FUNCTIONAL/QUALITATIVE PLATELET DISORDERS

Michele P. Lambert, MD MSTR

The Children's Hospital of Philadelphia

October 24, 2024

DISCLOSURES

- Lambert: Advisory board member for Octapharma, Novartis, Janssen, Sobi, PDSA, CdLS Foundation and the 22q Society
- Lambert: Consultant for Novartis, Sobi, argenx, Janssen
- Lambert: Research funding from Sysmex, Novartis, Janssen, Sobi, Rocket

QUALITATIVE PLATELET DEFECTS - OVERVIEW

Platelet Function Disorders come in two flavors:

- Inherited
- Acquired

QUALITATIVE PLATELET DEFECTS - OVERVIEW

Platelet Function Disorders come in two flavors:

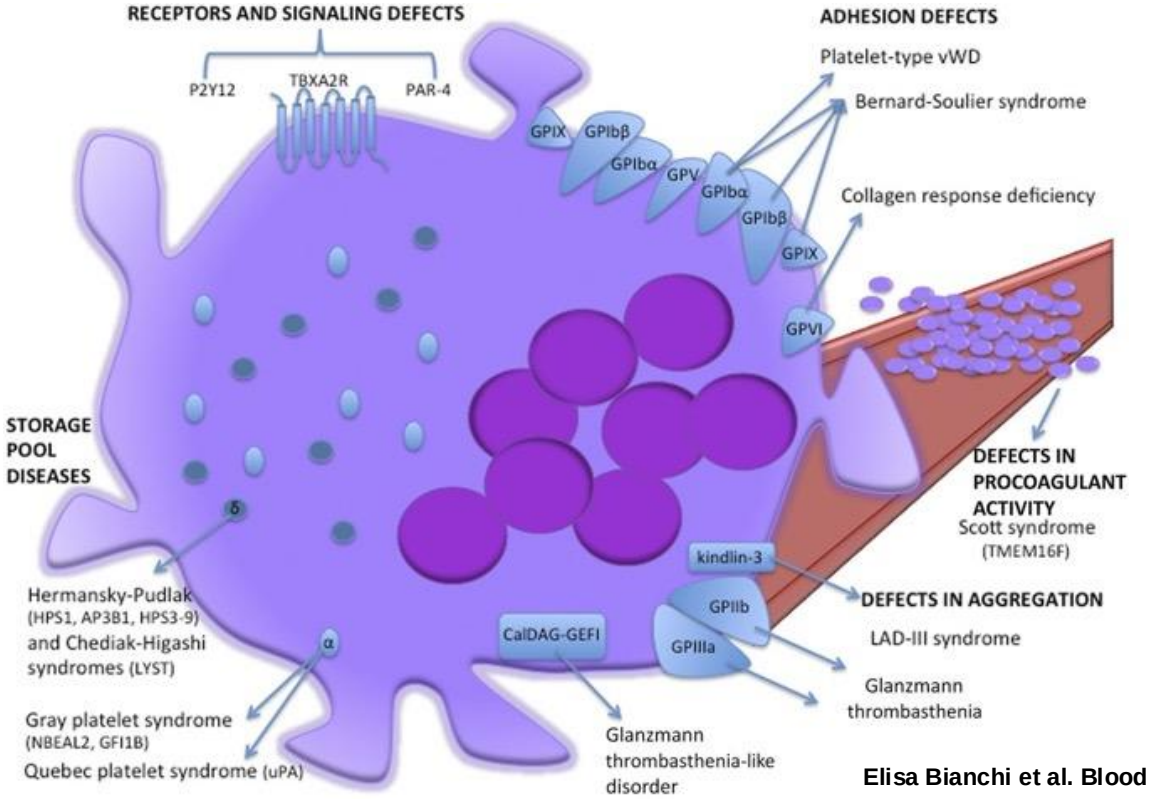
- Inherited Disorders of Platelet Function
  - Adhesion Defects
  - Aggregation Defects
  - Receptor/Signaling Defects
  - Granule Defects
- Acquired Disorders of Platelet Function
  - Drug-induced
  - Non drug-induced

QUALITATIVE PLATELET DEFECTS – GENERAL

- Clinical presentation:
  - Primary hemostasis defect so bleeding reflects primary defect – mucous membranes, skin
  - Bruising, petechiae
  - Epistaxis, mouth bleeding (gums/teeth)
  - GI bleeding
  - Menorrhagia

  - Increased bleeding with trauma and surgery

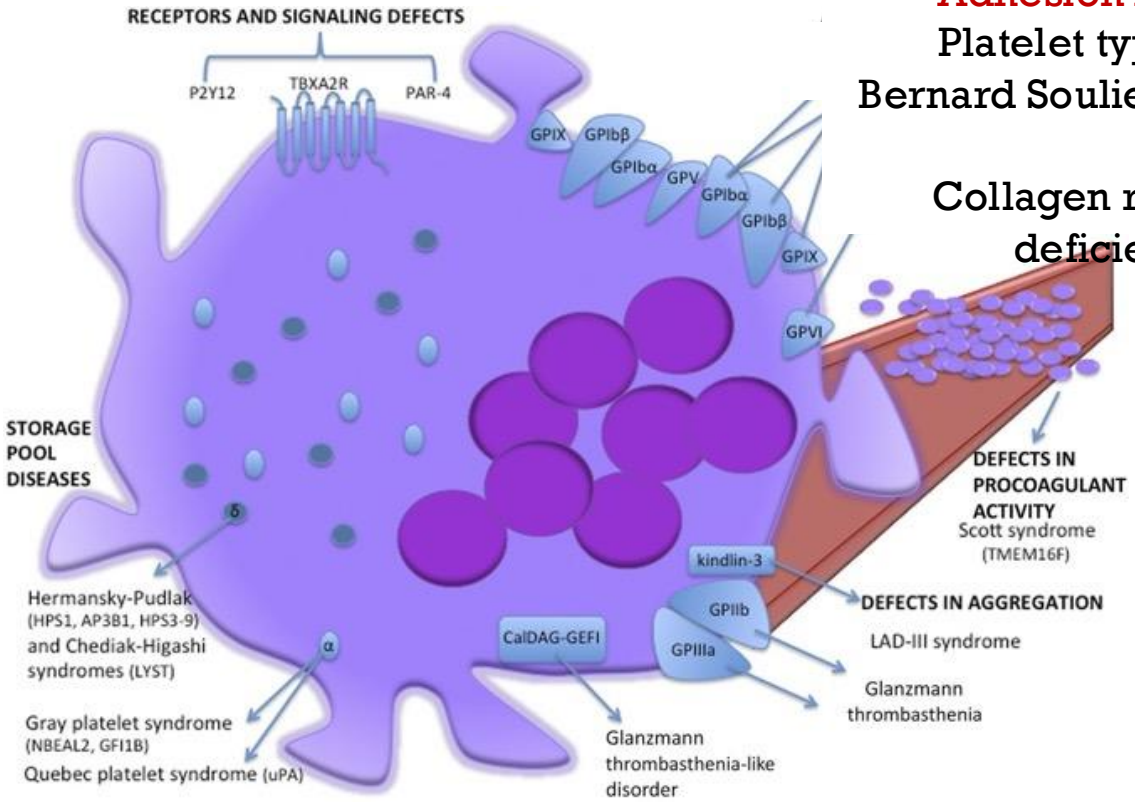
INHERITED PLATELET DISORDERS - OVERVIEW



Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW



Adhesion Defects:

Platelet type VWD

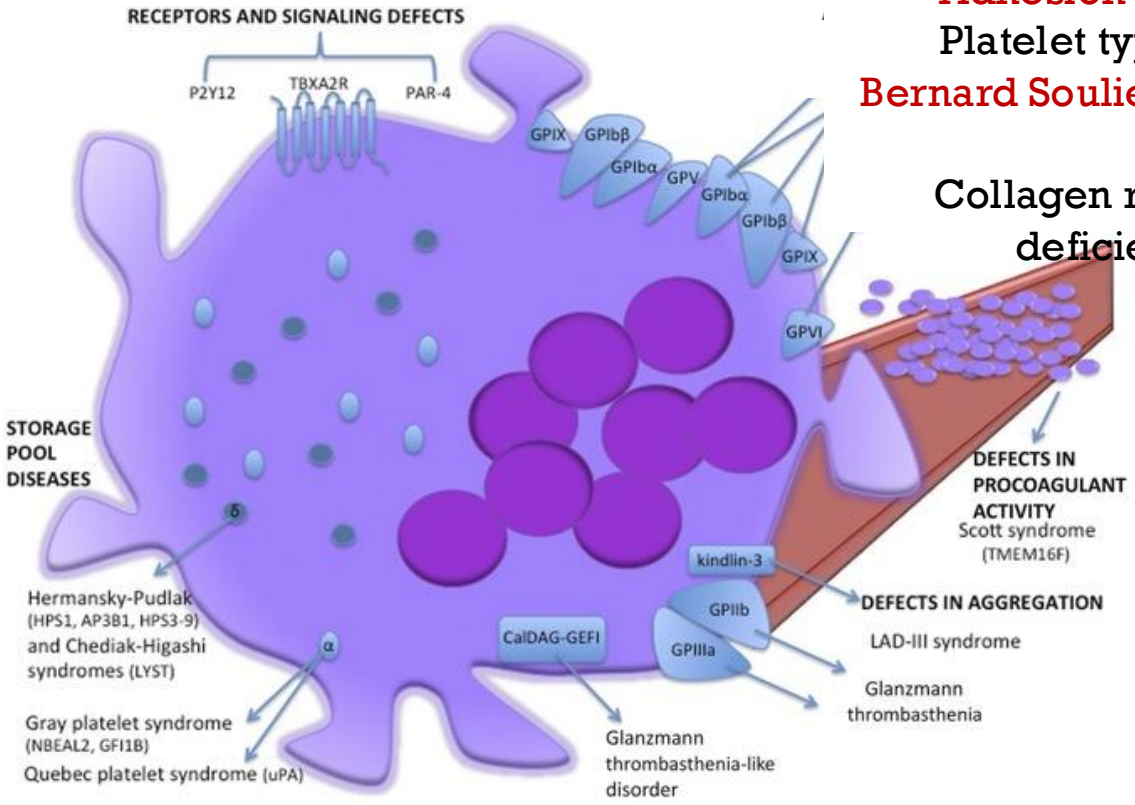
Bernard Soulier Syndrome

Collagen response deficiency

Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW



Adhesion Defects:

Platelet type VWD

Bernard Soulier Syndrome

Collagen response deficiency

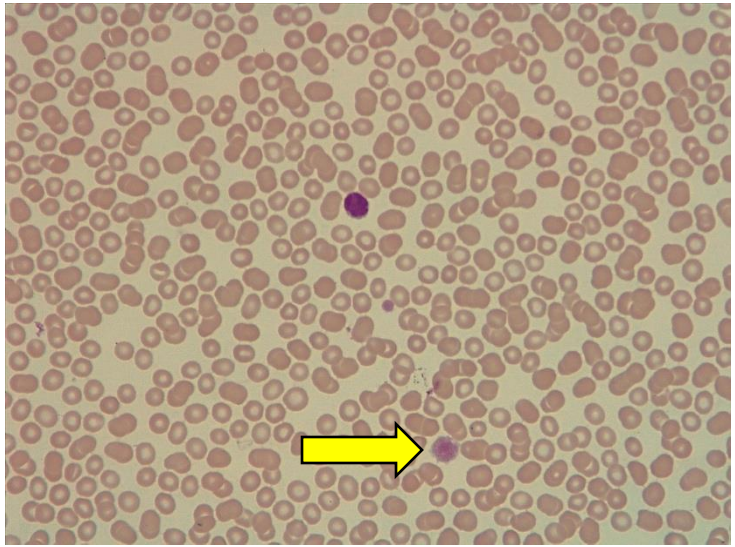
Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

BERNARD SOULIER SYNDROME

- 18 year-old-female with chronic thrombocytopenia initially noted around 15 months of age; platelet count 60-80k/mcL with giant platelets noted on smear; history of excessive bruising and abnormal uterine bleeding requiring iron supplementation and PRBC transfusion

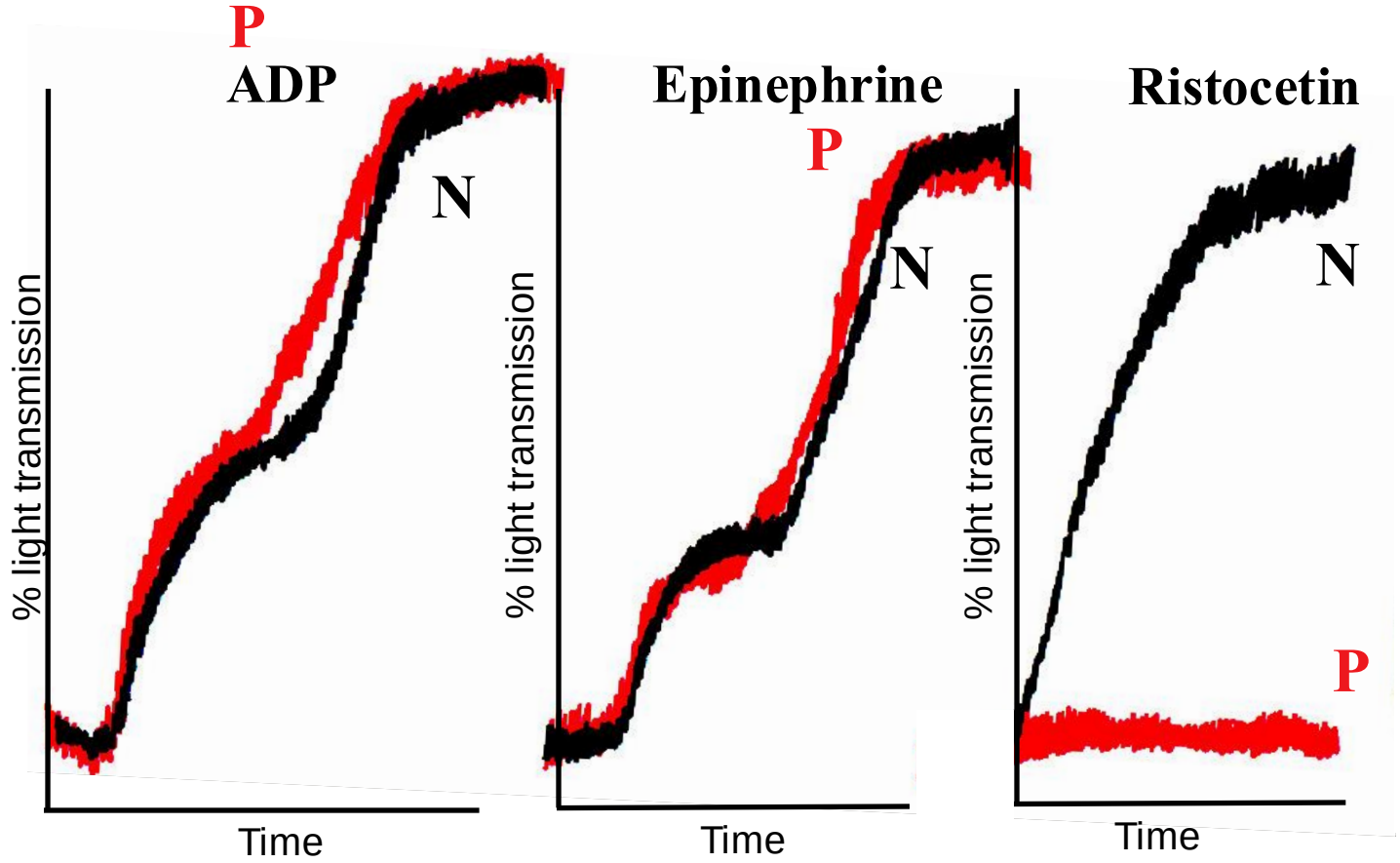
- Hemoglobin 10.2 g/dL
- Platelets 72k/mcL
- MPV 17 fL



BERNARD SOULIER SYNDROME – KEY POINTS

- Autosomal recessive inherited platelet disorder
- Defect in platelet agglutination due to variants in *GPIBA*, *GPIBB* or *GP9* genes
- The second-most diagnosed inherited platelet disorder in adults
- Commonly misdiagnosed as chronic ITP because bleeding manifestations are classically severe but can be moderate-mild
- Thrombocytopenia; increased platelet size
- Absent or markedly reduced aggregation response to ristocetin
- Normal response to ADP, epinephrine, collagen
- Impaired response at low thrombin concentration

BERNARD SOULIER SYNDROME – KEY POINTS

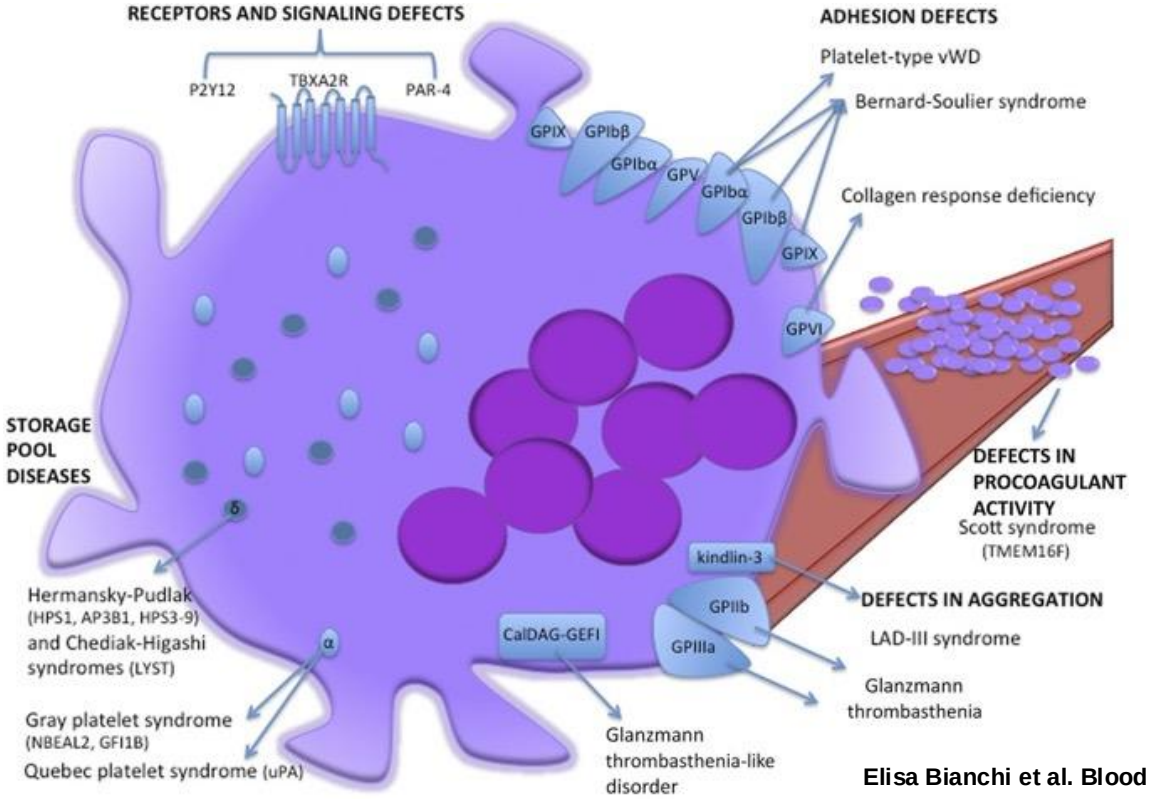


BERNARD SOULIER SYNDROME – BOARD PEARLS

- Low platelet count (but not crazy low)
- Normal coagulation studies
- Abnormal platelet function (agglutination)
- Abnormal bleeding
- Patients are older than GT

- BSS comes first in the alphabet, therefore defect is in GPIb/IX
- Agglutination is abnormal (ristocetin) but ***function*** is normal (IIb/IIIa is functional)

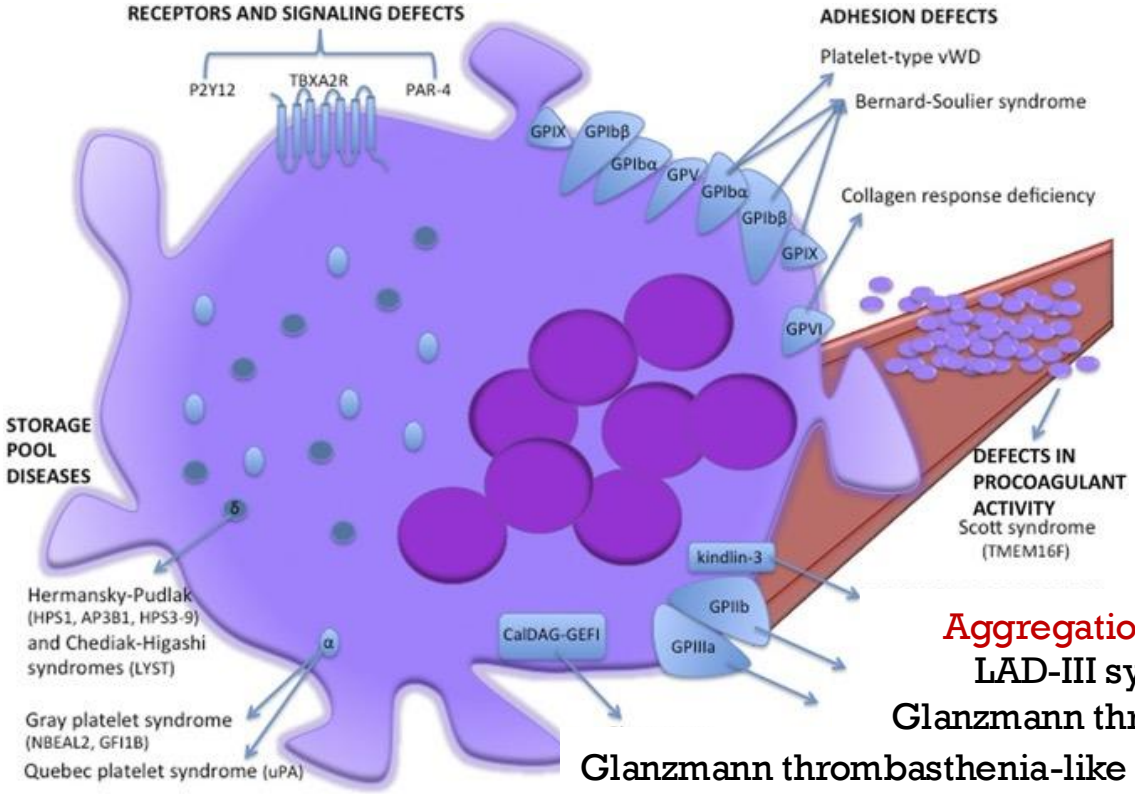
INHERITED PLATELET DISORDERS - OVERVIEW



Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW



Aggregation Defects:

LAD-III syndrome

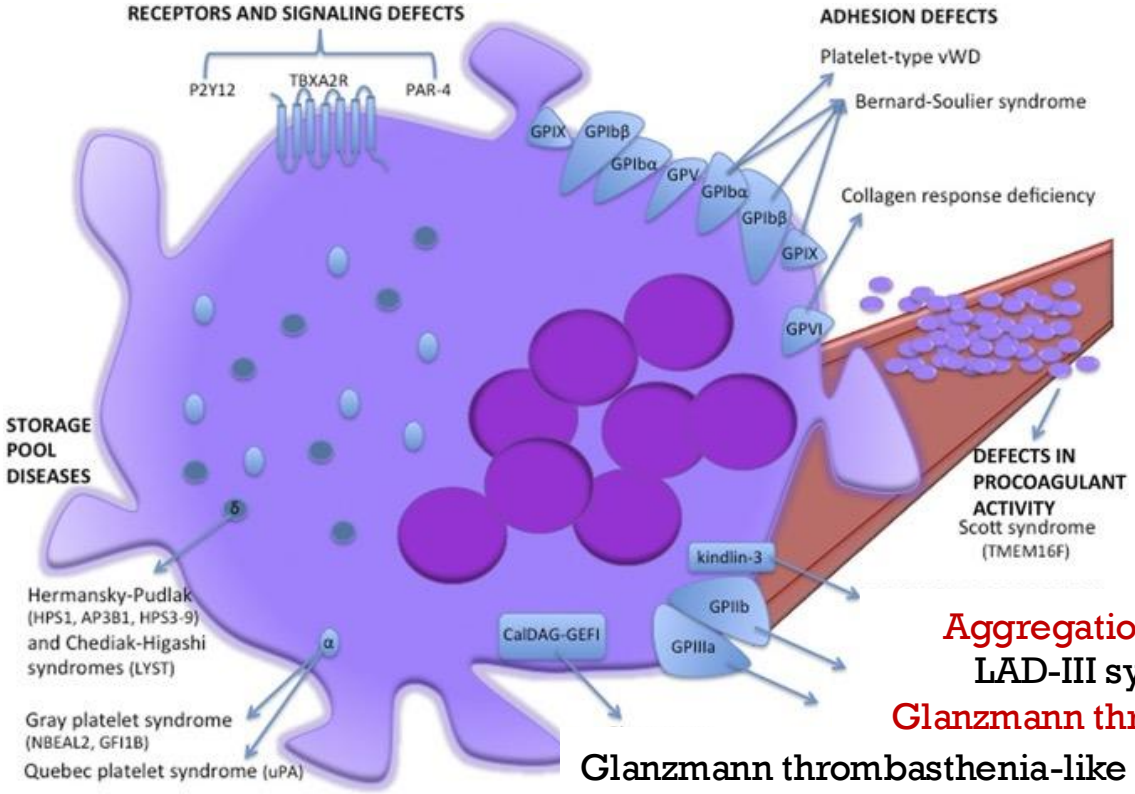
Glanzmann thrombasthenia

Glanzmann thrombasthenia-like disorder

Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW



Aggregation Defects:

LAD-III syndrome

Glanzmann thrombasthenia

Glanzmann thrombasthenia-like disorder

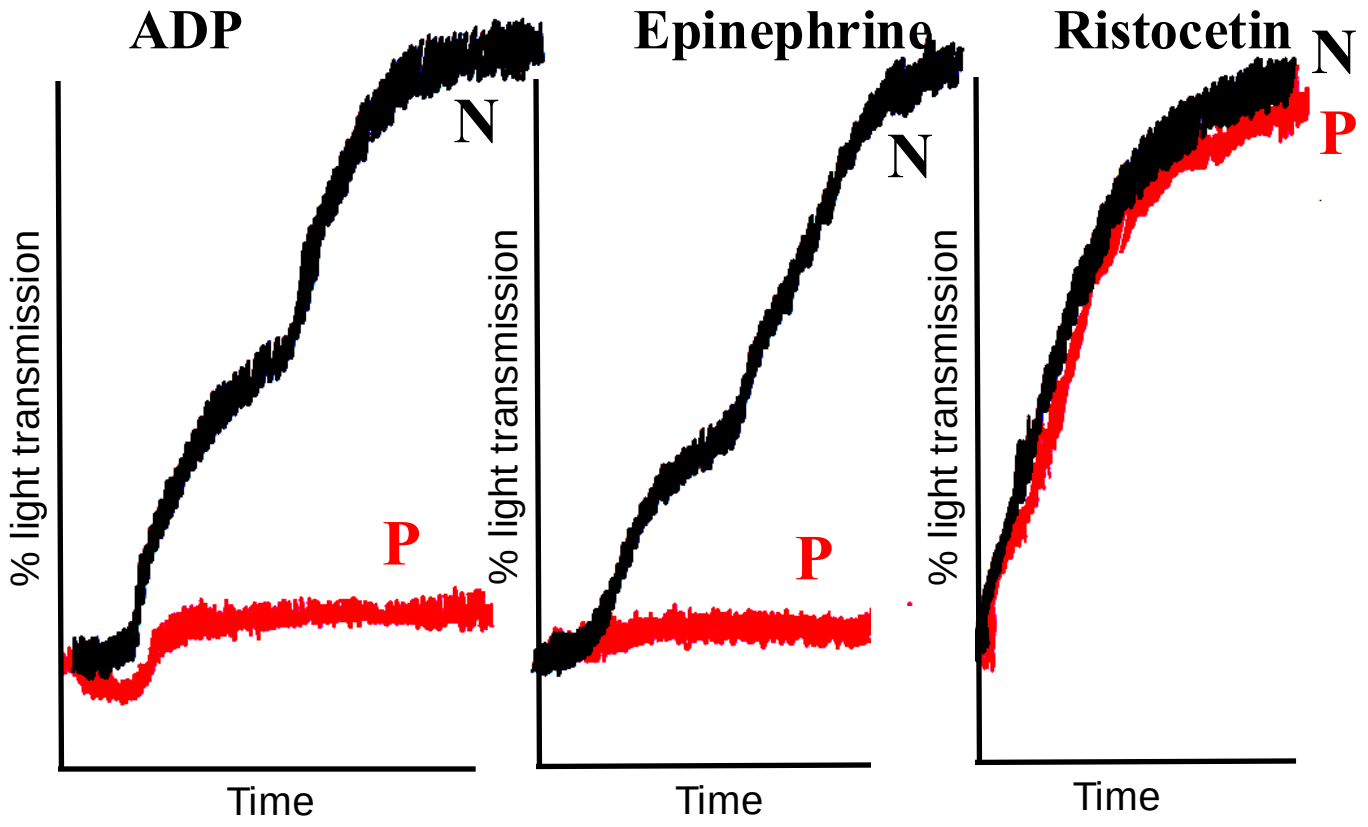
Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

GLANZMANN THROMBASTHENIA

- 9-month-old male presents with bruising, petechiae and epistaxis; PMD made a referral to CPS for suspected abuse due to unusual amount of bruising;
- Bleeding noted with tooth eruption;
- Episode of prolonged epistaxis requiring ED visit and packing
- Hemoglobin 9.7 g/dL with MCV 70.1 fL
- Platelet count 278k/mcL
- PT/PTT and von Willebrand Disease studies are normal

GLANZMANN THROMBASTHENIA – KEY POINTS



GLANZMANN THROMBASTHENIA – KEY POINTS

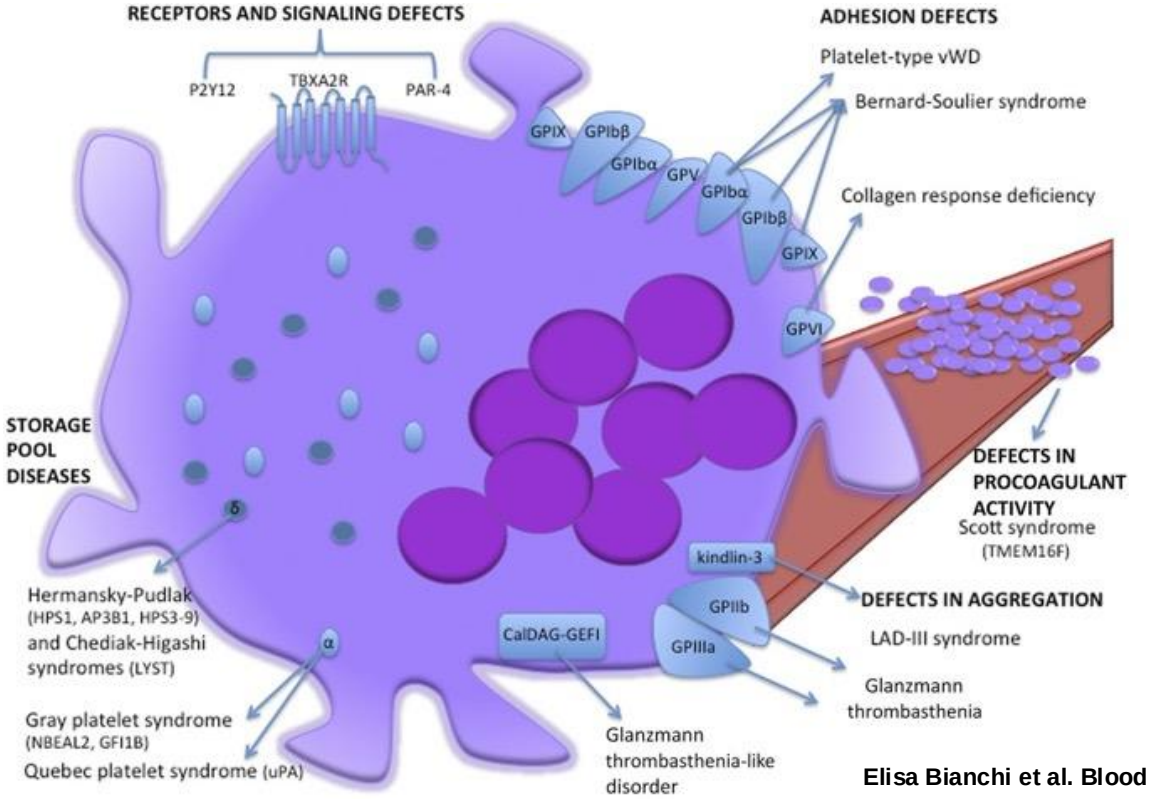
- Autosomal recessive inheritance
- No bleeding in heterozygotes
- Absent or markedly reduced aggregation responses: no primary wave
- Normal aggregation with ristocetin
- Impaired clot retraction in most
- Typically diagnosed in infancy
- Nosebleeds, menstruation and childbearing present special challenges

GLANZMANN THROMBASTHENIA – BOARD PEARLS

- Normal platelet count
- Normal coagulation studies
- Abnormal platelet function
- Abnormal bleeding
- Usually, a young patient

- GT comes second in the alphabet, therefore defect is in GPIIb/IIIa
- Because GPIIb/IIIa is ***THE*** major platelet receptor for aggregation, platelet aggregation is abnormal

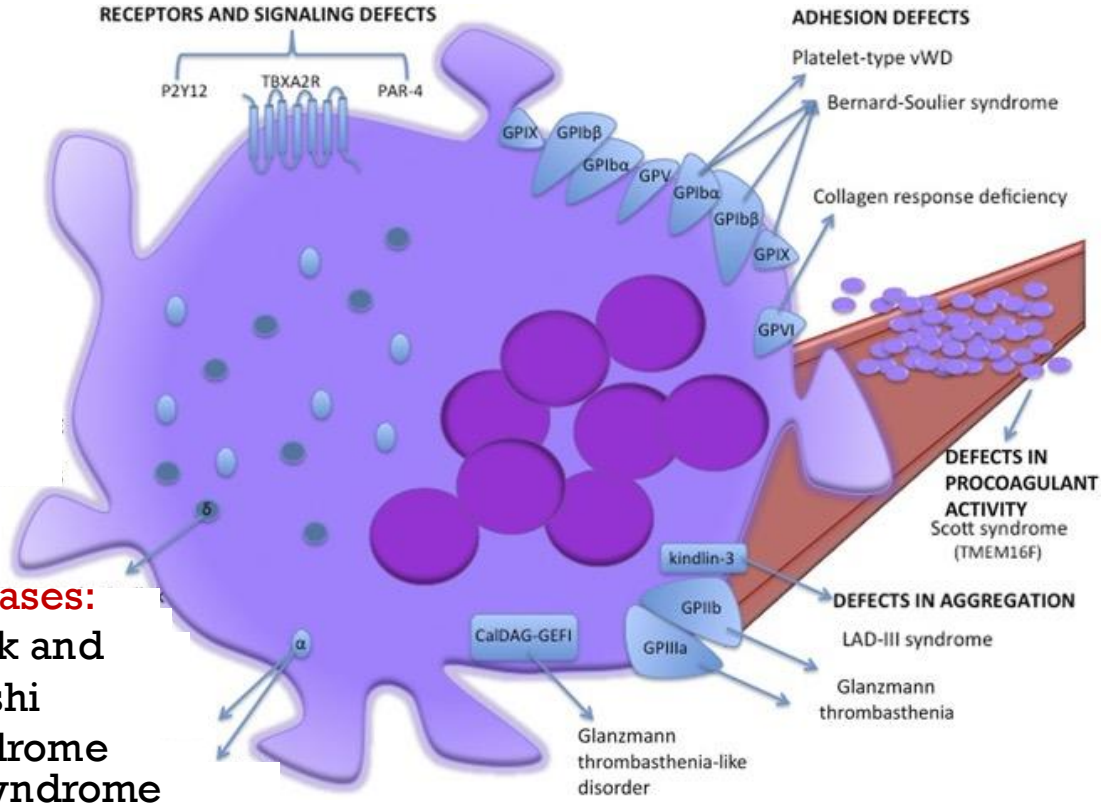
INHERITED PLATELET DISORDERS - OVERVIEW



Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW



Storage Pool Diseases:

Hermansky Pudlak and

Chediak Higashi

Grey Platelet Syndrome

Quebec Platelet Syndrome

Elisa Bianchi et al. Blood 2016;127:1249-1259

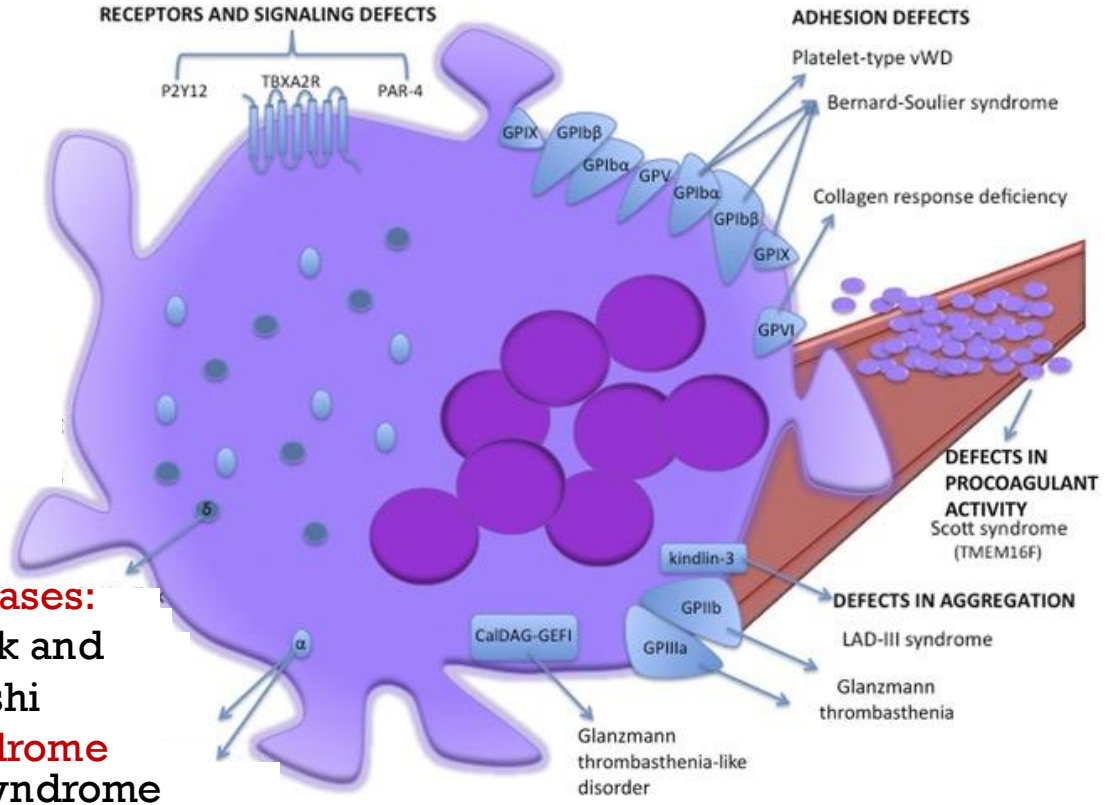
blood

INHERITED PLATELET DISORDERS – STORAGE POOL

- Platelet granules
  - α (red arrow)
  - δ (yellow arrow)
  - Lysosomes and T
- Mitochondria
- Open Canalicular System

Neumüller J, Ellinger A, Wagner T (2015). Transmission Electron Microscopy of Platelets FROM Apheresis and Buffy-Coat-Derived Platelet Concentrates, The Transmission Electron Microscope - Theory and Applications, Dr. Khan Maaz (Ed.), InTech, DOI: 10.5772/60673.

INHERITED PLATELET DISORDERS - OVERVIEW



Storage Pool Diseases:

Hermansky Pudlak and Chediak Higashi

Grey Platelet Syndrome

Quebec Platelet Syndrome

Elisa Bianchi et al. Blood 2016;127:1249-1259

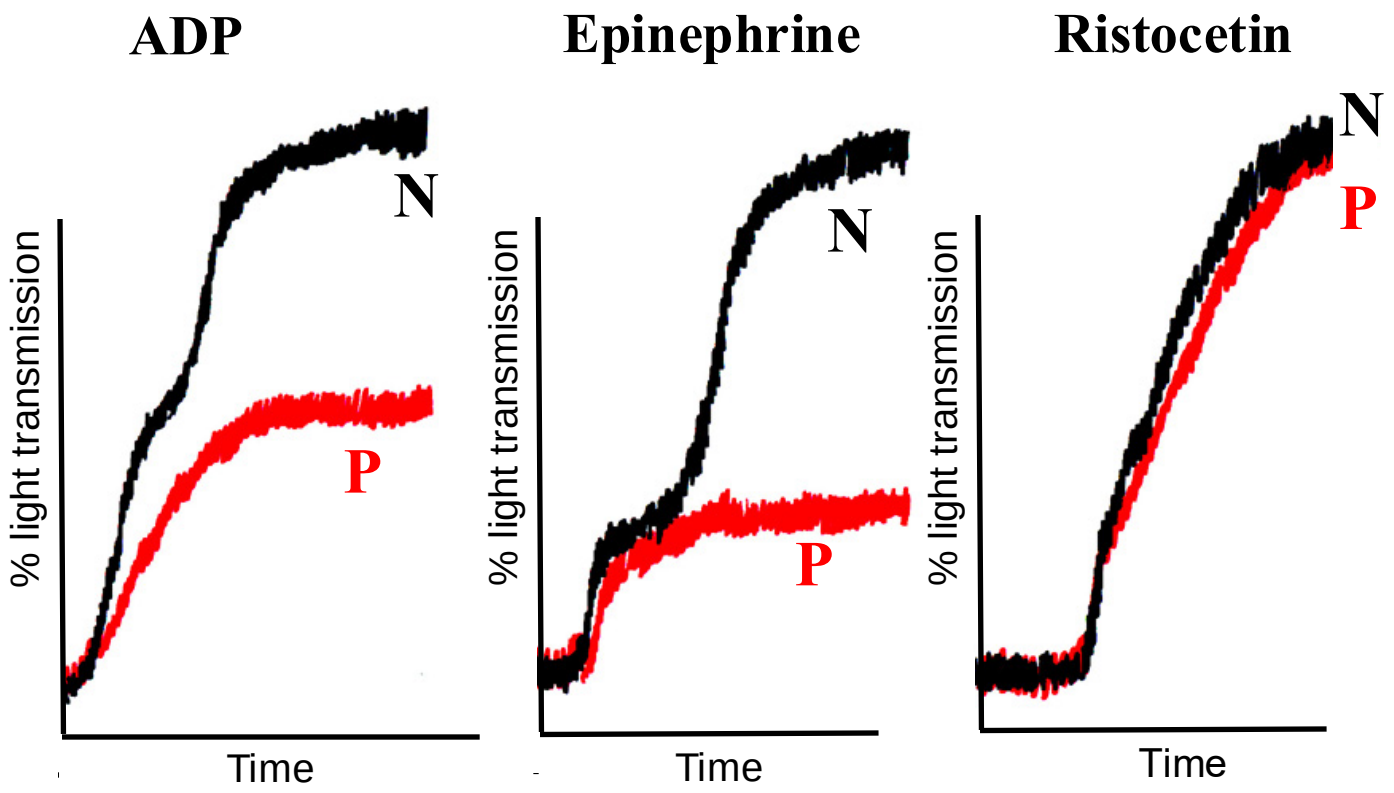
GREY PLATELET SYNDROME

- Moderate thrombocytopenia
- Mild to moderate bleeding diathesis
- Marked decrease in alpha granules in platelets
- Most AR
- myelofibrosis, inflammation

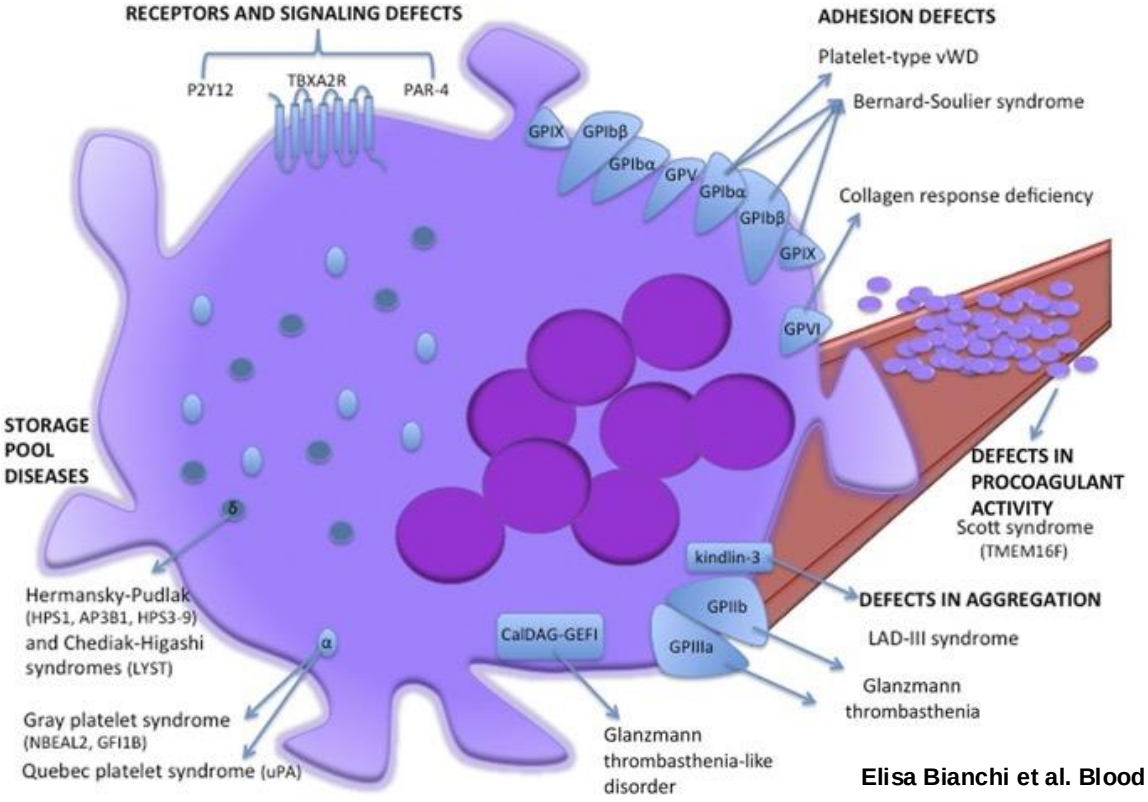
Walter H. A. Kahr, and Yigal Dror Blood 2012;120:2543

blood™

STORAGE POOL DEFICIENCY (GPS AND OTHERS)



INHERITED PLATELET DISORDERS - OVERVIEW



Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

INHERITED PLATELET DISORDERS - OVERVIEW

Receptor and Signaling Defects:

ADP (P2Y12)

Thromboxane A2

GPVI, GPIa/IIa

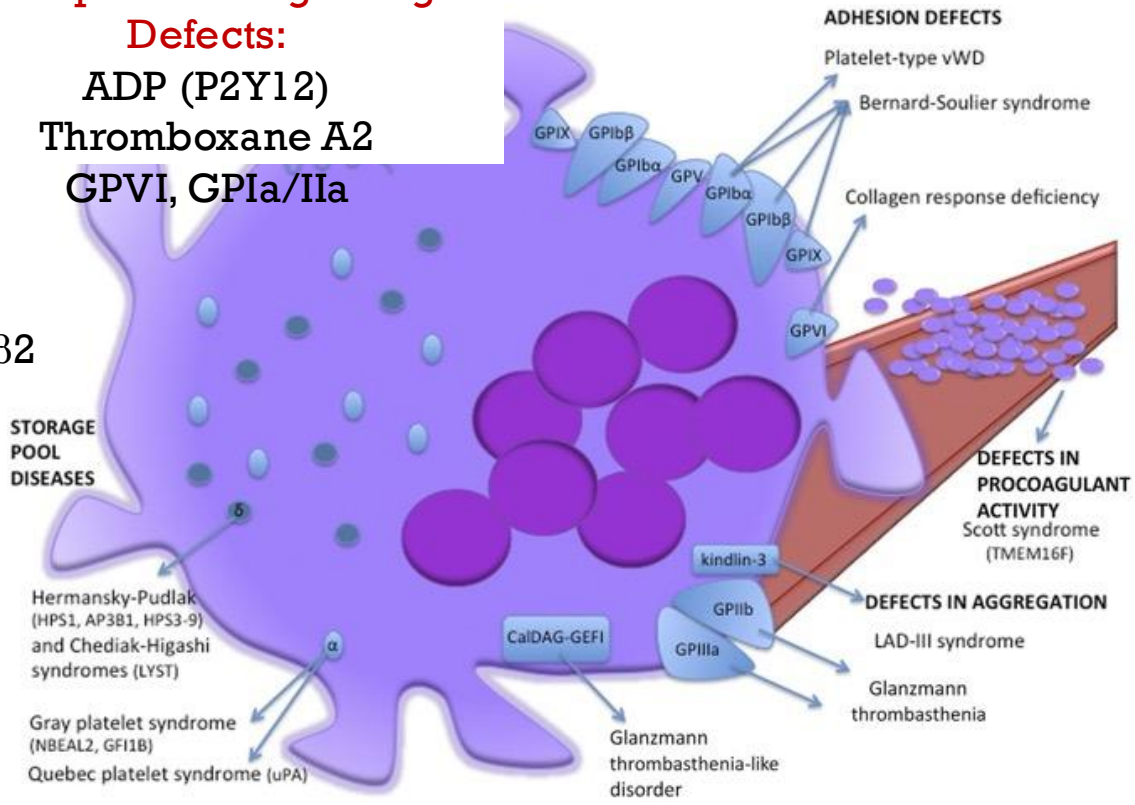
G proteins

Gαq, Gαi2, Gαs

Effector Enzyme Defects

Phospholipase C-β2

PKC-Θ



Elisa Bianchi et al. Blood 2016;127:1249-1259

blood

MISCELLANEOUS DISORDERS OF PLATELET FUNCTION

- Several other congenital platelet disorders are associated with abnormal platelet function:
  - Wiskott Aldrich Syndrome:
    - X-linked, immunodeficiency, thrombocytopenia, small platelets
    - Associated with eczema and increased ITP
  - RUNX1 – related platelet disorder
    - Variable thrombocytopenia
    - Variable platelet dysfunction
    - Increased risk of malignancy (primarily AML)

MANAGEMENT PRINCIPALS

- Individualized based on clinical features
- Platelet transfusions indicated in the management of bleeding episodes or surgical procedures
- Risk of developing specific anti-platelet antibodies (GT>>>BSS)
- Antifibrinolytics (aminocaproic acid and tranexamic acid)
- DDAVP (Desmopressin) → more for storage pool deficiency than GT
- Recombinant Factor VIIa (licensed for GT) → doses needed are high (90-270 mcg/kg) but prophylaxis can be be effective (3x/week) at reducing bleeding frequency and severity
  - rFVIIa works more effectively if given with platelet transfusion to reduce total transfusion needs

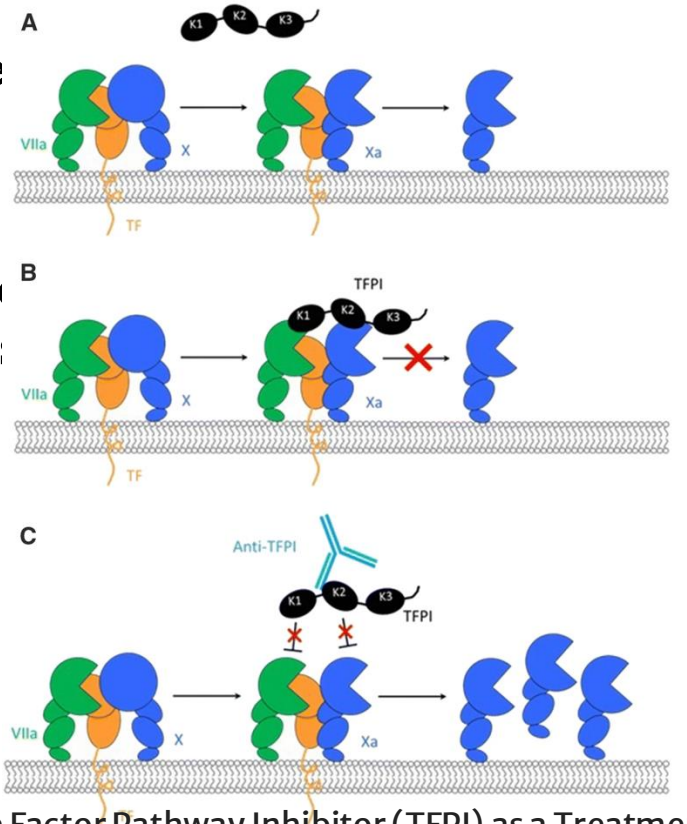
MANAGEMENT PRINCIPLES – NOVEL THERAPEUTICS

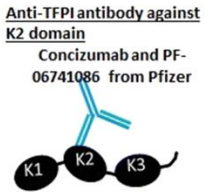
- Several therapies in development and being looked at specifically in GT

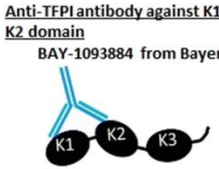
- TFPI inhibitors (concizumab and marstacimab) – block TFPI and therefore increase tissue factor-VIIa complex and generation of FXa

MANAGEMENT PRINCIPLES – NOVEL THERAPEUTICS

- Several therapie ecifically in GT
- TFPI inhibitors (PI and therefore increa ion of FXa







Chowdary, P. Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab. *Drugs* **78**, 881–890 (2018). https://doi.org/10.1007/s40265-018-0922-6

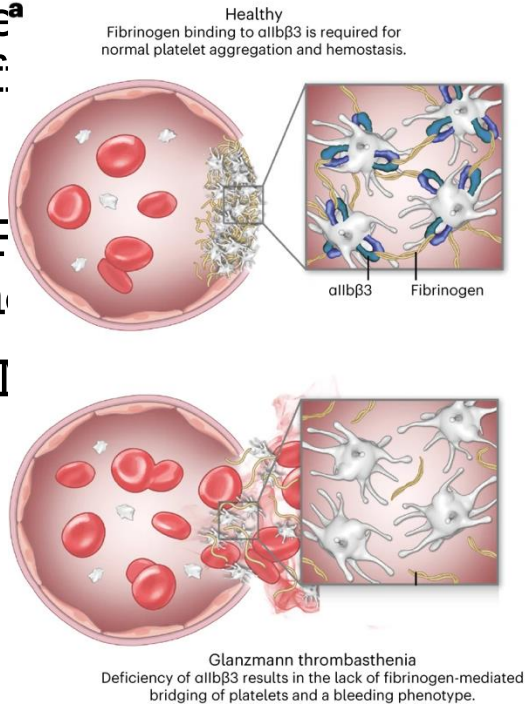
MANAGEMENT PRINCIPLES – NOVEL THERAPEUTICS

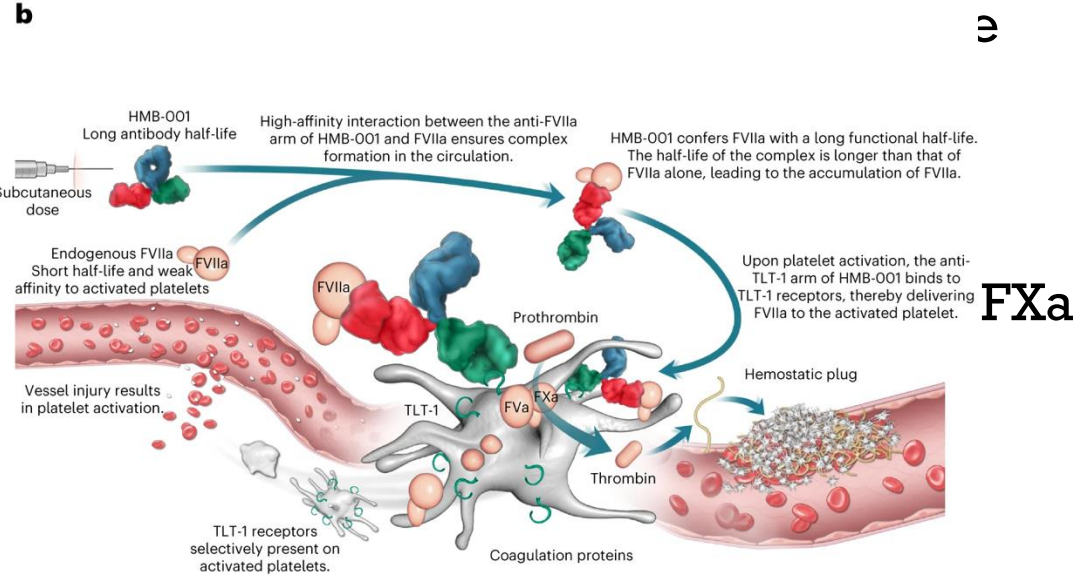
- Several therapies in development and being looked at specifically in GT

- TFPI inhibitors (concizumab and marstacimab) – block TFPI and therefore increase tissue factor-VIIa complex and generation of FXa
- HMB001 (FVII-TLT1 bispecific antibody) – brings factor VII to activated platelet surface to increase Xa generation and thrombin generation

MANAGEMENT PRINCIPLES – NOVEL THERAPEUTICS

- Se[a]
  ef
- TF
  th
- Hl





FXa

Gandhi, P.S., Zivkovic, M., Østergaard, H. *et al.* A bispecific antibody approach for the potential prophylactic treatment of inherited bleeding disorders. *Nat Cardiovasc Res* **3**, 166–185 (2024). https://doi.org/10.1038/s44161-023-00418-4

SUMMARY – CONGENITAL DISORDERS

- Glanzmann Thrombasthenia
  - Autosomal Recessive
  - Severe Bleeding (young)
  - Receptor Defect
  - GPIIb/IIIa
  - Abnormal Aggregation
  - Normal Ristocetin
- Bernard Soulier Syndrome
  - Autosomal Recessive
  - Severe Bleeding (older)
  - Receptor Defect
  - GPIb/IX
  - Normal Aggregation
  - Abnormal Ristocetin

SUMMARY – CONGENITAL DEFECTS

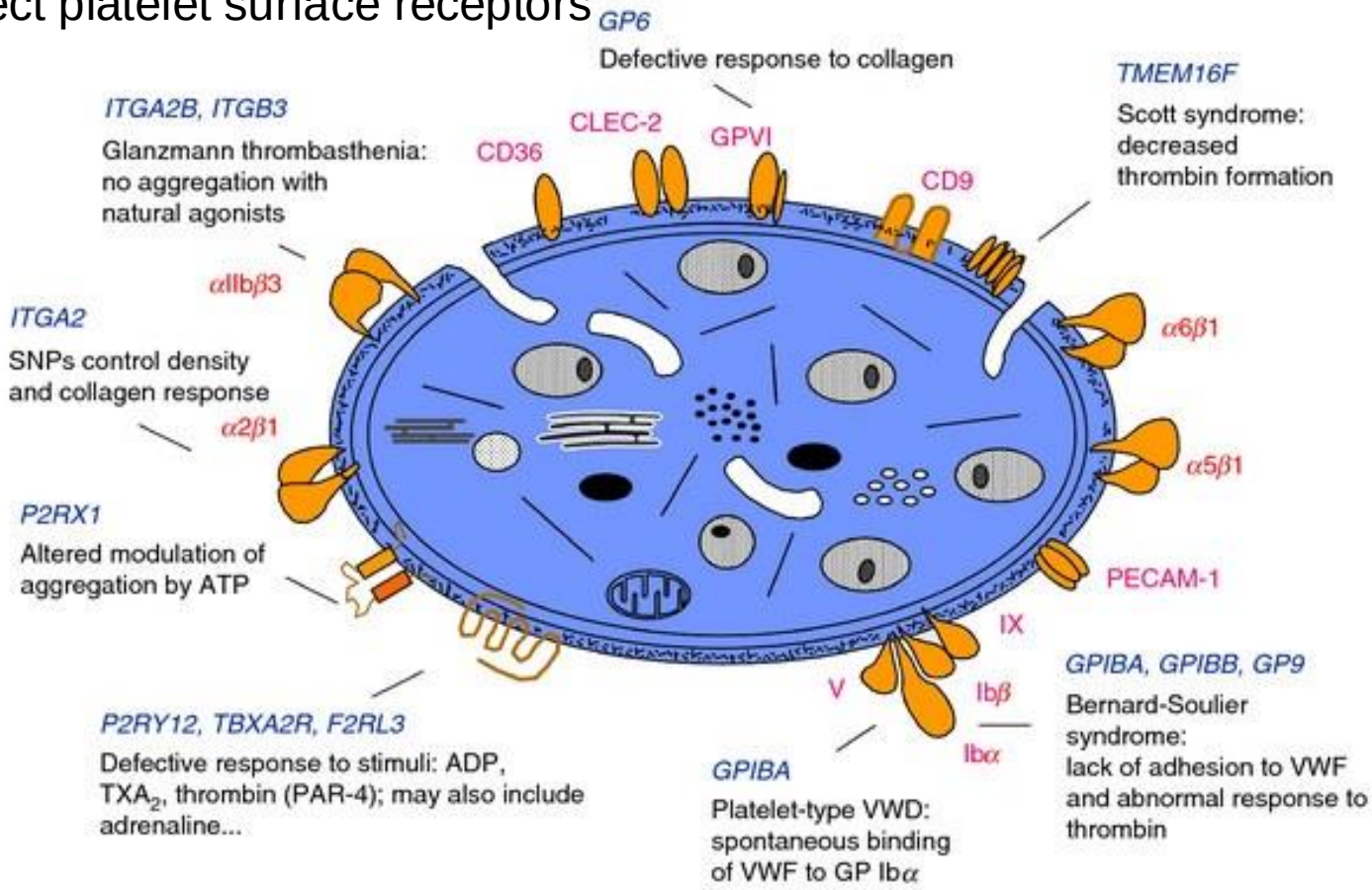
- Storage Pool
  - Absent second wave
  - Missing "chips"
  - Syndromic or non-syndromic
- Signaling Defects
  - Specific receptor defects
  - Often mimic medication effects

QUALITATIVE PLATELET DEFECTS - OVERVIEW

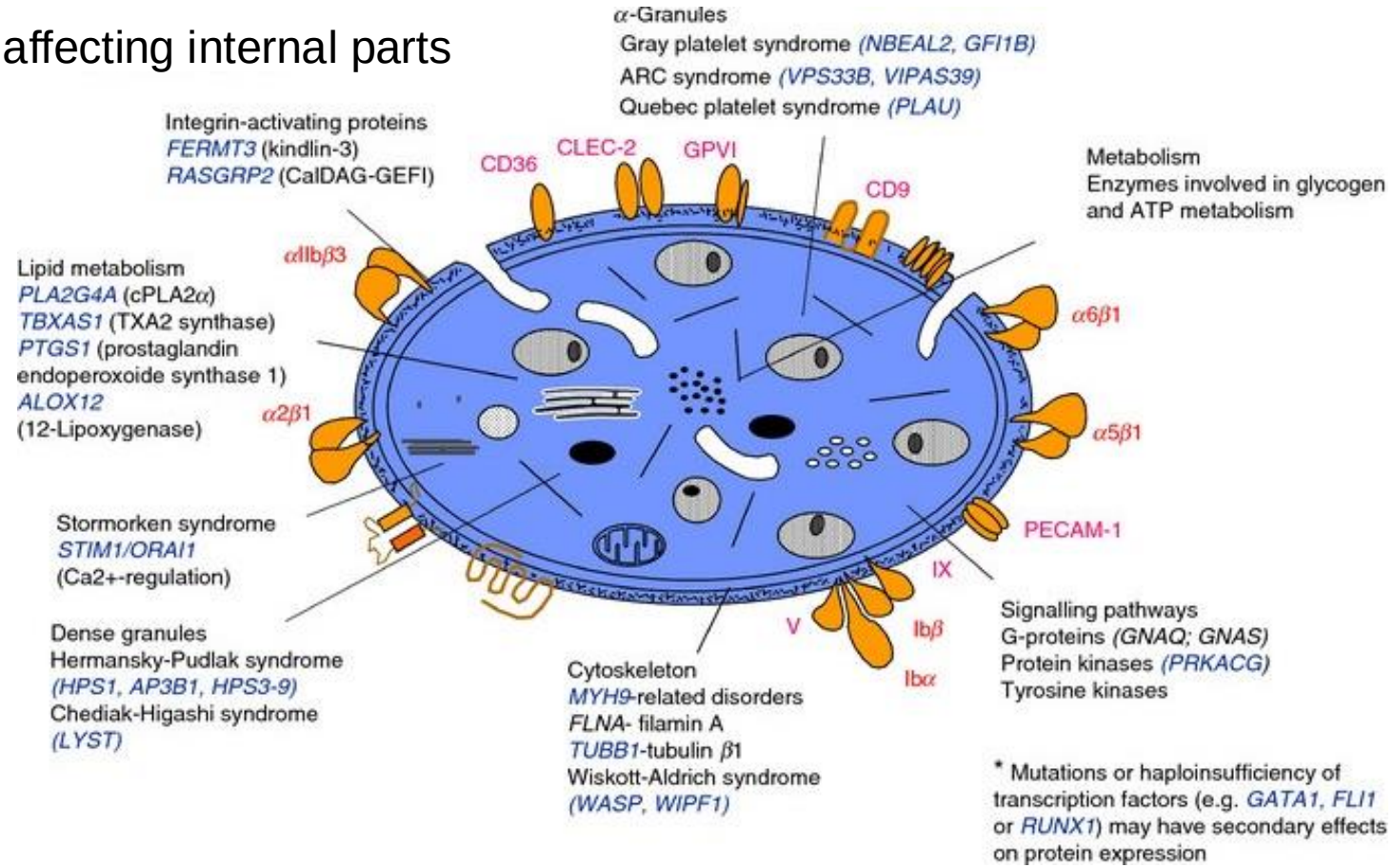
Platelet Function Disorders come in two flavors:

- Inherited Disorders of Platelet Function
  - Adhesion Defects
  - Aggregation Defects
  - Receptor/Signaling Defects
  - Granule Defects
- Acquired Disorders of Platelet Function
  - Drug-induced
  - Non drug-induced

Genes affect platelet surface receptors



Genes affecting internal parts



AND THE LIST OF GENES KEEPS GROWING

ACQUIRED DISORDERS OF PLATELET FUNCTION

- Medications
- Chronic renal disease
- Liver disease
- Bone marrow disease
- Cardiopulmonary bypass
- Antiplatelet antibodies
- Acquired storage pool disorders

ACQUIRED DISORDERS OF PLATELET FUNCTION

- Statistically, maybe more common
  - Congenital disorders are underdiagnosed and often missed
  - Mild congenital function disorders combined with inhibitory drugs may produce significantly more symptoms
- Most often medication related

ACQUIRED PLATELET DYSFUNCTION - DRUGS

- NSAIDS
- Antibiotics
- Cardiovascular Drugs
  - β-Adrenergic Blockers (propranolol)
  - Vasodilators (Nitroprusside, nitroglycerin)
  - Calcium Channel Blockers (Verapamil)
  - Quinidine
- Psychotropic Drugs
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Tricyclic Antidepressants (Imipramine)
  - Phenothiazines (Chlorpromazine)
- Anesthetics
  - Local (e.g., Dibucaine); General (e.g., Halothane)
- Chemotherapeutic Agents
  - Mithramycin, BCNU, Daunorubicin, MEK inhibitors
- Dextrans
- Ethanol
- Vitamin E
- Radiographic Contrast Media

NSAIDS AND BLEEDING

- Reversibly inhibit cyclooxygenase
- Variable binding to COX-1/COX-2 depending on drug so relative risk of bleeding varies
- Combined with other drugs may worsen bleeding – eg SSRIs
- Because binding is reversible, but same site as aspirin, can interfere with antithrombotic effect

SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS (SSRIS)

- Platelets incorporate serotonin into dense granules – by uptake from plasma
- SSRIs inhibit platelet function – prolong BT, inhibit aggregation - secretion, prolong PFA CT.
- Associated with increased risk of GI bleeds, transfusions following orthopedic surgery, and hospital admissions for bleeding

PLATELET DYSFUNCTION IN RENAL DISEASE

- Uremia classically associated with platelet dysfunction
  - Independent of platelet count
  - Platelet adhesion defect
    - Perhaps why DDAVP helps in bleeding Altered levels of endothelial NO and PGI2?
  - Decreased platelet secretion
    - Impaired arachidonic acid and prostaglandin metabolism
  - Storage pool defect Due to platelet activation during dialysis?
    - Decreased ADP, serotonin and TxA2 Due to circulating Arg-Gly-Arg containing peptides?
  - Defect in GPIIb/IIIa signaling
    - Impaired fibrinogen binding
- Can not forget importance of anemia in altering vascular rheology

CHRONIC RENAL FAILURE: THERAPEUTIC APPROACHES

- Increase in Hct by RBC transfusions and erythropoietin is associated with correction of BT and diminished clinical bleeding
- Dialysis (hemodialysis and peritoneal) effective in correcting the BT and platelet aggregation defect
- Platelet transfusions
- DDAVP shortens BT in 50-75% patients
- Cryoprecipitate shortens the BT in some studies
- Conjugated estrogens (IV or oral) reported to shorten prolonged BT

PLATELETS IN LIVER DISEASE

- 6% thrombocytopenia in chronic, non-cirrhotic liver disease
- 76% mild-moderate thrombocytopenia in cirrhosis
  - 13% severe thrombocytopenia (<50K/mcL platelet count)
- Platelet dysfunction
- 10-20% portal vein thrombosis; DVT and embolic disease

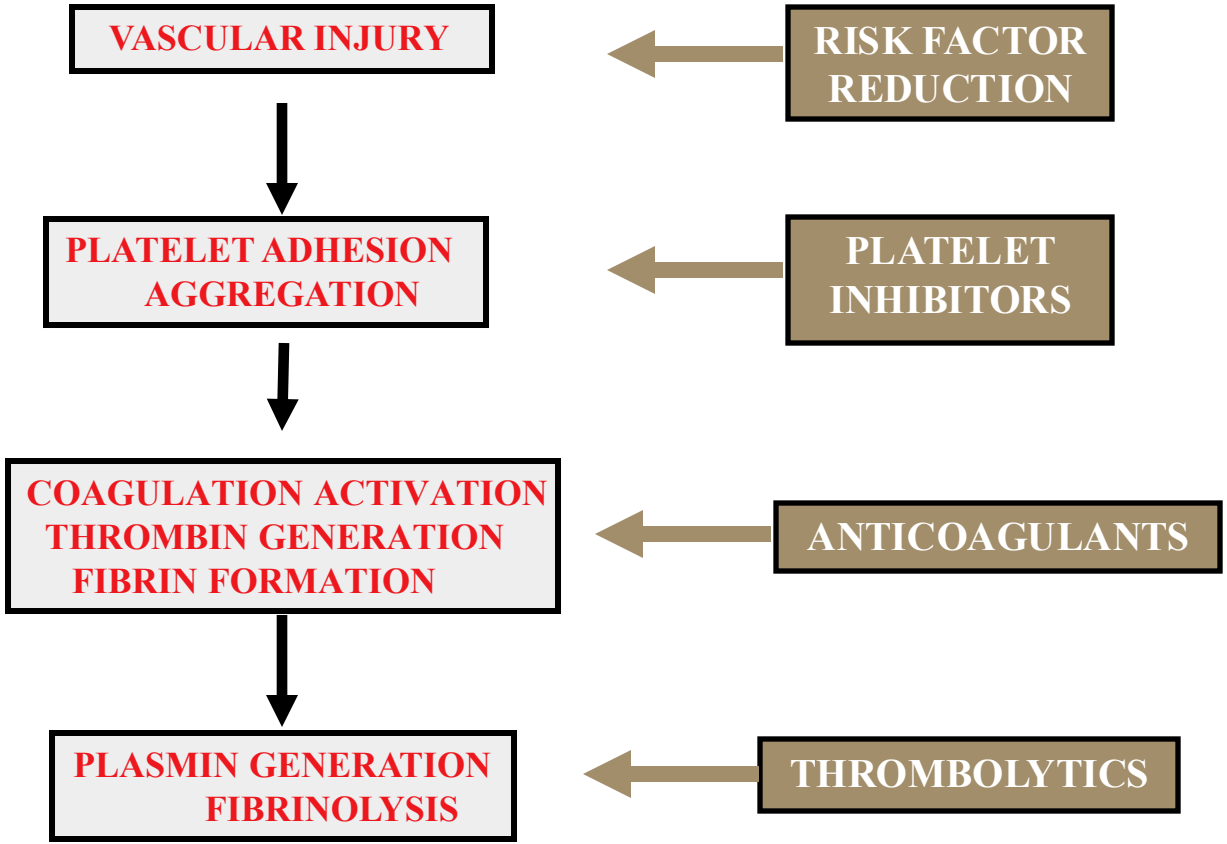
PLATELET DYSFUNCTION IN LIVER DISEASE

- Defects in thromboxane A2 synthesis
- Storage pool deficiency
- GP1b abnormalities

- ?role of anemia similar to renal disease

ANTI-PLATELET THERAPY

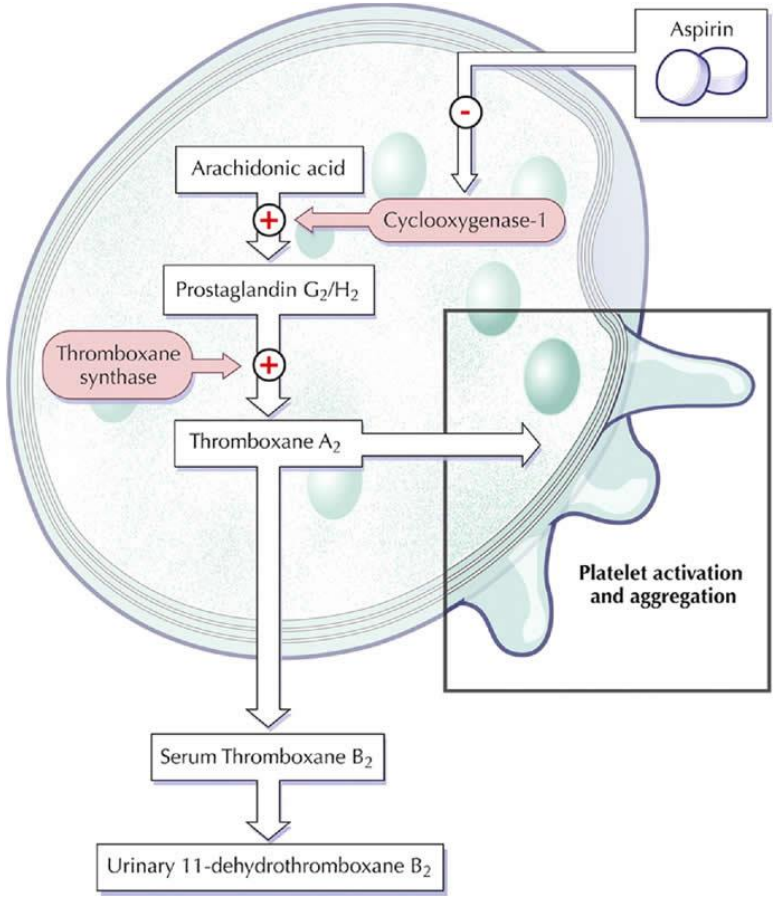
STRATEGIES FOR ANTITHROMBOTIC THERAPY



ANTI-PLATELET THERAPIES

- Aspirin
- Dipyridamole
- P2Y12 antagonists
  - *Thienopyridines:* Ticlopidine, Clopidogrel, Prasugrel
  - *Non-Thienopyridines:* Ticagrelor, Cangrelor
- *GPIIb/IIIa Inhibitors: Abciximab, Eptifibatide, Tirofiban*
- *PAR1 antagonists*
- *Cilostazol*

ASPIRIN MECHANISM



ASPIRIN PHARMACOKINETICS

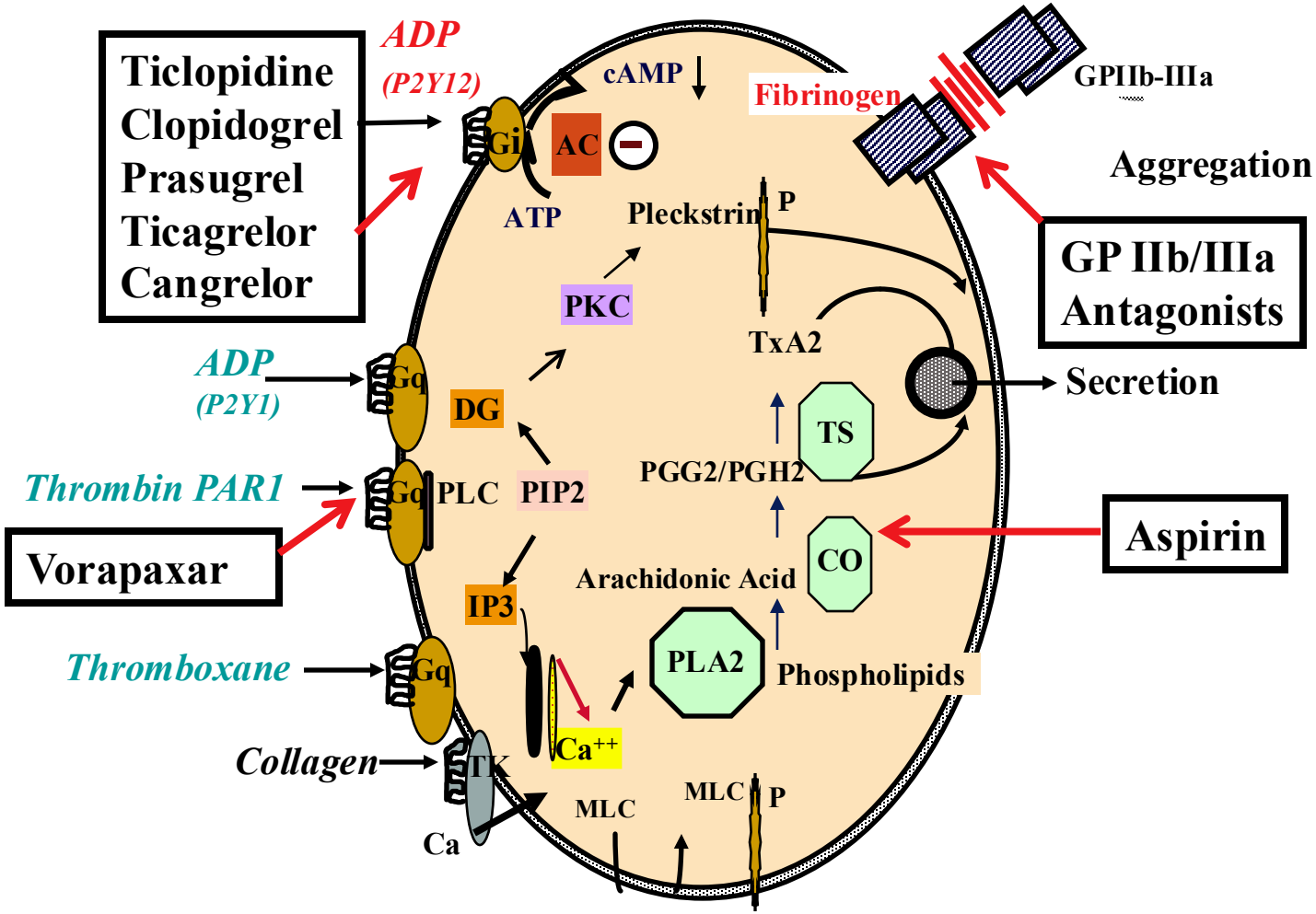
- Rapidly absorbed in stomach and small intestine
- Peak levels at 30-40 min after ingestion
- Plasma concentration decays: half-life of 15-20 min
- Inhibition of platelet function evident at 1 hour
- Irreversibly inactivates COX in platelets
- Acetylates the enzyme in megakaryocytes as well

ASPIRIN AS ANTITHROMBOTIC AGENT

- Effective in a wide range of arterial disorders
- Reduces vascular deaths by 15% and vascular events by 30% in high-risk patients
- Effective when used long-term in doses 50-100 mg/day
- No convincing evidence that higher doses are more effective
- Lower doses (300 mg) produce fewer GI side effects than higher doses (1200 mg)
- Bleeding risks increased with increasing aspirin dose (75-325 mg/d) with or without clopidogrel (CURE Trial)

ANTI-PLATELET THERAPIES

- Aspirin
- Dipyridamole
- P2Y12 antagonists
  - *Thienopyridines:* Ticlopidine, Clopidogrel, Prasugrel
  - *Non-Thienopyridines:* Ticagrelor, Cangrelor
- *GPIIb/IIIa Inhibitors: Abciximab, Eptifibatide, Tirofiban*
- *PAR1 Antagonists*
- *Cilostazol*


Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor
Cangrelor
ADP
(P2Y12)
Gi
AC
cAMP
ATP
Fibrinogen
GPIIb-IIIa
Aggregation
GP IIb/IIIa
Antagonists
Pleckstrin
P
PKC
TxA2
Secretion
ADP
(P2Y1)
Gq
DG
TS
Thrombin PAR1
Gq
PLC
PIP2
PGG2/PGH2
Vorapaxar
Aspirin
CO
Arachidonic Acid
IP3
PLA2
Phospholipids
Thromboxane
Gq
Ca++
Collagen
TK
MLC
P
MLC
Ca

P2Y12 ANTAGONISTS

Ticlopidine, Clopidogrel*, Prasugrel

- Prodrugs
- Converted to active metabolites by liver cytochrome P450 isozymes
- Irreversible Inhibitors

Ticagrelor, Cangrelor

- Direct acting
- Reversible inhibitors
- Ticagrelor: oral
- Cangrelor: IV

*AE: TTP associated with clopidogrel

KEY ANTI-PLATELET MEDICATION NOTES

- Clopidogrel associated with TTP
- Cilostazol increases platelet cAMP (phosphodiesterase III inhibitor)
  - alters platelet responses to most agonists
- IIB/IIIa associated with "ITP" (drug - induced thrombocytopenia)
  - Tirofiban and eptifibatide: drug binding induces neoepitobe
  - Abciximab: chimeric human-mouse Fab and antibodies are against murine Fab

ACQUIRED DISORDERS OF PLATELET FUNCTION

- Medications
- Chronic renal disease
- Liver disease
- Bone marrow disease
- Cardiopulmonary bypass
- Antiplatelet antibodies
- Acquired storage pool disorders

SUMMARY – ACQUIRED PLATELET DEFECTS

- Common cause of platelet dysfunction
- Suspect in a patient with new onset bleeding symptoms
- Careful medication history is important (any medication could be culprit, but most not associated with clinical bleeding)
- Not always ***unintended*** effect of therapy (although bleeding is not generally the goal)
- Liver and renal disease are potentially associated with platelet dysfunction
- Acquired platelet dysfunction with cardiopulmonary bypass beyond thrombocytopenia
- Bone marrow disease associated with acquired storage pool disease

THANK YOU