Stolling anno 2008

(Hemostase anno 2008)

A. Sturk & R. Nieuwland

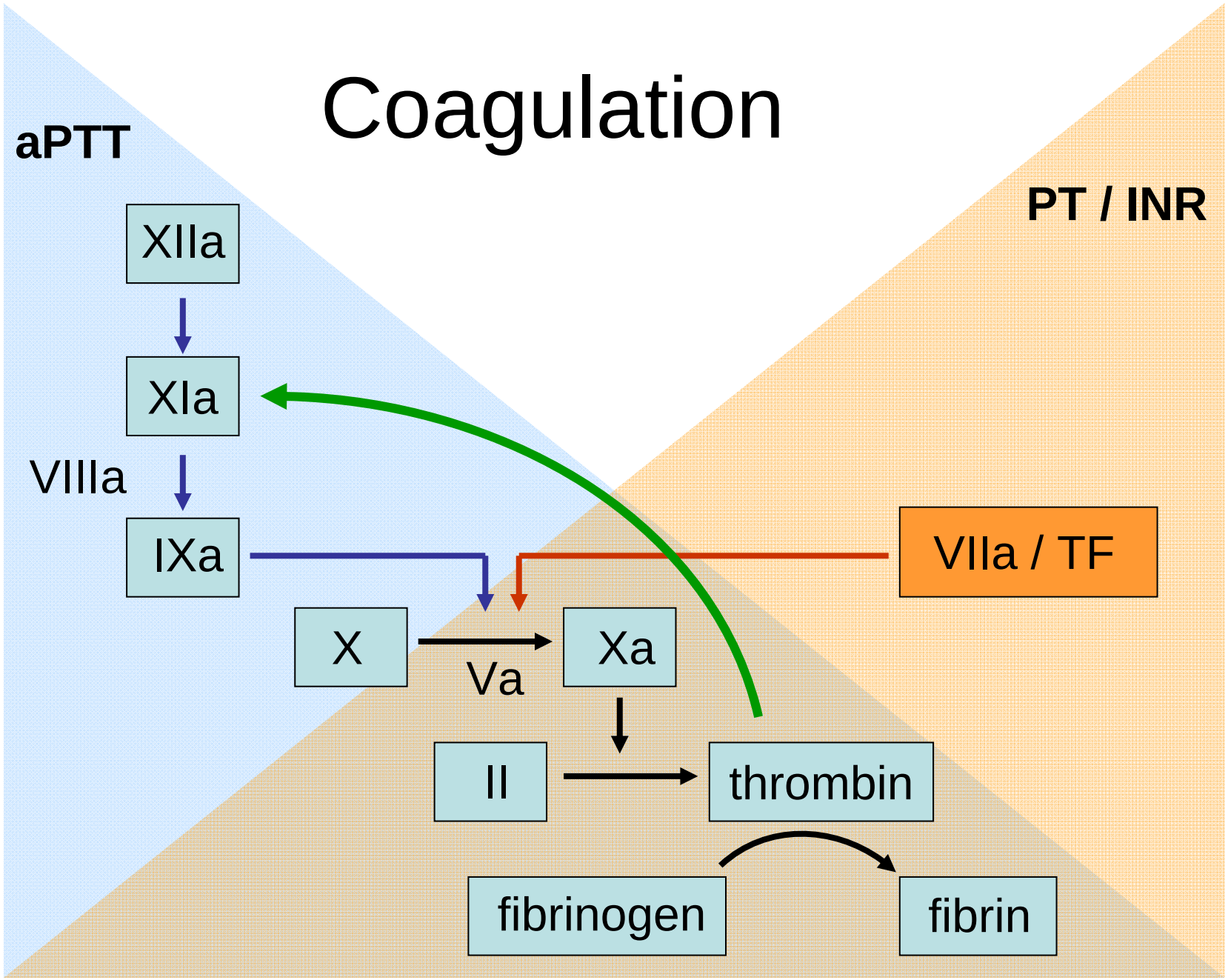
Recent reviews

- Platelet activation and atherothrombosis

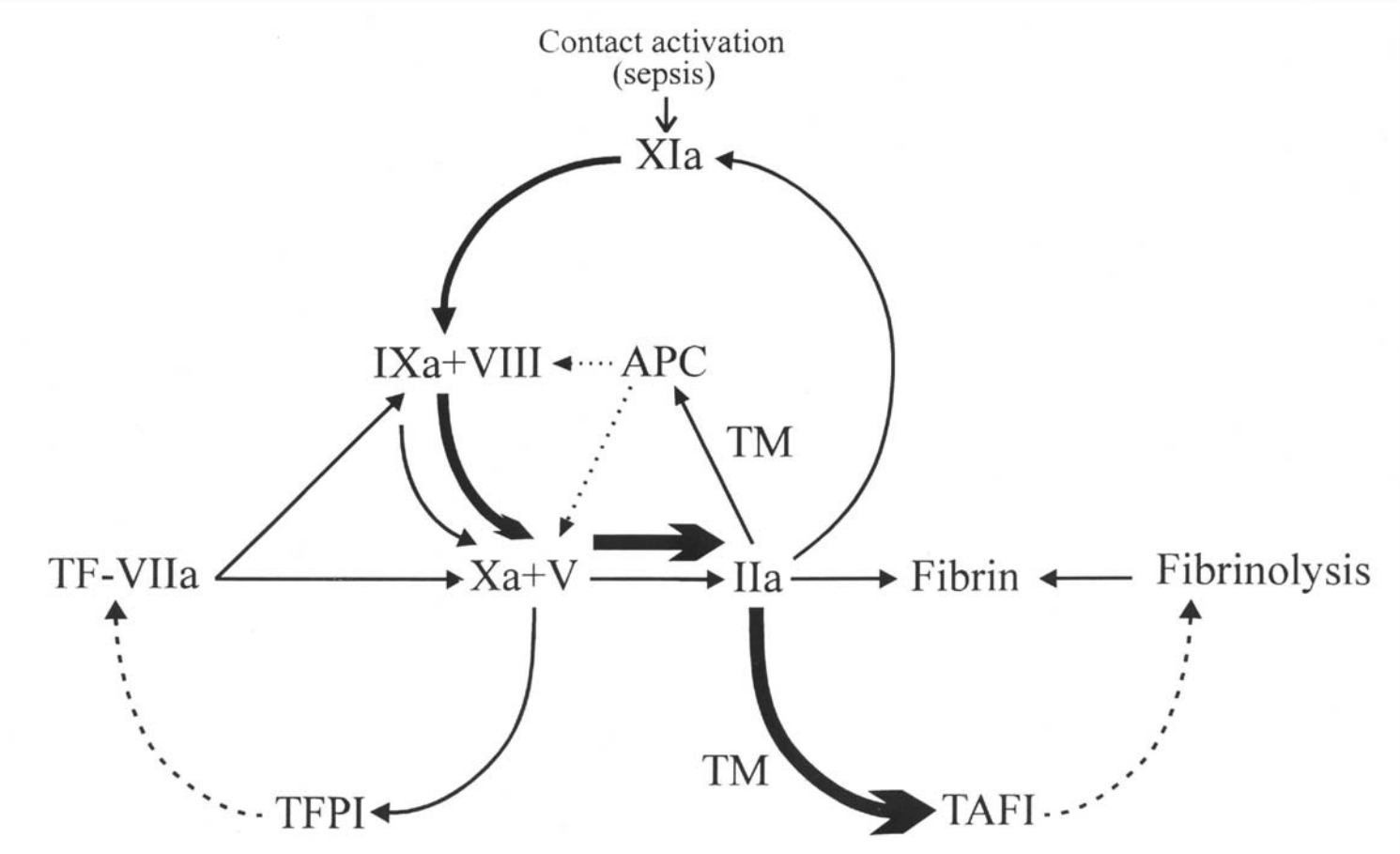
  G. Davi, C. Patrono. *N Eng J Med 2007; 357:2482-2494*.

- Mechanisms of thrombus formation

  B. Furie, B.C. Furie. *N Eng J Med 2008; 359: 938-949*.


Coagulation
aPTT
PT / INR
XIIa
XIa
VIIIa
IXa
VIIa / TF
X
Va
Xa
II
thrombin
fibrinogen
fibrin

Coagulation 1996



Thesis P.A.Kr. von dem Borne, 1996

Feedback activation of factor XI by thrombin does not occur in plasma

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Communicated by Nancy Kleckner, Harvard University, Cambridge, MA, June 25, 2007 (received for review March 15, 2007)

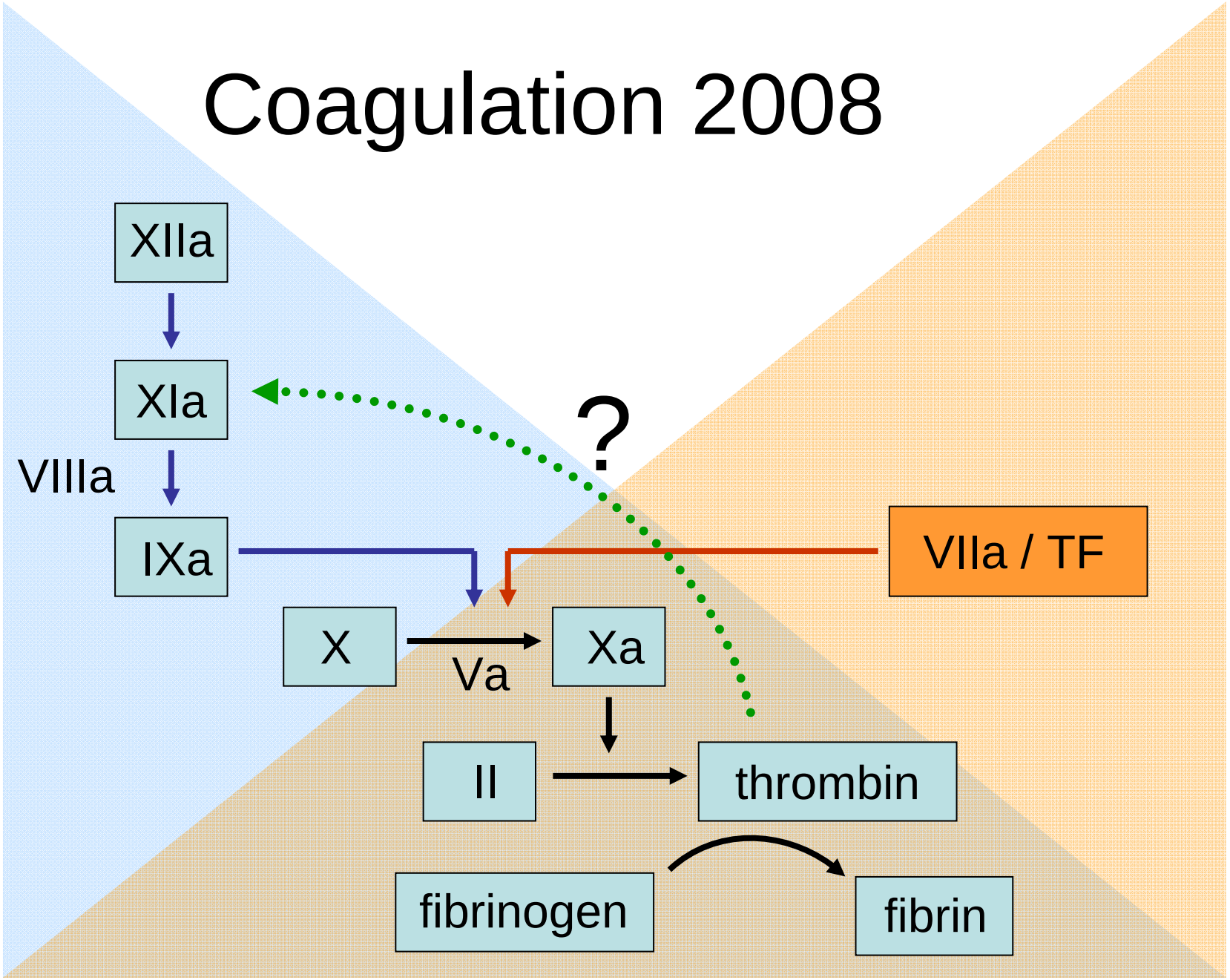
In this study, we tested the hypothesis that factor XI (FXI) activation occurs in plasma following activation of the extrinsic pathway by thrombin-mediated feedback activation. We used two different assays: (*i*) a direct measurement of activated FXI by ELISA and (*ii*) a functional assay that follows the activation of the coagulation cascade in the presence or absence of a FXI inhibiting antibody by monitoring thrombin activity. We failed to detect any FXI activation or functional contribution to the activation of the coagulation cascade in platelet poor or platelet-rich plasma, when activation was initiated by thrombin or tissue factor. Additionally, we found that, in the absence of a contact system inhibitor during blood draw, contact activation of FXI can mistakenly appear as thrombin- or tissue-factor-dependent activation. Thus, activation of FXI by thrombin in solution or on the surface of activated platelets does not appear to play a significant role in a plasma environment. These results call for reevaluation of the physiological role of the contact activation system in blood coagulation.

In accordance with this hypothesis, several studies have demonstrated that FXI contributes to the activation of the coagulation cascade in plasma by low concentrations of tissue factor (TF) (7–9). This observation is particularly significant because TF, which is exposed to blood during injury, initiates hemostatic blood clot formation through the extrinsic pathway. Furthermore, FXI was also found to inhibit fibrinolysis by promoting activation of thrombin-activatable fibrinolysis inhibitor (9–11). The involvement of thrombin mediated FXI activation in these processes was questioned, however, because no FXI activation was detected in plasma even when high concentrations of TF and thrombin were added (12). Furthermore, it was found that physiological concentrations of plasma proteins such as fibrinogen and HK (which is complexed with FXI under physiological conditions) interfere with FXI activation by thrombin (5, 13).

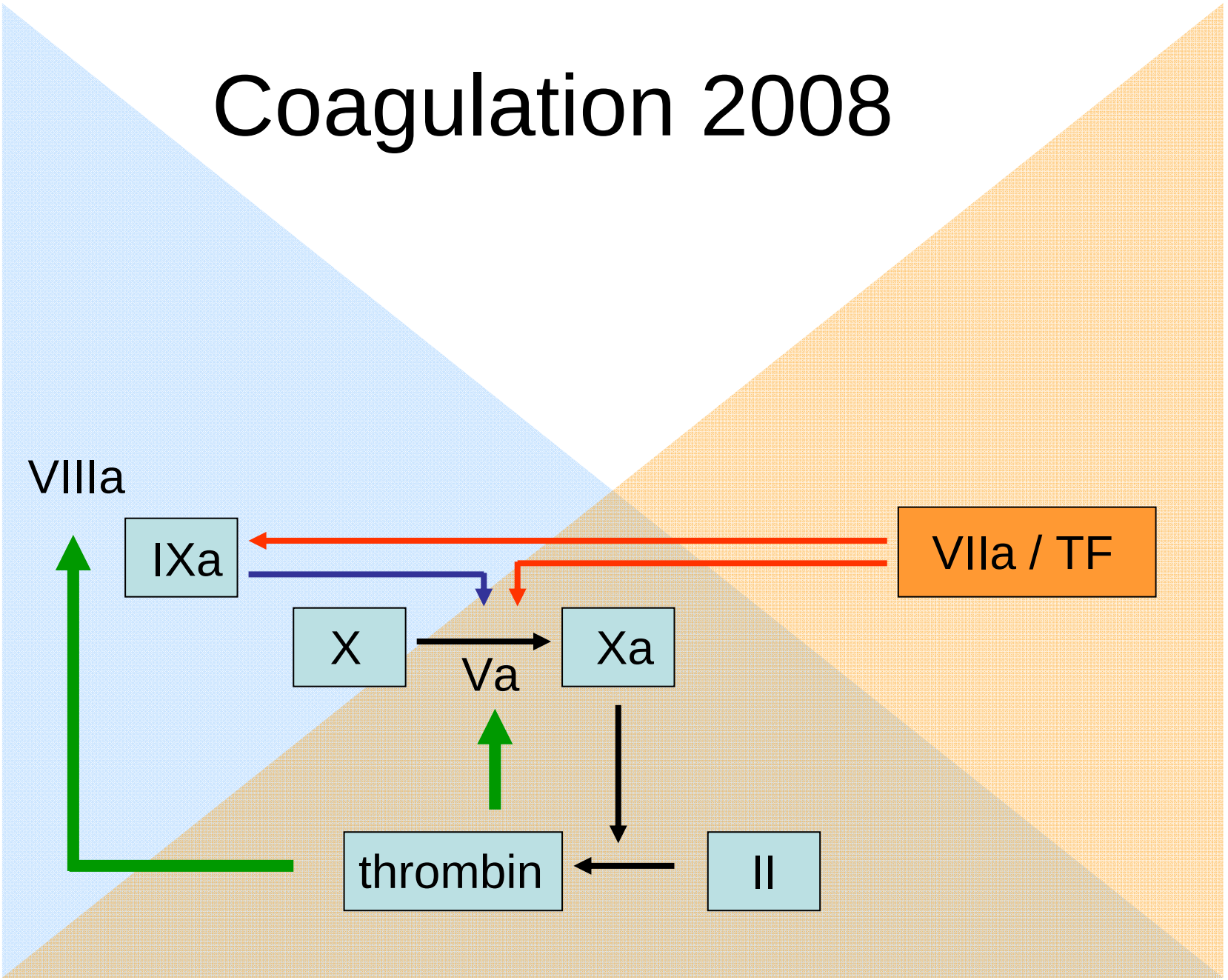
An apparent solution to the discrepancy was offered by the observation that FXI activation by thrombin is enhanced several

PNAS 2007;104:12855-60

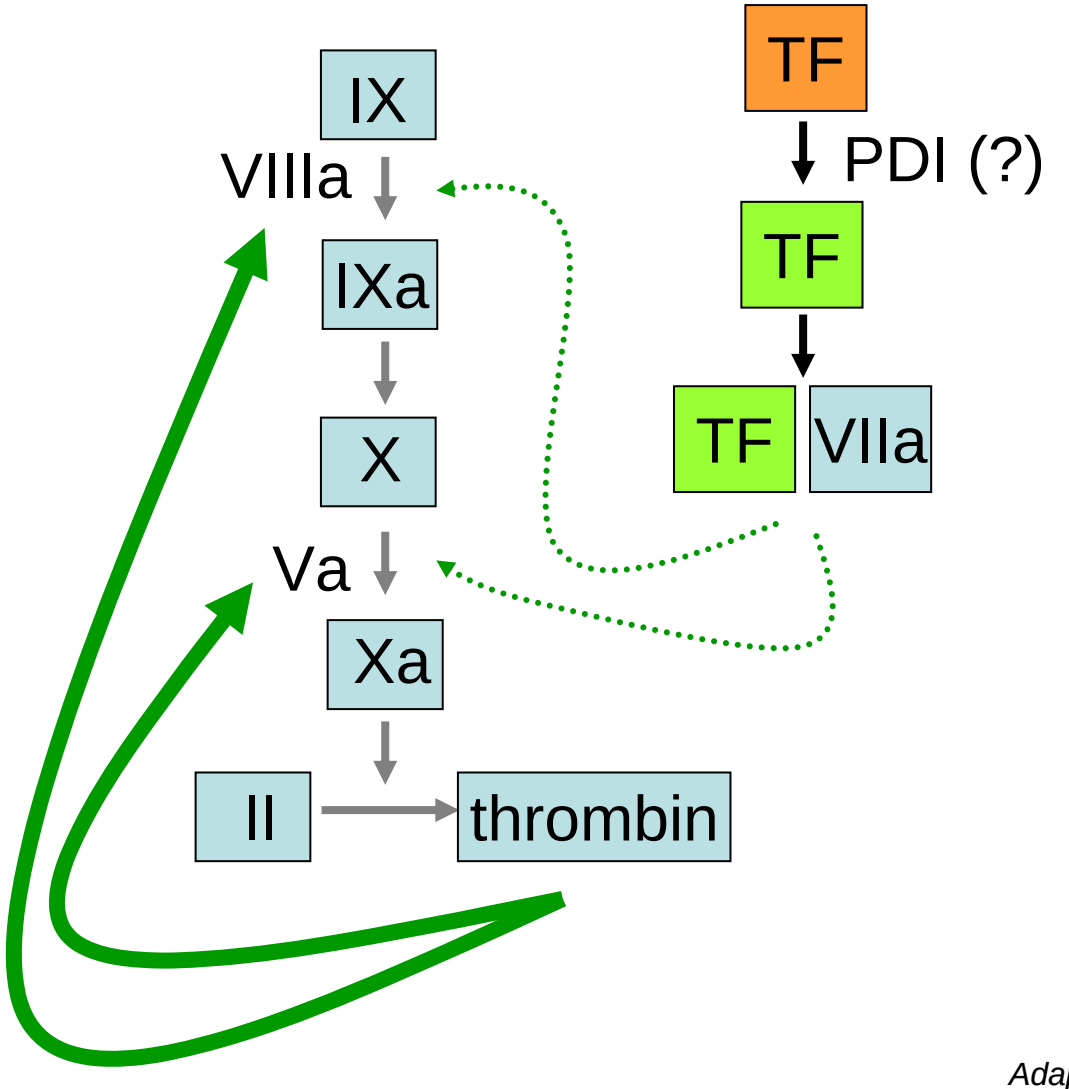
Coagulation 2008



Coagulation 2008

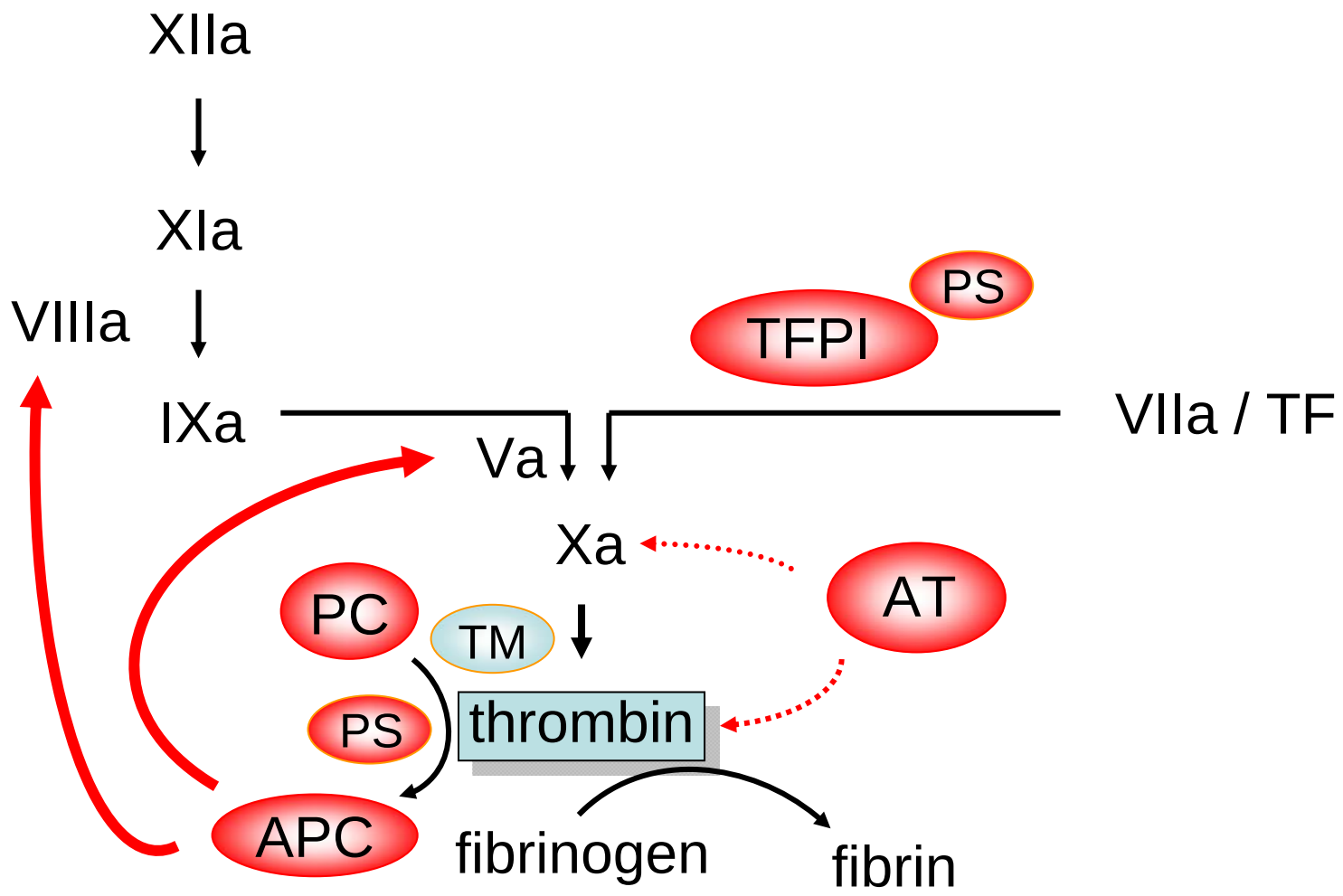


Coagulation 2008

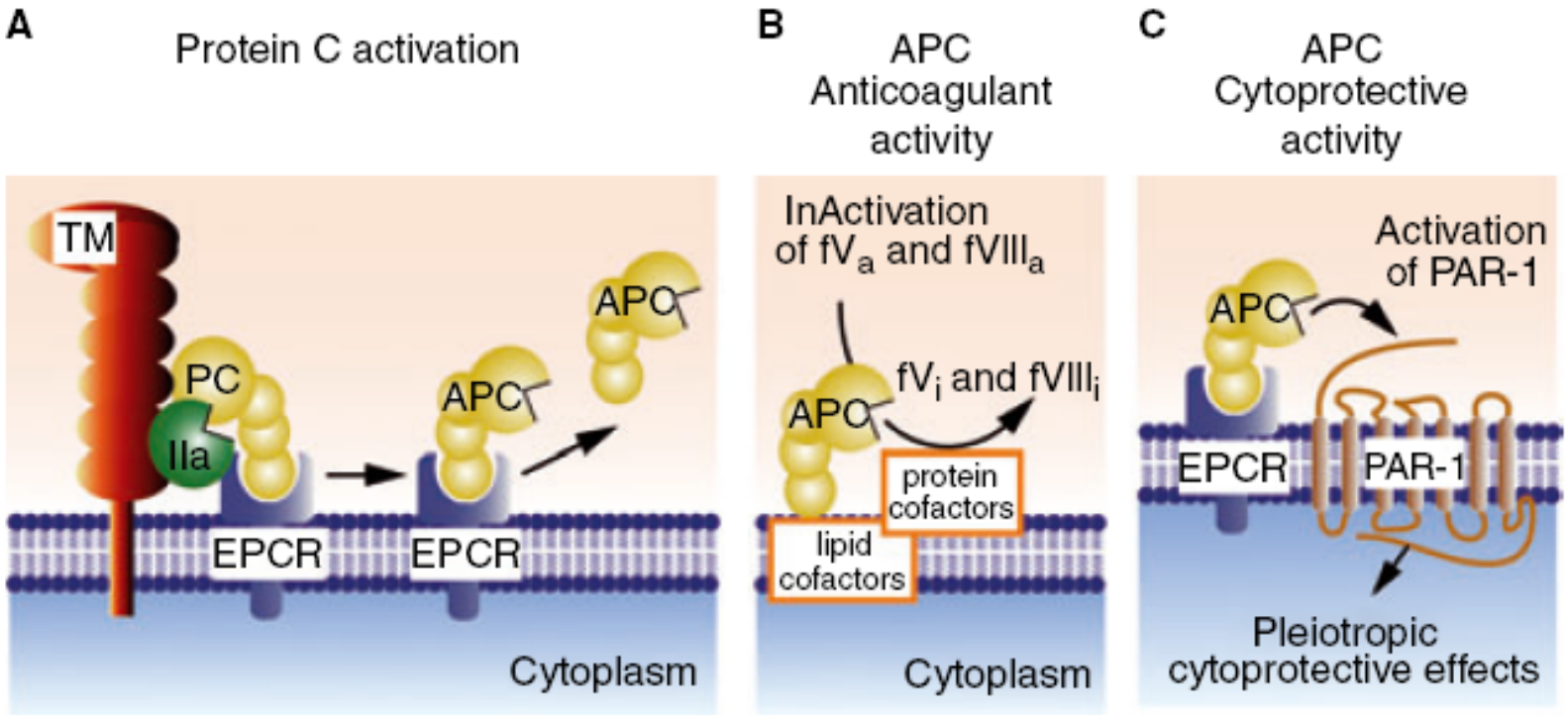


Adapted from Furie & Furie.
N. Eng. J. Med. 2008; 359: 938-49

Natural coagulation inhibitors

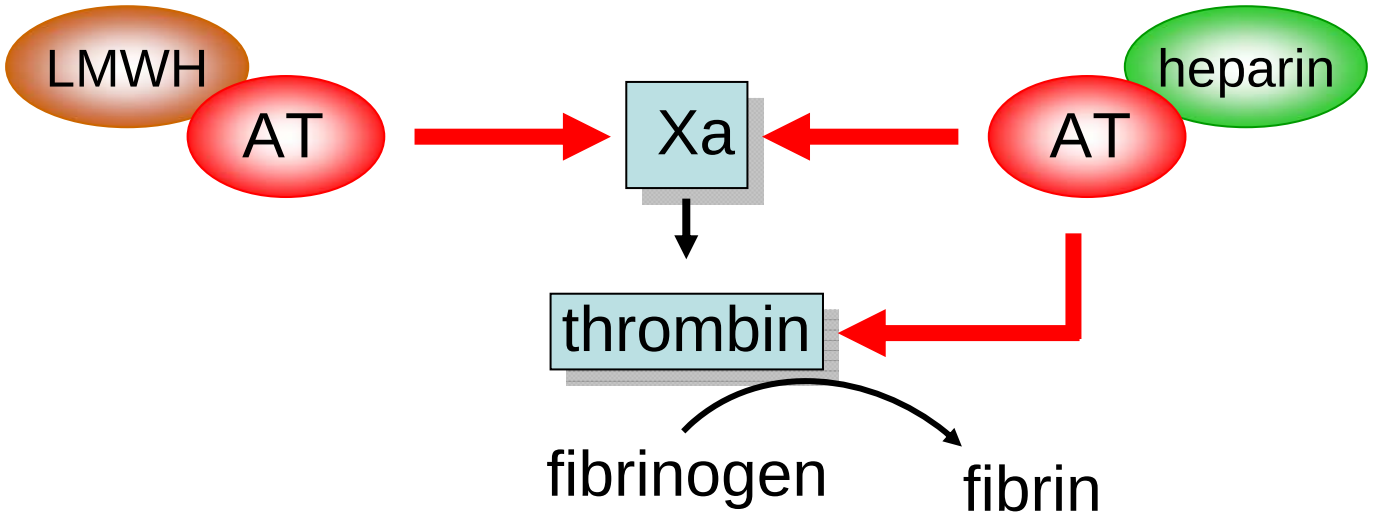


Natural coagulation inhibitors
Protein C

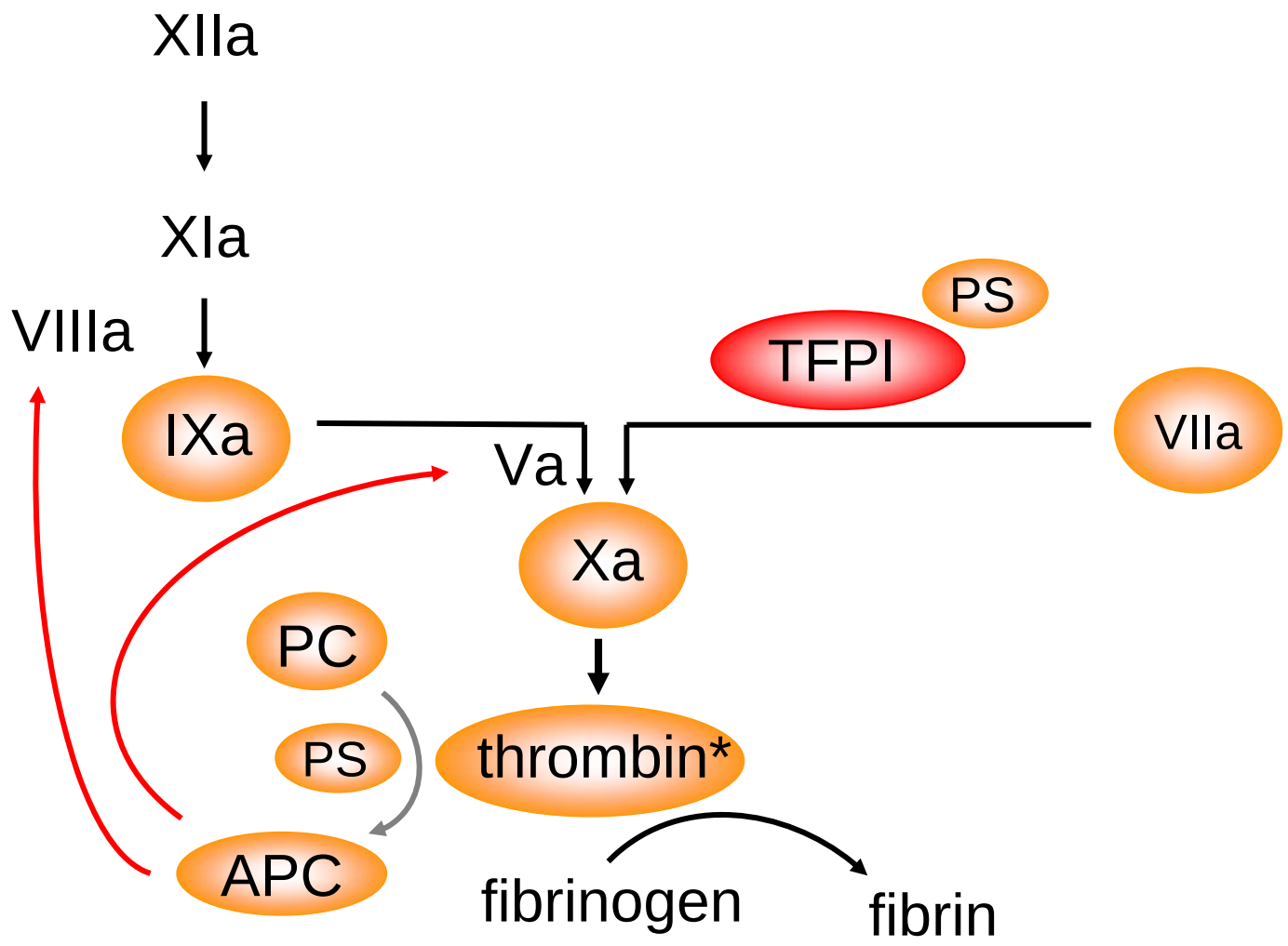


J Thromb Haem 2007; 5: 73-80

Anticoagulation with heparin and LMWH

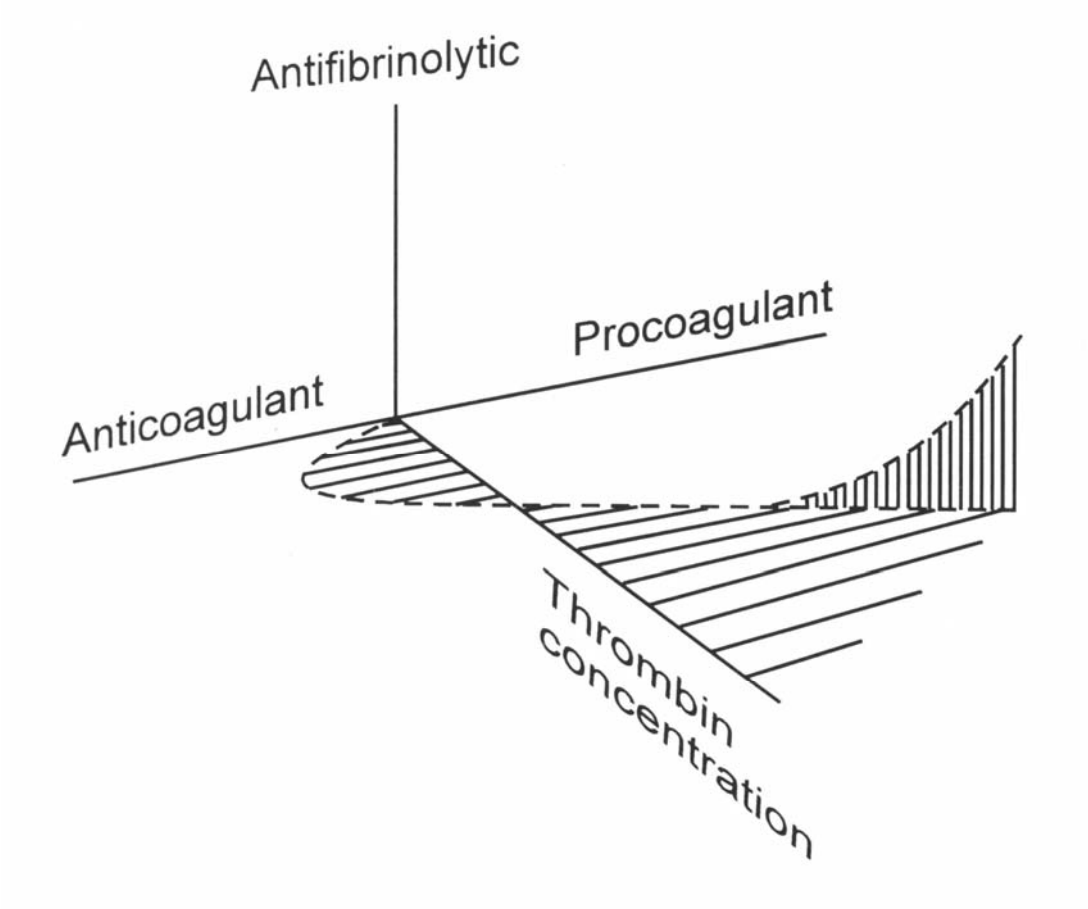


Orale antistolling



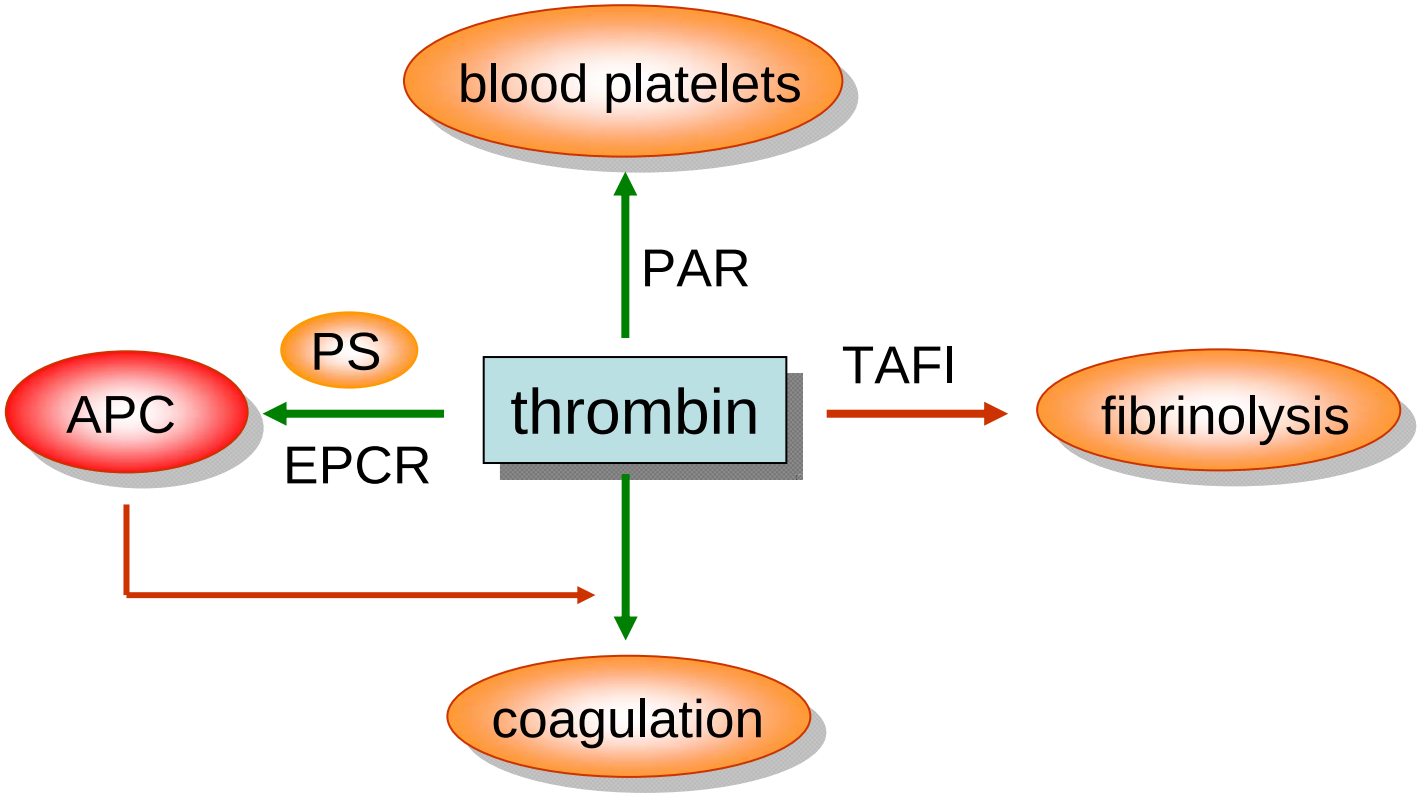
*prothrombin (factor II)

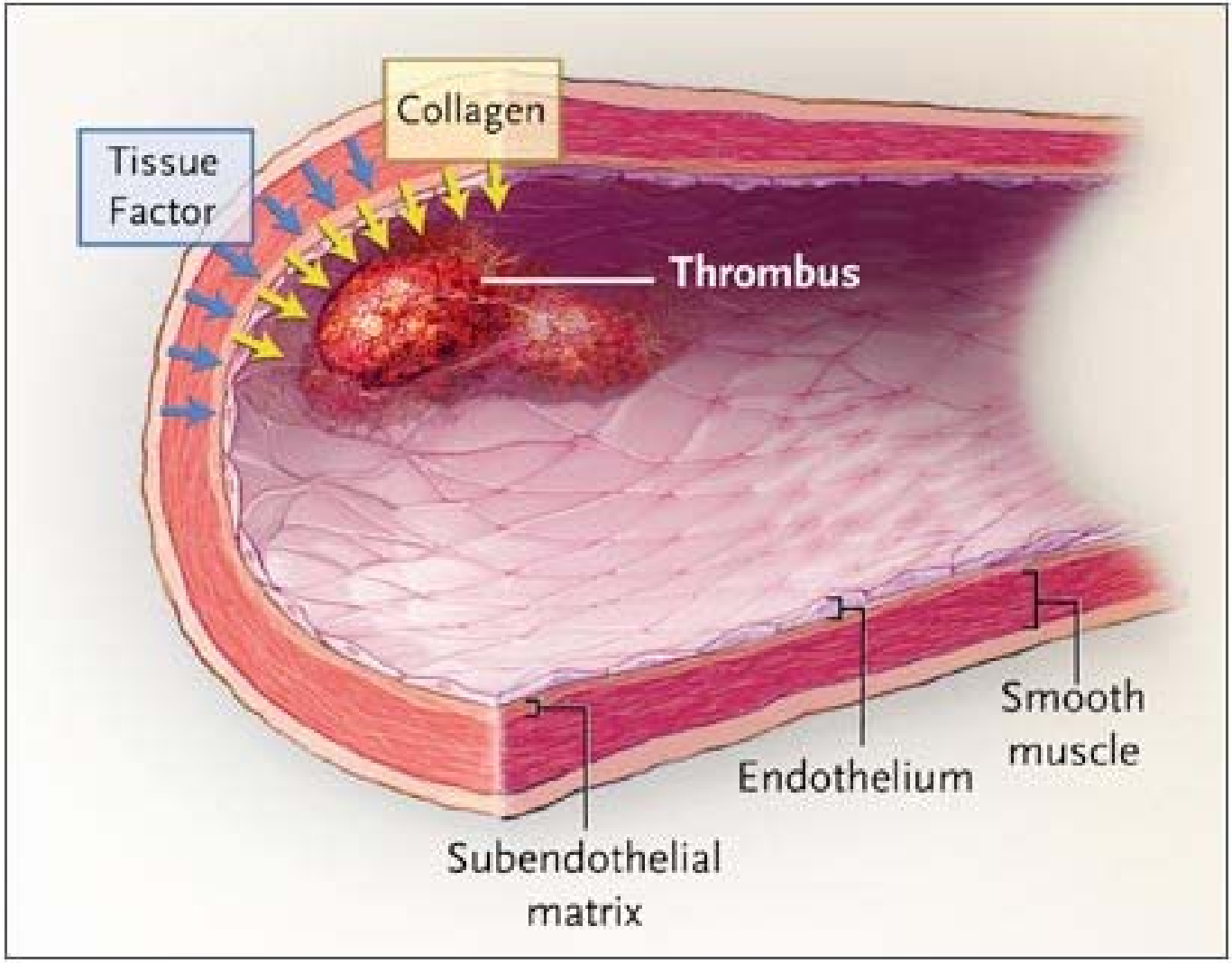
Thrombin



Thesis P.A.Kr.von dem Borne, 1996

Thrombin: more than coagulation



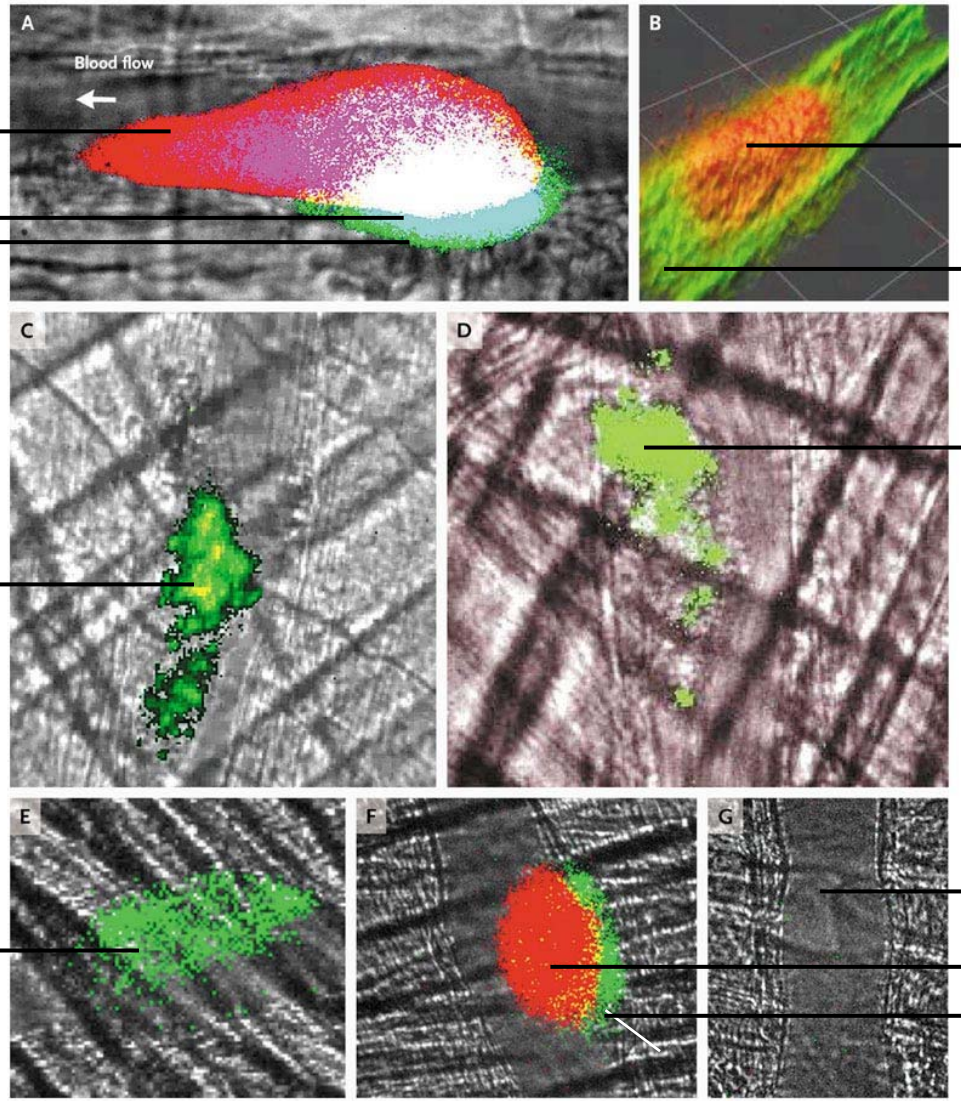

Collagen
Tissue Factor
Thrombus
Smooth muscle
Endothelium
Subendothelial matrix

Hemostasis

- Hemostasis: "*the process that maintains the integrity of a close, high-pressure circulatory system after vascular damage*".
  - Circulating platelets are recruited to the site of injury, where they become a major component of the developing thrombus"

    ("*primary hemostasis*")
  - Blood coagulation, initiated by tissue factor, culminates in the generation of thrombin and fibrin ("*secundary hemostasis*")
  - "These events *occur concomitantly*"

Thrombus formation *in vivo*



Platelets

Fibrin

TF

Platelet thrombus

Endothelium

Calcium mobilization in platelets

Accumulation of TF-exposing MP

PDI during thrombus formation

+ anti-PDI

Platelets

Fibrin

N Engl J Med 2008;359:938-949

What is the origin of TF?

- Extravascular origin (unlikely)
- Intravascular origin (“blood-borne TF”)
  - Endothelial cells (and monocytes)
  - Platelets? Granulocytes?
  - Cell-derived microparticles
    - Expose ***inactive*** TF

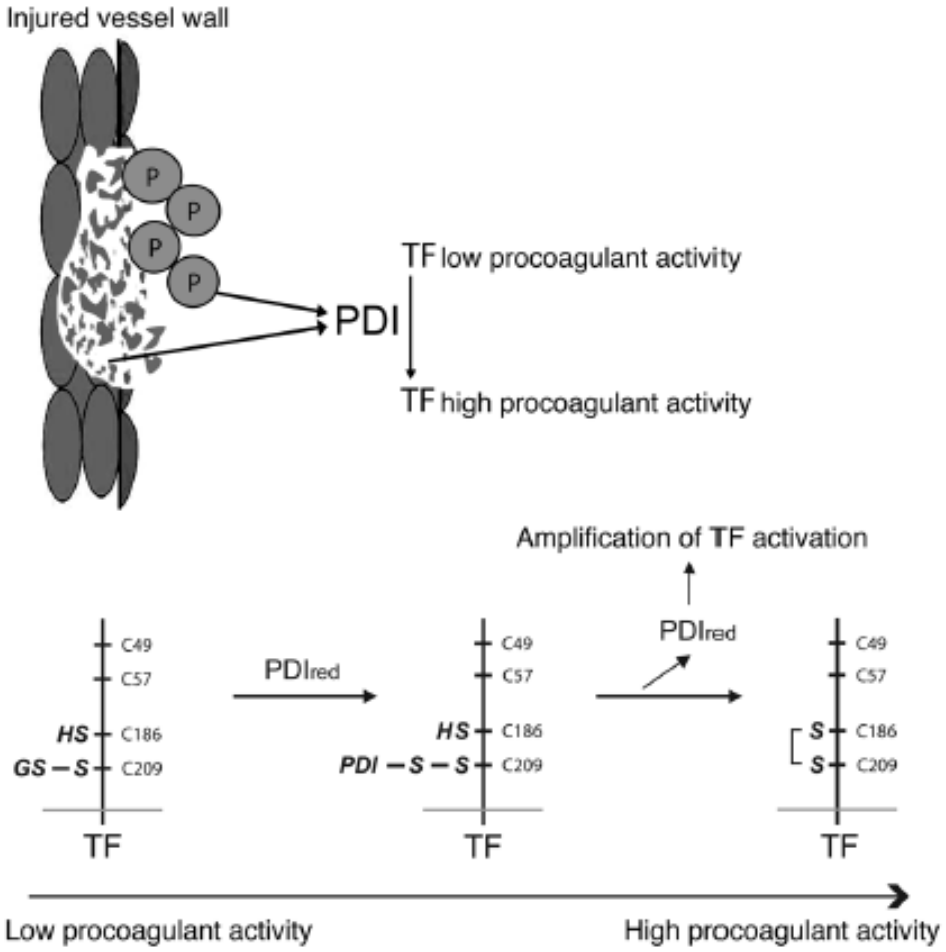
      “There is no detectable TF activity in normal blood, yet TF-bearing MP circulate in healthy persons. Perhaps TF-bearing MP contain inactive TF, which may become activated only when the particles are recruited to the site of vascular injury”
    - Expose ***active*** TF

      “Pathologic MP may bear active TF, which may confer a predisposition to thromboembolic events”

Activation of intravascular (latent) TF?

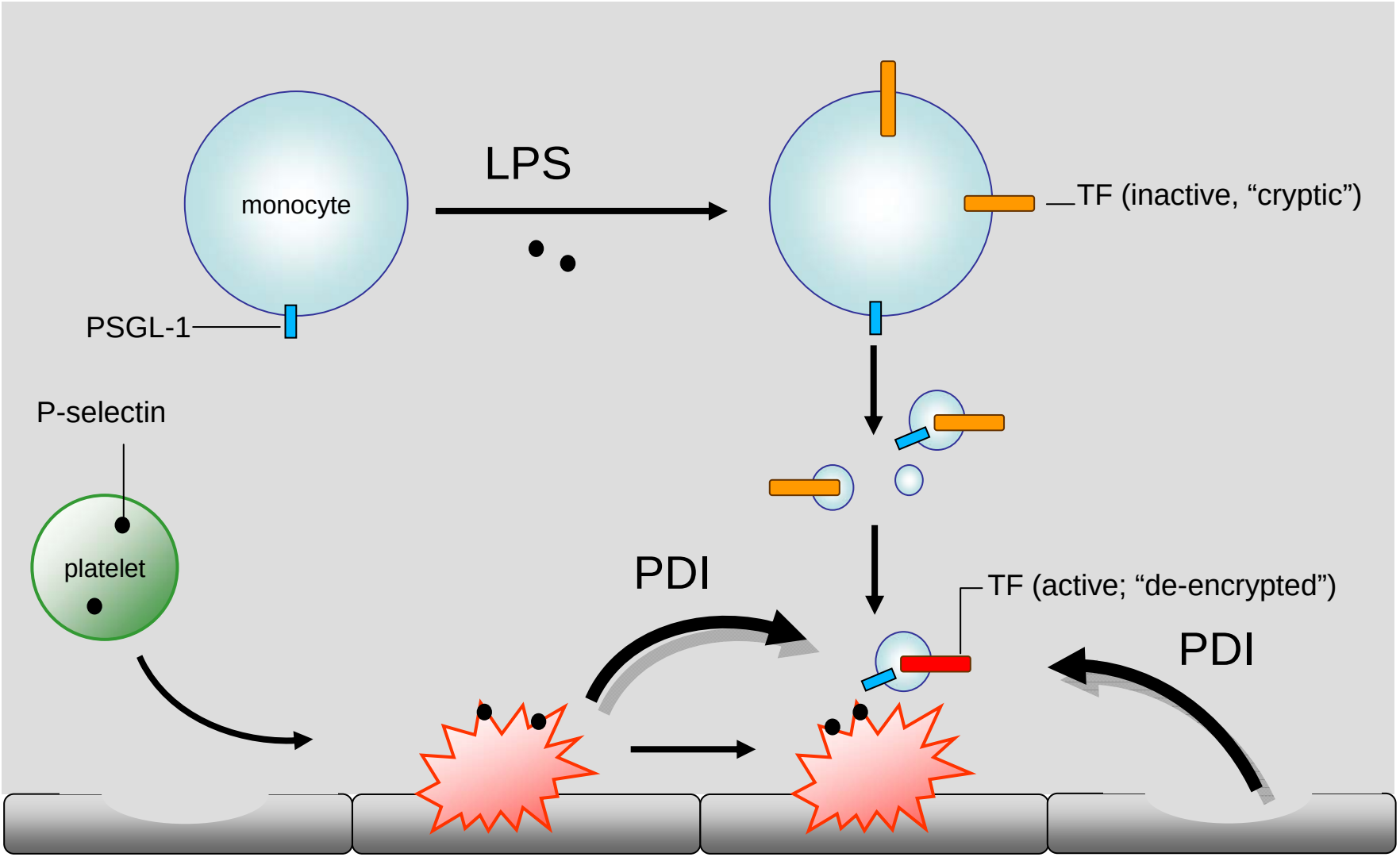
- TF can be present in a functionally latent (encrypted, cryptic) form, despite binding of factor VII.
- How can TF switch from latent to active form?
  - Lipid reorganisation (bilayer distribution of PS)
  - Dimerization
  - Association with lipid rafts
  - Secretion of TF-rich granules
  - Protein disulfide isomerase (PDI)
    - “catalyzes cleavage or formation of disulfide bonds between cysteine residues”

PDI and coagulation



J Clin Invest 2008; 3: 1110-22

Activation of MP-exposed TF in hemostasis



Conclusions

- The PT and aPTT are still the overall coagulation assays of choice.
- These assays artificially divide the coagulation system in pathways presently believed not to exist.
- TF is the initiator of the coagulation system in-vivo, positive feed back loops of thrombin on factors V and VIII, and possibly XI, propagate the coagulation system.
- PDI may regulate the coagulation active – non-active TF conformations.
- Hemostasis, i.e. thrombus formation in-vivo, is a complicated, dynamic process with simultaneous coagulation and platelet involvement.