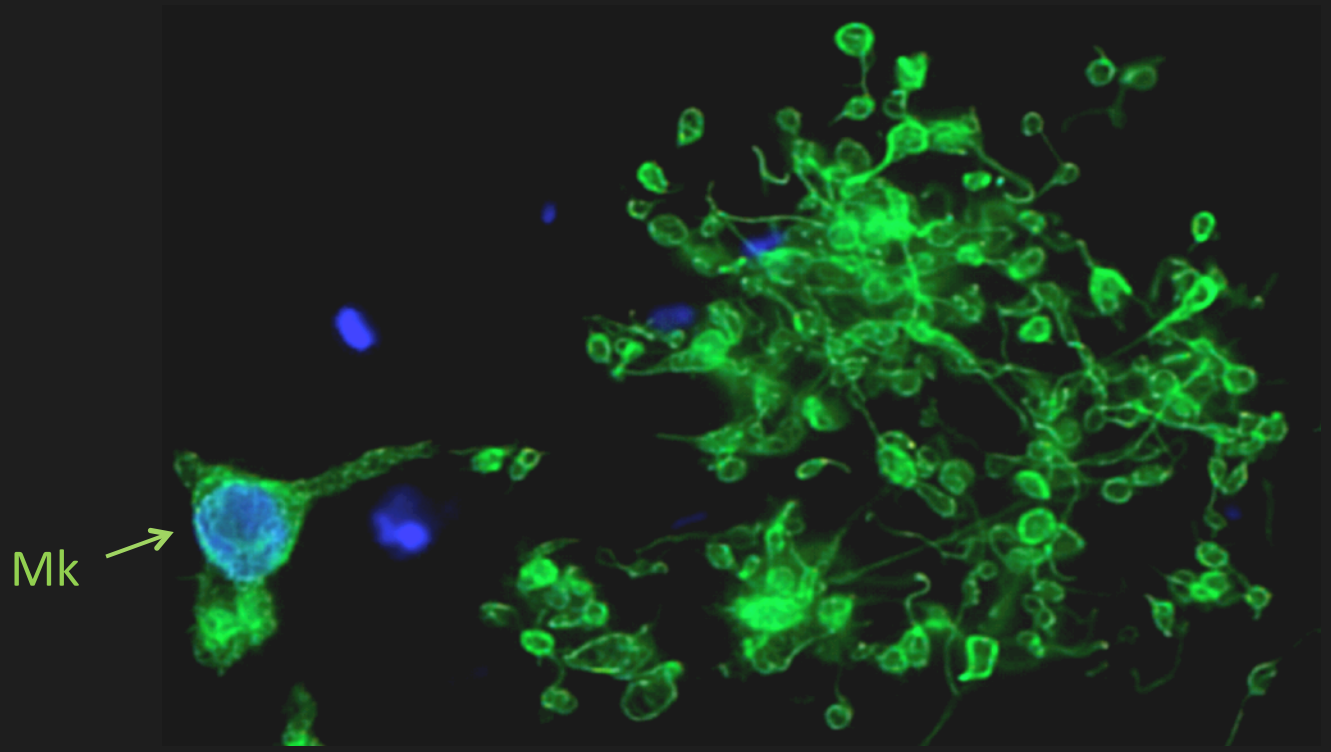
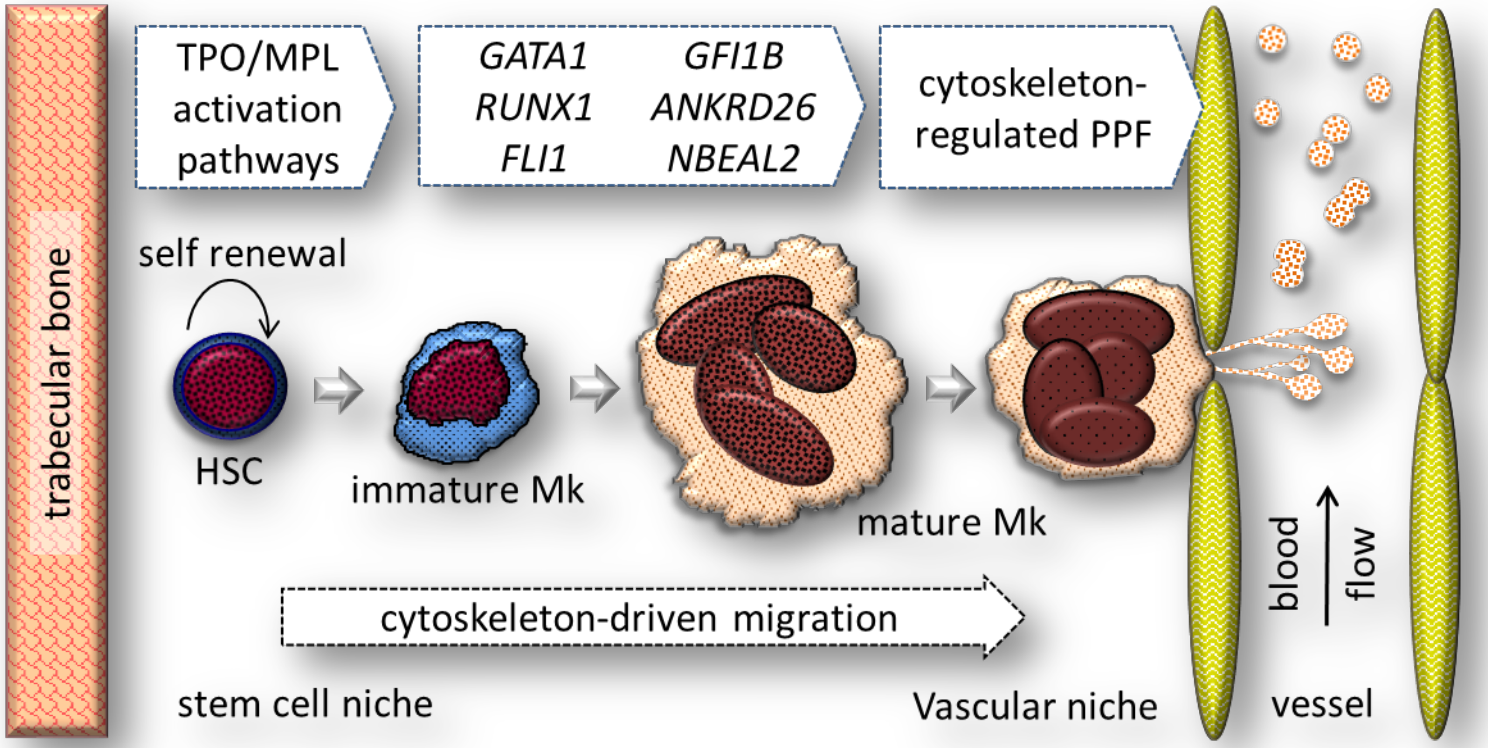
Megakaryopoiesis and platelet production




Mk
Proplatelets

Megakaryopoiesis and platelet production



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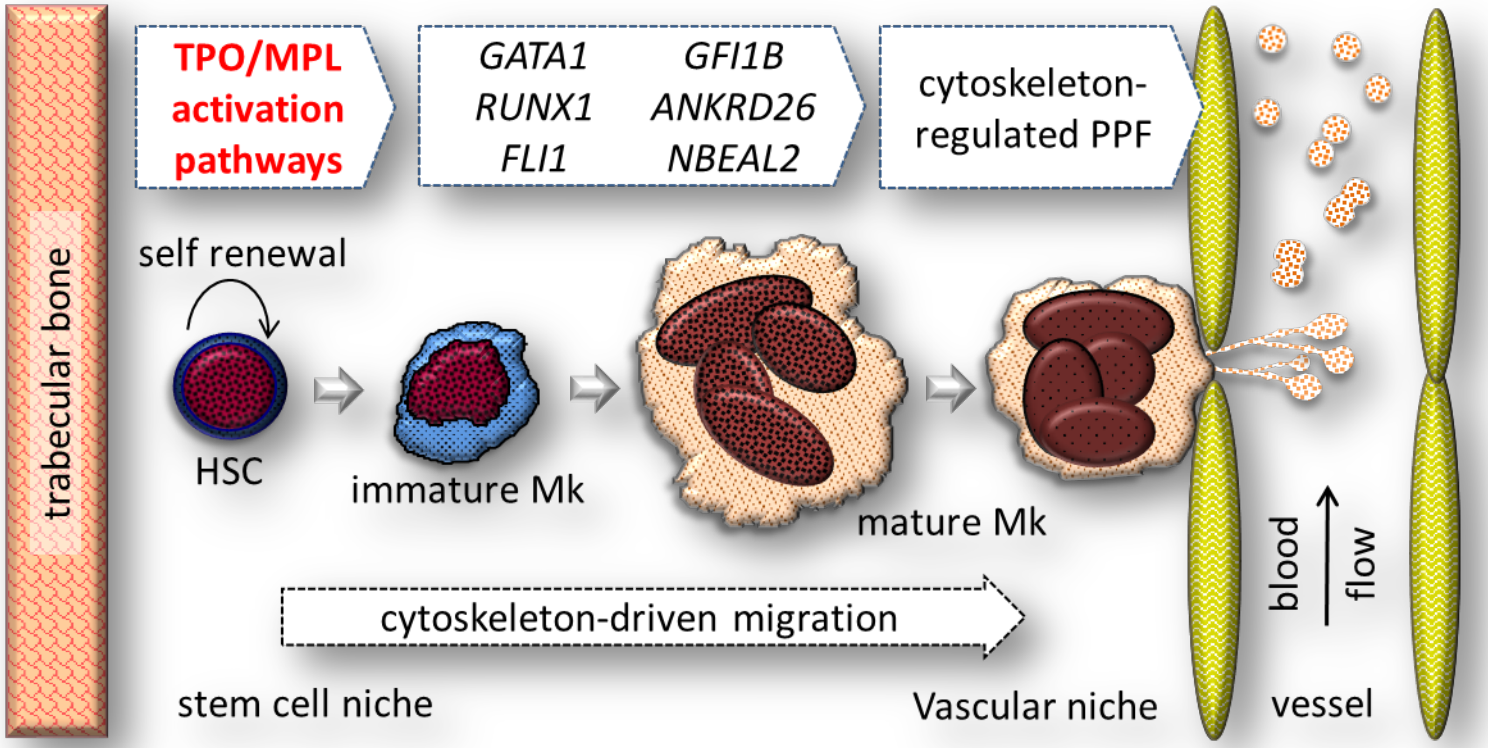

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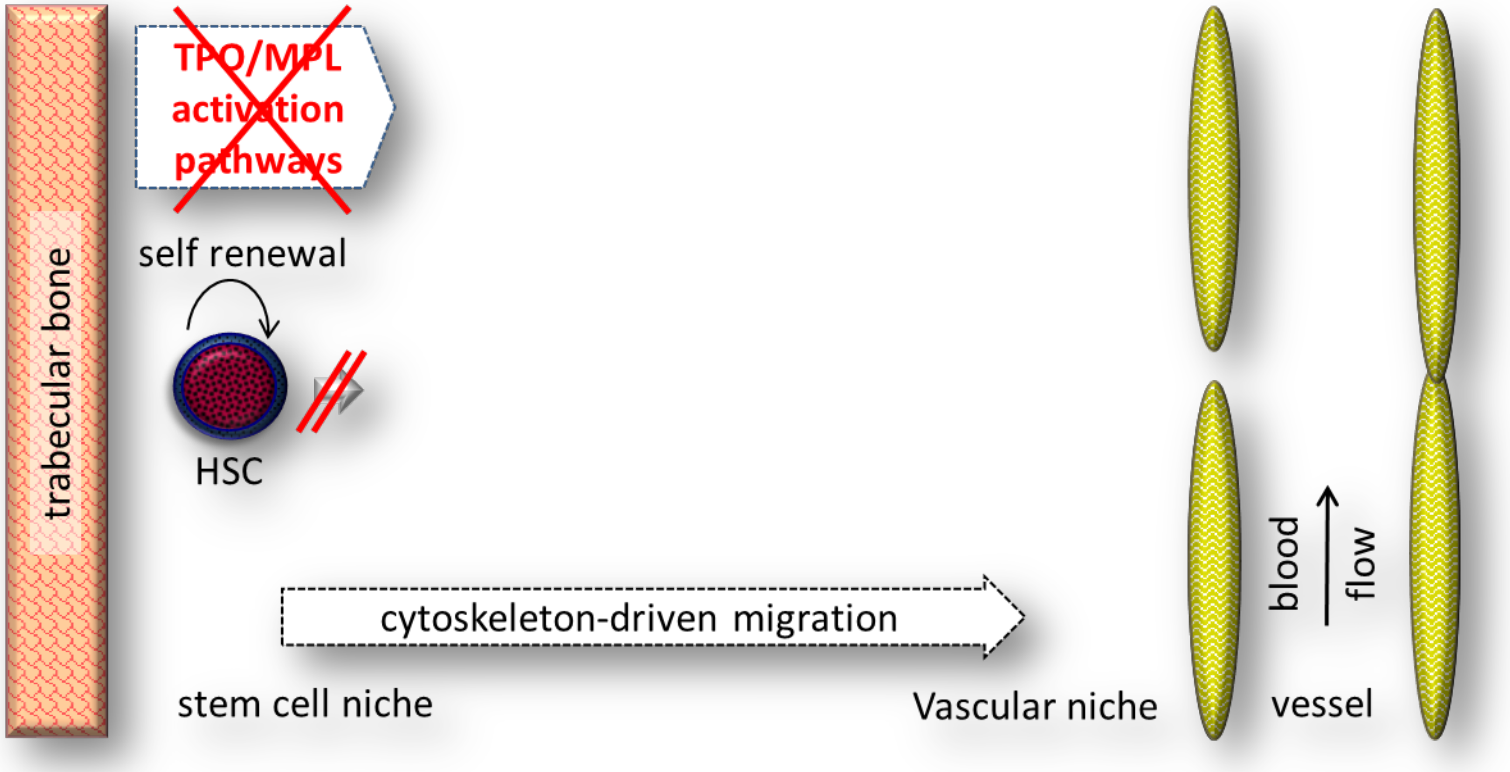
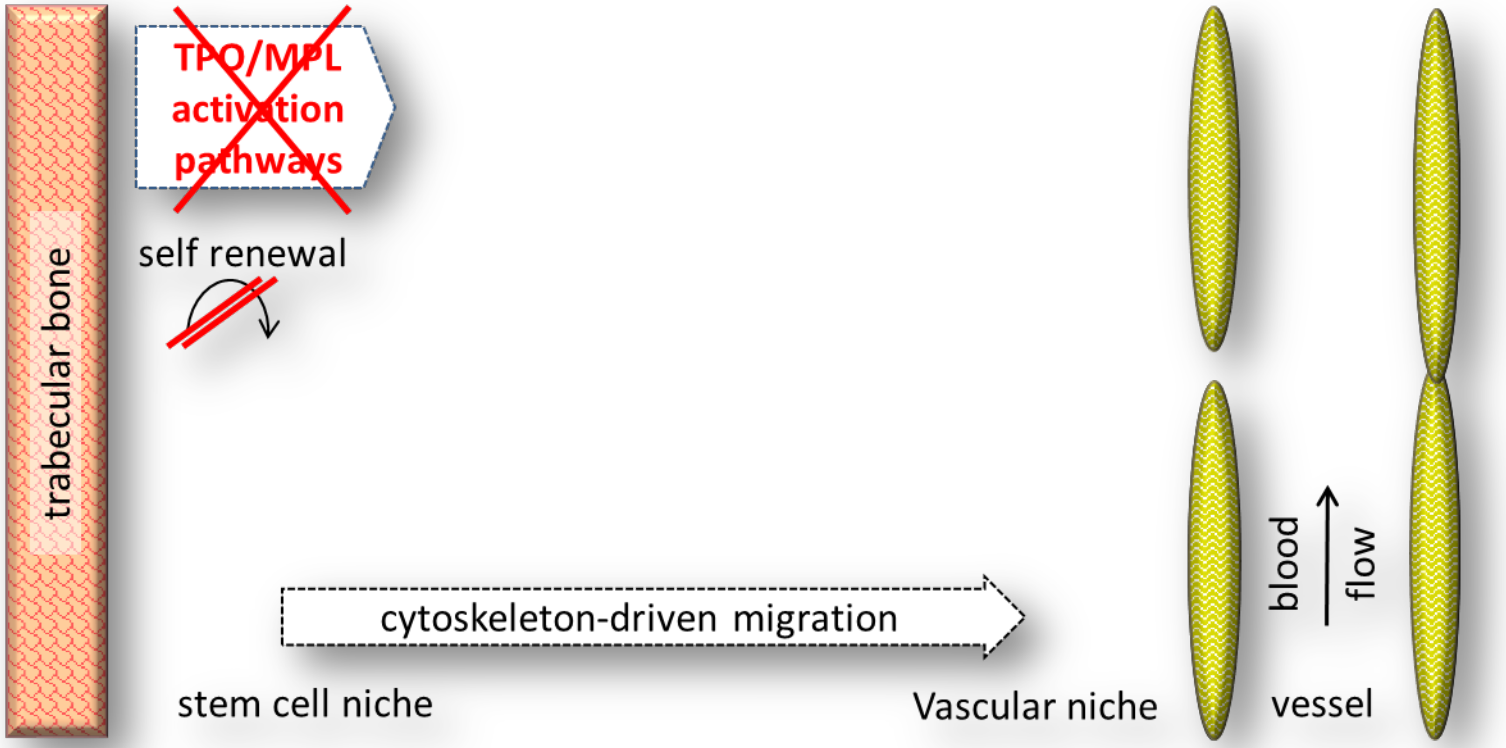


Megakaryopoiesis and platelet production



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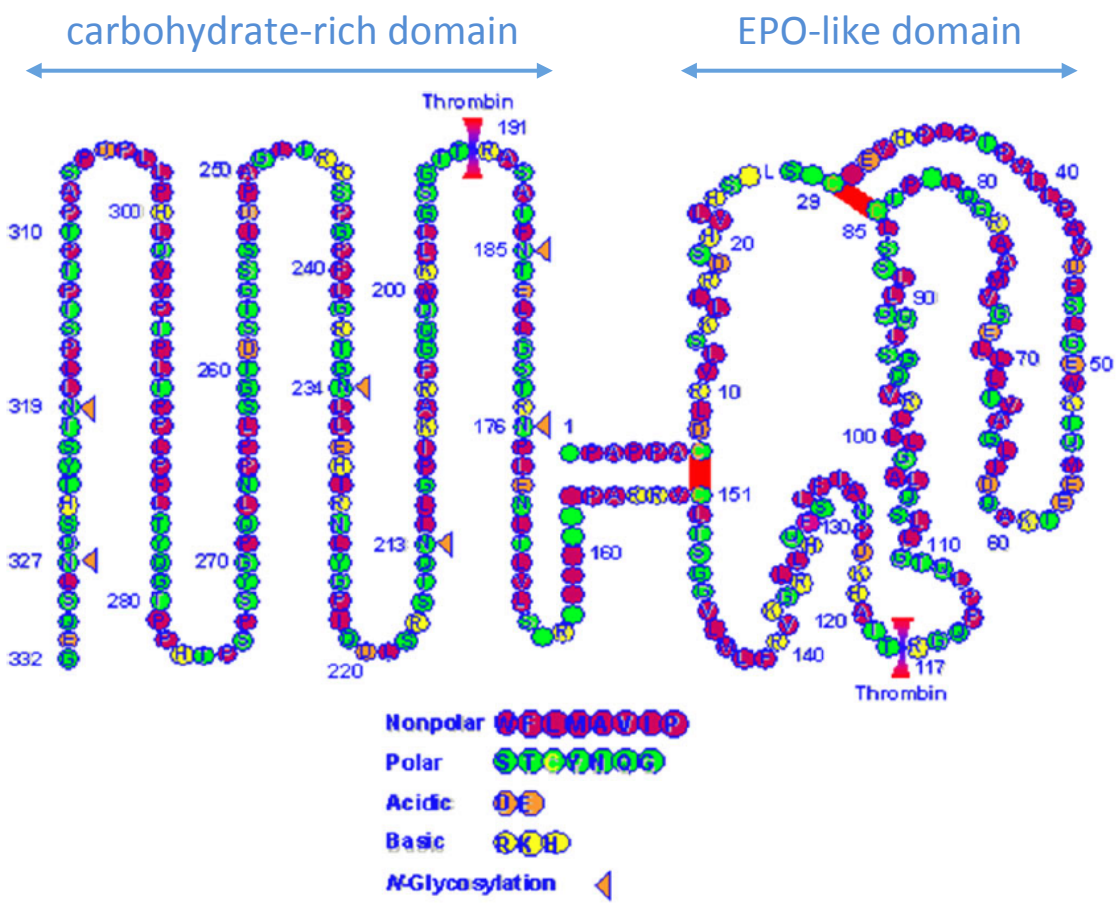
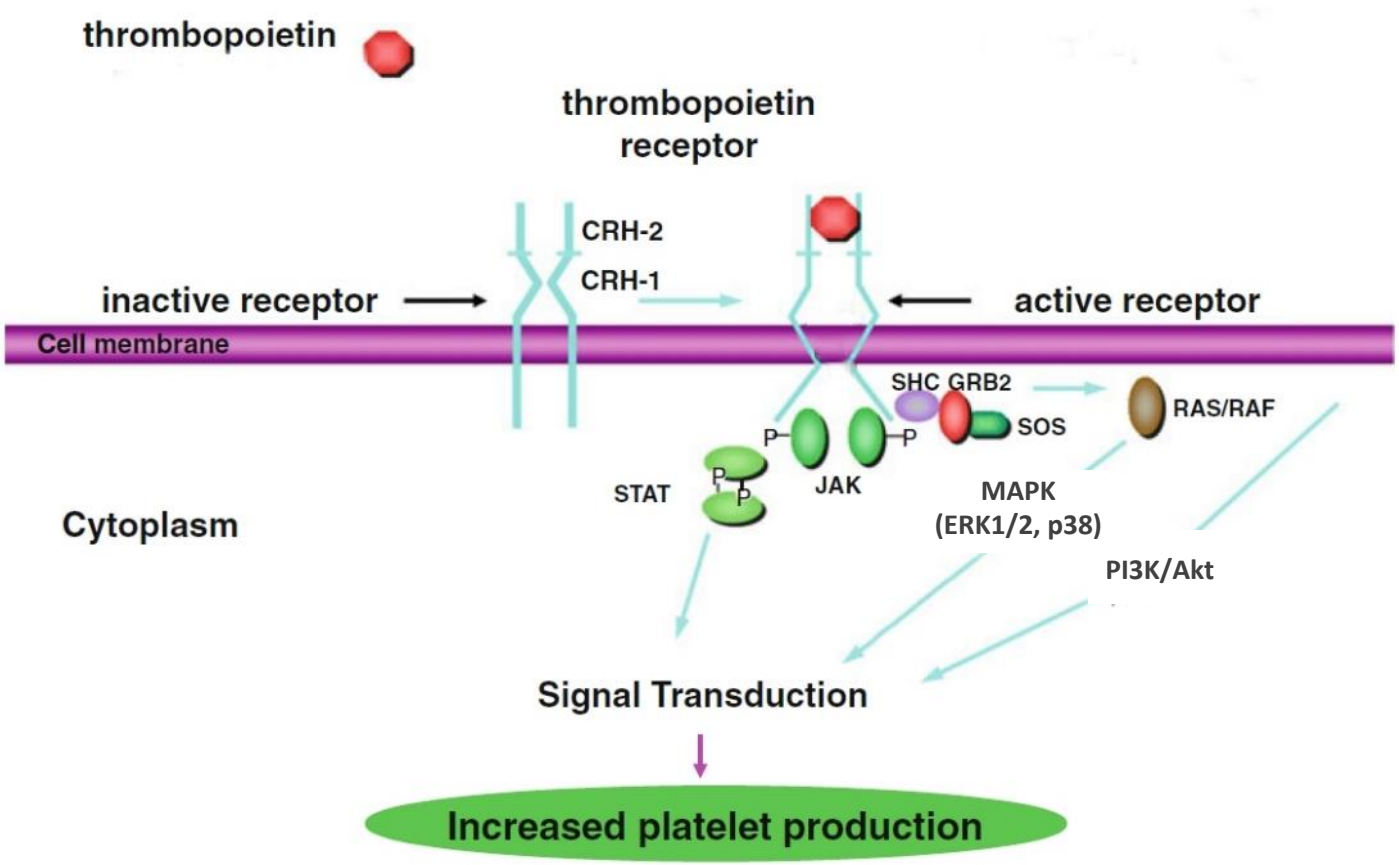
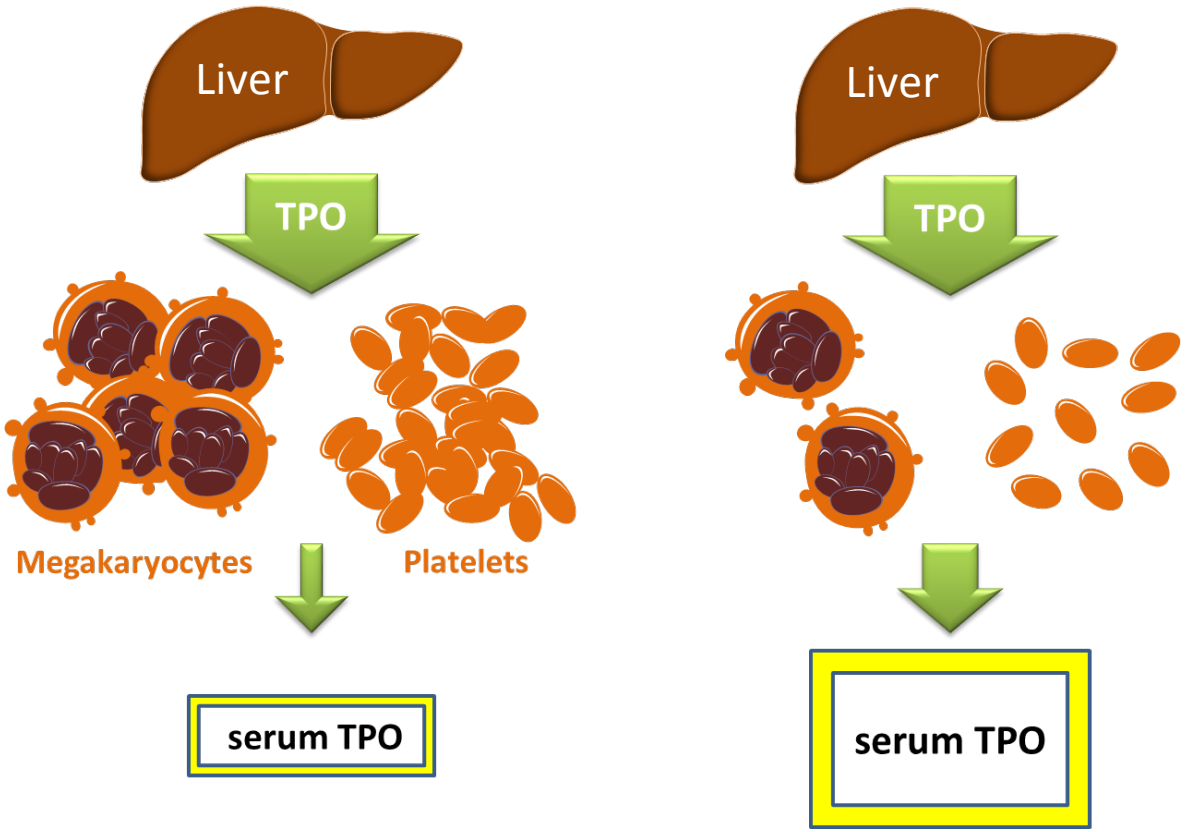
Thrombopoietin structure



MPL: the thrombopoietin receptor



Regulation of serum TPO level

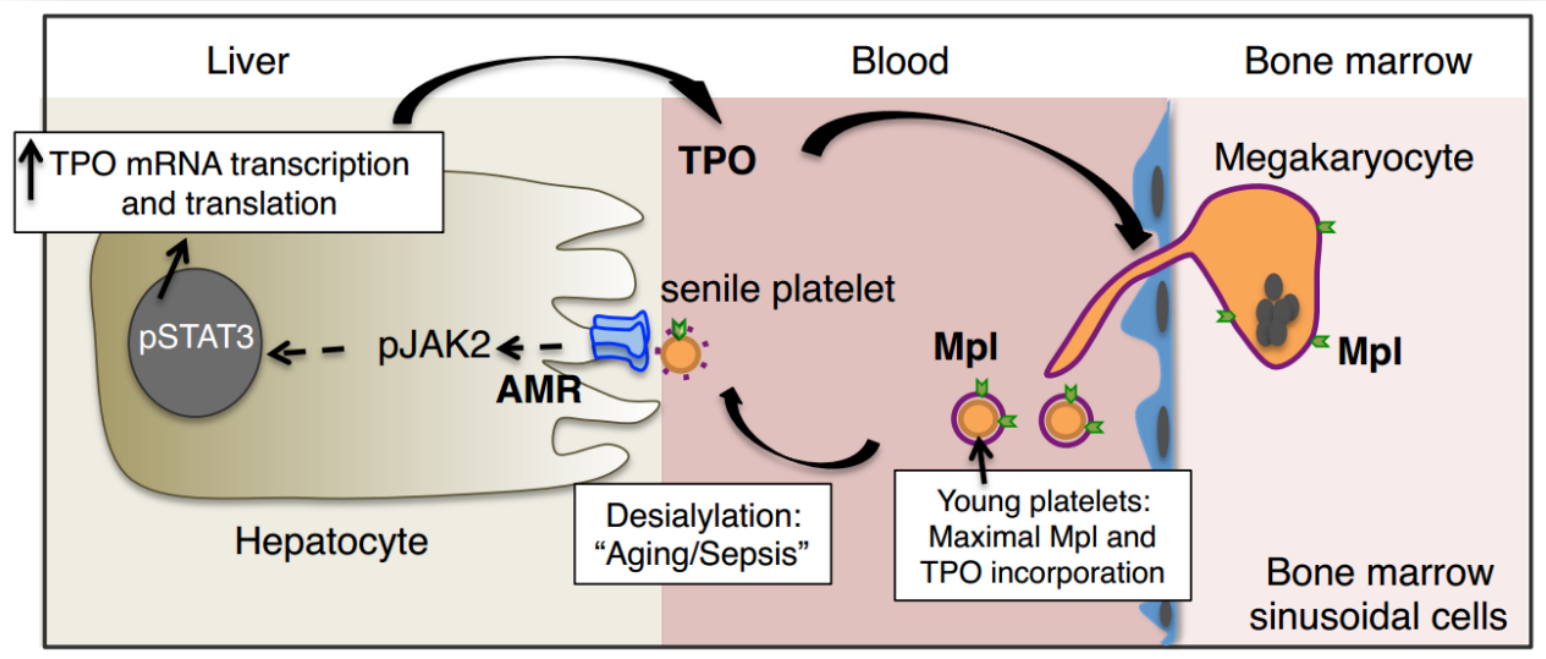


nature medicine

2015 January ; 21(1): 47–54

The Ashwell-Morell receptor regulates hepatic thrombopoietin production via JAK2-STAT3 signaling

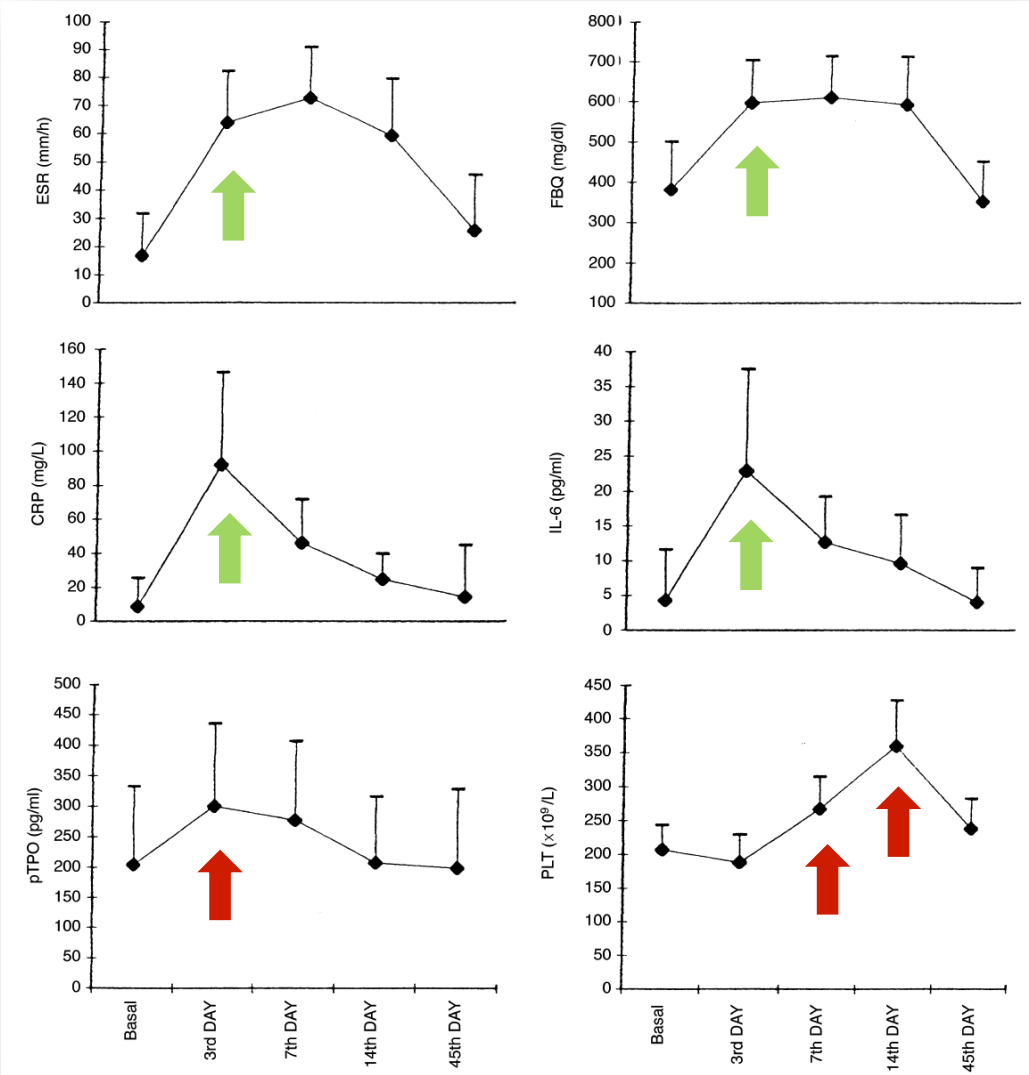
Renata Grozovsky[1], **Antonija Jurak Begonja**[1,#], **Kaifeng Liu**[2], **Gary Visner**[2], **John H. Hartwig**[1], **Hervé Falet**[1], and **Karin M. Hoffmeister**[1]



Clin. Lab. Haem.
1999, **21**, 271–275

Circulating thrombopoietin in reactive conditions behaves like an acute phase reactant

A. CERUTTI*
P. CUSTODI†
M. DURANTI*
M. CAZZOLA‡
C.L. BALDUINI‡



Three mechanisms regulate serum TPO levels

- **TPO internalization by platelet and megakaryocyte** 
- **Hepatic synthesis stimulated by desialylated platelets (old platelets)** 
- **Hepatic syntesis stimulated by IL-6 (inflammation)** 

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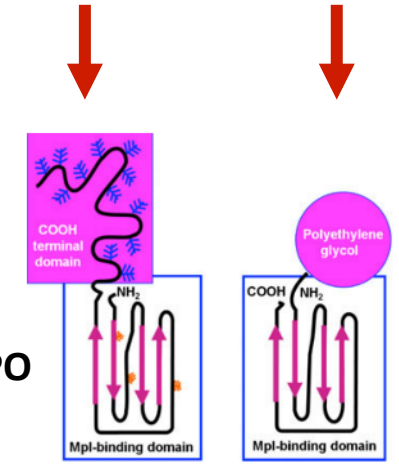
Discovering of TPO (1994)

Recombinant TPO



rhTPO **PEG-rhMGDF**

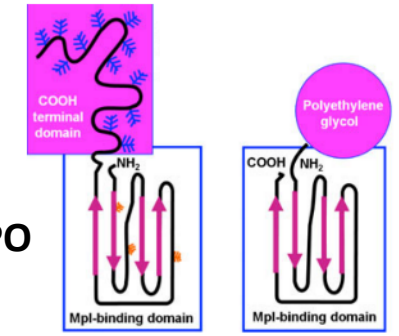
Blood

2001;98:3241-8

X

Discovering of TPO (1994)

Recombinant TPO



rhTPO

PEG-rhMGDF

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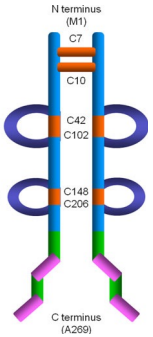
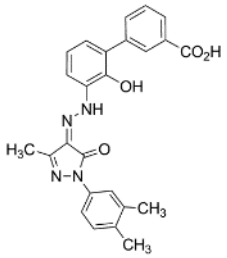
X

TPO mimetics



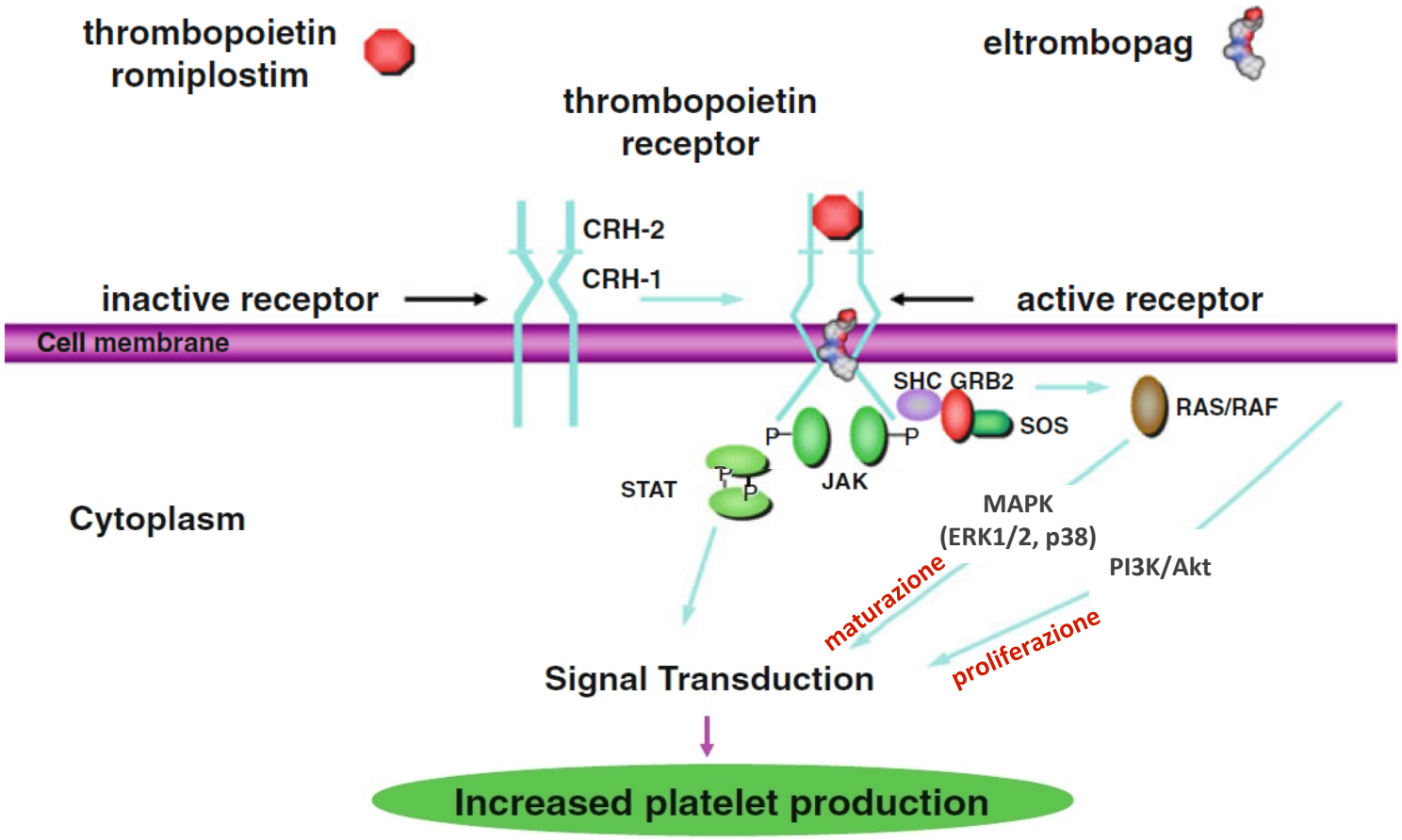


Romiplostim
AMP-2
AMG-531
Nplate

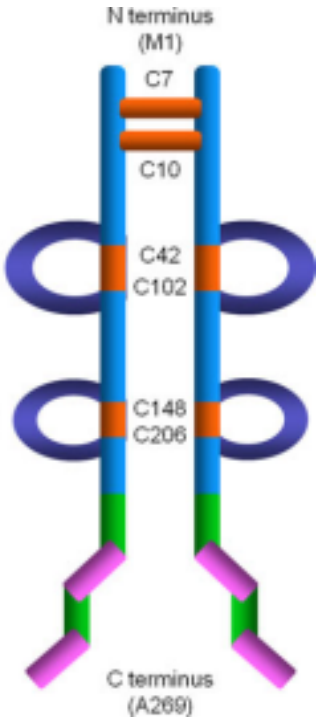
Approved in
2008 for ITP

Eltrombopag
SB497115
Promacta
Revolade

Approved in
2008 for ITP

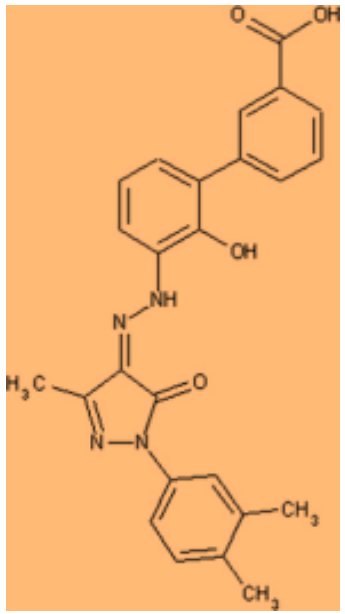

thrombopoietin
romiplostim
eltrombopag
thrombopoietin
receptor
CRH-2
CRH-1
inactive receptor
active receptor
Cell membrane
SHC GRB2
SOS
RAS/RAF
P
P
STAT
JAK
Cytoplasm
MAPK
(ERK1/2, p38)
PI3K/Akt
maturazione
proliferazione
Signal Transduction
Increased platelet production

Romiplostim



- **Peptibody with no sequence homology with endogenous TPO**
- **Similar effect of intravenous and subcutaneous administration**
- **Recycled by FcRn on endothelial cells (T1/2=120-140 h)**
- **Terminally cleared by reticuloendothelial system**
- **No known effect of renal or hepatic dysfunction on its half-life**
- **Competes with TPO for binding to MPL**
- **In healthy subjects, platelet count rises 5 d after a single subcutaneous administration and peaks on day 12-14**

Eltrombopag



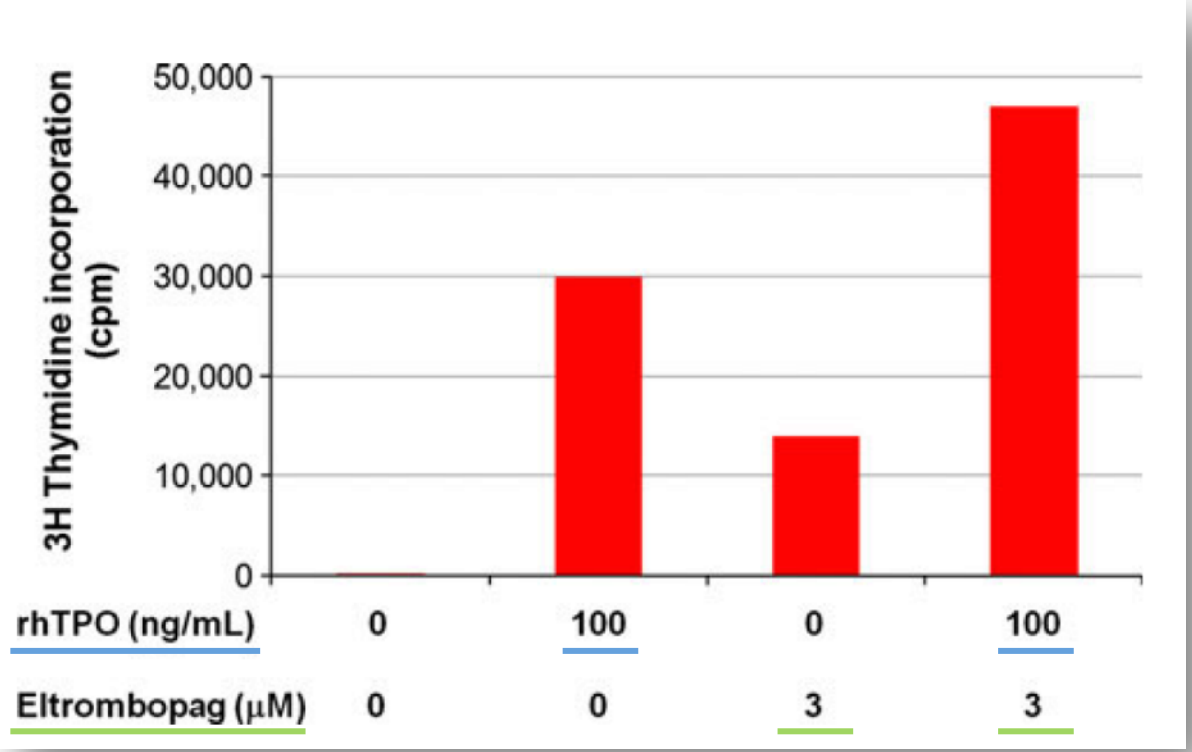
- Non-peptide molecule

- Oral administration
- Metabolism: 60% hepatic; 31% renal (T1/2=21-32 h)
- Plasma levels rise in proportion to reduction in hepatic function
- Pharmacologic interactions

- It does not compete with TPO for binding to MPL

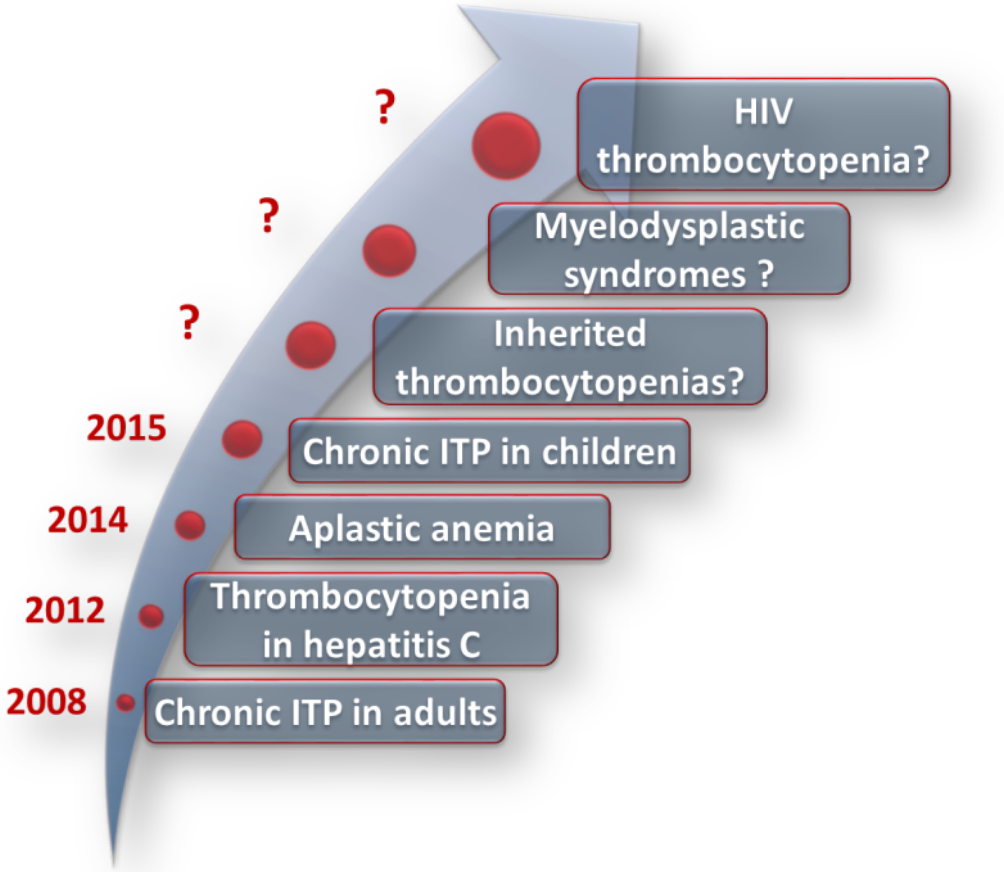
- Administration of 75 mg daily to healthy humans for 10 days produces a maximal dose-dependent rise in platelet counts of $150x10^9$/L over baseline

Eltrombopag effect is additive to that of rhTPO in a TPO-dependent cell line



Int J Hematol 2013;98:10-23

The increasing indications for thrombopoietin mimetics



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Potential adverse effects of TPO-mimetics

Thrombosis

Stimulation of growth of solid tumors

Stimulation of growth of leukemic cells

Increased bone marrow reticulin

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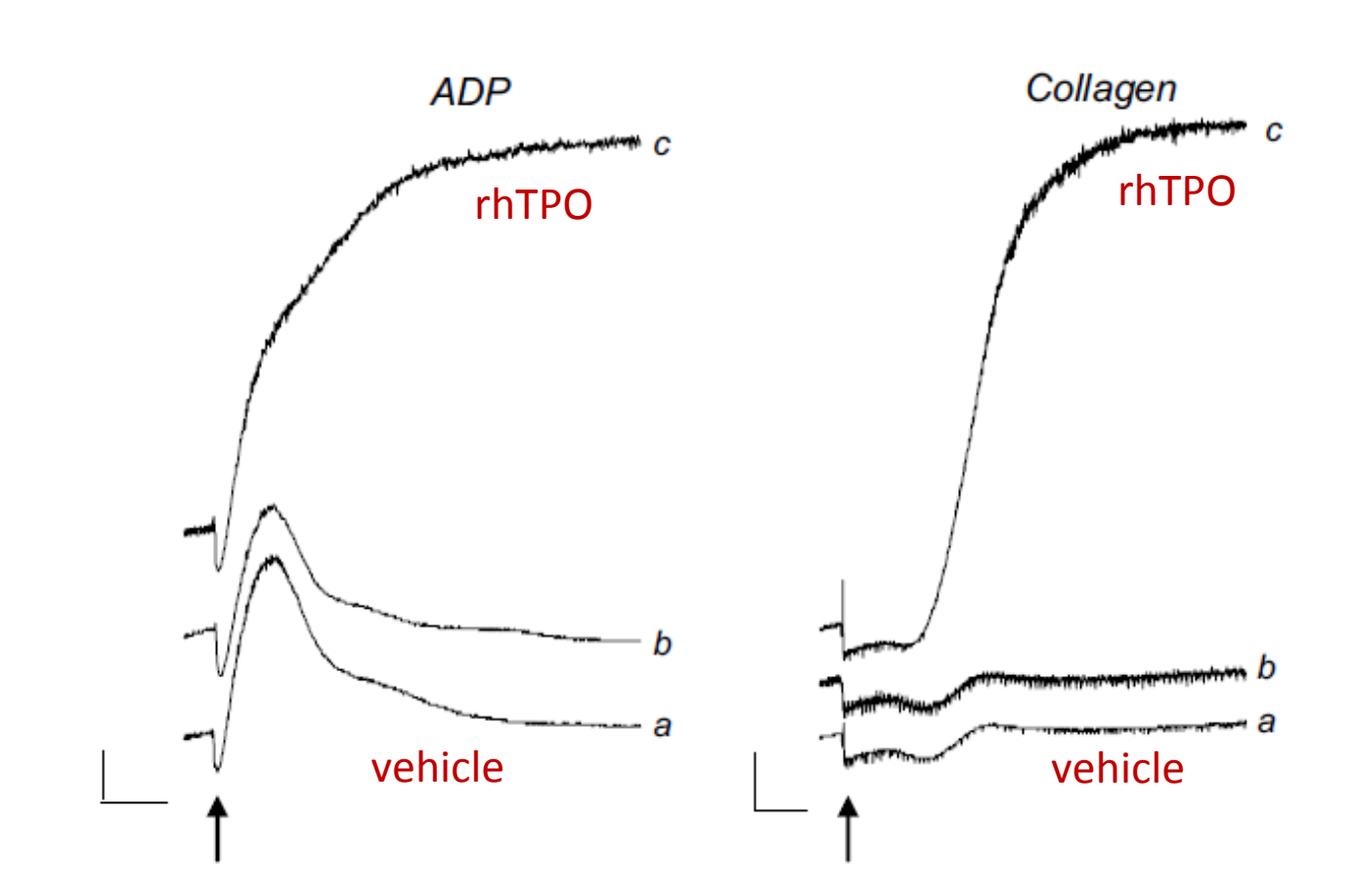
In vitro effect of rhTPO and eltrombopag on aggregation of human platelets



Exp Hematol 2009;37:1030-7

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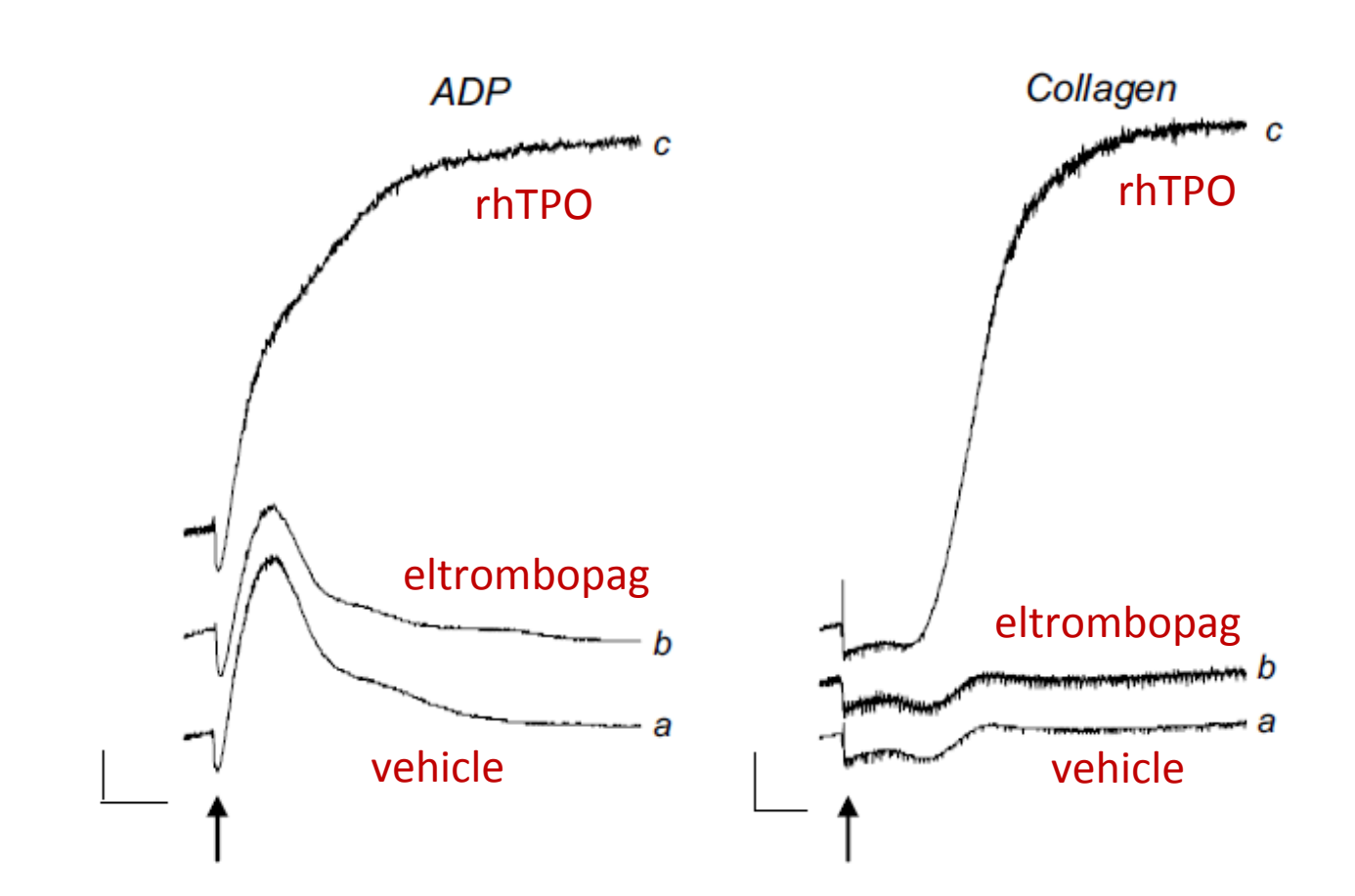
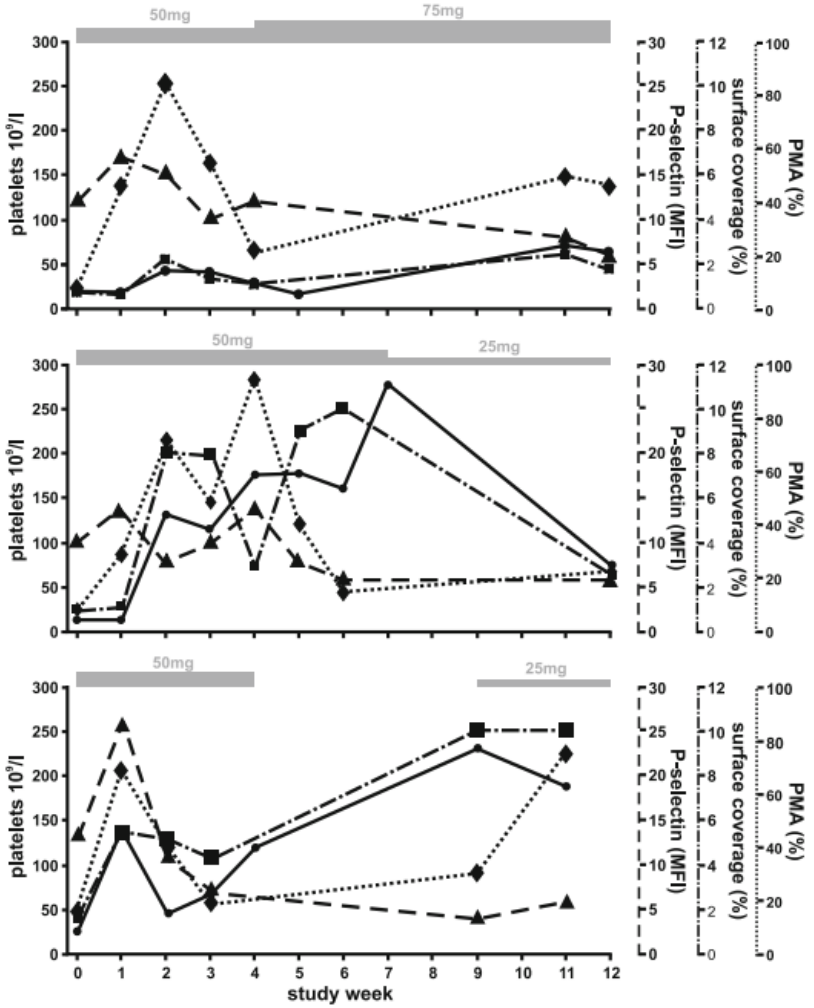


Exp Hematol 2009;37:1030-7

Platelet activation during eltrombopag treatment



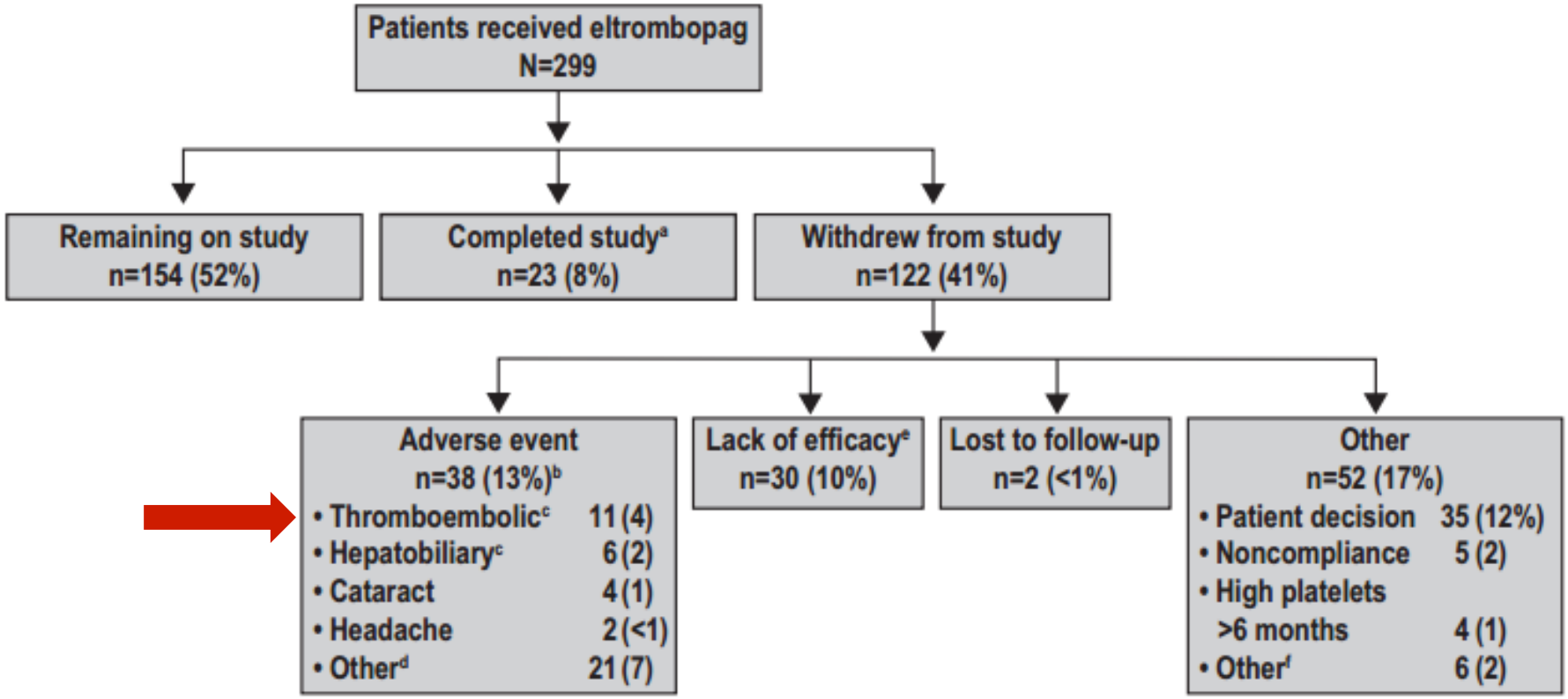
Ann Hematol 2012;91:109-13

Regular Article Blood 2013;121(3):537-545

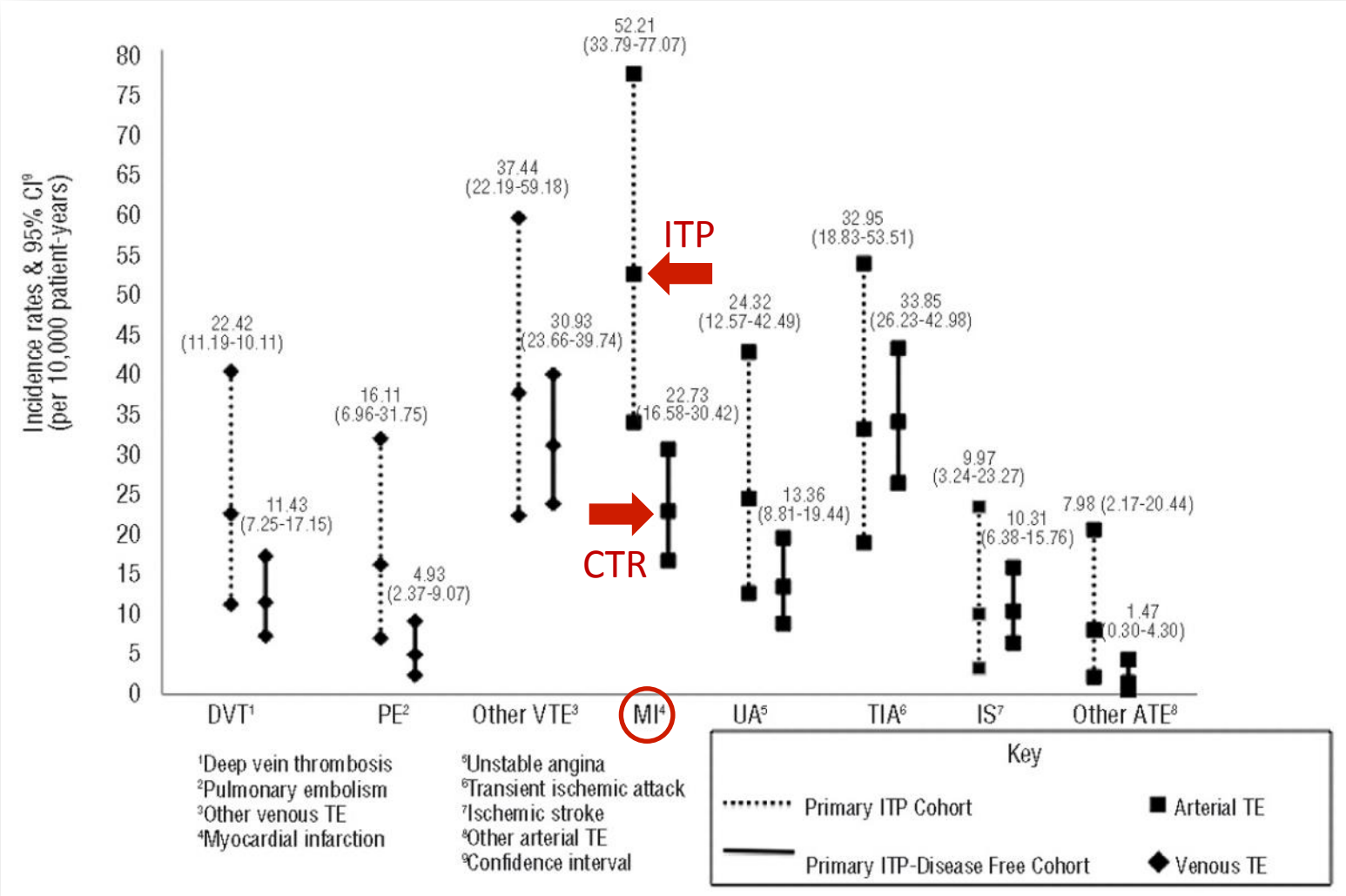
PLATELETS AND THROMBOPOIESIS

Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study

Mansoor N. Saleh,[1] James B. Bussel,[2] Gregory Cheng,[3] Oliver Meyer,[4] Christine K. Bailey,[5] Michael Arning,[5] and Andres Brainsky,[5] on behalf of the EXTEND Study Group



Incidence rates of venous and arterial thromboembolic events (TE) in the primary ITP and primary ITP-disease free cohorts



Ameet Sarpatwari et al. Haematologica 2010;95:1167-1175

haematologica
the hematology journal

Long-term safety in patients with chronic ITP treated with romiplostim

	ROMIPLOSTIM			OTHER TREATMENTS		
	$N = 994$; pt-yr = 1520			$N = 138$; pt-yr = 110		
	#	*r*	95 % CI	#	*r*	95 % CI
All AE	17,129	1127.1	1110–1144	1268	1152.3	1090–1218
Serious AE	910	60	56–64	107	97	80–118
Fatal AE	40	2.6	1.9–3.6	8	7.3	3.1–14.3
Treatment-related AE[a]	1739	114.4	109–120	168	152.7	131–178
Treatment-related serious AE[a]	118	7.8	6.4–9.3	18	16.4	9.7–25.9
Treatment-related fatal AEs[a]	5	0.3	0.1–0.8	0	0	0.0–2.7
AE leading to D/C IP (treatment-related)	83 (40)	5.5 (2.6)	4.4–6.8 (1.9–3.6)	8 (4)	7.3 (3.6)	3.1–14.3 (1.0–9.3)
AE leading to D/C study (treatment-related)	65 (35)	4.3 (2.3)	3.3–5.5 (1.6–3.2)	4 (0)	3.6 (0)	1.0–9.3 (0.0–2.7)
Haemorrhage						
Any grade	3115	205	198–212	289	263	233–295
Grade 3 or greater	182	12	10–14	19	17	10–27
Serious haemorrhage	151	9.9	8.4–11.7	15	13.6	7.6–22.5
Thrombotic/thromboembolic events	83	5.5	4.4–6.8	6	5.5	2.0–11.9
Serious thrombotic/thromboembolic events	61	4.0	3.1–5.2	2	1.8	0.2–6.6
Bone marrow reticulin/collagen[b]	18	1.3	0.8–2.1	1	0.9	0.0–5.1
Non-haematological tumours	34	2.2	1.6–3.1	4	3.6	1.0–9.3
Haematological malignancies/MDS	7[c]	0.5	0.2–1.0	3[d]	2.7	0.6–8.0
Cataracts	34	2.2	1.6–3.1	1	0.9	0.0–5.1

Int J Hematol 2015;102:259–270

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Int J Hematol 2015;102:259–270

Am J Hematol. 2016 Jan;91(1):39-45. doi: 10.1002/ajh.24234. Epub 2015 Nov 26.

Is ITP a thrombophilic disorder?

Rodeghiero F[1].

⊕ Author information

Abstract

Immune thrombocytopenia (ITP) represents the epitome of acquired bleeding diseases for the hematologist. Stemming from the interest for the safety of thrombopoietin-receptor agonists (TPO-ra) romiplostim and eltrombopag, recent data have investigated if thrombotic risk is also increased in this disorder. In patients not treated with TPO-ra, a slightly higher risk of venous thrombosis (VTE) is consistently found in ITP, but not to a rate demanding special attention in the generality of cases. No significant increase of arterial thrombosis (AT) is apparent. However, age, splenectomy, and personal risk factors may put some ITP patient to a particularly higher risk of venous and arterial thrombosis (three to four times higher than the average subject). Patients exposed to TPO-ra present indirect evidence of a much higher risk of both AT and VTE. Unfortunately, no matched control population is available and the prospective and registrative nature of these studies may have emphasized the incidence of thrombosis, which was recorded as adverse event. The clinician should be able to individualize the best treatment for the patient, taking also into account the thrombotic risk, limiting active treatment of ITP to those patients really at risk of bleeding. Am. J. Hematol. 91:39-45, 2016. © 2015 Wiley Periodicals, Inc.

Potential adverse effects of TPO-mimetics

Thrombosis

Stimulation of growth of solid tumors

Stimulation of growth of leukemic cells

Increased bone marrow reticulin

TPO expression in human cancer cell lines and primary tissues

Cell line type	*c-mpl* expression
Breast-derived cell lines	
BT-474: ductal carcinoma	–
ZR-75-30: breast carcinoma	–
ZR-75-1: breast carcinoma	–
Neural tissue-derived cell lines	
SW 1088: astrocytoma	–
CCF-STTG1: astrocytoma, grade IV	–
T98G: glioblastoma	–
TE671: medulloblastoma	–
DAOY: medulloblastoma	–
A172: glioblastoma	–
SK-N-SH: neuroblastoma, metastasis to bone marrow	–
H4: neuroglioma, brain	–
Lung cancer cell lines	
NCI-H146: lung, small cell carcinoma	–
NCI-H345: lung, small cell carcinoma	–
Miscellaneous Cancer Cell Lines:	
HT-15: adenocarcinoma, colon	–
Hep G2: hepatocellular carcinoma	–
Hep 3B: hepatocellular carcinoma	+
Hs294T: melanoma, metastasis to lymph node	–
HM-1: melanoma	–
HeLa: cervix, epitheloid carcinoma	–
AN3 CA: endometrial adenocarcinoma, metastatic	–
NIH:OVCAR-3: ovary, adenocarcinoma	–
TERA-1: embryonal carcima	–
DU 145: prostate, carcinoma	–
Embryonal and placental cell lines	
FSH 173 SE: whole human embryo	–
WRL: human embryonal liver	–

Primary tissues	*c-mpl* expression
Hodgkin's lymphoma	–
Non-Hodgkin's lymphoma	–
Kaposi sarcoma	–
Pancreatic adenocarcinoma	–
Colon adenocarcinoma	–
Liver adenocarcinoma	–
Breast adenocarcinoma	–
Lung adenocarcinoma	–
Adenocarcinoma of thyroid	–
Malignant melanoma	–

Cancer Research 1995;55:3509-12

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Cancer 2000 Feb 1;88(3):570-6.
Expression of thrombopoietin and its receptor (c-mpl) in chronic myelogenous leukemia: correlation with disease progression and response to therapy.
Kaban K, Kantarjian H, Talpaz M, O'Brien S, Cortes J, Giles FJ, Pierce S, Albitar M.

Leukemia 1996 Sep;10(9):1405-21.
Thrombopoietin: expression of its receptor MPL and proliferative effects on leukemic cells.
Drexler HG1, Quentmeier H.

Hum Cell 1996;9:309-16
Use of human leukemia-lymphoma cell lines in hematological research: effects of thrombopoietin on human leukemia cell lines.
Drexler HG1, Quentmeier H.

Leukemia 1997;11:541-51
Thrombopoietin supports the continuous growth of cytokine-dependent human leukemia cell lines.
Drexler HG1, Zaborski M, Quentmeier H.

Pathology & Oncology Research
April 2014, Volume 20, Issue 2, pp 309-317

Date: 02 Oct 2013

The TPO/c-MPL Pathway in the Bone Marrow may Protect Leukemia Cells from Chemotherapy in AML Patients

Zeng Dong-Feng, Liu Ting, Zhang Yong, Chang Cheng, Zhang Xi, Kong Pei-Yan

Leukemia 1996;10:297-310.
Expression of the receptor MPL and proliferative effects of its ligand thrombopoietin on human leukemia cells.
Quentmeier H, Zaborski M, Graf G, Ludwig WD, Drexler HG.

NEOPLASIA Blood 2006;107:2525-30

Circulating thrombopoietin as an in vivo growth factor for blast cells in acute myeloid leukemia

Francis Corazza, Christophe Hermans, Stéphanie D'Hondt, Alina Ferster, Alain Kentos, Yves Benoît, and Eric Sariban

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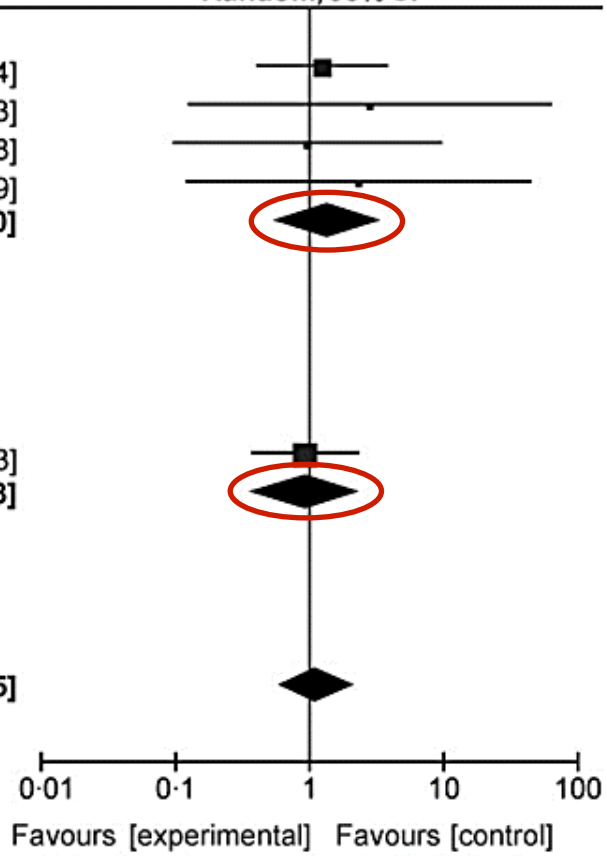
Treatment-related fatal AEs[a]	5	0.3	0.1–0.8	0	0	0.0–2.7
AE leading to D/C IP (treatment-related)	83 (40)	5.5 (2.6)	4.4–6.8 (1.9–3.6)	8 (4)	7.3 (3.6)	3.1–14.3 (1.0–9.3)
AE leading to D/C study (treatment-related)	65 (35)	4.3 (2.3)	3.3–5.5 (1.6–3.2)	4 (0)	3.6 (0)	1.0–9.3 (0.0–2.7)
Haemorrhage						
Any grade	3115	205	198–212	289	263	233–295
Grade 3 or greater	182	12	10–14	19	17	10–27
Serious haemorrhage	151	9.9	8.4–11.7	15	13.6	7.6–22.5
Thrombotic/thromboembolic events	83	5.5	4.4–6.8	6	5.5	2.0–11.9
Serious thrombotic/thromboembolic events	61	4.0	3.1–5.2	2	1.8	0.2–6.6
Bone marrow reticulin/collagen[b]	18	1.3	0.8–2.1	1	0.9	0.0–5.1
Non-haematological tumours	34	2.2	1.6–3.1	4	3.6	1.0–9.3
Haematological malignancies/MDS	7[c]	0.5	0.2–1.0	3[d]	2.7	0.6–8.0
Cataracts	34	2.2	1.6–3.1	1	0.9	0.0–5.1

Int J Hematol 2015;102:259–270

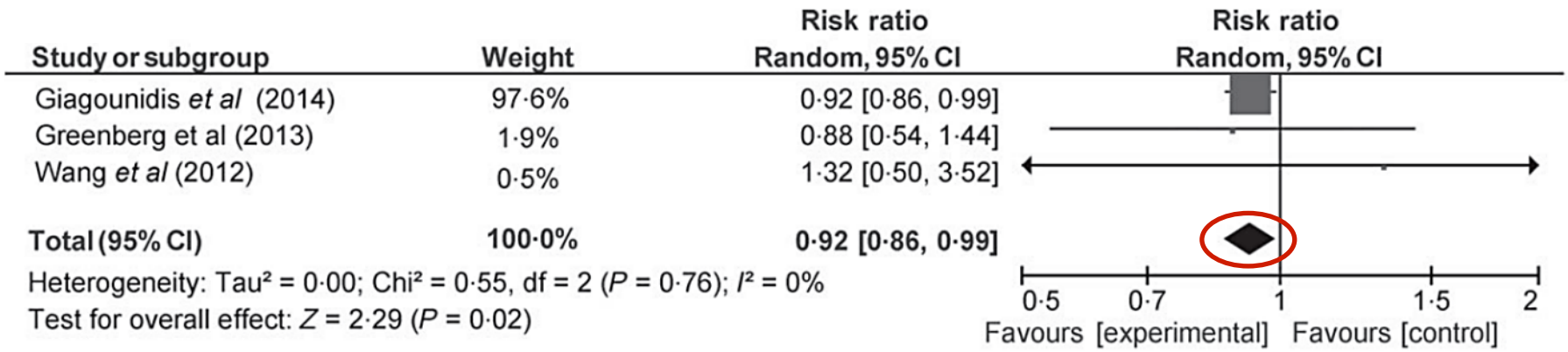
AML progression/increased blast percentage in patients with myelodysplastic syndromes receiving TPO-mimetics

Study or subgroup	Romiplostim Events	Total	Control Events	Total	Weight	Risk ratio Random, 95% CI
1.22.2 Romiplostim						
Giagounidis *et al* (2014)	10	167	4	83	33·2%	1·24 [0·40, 3·84]
Greenberg *et al* (2013)	1	15	0	14	4·3%	2·81 [0·12, 63·83]
Kantarjian *et al* (2010b)	2	27	1	13	8·0%	0·96 [0·10, 9·68]
Wang *et al* (2012)	2	27	0	12	4·8%	2·32 [0·12, 44·99]
Subtotal (95% CI)		**236**		**122**	**50·4%**	**1·36 [0·54, 3·40]**
Total events	15		5			
Heterogeneity: Tau² = 0·00; Chi² = 0·45, df = 3 (*P* = 0·93); *I*² = 0%						
Test for overall effect: *Z* = 0·66 (*P* = 0·51)						
1.22.3 Eltrombopag						
Platzbecker *et al* (2013)	5	9	3	5	49·6%	0·93 [0·37, 2·33]
Subtotal (95% CI)		**9**		**5**	**49·6%**	**0·93 [0·37, 2·33]**
Total events	5		3			
Heterogeneity: Not applicable						
Test for overall effect: *Z* = 0·16 (*P* = 0·87)						
Total (95% CI)		**245**		**127**	**100·0%**	**1·12 [0·59, 2·15]**
Total events	20		8			
Heterogeneity: Tau² = 0·00; Chi² = 0·86, df = 4 (*P* = 0·93); *I*² = 0%						
Test for overall effect: *Z* = 0·35 (*P* = 0·73)						
Test for subgroup differences: Chi² = 0·33, df = 1 (*P* = 0·56), *I*² = 0%						



BJH 2014;167:626-38

Bleeding events and platelet transfusions in patients with myelodysplastic syndromes receiving TPO-mimetics



BJH 2014;167:626-38

Potential adverse effects of TPO-mimetics

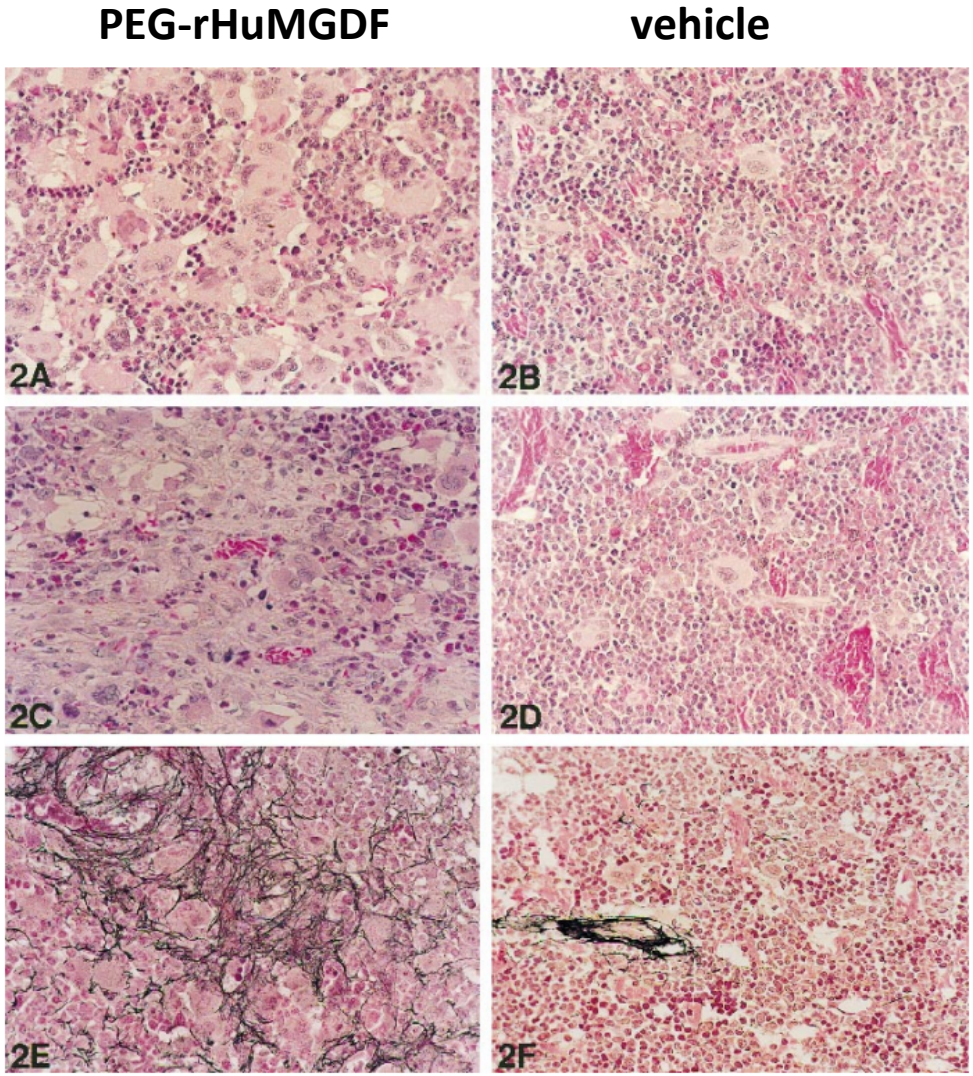
Thrombosis

Stimulation of growth of solid tumors

Stimulation of growth of leukemic cells

Increased bone marrow reticulin

Morphological changes induced by PEG-rHuMGDF in rats' bone marrow



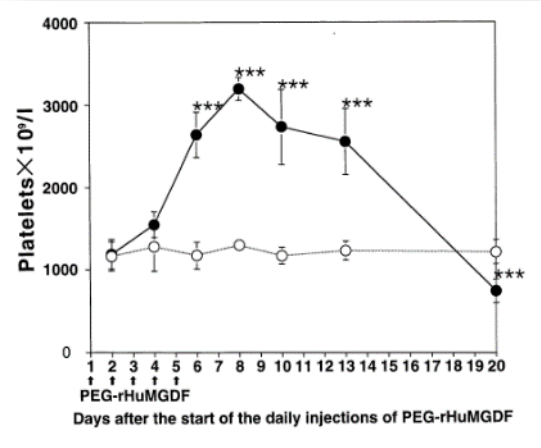
haematoxylin and eosin

Watanabe's reticulin stain

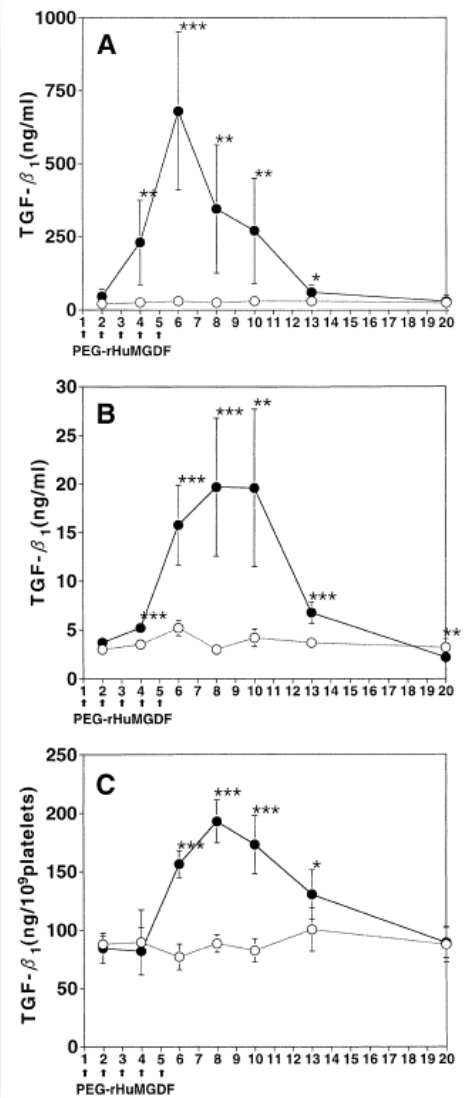
Br J Haematol 1997;99:739-45

Changes in platelet count and TGFβ1 induced by PEG-rHuMGDF

platelet count



TGFβ1



bone marrow

plasma

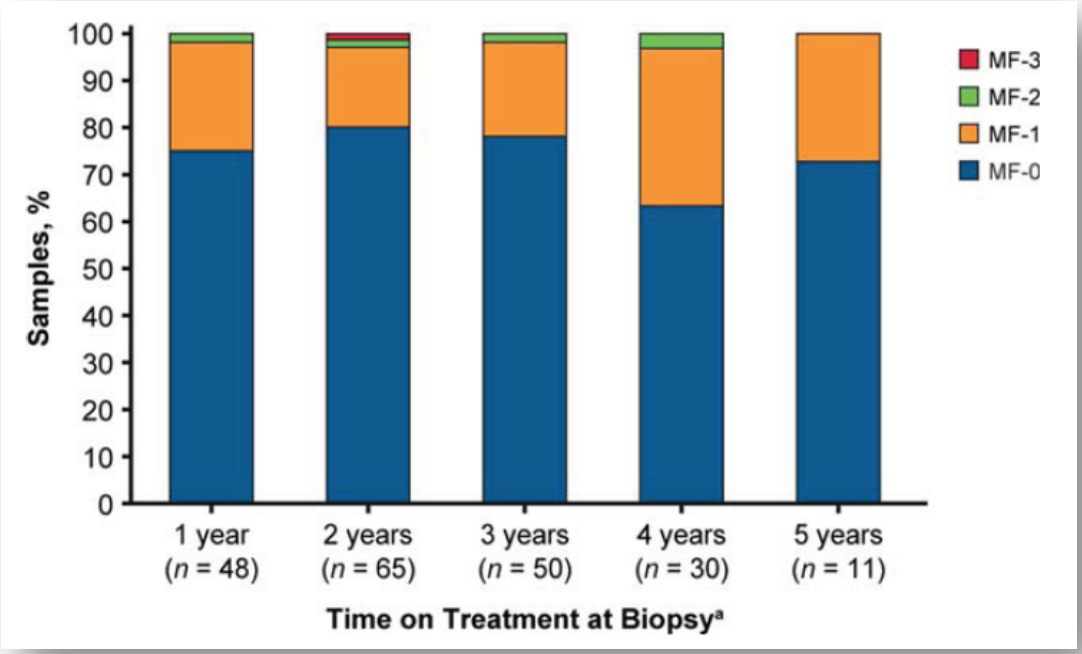
platelets

Br J Haematol 1997;99:739-45

RESEARCH ARTICLE Am. J. Hematol. 90:598–601, 2015.

Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenia treated with eltrombopag: Data from the EXTEND study

Russell K. Brynes,[1]* Attilio Orazi,[2] Dickens Theodore,[3] Paul Burgess,[4] Christine K. Bailey,[5] Maung M. Thein,[1] and Kalpana K. Bakshi[5]



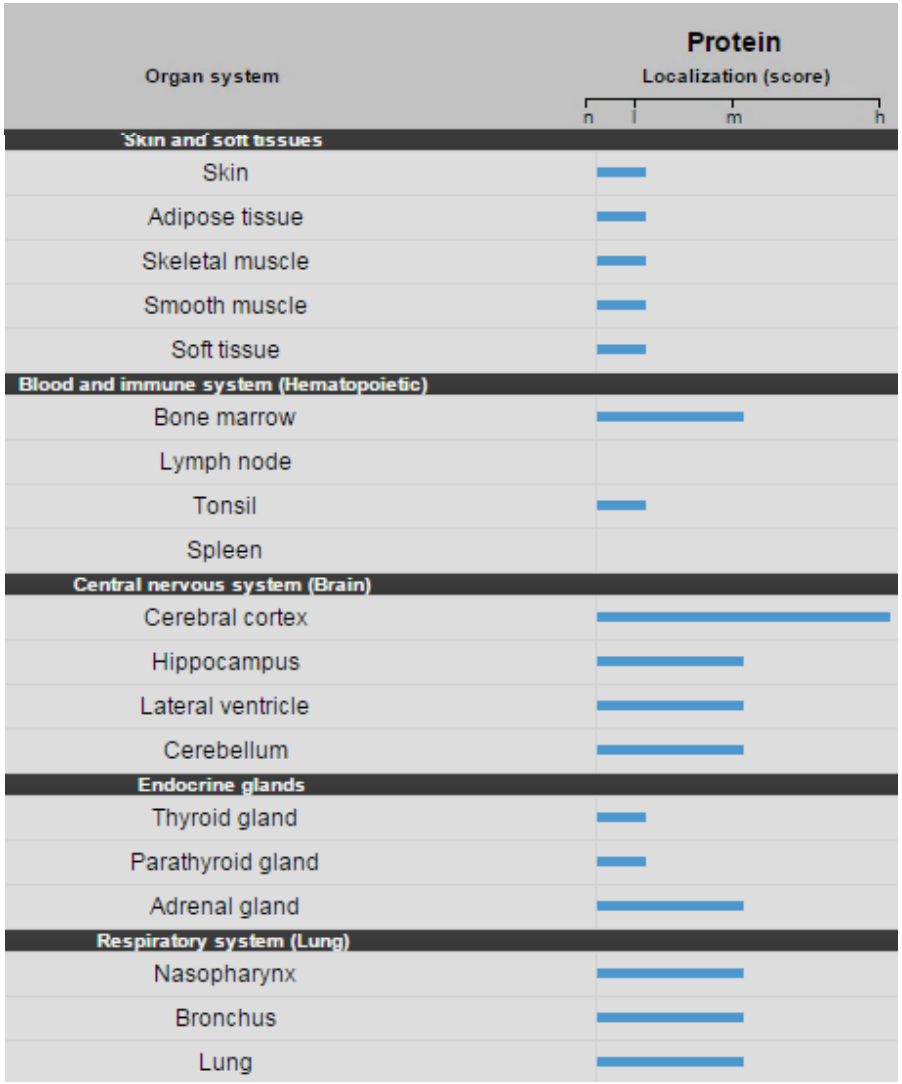
Meccanismo d'azione dei TPO RA: dalla biologia all'applicazione clinica

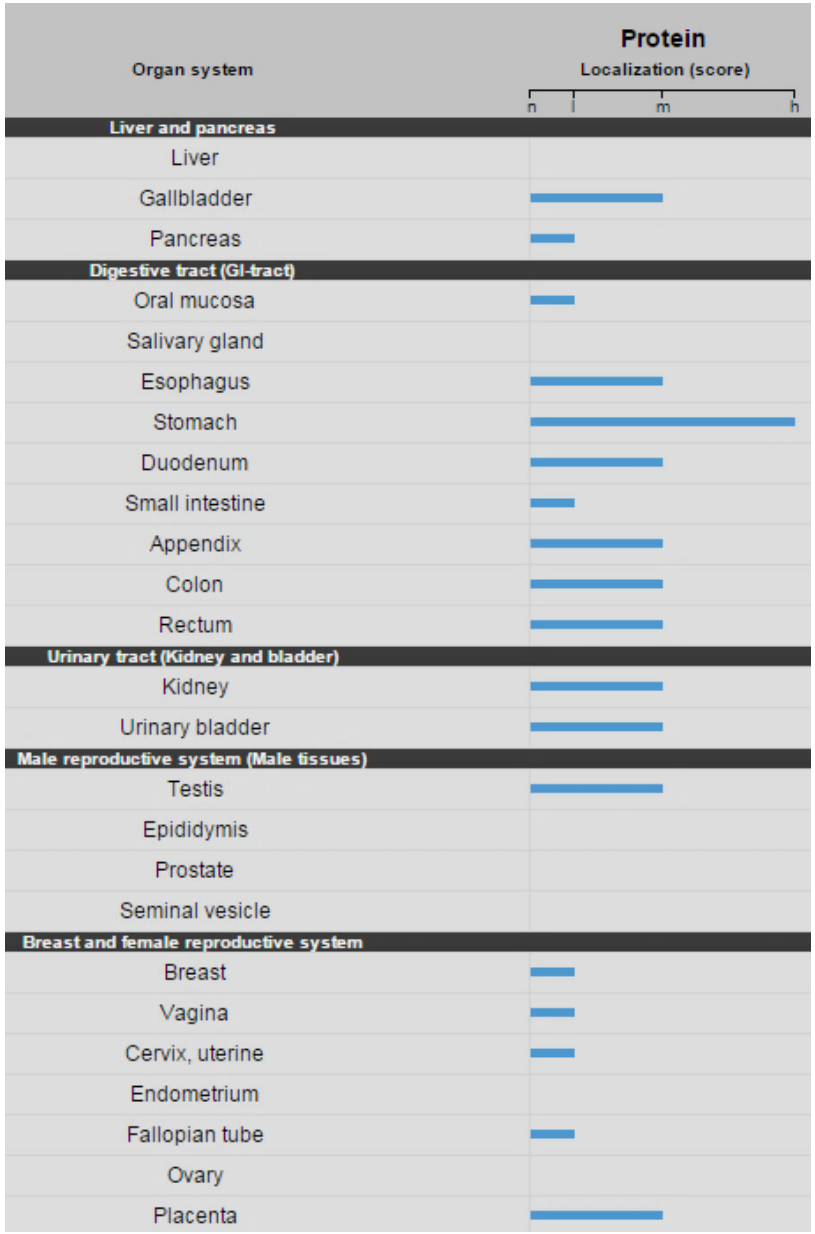
Indice

- La megacariopoiesi
- La trombopoietina ed il suo recettore (MPL)
- Trombopoietino-mimetici e loro meccanismo d'azione
  - Romiplostim
  - Eltrombopag
- Potenziali effetti indesiderati dei trombopoietino-mimetici
- Nuove possibili indicazioni dei trombopoietino-mimetici

THE HUMAN PROTEIN ATLAS

MPL





Cardioprotective effects of thrombopoietin

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Thrombopoietin improved ventricular function and regulated remodeling genes in a rat model of myocardial infarction.
Int J Cardiol 2013;167:2546-54

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Thrombopoietin protects the brain and improves sensorimotor functions: reduction of stroke-induced MMP-9 upregulation and blood-brain barrier injury.

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Lesion-targeted thrombopoietin potentiates vasculogenesis by enhancing motility and enlivenment of transplanted endothelial progenitor cells via activation of Akt/mTOR/p70S6kinase signaling pathway.
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Matsuo R, Nakano Y, Ohkohchi N.
Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy.
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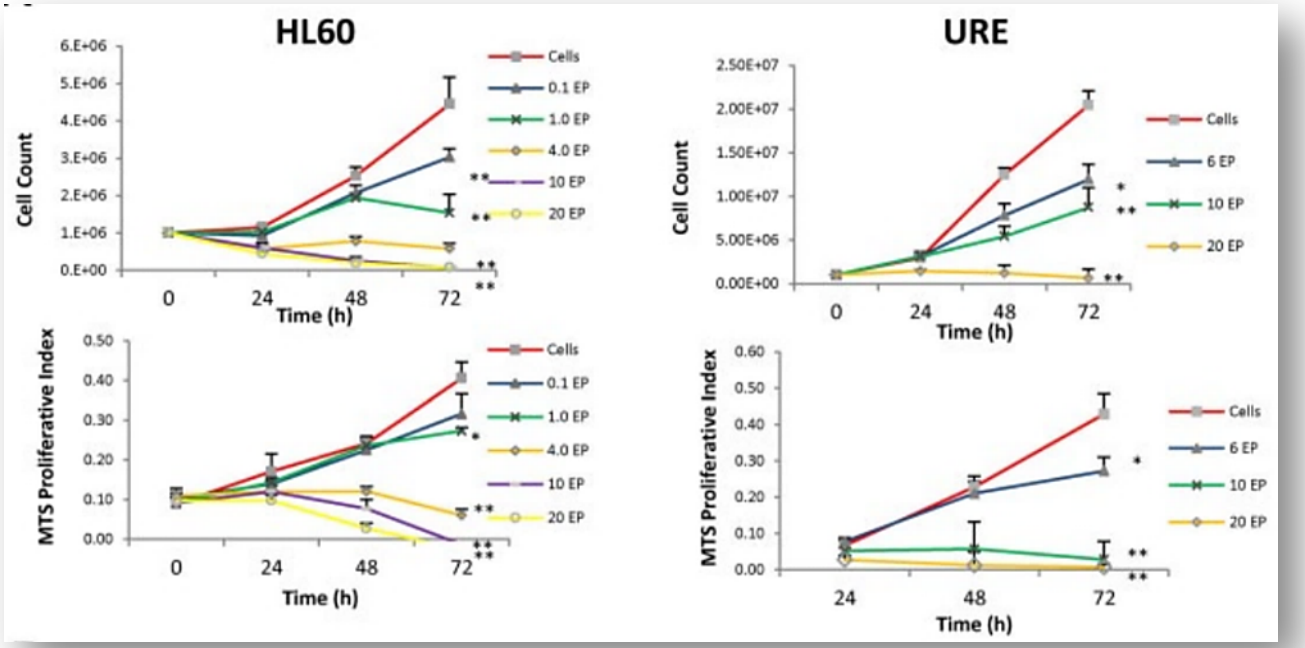
Watanabe M, Murata S, Hashimoto I et al
Platelets contribute to the reduction of liver fibrosis in mice.
J Gastroenterol Hepatol. 2009 Jan;24(1):78-89.

Maruyama T, Murata S, Takahashi K et al
Platelet transfusion improves liver function in patients with chronic liver disease and cirrhosis.
Tohoku J Exp Med. 2013;229:213-20

Murata S, Hashimoto I, Nakano et al
Single administration of thrombopoietin prevents progression of liver fibrosis and promotes liver regeneration after partial hepatectomy in cirrhotic rats.
Ann Surg. 2008;248:821-8

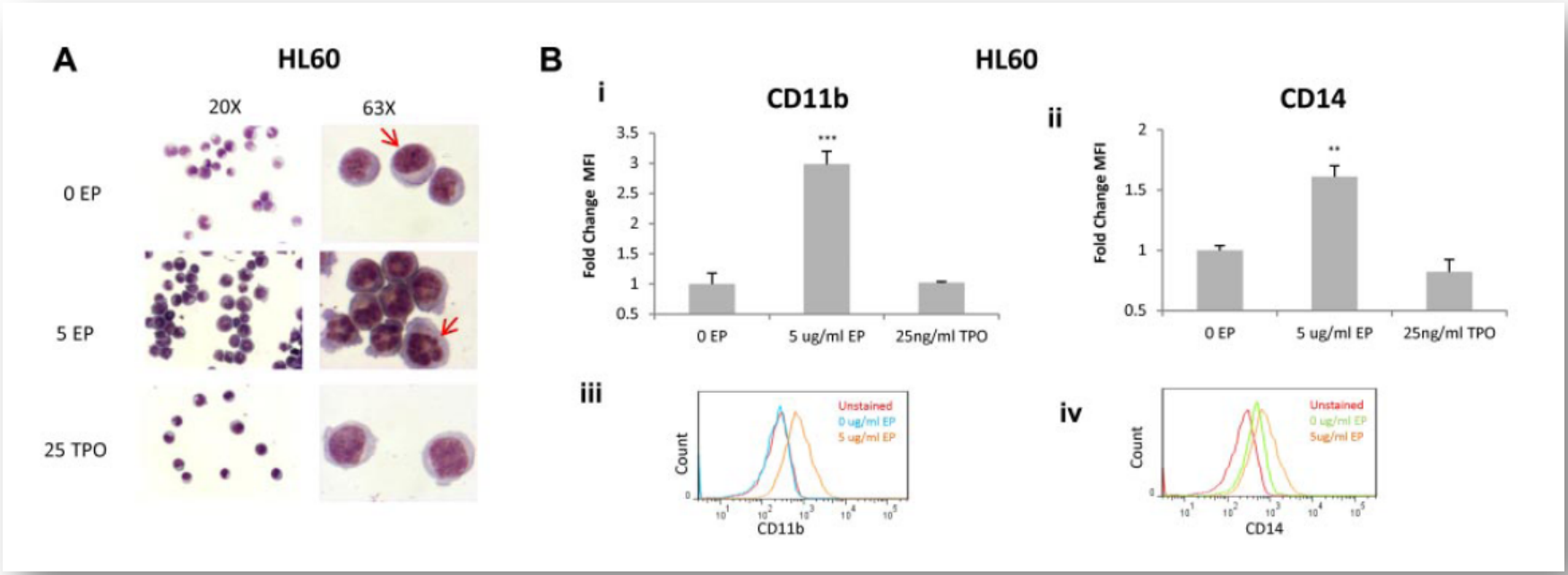
Eltrombopag and leukemic cells

Eltrombopag (EP) inhibits the growth of human (HL60) and murine (URE) leukemia cells



Blood 2012;120:386

Eltrombopag (EP) induces differentiation of human leukemia cell lines



Blood 2012;120:386

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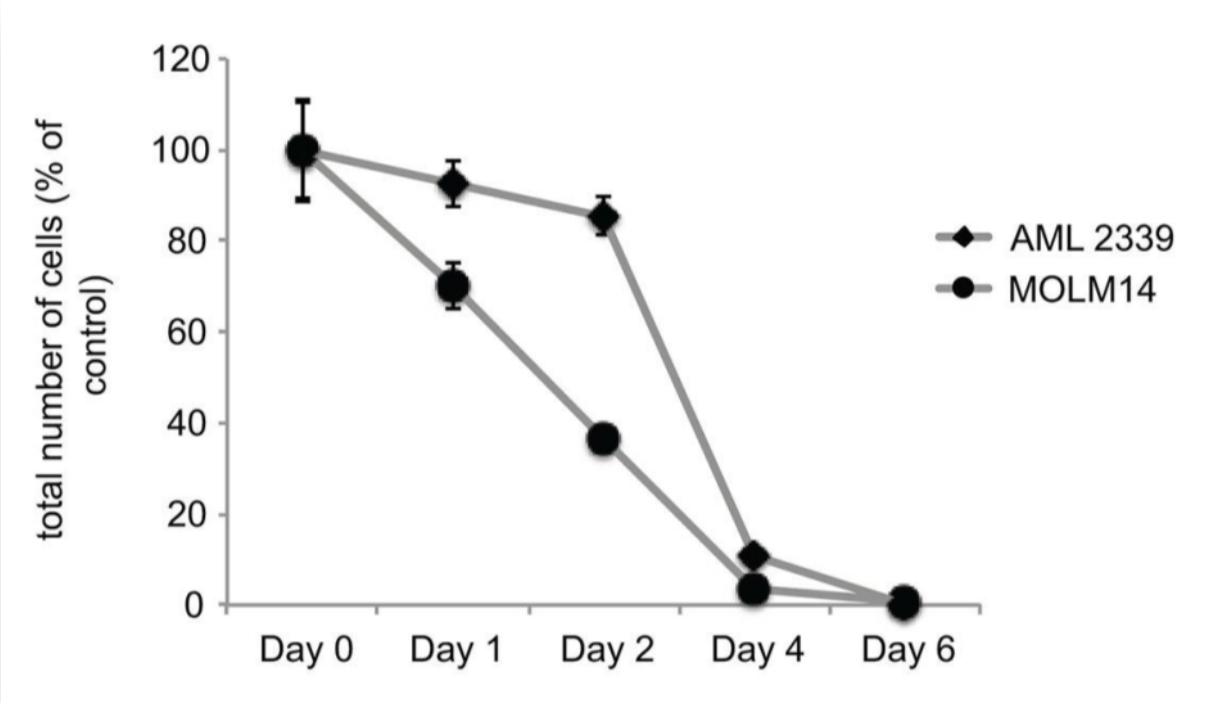
Published online 2015 Apr 27. doi: 10.1371/journal.pone.0126691

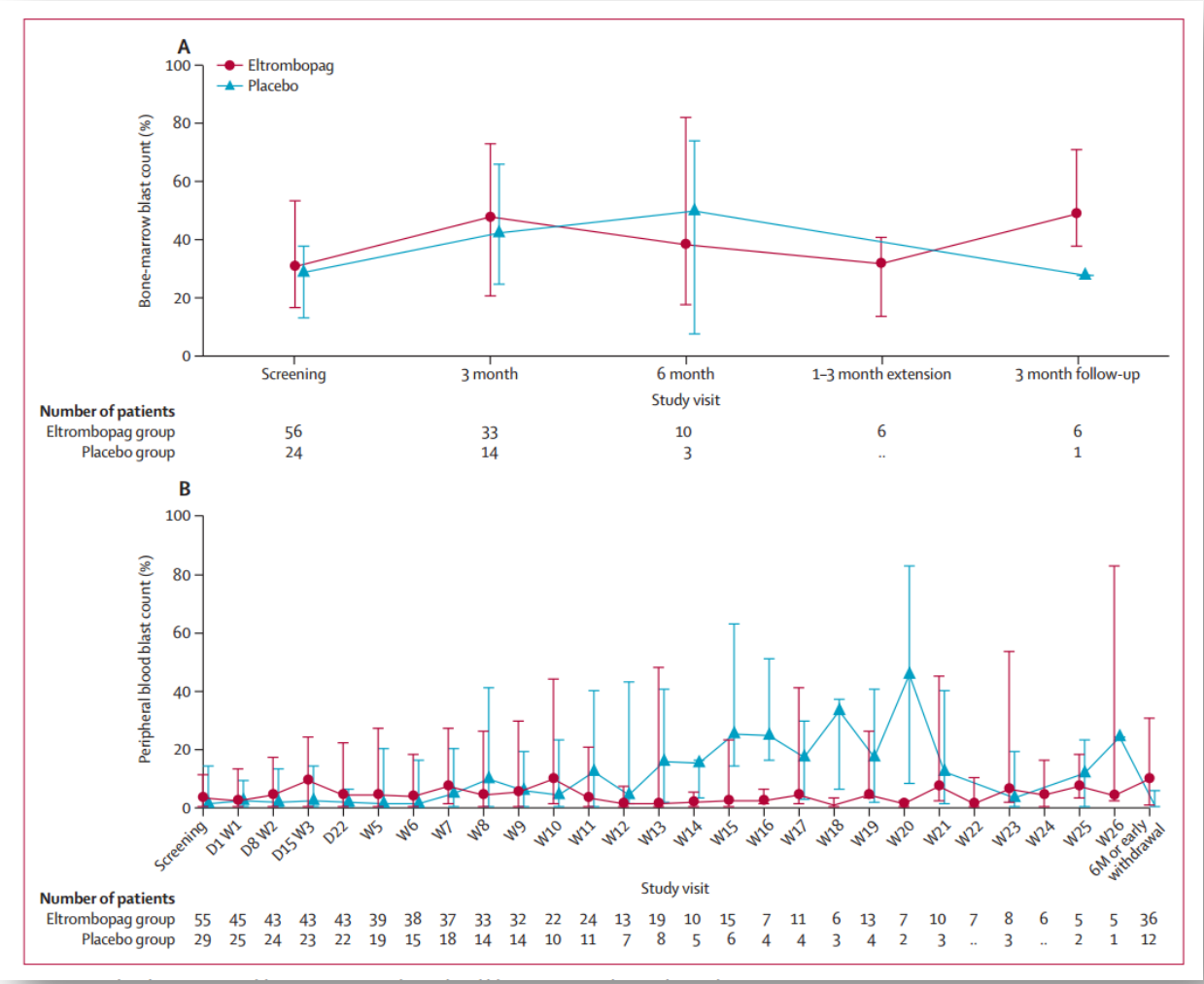
Eltrombopag Modulates Reactive Oxygen Species and Decreases Acute Myeloid Leukemia Cell Survival

Anna Kalota,[1] Mary A. Selak,[2] Laura A. Garcia-Cid,[1] and Martin Carroll[1,*]

Time course of the response to 5 µM eltrombopag in representative primary AML sample and MOLM14 cell line



Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia *Lancet Haematol 2015 2: e417–26*



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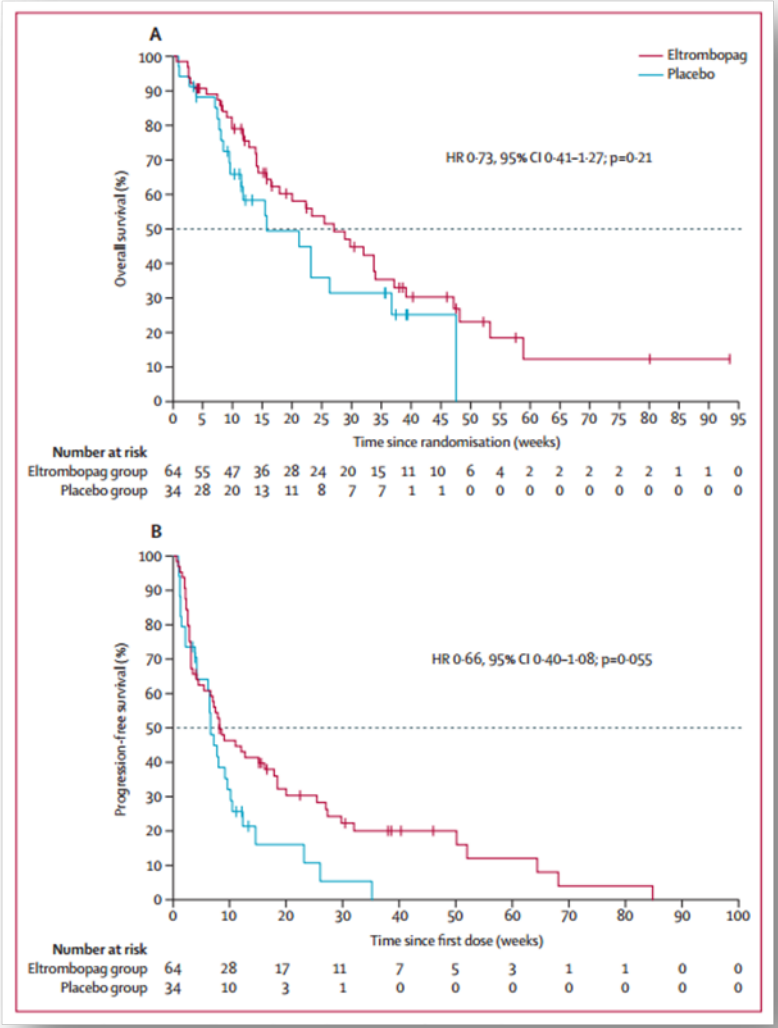
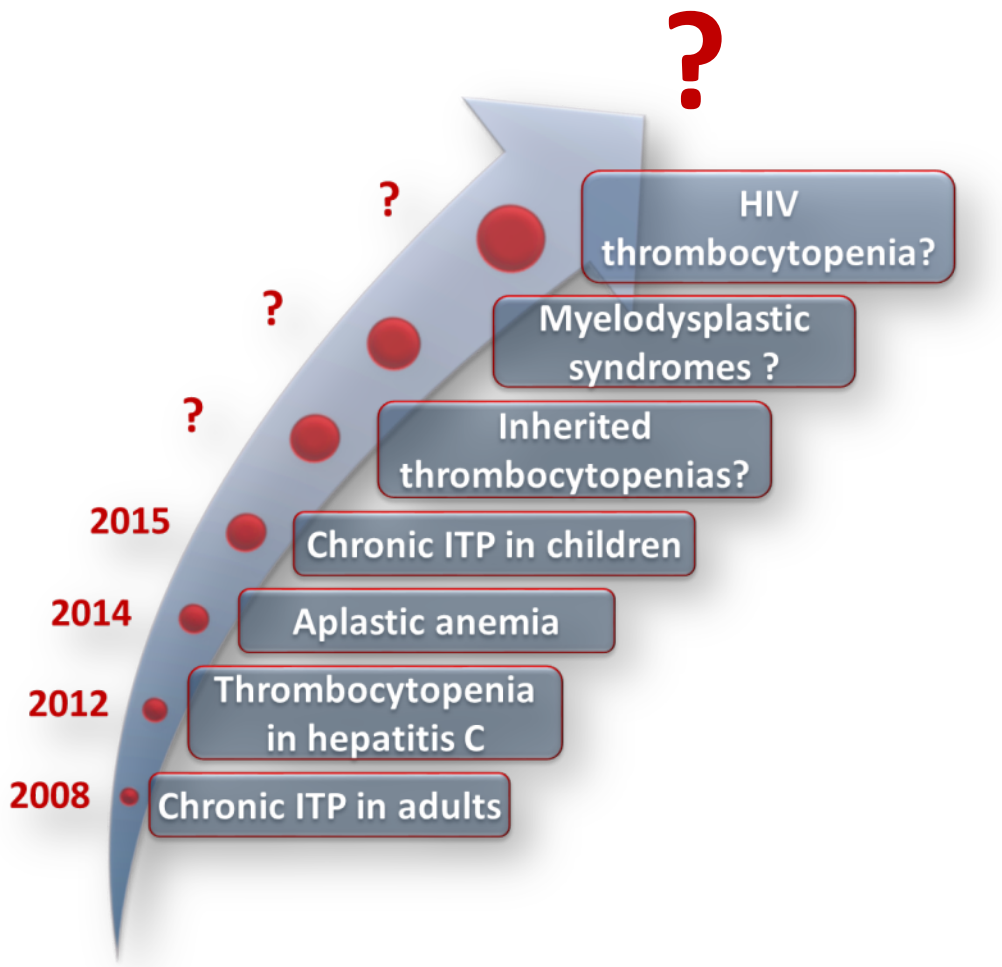


The increasing indications for thrombopoietin mimetics



I TPO MIMETICI

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