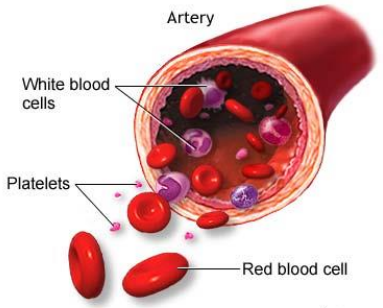
Imperial College London

Platelets, numbers and alternative functions 2018

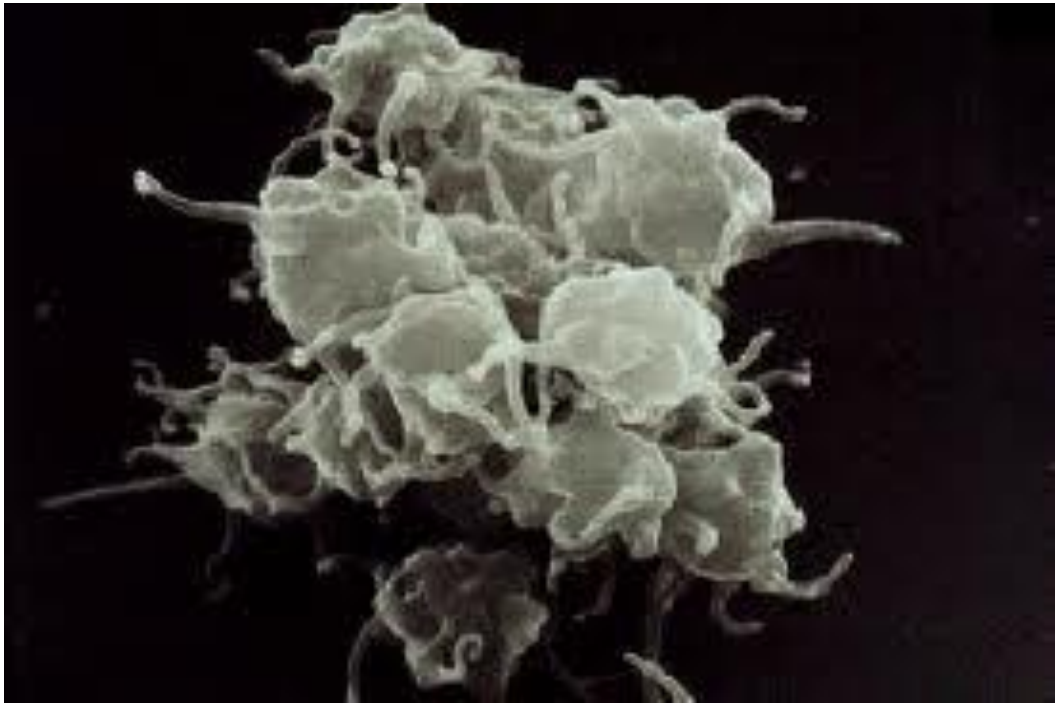
Nichola Cooper
Hammersmith Hospital
Imperial College

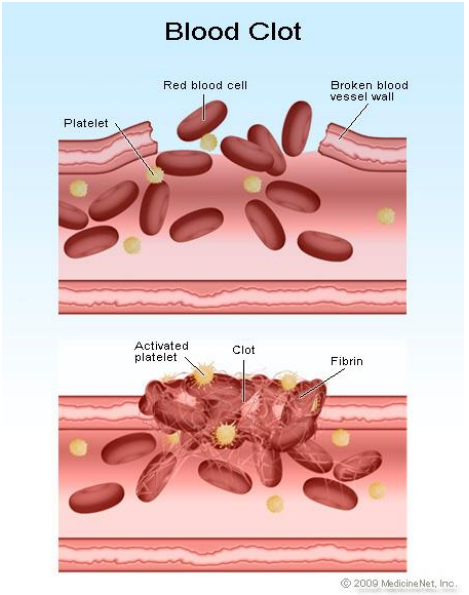


Discussion points today

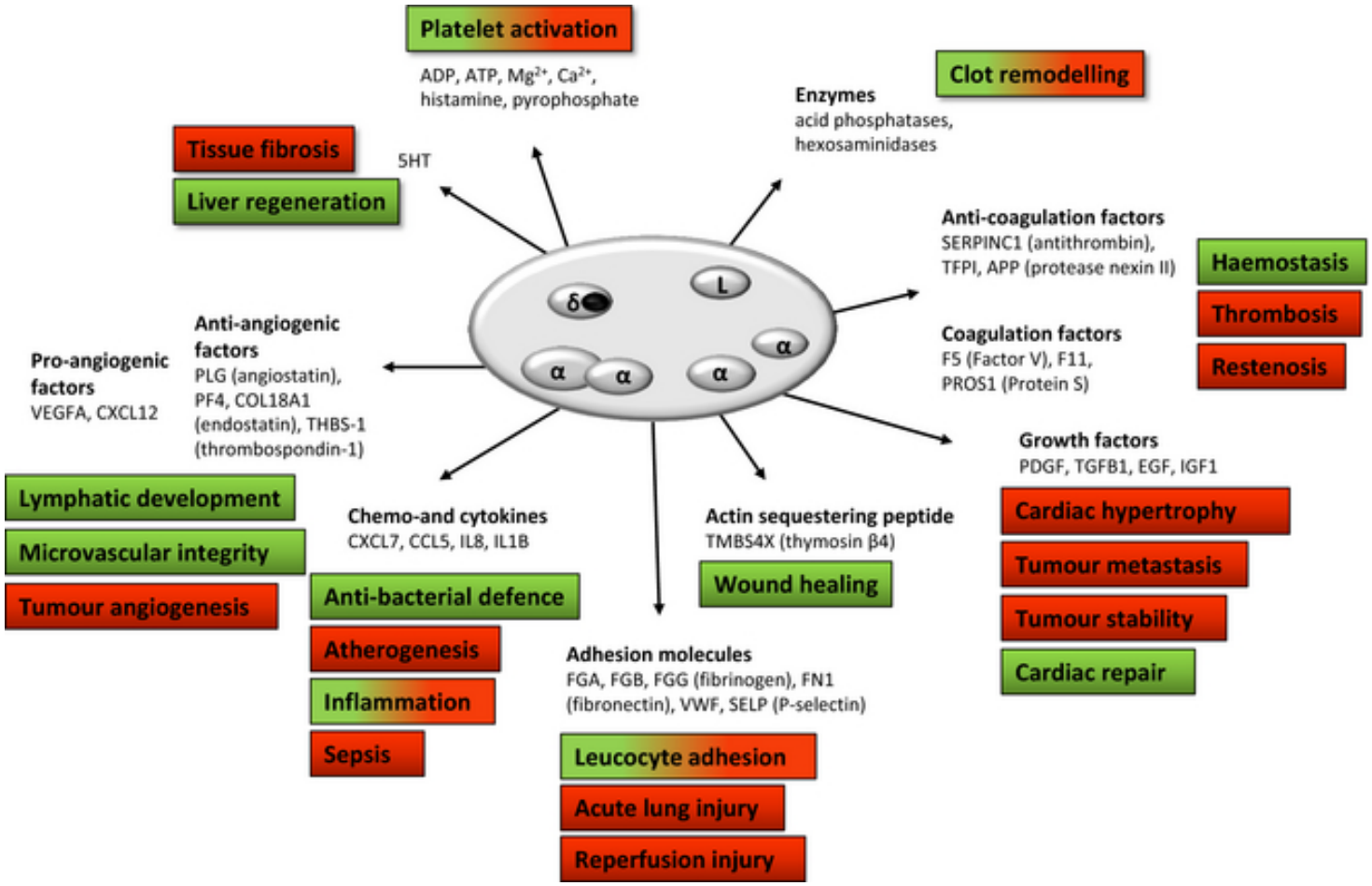
- What do platelets do beyond clot formation?
- How are platelets made?
- How is the platelet count regulated? TPO
- What is the relationship of platelet count and bleeding?
- How does this relate to disease?
  - Types of thrombocytopenia
  - ITP: pathogenesis, counts and treatment

Understood role of the platelet: platelet activation and aggregation to produce a blood clot and stop/prevent bleeding





Secrets of platelet exocytosis – what do we really know about platelet secretion mechanisms?



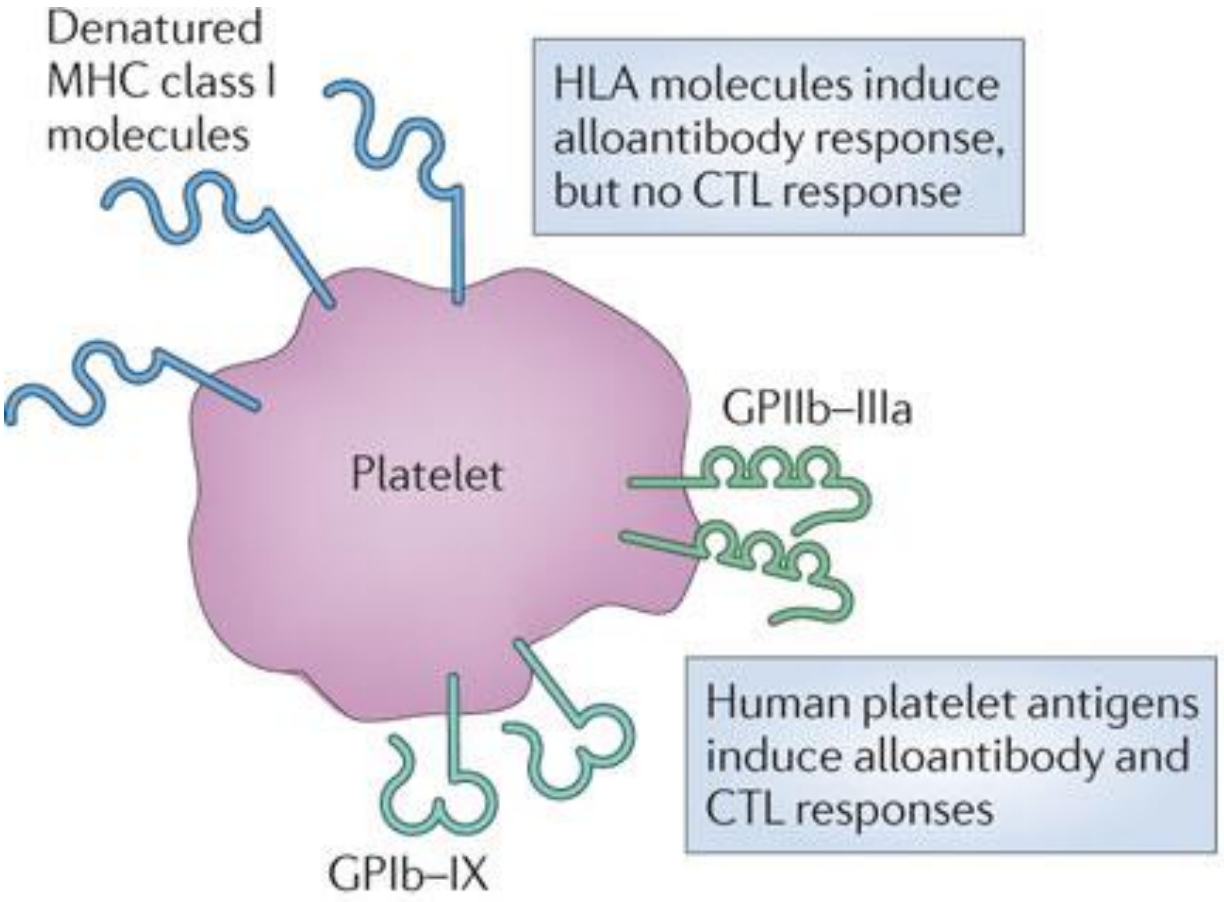
Ewelina M. Golebiewska* andAlastair W. Poole*

British Journal of Haematology
30 NOV 2013 DOI: 10.1111/bjh.12682
http://onlinelibrary.wiley.com/doi/10.1111/bjh.12682/full#bjh12682-fig-0001

Platelets and the immune continuum

John W. Semple, Joseph E. Italiano, Jr & John Freedman

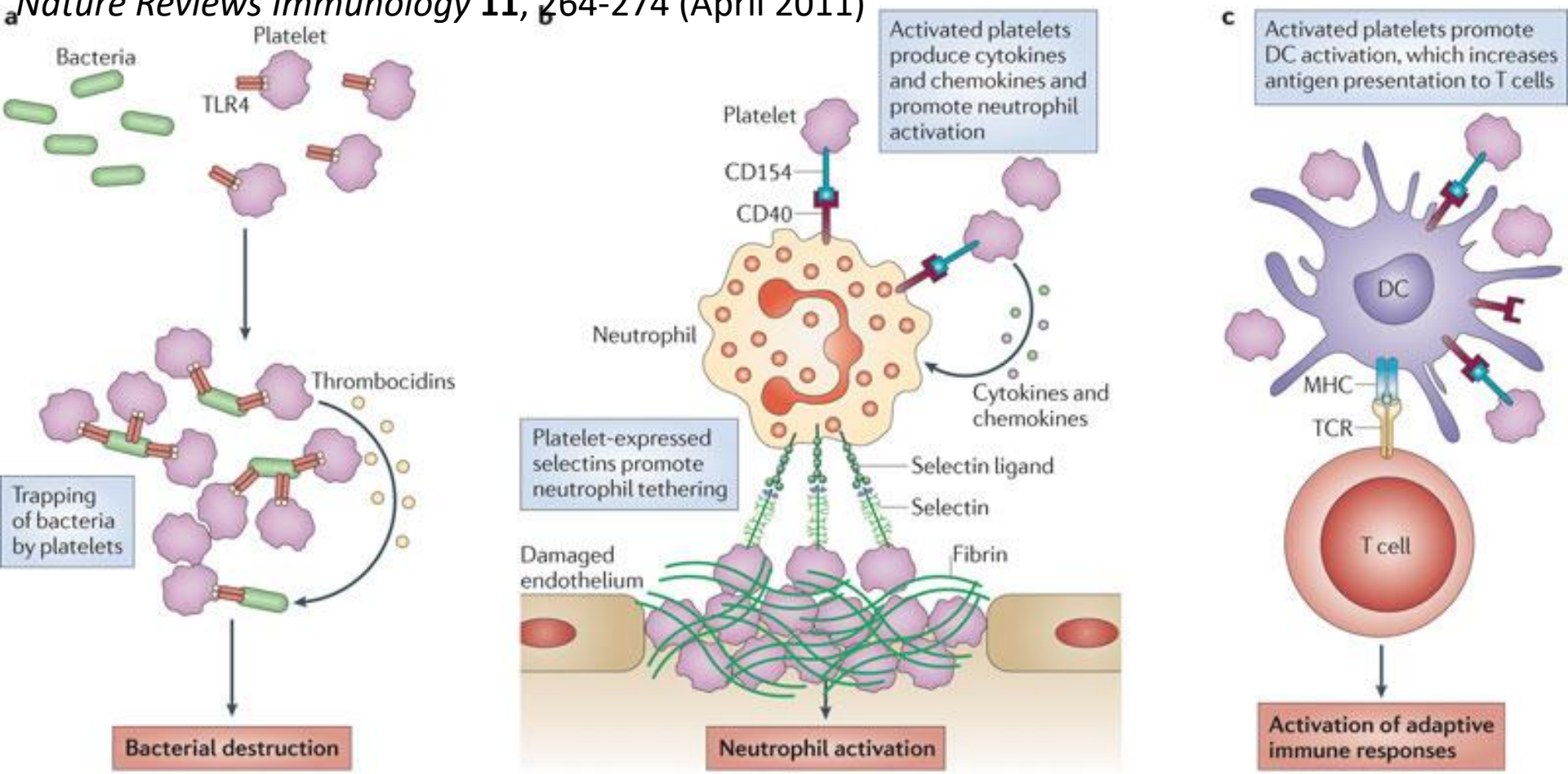
Nature Reviews Immunology **11**, 264-274 (April 2011)



Platelet interactions with the immune system

From: Platelets and the immune continuum

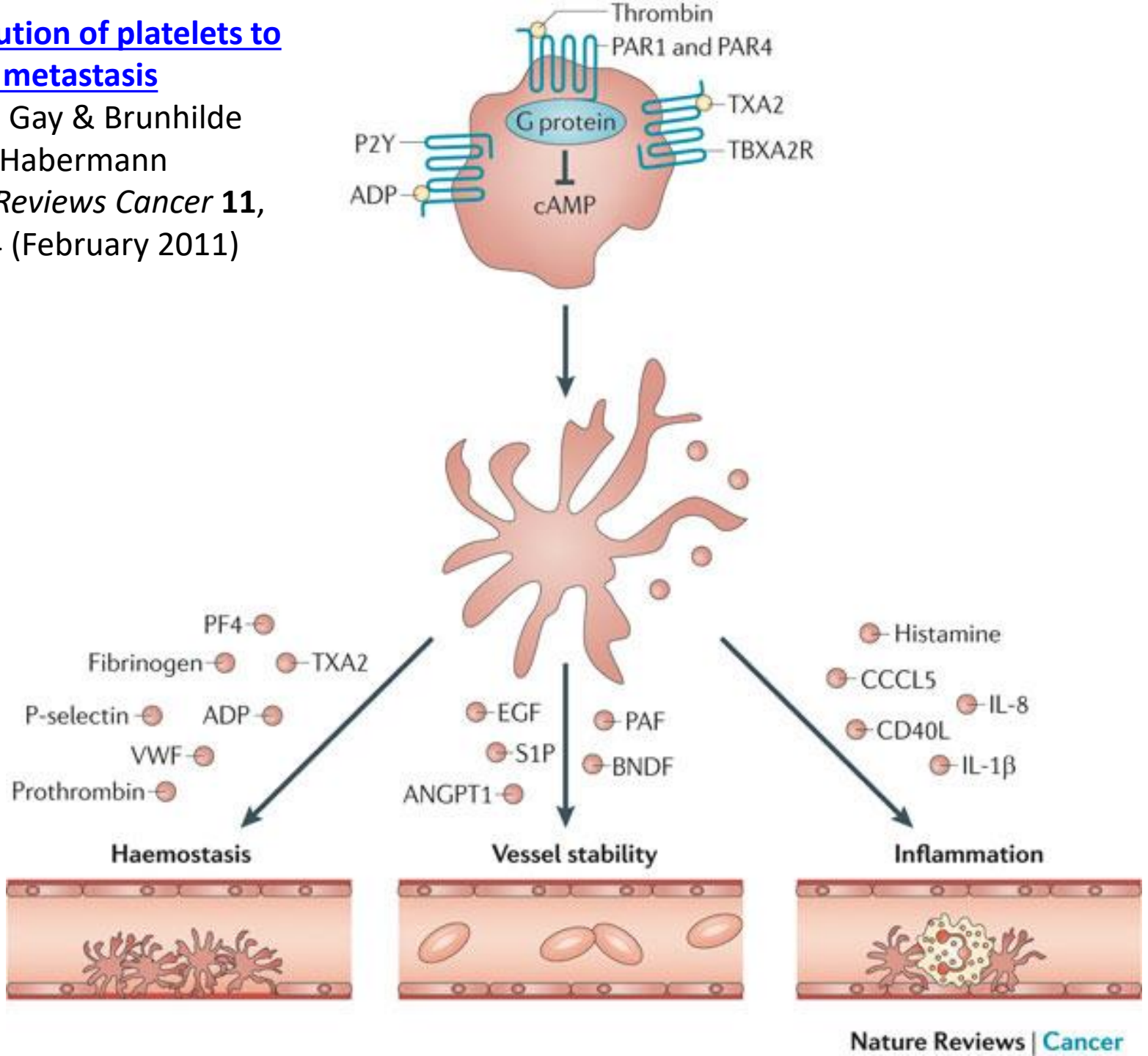
John W. Semple, Joseph E. Italiano, Jr & John Freedman
Nature Reviews Immunology **11**, 264-274 (April 2011)

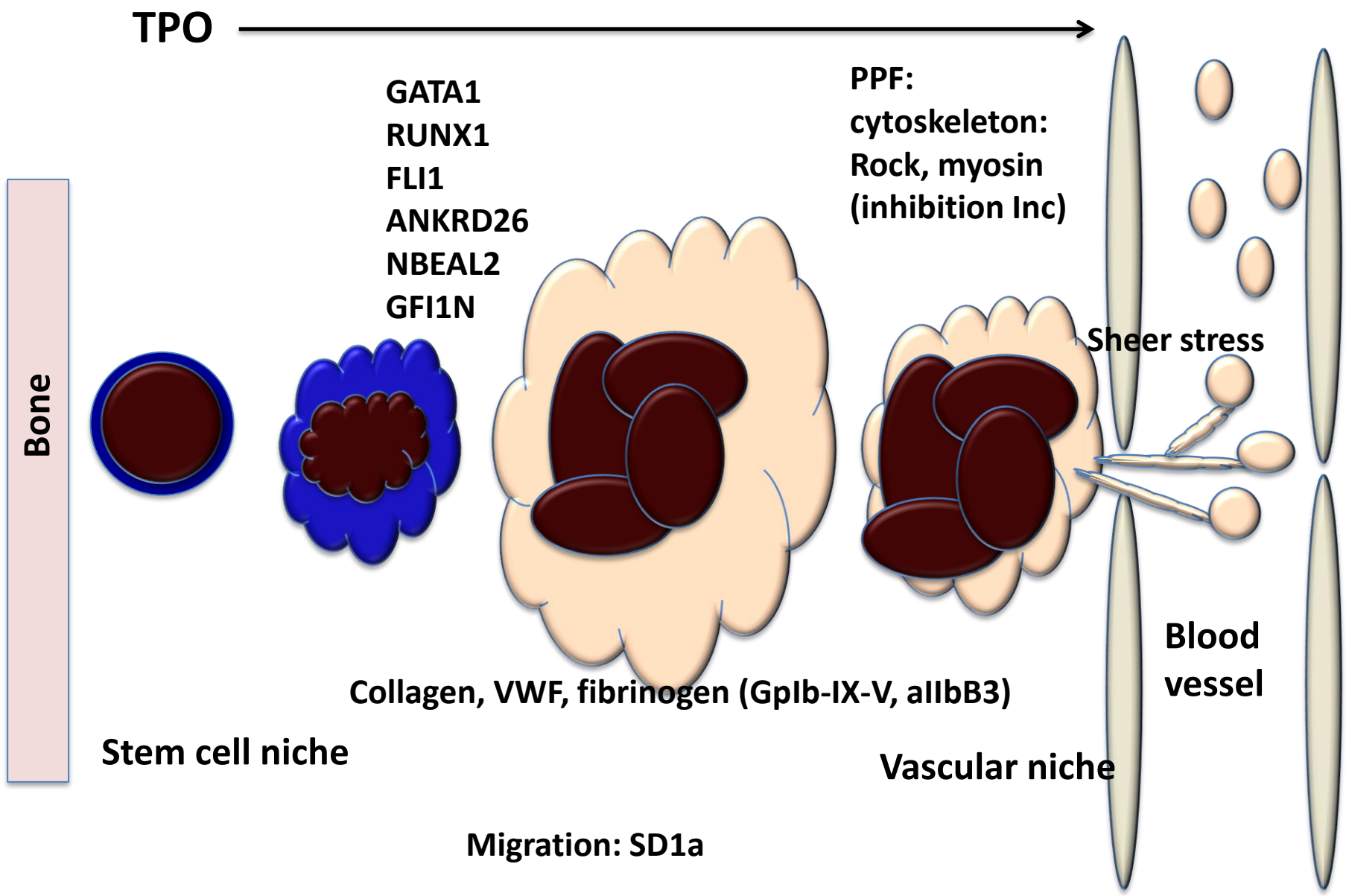


Contribution of platelets to tumour metastasis

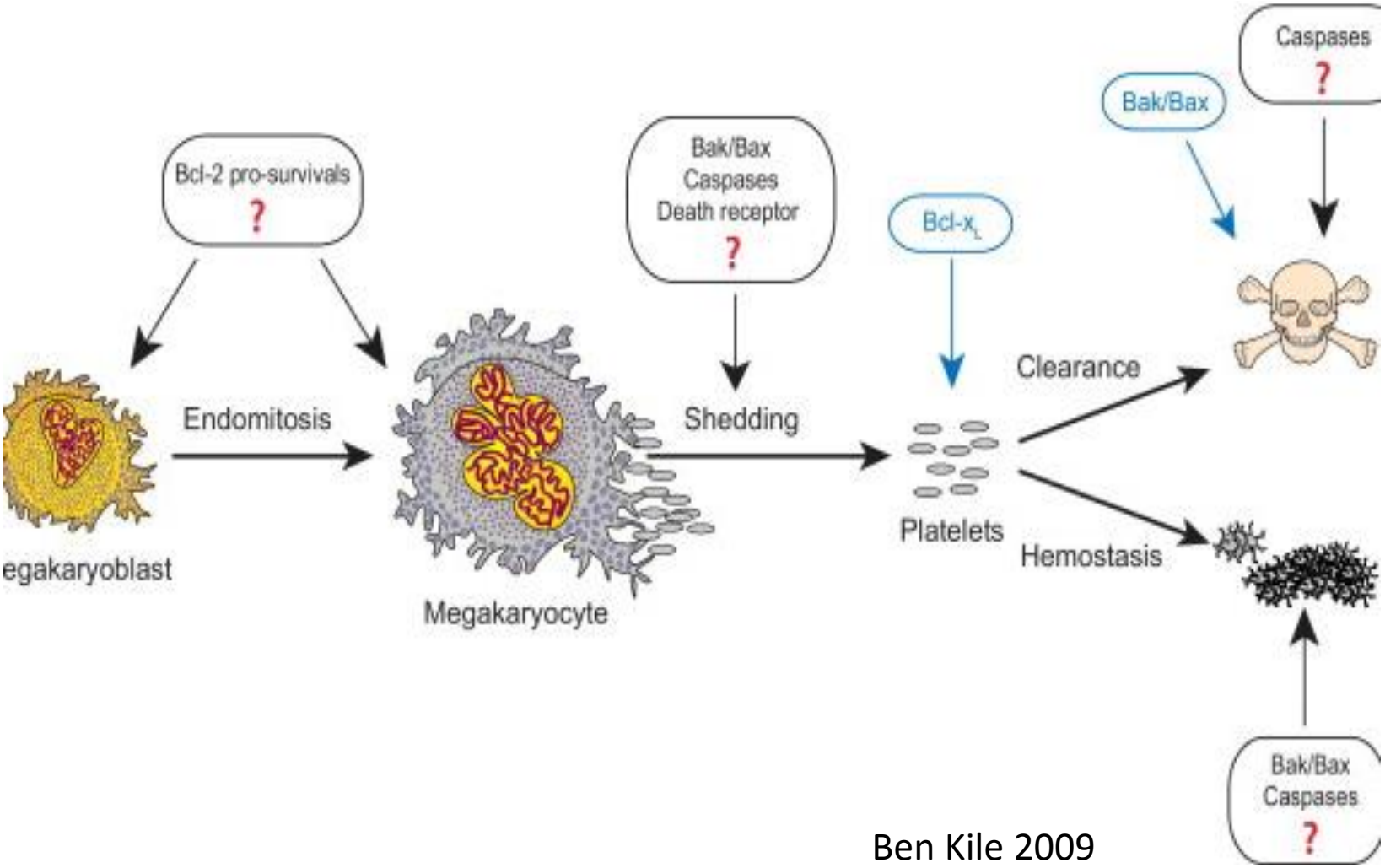
Laurie J. Gay & Brunhilde Felding-Habermann

Nature Reviews Cancer **11**, 123-134 (February 2011)




TPO
GATA1
RUNX1
FLI1
ANKRD26
NBEAL2
GFI1N
PPF:
cytoskeleton:
Rock, myosin
(inhibition Inc)
Bone
Sheer stress
Blood
vessel
Collagen, VWF, fibrinogen (GpIb-IX-V, aIIbB3)
Stem cell niche
Vascular niche
Migration: SD1a
Can you Influence this part?: MSCs, Notch, Stem Regenin-1, HES-1, PU.1

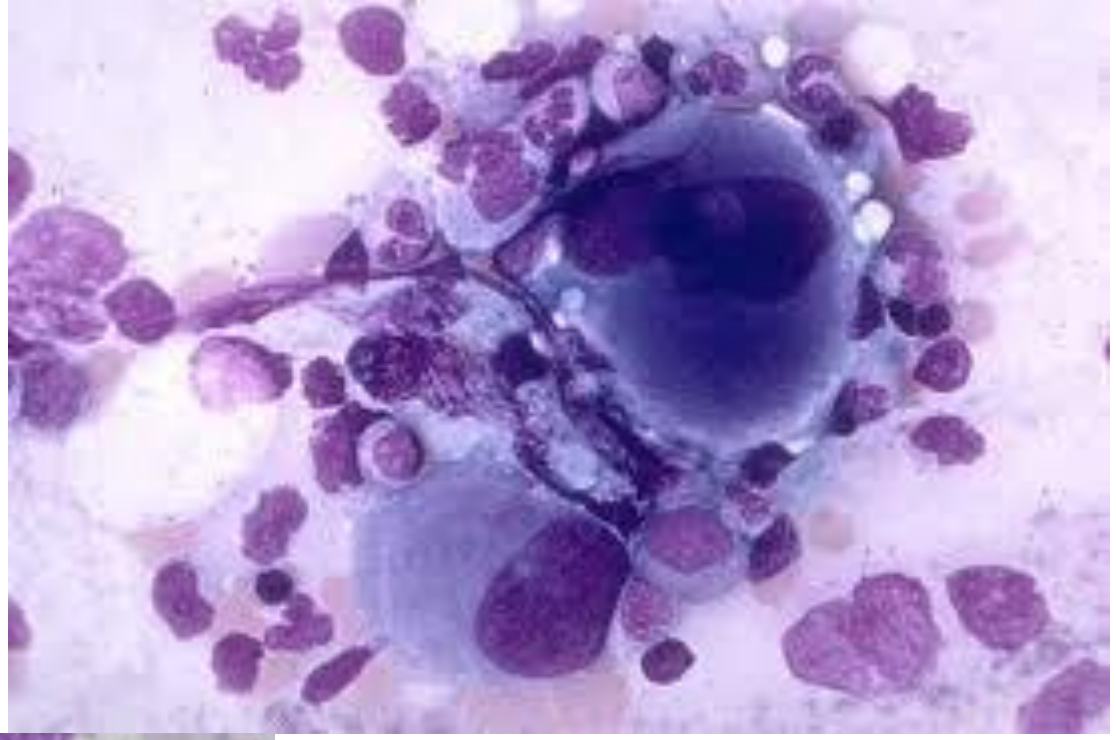
The platelet has a specific life span of 10 days, then is programmed to be cleared (if not activated)

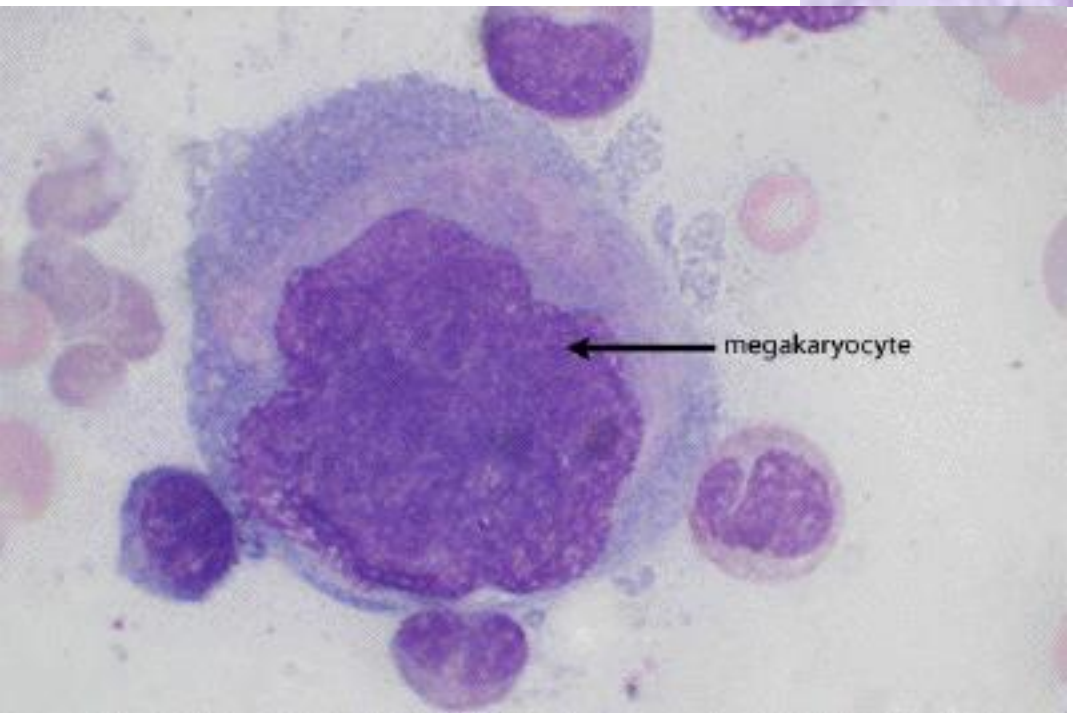


Ben Kile 2009

Each megakaryocyte produces 2000 to 3000 platelets

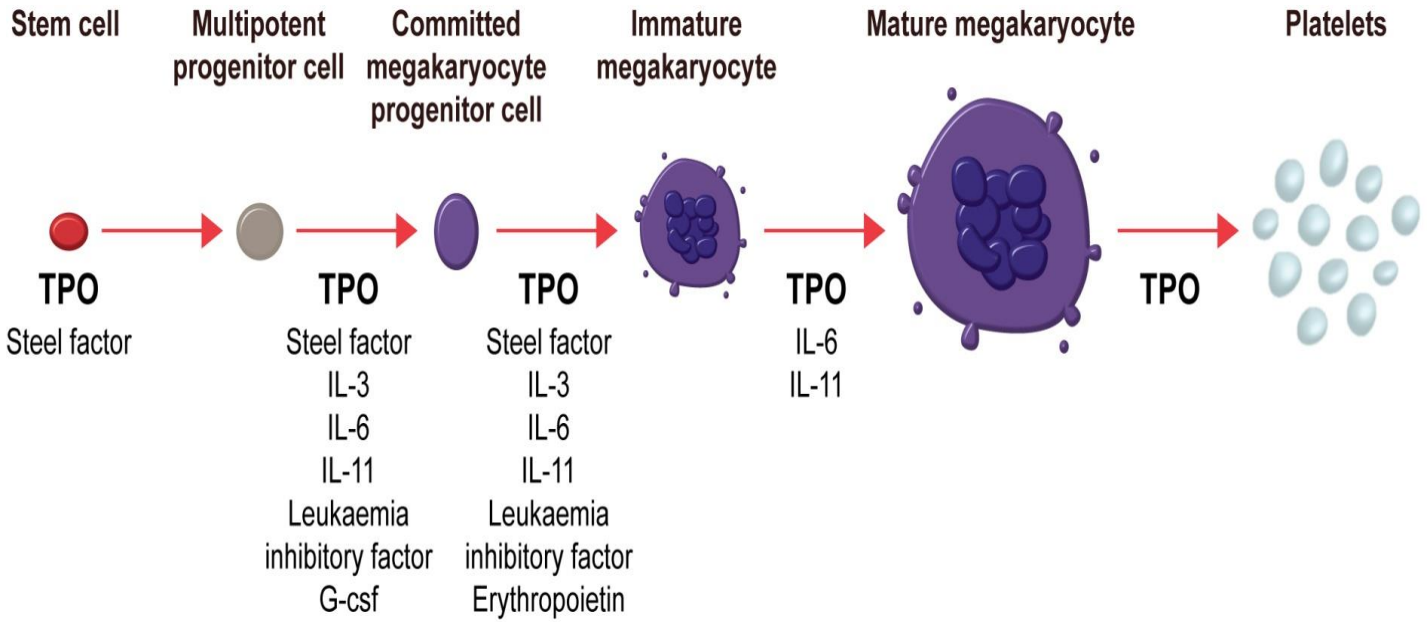
Platelets circulate for 7 to 10 days





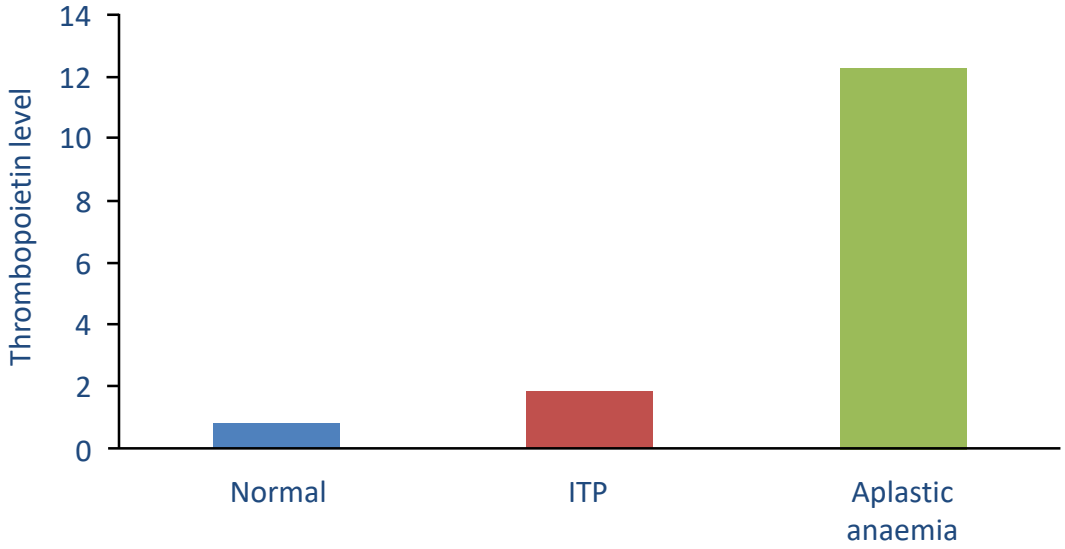
About a third of platelets are kept in the spleen

TPO – principle regulator of platelet production



1. Afdhal N.H. and McHutchison. Aliment Pharmacol Ther 2007.**26** (Suppl 1), 29-39: 2. Newland, A. Semin Hematol **44**(Suppl 5):S35-s45

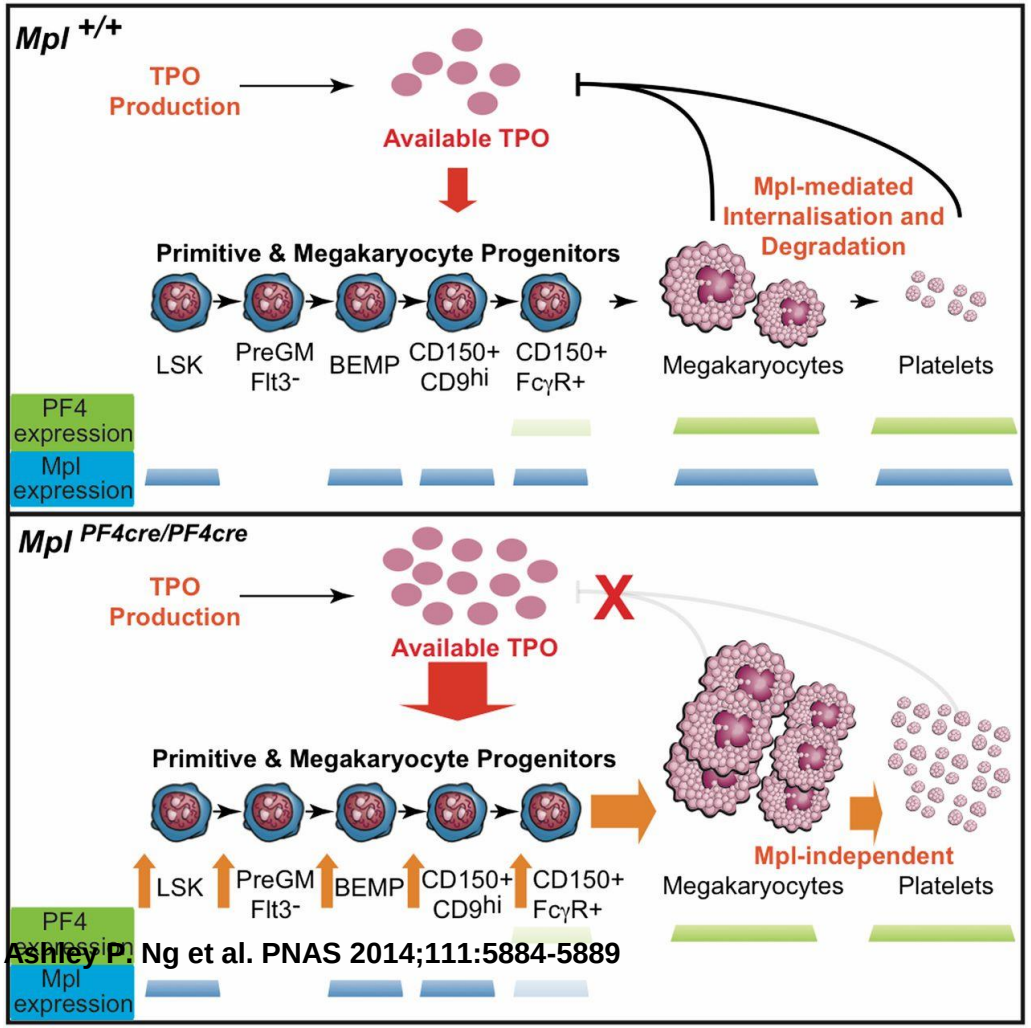
Thrombopoietin is lower in ITP than other thrombocytopenic disorders



- No correlation between platelet count and TPO levels in patients with ITP[1]
- No significant difference in TPO levels between patients with ITP and controls[2]

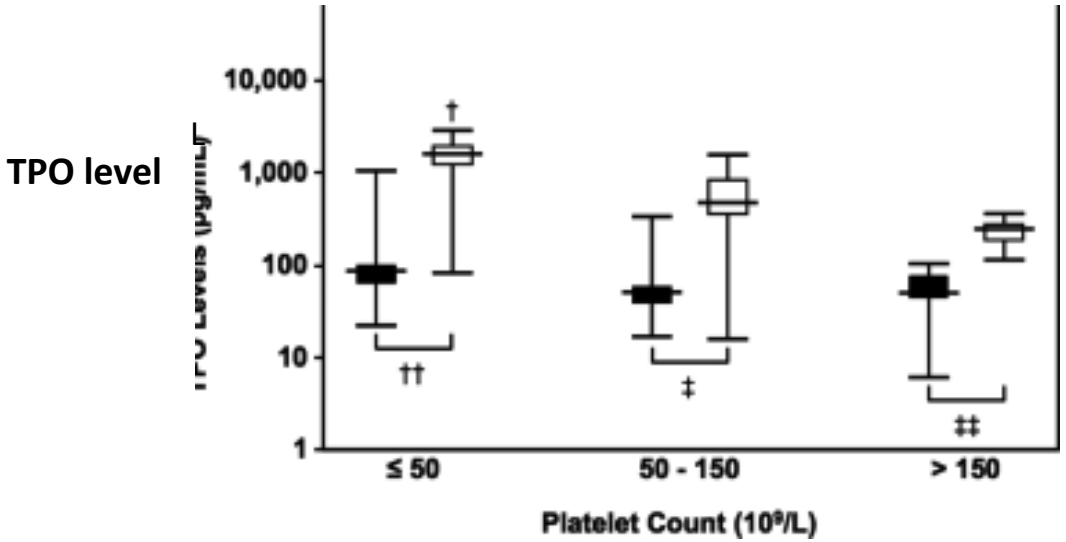
- 1. Kosugi S *et al. Br J Haematol* 2003;93:704–706;
  2. Aledort LM *et al. Am J Hematol* 2004;76:205–213

Model for regulation of TPO and control of megakaryopoiesis.



Ashley P. Ng et al. PNAS 2014;111:5884-5889

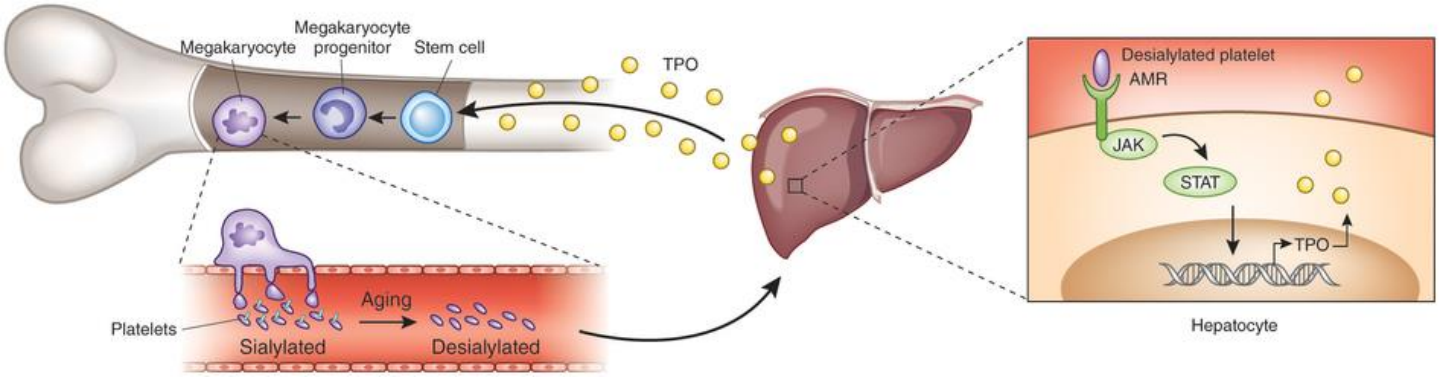
Thrombopoietin levels may distinguish between consumptive or hypoproliferative causes of thrombocytopenia



■ Consumptive ☐ Hypoproliferative

Maker et al Haematology 2013: Thrombopoietin levels in patients with disorders of platelet production: Diagnostic potential and utility in predicting response to TPO Receptor agonists

Ashwell–Morell receptor in hepatocytes: A possible method of platelet regulation

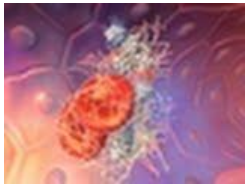


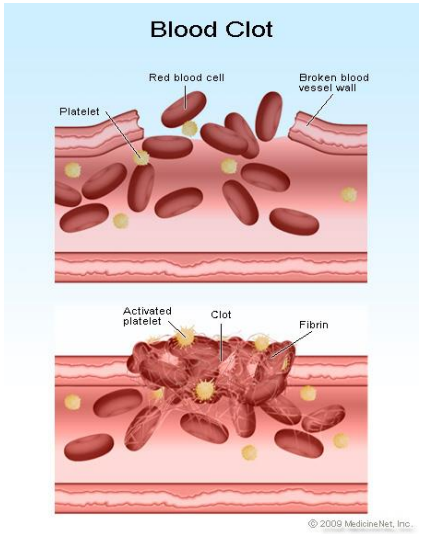
Old platelets are recognized by the Ashwell–Morell receptor (AMR) in hepatocytes causing thrombopoietin production

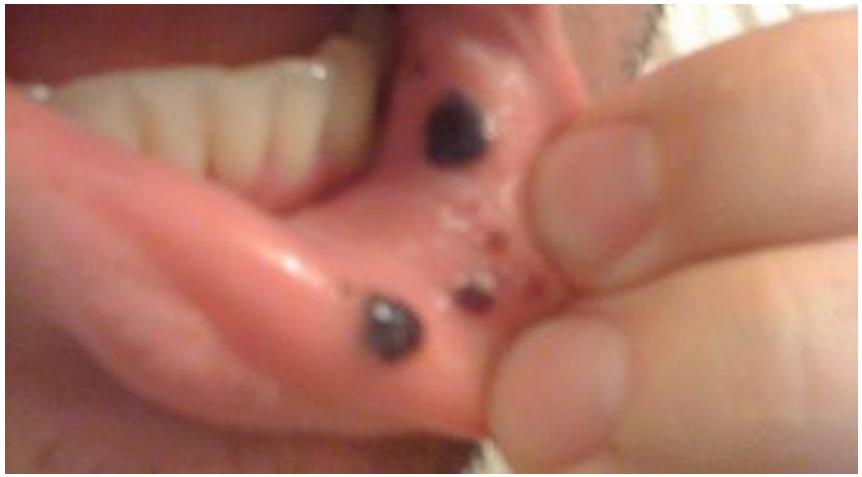
Kile BT. *Nat Med* 2015;21:11–12

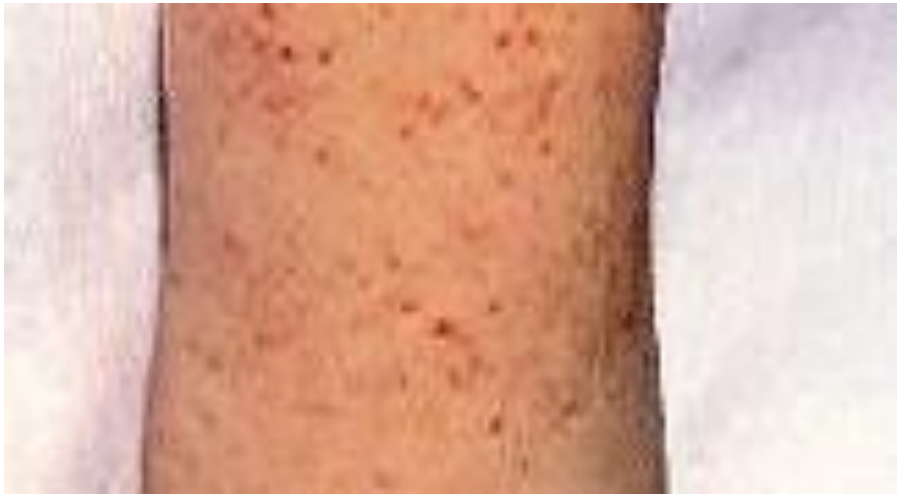
Small platelets MPV <7fL	Normal platelets MPV 7-11 fL	Large/Giant platelets, MPV >11 fL
Wiskott-Aldrich syndrome	Familial platelet disorder/AML	MHY9-related diseases May-Hegglin anomaly Sebastian syndrome Fechtner syndrome Epstein syndrome
X-linked thrombocytopenia	Chromosome 10/THC2	Bernard-Soulier syndrome
	Congenital Amegakaryocytic thrombocytopenia	Paris-Trousseau thromboctopenia/Jacobsen syndrome
	Thrombocytopenia and absent radii	Velcardiofacial/DiGeorge syndrome
		GATA1 mutation
		Grey platelet syndrome

Relative bleeding risk at different platelet counts









Is there a platelet count at which serious bleeding occurs?

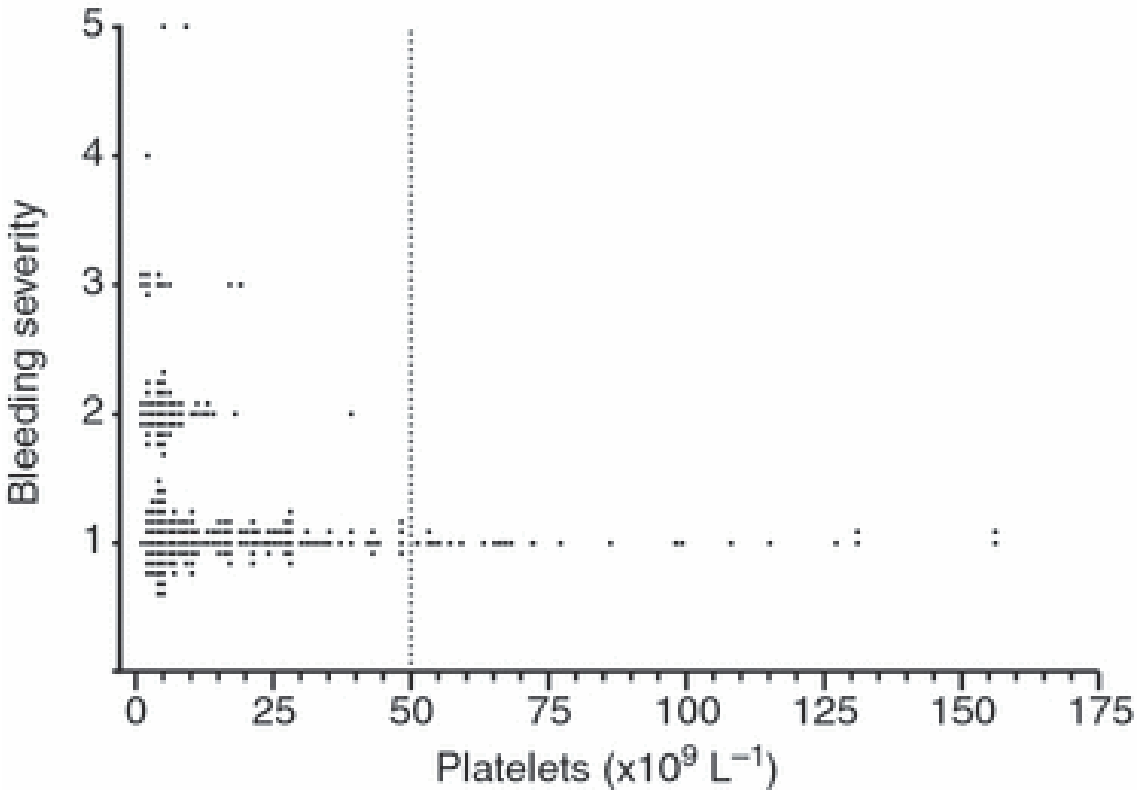
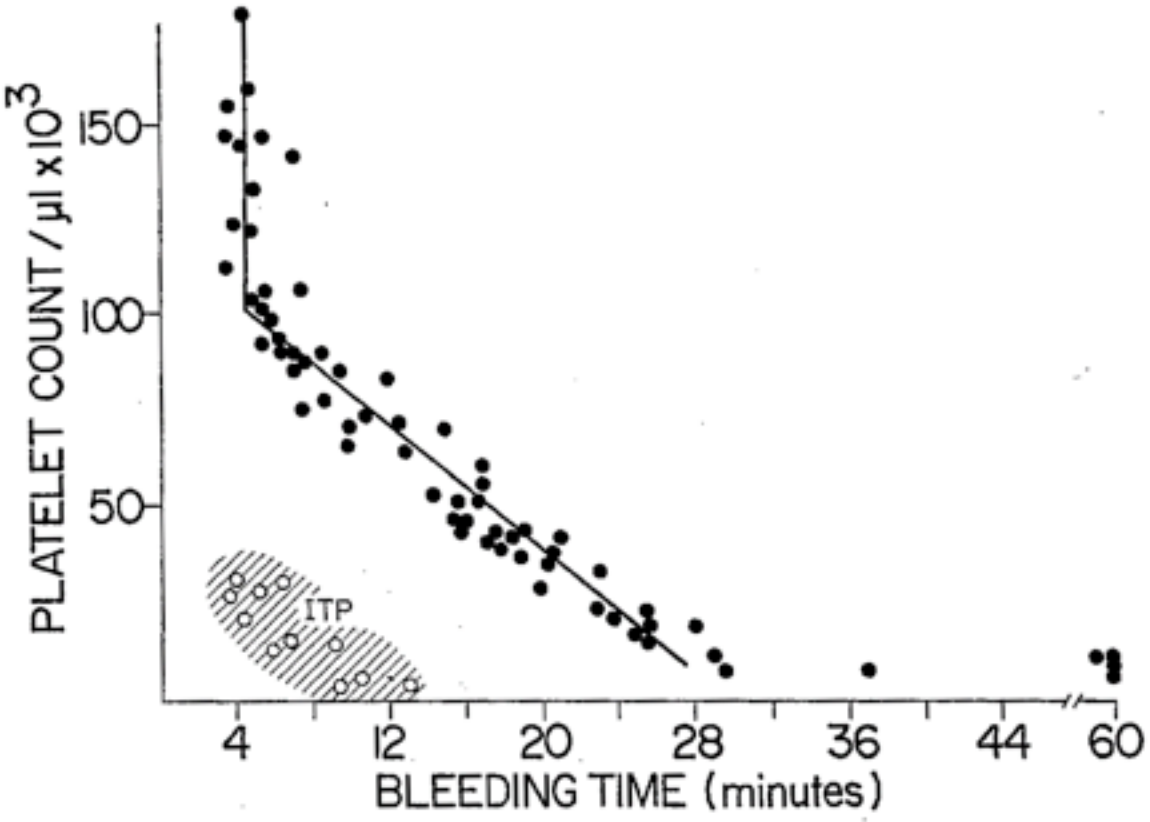


Figure 3. Distribution of bleeding adverse events by severity and platelet count in both treatment groups in the phase 3 studies. Each point represents one bleeding adverse event. One grade 1 bleeding adverse event that occurred at a platelet count of 505 × 10^9 L^{-1} is not shown

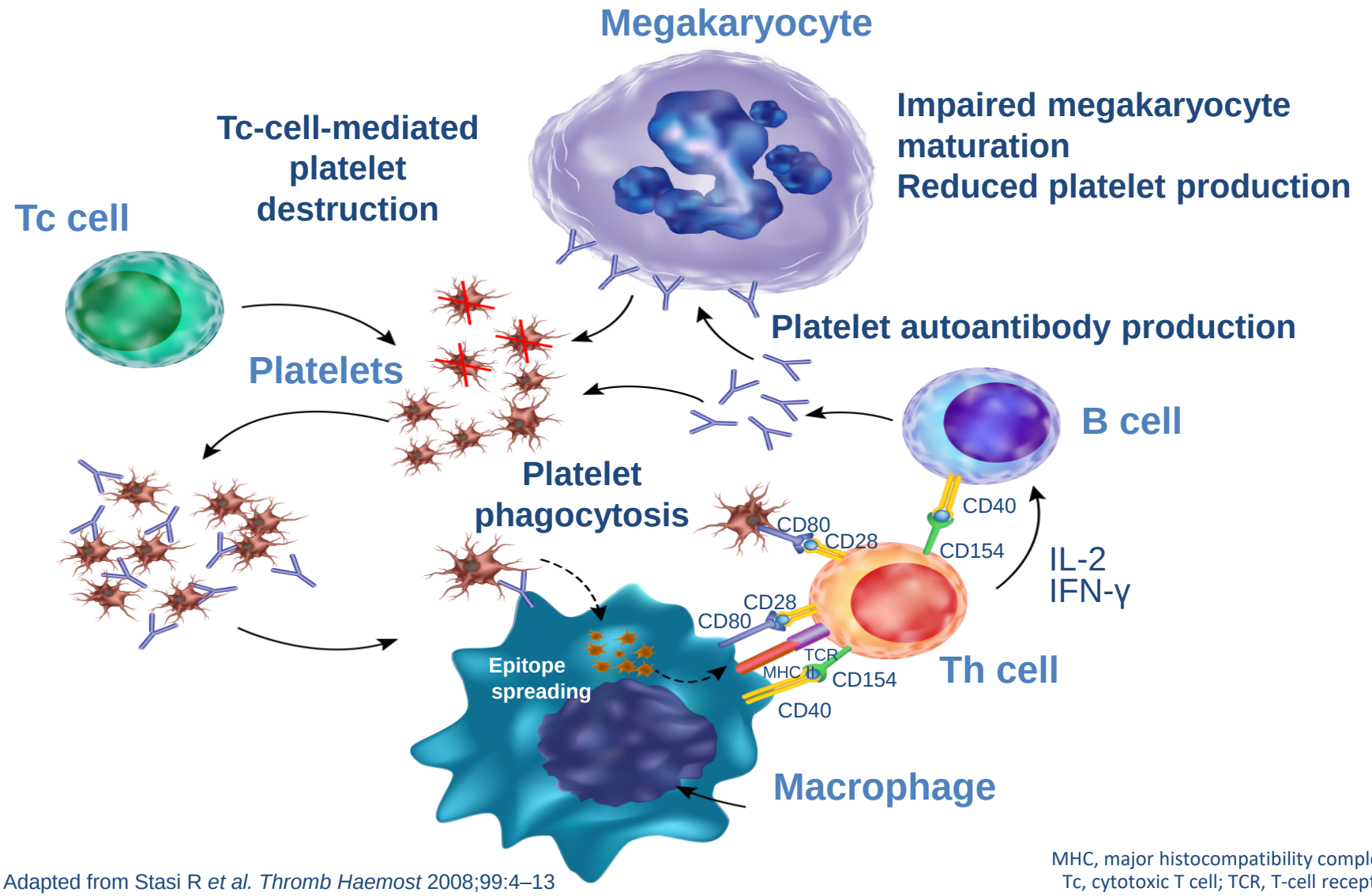
GERNSHEIMER, JTH 2010

Imperial College
London

Bleeding and ITP



Immune thrombocytopenia pathophysiology is complex involving different pathways

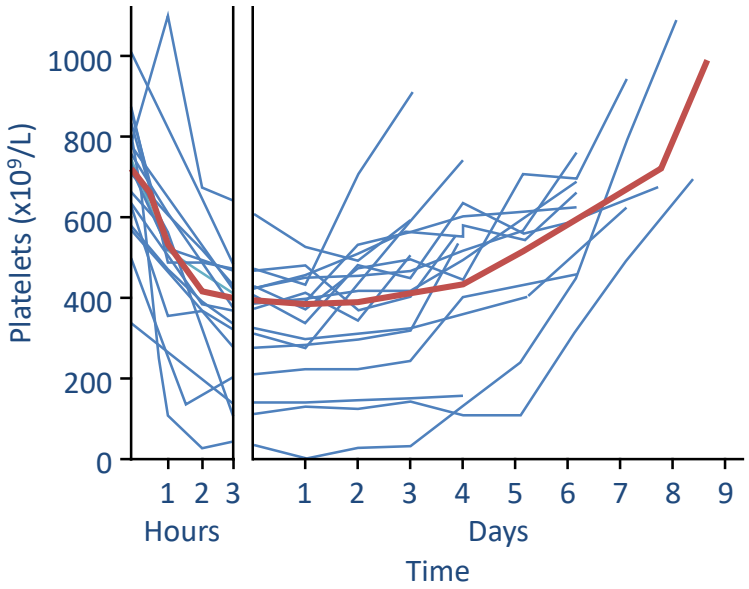


Adapted from Stasi R *et al. Thromb Haemost* 2008;99:4–13

MHC, major histocompatibility complex; Tc, cytotoxic T cell; TCR, T-cell receptor

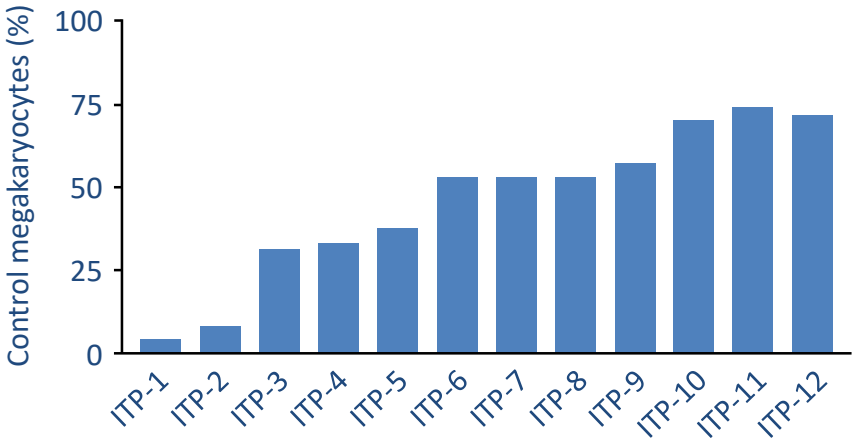
What is the evidence for immune pathology in ITP? B-cell disease

Antiplatelet antibodies: 1951[1]



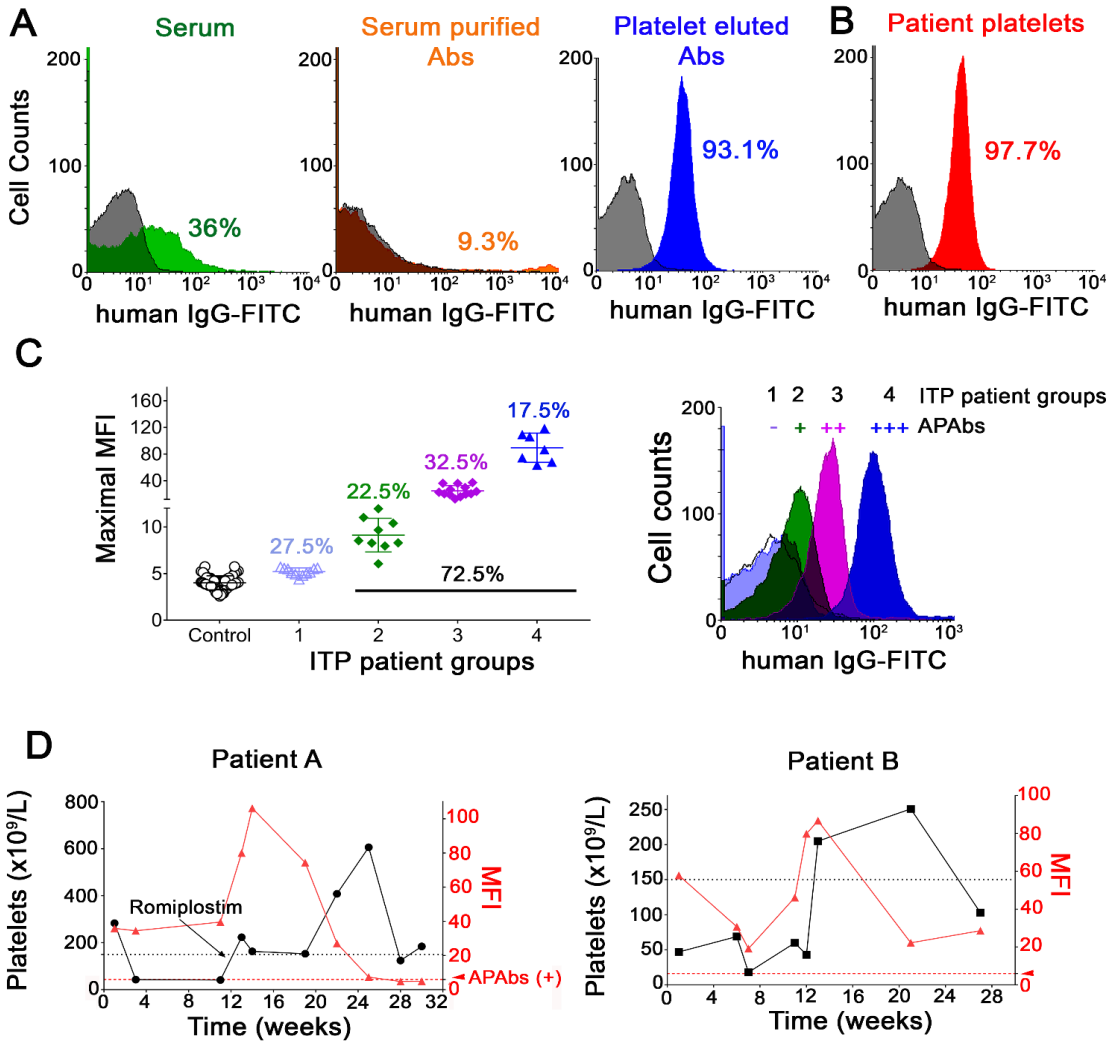
Platelet count after infusion with patient plasma

Inhibition of megakaryocytes by plasma from ITP patients: 2004[2]



1. Harrington WJ *et al. J Lab Clin Med* 1951;38:1–10;
2. McMillan R *et al. Blood* 2004;103:1364–1369

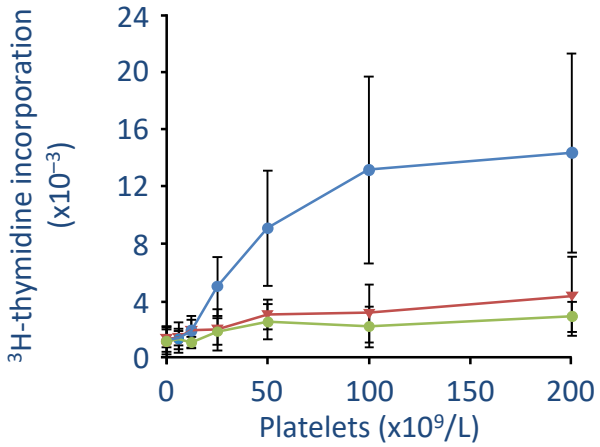
Over 70% of patients have antibodies eluted from platelets – suggestive of other specificities



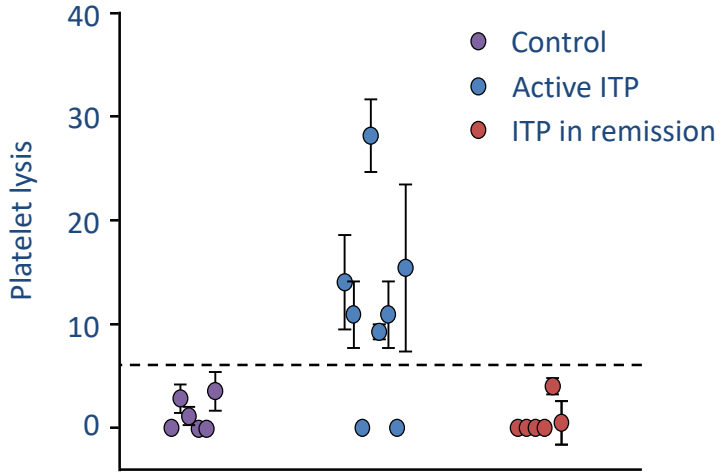
Adrienn Teraz-Orosz BJJH 2018

What is the evidence for T-cell-mediated platelet destruction in ITP?

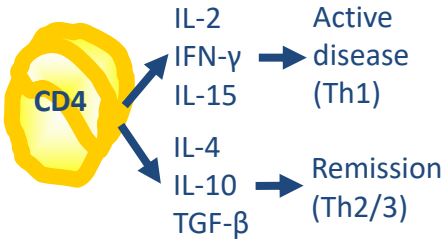
T-cell proliferation in response to own platelets and Th1-mediated disease: 1990s[1]



Cytotoxic T-cell attack against platelets: 2003[2]



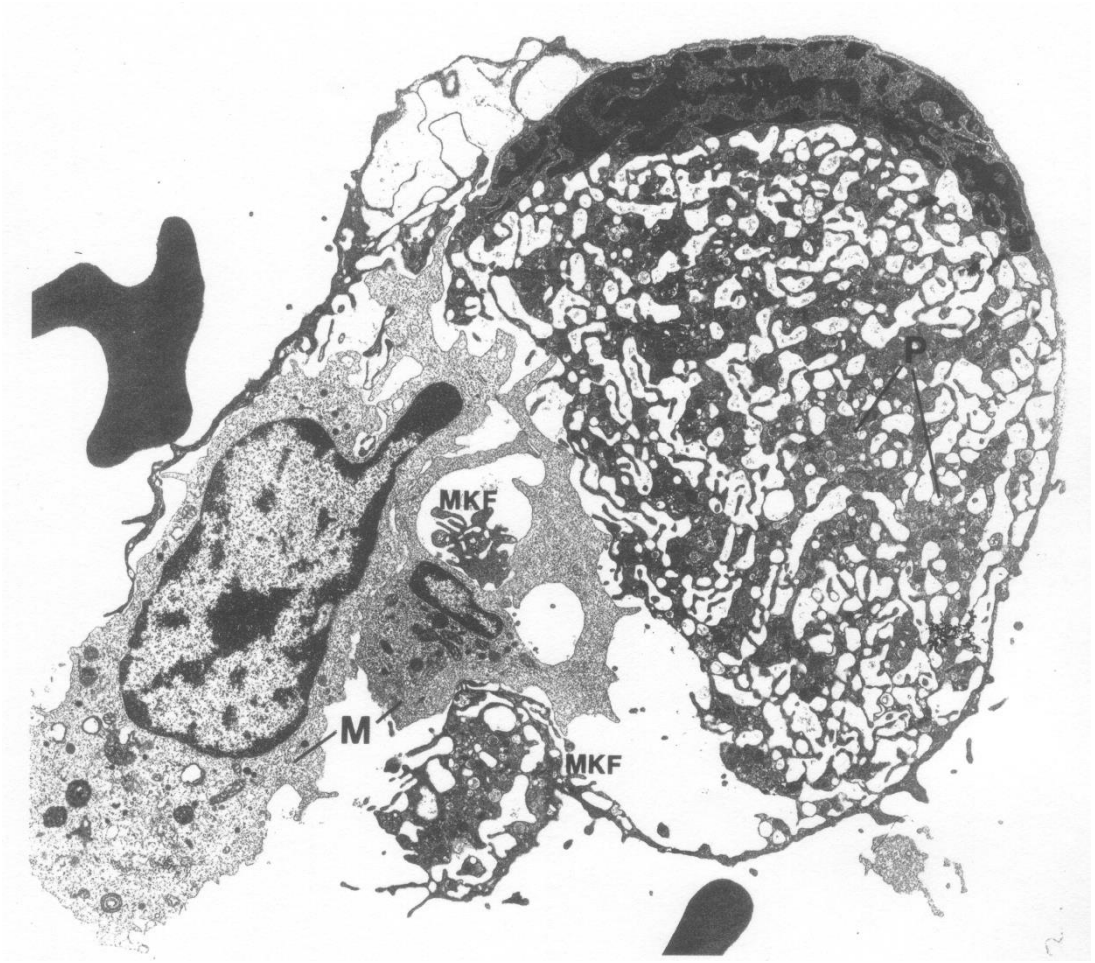
Note: Please provide reference for graph



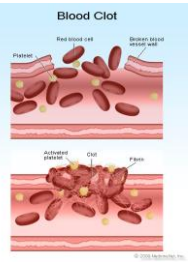
1. Semple JW & Provan D. *Curr Opin Hematol* 2012;19:357–362;
2. Olsson B *et al. Nat Med* 2003;9:1123–1124

CD, cluster of differentiation; IFN-γ, interferon-γ; IL, interleukin; TGF-β, transforming growth factor-β; Th, helper T cell

Increased apoptosis in megakaryocytes from patients with ITP

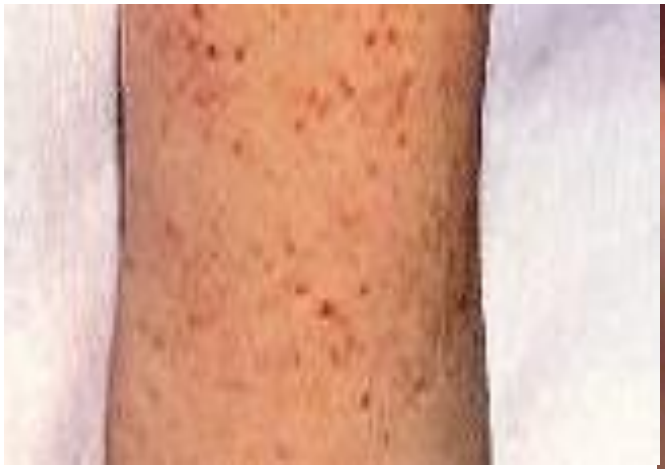


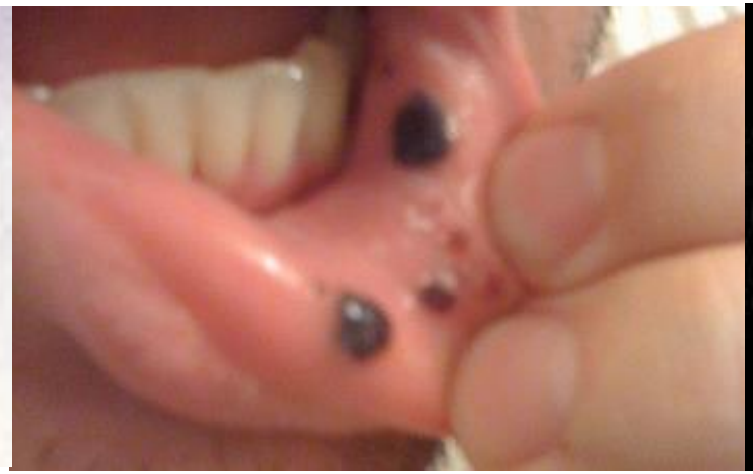
Reproduced from Stahl CP, et al. *Blood.* 1986;67:421–428, with permission from Springer.

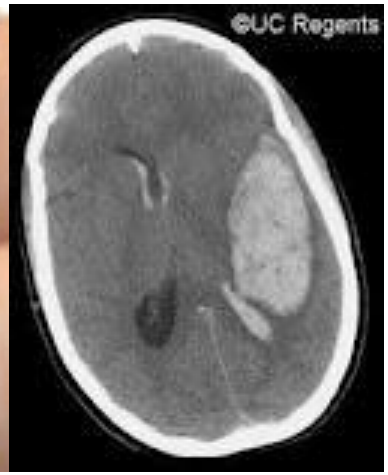


Morbidity/mortality ITP

- Majority of patients are asymptomatic despite low platelet counts
- Increased mortality only in patients with persistently low platelet counts
- Morbidity and mortality as much from complications of immunosuppressive treatment as from bleeding [1, 2]



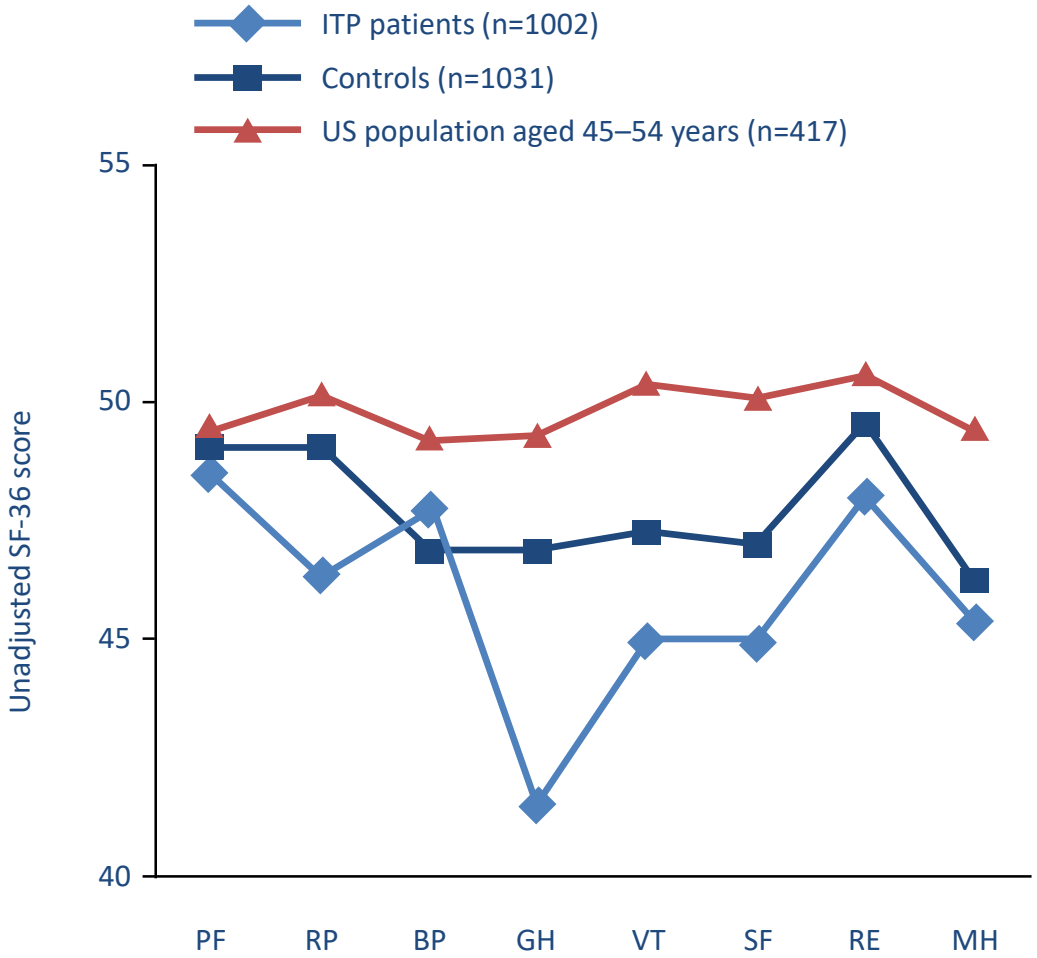




[1]Portejle et al 2000, [2]Cohen et al 2002

Patients with ITP have poor HRQoL

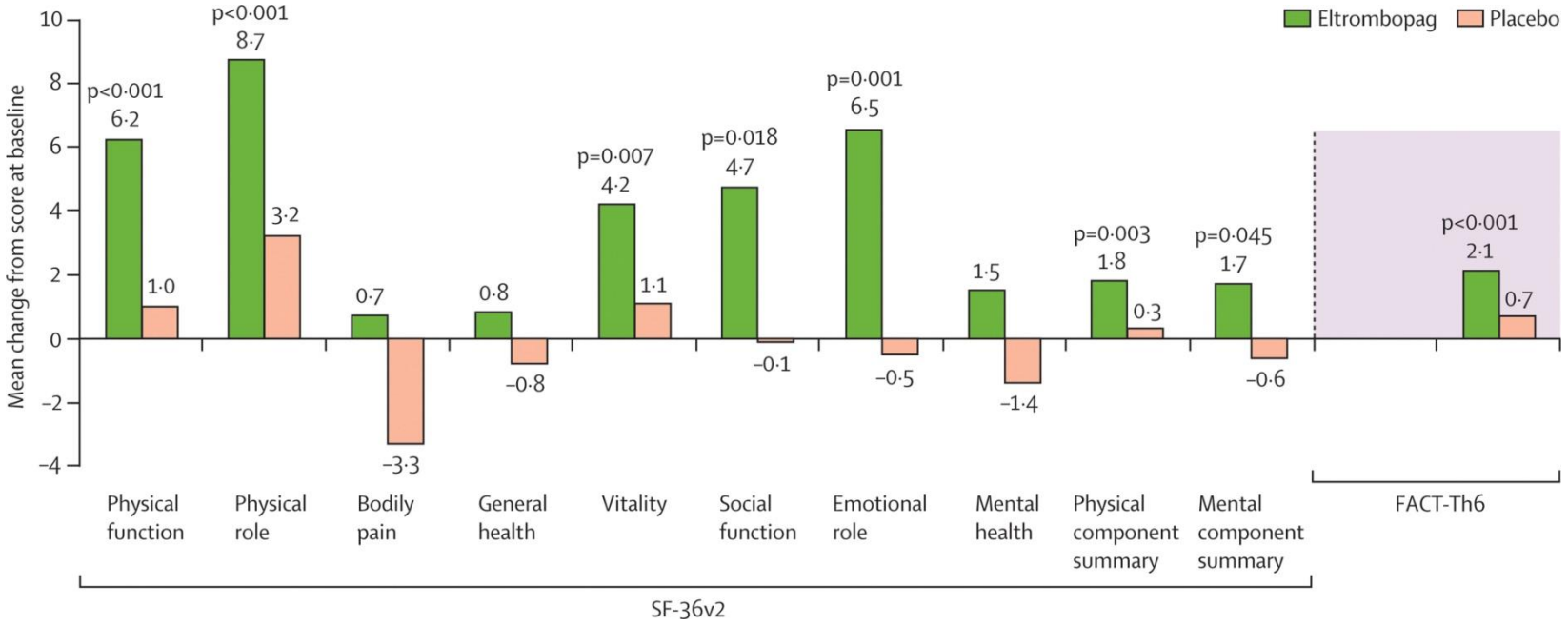
- The aim for patients with chronic ITP should be to minimize impact on HRQoL
- Treatment decisions should be based on the treatment side effects, both short and long term
- There are currently no data on this



BP, bodily pain; GH, general health; HRQoL, health-related quality of life; MH, mental health; PF, physical function; RE, role function – emotional; RP, role function – physical; SF, social function; VT, vitality

Snyder CF *et al. Curr Med Res Opin* 2008;24:2767–2776

Quality of life changes with Eltrombopag adults



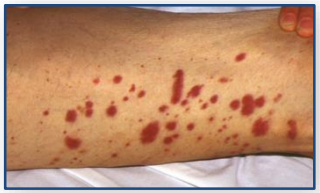
Cheng Lancet 2010

Risk of fatal/severe bleeding in ITP is VERY RARE

- Presence of other conditions such as hypertension or cerebrovascular disease
- Rate of fatal haemorrhage increases with age
  - <40 years: 0.004 per patient-year
  - 40–60 years: 0.012 per patient-year
  - >60 years: 0.130 per patient-year
- Increased risk of venous thromboembolism in people with increased risk factors

George JN. *J Thromb Haemost* 2006;4:1664–1672; Cohen YC *et al. Arch Intern Med* 2000;160:1630–1638; Sarpatwari A *et al. Haematologica* 2010;95:1167–1175

Treatment recommendations based on platelet count



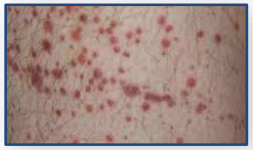
Platelet count

0 | $10x10^9/L$ | $30x10^9/L$ | $150x10^9/L$

Treat adults

Treatment depends on individual patient factors: Age, other comorbidity, success of treatment

Only treat if bleeding, requiring surgery or requiring anticoagulation or antiplatelet agents



Only treat children with symptoms

Images courtesy of N Cooper

Current ‘guidelines’

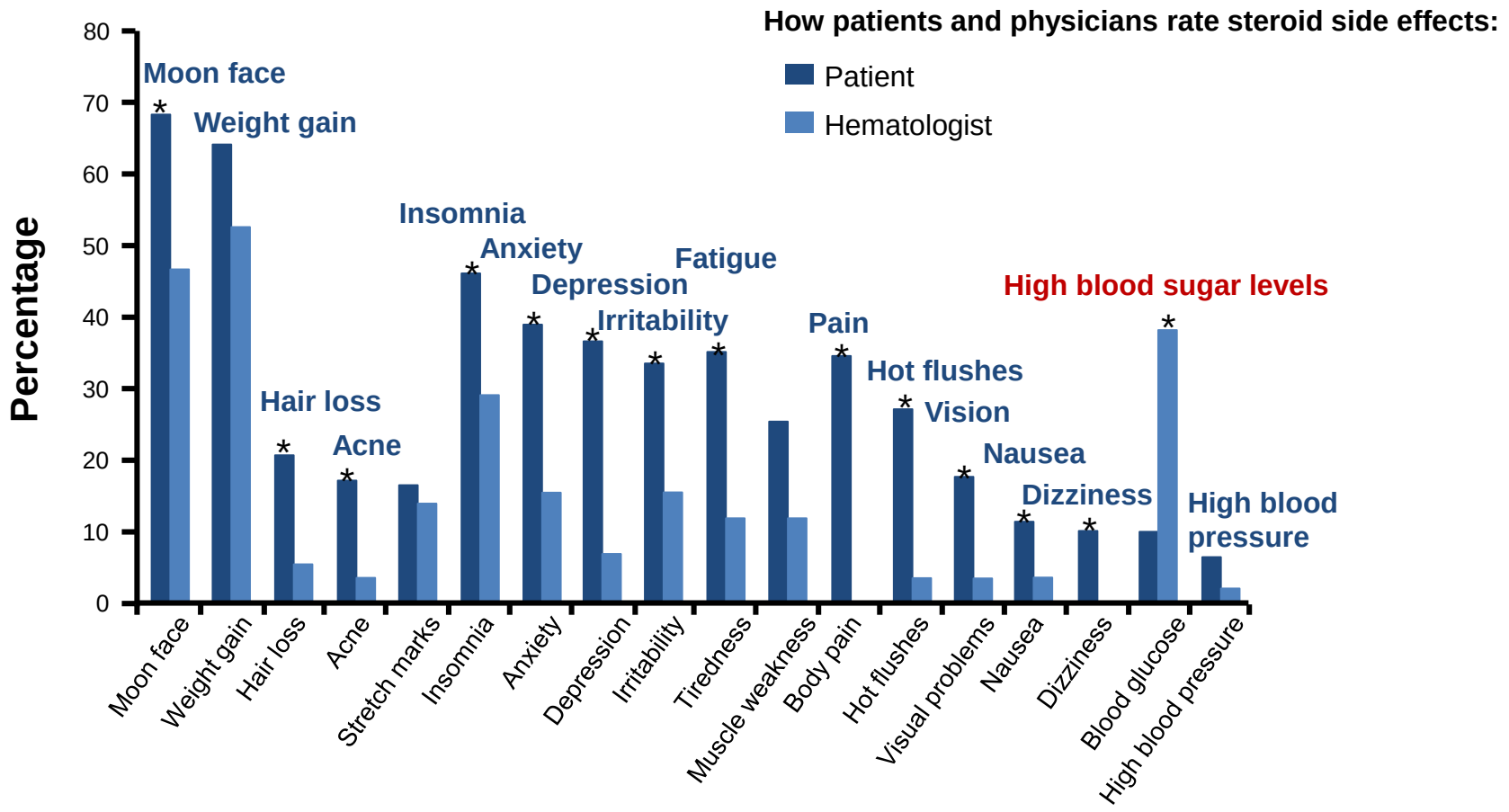
International consensus report on the investigation and management of primary immune thrombocytopenia

Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. *Blood* 2010;115:168–186

The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia

Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. *Blood* 2011;117:4190–4207

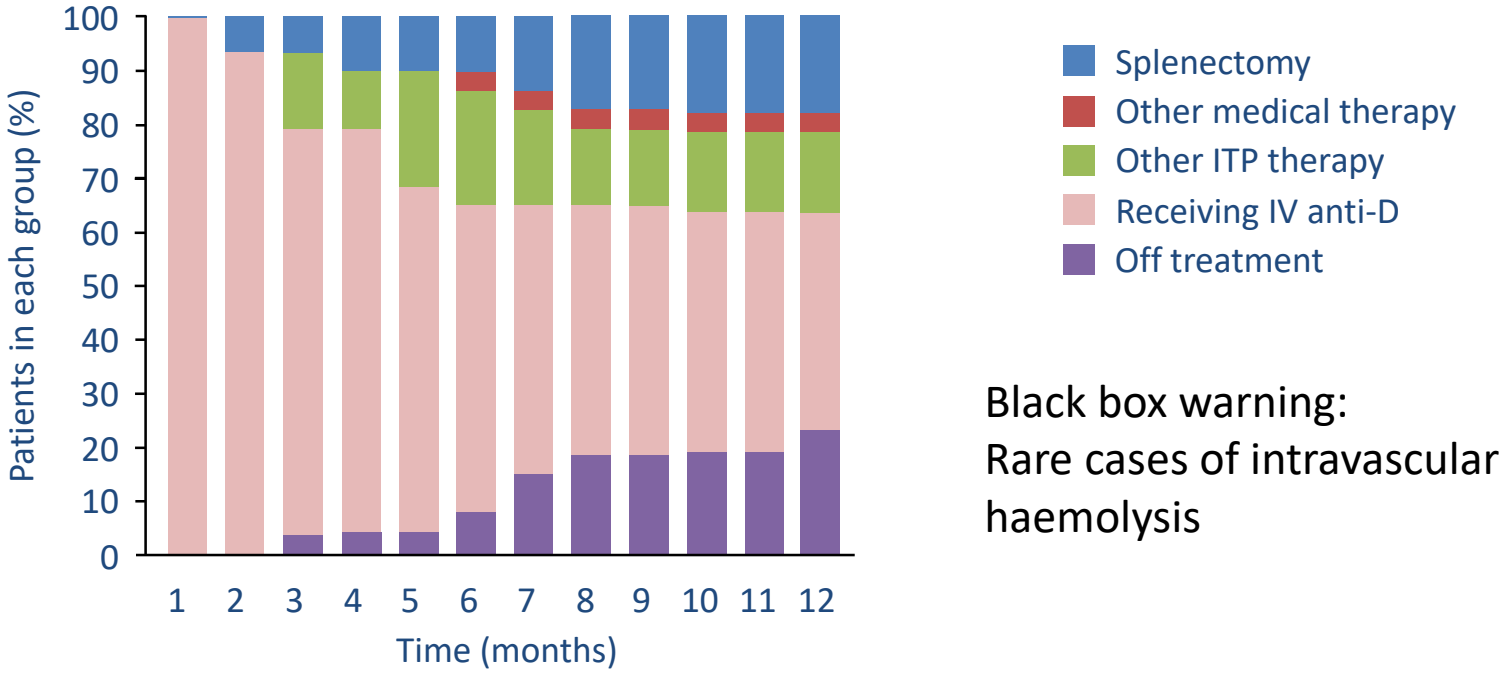
Patients and physicians consider different side effects of steroid treatment burdensome



*p<0.05 hematologist vs. patient.
Figure reproduced from Guidry JA, *et al. Eur J Haematol* 2009;83:175–182.

About 30% of patients go into remission with any treatment

Long-term outcome of patients receiving monthly IV anti-D



Black box warning:
Rare cases of intravascular haemolysis

Patients with newly diagnosed ITP should be given treatment most likely to achieve a platelet response and least likely to have a long-term impact (such as splenectomy)

Cooper N *et al. Blood* 2002;99:1922–1927

Second-line options in persistent ITP

- Common morbidity in persistent ITP is infection or other steroid-related complications
- Steroid-sparing agents:
  - Rituximab
  - Immunosuppression (azathioprine, MMF)
  - Thrombopoietin receptor agonists
  - Splenectomy

Management of ITP

Thrombocytopenia
Diagnosis: Infection, drugs, inherited, acquired

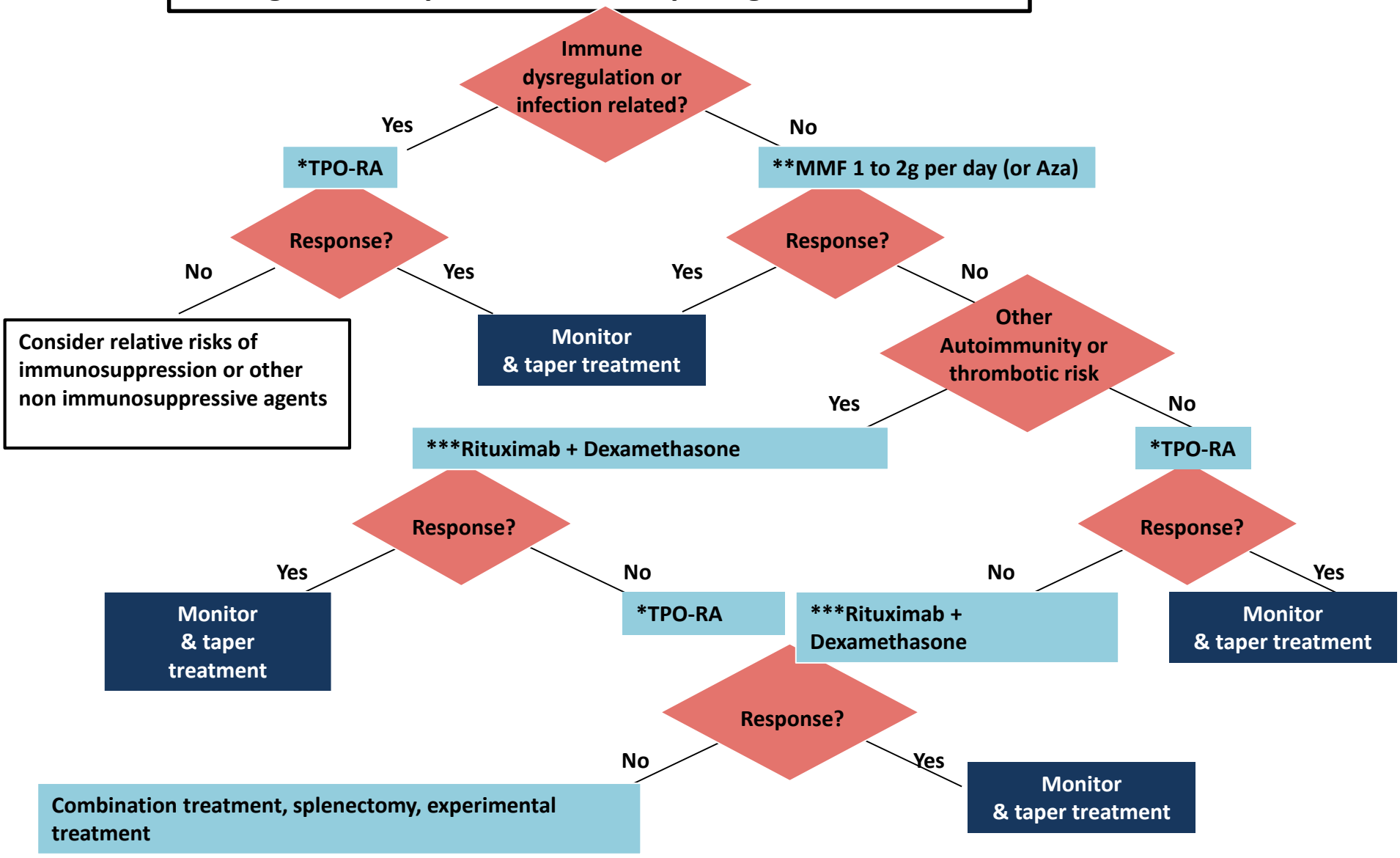
Newly diagnosed ITP (0–3 months)
Steroids or IVIg

Persistent ITP (3–12 months)
MMF or TPO-RAs or rituximab

Chronic ITP (>12 months)
Continuous TPO-RAs
Repeated rituximab (± dexamethasone)
Continuous MMF
Other: Danazol, dapsone, hydroxychloroquine
Splenectomy

Courtesy of N Cooper

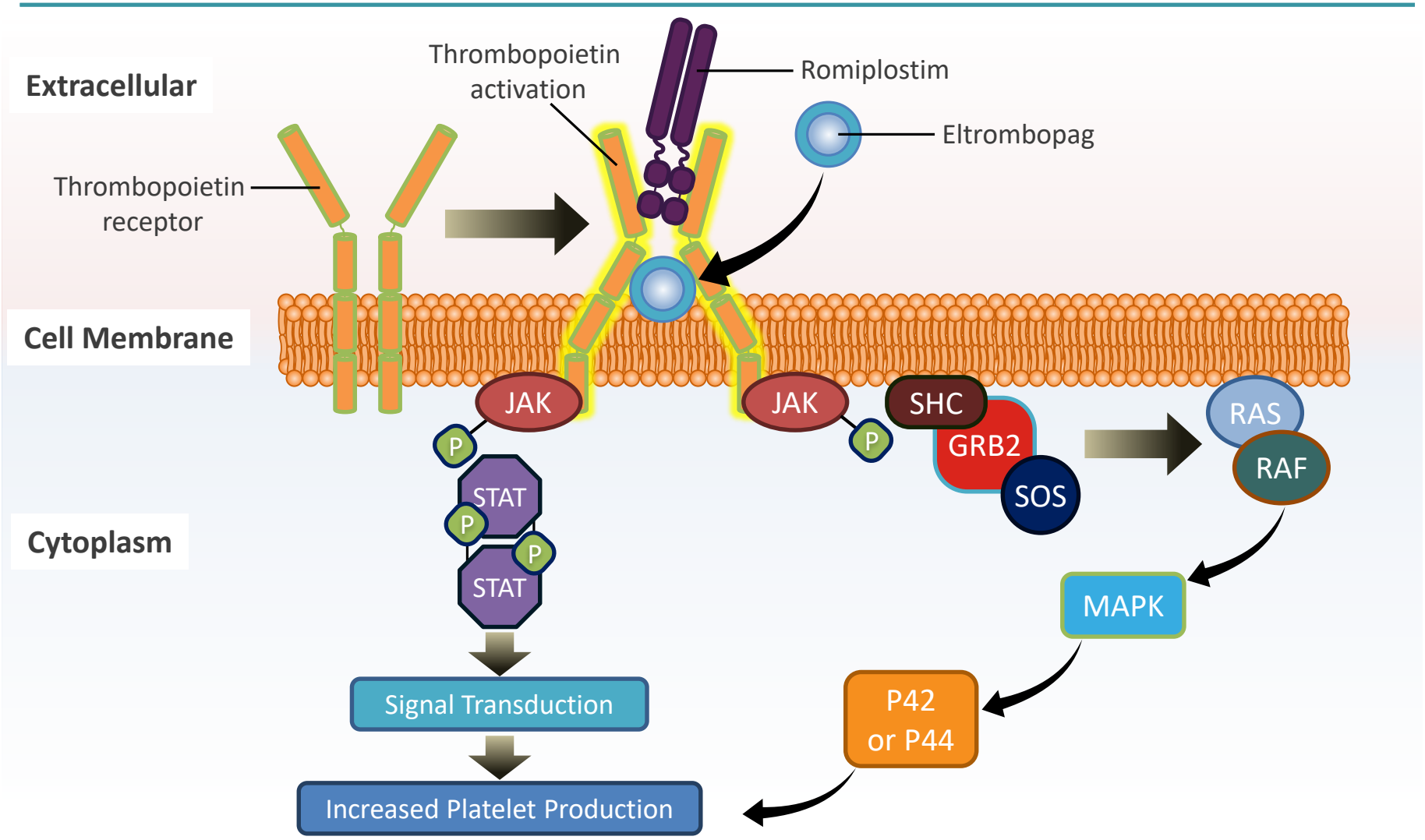
Management of persistent ITP requiring treatment



Responders: Monitor every 2 – 8 weeks for bleeding and infections. Emergency access if bleeding. Taper treatment after 12 to 18 months.

Cooper BJH 2017

Mechanism of Action of TPO-RAs



Kistanguri G, et al. *Hematol Oncol Clin North Am*. 2013;27:495-520.

The role of cytokines released from platelets:

Does increasing the platelet count using TPO-RA result in restoration of immune tolerance to platelets by increasing TGFb?

Figure 6

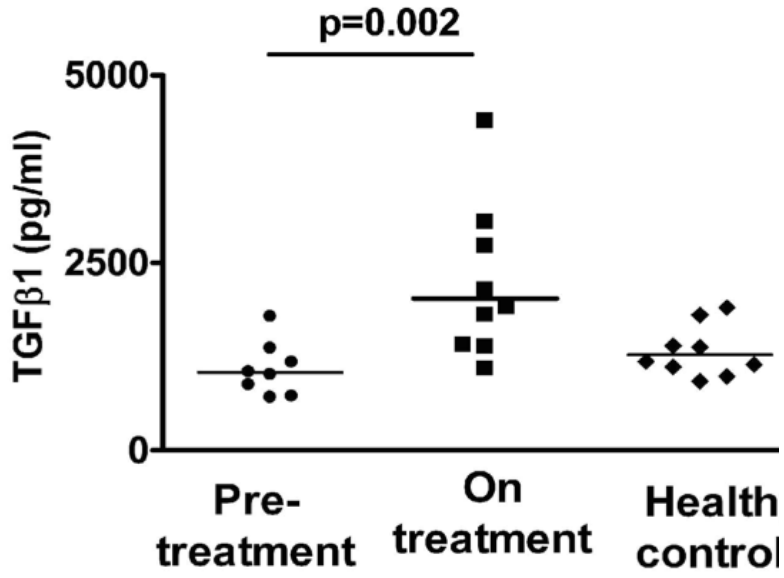
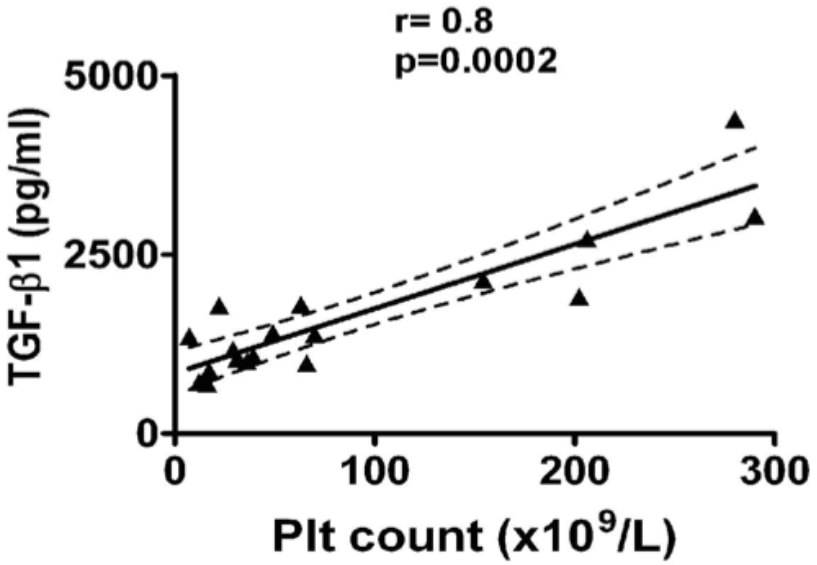


Figure 5



Bao et al Blood 2010

Some patients, even with refractory disease, have only needed TPOs for a short time

TPO-Ras (romiplostim and eltrombopag)[1, 2, 3]

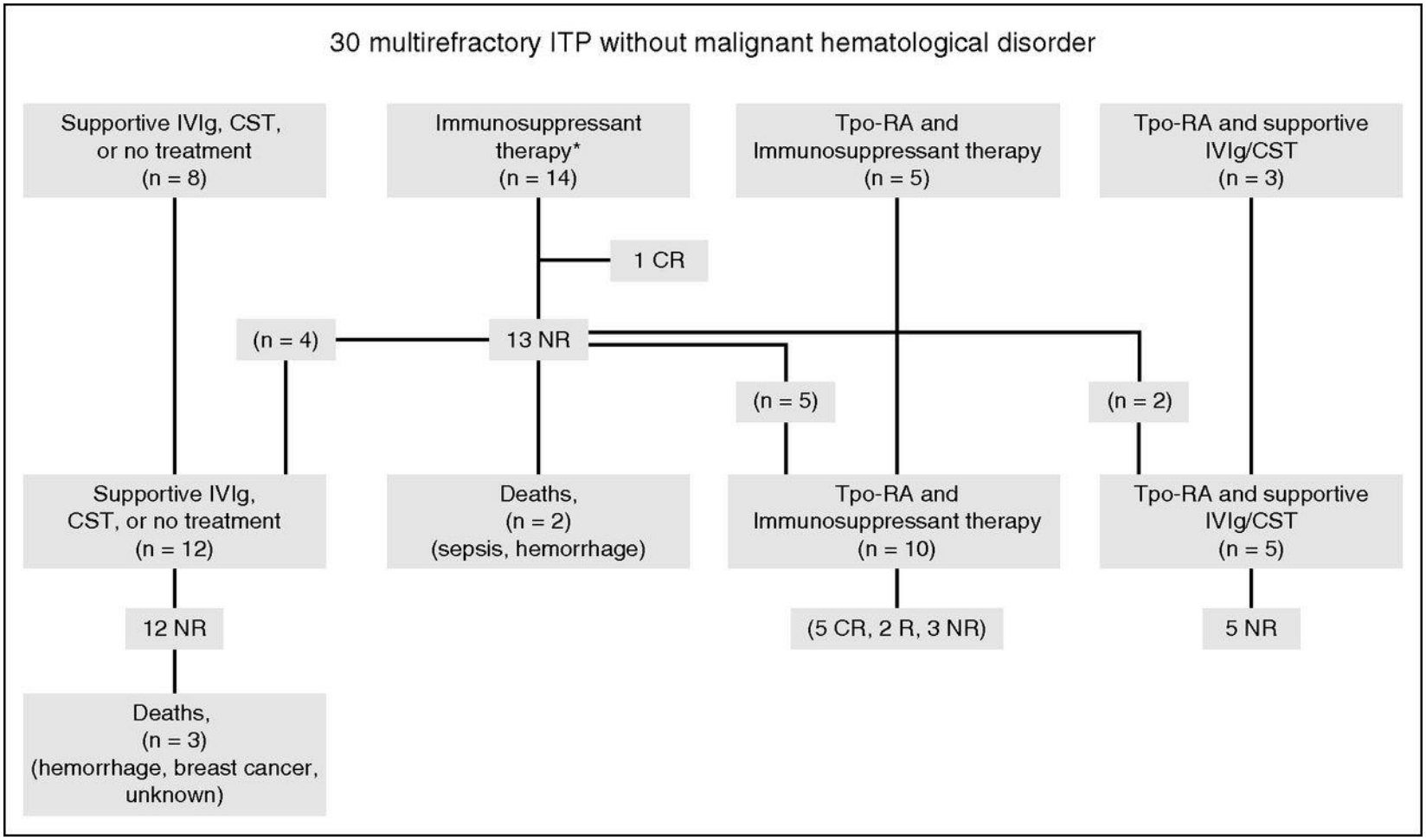
- 30% of patients could come off treatment
- Patients had ITP for an average of 7.8 years and had failed an average of four prior therapies, including eight patients who had a splenectomy

No predictive factors of sustained response were identified

1. Ghadaki B *et al*. *Transfusion* 2013;53:2807–2812;
2. Gonzales-Lopez TJ *et al*. *Am J Hematol* 2015;90:E40–E43;
3. Newland A *et al. Br J Haematol* 2016;172:262–273

Platelet counts drop when TPO-RAs are stopped.
They should be reduced with caution

Response to therapy in patients with a multi-refractory ITP: combination of TPO and immunosuppression

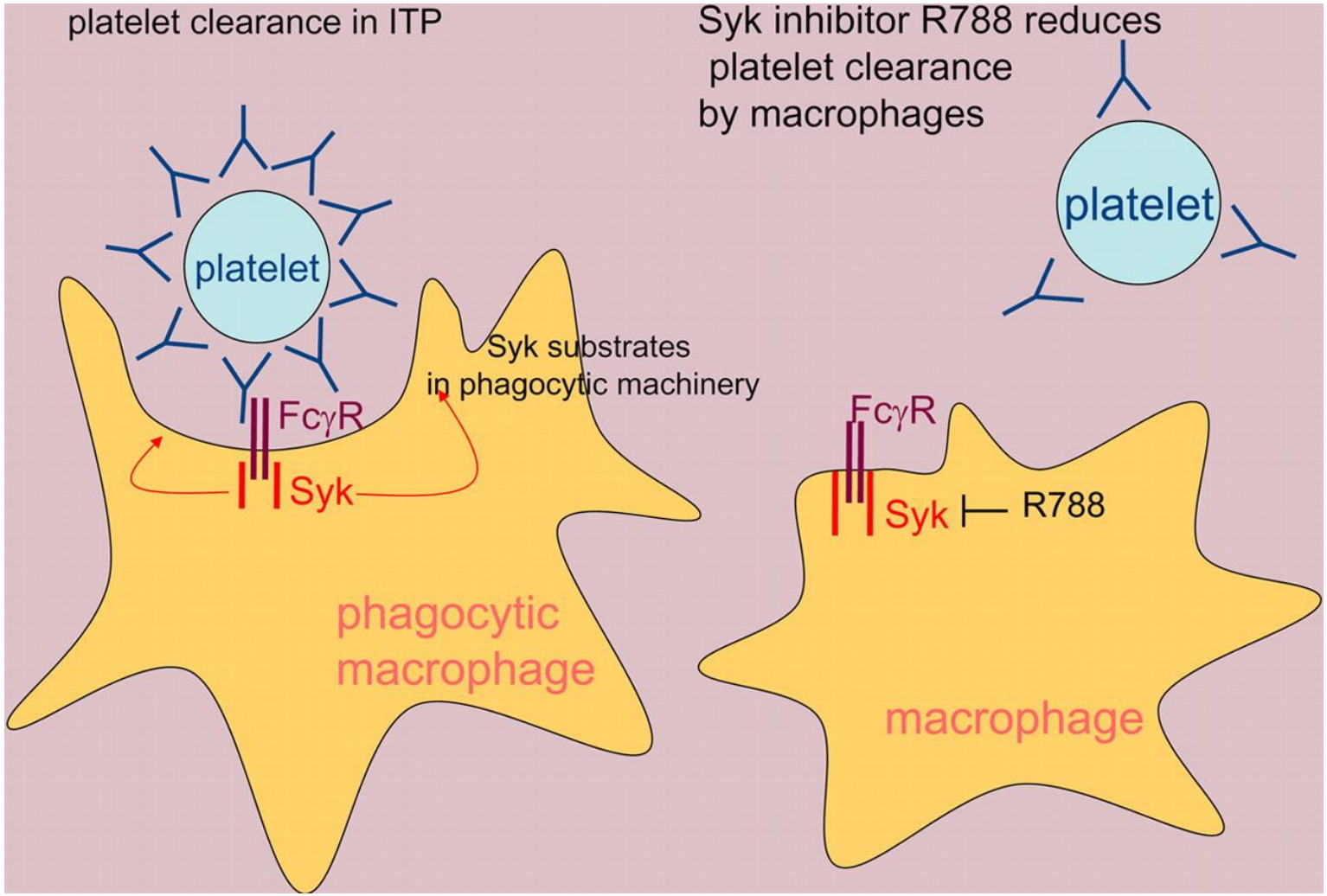


Matthieu Mahévas et al. Blood 2016;128:1625-1630

***Cyclophosphamide, n = 1; azathioprine, n = 4; cyclosporine, n = 1; mycophenolate mofetil, n = 2; alemtuzumab, n = 1; high-dose cyclophosphamide followed by autologous HSCT, n = 1.**

blood

Fostamatinib inhibits Immune-mediated clearance of antibody-opsonized platelets in patients with ITP receptors



blood

Donna S. Woulfe Blood 2009;113:3133-3134

Summary

- Stem cells develop in to megakaryocytes via complex regulatory system
- Thrombopoietin is the critical Factor for MK development
- Megakaryocytes migrate to blood vessel and platelets released in to the vessel by unclear regulation
- Regulation of platelet number not fully understood
- Life span of platelets regulated by apoptotic pathways
- Many genes involved in megakaryocyte development and platelet production
- Many roles of platelets, besides coagulation
- The role of platelets in infection may results in their premature destruction – resulting in ITP
- Most patients with ITP do not bleed, treatment is complicated

- (Megakaryocyte/platelet supplement with the BJH April 2014)
- How I manage ITP BJH 2017

Imperial College London

NORD

The ITP Support Association
Immune Thrombocytopenia