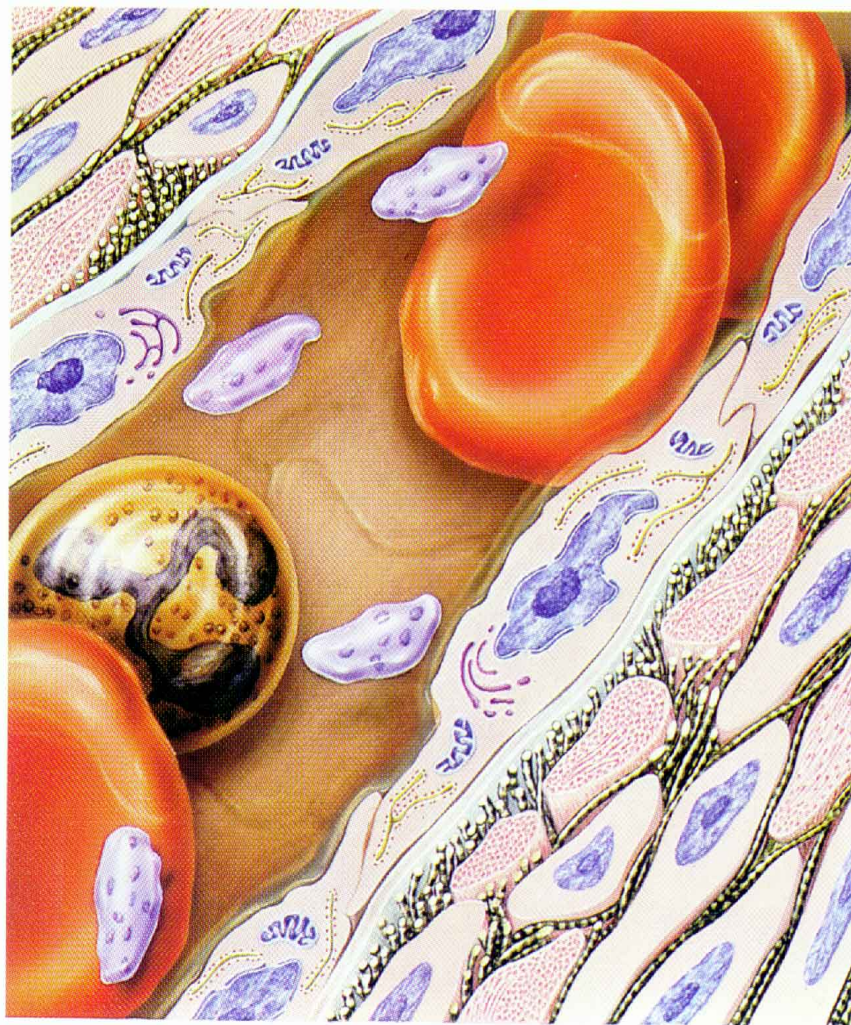


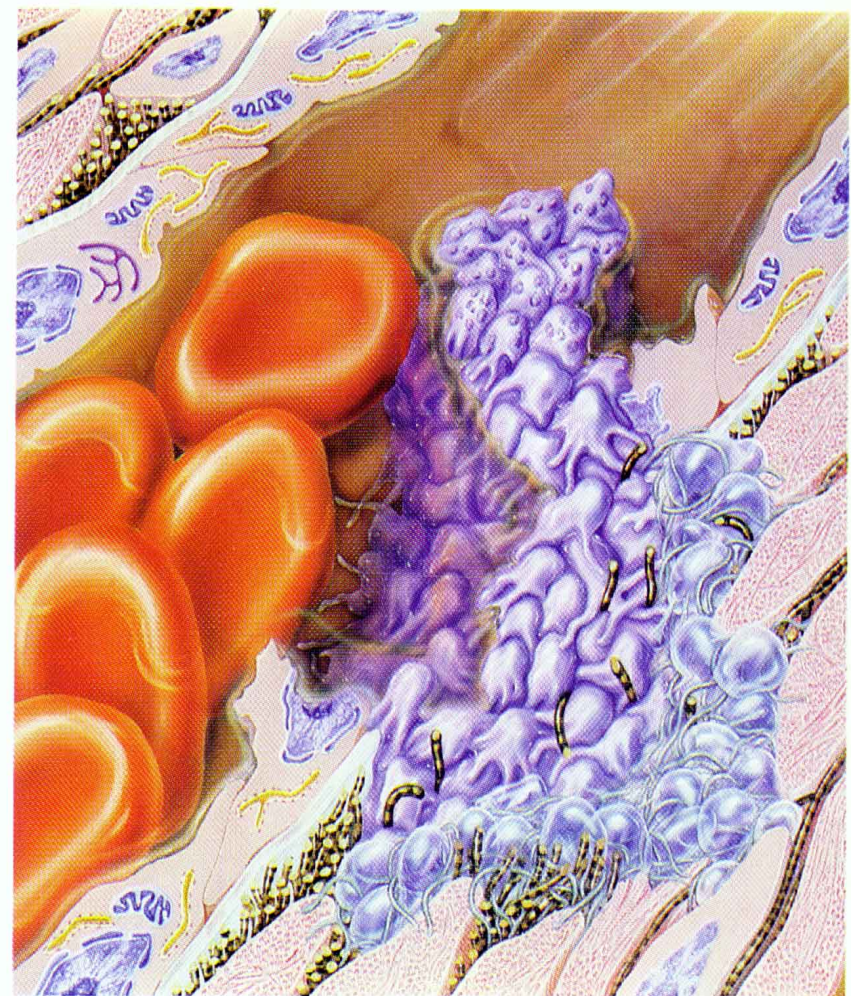
Disorders of Platelet Function

A. Koneti Rao, M.D.

**Sol Sherry Professor of Medicine
Co-Director, Sol Sherry Thrombosis Research Center
Chief, Hematology Section
Temple University School of Medicine
Philadelphia**

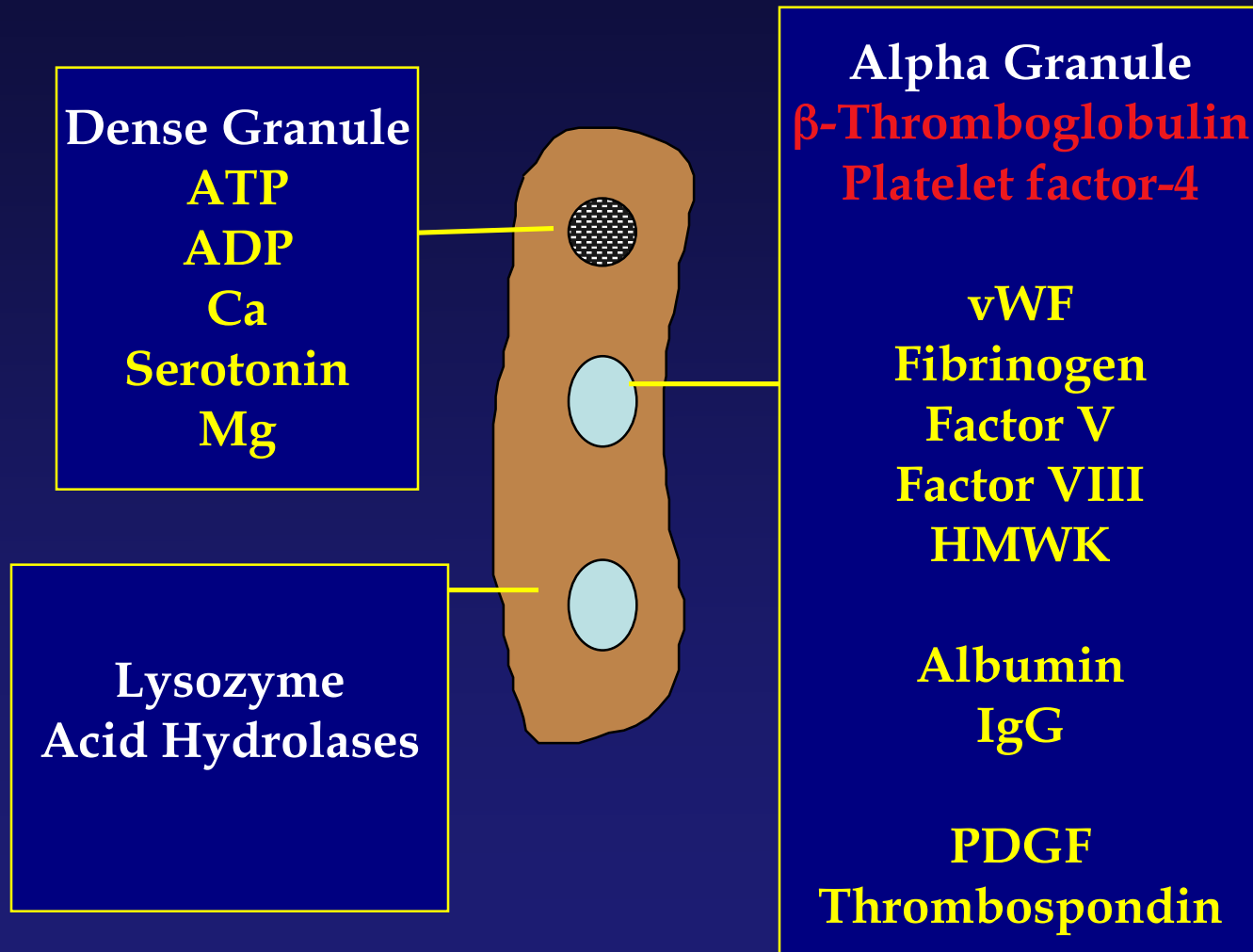


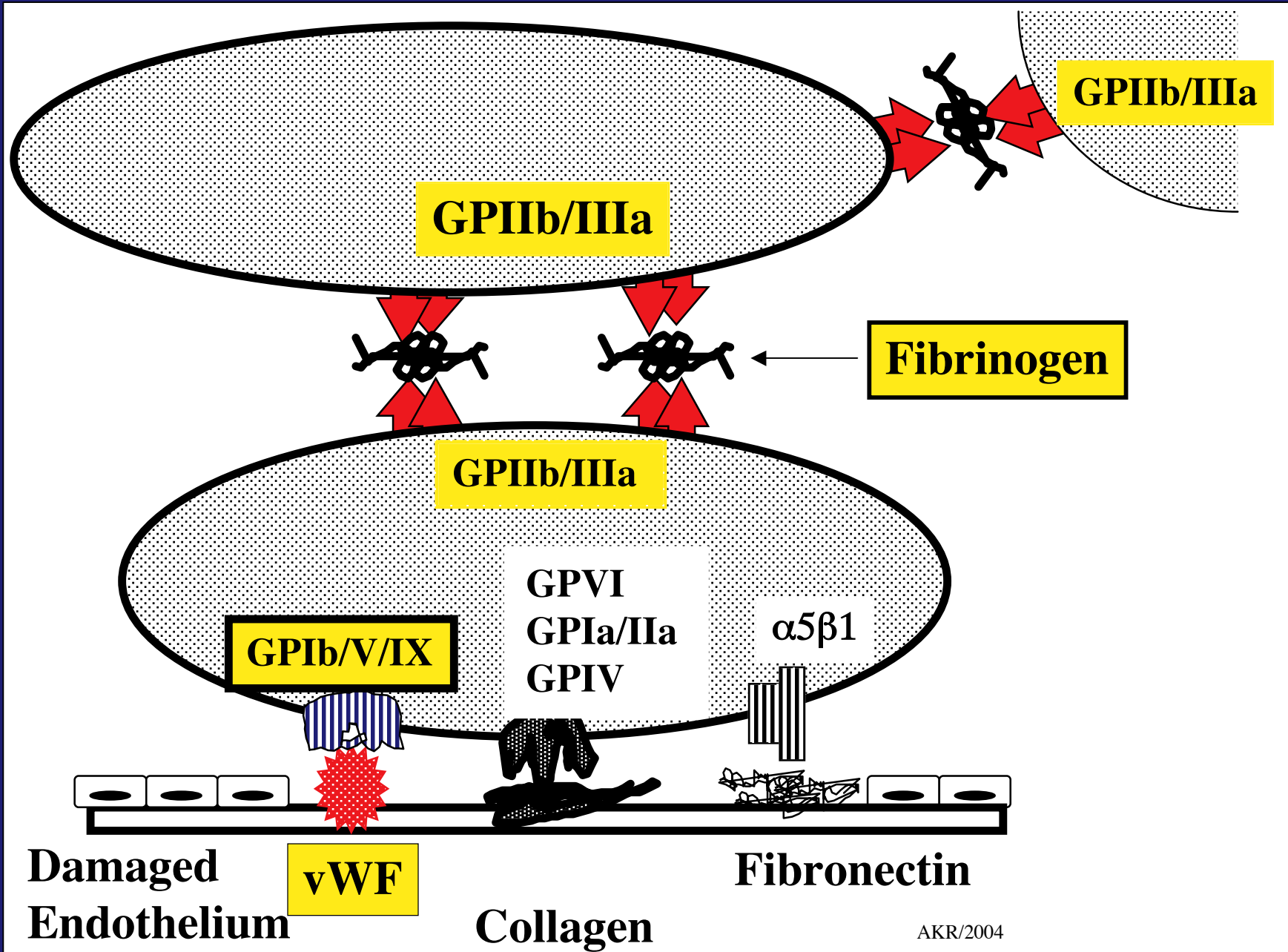
Akkerman JW, Bouma BN, Sixma JJ. Atlas of Hemostasis, 1979.



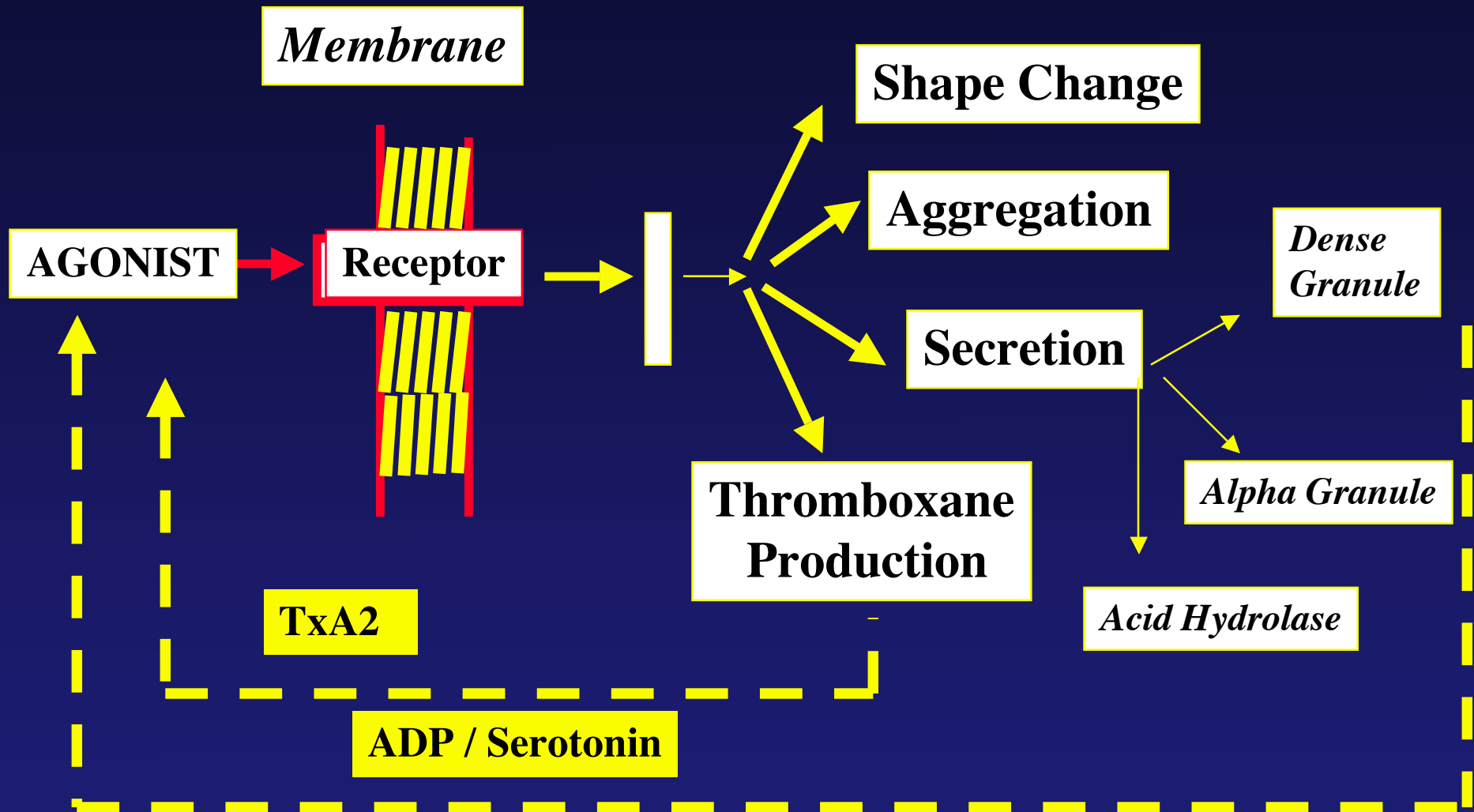
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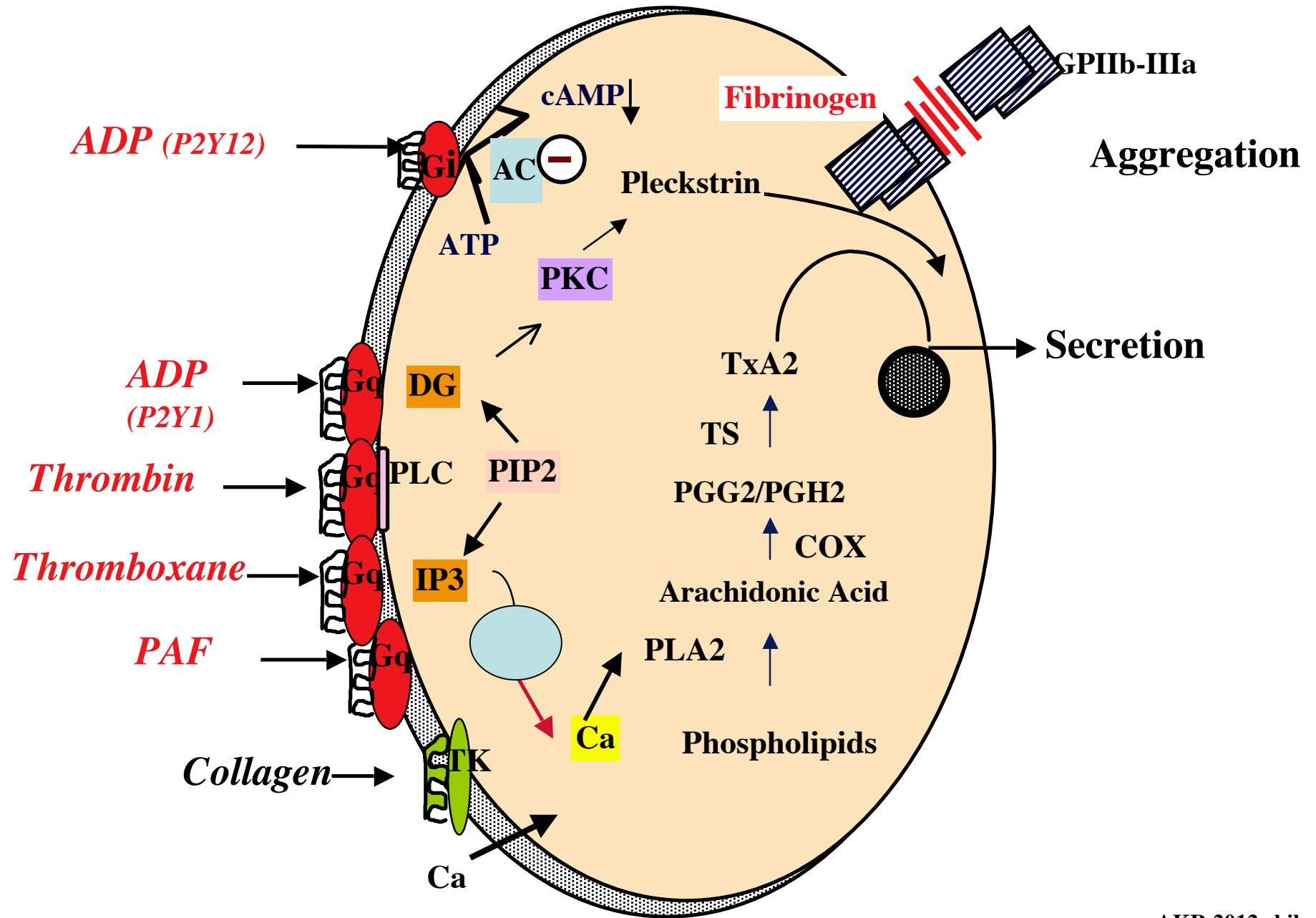
Platelet Granule Constituents





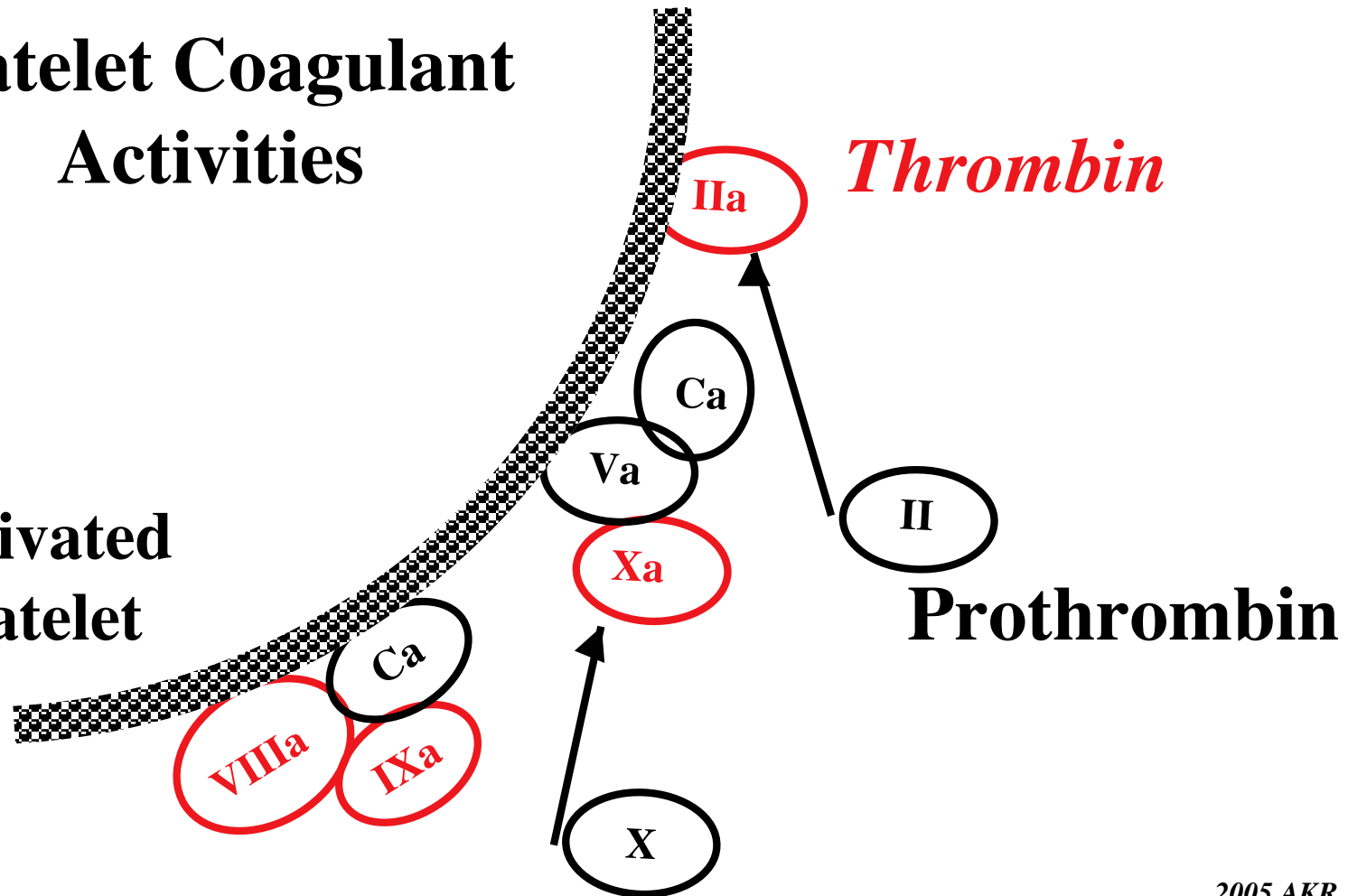
Platelet Responses to Activation





Platelet Coagulant Activities

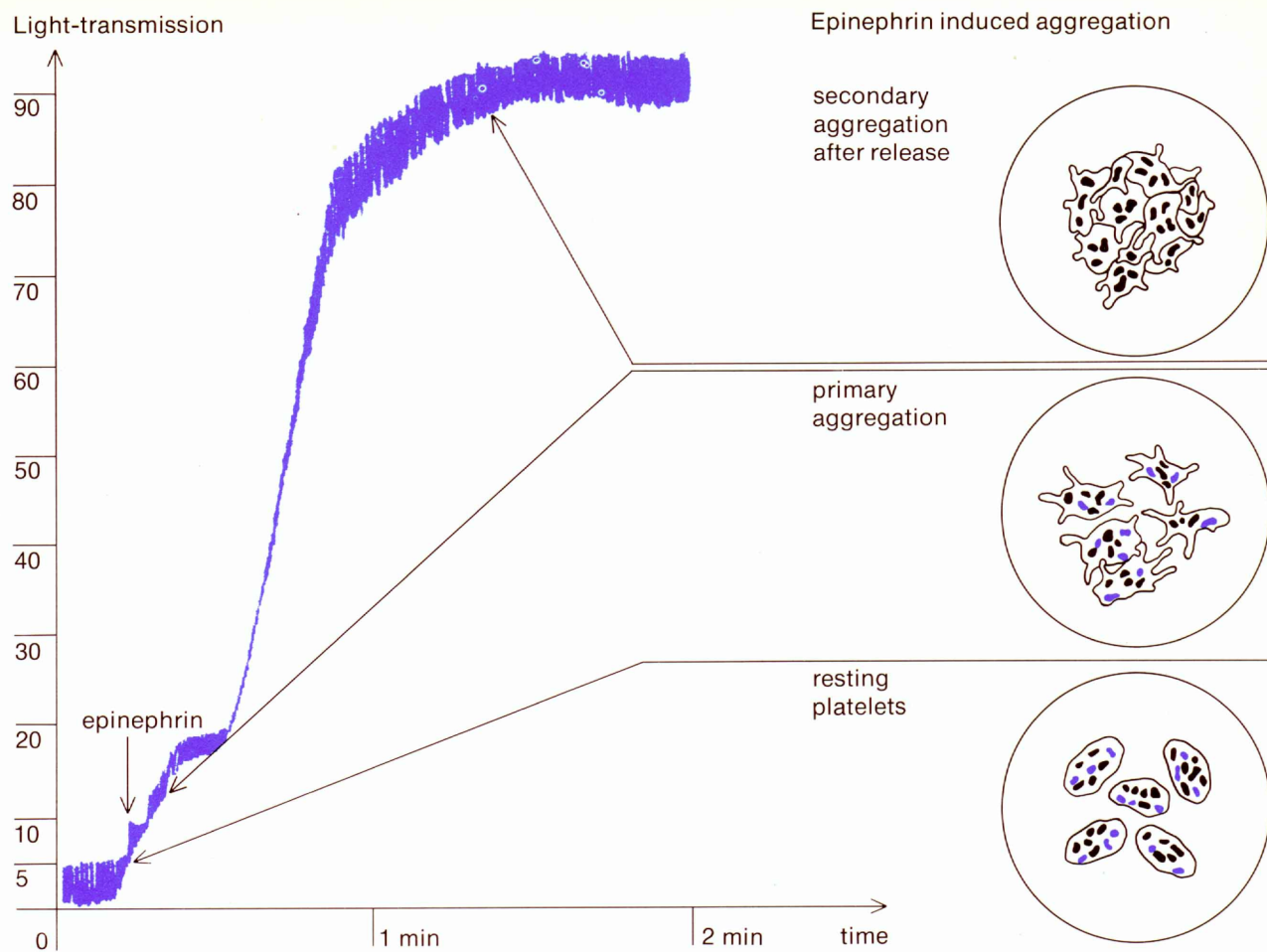
Activated Platelet



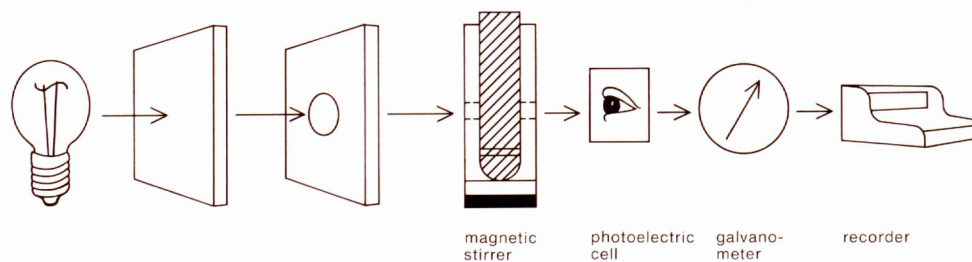
Platelet -Vessel Wall Disorders

Laboratory Tests

- **Platelet Counts**
- **Bleeding time**
- **Platelet Aggregation Studies**
- **Platelet Secretion Studies**
- **Platelet Function Analyzer**



Principle



Akkerman JW, Bouma BN, Sixma JJ. Atlas of Hemostasis, 1979

Congenital Disorders of Platelet Function

General Characteristics

- **Mucocutaneous Bleeding Manifestations**
- **Marked Variability in Bleeding Manifestations**
- **Normal Platelet Counts**
- **Prolonged Bleeding Times**
- **Abnormal Platelet Aggregation/Secretion Responses**



Akkerman JW, Bouma BN, Sixma JJ. Atlas of Hemostasis, 1979

Congenital Disorders of Platelet Function

1. Defects in Platelet-Vessel Wall Interaction

- **von Willebrand Disease**
- **Bernard-Soulier Syndrome**

2. Defects in Platelet-Platelet Interaction

- **Congenital Afibrinogenemia**
- **Glanzmann Thrombasthenia**

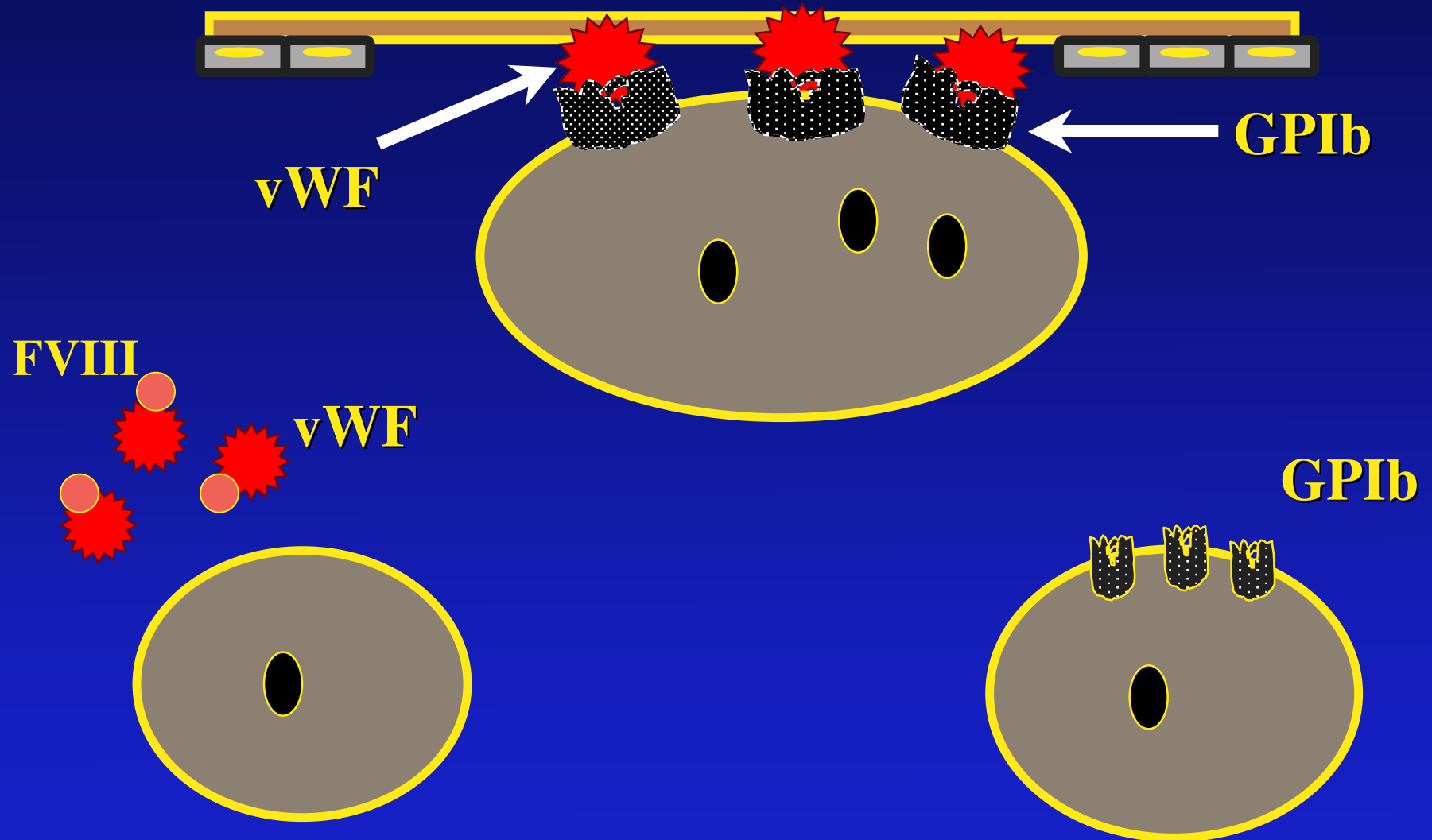
3. Defects in Platelet Secretion and Signal Transduction

- **Abnormalities of Granules**
- **Signal Transduction Defects**
- **Abnormalities in Arachidonate Pathways and Thromboxane synthesis**

4. Disorders of Platelet Coagulant-Protein Interactions

5. Miscellaneous Disorders

Disorders of Adhesion



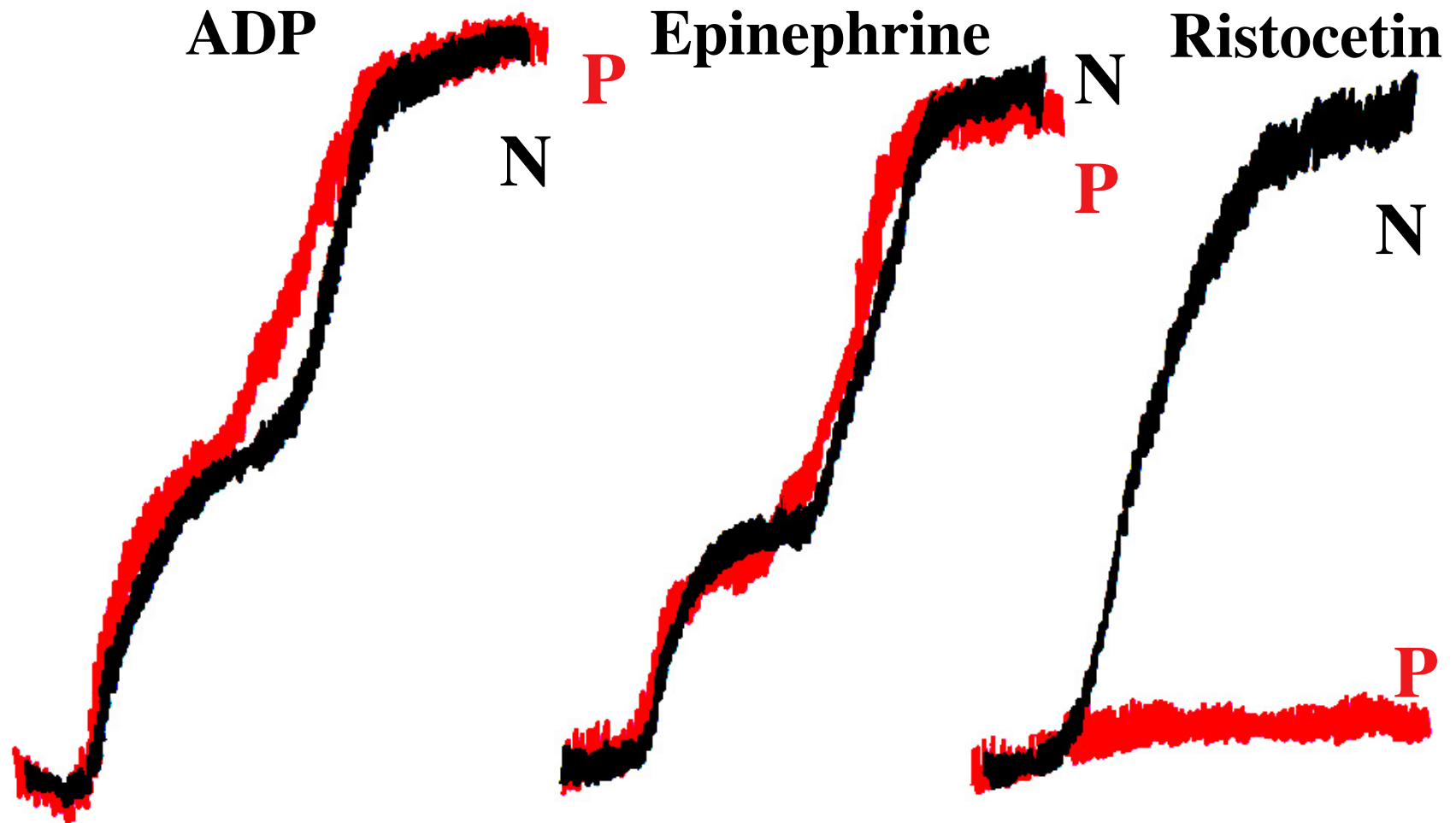
Bernard Soulier Syndrome

Von Willebrand Disease

Bernard Soulier Syndrome

- **Autosomal recessive inheritance**
- **Deficiency of GPIb-IX-V complex**
- **Thrombocytopenia; *increased platelet size***
- **Absent or markedly reduced aggregation response to ristocetin**
- **Normal response to ADP, epinephrine, collagen**
- **Impaired response at low thrombin concentration**

von Willebrand Disease/ Bernard Soulier Syndrome



Congenital Disorders Of Platelet Function

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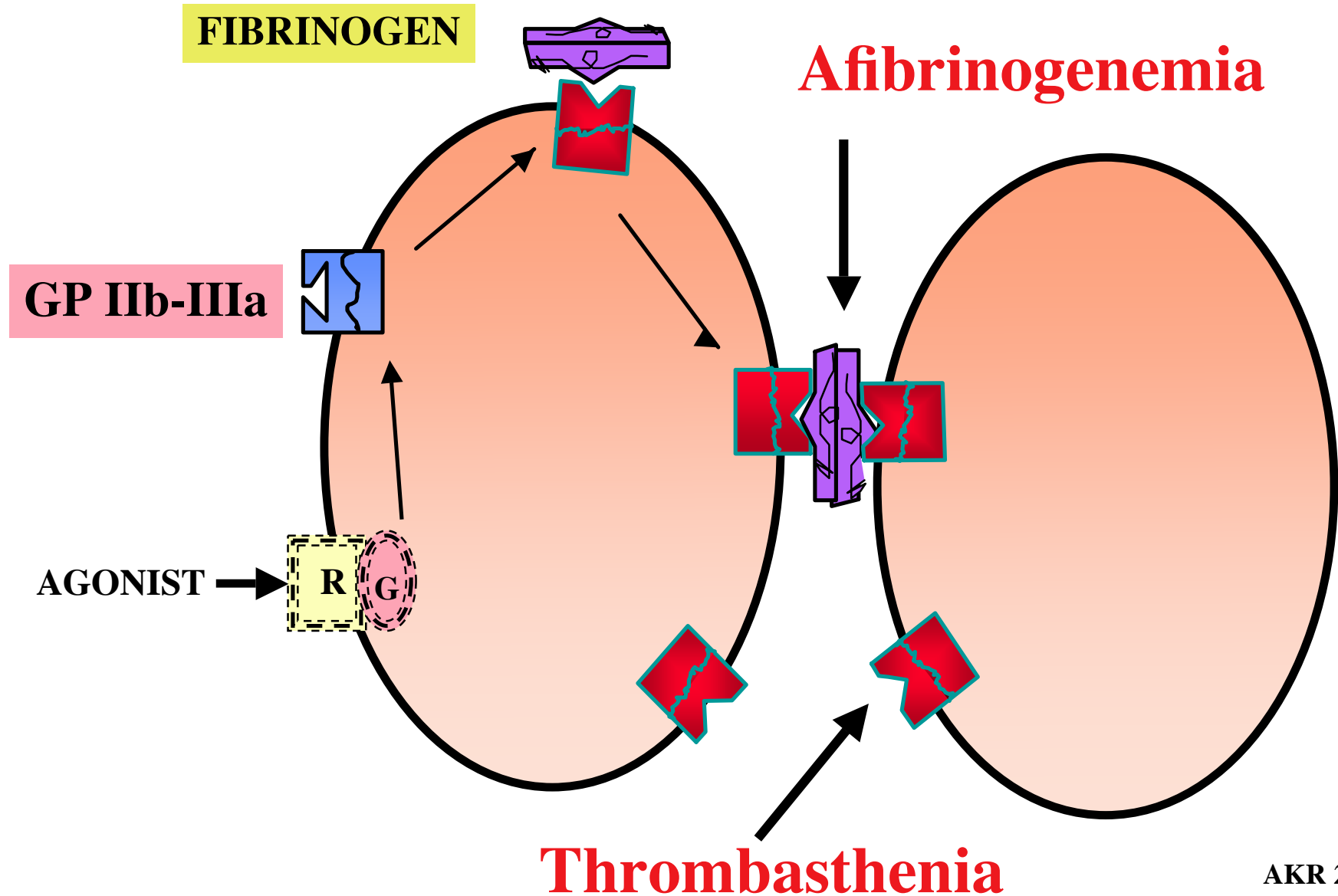
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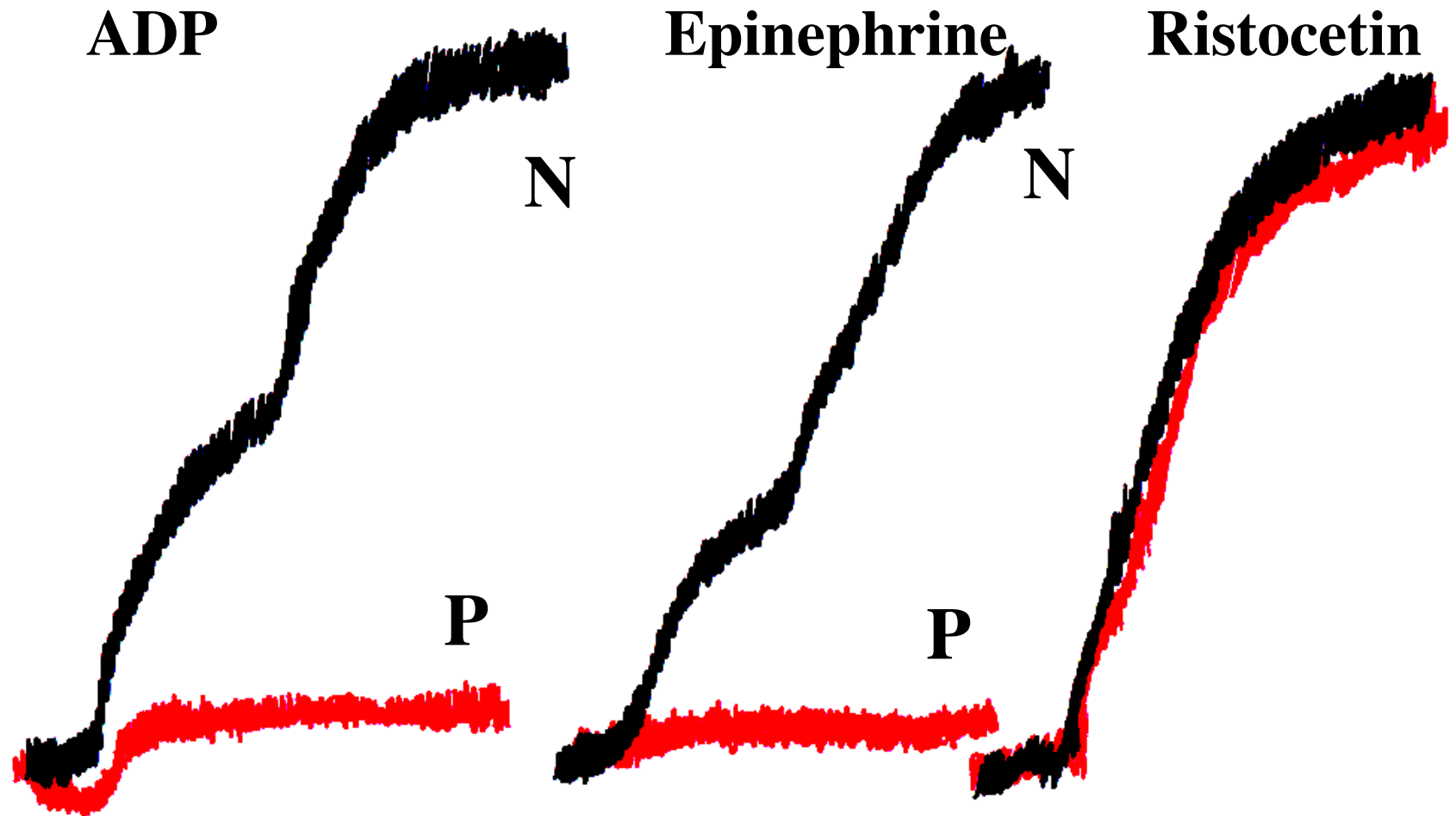
Disorders of Aggregation



Glanzmann Thrombasthenia

- 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

Thrombasthenia/Afibrinogenemia



Congenital Disorders Of Platelet Function

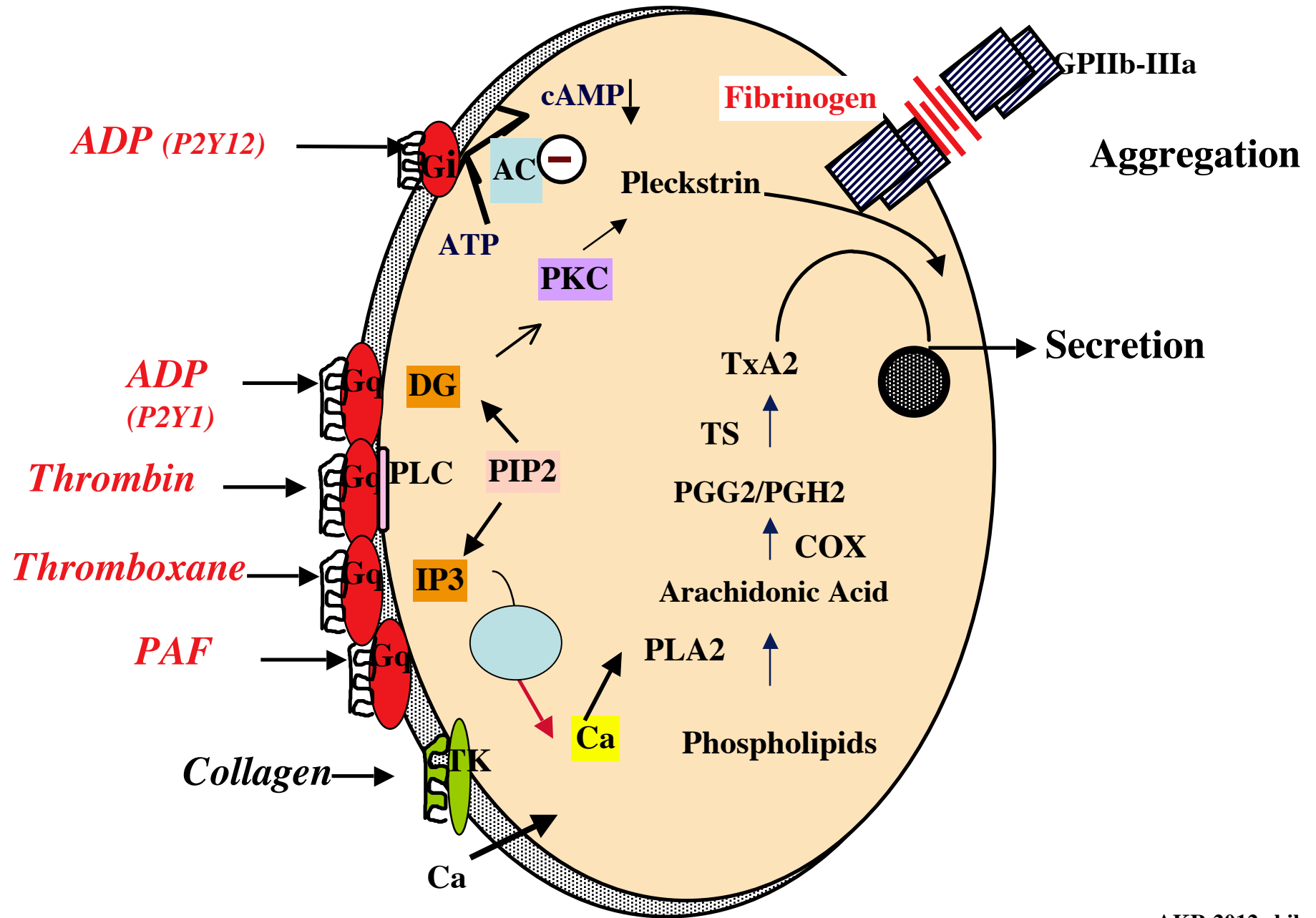
3. Disorders of Platelet Secretion / Signal Transduction

a. Abnormalities of Granules

Storage Pool Deficiency (δ , α , $\alpha\delta$)
Quebec Platelet Disorder

b. Signal Transduction Defects (Activation Defects)

c. Abnormalities in Arachidonic Acid Pathways and in Thromboxane Synthesis



Storage Pool Disease/ Secretion Defects

ADP



Epinephrine



Ristocetin



Congenital Disorders Of Platelet Function

3. Disorders of Platelet Secretion / Signal Transduction

a. Abnormalities of Granules

Storage Pool Deficiency (δ , α , $\alpha\delta$)
Quebec Platelet Disorder

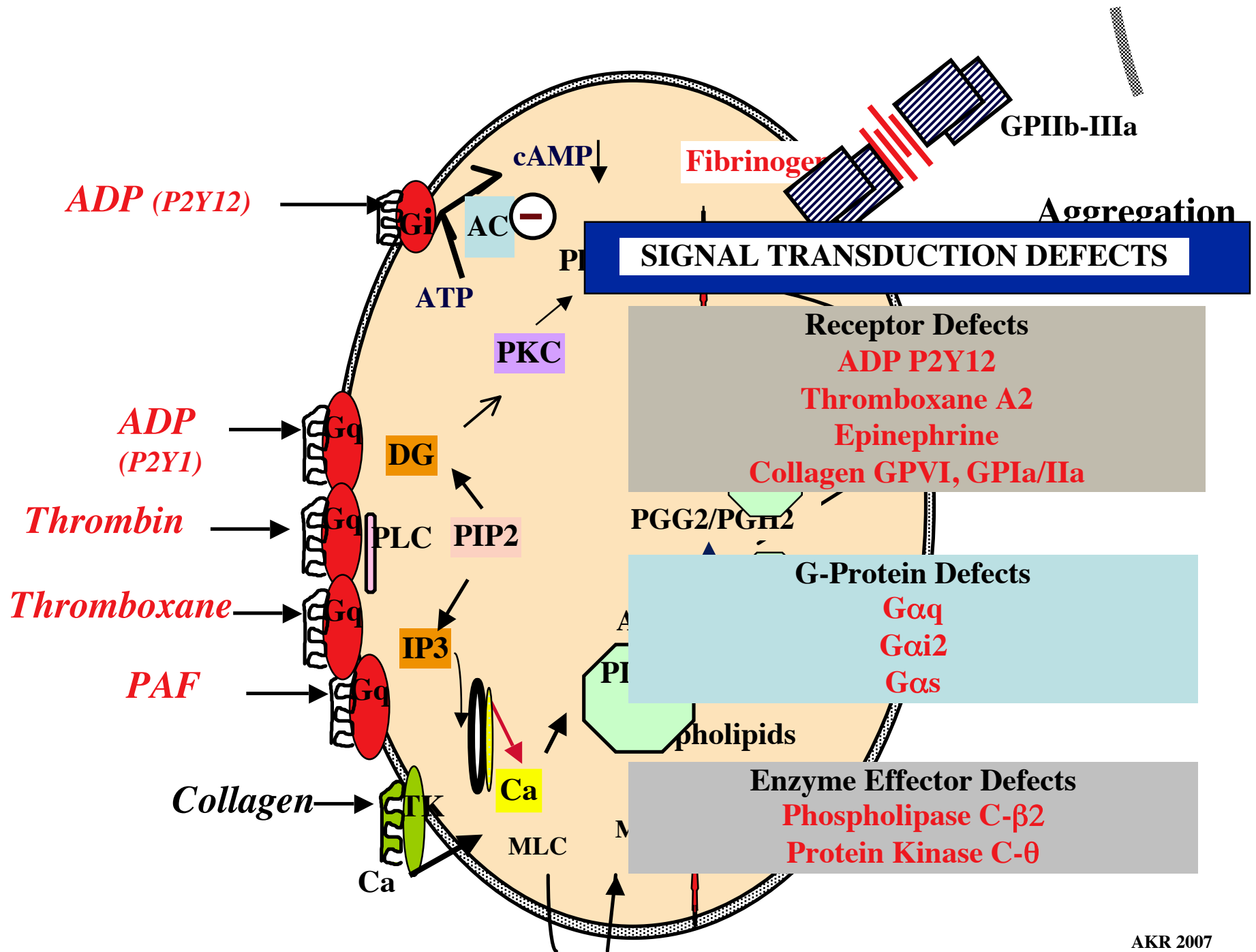
b. Signal Transduction Defects (Activation Defects)

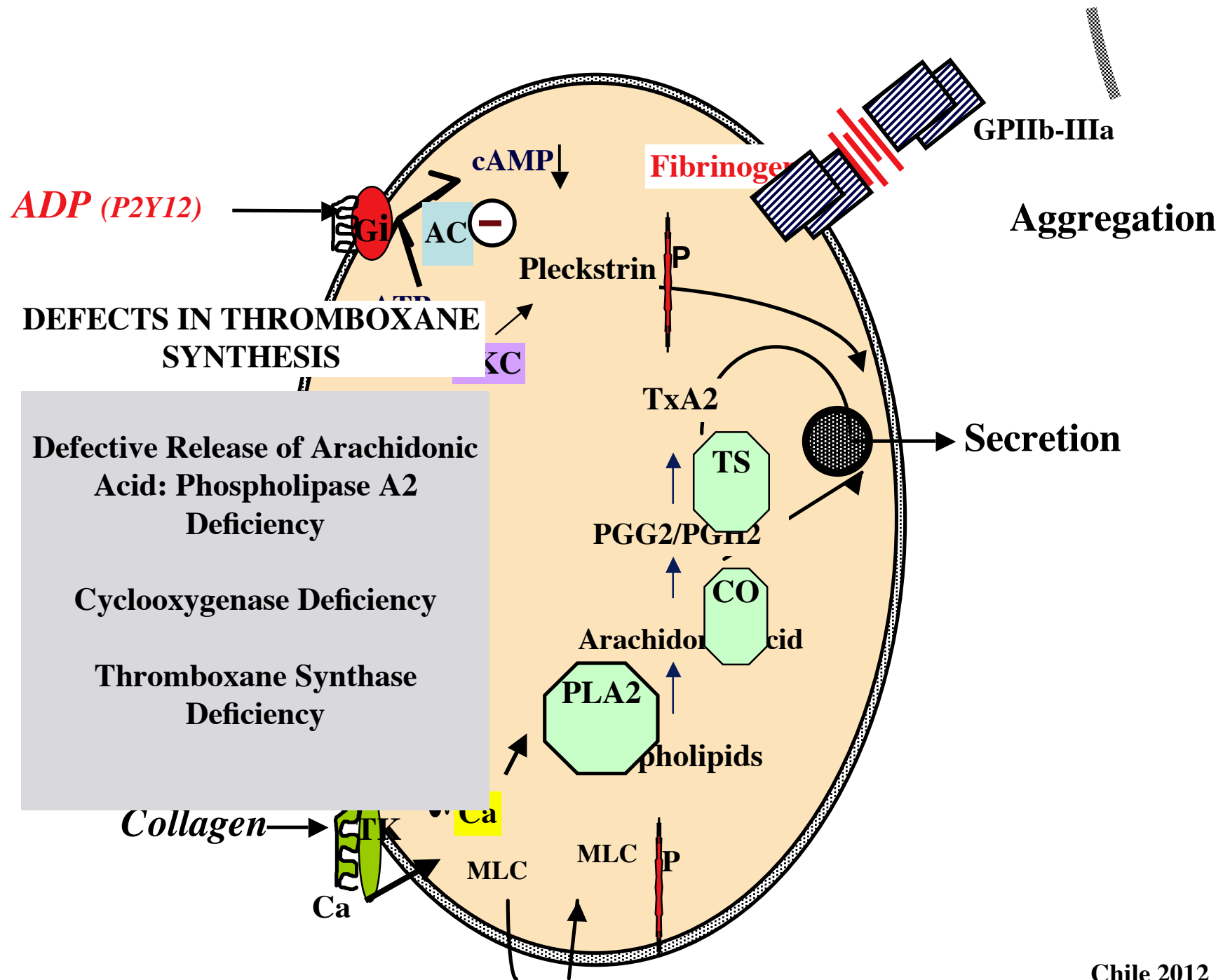
c. Abnormalities in Arachidonic Acid Pathways and in Thromboxane Synthesis

Disorders of Platelet Granules

Storage Pool Deficiency

- **Platelets deficient in dense granules, alpha granules or both types of granules**
- **Grey Platelet syndrome: deficiency of only alpha granules**
- **Hermansky-Pudlak syndrome: Dense granule deficiency with Oculocutaneous albinism, nystagmus.**
- **HPS: Autosomal recessive; Pocket in north-west Puerto Rico**





Congenital Platelet Function Disorders

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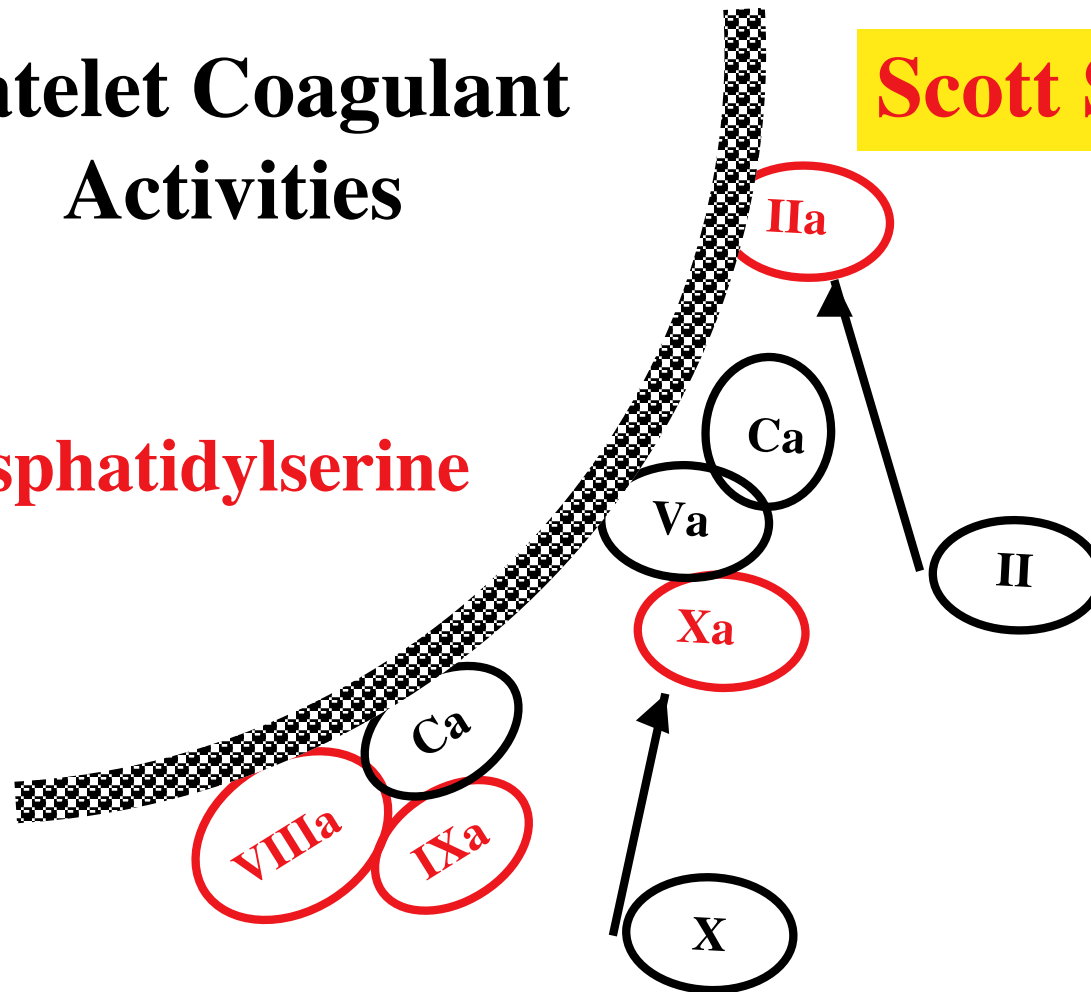
4. Disorders of Platelet Coagulant-Protein Interactions

5. Miscellaneous Disorders

Platelet Coagulant Activities

Scott Syndrome

Phosphatidylserine



Congenital Disorders Of Platelet Function

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Congenital Disorders Of Platelet Function

Miscellaneous Disorders

1. Abnormalities of Cytoskeletal/ Structural proteins

- Wiskott-Aldrich Syndrome
- β 1-Tubulin Deficiency

2. Defects in Transcription factors:

Thrombocytopenia

- RUNX1: Familial platelet defect with predisposition to AML
- GATA-1
- FLI1: Dysmorphic platelets with giant α -granules

Congenital Disorders of Platelet Function: Management Principles

- **Individualized based on clinical features**
- **Platelet transfusions indicated in the management of bleeding episodes or surgical procedures**
- **Risk of developing specific anti-platelet antibodies**
- **DDAVP (Desmopressin)**
- **Recombinant Factor VIIa**

Congenital Disorders of Platelet Function

Therapeutic Options

- **DDAVP (Desmopressin)**
 - Shortens the bleeding time in some patients with platelet function defects
 - Induces a rise in plasma VWF, FVIII, tPA
- **Recombinant Factor VIIa**

Rao AK et al. *Thromb Haemost.* 1995;74: 1071-1078.

Mannucci PM. *N Engl J Med.* 1998;339: 245-253.

Mannucci PM, Levi. *N Engl J Med.* 2007; 356: 2301-2311.

Poon, MC. *Semin Hematol.* 2001, 38 (Suppl 4): 12-15.

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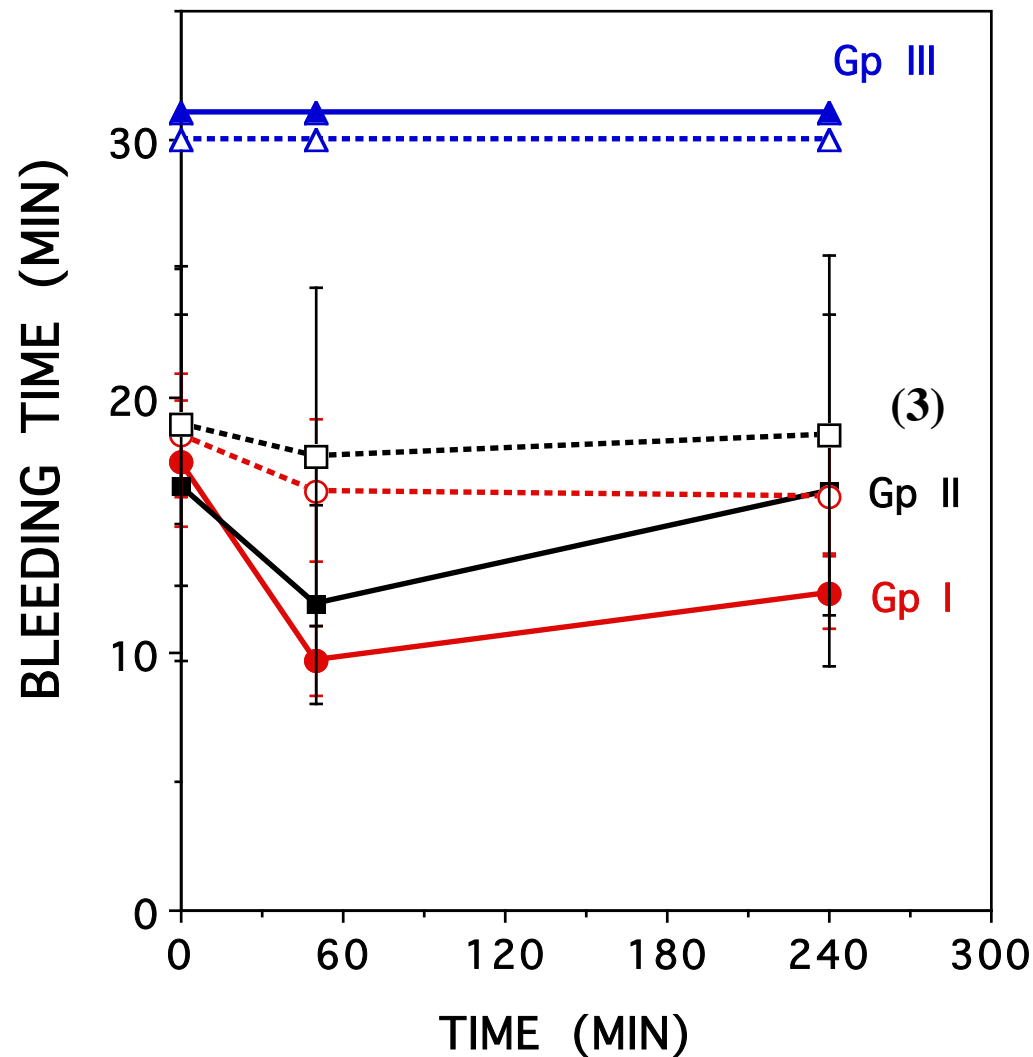
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Effect of DDAVP on Bleeding Time of Patients with Congenital Platelet Defects



Group III:
Storage Pool Deficiency

Group II:
Decreased Thromboxane
Production

Group I:
Primary Secretion Defects

..... Placebo
—— DDAVP

Rao, AK et al, 1995, Thrombos Haemost 75:76-82.

Congenital Disorders Of Platelet Function

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Thank You

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