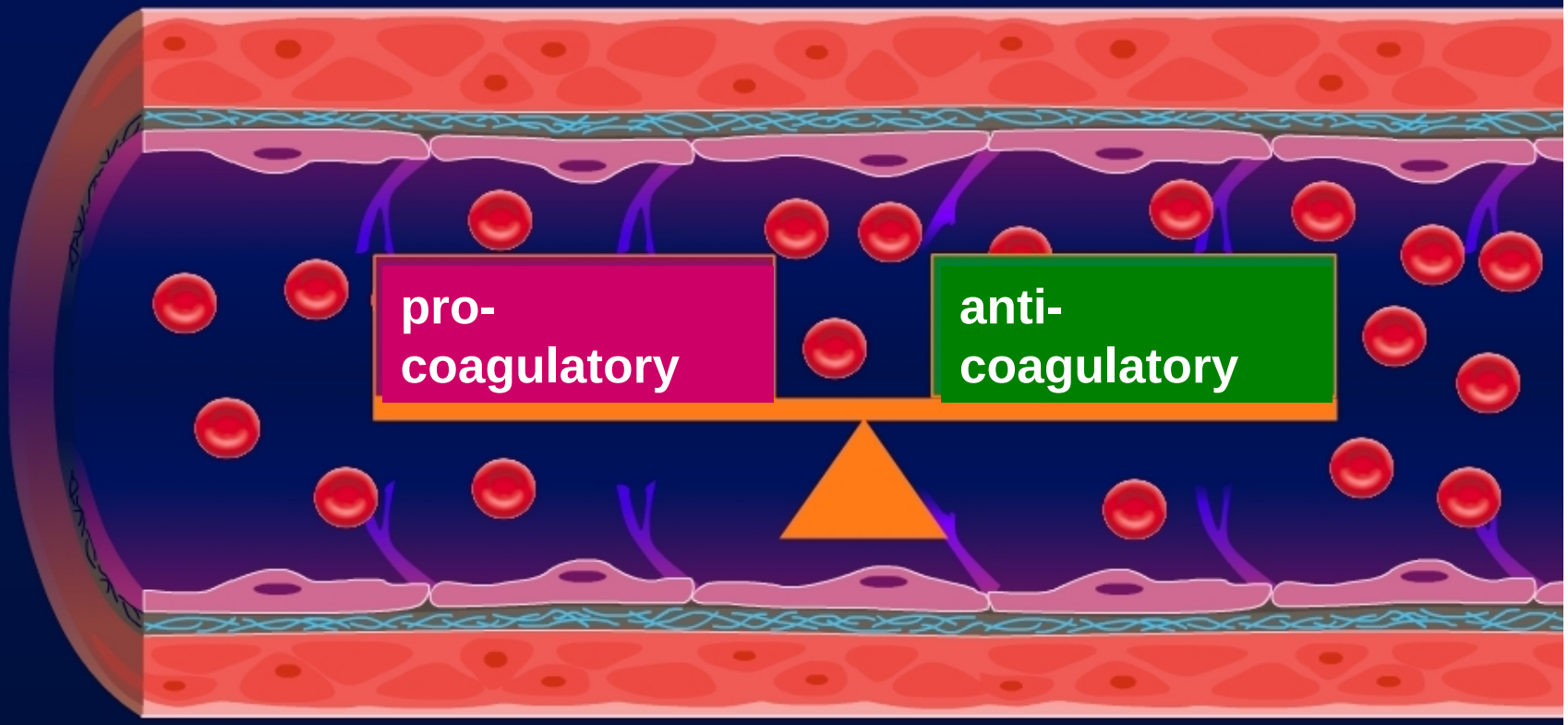
Coagulation Disorders: Diagnosis and Therapy

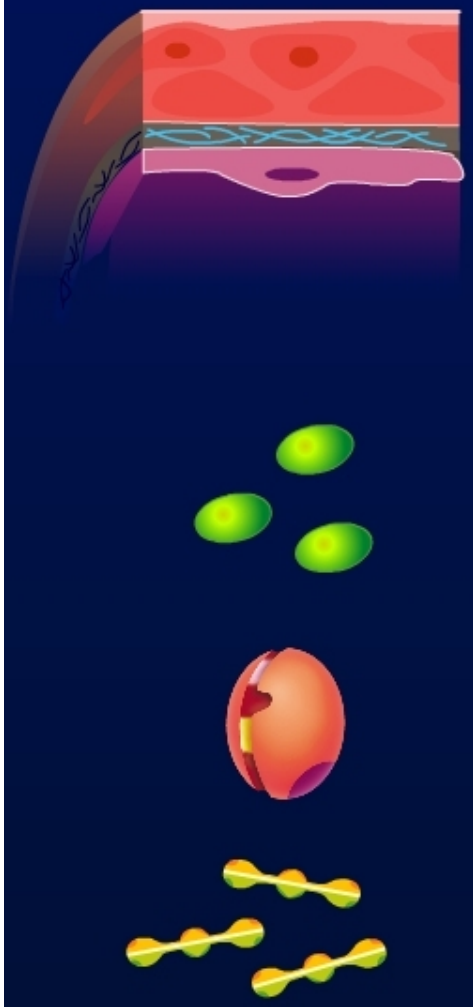
PD Dr.med. Torsten Tonn

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

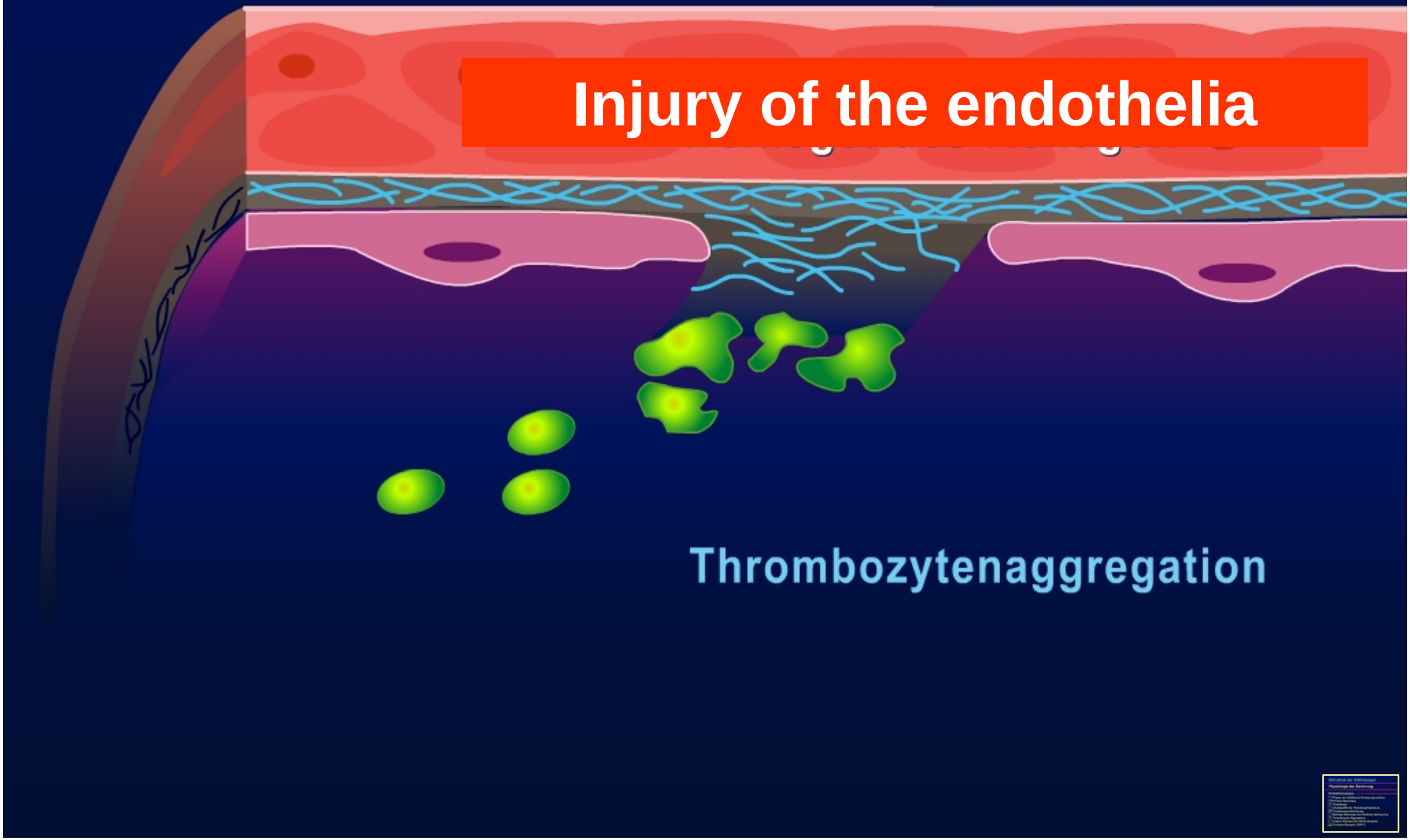
Endothelia: Barrier function, membrane bound factors and mediators.

Platelets: Aggregation, secretion, phospholipids

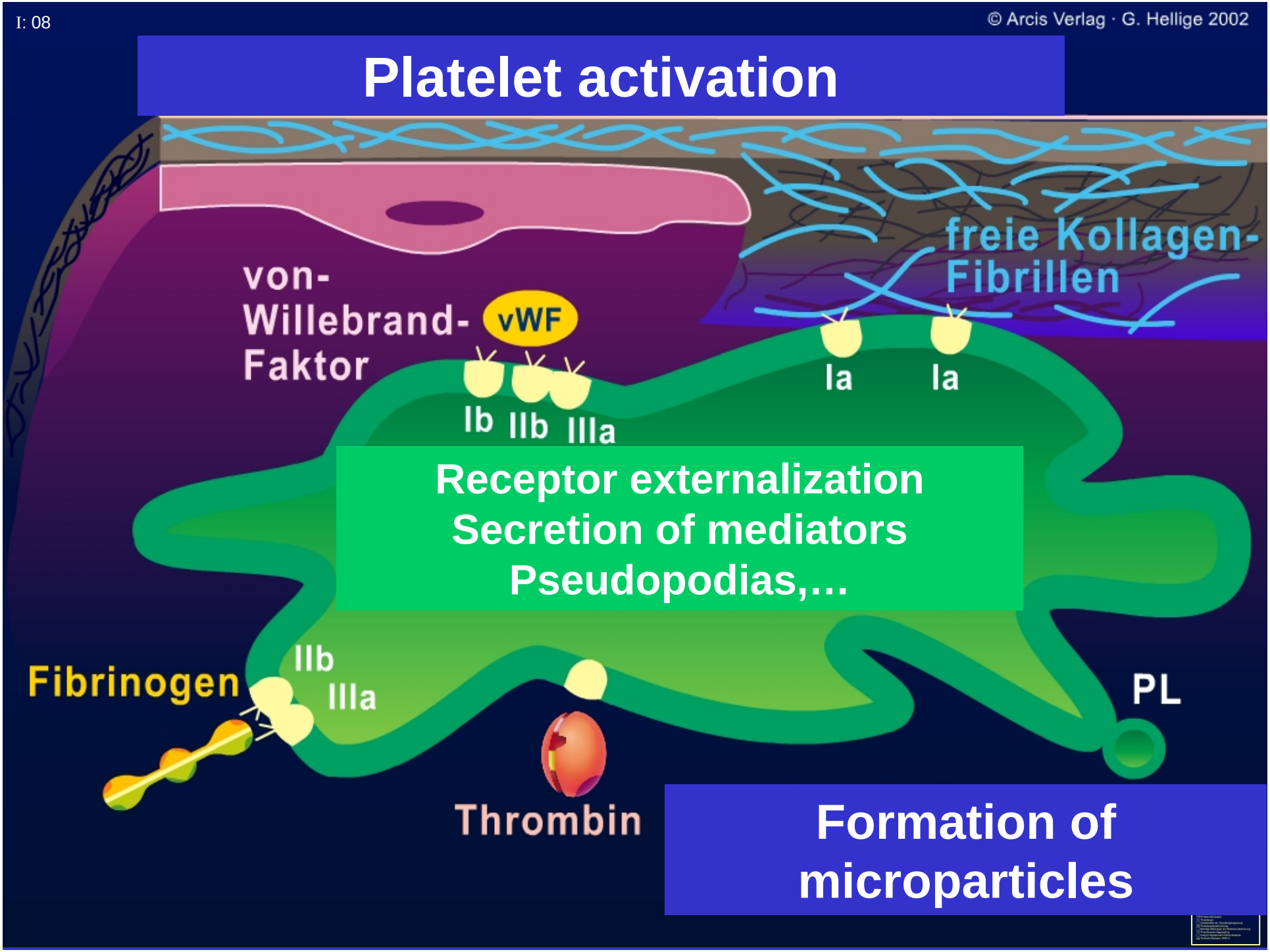
Coagulation Factors: Activatable proteases and protease inhibitors, i.e. thrombin, antithrombin…

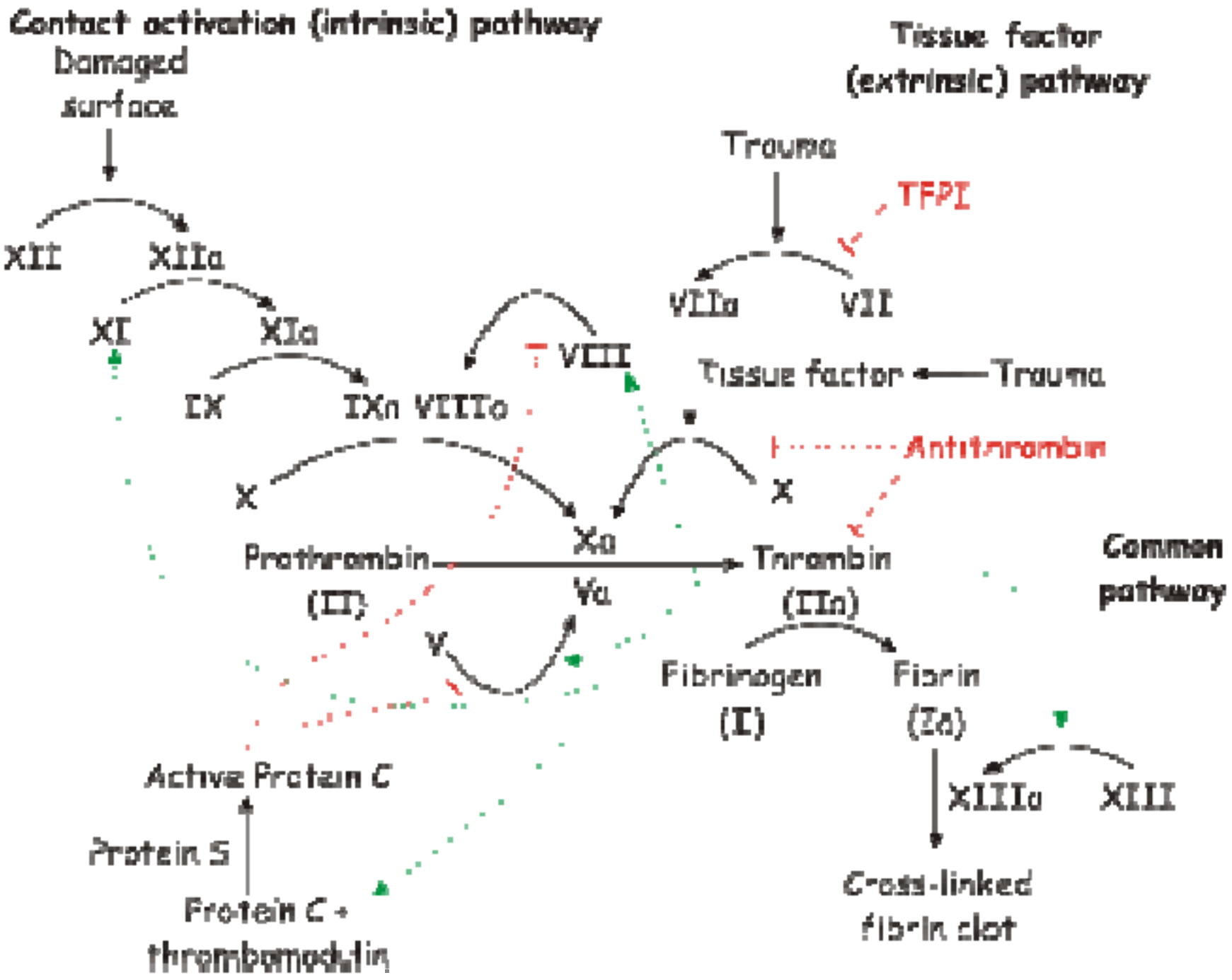
Fibrinogen

Primary hemostasis

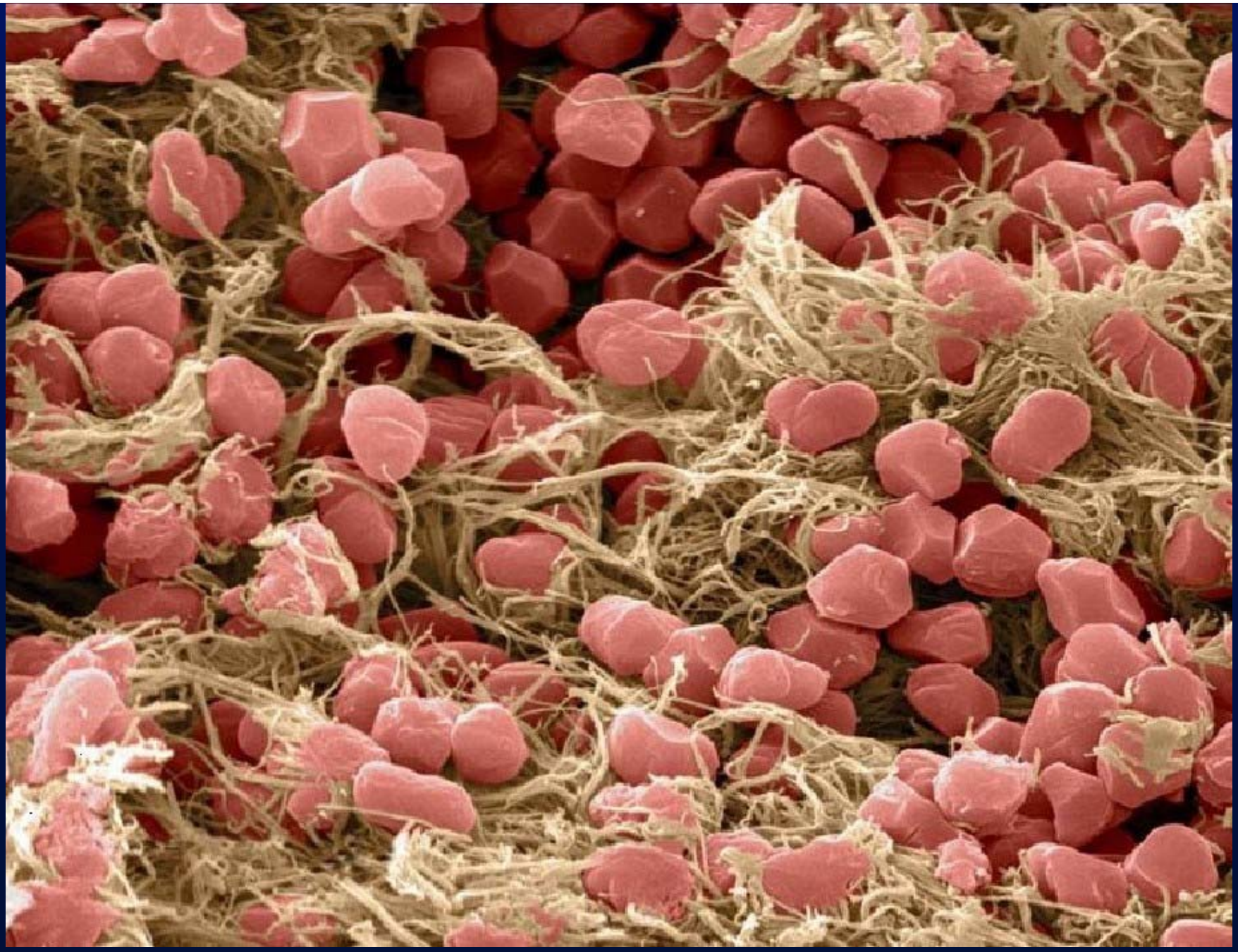


Platelet activation

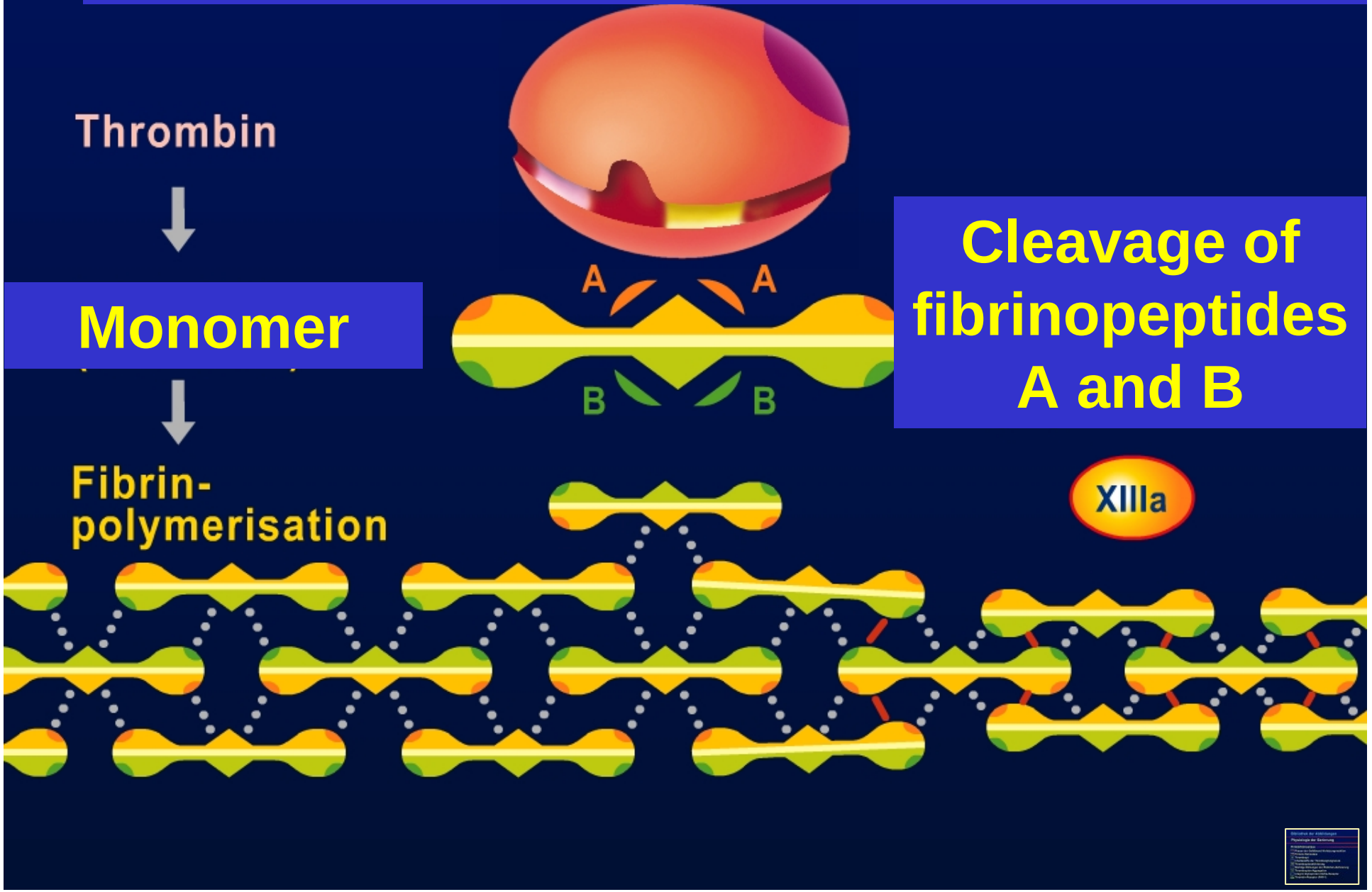



Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
X
Xa
Va
V
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
Common pathway
Activated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

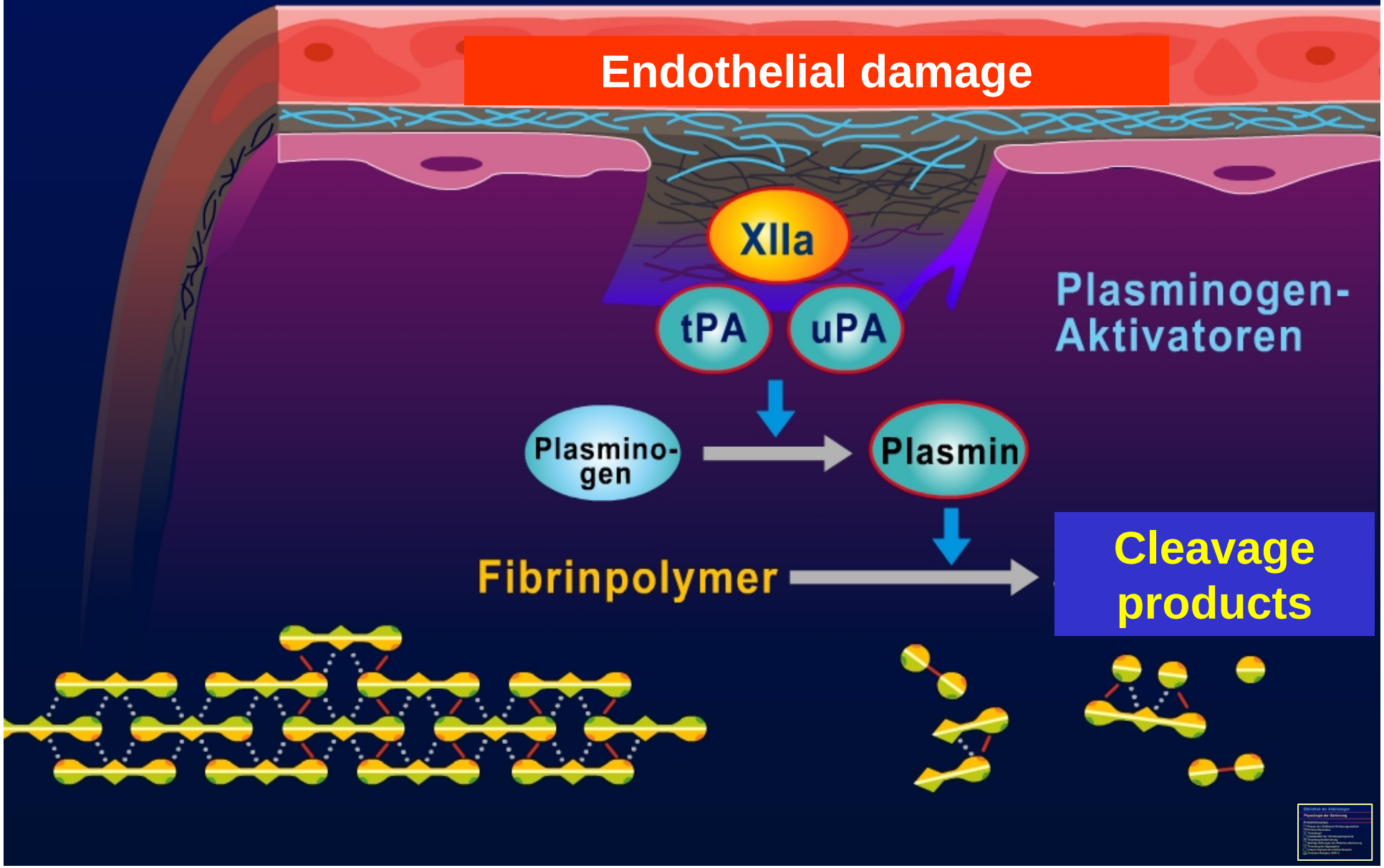
I: 14



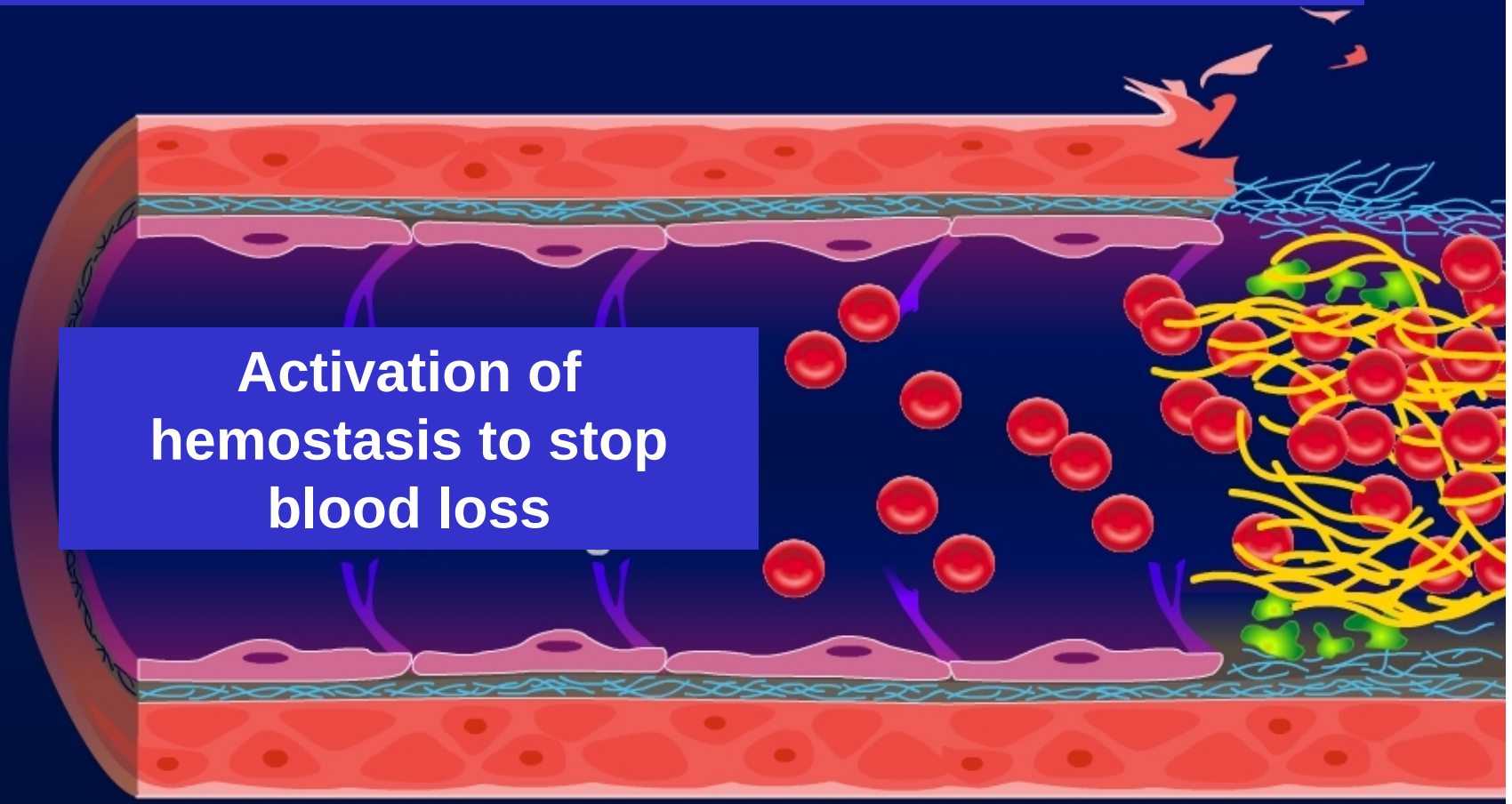
Fibrin generation and cross-linking



Endogenous biological fibrinolysis

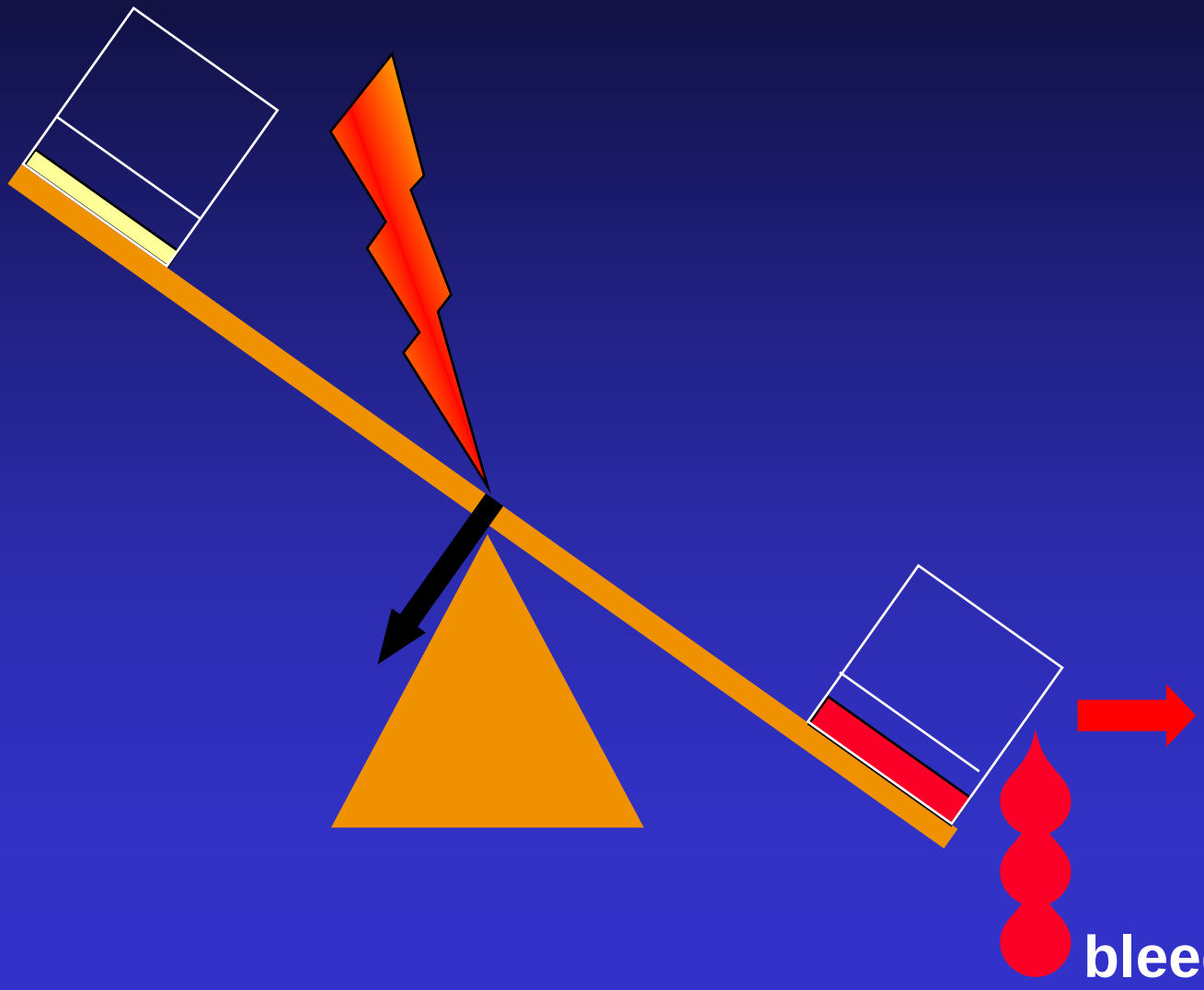


Reaction to Injury



Activation of hemostasis to stop blood loss

Disturbance of Balance



Types of Bleeding

- **Plasmatic type:**
  - Joint and muscle bleedings
  - hematoma
  - Ekchymosis

- **Platelet or vascular type**
  - Petechia, epistaxis
  - Menorrhagia

Thrombocytopenia

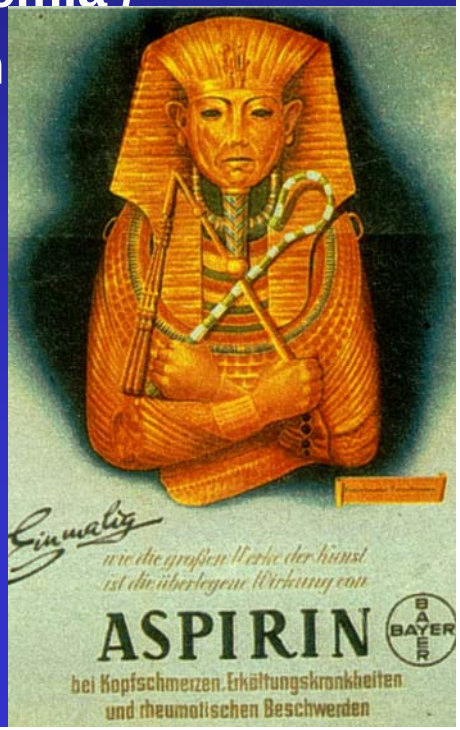
- Disturbed generation in bone marrow
- Increased consumption
- Pooling in spleen
- Combination of causes, as in alcoholism

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 aggregation (Aspirin, Ticlopidin, Clopidogrel, GP IIb/IIIa-antagonists, ...)**
  - **B-cell type leukemia / M. Waldenström**
  - **Dextran, u.a.**
  - **Uremia**
  - **ET, DIC,**
  - **...**



Hemorrhagic Diathesis

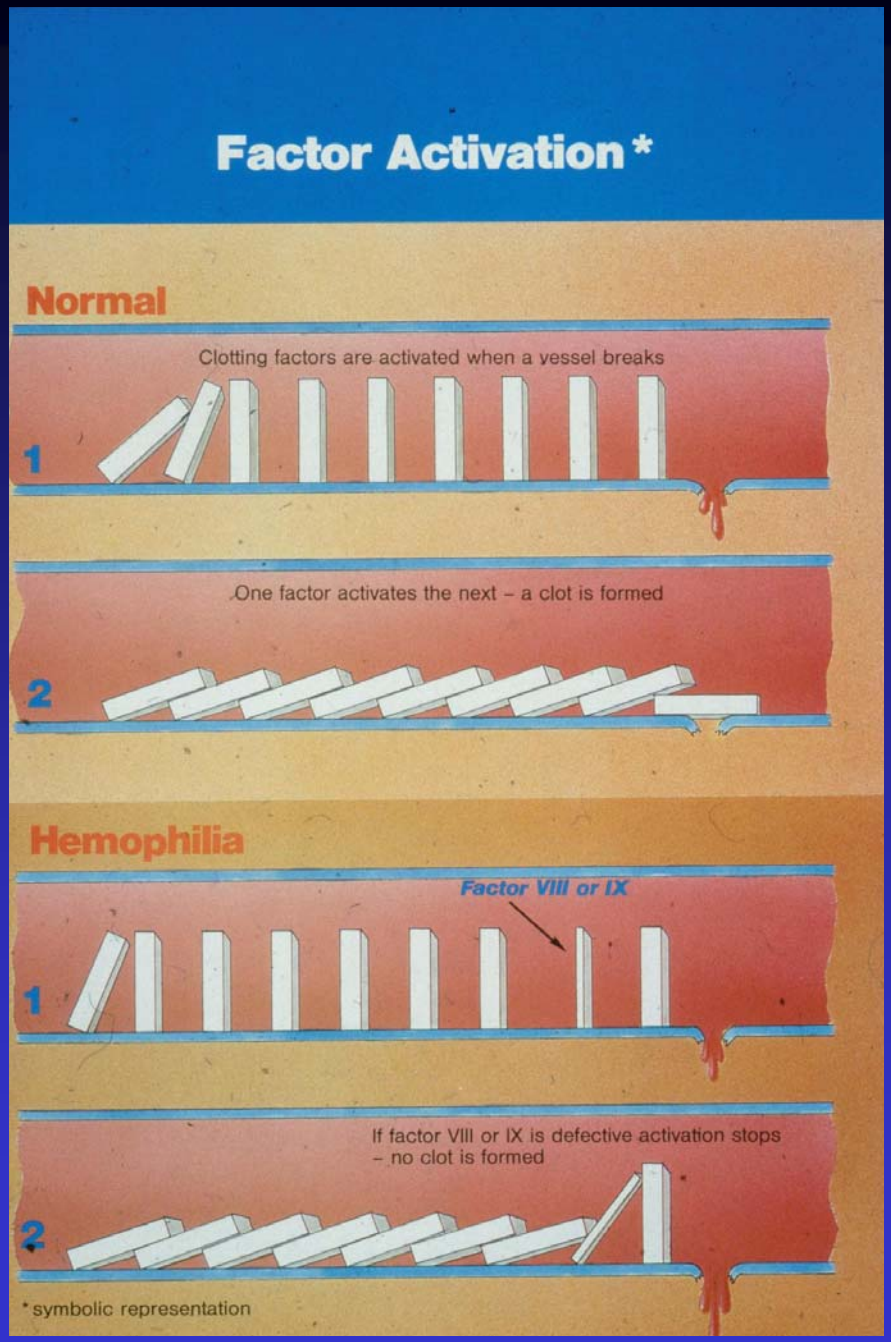
Frequent (classical) forms

- 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 Mil

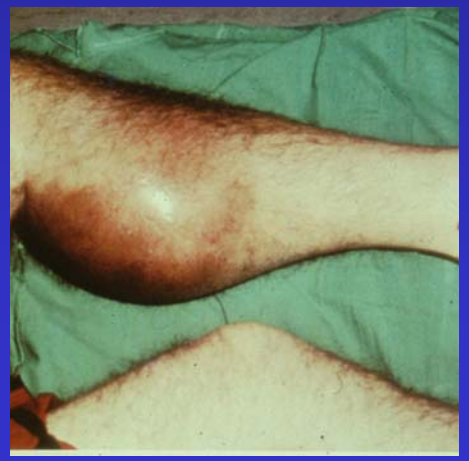
Review Oldenburg & Schwaab Sem Thromb Haemost 2001


Factor Activation *
Normal
Clotting factors are activated when a vessel breaks
1
One factor activates the next – a clot is formed
2
Hemophilia
Factor VIII or IX
1
If factor VIII or IX is defective activation stops
– no clot is formed
2
* symbolic representation

Hemophilia A

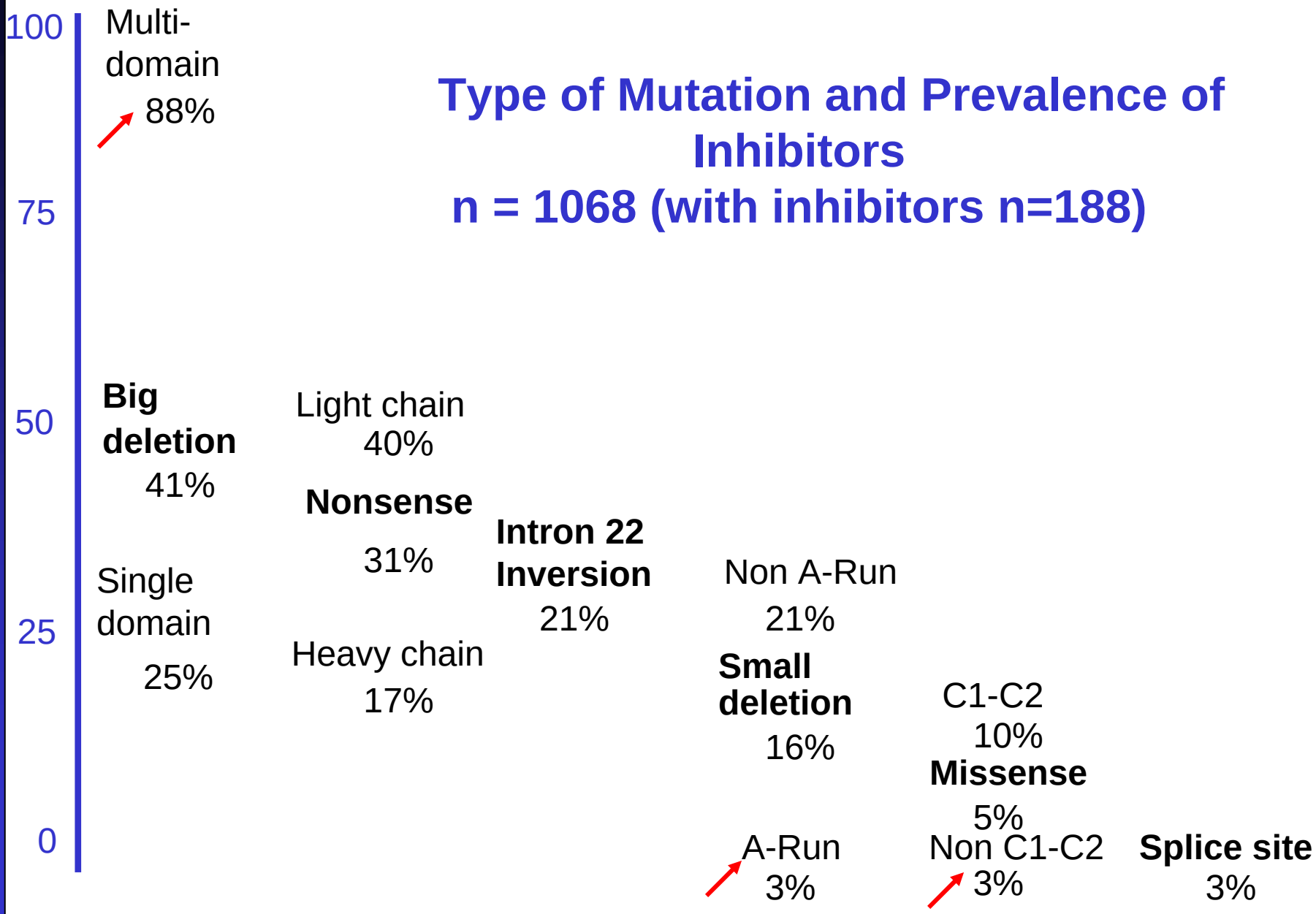
Bleeding into joints and muscle

- **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

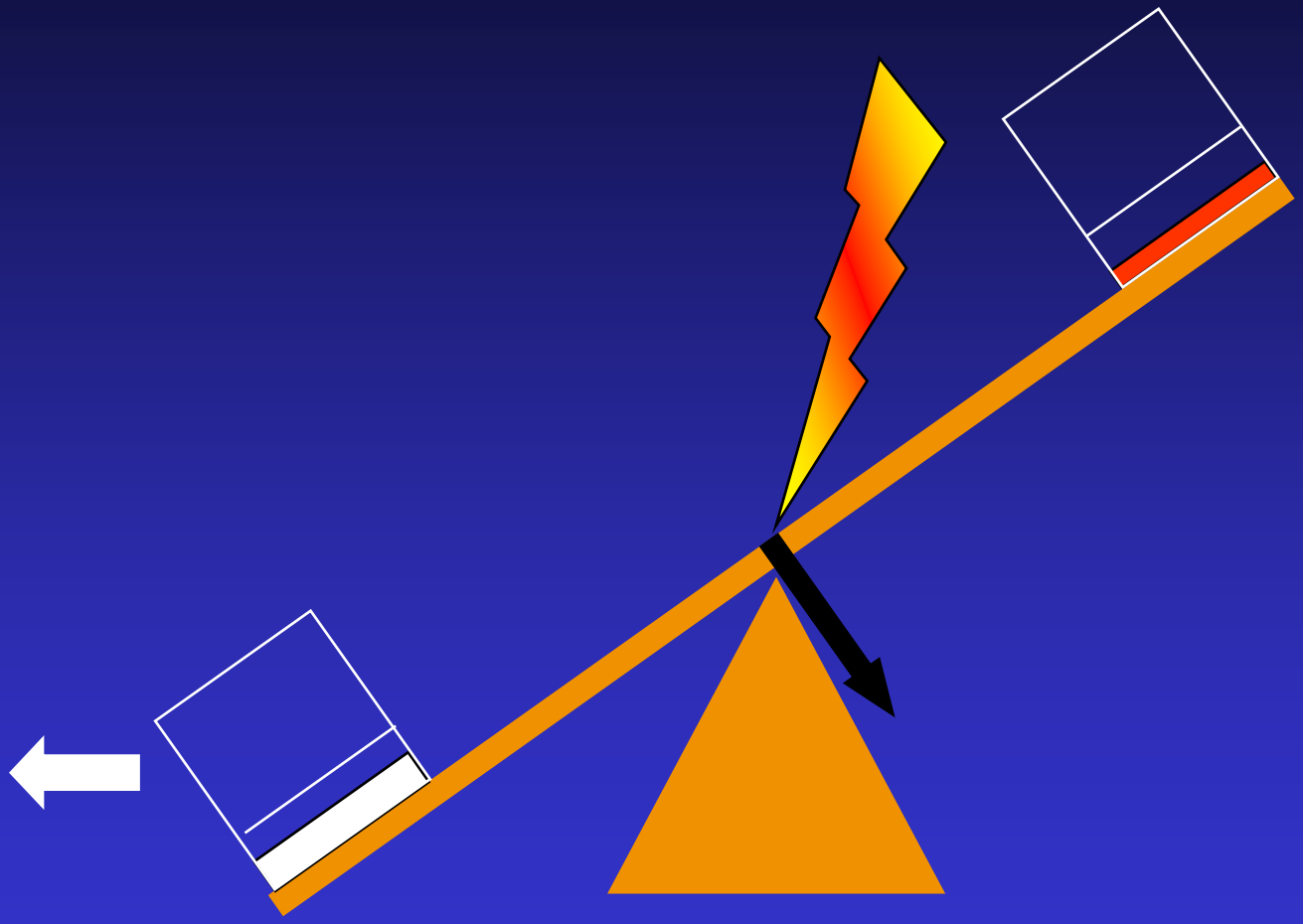


Oldenburg et al., Haematologica, 2000

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)

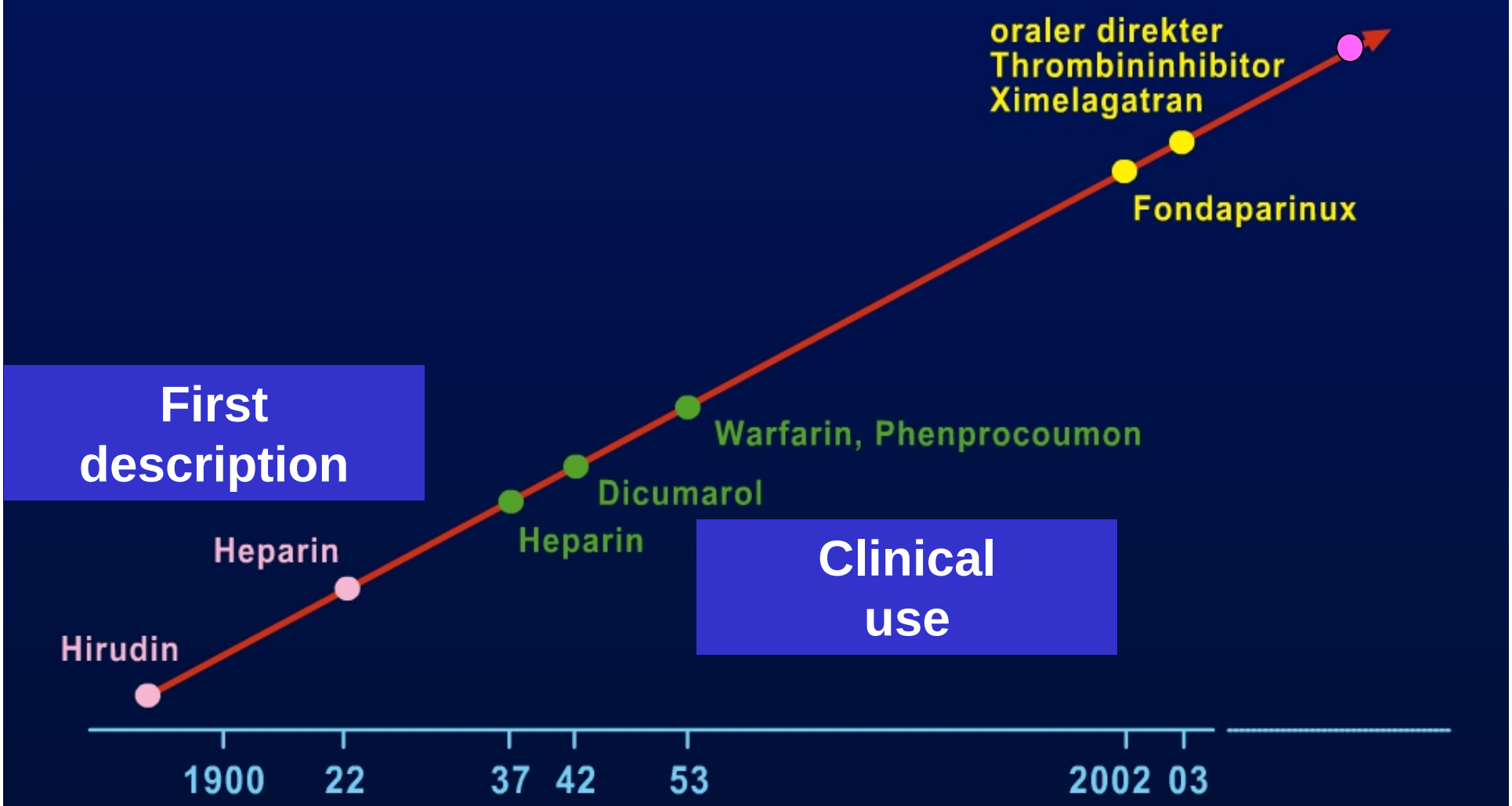
		Patients	Controls	Relative Risk
	U/ml	% (N=474)	% (N=474)	
Antithrombin	2x <0.8	1,1	0,2	5.0
Protein C	2x <0.67	3,1	0,8	3.8
	<0.67 + PCR	2,7	0,4	6.5
Protein S g /fr	<0.67/0.57	1,2	0,7	1.7
Faktor V Leiden	heterocygous	20 (N=347)	5 (N=310)	7.4
	homocygous	0,2	0	estimated 80 (Hardy/Weinberg)
Prothrombin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

FV-Leiden Mutation and Prothrombin-Mutation

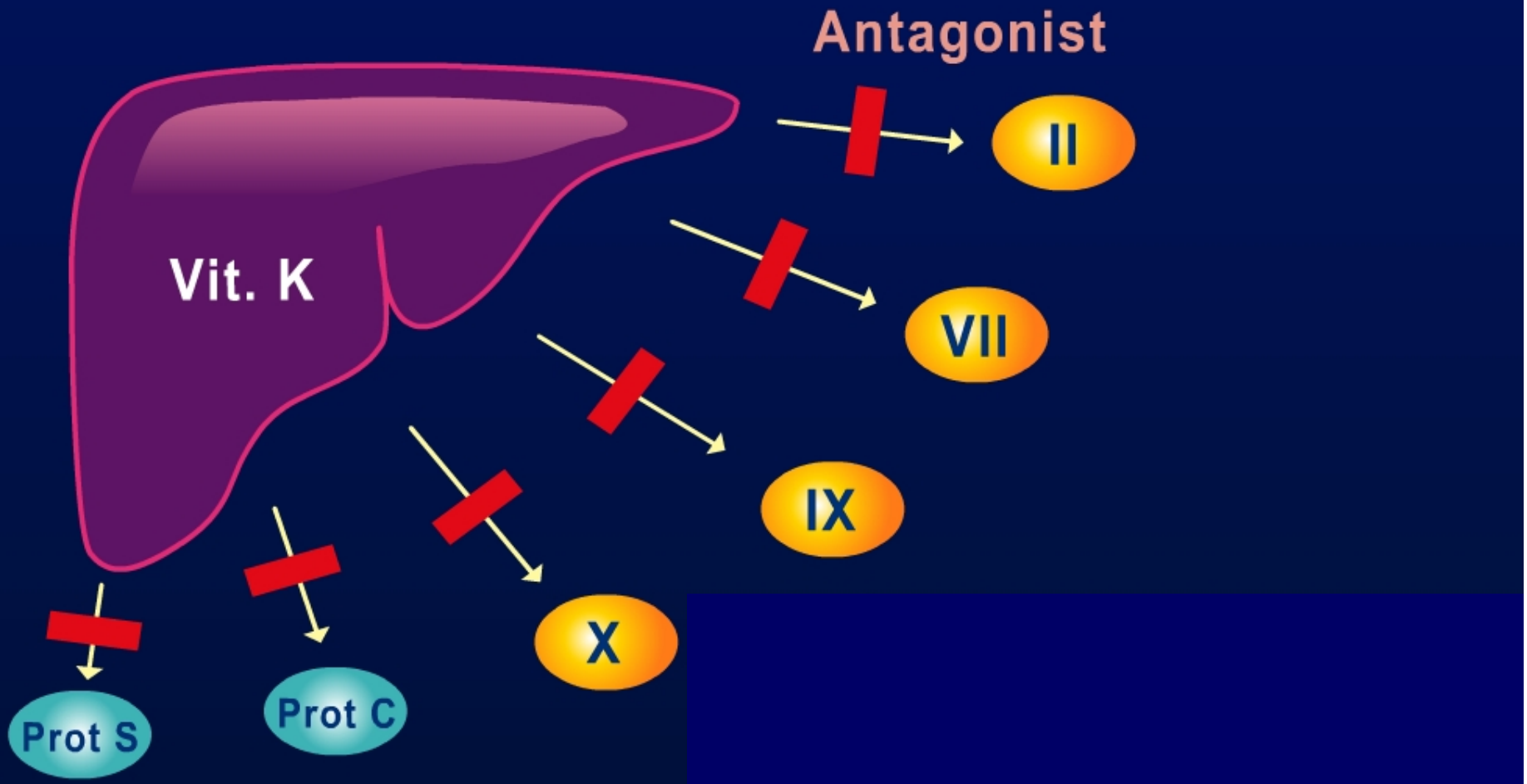
- Founder-Mutations – appeared 60.000-70.000 B.C.
- frequent in general population (FVL ~ 10%, PT ~ 4%)
- 3-fold (heterocygote) up to 80-fold risk for thromboembolic disease
- manifestation together with other risk factors
- 90% of carriers never develop thrombosis

Development of Anticoagulants

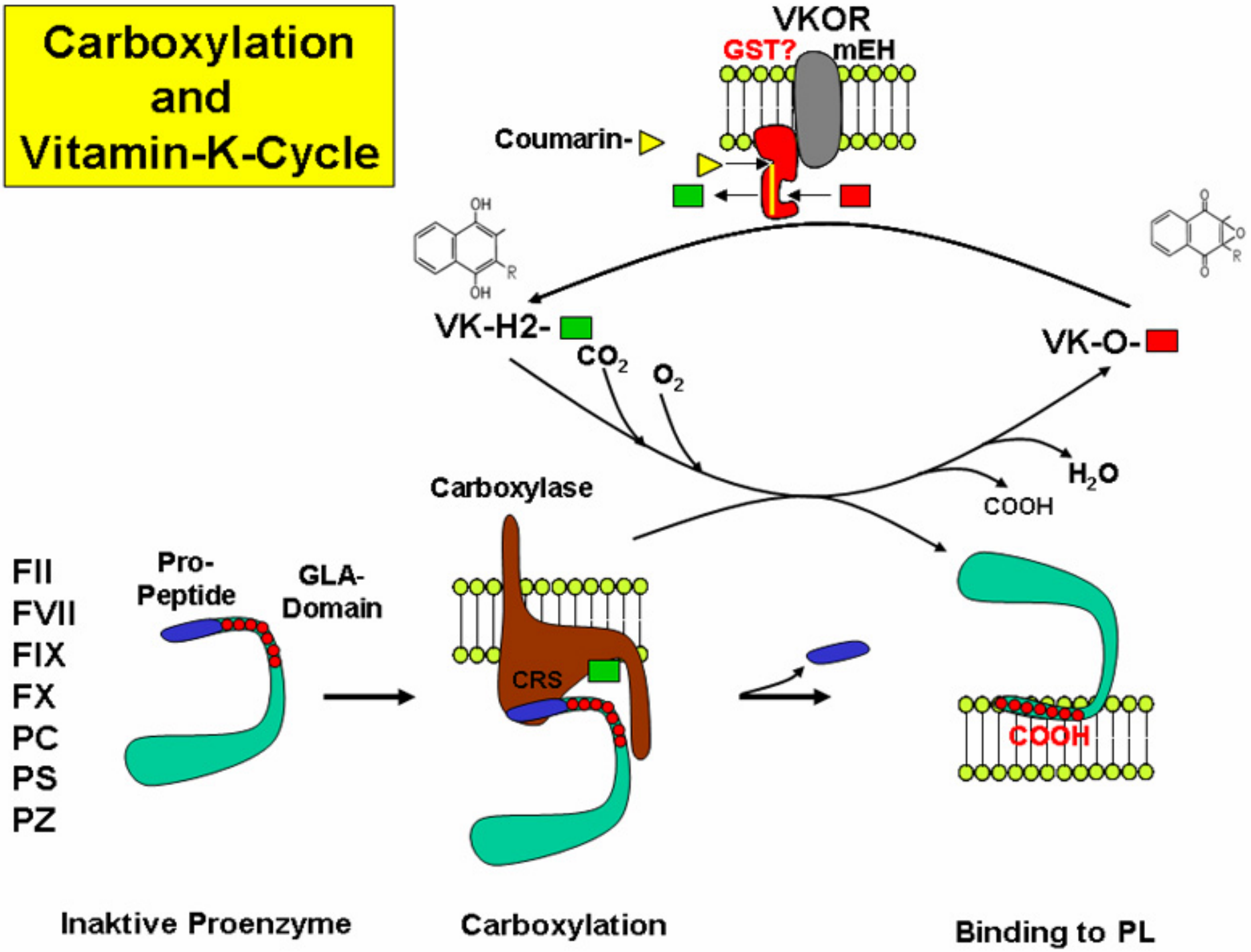
u.a.



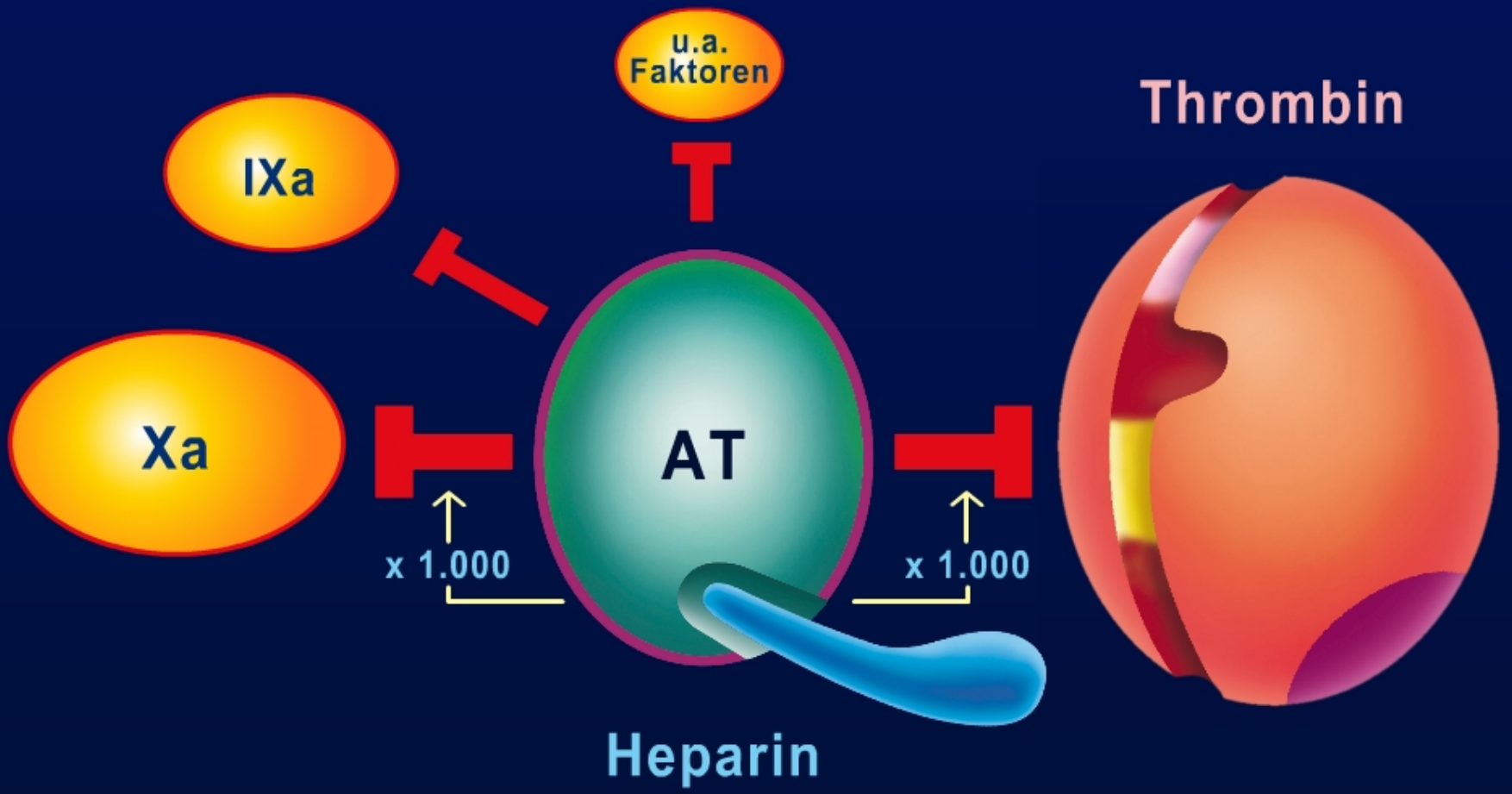
Vitamine K-dependent coagulation factors



Carboxylation and Vitamin-K-Cycle

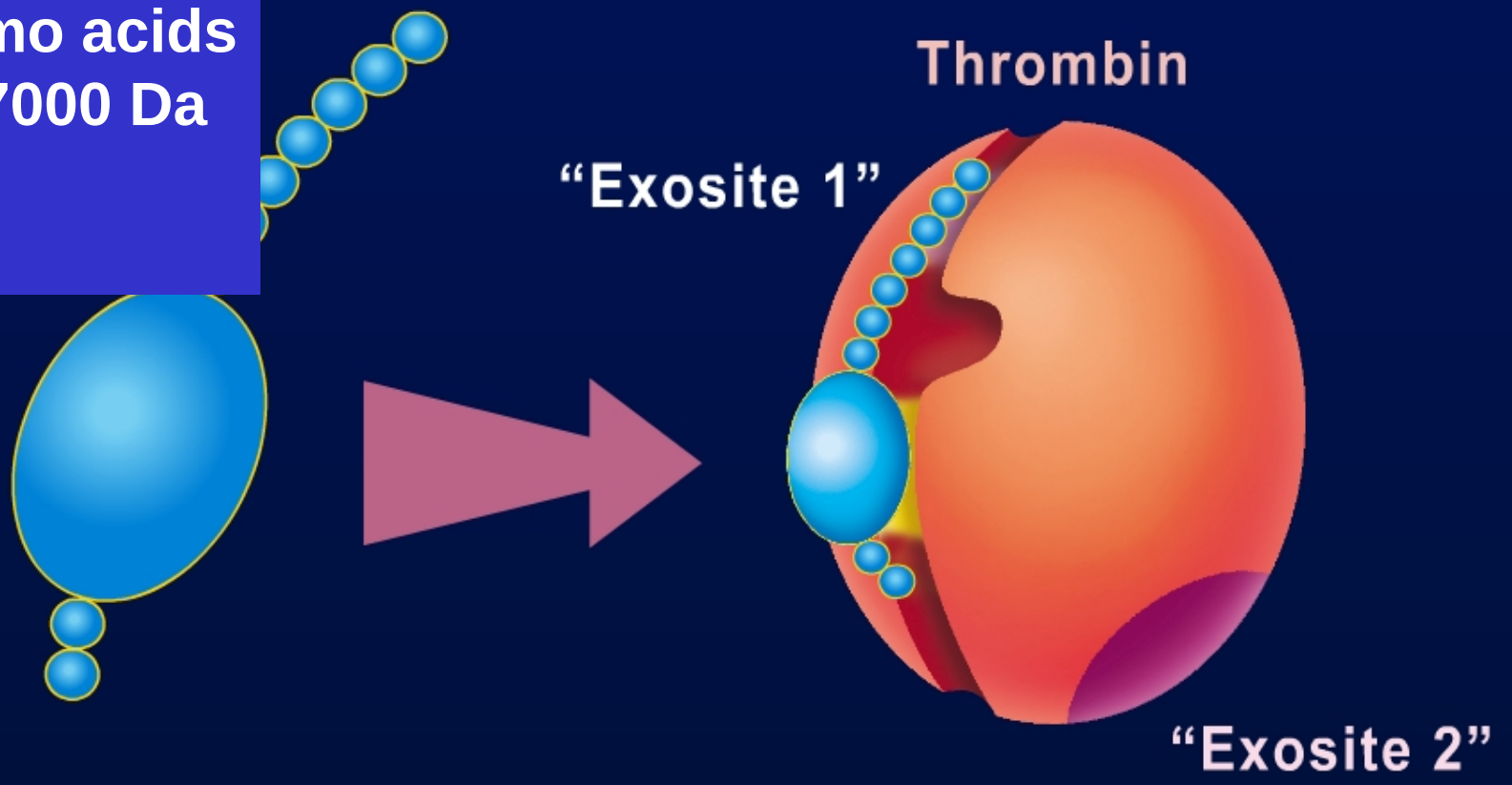


Agonistic Action of Heparin and Antithrombin



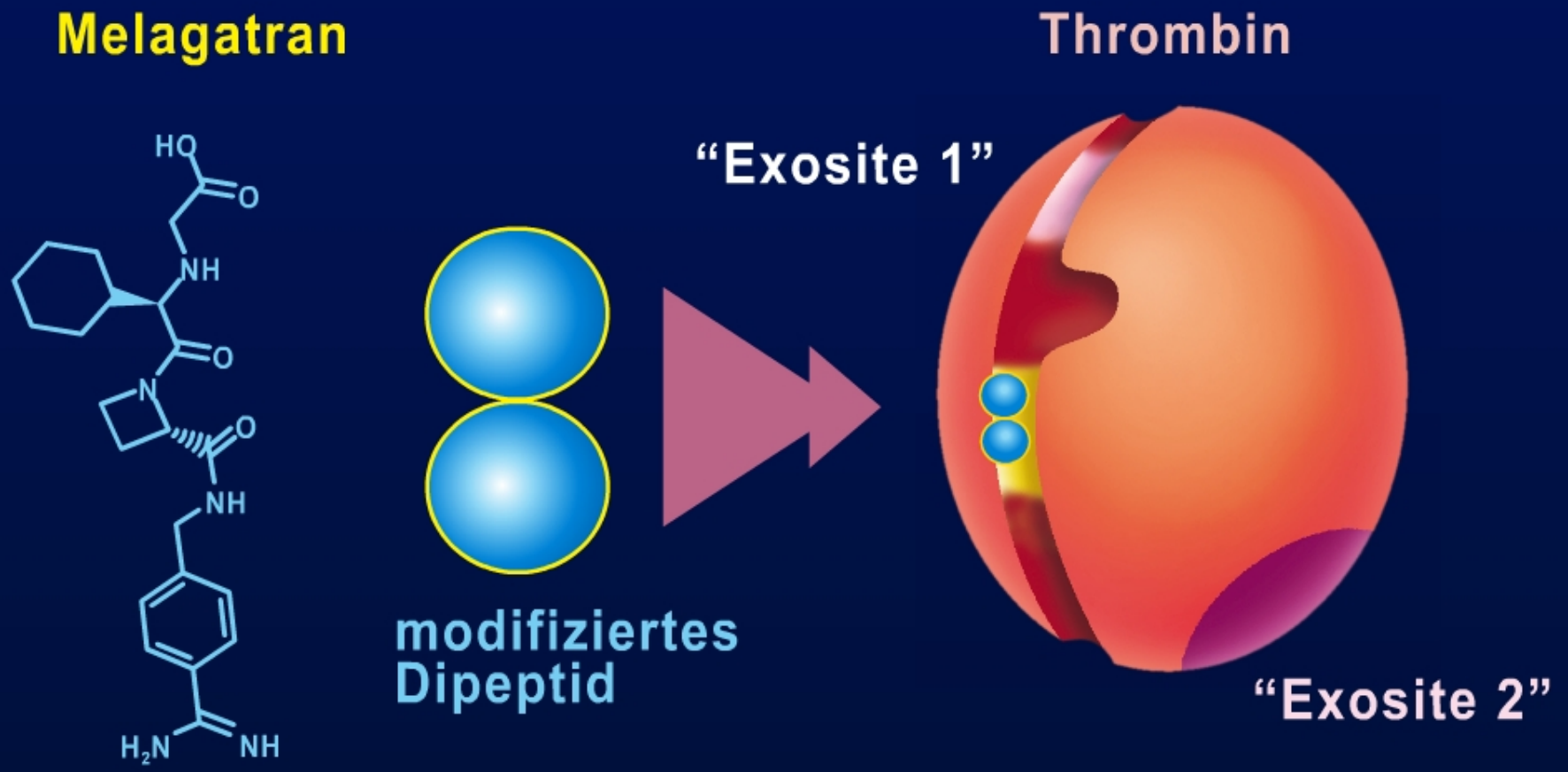
Mechanism of Action of Hirudin

65 animo acids
MW: 7000 Da



Direct binding to active site

Melagatran: Mechanism of Action



Reversable binding to active site

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Question 1

Which is the prevalence of the thrombosis risk factor “FV Leide mutation“ in the Caucasian population?

1. 1:1000
2. 1:500
3. 1:100
4. 1:50
5. 1:10

Question 2

A defect in which gene does not lead to a higher risk of venous thrombosis?

1. Protein C
2. Protein S
3. Factor IX
4. Factor V
5. Prothrombin (Factor II)

Question 3

Which is not a typical characteristic for a polymorphism?

1. It is a mutation
2. It has a frequency < 1%
3. It is a genetic marker
4. It usually has no relevance to any disease
5. It can be a CA-repeat