

HEMATOLOGY REVIEWS

Qualitative Platelet Defects



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DISCLOSURES

- Lambert: Advisory board member for Octapharma, Novartis, Shionogi, Rigel, Principia, PDSA, CdLS Foundation and the 22q Society
- Lambert: Consultant for Novartis, Shionogi, Dova, Principia, Argenx, Rigel
- Lambert: Research funding from Sysmex, Novartis, Rigel, Argenx, Principia, Dova and Astra Zeneca
- Poncz: Consultant for Sanofi, Johnson & Johnson
- Poncz: Research funding from Astra Zeneca, Alexion, NIH (P01, R35 and R01).



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



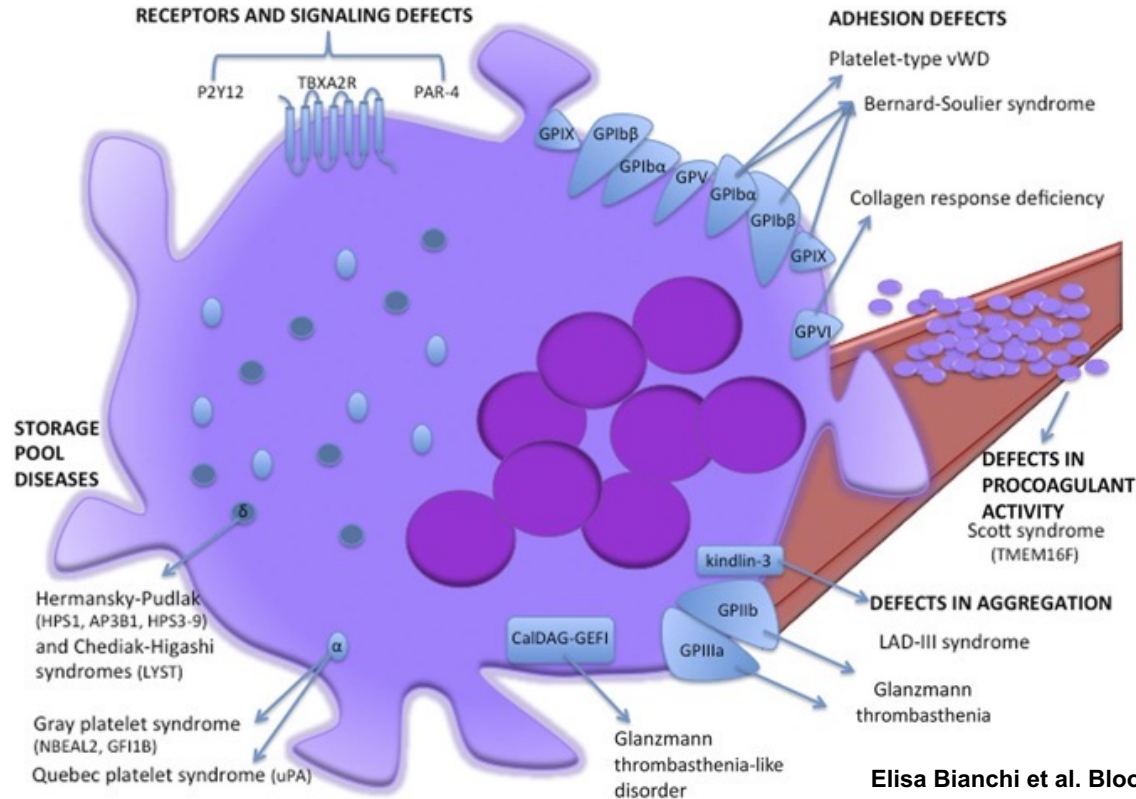
QUALITATIVE PLATELET DEFECTS – GENERAL

- **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

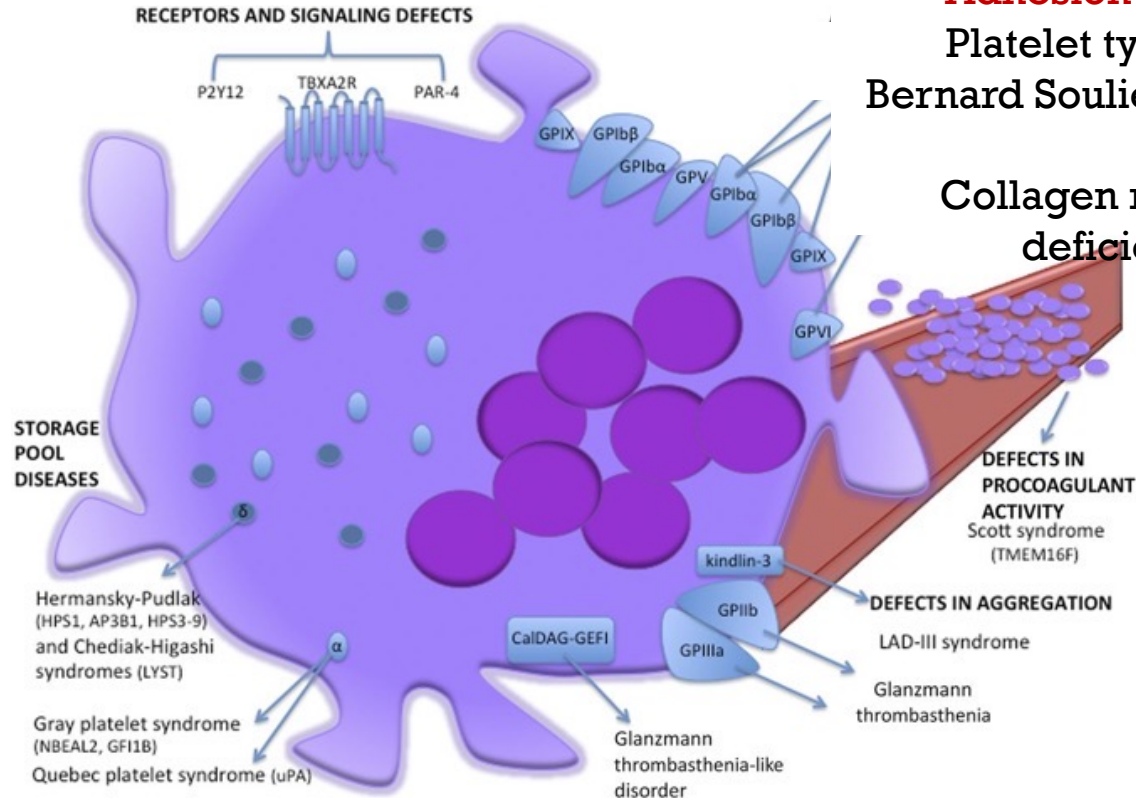
INHERITED PLATELET DISORDERS - OVERVIEW

Adhesion Defects:

Platelet type VWD

Bernard Soulier Syndrome

Collagen response
deficiency

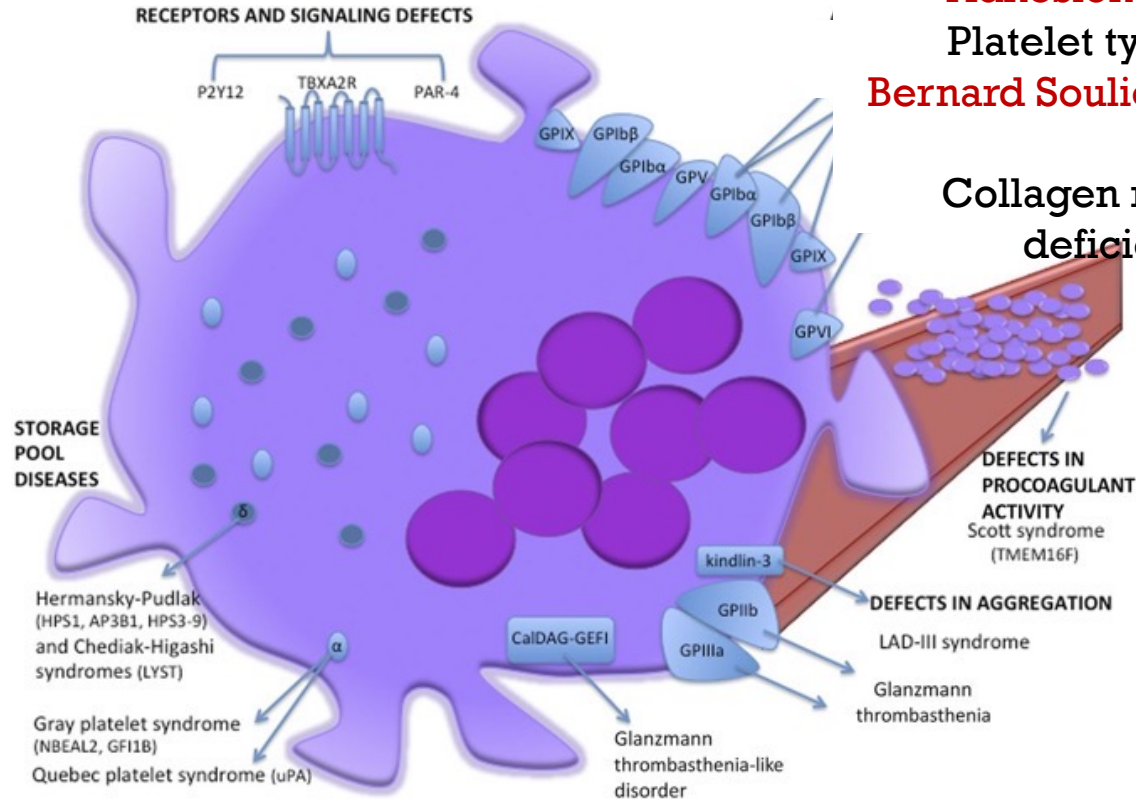


INHERITED PLATELET DISORDERS - OVERVIEW

Adhesion Defects:

Platelet type VWD

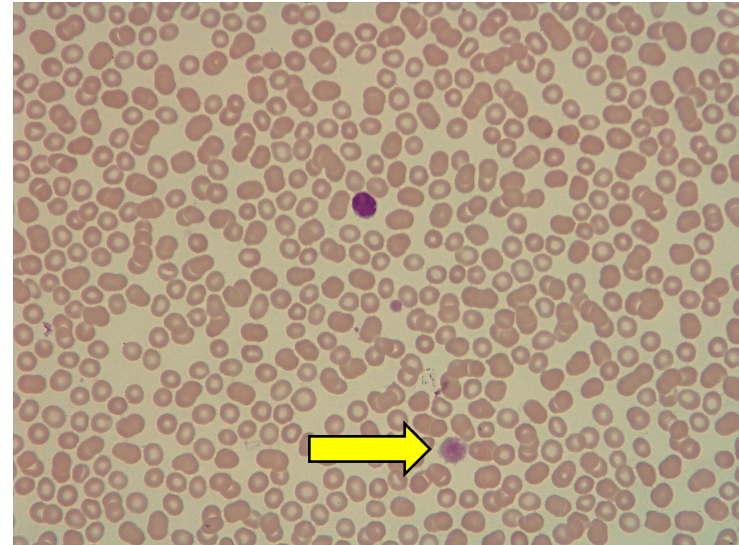
Bernard Soulier Syndrome



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

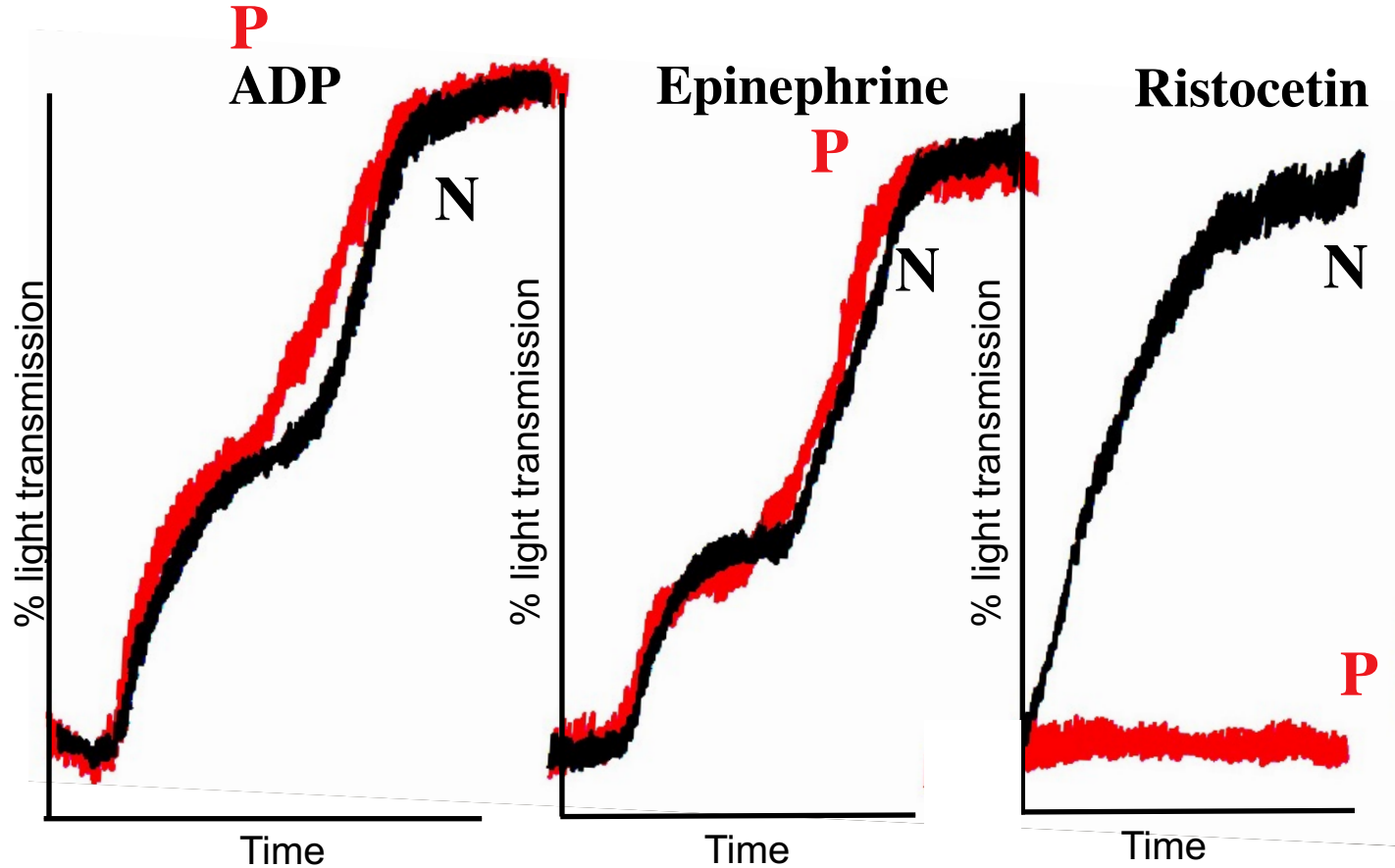


BERNARD SOULIER SYNDROME – KEY POINTS

- 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

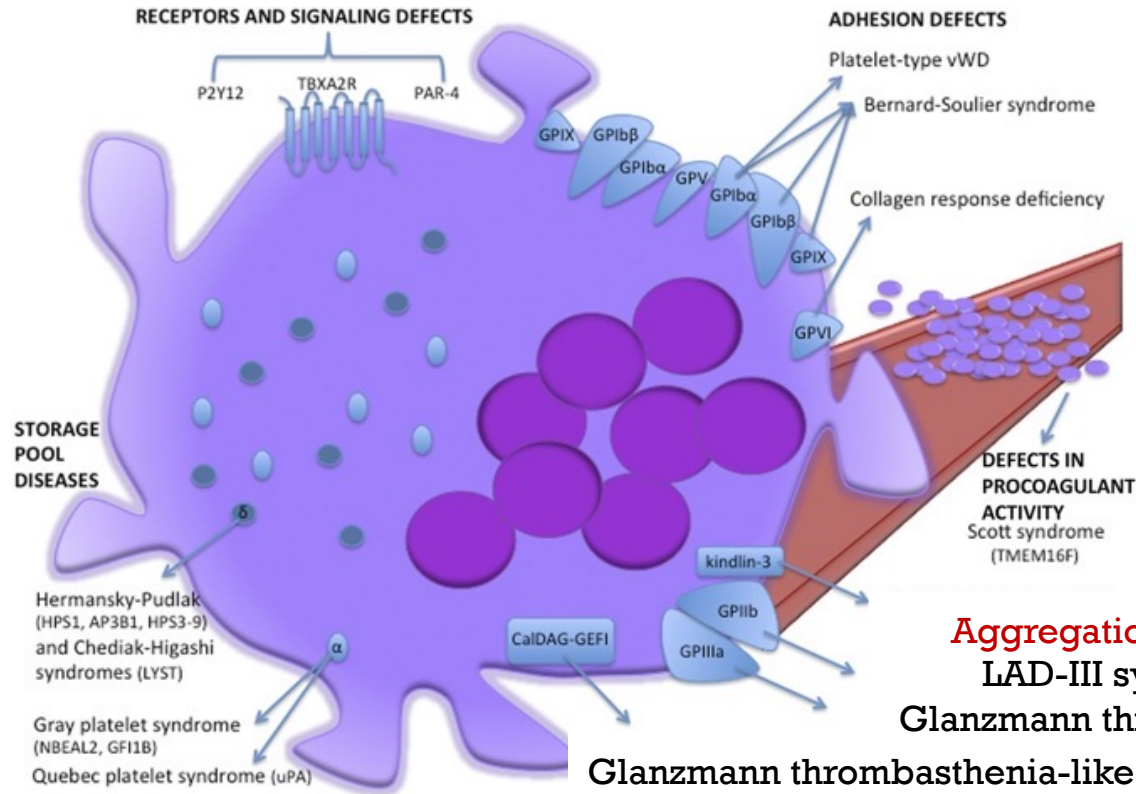


BERNARD SOULIER SYNDROME — BOARD PEARLS

- 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



Aggregation Defects:

LAD-III syndrome

Glanzmann thrombasthenia

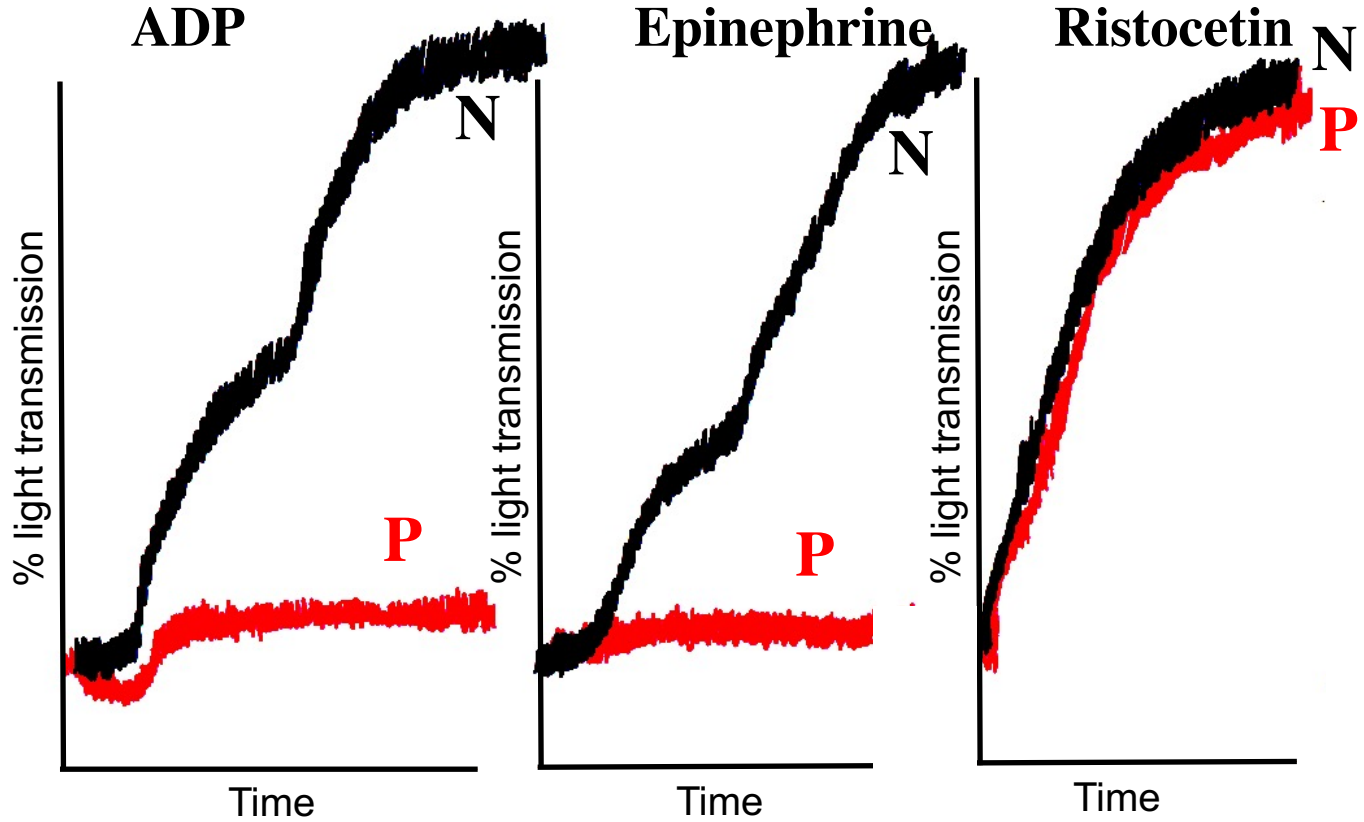
Glanzmann thrombasthenia-like disorder

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

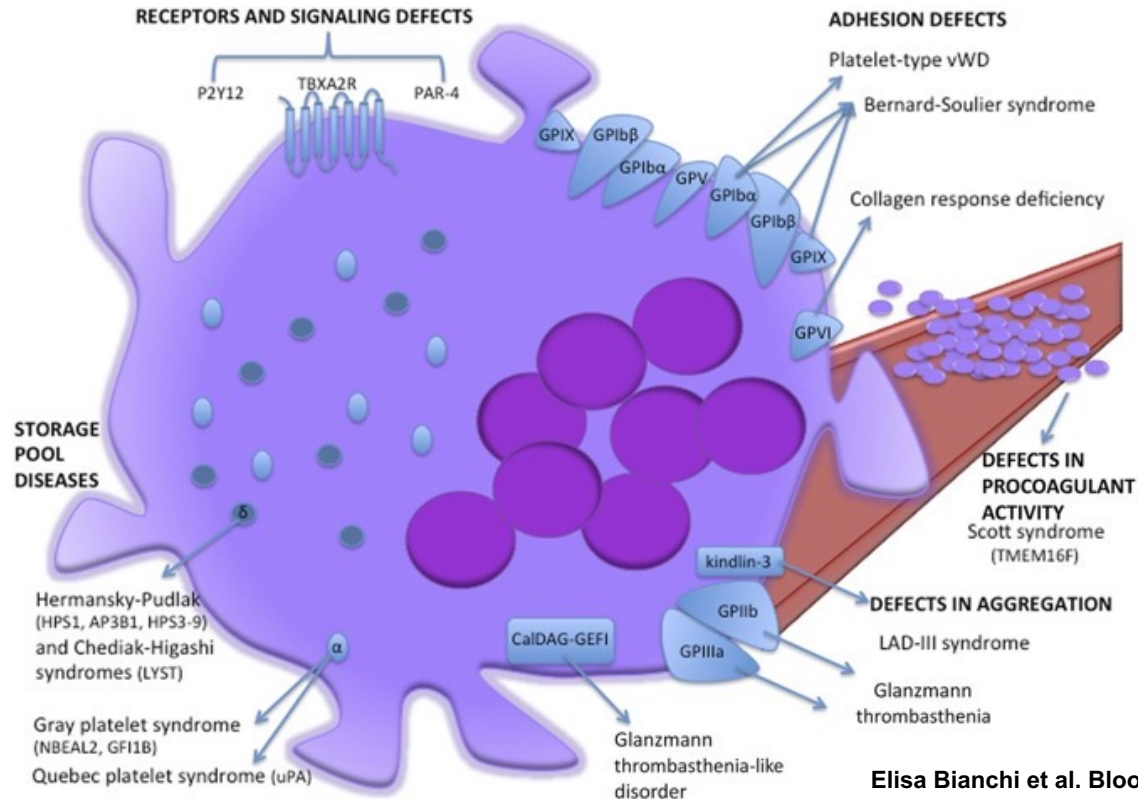


GLANZMANN THROMBASTHENIA — BOARD PEARLS

- 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



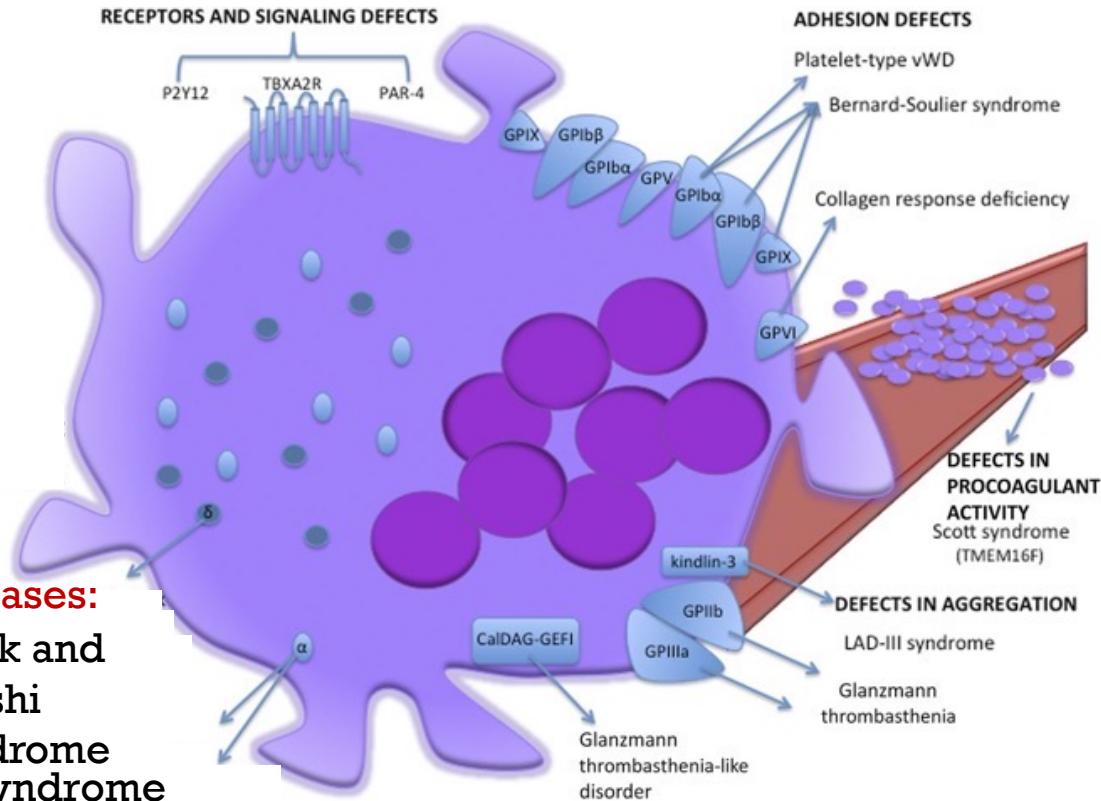
INHERITED PLATELET DISORDERS - OVERVIEW



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

INHERITED PLATELET DISORDERS - OVERVIEW

Storage Pool Diseases:
 Hermansky Pudlak and
 Chediak Higashi
 Grey Platelet Syndrome
 Quebec Platelet Syndrome



INHERITED PLATELET DISORDERS – STORAGE POOL

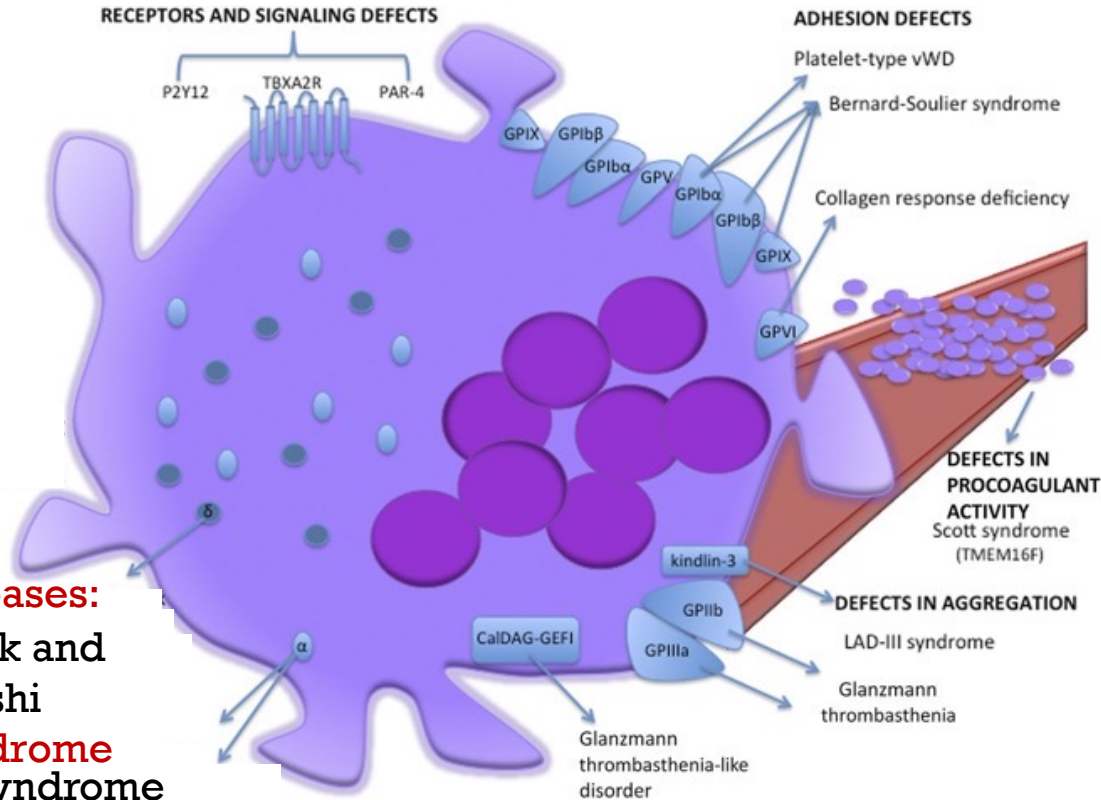
- Platelet granules
 - α (red arrow)
 - δ (yellow arrow)
 - Lysosomes and T
- Mitochondria
- Open Canalicular System



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:
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 Grey Platelet Syndrome
 Quebec Platelet Syndrome

GREY PLATELET SYNDROME

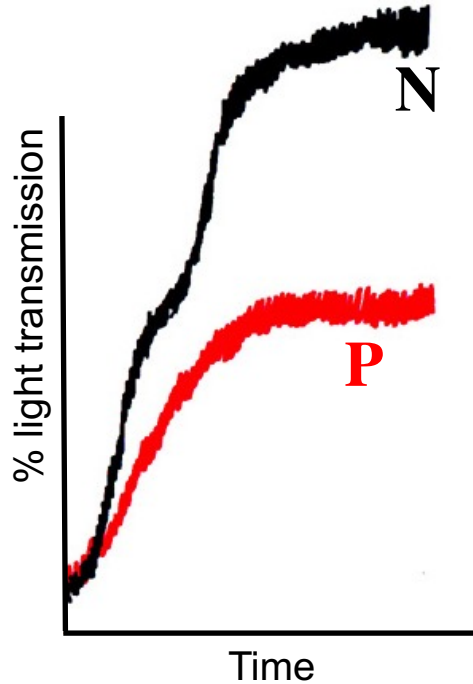
- Moderate thrombocytopenia
- Mild to moderate bleeding diathesis
- Marked decrease in alpha granules in platelets
- Most AR
- myelofibrosis, inflammation

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

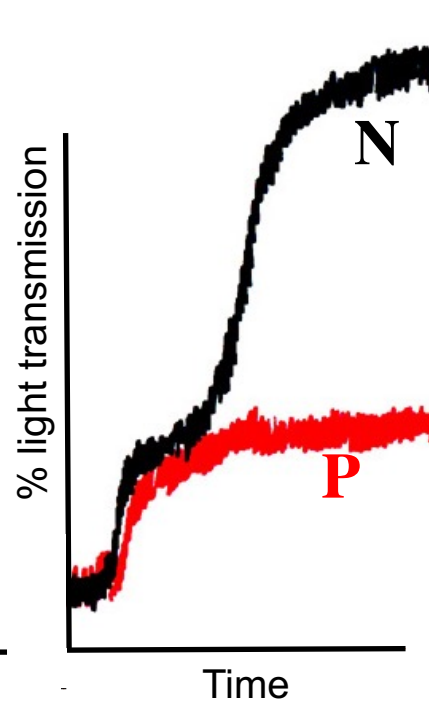


STORAGE POOL DEFICIENCY (GPS AND OTHERS)

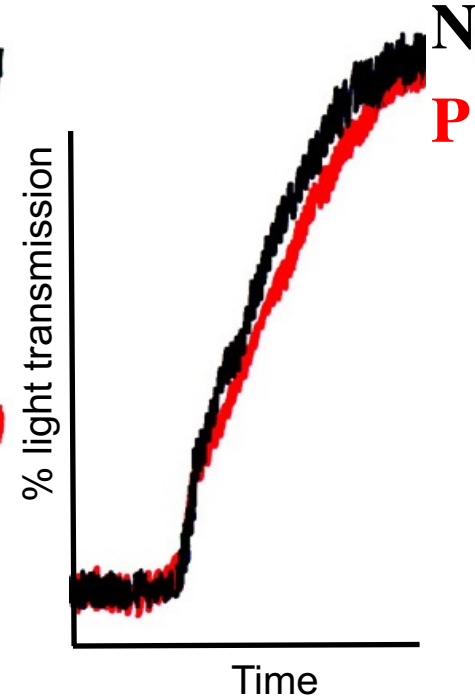
ADP



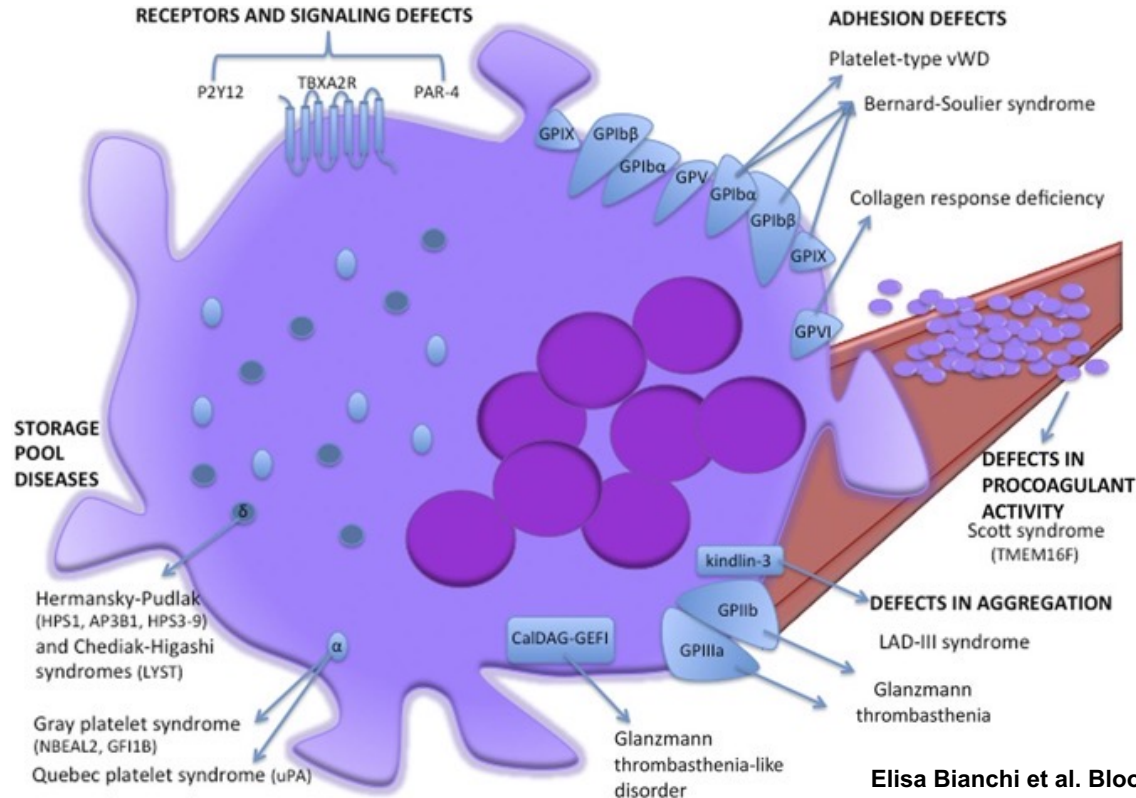
Epinephrine



Ristocetin



INHERITED PLATELET DISORDERS - OVERVIEW



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INHERITED PLATELET DISORDERS - OVERVIEW

Receptor and Signaling

Defects:

ADP (P2Y₁₂)

Thromboxane A₂

GPVI, GPIa/IIa

G proteins

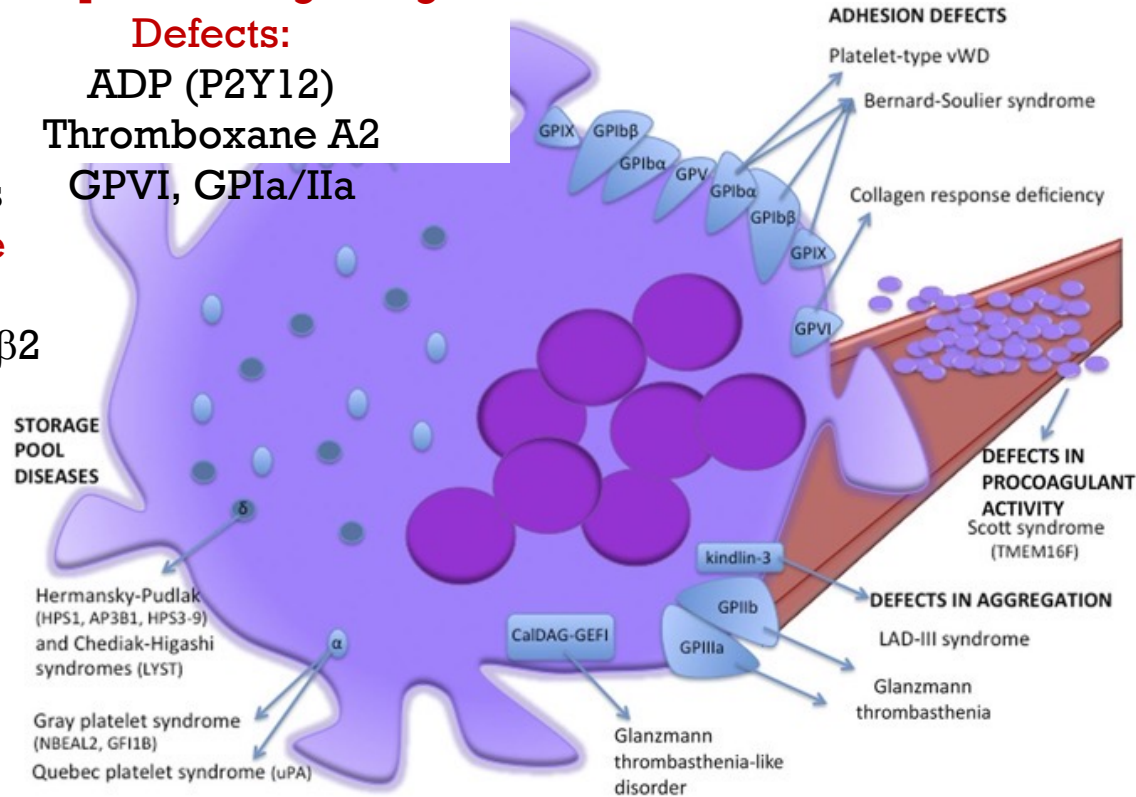
G α_q , G α_i2 , G α_s

Effector Enzyme

Defects

Phospholipase C- β 2

PKC- θ



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
- DDAVP (Desmopressin)
- Recombinant Factor VIIa



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



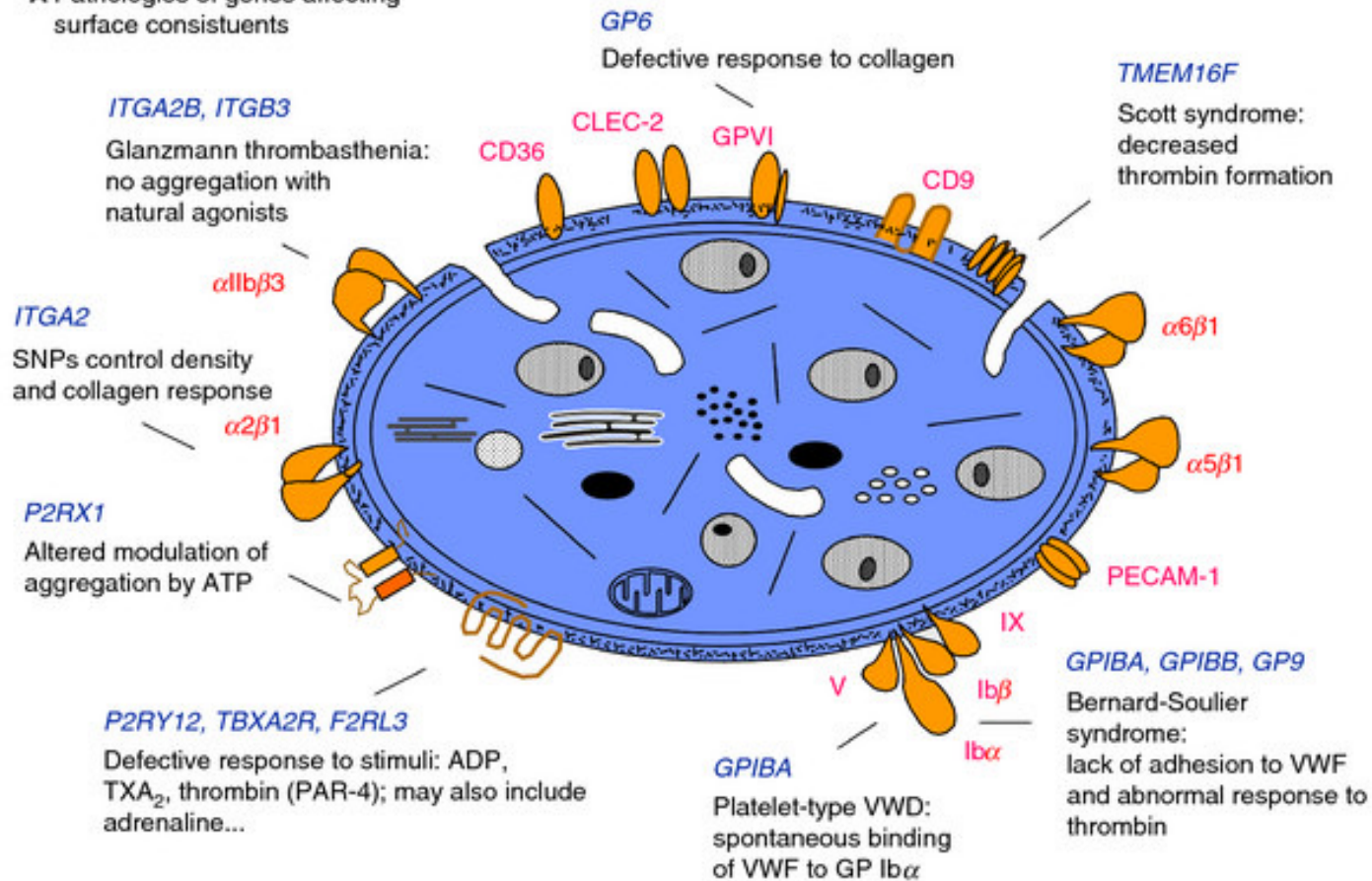
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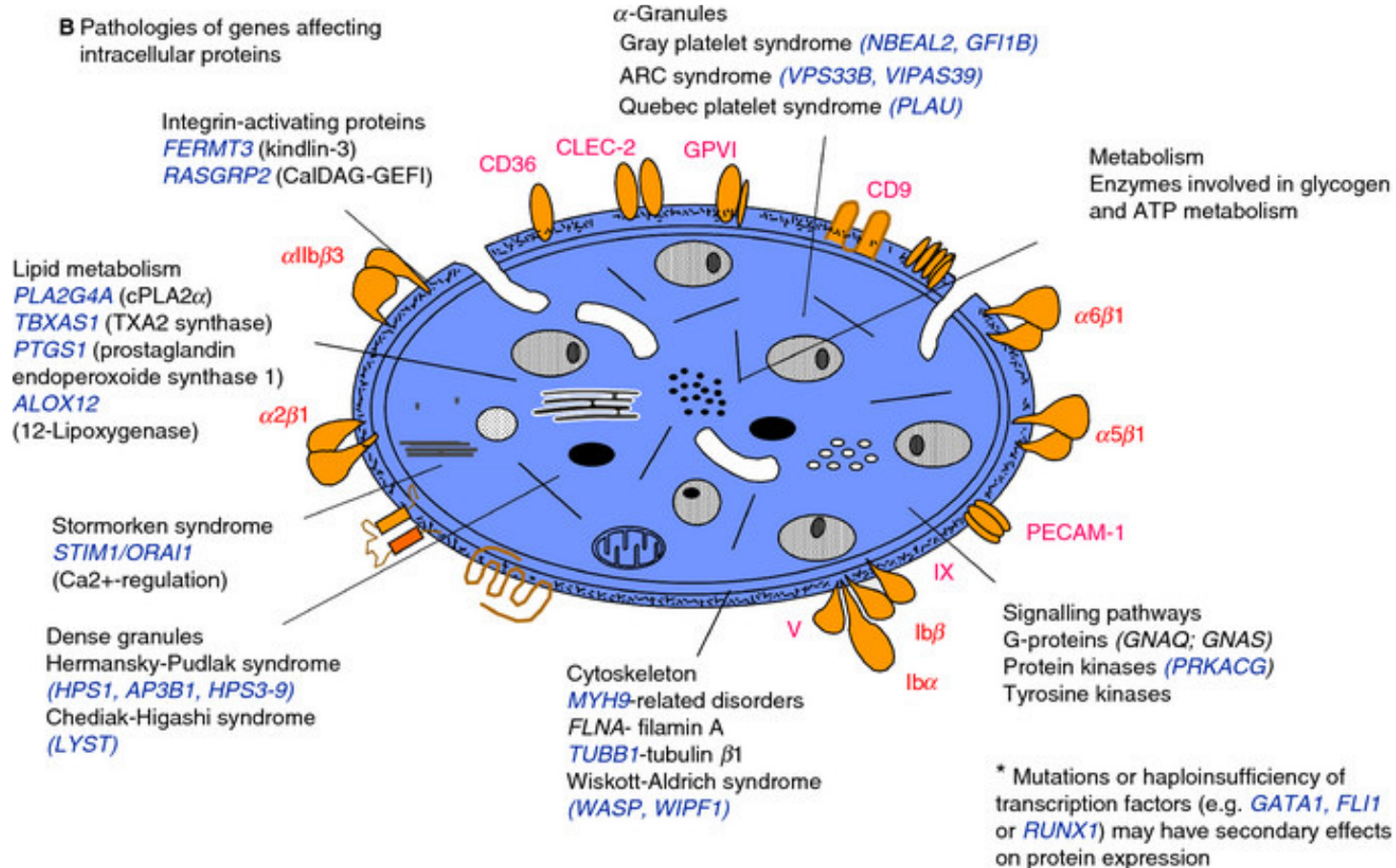
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A Pathologies of genes affecting surface constituents



B Pathologies of genes affecting intracellular proteins



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 *Due to platelet activation during dialysis?*
 - Storage pool defect
 - 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

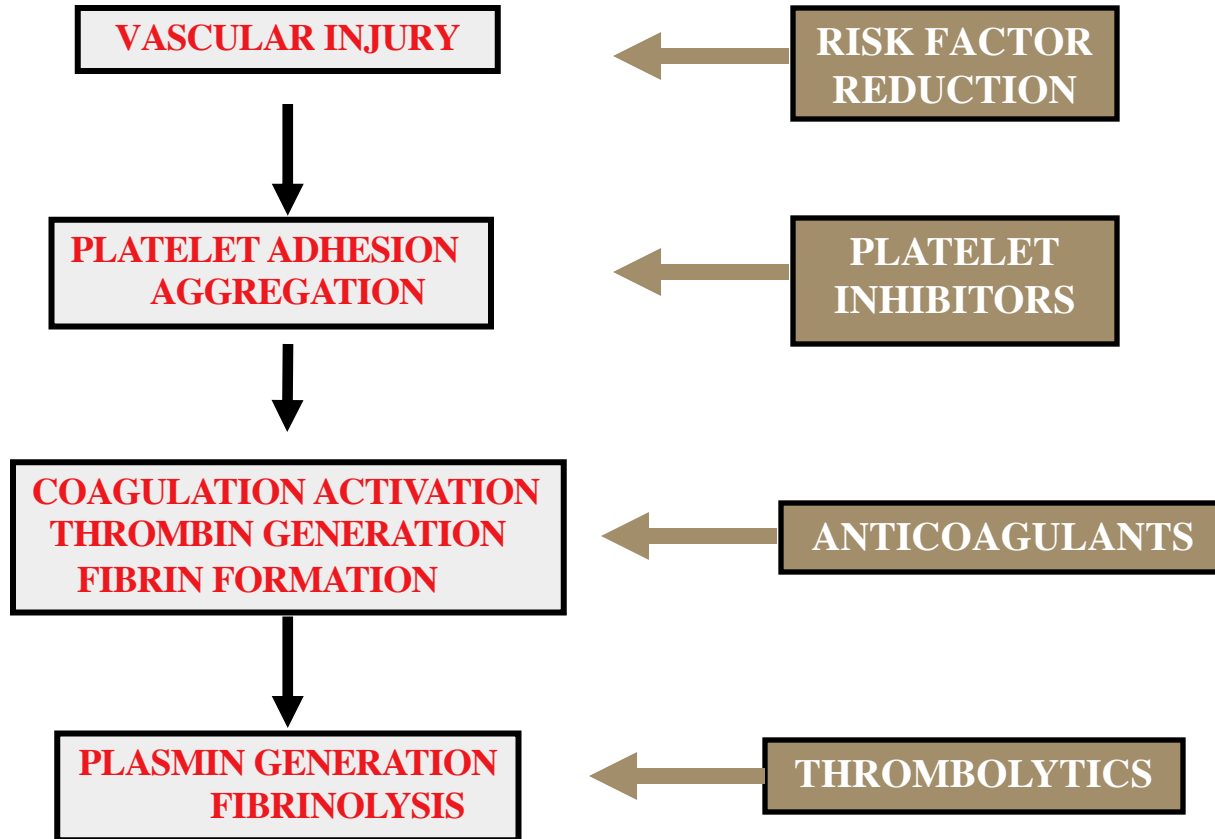
- ?role of anemia similar to renal disease



ANTI-PLATELET THERAPY



STRATEGIES FOR ANTITHROMBOTIC THERAPY

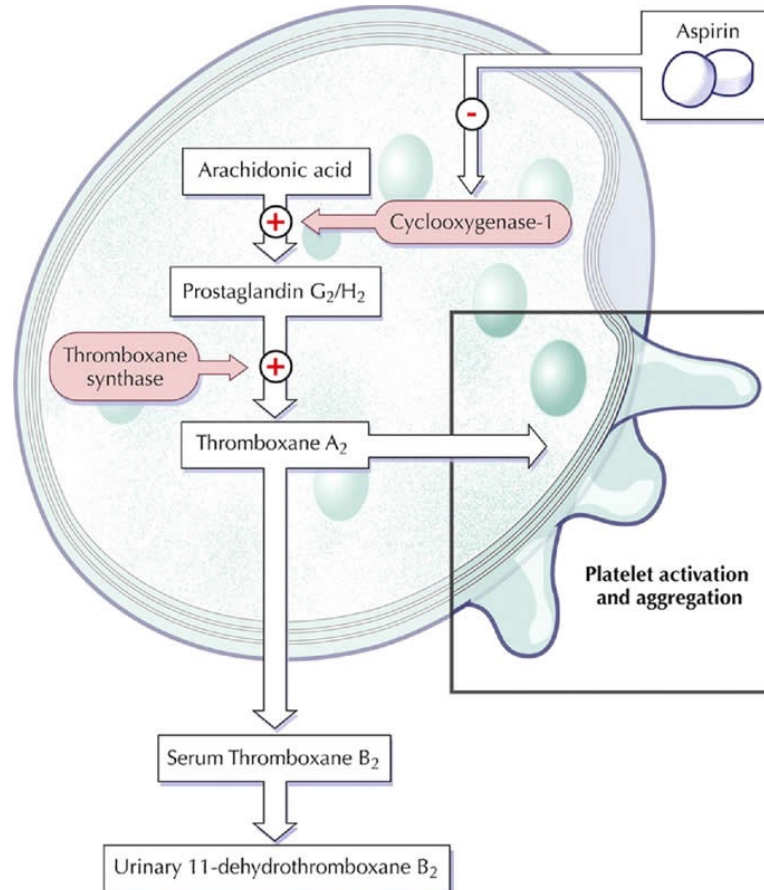


ANTI-PLATELET THERAPIES

- 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

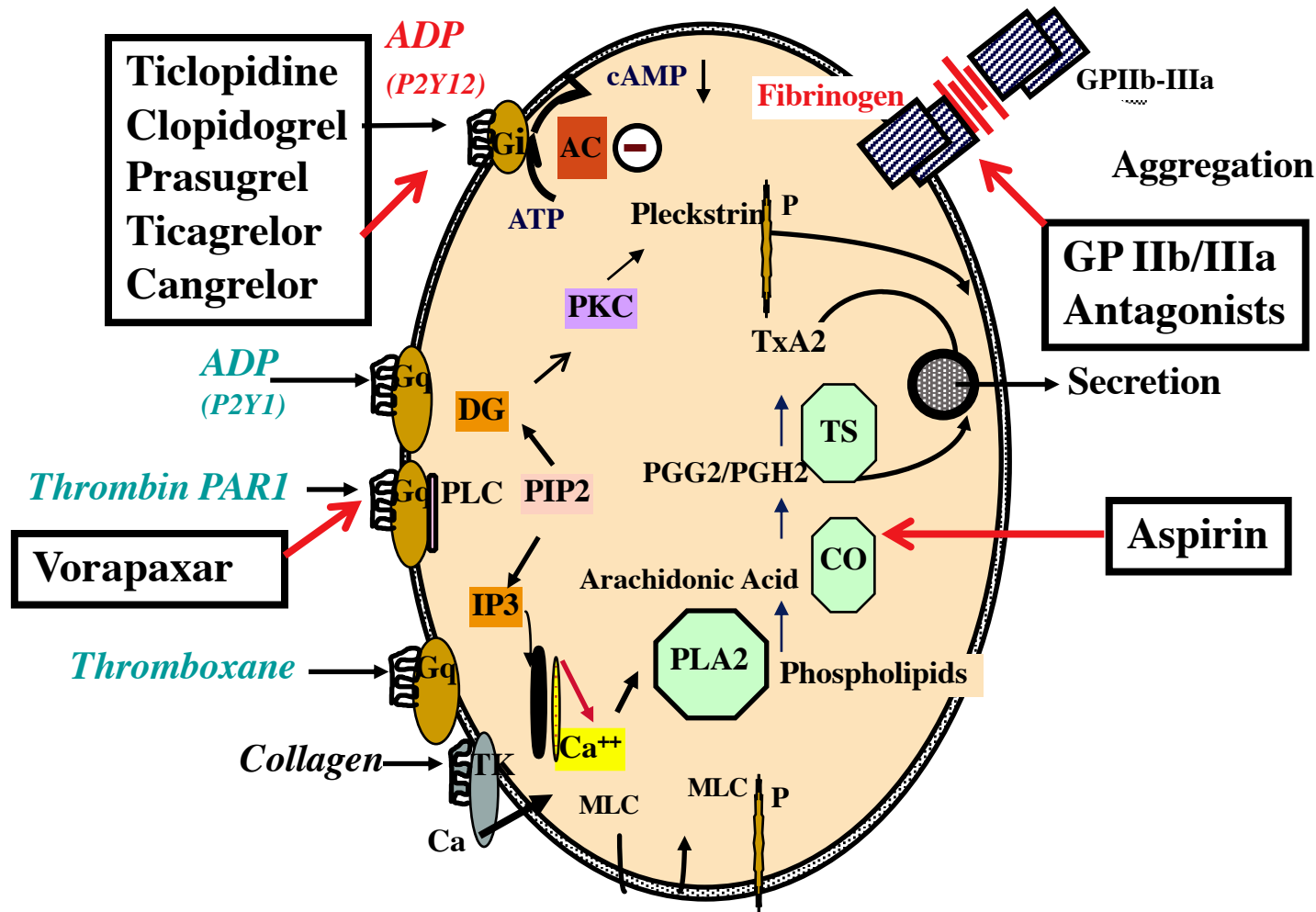
- Effective in a wide range of arterial disorders
- Reduces vascular deaths by 15% and vascular events by 30% in high-risk patients
- Effective when used long-term in doses 50-100 mg/day
- No convincing evidence that higher doses are more effective
- Lower doses (300 mg) produce fewer GI side effects 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

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- *PAR1 Antagonists*
- *Cilostazol*





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 neoepitope
 - 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

