Congenital Platelet Disorders

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Inherited platelet disorders

- True prevalence is underestimated
- Many lack a family history
- Many de novo mutations (eg 20-30% in MYH9)
- Variable bleeding tendency
- Not all present in childhood

Platelet Disorders

- Reduced function
  - Thrombocytopathy (term not used much)

- Reduced count
  - Thrombocytopenia

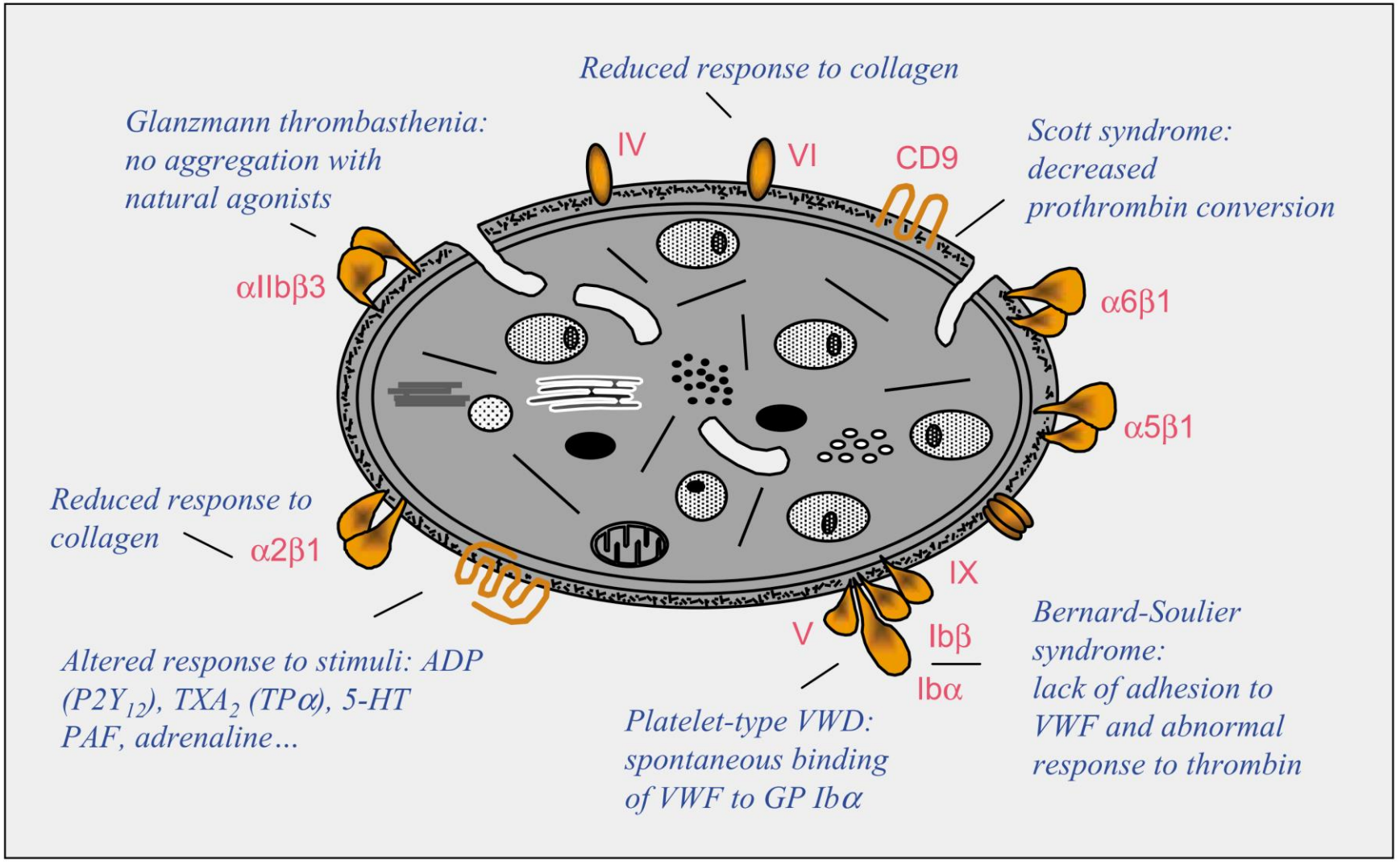
UK registered patients

Disorders	Number of patients
Haemophilia A	7,700
Haemophilia B	1,707
VWD	10,598
Glanzmann Thrombasthenia	125
Bernard Soulier syndrome	85
Other platelet disorders	2,222

UK population: 66 million

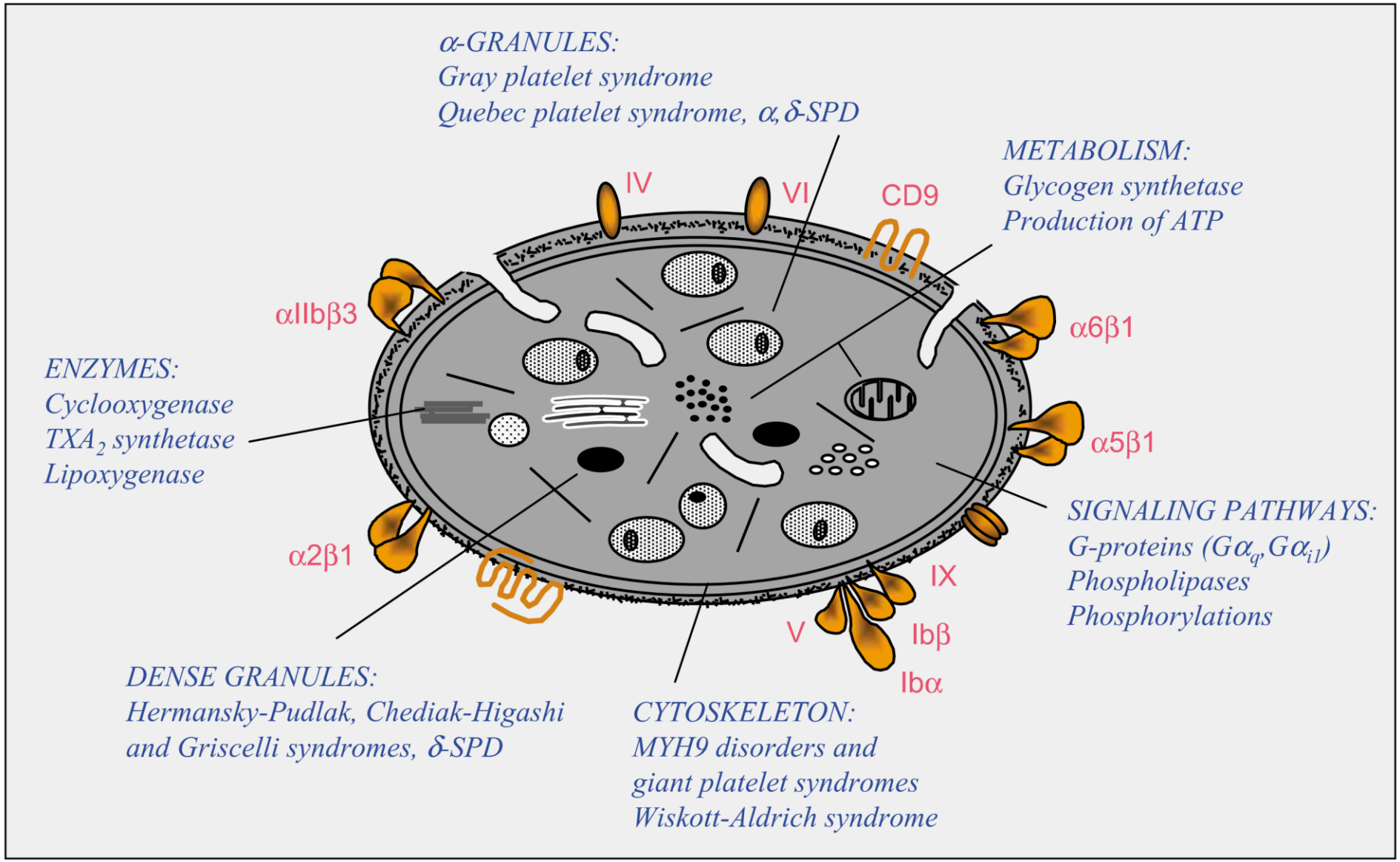
Disorders of platelet function

Disorders that mainly affect surface components of platelets



Nurden P & Nurden AT. T&H 2008; 99:253-263

Disorders that mainly affect intracellular components of platelets

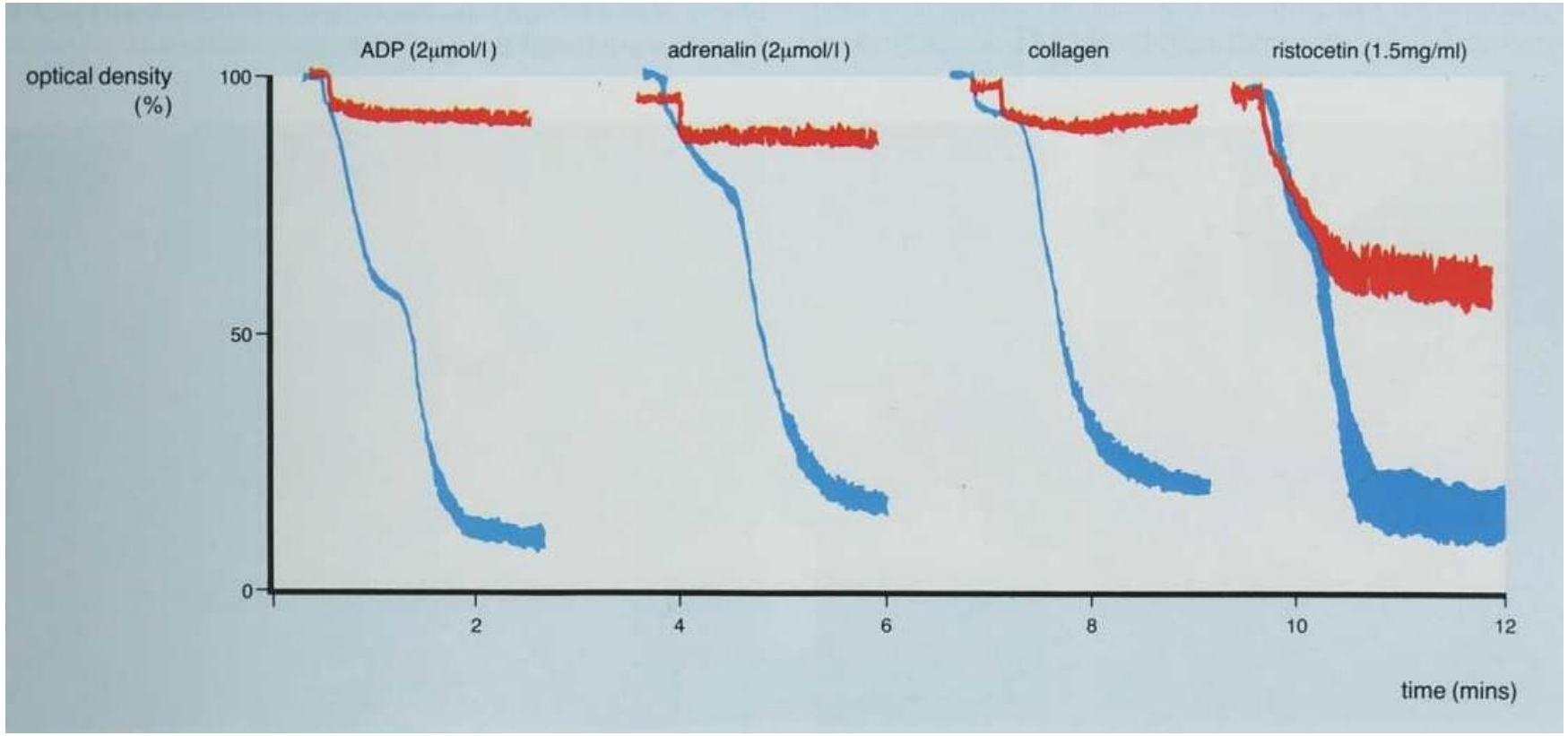


Nurden P & Nurden AT. T&H 2008; 99:253-263

Glanzmann Thrombasthenia

- Autosomal recessive
- Rare (1 in 1 million)
  - exc in countries with consanguinity
- Primary haemostatic defect
- Mostly severe
- Abnormality in platelet glycoprotein IIb/IIIa (αIIb/β3)
- Treat with platelet transfusion or recombinant VIIa
- Risk of alloantibodies against IIb/IIIa

Glanzmann Thrombasthenia platelet aggregation



Classification of Glanzmann Thrombasthenia

Type	Proportion %	αIIb/β3
I	75	Absent or trace (<5%)
II	15	Substantially reduced (5-20%)
Variant	10	Abnormal (>20%)

Type of bleeding in Glanzmann Thrombasthenia

Symptom	% of patients reporting this symptom
Menorrhagia	80-95 (of menstruating females!)
Epistaxis	80
Gum bleeding	60
Easy bruising	50
Gastrointestinal bleeding	20
Muscle haematoma	10

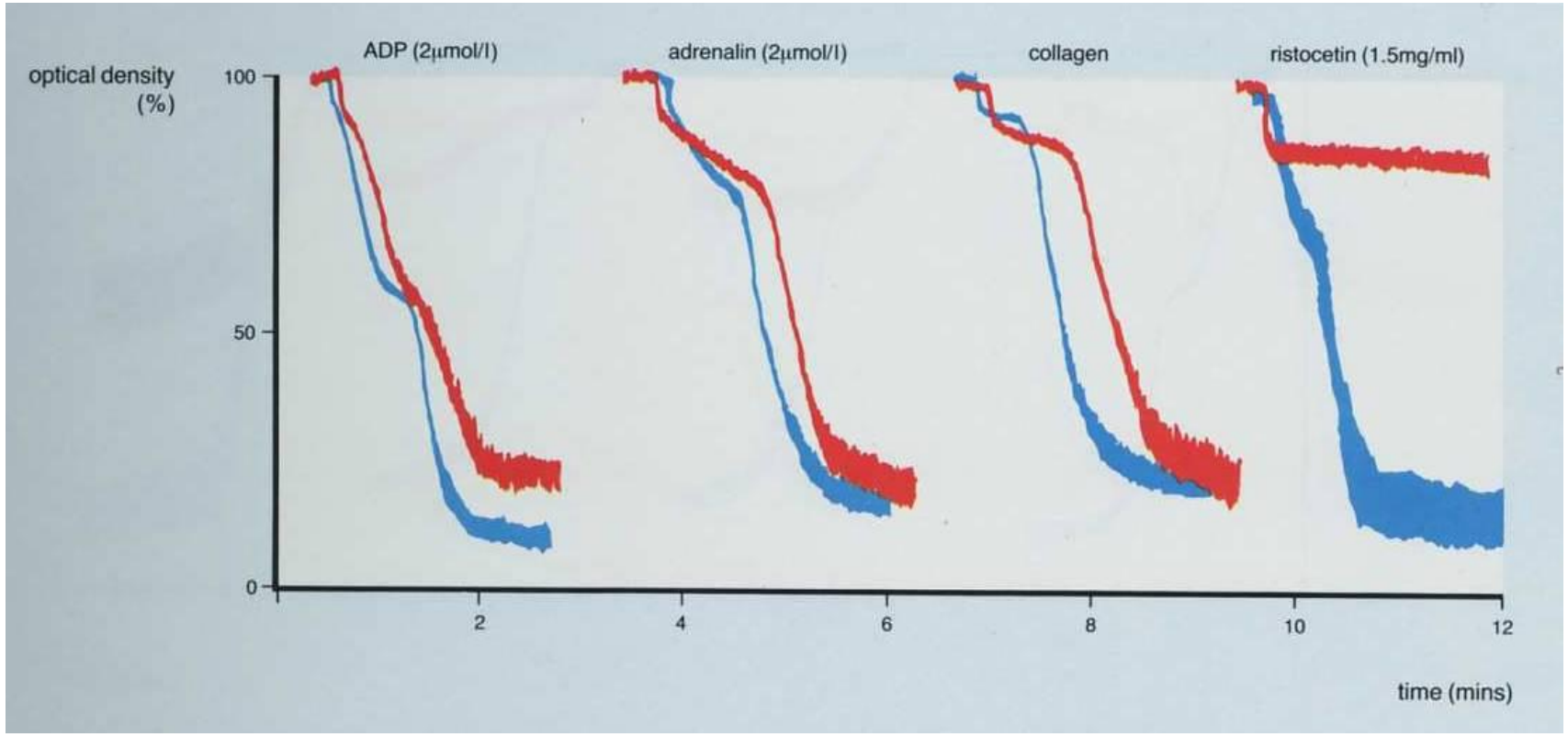
Pregnancy in Glanzmann Thrombasthenia

- Risk of bleeding at delivery
- Risk of affected baby
  - Will depend if there is consanguinity
- During pregnancy baby platelets (heterozygous) cross the placenta
- Mum can mount immune response
  - Develops anti-IIb/IIIa alloantibodies
- Mum with platelet alloantibodies
  - Will not respond to platelet transfusions
  - Antibodies cross the placenta – risk of bleeding in baby

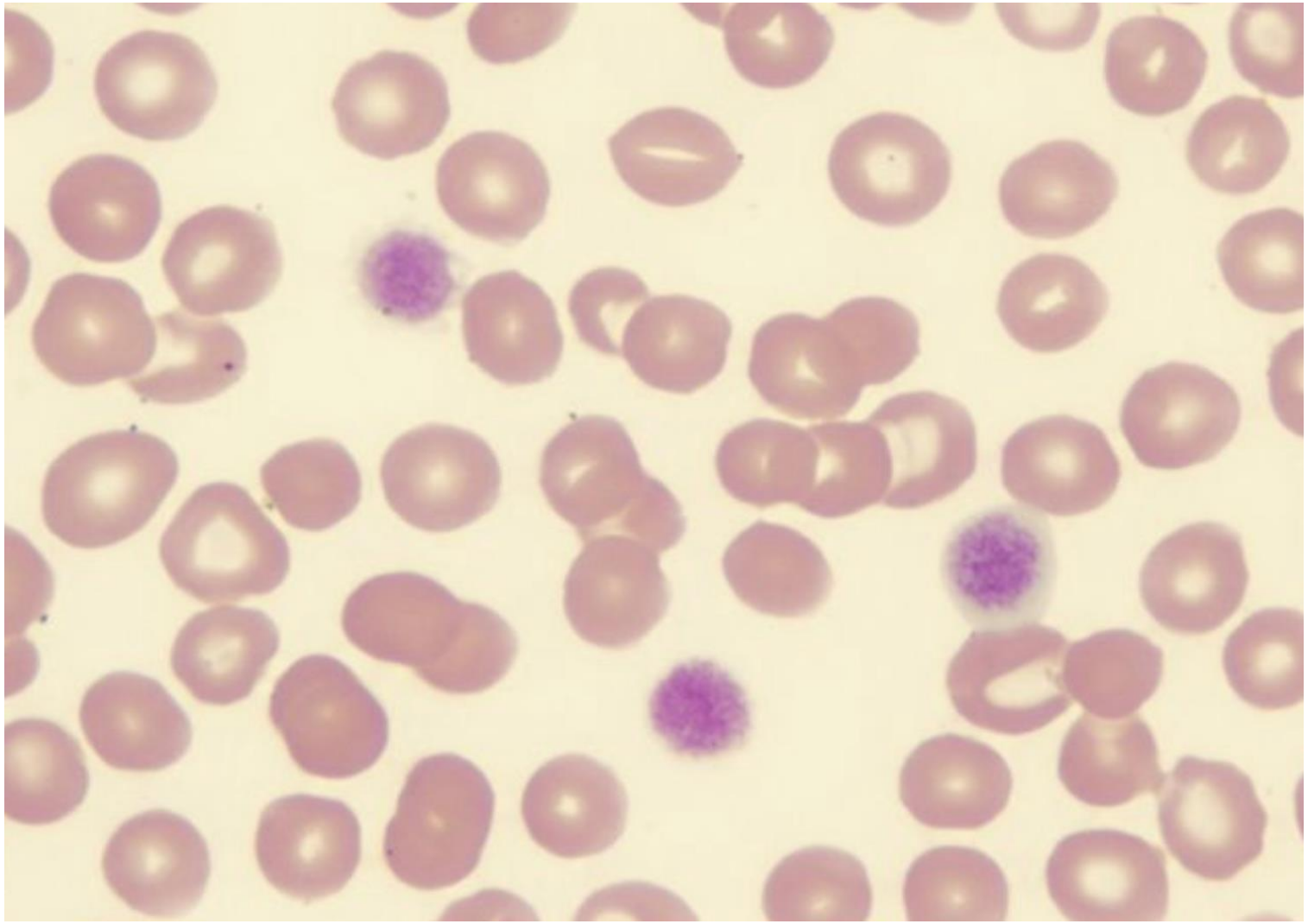
Bernard Soulier syndrome

- Autosomal recessive
- Rare (1 in 1 million)
  - exc in countries with consanguinity
- Primary haemostatic defect
  - Prolonged bleeding time with variable thrombocytopenia
- Giant platelets
- Abnormality in platelet glycoprotein Ib/V/IX
- Treat with platelet transfusion or recombinant VIIa

Bernard Soulier Syndrome platelet aggregation



Giant platelets in Bernard Soulier syndrome

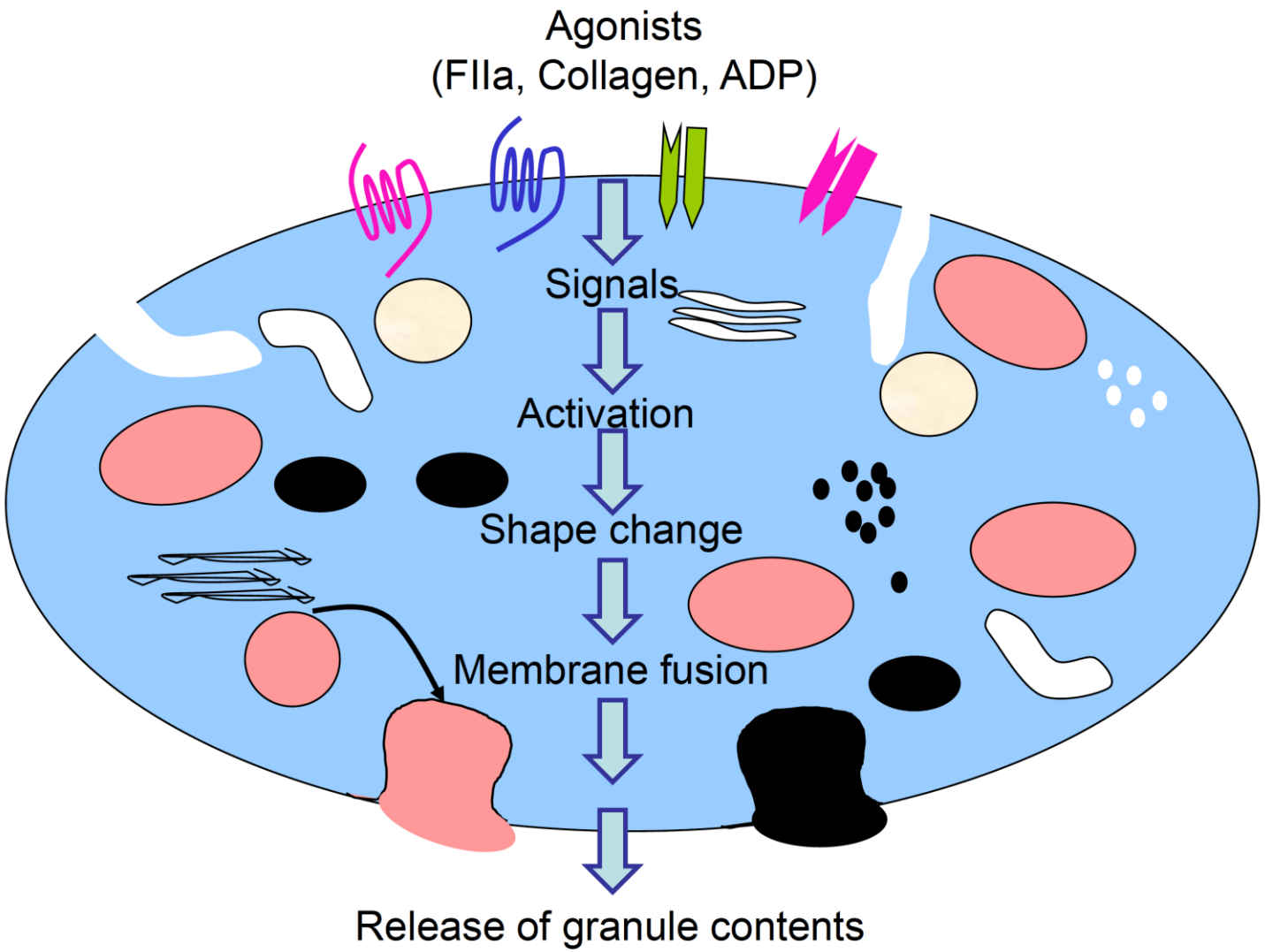


Platelet storage pool disease

Deficiency of:

- Dense granules (δ-SPD)
- Alpha granules (α-SPD)
- Both granules (αδ-SPD)

Platelet granule release



Platelet storage organelles

α granules

Adhesive proteins

Clotting factors and their inhibitors

Fibrinolytic factors and their inhibitors

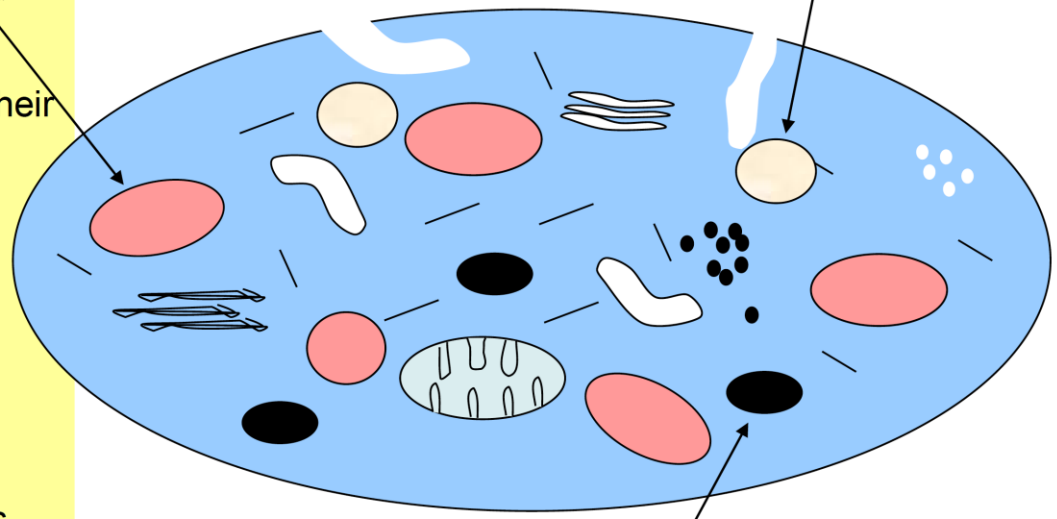
Proteases and antiproteases

Growth and mitogenic factors

Chemokines, cytokines

Anti-microbial proteins

Membrane glycoproteins



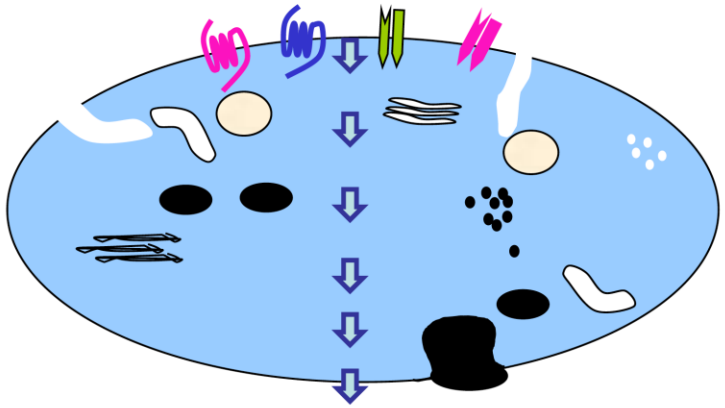
lysosomes

Enzymes including
cathepsins
acid hydrolases

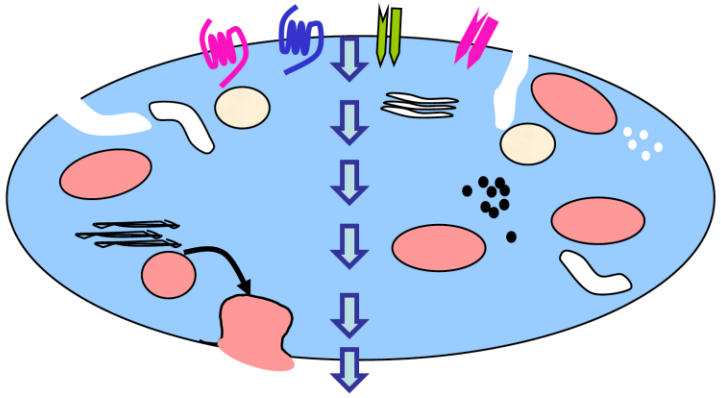
dense (δ) granules

ADP/ATP
Serotonin
histamine
inorganic polyphosphate

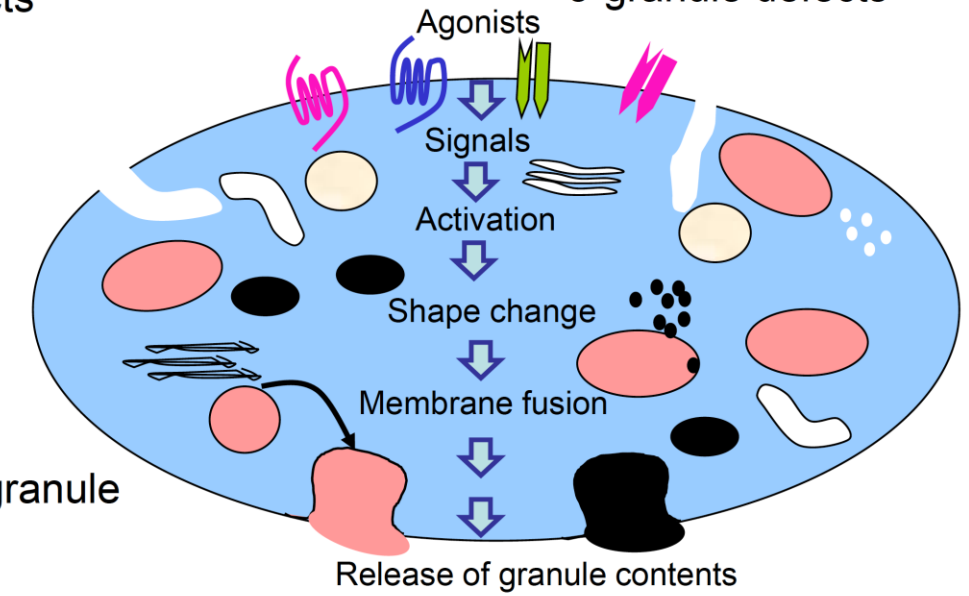
Types of platelet secretion defects



α-granule defects



δ-granule defects



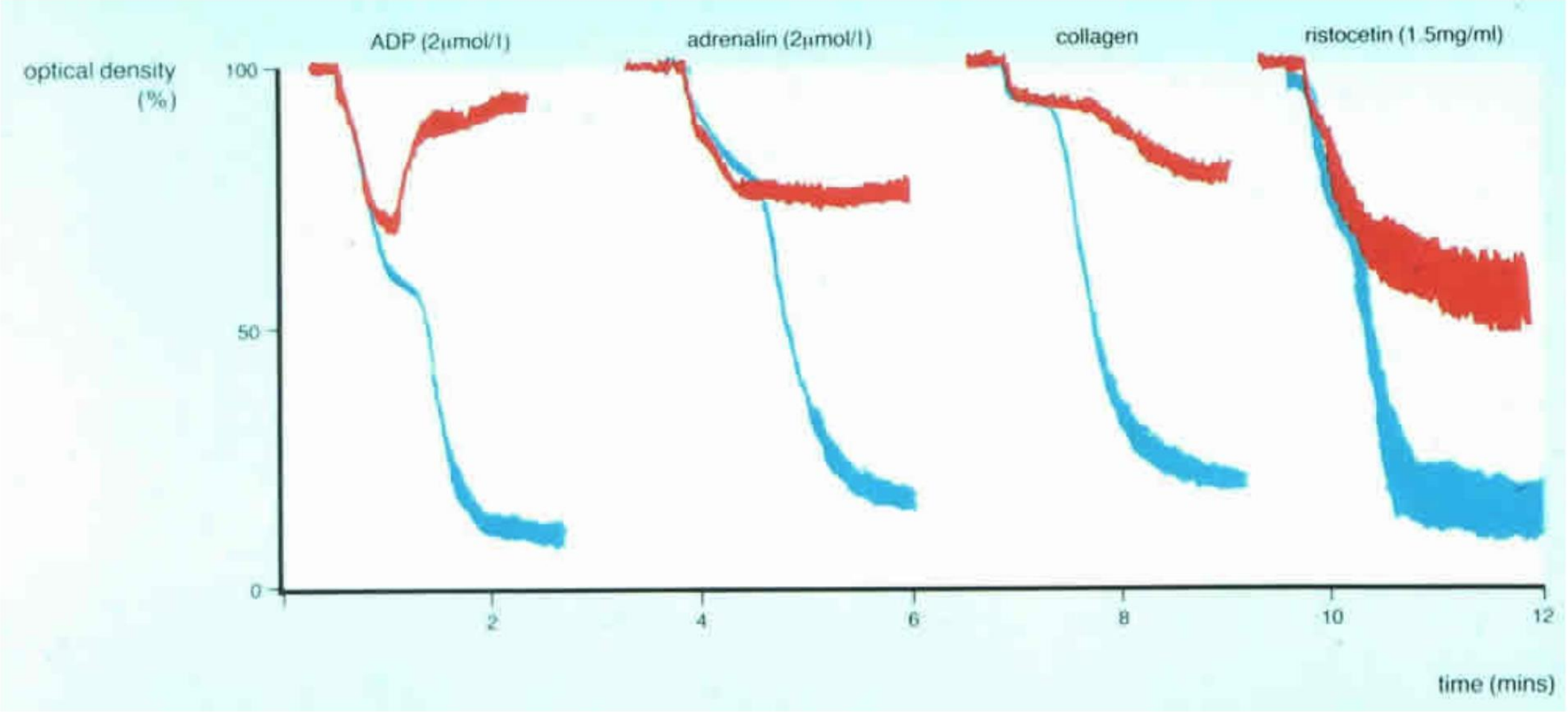
Receptor, signalling or granule trafficking defects

Release of granule contents

Platelet storage pool disease

- Mild bleeding disorder
- Can be isolated – often due to Fli-1 mutations
- Can be syndromic eg Hermansky Pudlak syndrome
- Treatment
  - Desmopressin
  - Tranexamic acid
  - Platelet transfusion

Platelet storage pool disease aggregation

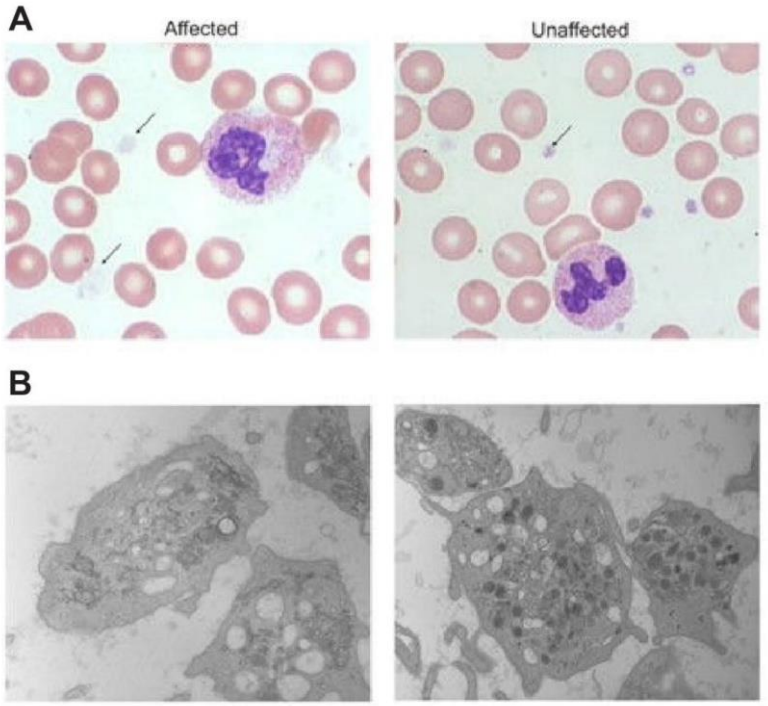


Hermansky-Pudlak syndrome

- Autosomal recessive
- Worldwide 2 per million (but 1 in 1800 in Puerto Rico)
- Symptoms
  - Albinism
  - Platelet dense granule deficiency
  - Pulmonary fibrosis, granulomatous colitis, nystagmus
- 8 HPS genes
  - 90% of cases are due to HPS1 mutations

Grey platelet syndrome

- Autosomal recessive
- Mild to moderate bleeding
- Severe deficiency of α-granules
- Macrothrombocytopenia
- Myelofibrosis
- Due to *NBEAL2* mutations



Other platelet function defect disorders

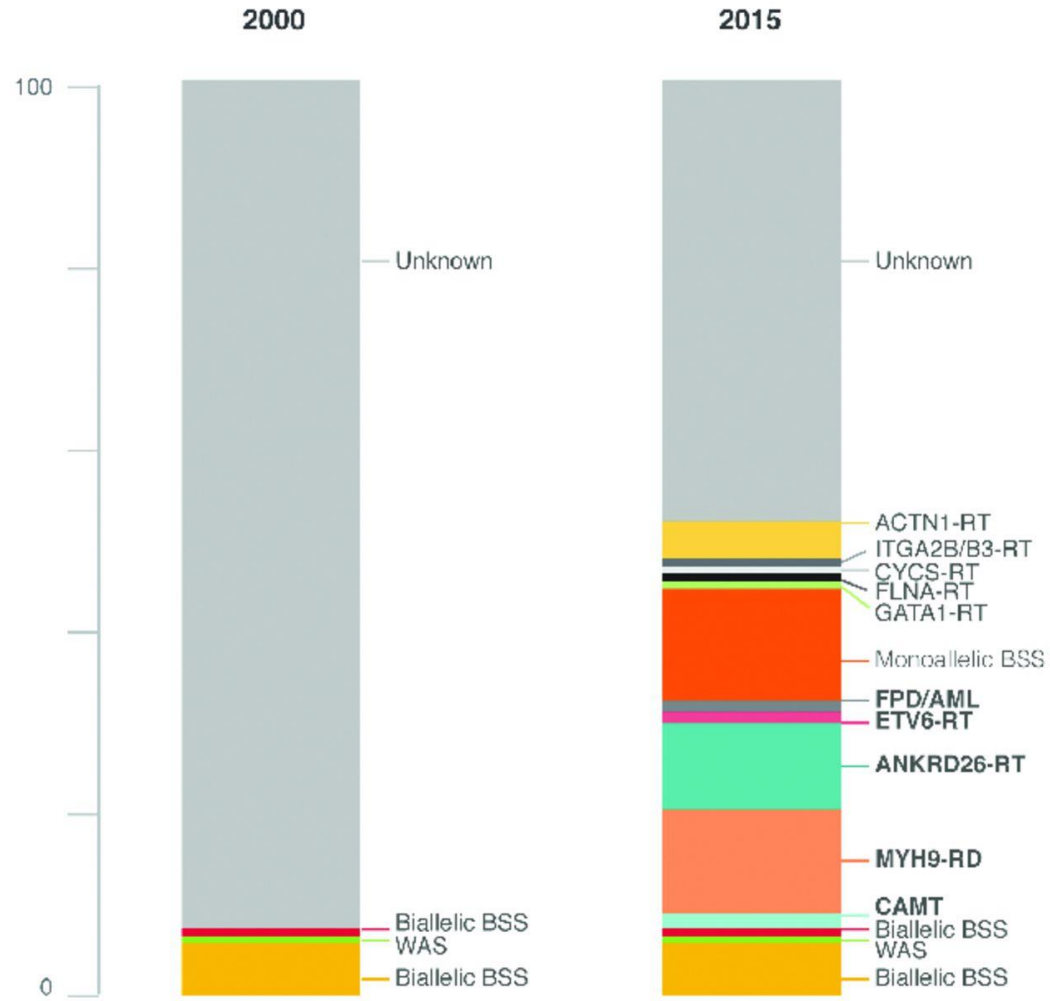
- Mild
- Not always well defined
- Precise definition only for a minority
- Often mildly abnormal platelet aggregation
- Usually no treatment required
- Treatment:
  - Desmopressin and tranexamic acid
  - If significant bleeding despite this – platelet transfusion

Disorders of platelet number

Inherited thrombocytopenia

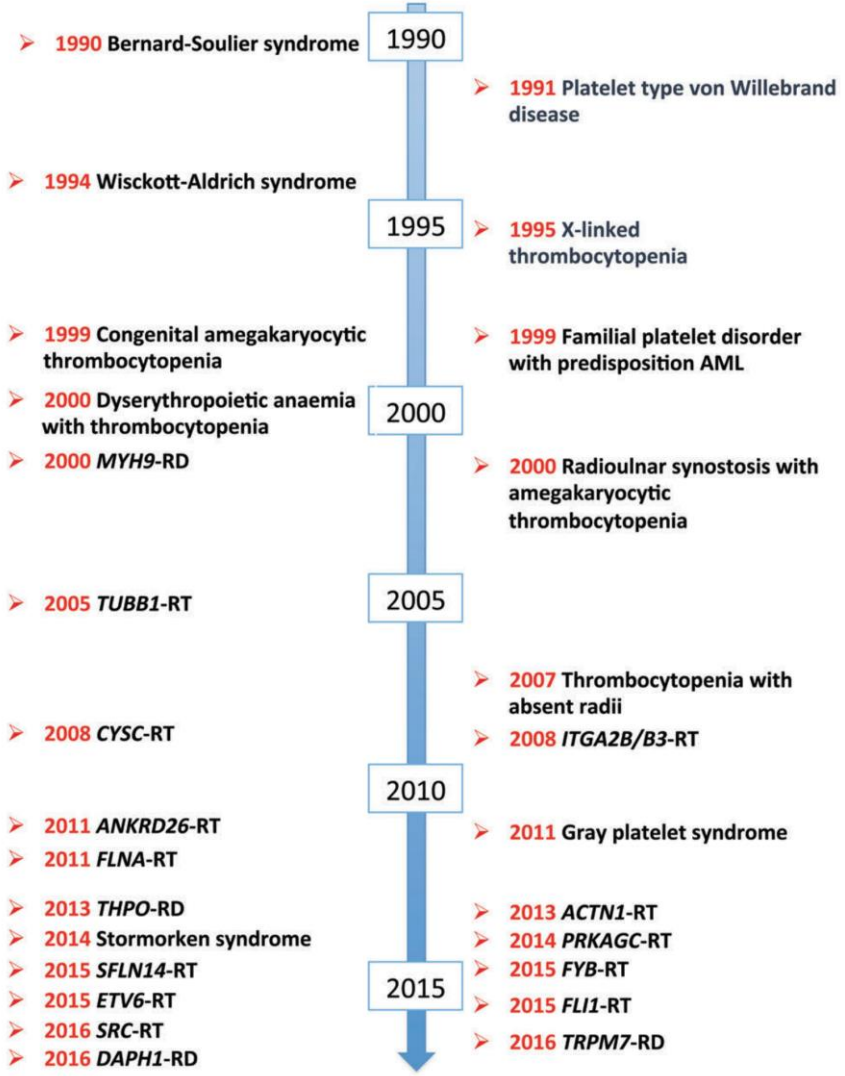
- Commoner than generally believed
- Mostly mild bleeding tendency
- Variable platelet size
- Most disorders identified very recently
- Molecular genetic diagnosis
- Many are syndromic

The evolving view of inherited thrombocytopenias



Balduini CL Haematologica 2016;101:2-4

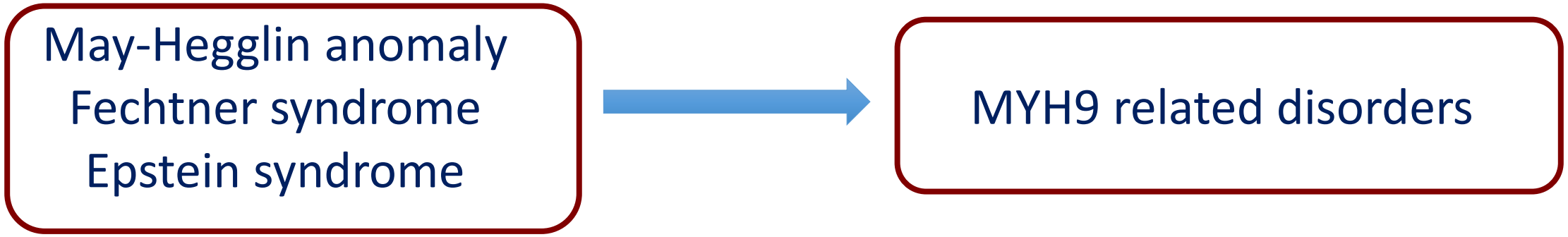
The molecular identification of inherited platelet disorders



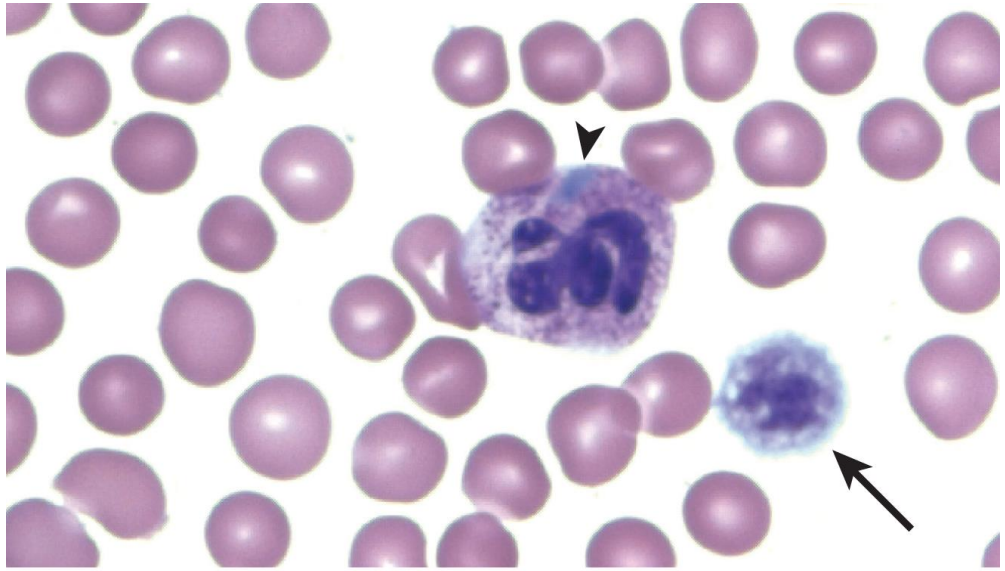
Balduini CL. Haematologica 2017 (in press)

Pattern of inheritance

- X-linked
  - Wiskott-Aldrich syndrome
  - X-linked thrombocytopenia
- Autosomal dominant
  - MYH9 defects
  - FLI1 defects
- Autosomal recessive
  - Glanzmann Thrombasthenia
  - Bernard Soulier syndrome

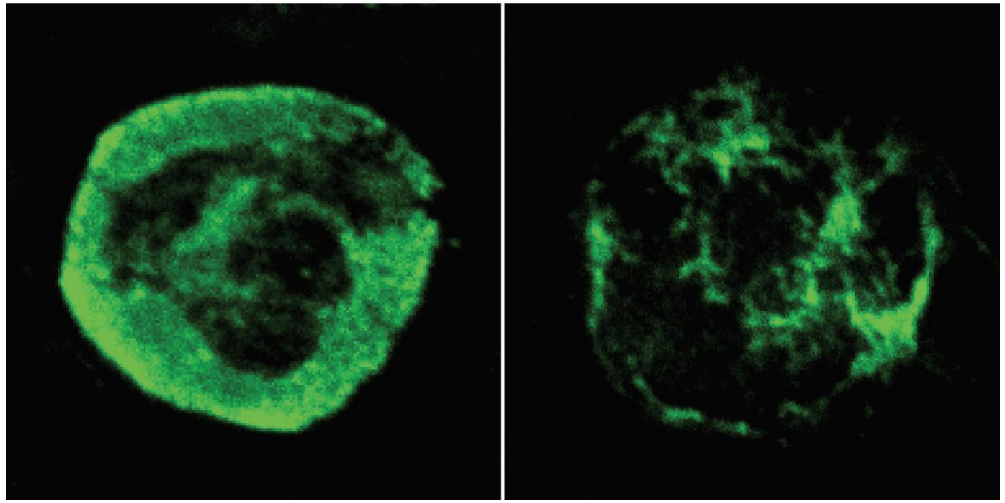

May-Hegglin anomaly
Fechtner syndrome
Epstein syndrome
MYH9 related disorders

Peripheral blood in MYH9 thrombocytopenia



(a)

Neutrophil inclusion
and
Large platelet



Normal immunofluorescence for non-muscle myosin heavy chain IIA

Speckled staining in patients with MYH9 defects

MYH9 related thrombocytopenia

- Macrothrombocytopenia
- Mild bleeding disorder
- Defect in non-muscle myosin chain IIA
- Neutrophil inclusions
- Autosomal dominant
- Associated with:
  - Renal defects
  - Sensorineural deafness
  - Cataracts at a young age

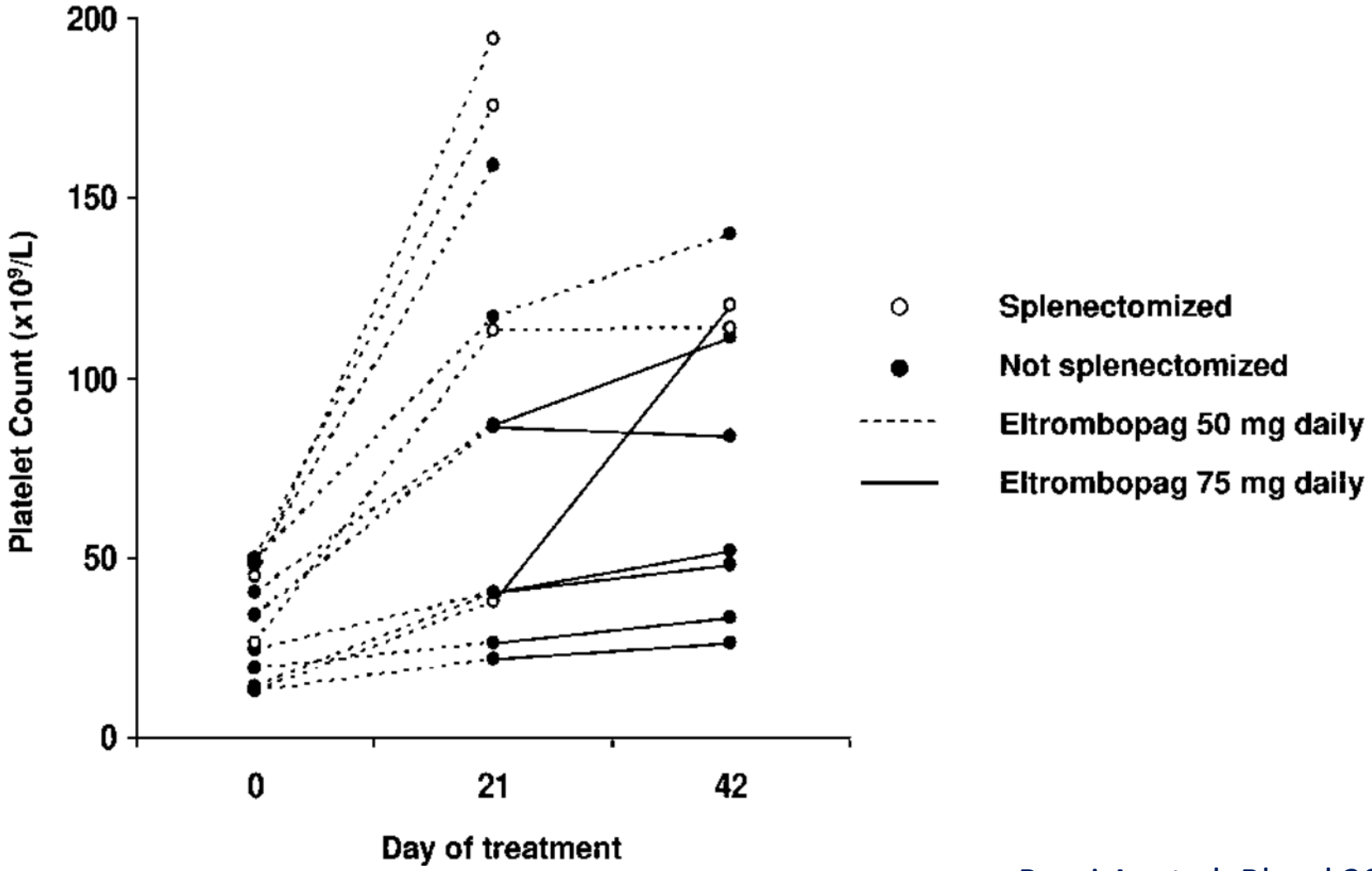
Inherited thrombocytopenia associated with haematological malignancy

- RUNX1 (AML1)
  - Familial platelet disorder with propensity to acute myeloid leukaemia (FPD-AML)
  - AML or MDS in 40%
- ETV6
  - ALL in 20%
- ANKRD26
  - AML in 8%

Treatment of inherited thrombocytopenias

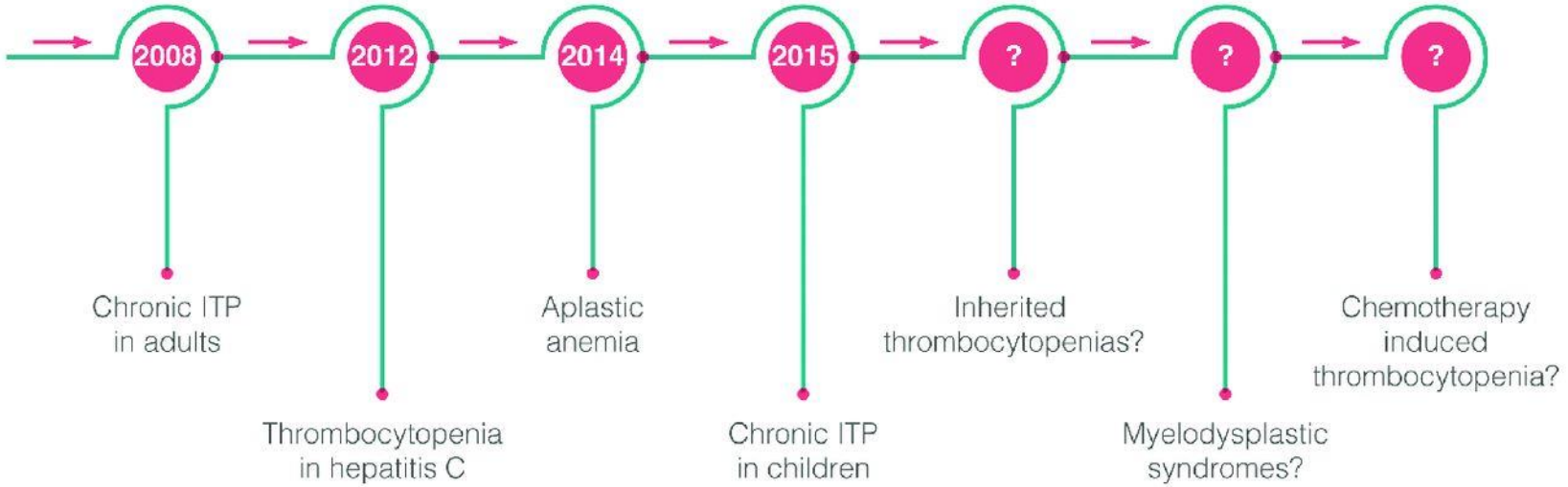
- Often no treatment is required
  - Platelet count is relatively high
  - Macrothrombocytopenia leads to increased surface area
- Topical measures and pressure
- Tranexamic acid
- Eltrombopag
- Romiplostim
- For some disorders eg Wiskott-Alrich
  - Splenectomy, stem cell transplant, gene therapy

Eltrombopag for MYH9 thrombocytopenia



Pecci A, et al. Blood 2010; 116:5832

The increasing indications for thrombopoietin mimetics



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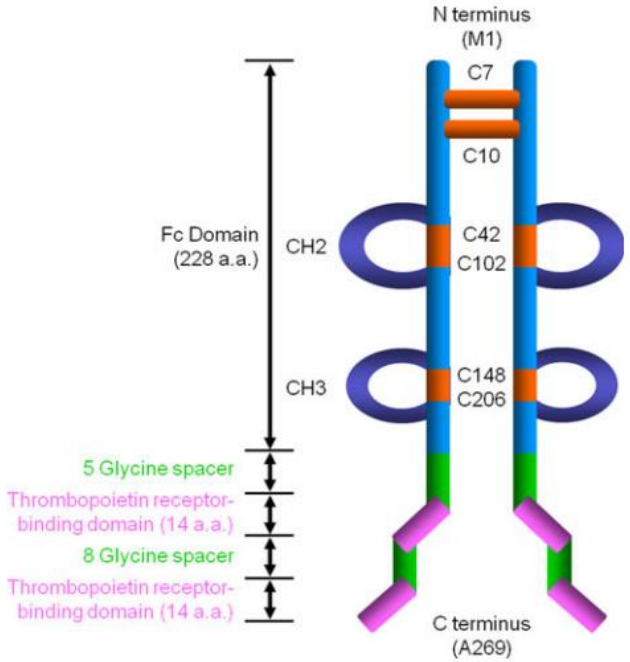
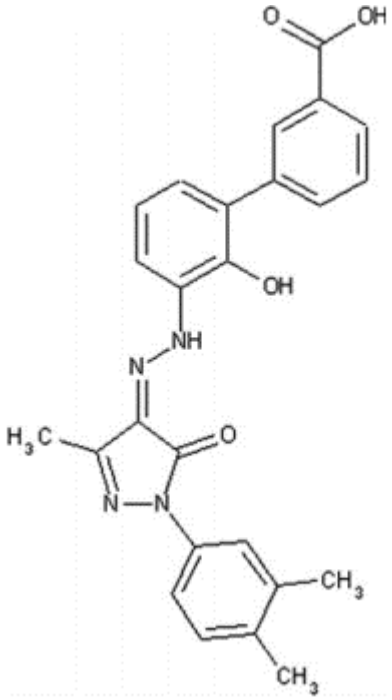
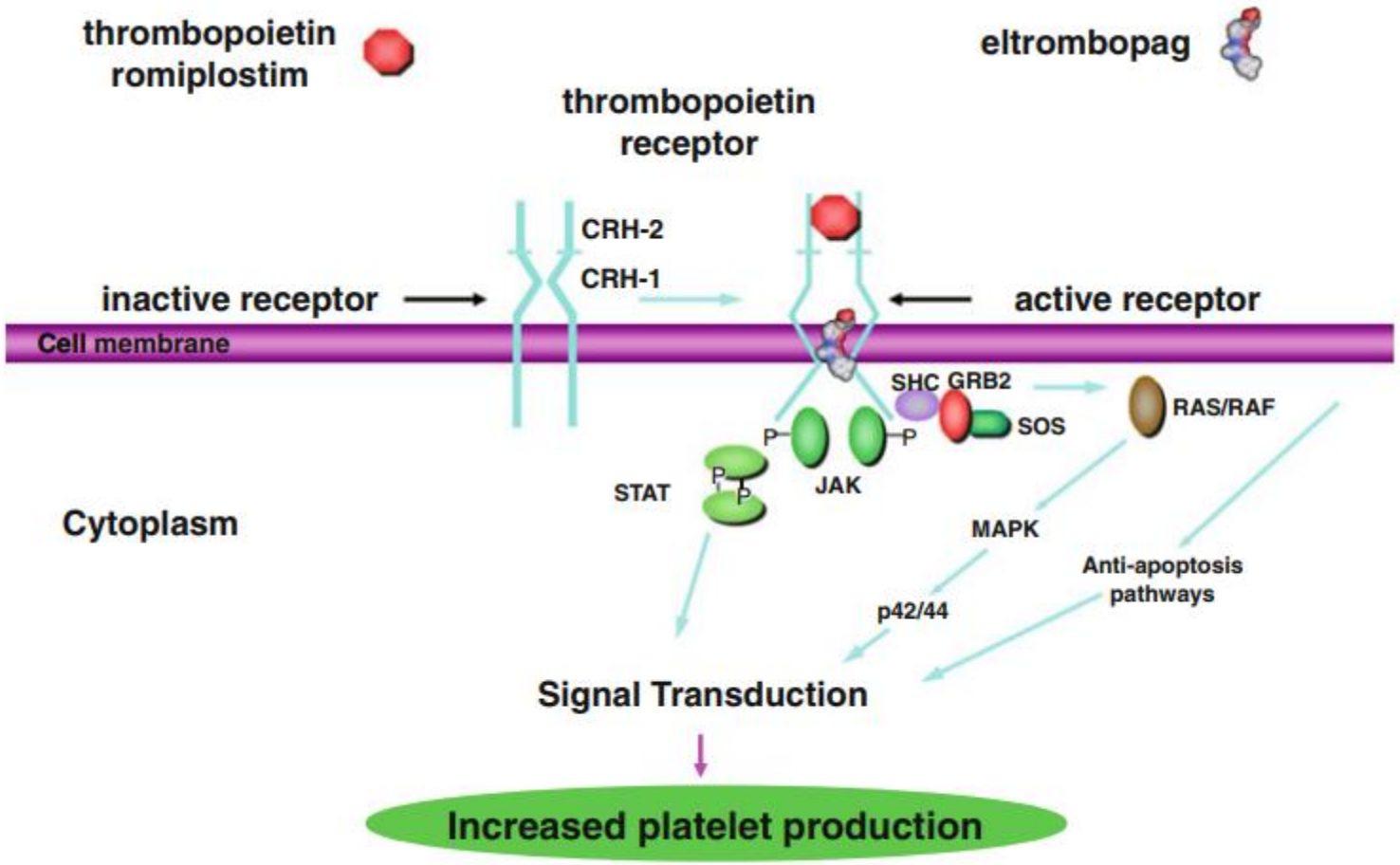


Romiplostim



Eltrombopag



Kuter DJ. Int J Hematol 2013; 98:10-23

Eltrombopag use in inherited thrombocytopenia

- Useful for surgery or in those with frequent bleeding
- Start 3 weeks before surgery
- Most need 75mg once daily
- MYH9: Most respond
- ANKRD26: Most respond
- Wiskott Aldrich and XLT: some respond

- Only use short term in conditions associated with malignancy