# Coagulation Disorders: Diagnosis and Therapy

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# Overview

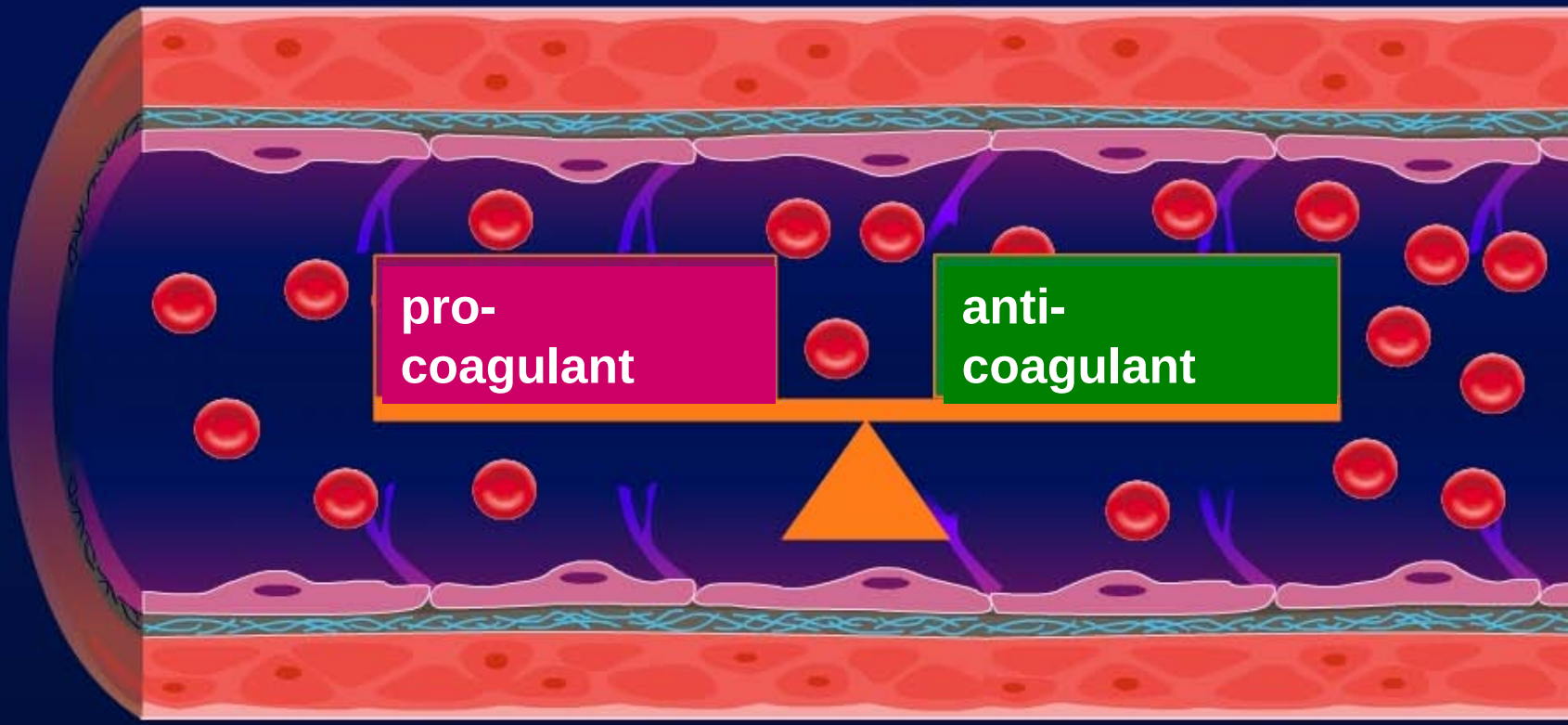
## Physiology of coagulation

## Thrombosis

- Diagnosis
- Therapy

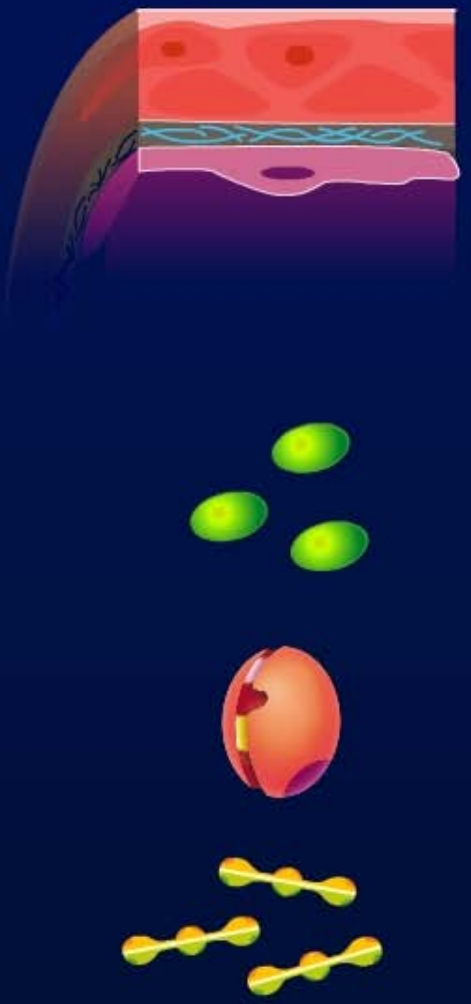
- **Bleeding**
  - Diagnosis
  - Therapy

**Hemostasis should maintain the regular blood flow and Prevent bleeding in case of injury**




**Balance of pro- and anti-coagulant mechanisms**

# Structures involved



**Vessel wall:** Tissue factor, collagen

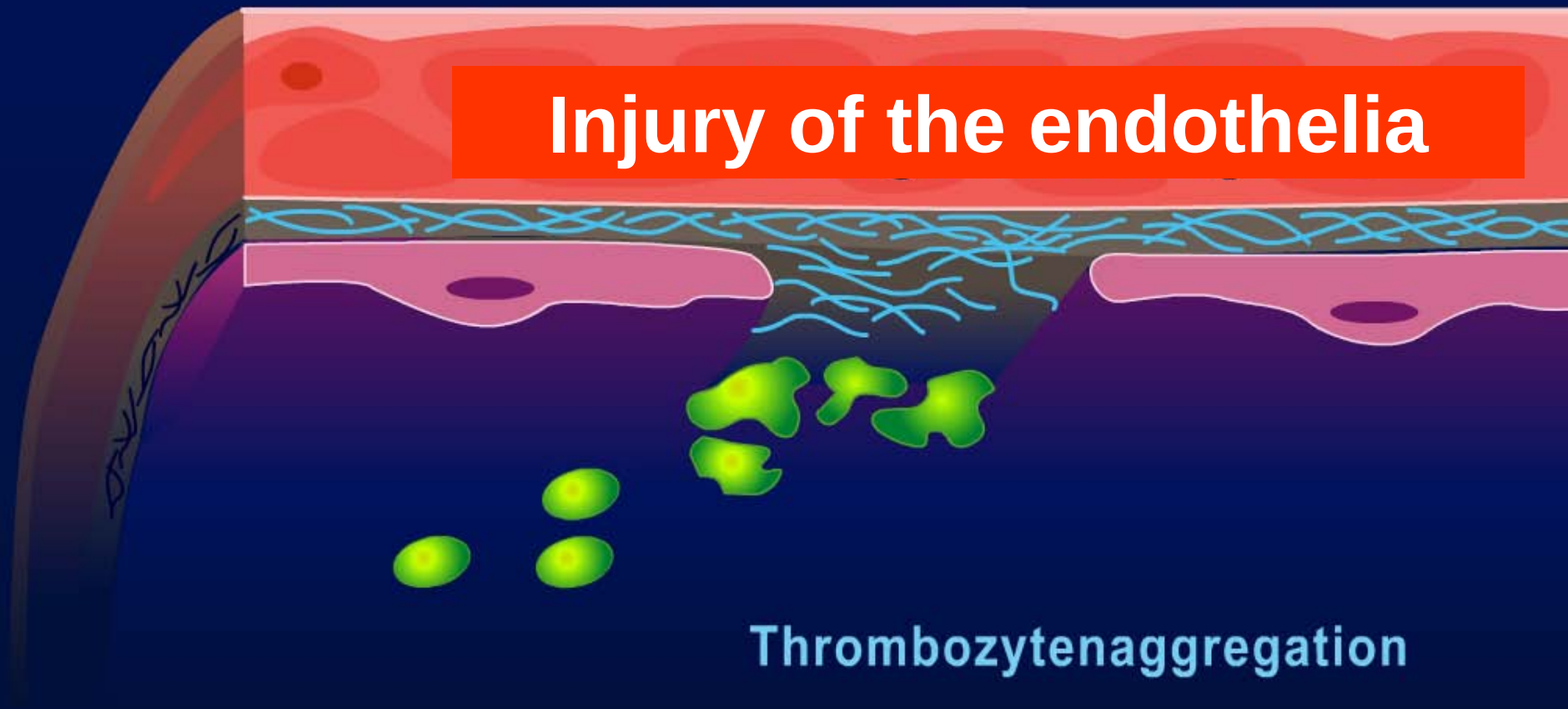
**Endothelia:** Barrier function, membrane bound factors and mediators.

**Platelets:** Aggregation, secretion, phospholipids

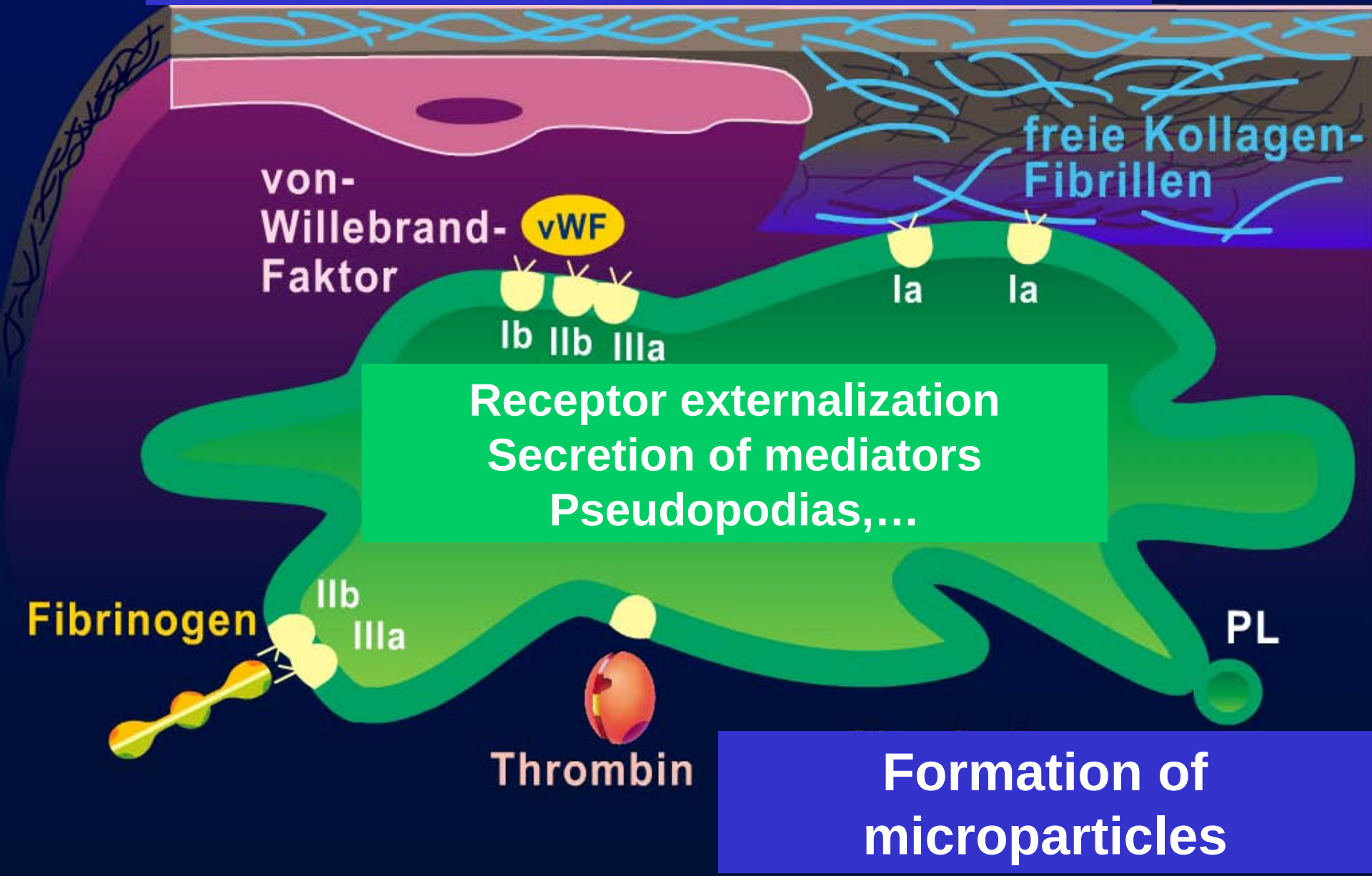
**Coagulation Factors:** Activatable proteases and protease inhibitors, i.e. thrombin, antithrombin…

**Fibrinogen**

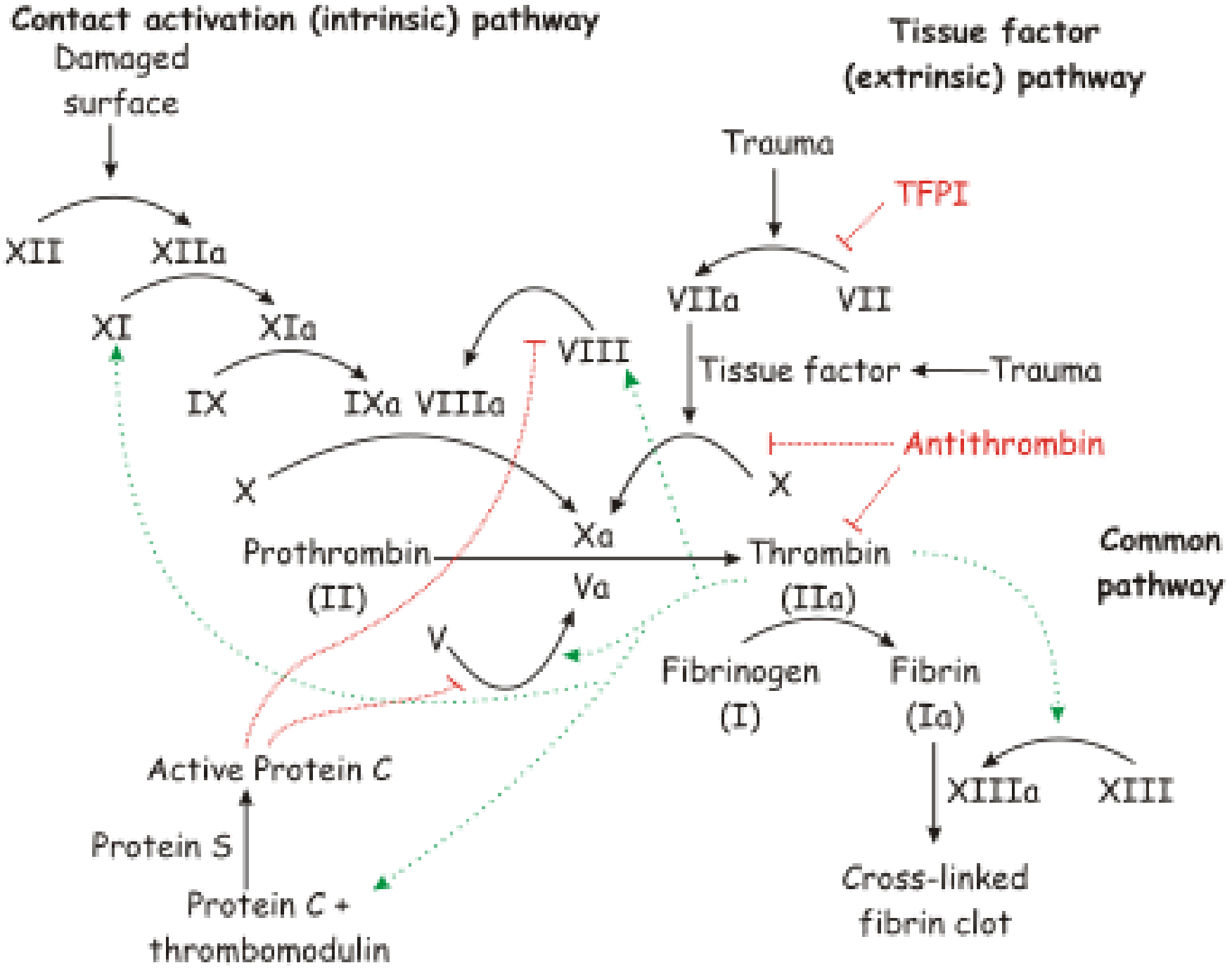
# Primary hemostasis



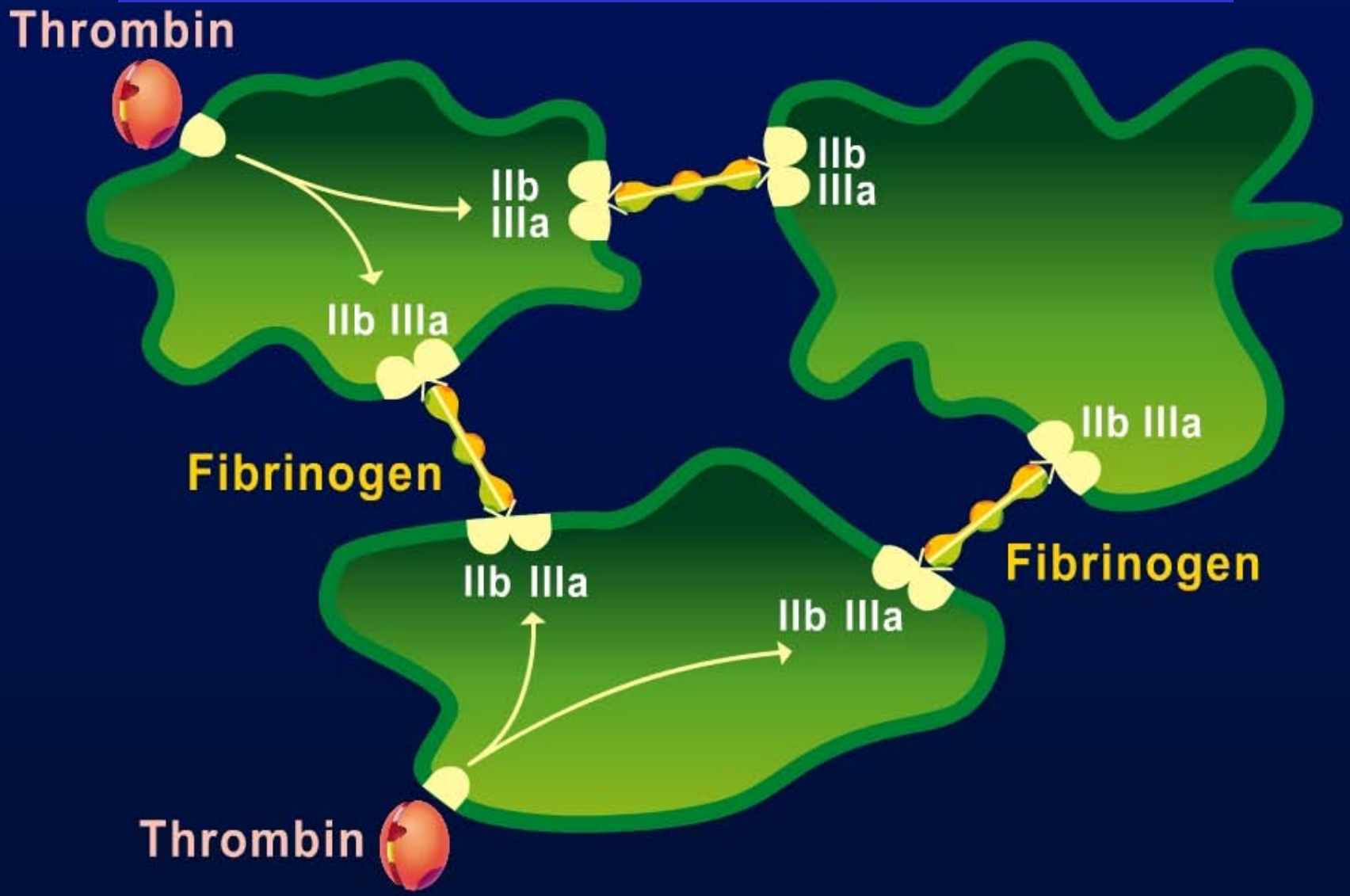
# Platelet activation



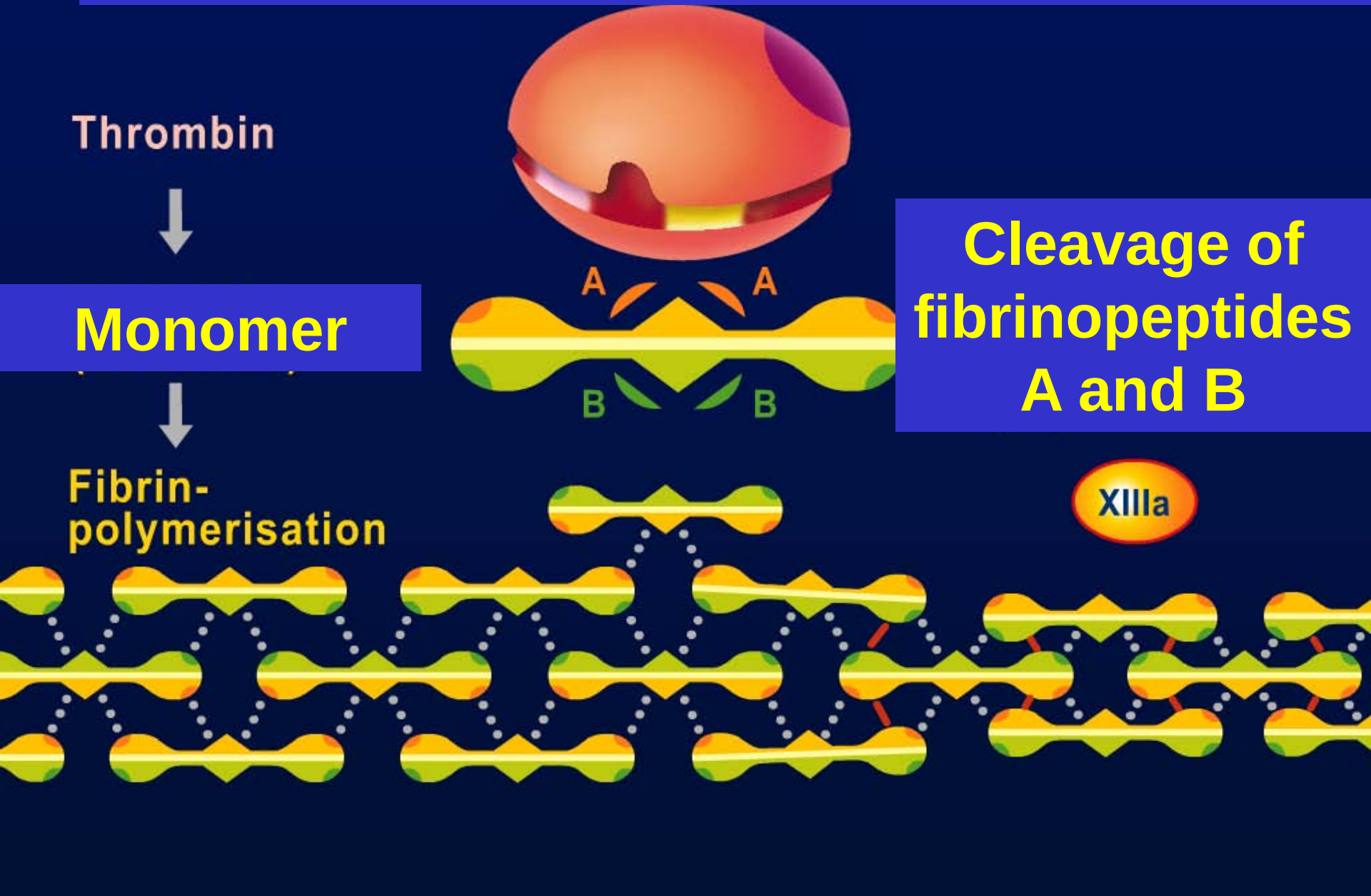

**Formation of microparticles**

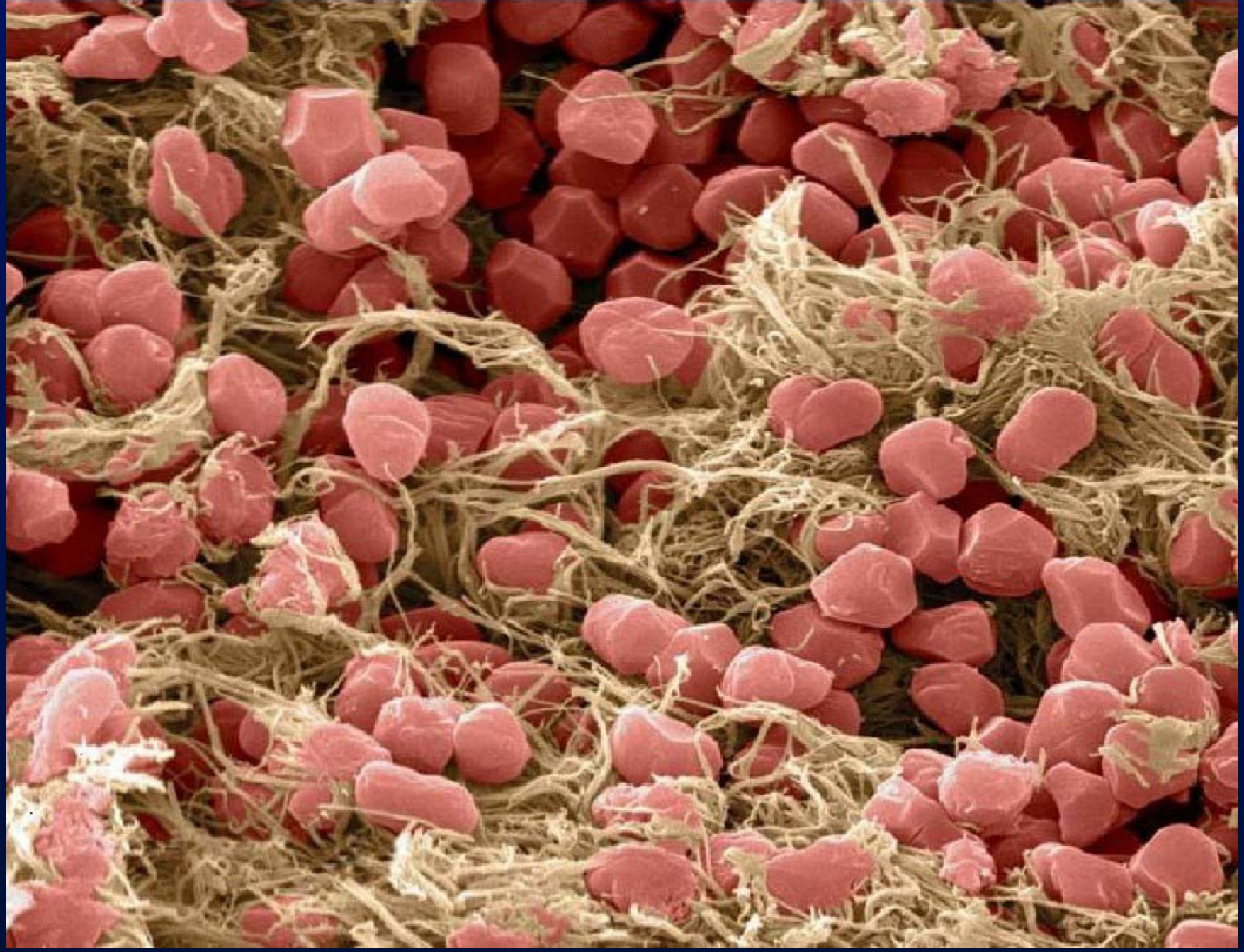

Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa VIIIa
VIII
X
Xa
Va
Prothrombin (II)
Thrombin (IIa)
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Common pathway

# Platelet aggregation

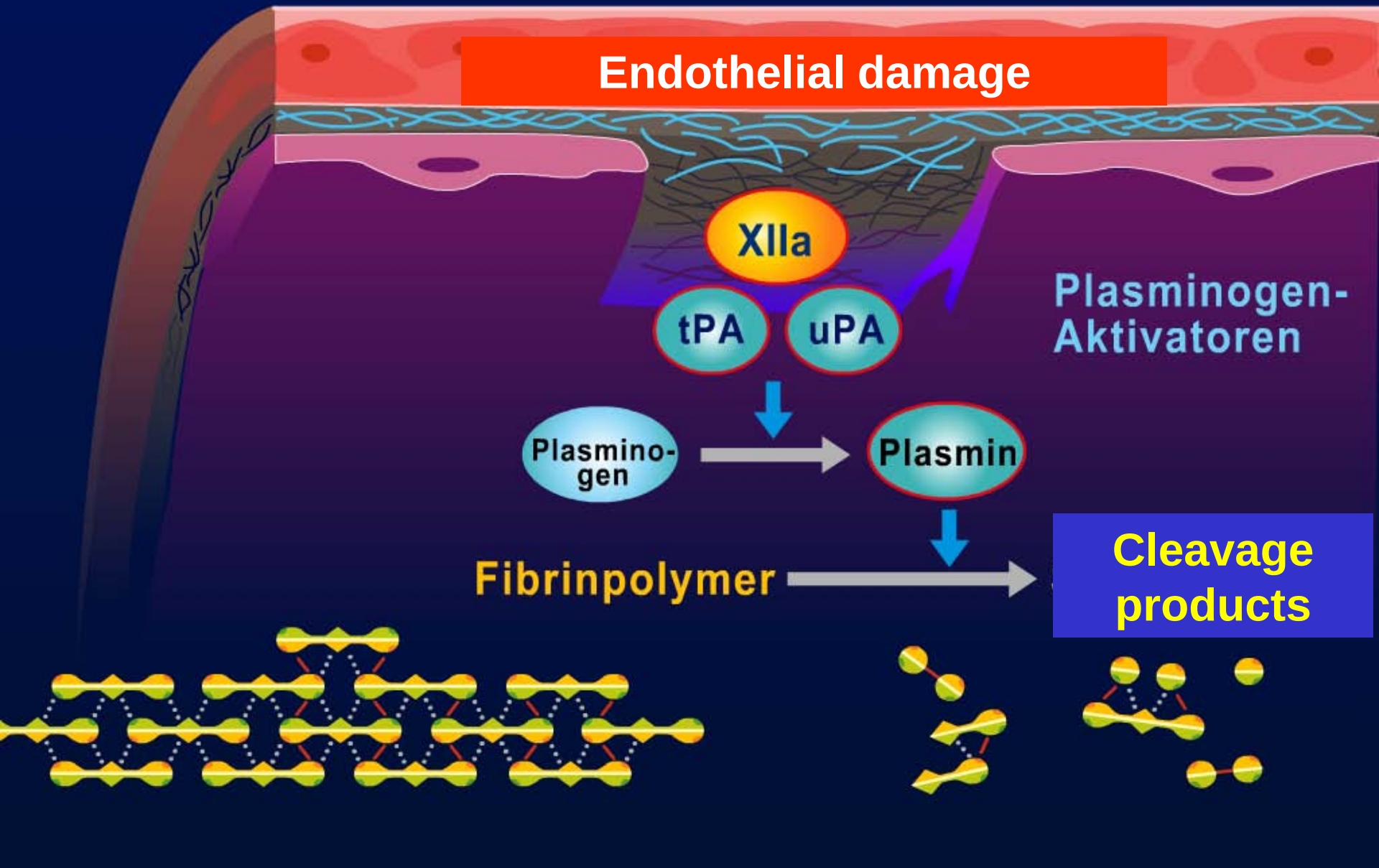


# Fibrin generation and cross-linking

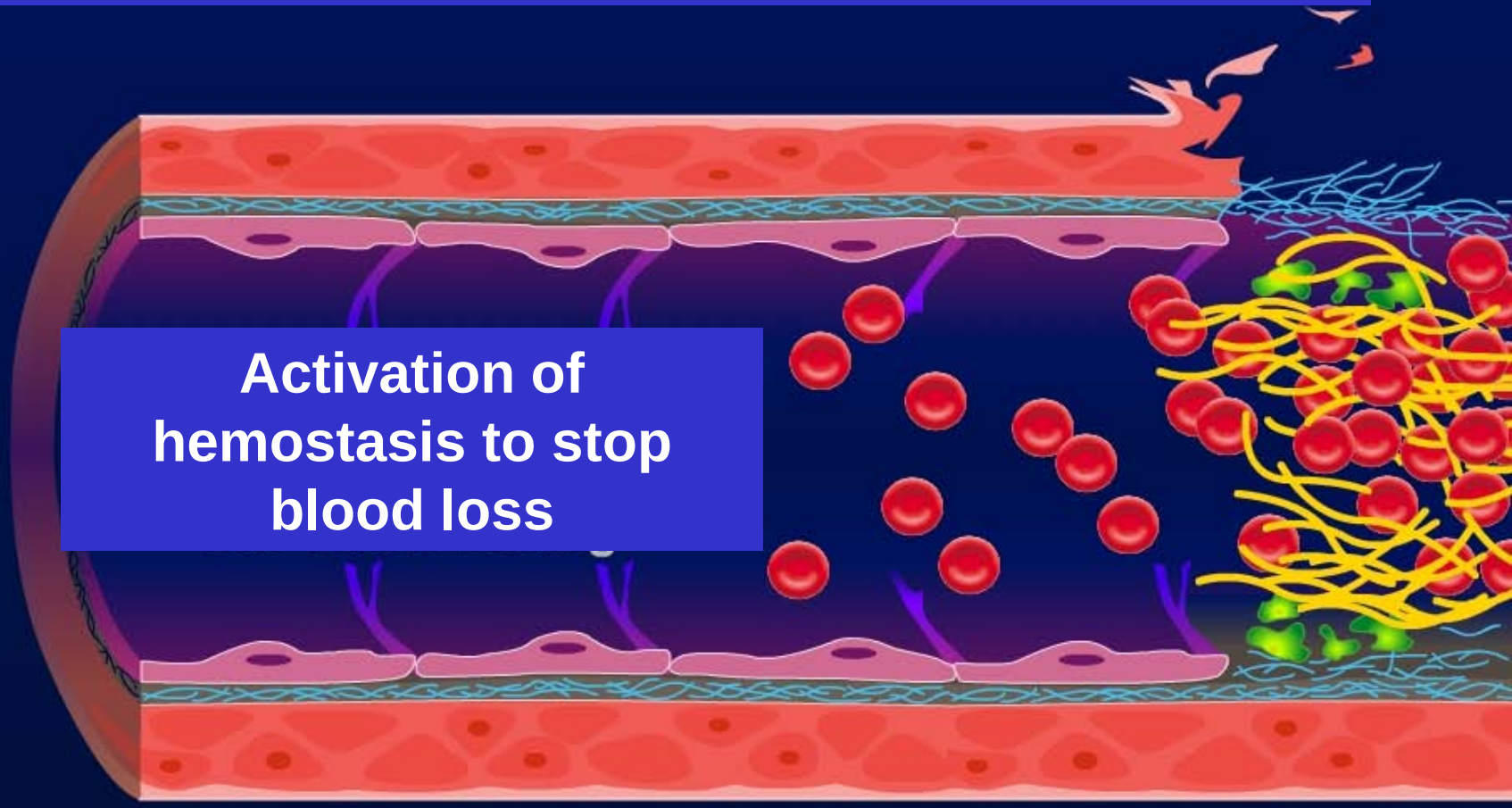




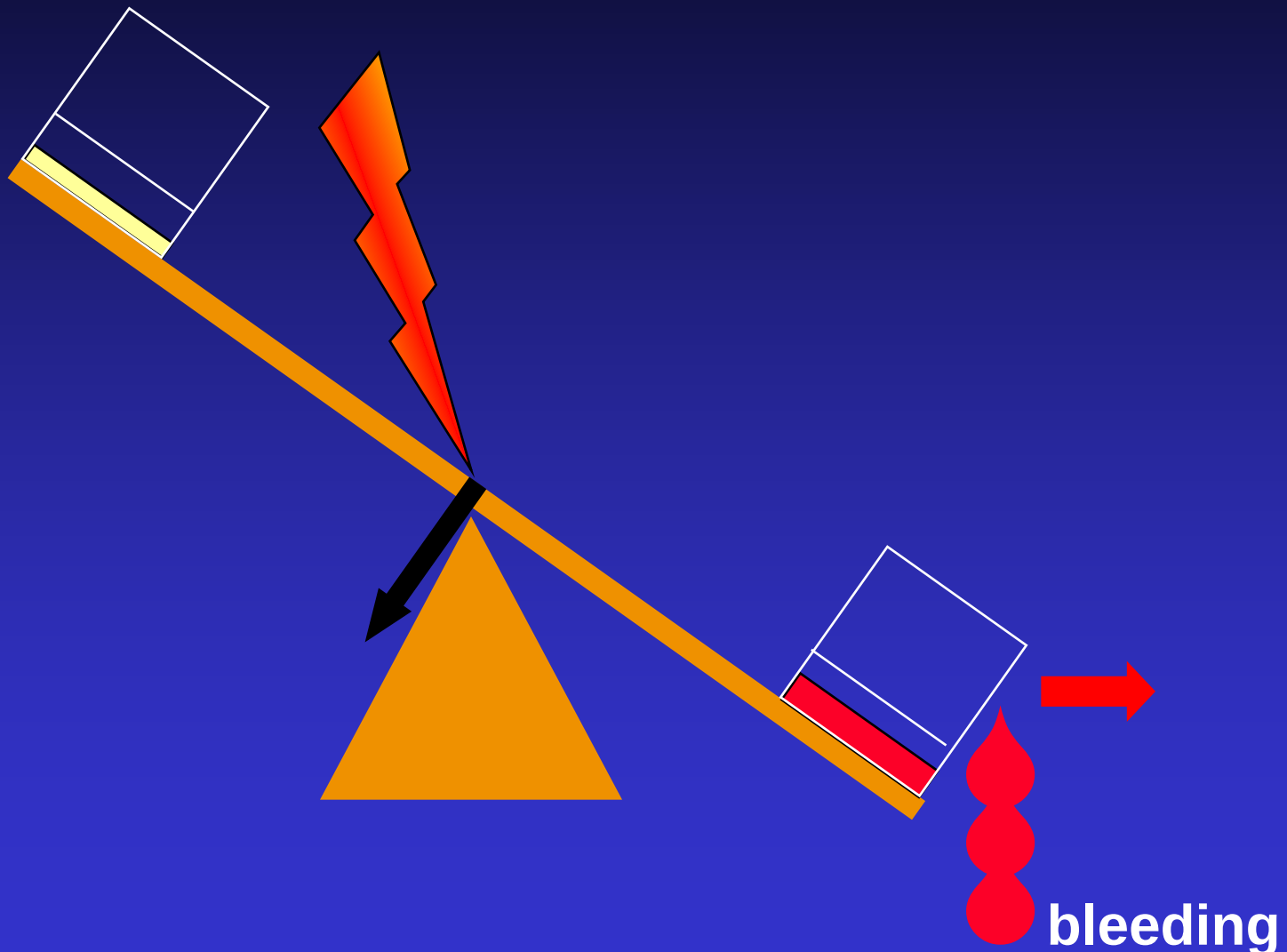
# Endogenous biological fibrinolysis



# Reaction to Injury

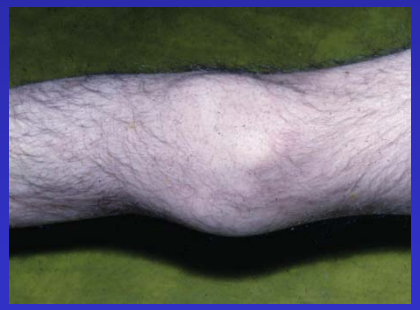
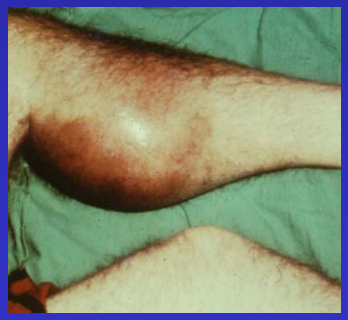
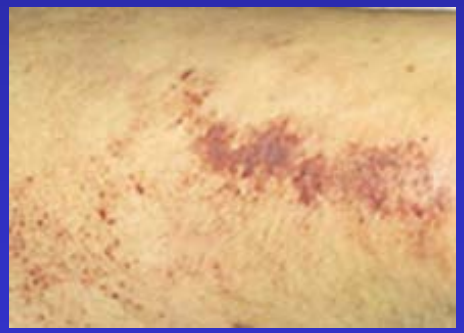
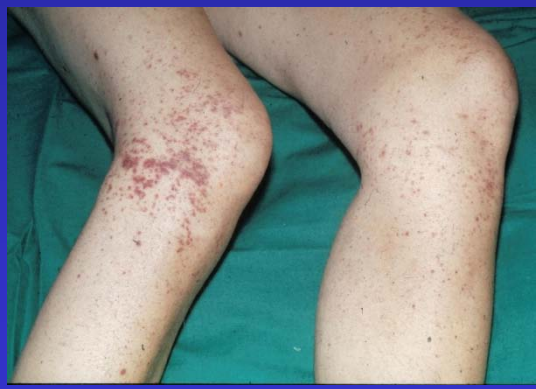


# Disturbance of Balance



# Types of Bleeding

- **Plasmatic type:**
  - Joint and muscle bleedings
  - hematoma
  - Ekchymosis
- **Platelet or vascular type**
  - Petechia, epistaxis
  - Menorrhagia

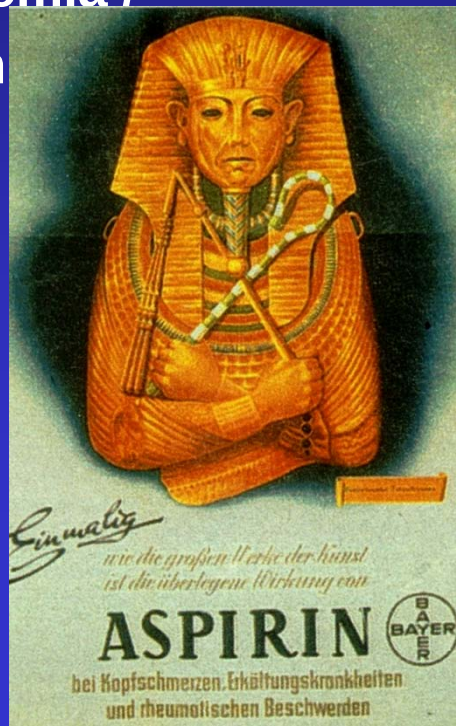
# Thrombocytopenia

- Disturbed generation in bone marrow
- Increased consumption
- Pooling in spleen
- Combination of causes, as in alcoholism

# Thrombocyte Preparations

# Thrombocytopathies

- **Heriditary**
  - **Thrombasthenia Glanzmann-Naegeli (GP IIb/IIIa deficiency)**
  - **Megalothrombopathy-**
    **(GP Ib/V/IX-complex def.):**
    - **Bernard-Soulier-Syndrom**
    - **May-Hegglin-Syndrom**
  - **Storage pool disease (diminished. ADP in granula)**
  - **Aspirin like defect (COX-deficiencyl)**
  - **...**
- **Acquired**
  - **Inhibitors of platelet aggreagation (Aspirin, Ticlopidin, Clopidogrel, GP IIb/IIIa-antagonists, ...)**
  - **B-cell type leukemia / M. Waldenström**
  - **Dextran, u.a.**
  - **Uremia**
  - **ET, DIC,**
  - **...**



# Hemorrhagic Diathesis

## Frequent (classical) forms

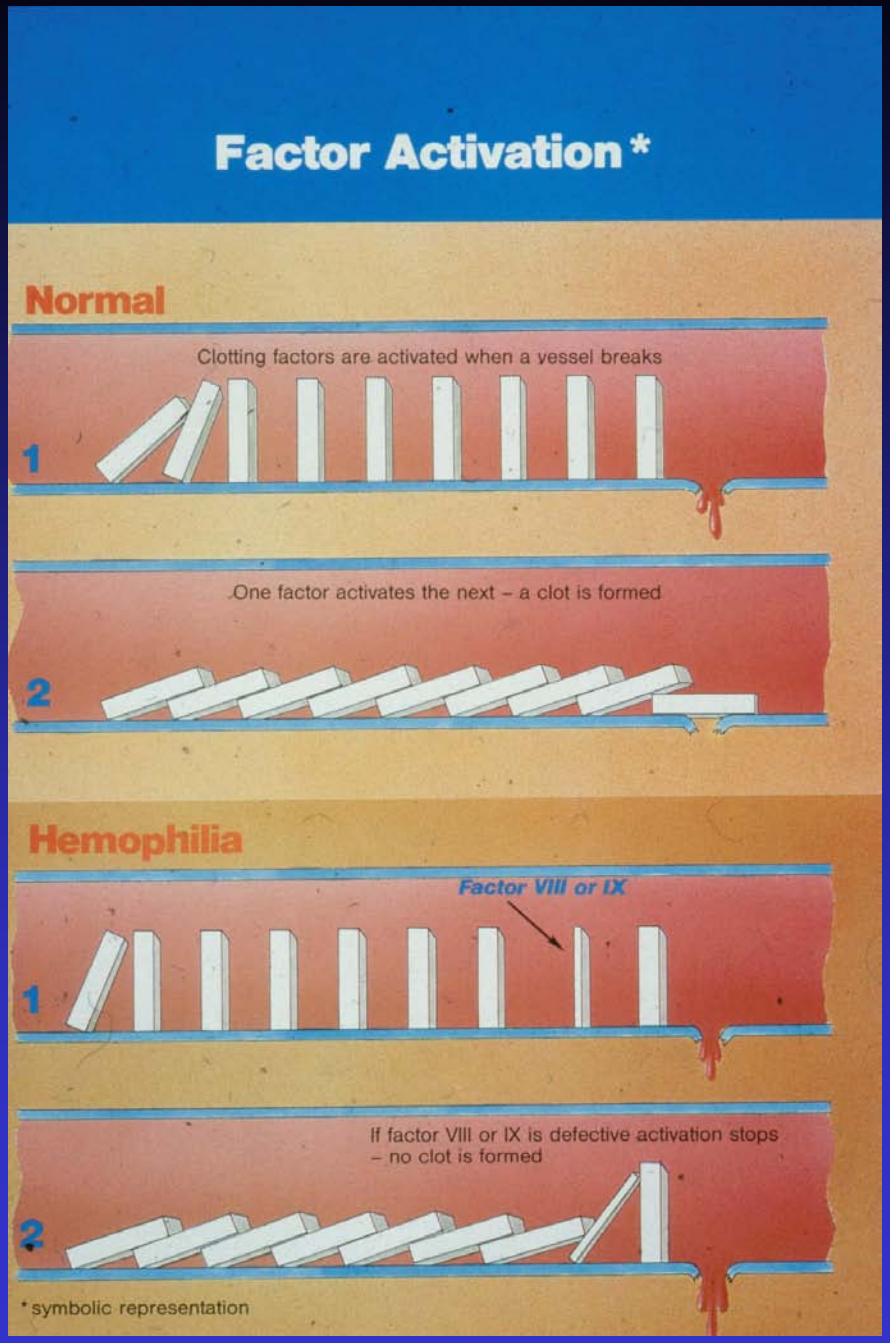
- Hemophilia A, Factor VIII deficiency, X-chromosomal, 1:5000
- Hemophilia B, Factor IX deficiency, X-chromosomal, 1:25.000
- Von Willebrand Disease, VWF-deficiency, autosomal, Typ III 1:100.000

## Rare Forms

- Deficiency of fibrinogen, FII, V, VII, X, XI, XIII, autosomal recessiv, 1: 1 Mill

Review Oldenburg & Schwaab Sem Thromb Haemost 2001

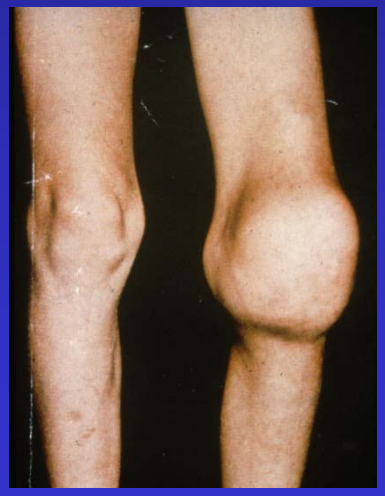
# Factor Activation *

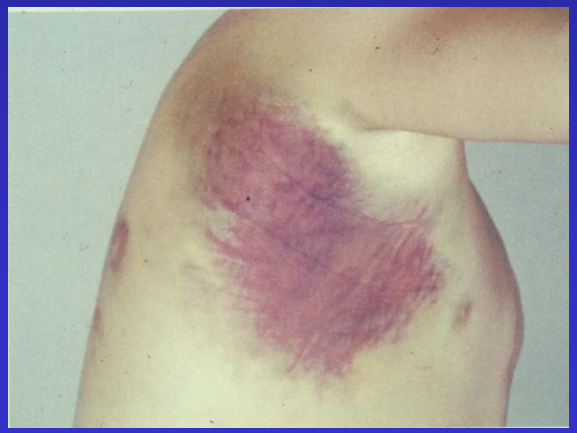


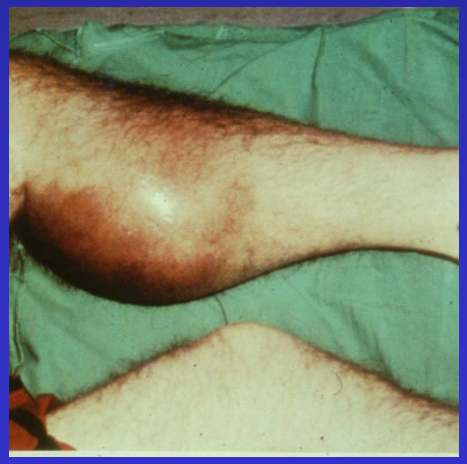
# Hemophilia A

**Bleeding into joints and muscle**

- **Deficiency of coagulation factor VIII**
- **Therapy by intravenous infusion of FVIII**
- **In Germany 4000 families with 6000 patients**



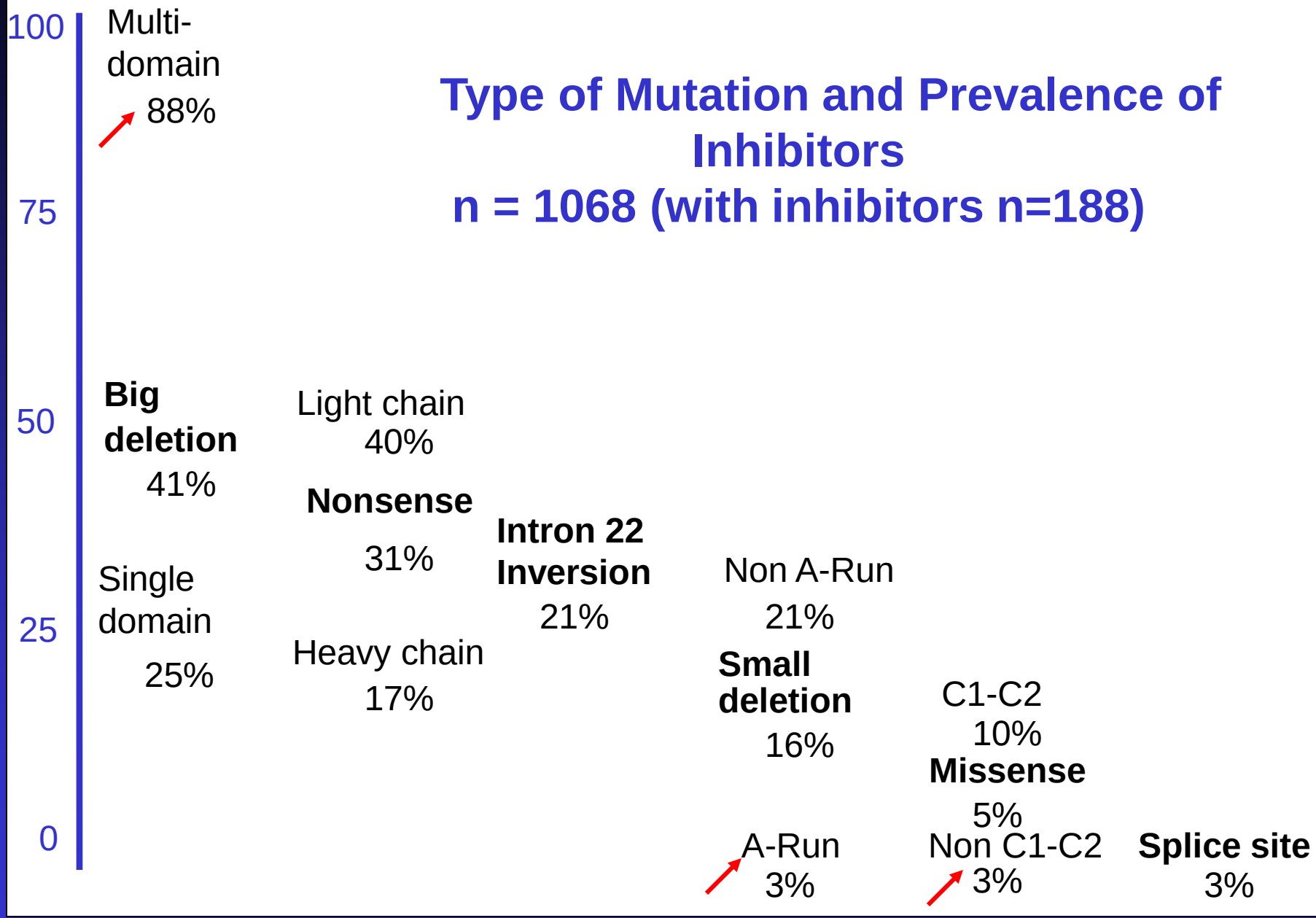




# Formation of inhibitory antibodies to FVIII

- Most frequent severe complication
- 20-30% of patients with severe hemophilia A
- Rare also as auto-antibody in elder patients
- Neutralization of substituted faktor-VIII-protein (Inhibitor formation)
- Alternative (Bypass-)therapy options, but no possibility of prophylaxis to avoid bleedings
- Eradication therapy of inhibitors

## Prevalence of inhibitors



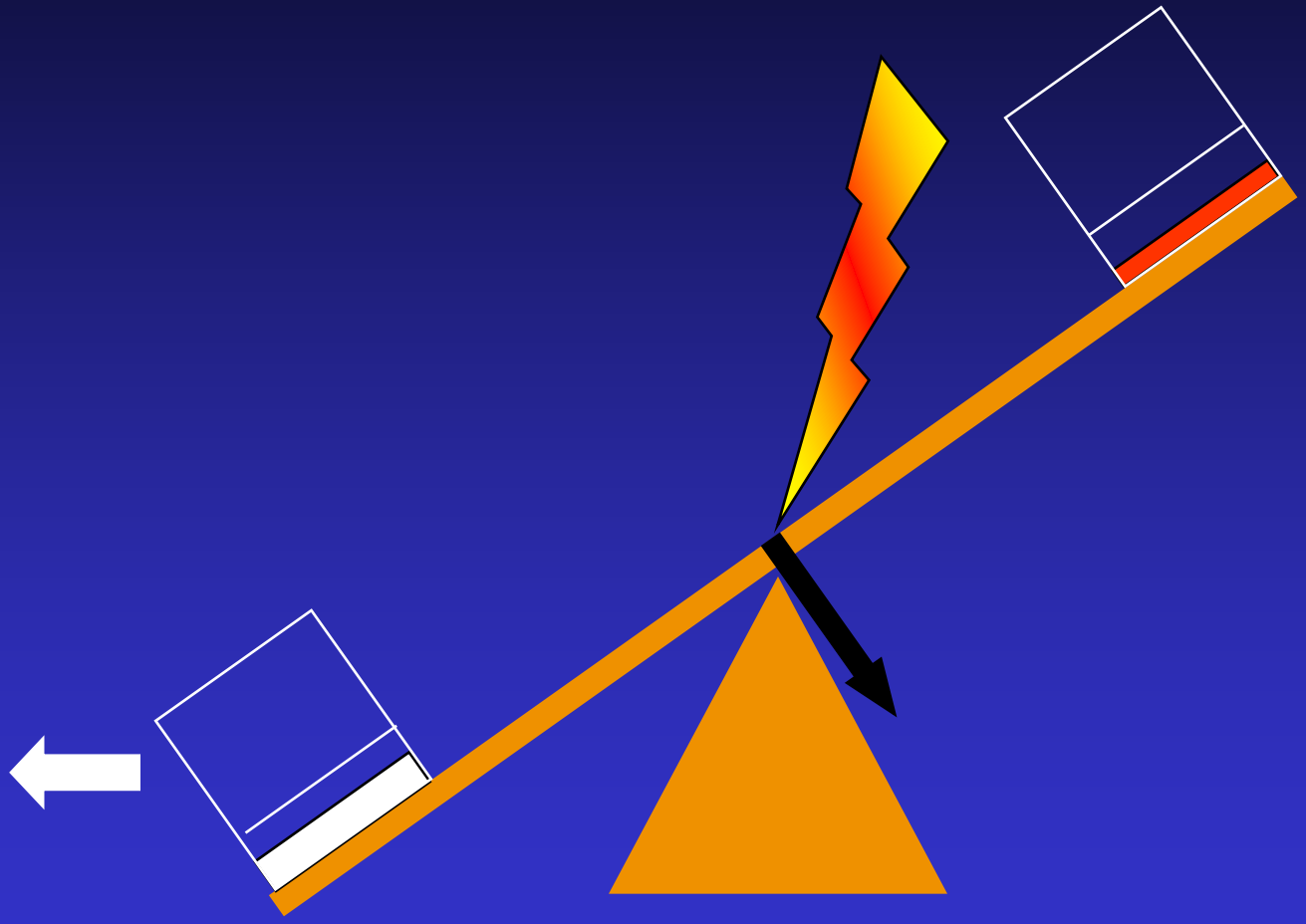

## Type of Mutation and Prevalence of Inhibitors
## n = 1068 (with inhibitors n=188)

Oldenburg et al., Haematologica, 2000

# Coagulation Factor Concentrates

| | |
|---|---|
| • Hemophilia A | FVIII (plasmatic or recomb.) |
| • Hemophilia B | FIX (plasmatic or recomb.) |
| • Von Willebrand | FVIII (vWF-cont., only plasmactic) |
| • Vit K factors | PPSB ( Vit K dep. FII, FVII, FIX, FX) |
| • Fibrinogen deficieny | Fibrinogen |
| • FXIII deficiency | FXIII |
| • AT deficiency | AT |
| • Protein C deficiency | PC/APC |
| • Inhibitors, uncontrolled bleeding | rFVIIa, Feiba (Factor eight inh. bypassing act.) |
| • FV and FXI deficiency | FFP |

# Disturbance of Balance



# Thrombosis Risk – multi-factorial

## Exogenous Factors

Surgery, injuries, hospitalization
Immobilisation (long travels, flights, etc.)

## Acquired Factors

Adipositas, varicosis , pregnancy
Hemiplegia, stroke, autoimmune diseases, tumors
oral anti-conception
Anit-phospolipid antibodies , high levels of FVIII or fibringoen

## Hereditary Factors

Factor V Leiden, Antithrombin -, Protein C-, Protein S-deficiencies, prothrombin G20210A,homocysteinemia

# Prevalence and thrombosis risk of heriditary defects of hemostasis

- LEIDEN -Thrombophilia-Study (LETS) - v. d. Meer et al, Thromb Haemostas 78, 631 (1997)

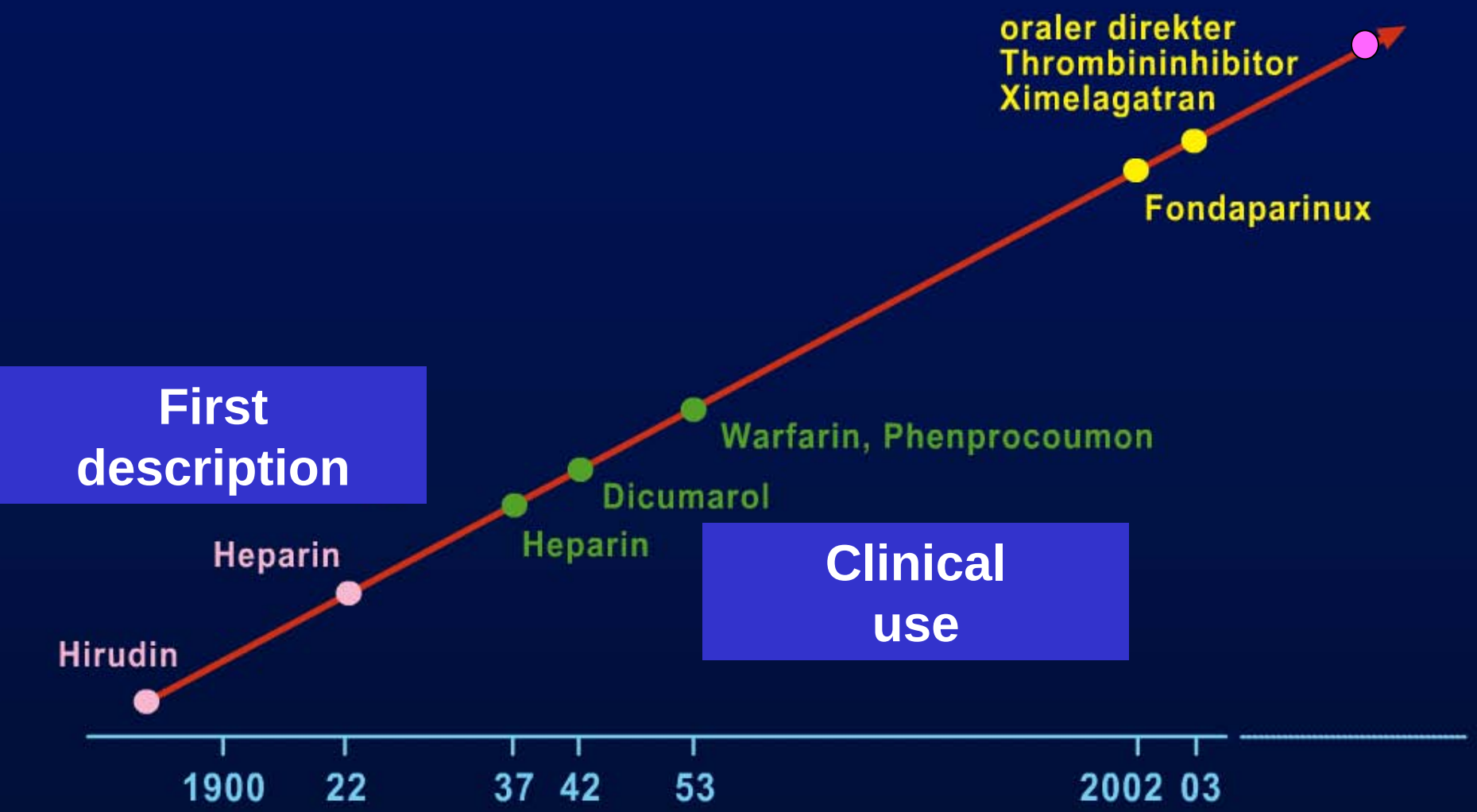
| | | Patients | Controls | Relative Risk |
|---|---|---|---|---|
| | U/ml | % (N=474) | % (N=474) | |
| Antithrombin | 2x <0.8 | 1,1 | 0,2 | 5.0 |
| Protein C | 2x <0.67 | 3,1 | 0,8 | 3.8 |
| | <0.67 + PCR | 2,7 | 0,4 | 6.5 |
| Protein S g / fr | <0.67/0.57 | 1,2 | 0,7 | 1.7 |
| Faktor V Leiden | heterocygous | 20 (N=347) | 5 (N=310) | 7.4 |
| | homocygous | 0,2 | 0 | estimated 80 (Hardy/Weinberg) |
| Prothrombin G20210A | | 6,2 | 2,3 | 2.8 |

# FV-Leiden Mutation and Prothrombin-Mutation

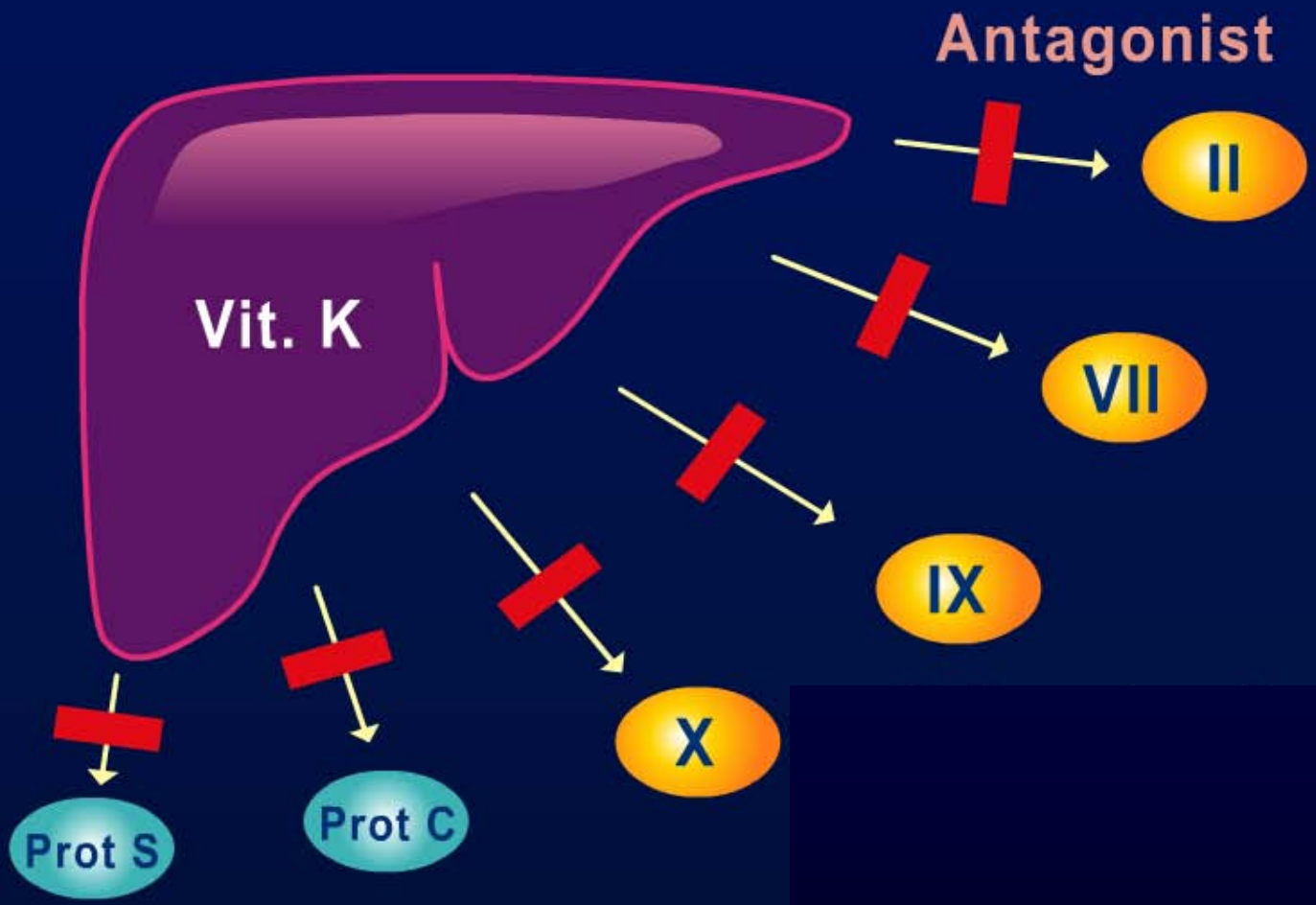
- Founder-Mutations – appeared 60.000-70.000 B.C.
- frequent in general population (FVL ~ 10%, PT ~ 4%)
- 3-fold (heterocygote) up to 80-fold risk for thromboembolic disease
- manifestation together with other risk factors
- 90% of carriers never develop thrombosis

# Development of Anticoagulants

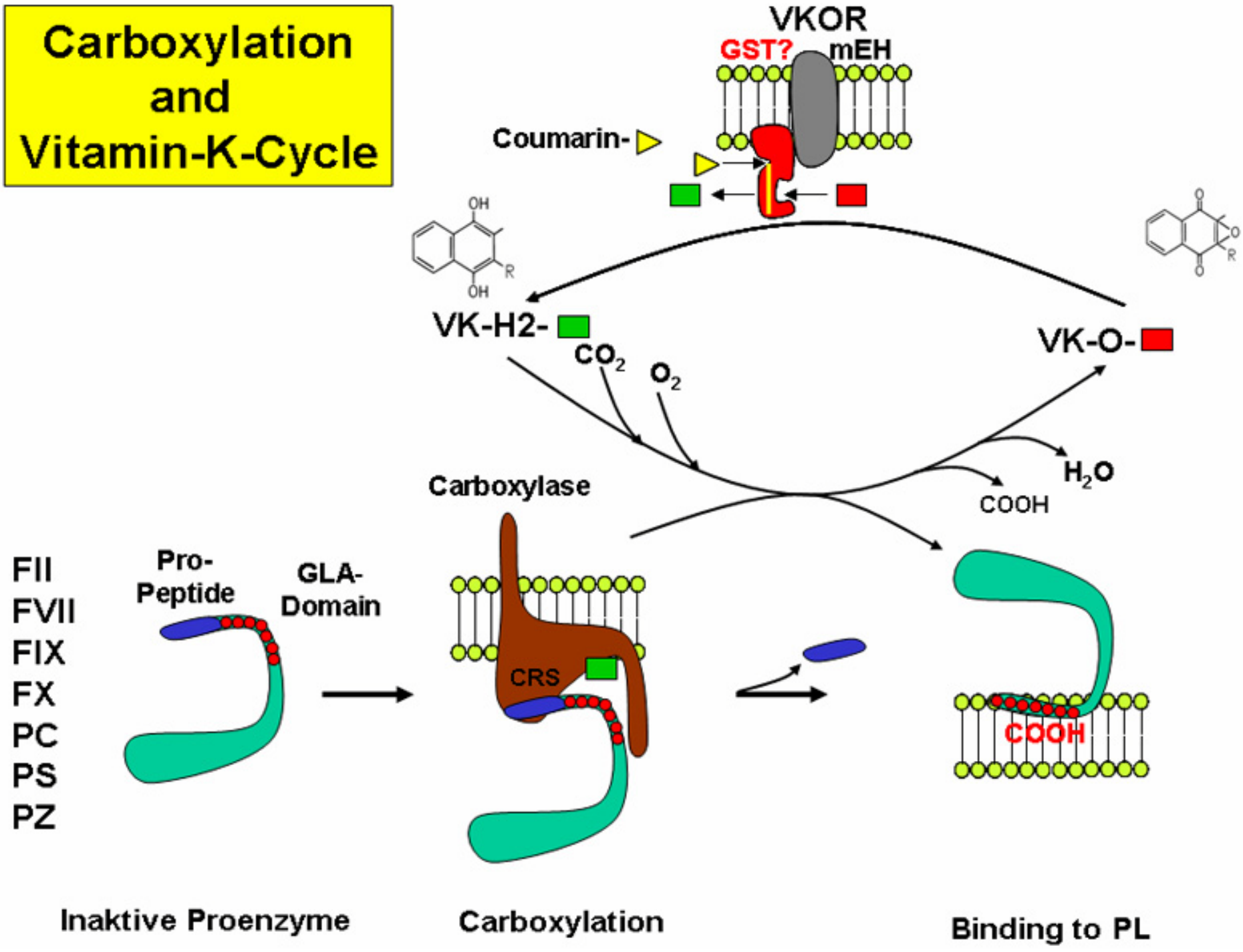
u.a.



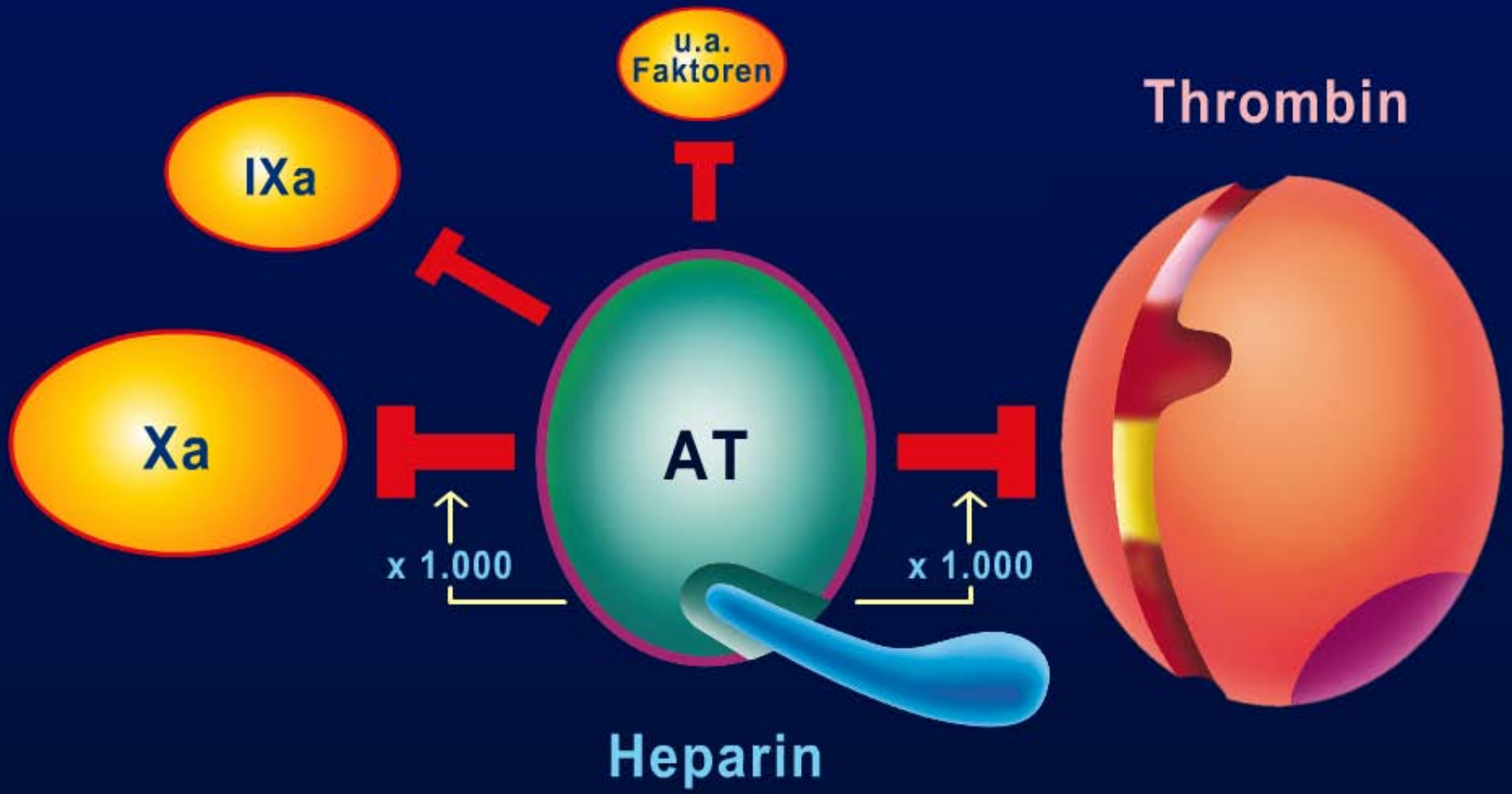
# Vitamine K-dependent coagulatino factors



# Carboxylation and Vitamin-K-Cycle

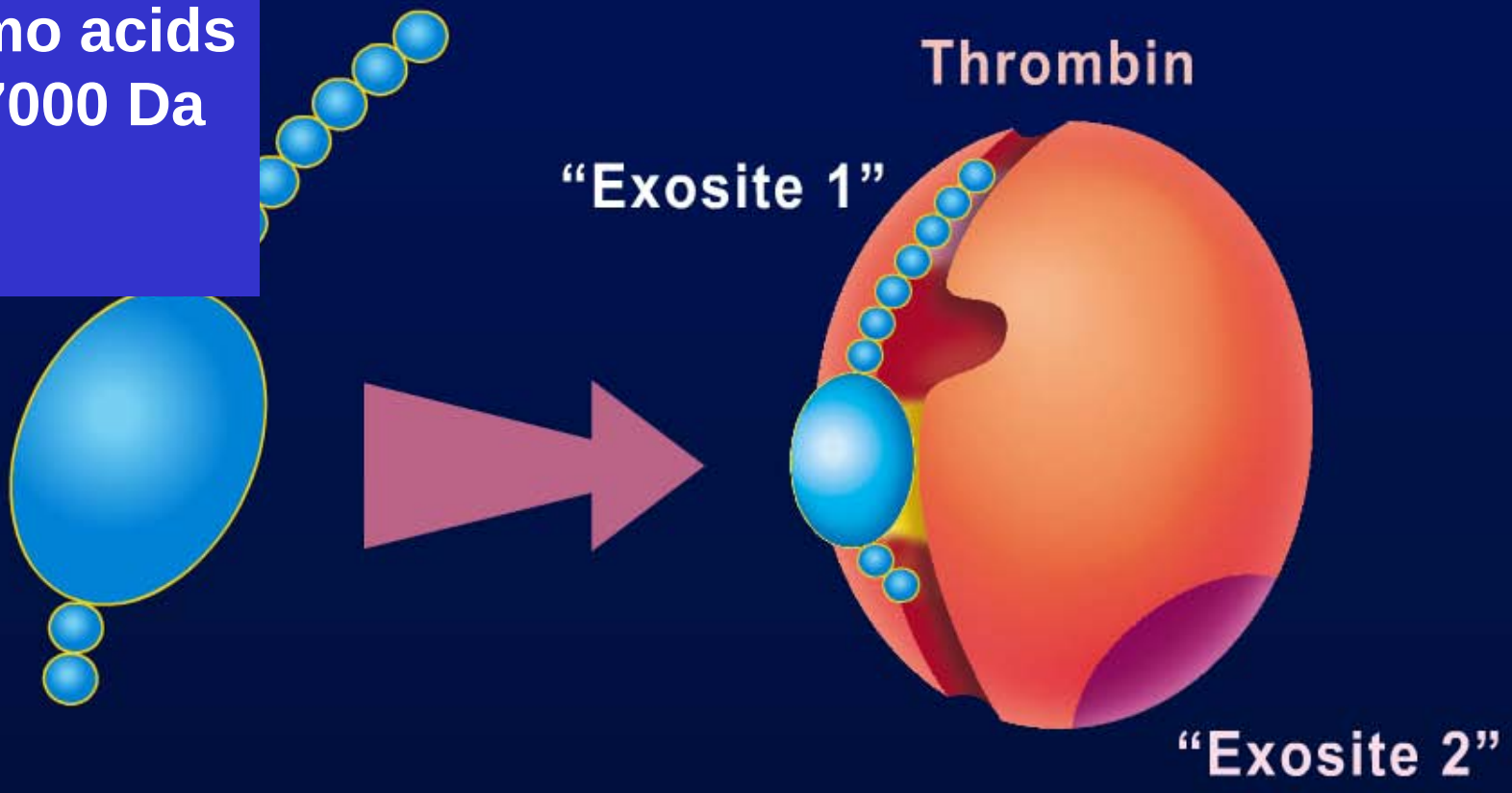


# Agonistic Action of Heparin and Antithrombin



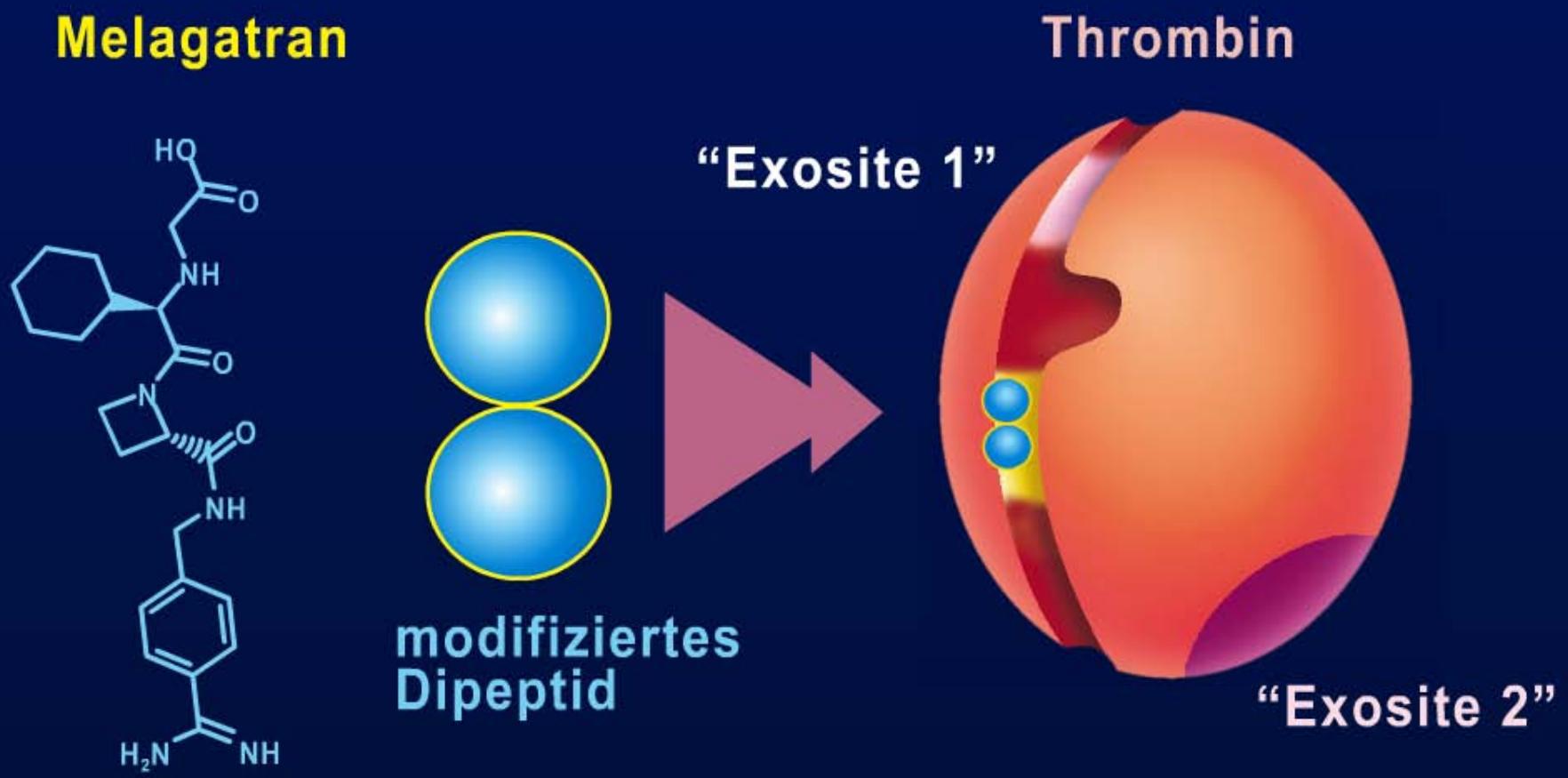
# Mechanism of Action of Hirudin

**65 animo acids**
**MW: 7000 Da**




**Direct binding to active site**

# Melagatran: Mechanism of Action

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