La coagulation en 2016

PE Morange
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Marseille

Déclaration de conflits d'intérêts

Nom : Pierre Morange

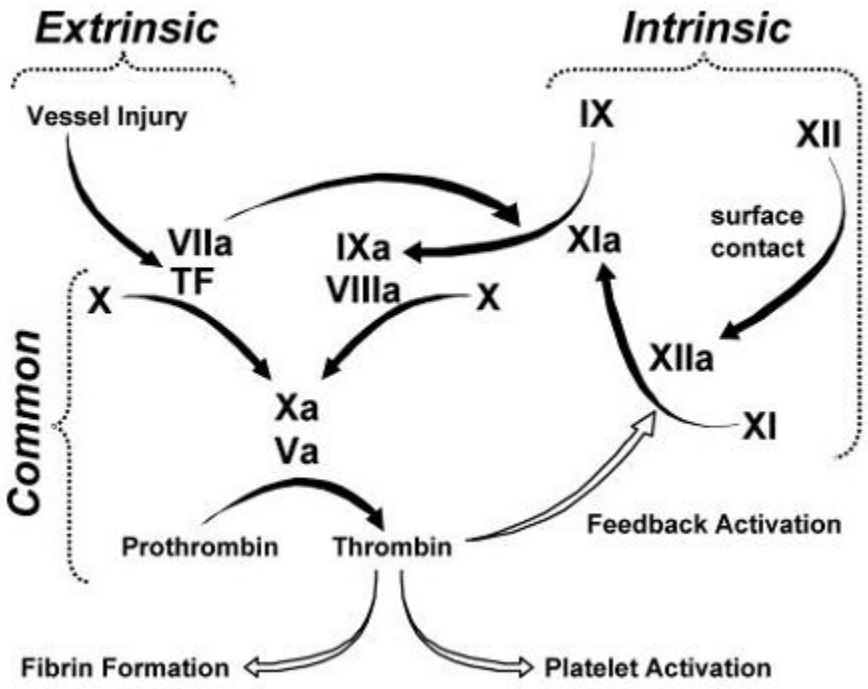
☐ **J'ai, ou ai eu** durant les trois dernières années, une affiliation, des intérêts financiers ou autres intérêts avec un organisme industriel ou commercial de type :

- ☐ Rémunération / Bourse / Honoraires
  - ☐ Orateur / Consultant
- ☐ Autre :

Nom de l'organisme / des organismes :

x **Je n'ai pas de conflit d'intérêt**

Schéma de la coagulation il y a 50 ans



Le déficit total en Facteur XII n’est pas associé à un syndrome Hémorragique

John Hageman - 1955

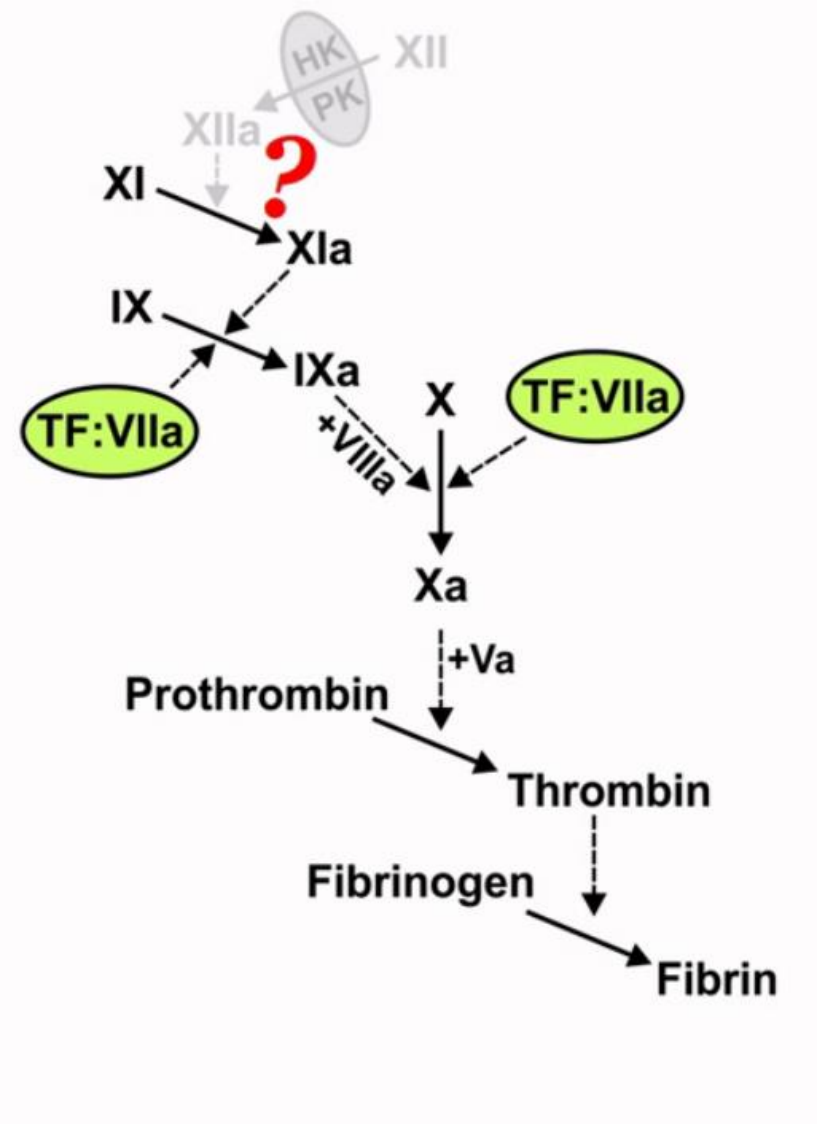
L’activation de la phase contacte n’est elle qu’un artéfact ?

Le déficit constitutionnel en Facteur XI : Hémophilie C

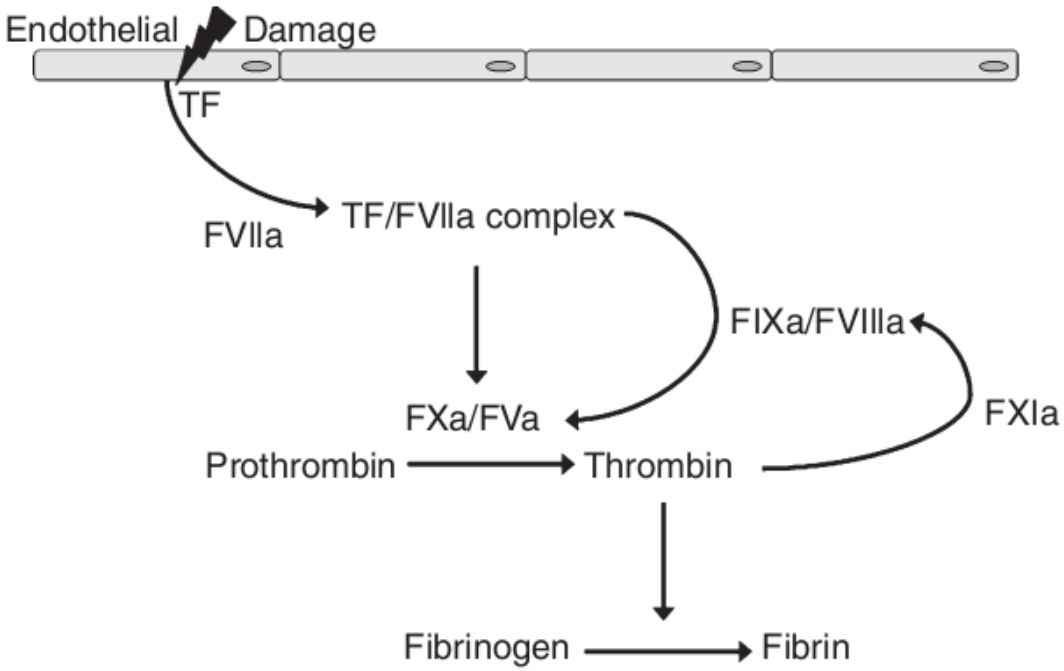
Deficiency	Estimated prevalence (geographic variation)	Location of gene(s) on chromosome	Clinical features (where factor is very low or undetectable)	Hemostatic level (iu/dl except fibrinogen)	Half life of transfused factor [24]
Afibrinogenemia	1 in 1 million	4 (three separate genes)	Severe	0.5 g/l	2–4 days
Prothrombin	1 in 2 million	11	Severe	20–30	3–4 days
Factor V	1 in 1 million	1	Severe	15–20	36 hours
Factors V plus VIII	1 in 1–2 million	18 2	Moderate	As for individual factors	NA
Factor VII	1 in 500,000	13	Severe	15–20	4–6 hours
Factor X	1 in 1 million	13	Severe	15–20	40–60 hours
Factor XI	Common in Ashkenazy Jews	4	Moderate to mild	15–30	40–70 hours
Factor XII	Common in Asia and mild deficiency common in the general population	5	No bleeding complications	NA	NA
Factor XIII	1 in 1–2 million	A subunit 6 B subunit 1	Severe	Not known	11–14 days

Un déficit constitutionnel sévère en FXI est associé à un syndrome hémorragique de type cutanéo-muqueux

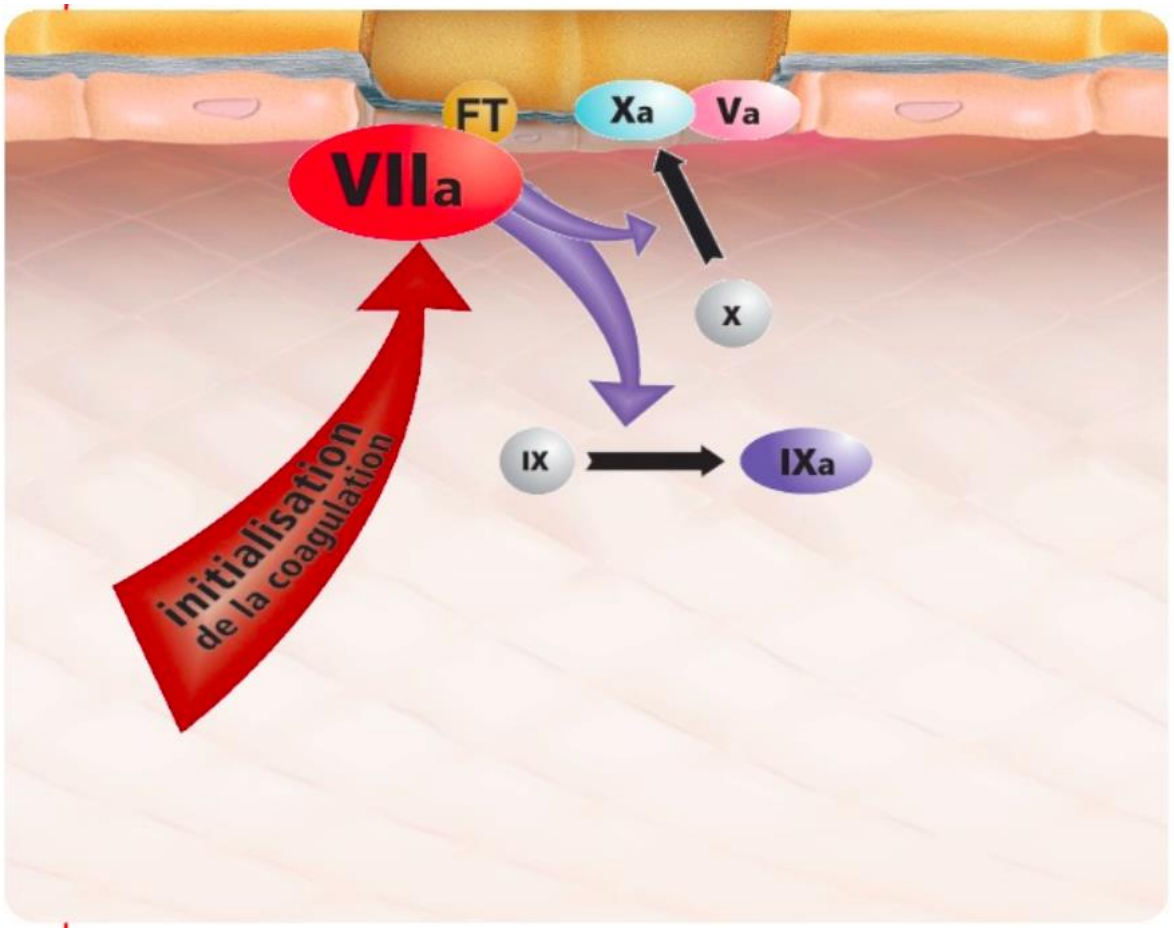
Comment est activé le FXI dans l'Hémostase ?



1991 : 'Le Tout Facteur Tissulaire'



1. Gailani & Broze. Factor XI activation in a revised model of blood coagulation. *Science* **253:**909-912 (1991).
2. Naito & Fujikawa. Activation of human blood coagulation factor XI independent of factor XII. Factor XI is activated by thrombin and factor XIa in the presence of negatively charged surfaces. *J Biol Chem* **266:**7353-7358 (1991).

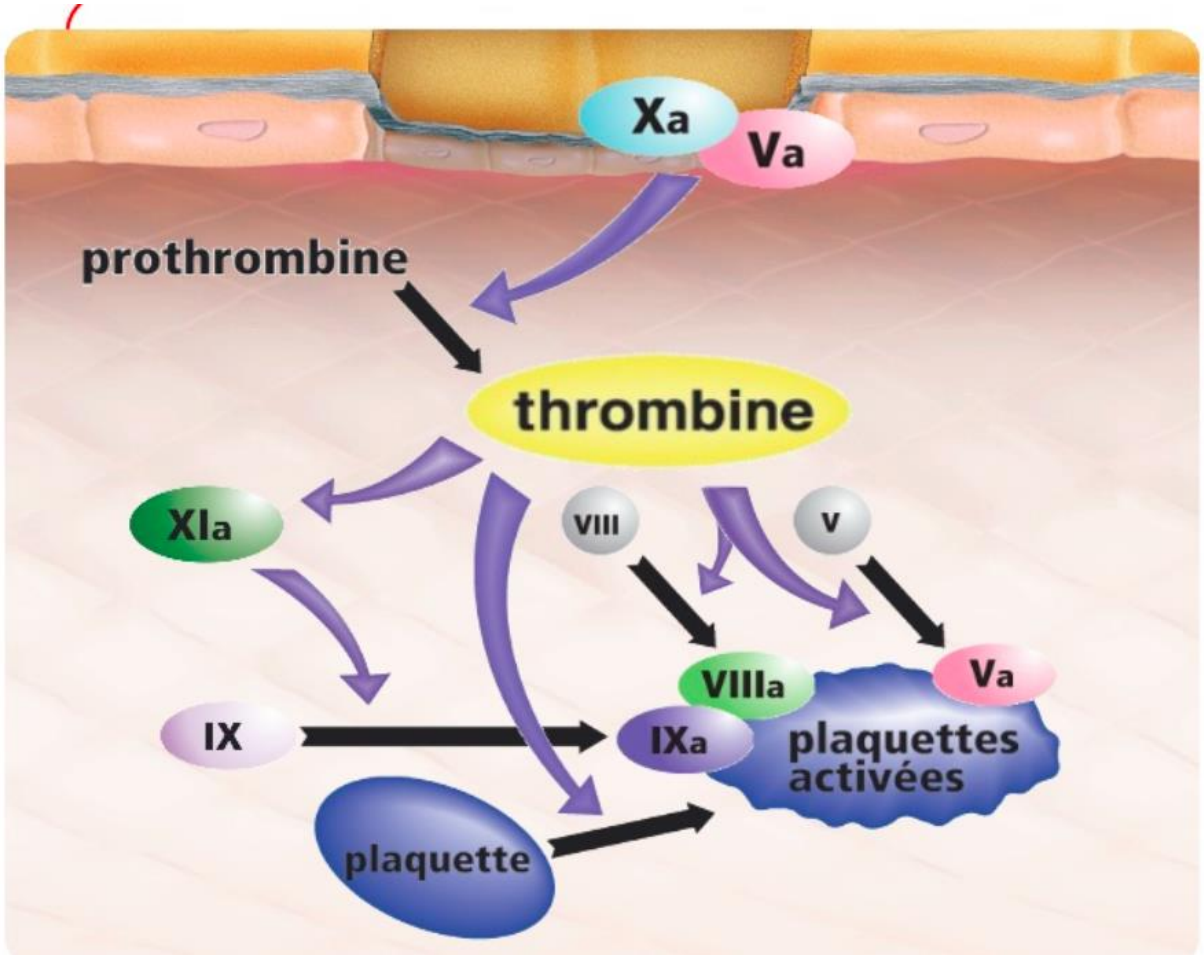


Une altération de la paroi vasculaire est à l'origine d'un contact entre le sang et les cellules sous-endothéliales.

Le facteur tissulaire (FT) est exposé et se lie au FVIIa ou FVII, qui est ensuite activé en FVIIa.

Le complexe entre le FT et le FVIIa active le FIX et le FX.

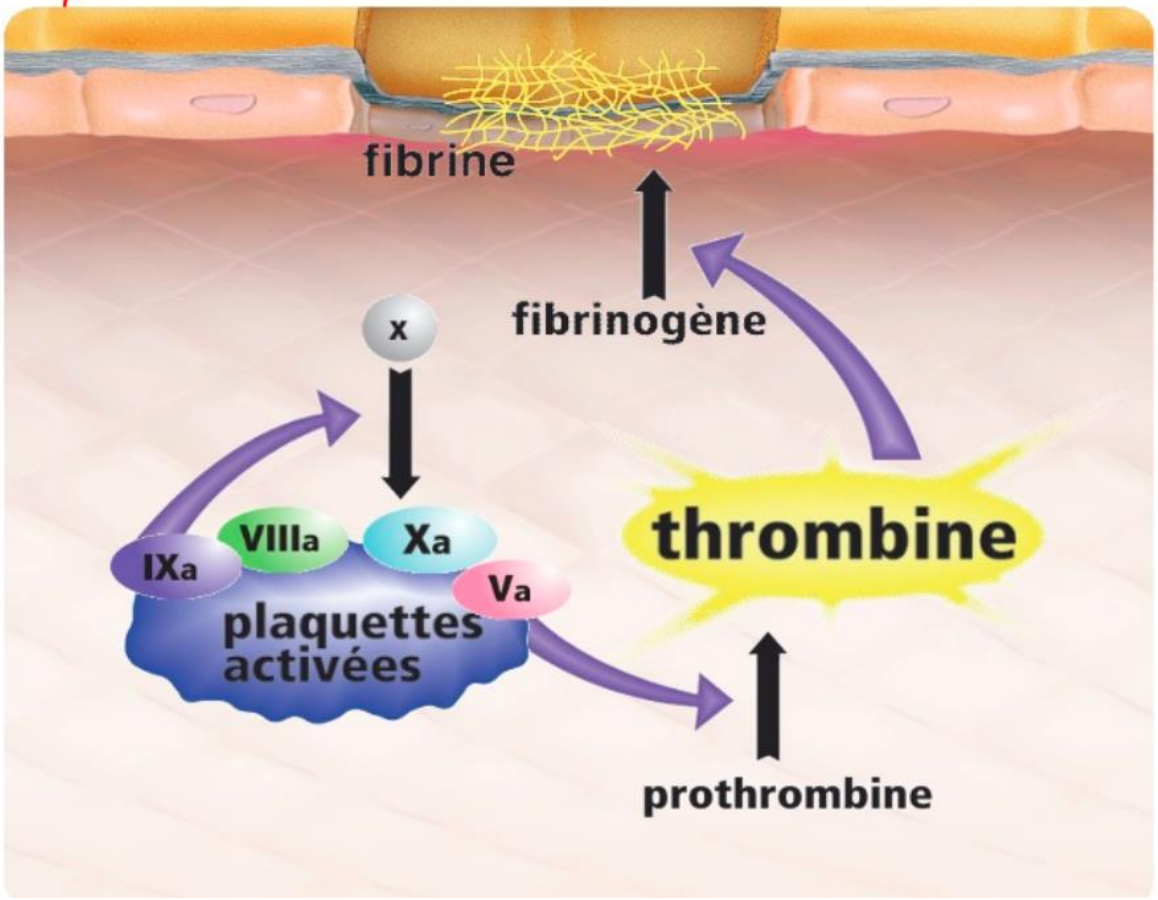
Le FXa se lie au FVa sur la surface cellulaire.



Le complexe FXa/FVa transforme de faibles quantités de prothrombine en thrombine.

La faible quantité de thrombine générée active localement les FVIII, FV, FXI et les plaquettes. Le FXIa transforme le FIX en FIXa.

Les plaquettes activées fixent les FVa, FVIIIa et FIXa.



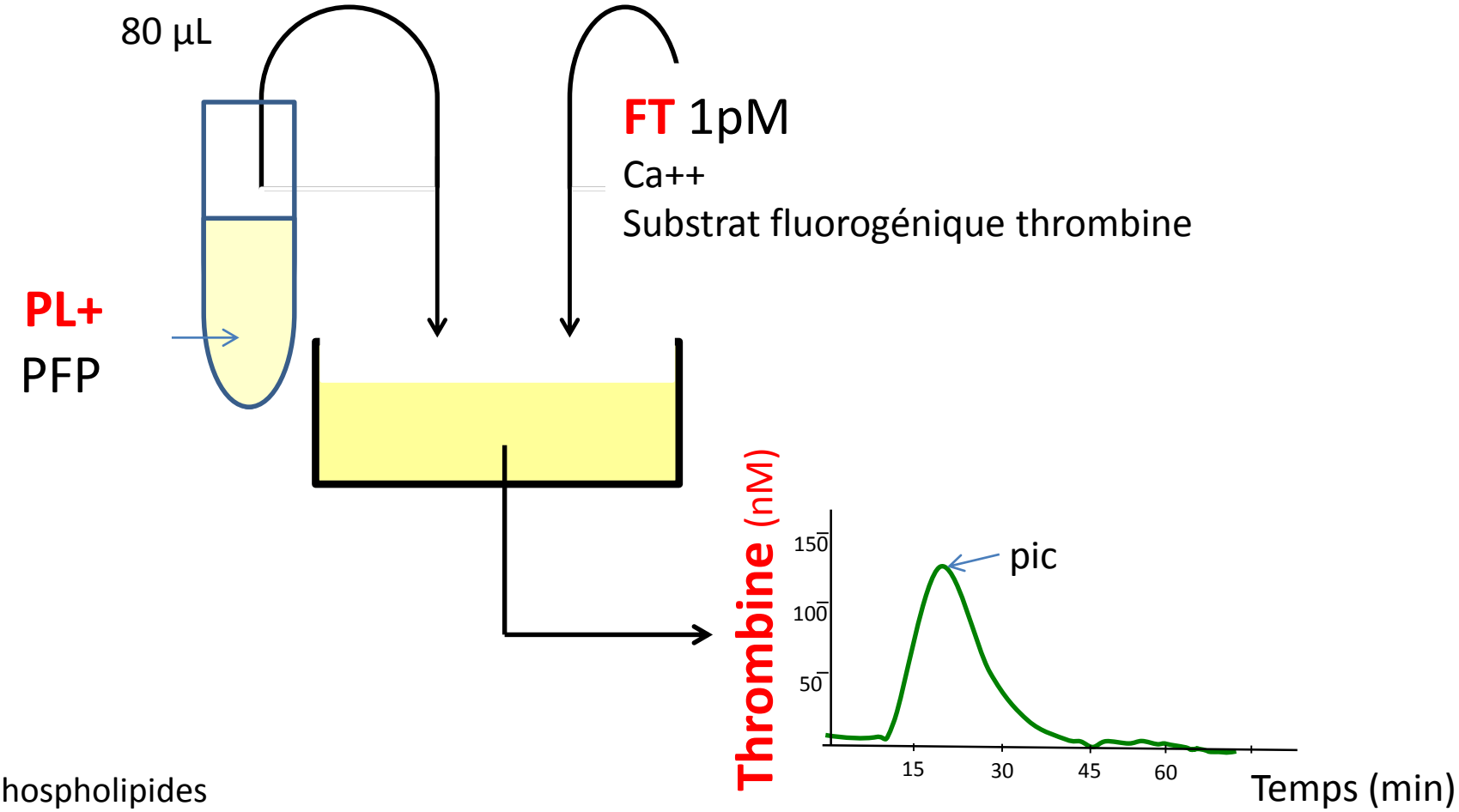
Le complexe FVIIIa/FIXa active le FX à la surface des plaquettes activées.

Le FXa, en association au FVa, transforme d'importantes quantités de prothrombine en thrombine, engendrant ainsi un "pic de thrombine".

Le "pic de thrombine" provoque la transformation du fibrinogène en fibrine aboutissant à la formation d'un caillot de fibrine stable.

Génération de Thrombine

Calibrated Automated Thrombogram® (CAT)

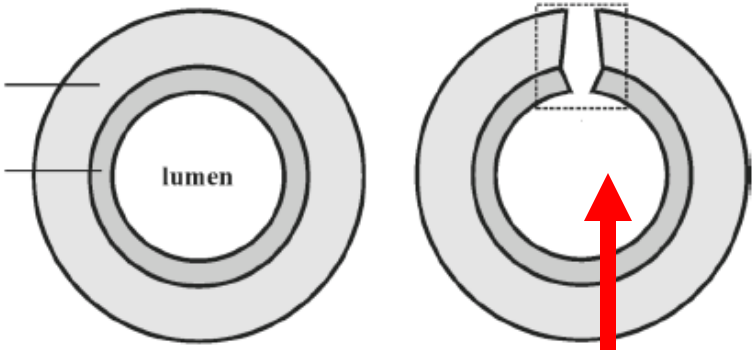


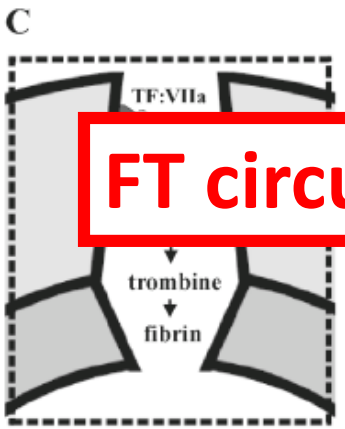
PL : Phospholipides

FT barrière hémostatique

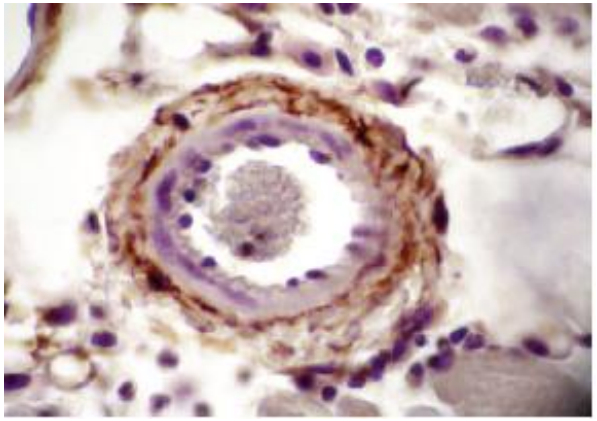
Adventice TF(+)

Intima TF(-)





FT circulant ?



immuno histochimie anti FT

FT circulant

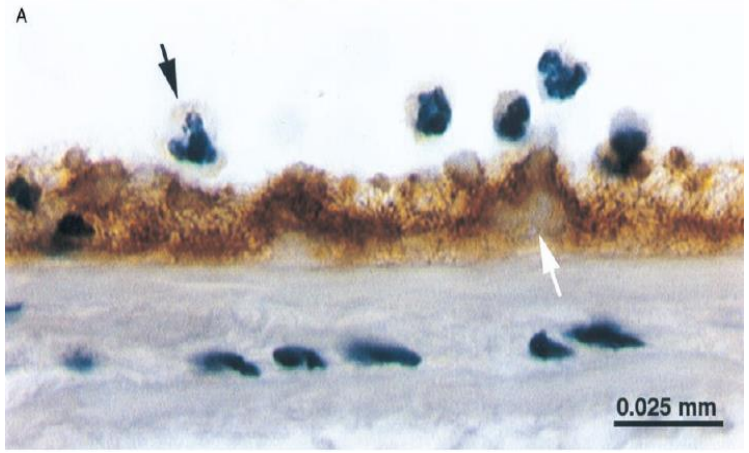
Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 2311–2315, March 1999
Medical Sciences

Blood-borne tissue factor: Another view of thrombosis

PETER L. A. GIESEN*, URSULA RAUCH*, BERND BOHRMANN†, DOROTHEE KLING†, MERCE ROQUÉ‡,
JOHN T. FALLON‡§, JUAN J. BADIMON‡, JACQUES HIMBER†, MARKUS A. RIEDERER†, AND YALE NEMERSON*¶

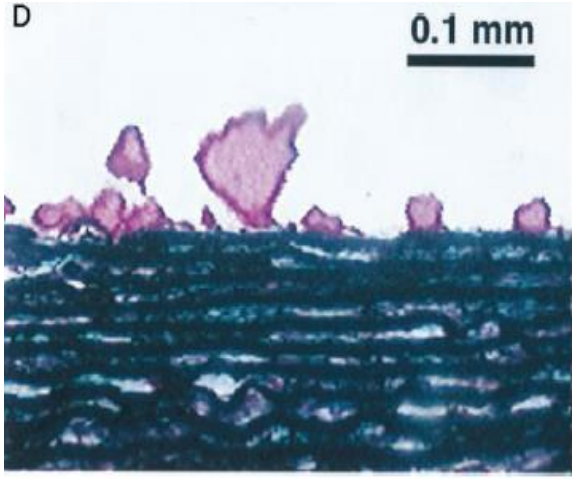
- **Formation d'un thrombus en l'absence d'apport de FT**
  - sur media dépourvue de FT
  - ou sur lame de verre coatée au collagène (pas de FT)
  - avec sang total
- **5 minutes : coloration FT+++:**
  - Polynucléaires neutrophiles et monocytes
  - Phénomène indépendant de GPIIbIIIa
- **GB = source principale de FT in vivo?**

FT circulant



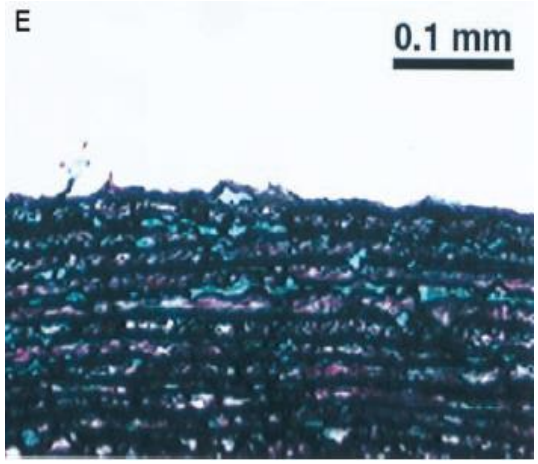
Dans un système sans apport de FT
Marquage FT intense dont polynucléaires

Perfusion of human native whole blood



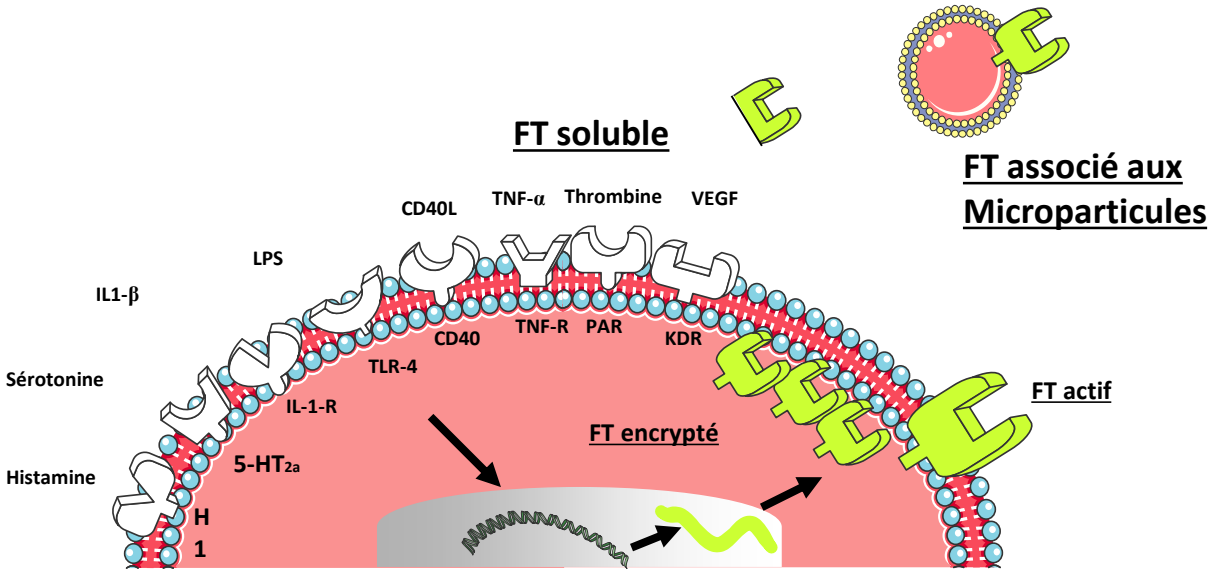
Inhibition de la formation du caillot + anti TF

Perfusion of human whole blood + anti TF



FT «circulant »

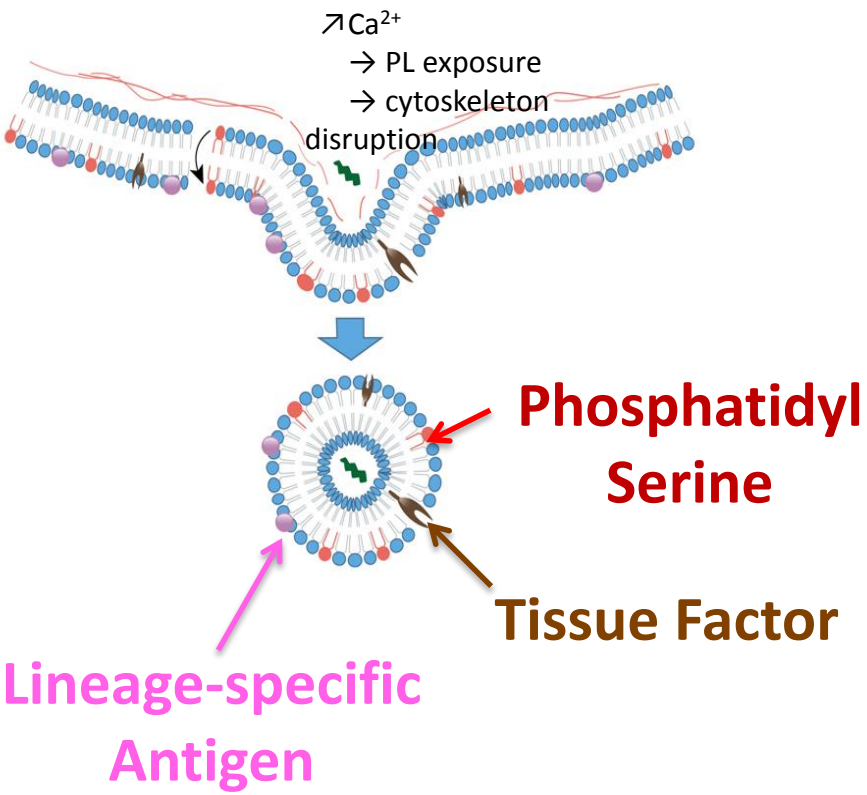
- Dans le plasma (potentiellement) FT= acellulaire:
  - lié aux MP endothéliales, monocytaires, plaquettaires
  - soluble résultat de l'épissage alternatif
  - soluble fragment de protéolyse



- Présence de FT dans le plasma de sujets sains?

Définition des microparticules

- Extracellular vesicles resulting from blebbing of the cell membrane in response to activation or apoptosis
- Heterogeneous size – diameter 0.1 to 1µm
- Expression of phosphatidylserine (PS) and antigens representative of their parent cells



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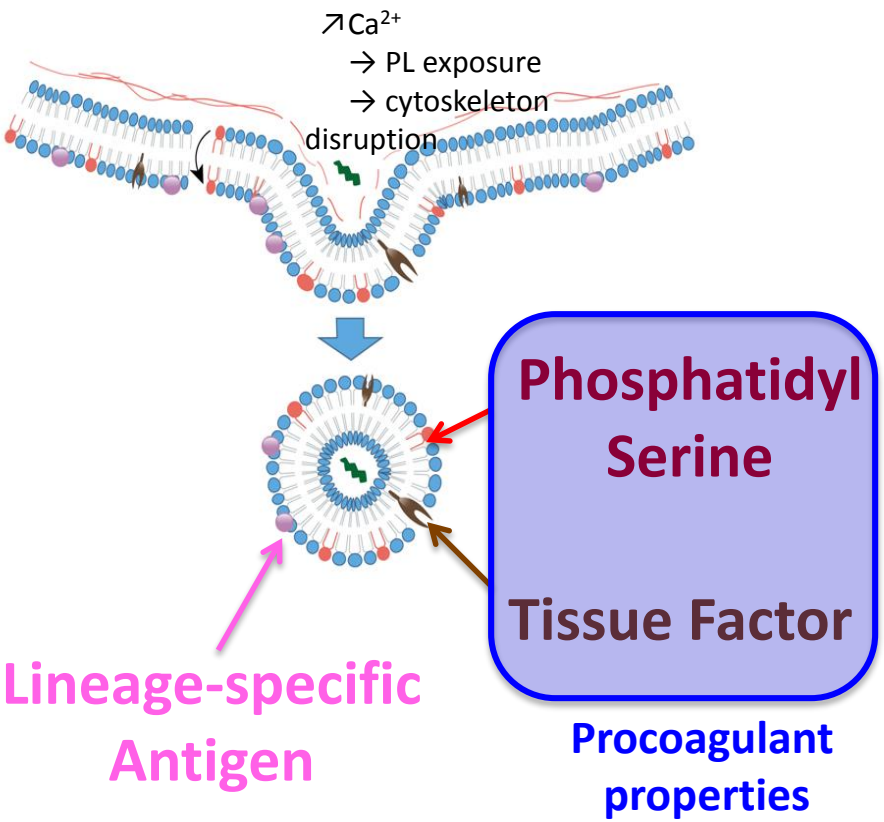

Génération de Thrombine

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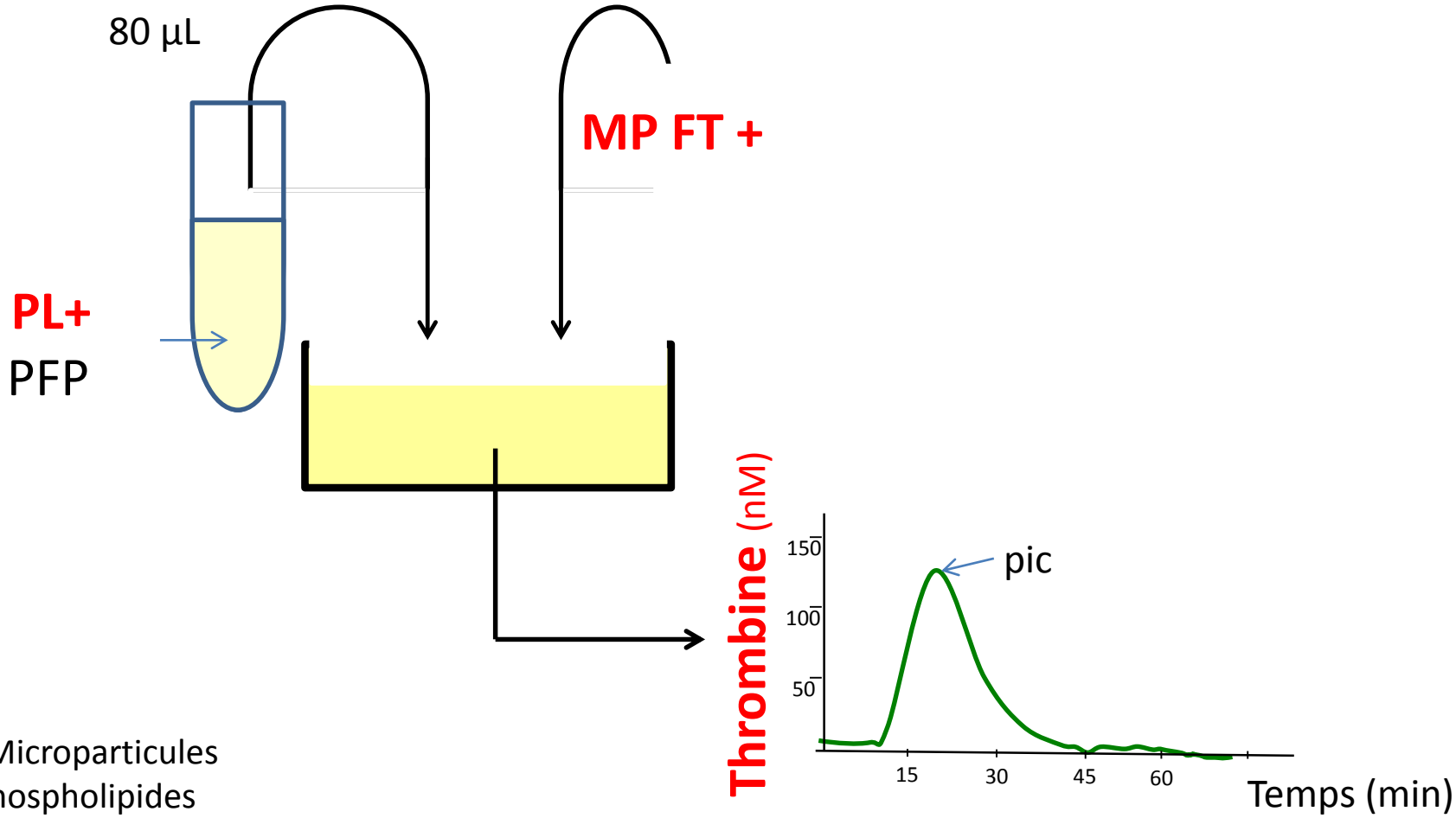


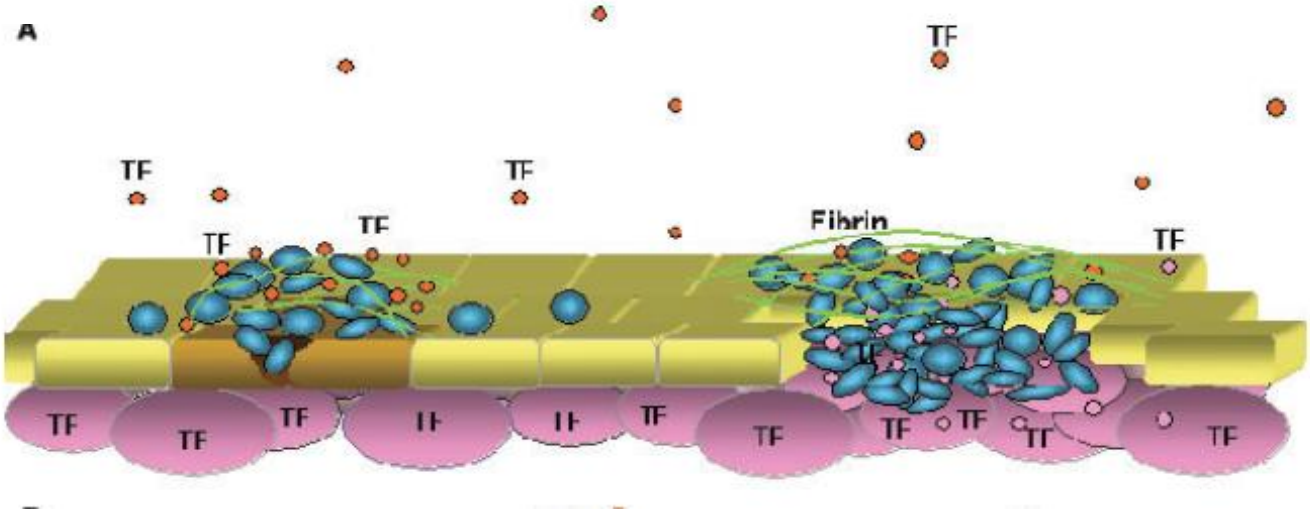
MP : Microparticules
PL : Phospholipides
CTI : Corn Trypsin Inhibitor

FT croissance du thrombus et importance de la lésion endothéliale

Lésion limitée: FT circulant+++

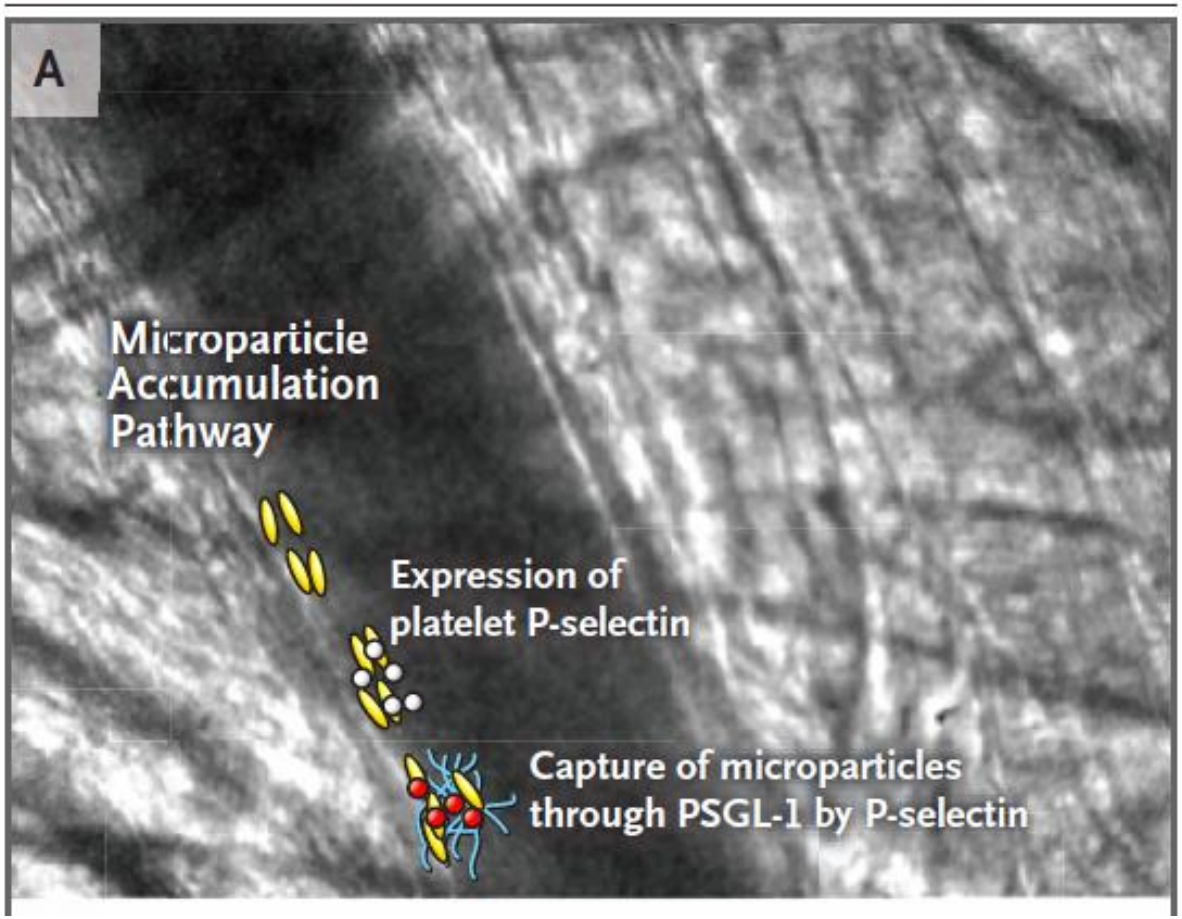
Lésion importante:

FT de la paroi +++



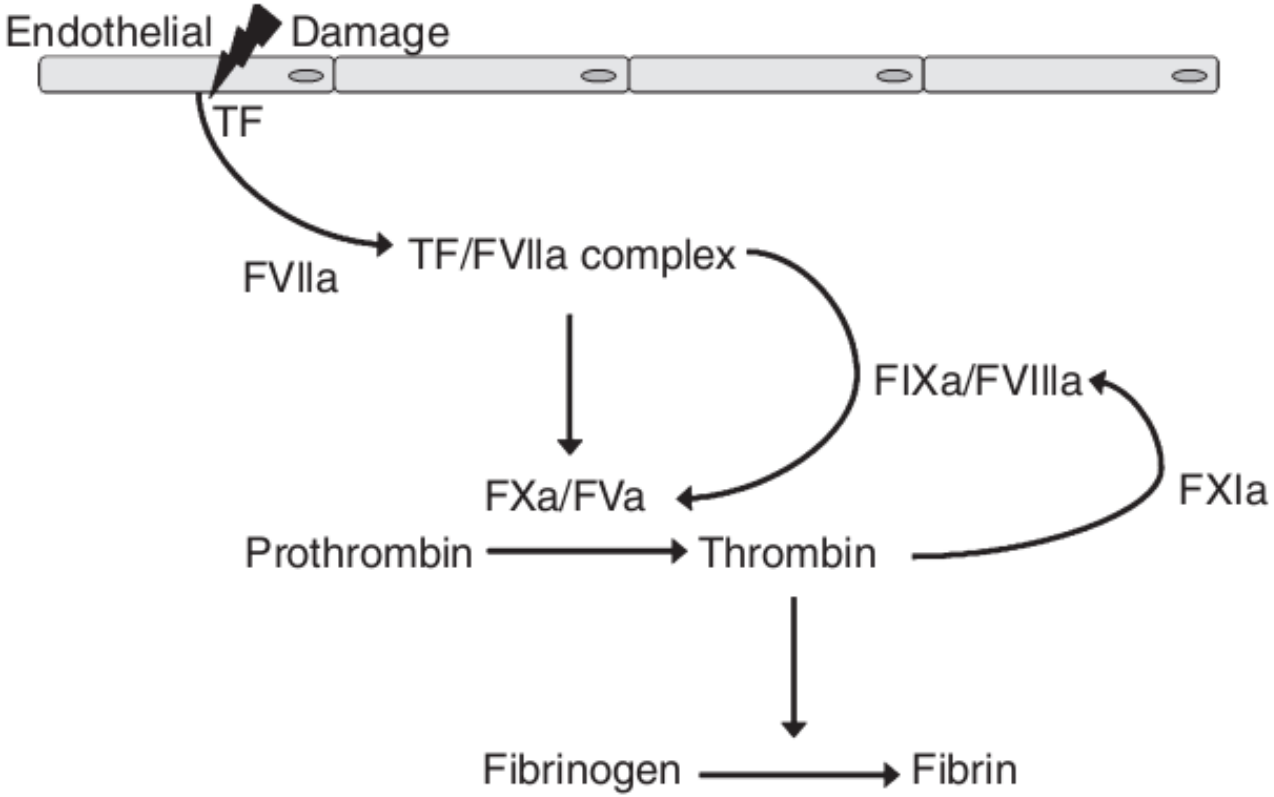
Polgar J, J Thromb Haemost, 2005

Microparticules et Hémostase

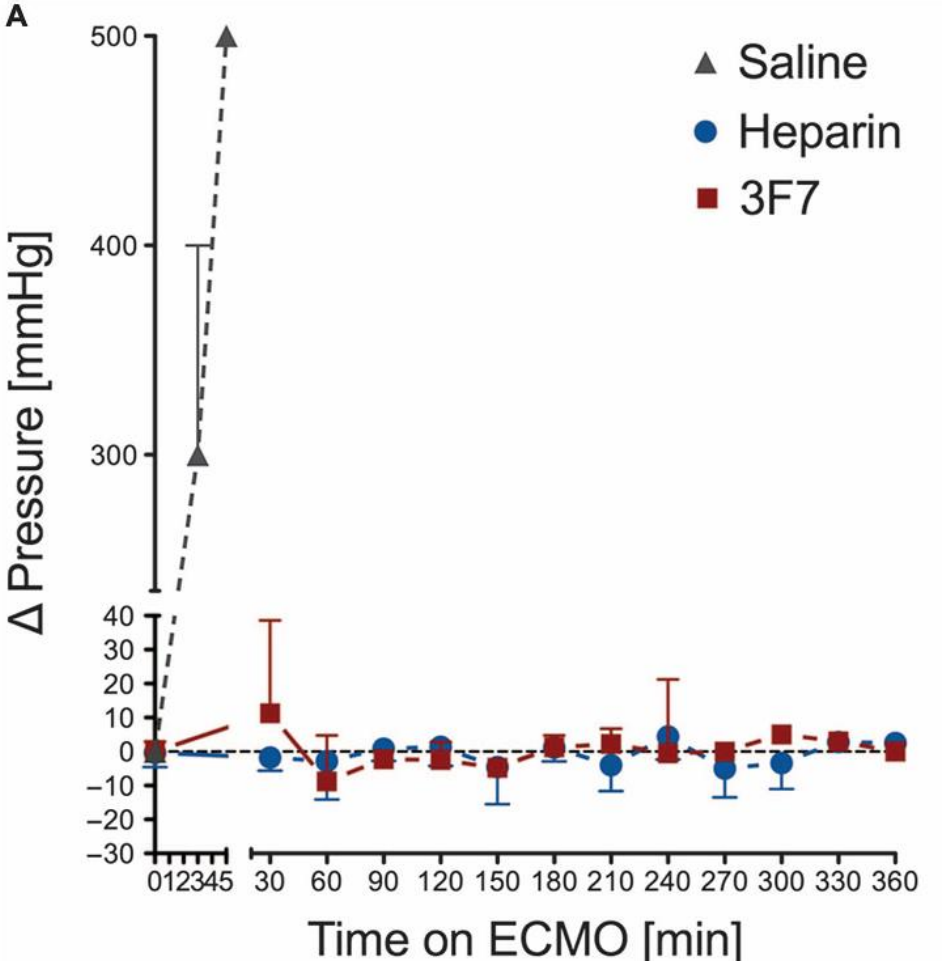


Furie B, Furie B. N Engl J Med 2008

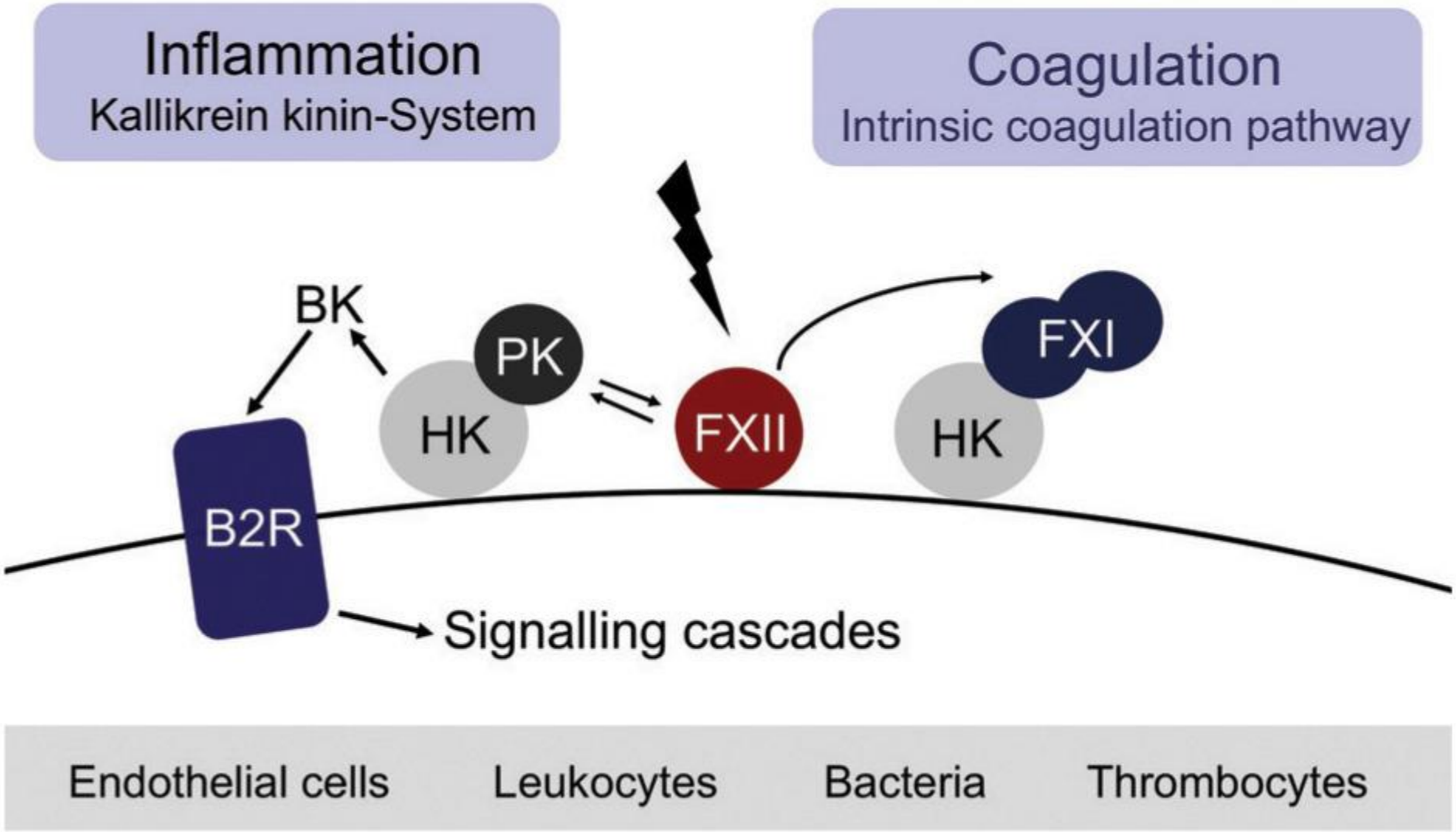
‘Le Tout Facteur Tissulaire’



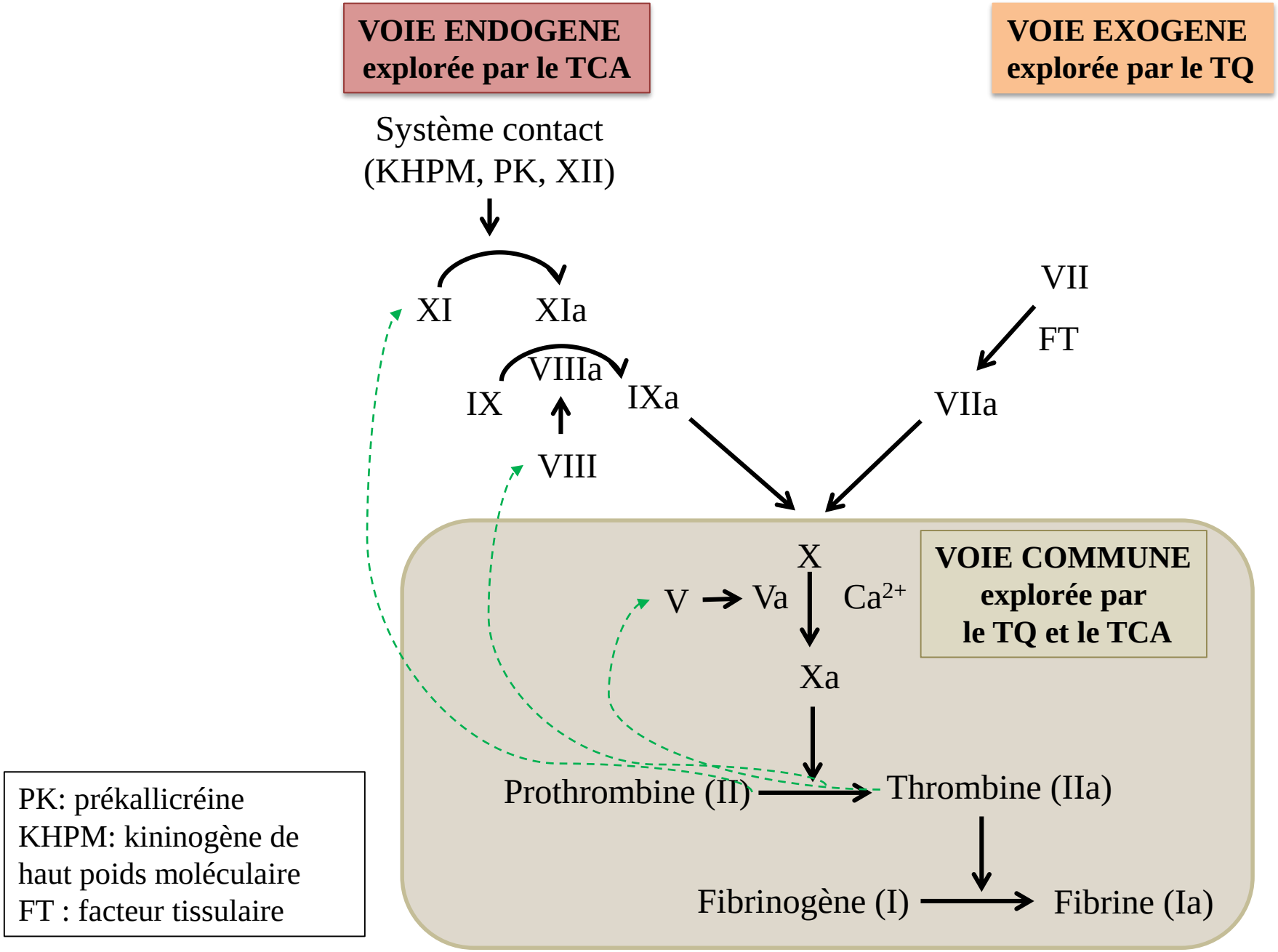
Comme l'Héparine, un anticorps ciblant le FXII inhibe la thrombose dans un système ECMO chez le lapin



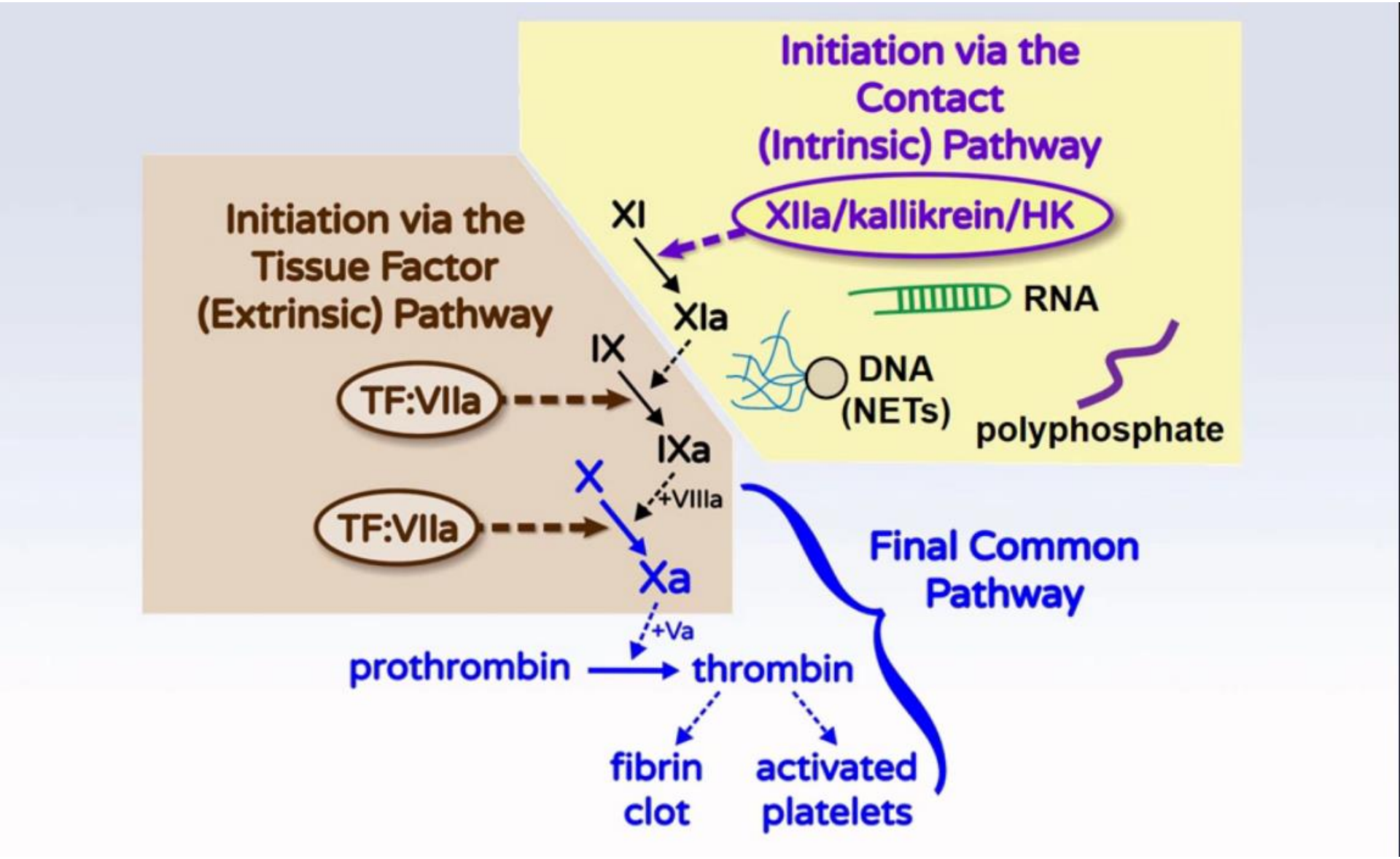
Larsson Sci Trans Med 2014



Copyright © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

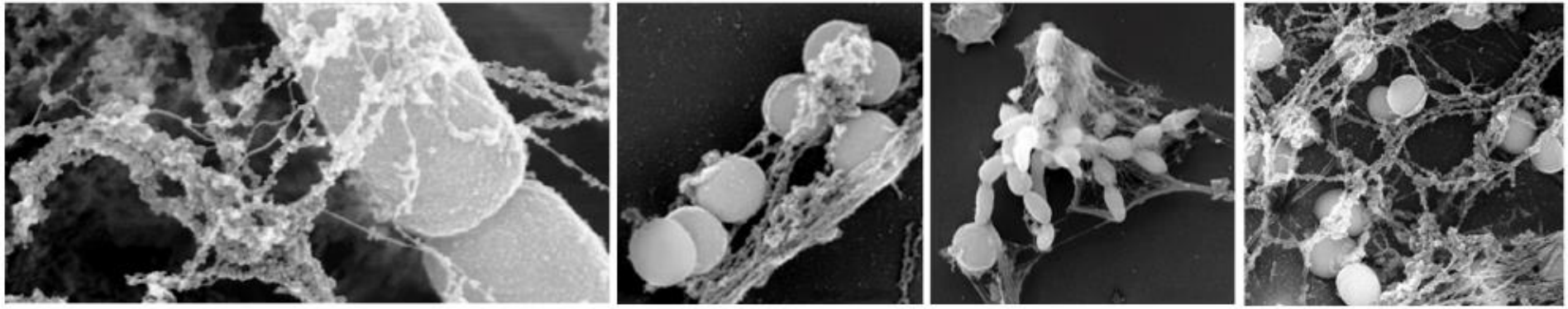

VOIE ENDOGENE
explorée par le TCA
VOIE EXOGENE
explorée par le TQ
Système contact
(KHPM, PK, XII)
XI
XIa
VIII
IX
VIIIa
IXa
VII
FT
VIIa
VOIE COMMUNE
explorée par
le TQ et le TCA
X
V
Va
Ca2+
Xa
Prothrombine (II)
Thrombine (IIa)
Fibrinogène (I)
Fibrine (Ia)
PK: prékallicréine
KHPM: kininogène de
haut poids moléculaire
FT : facteur tissulaire

La phase contacte est activée in vivo



Morrissey ISTH 2015

La « NETose »
Neutrophil Extracellular TrapS

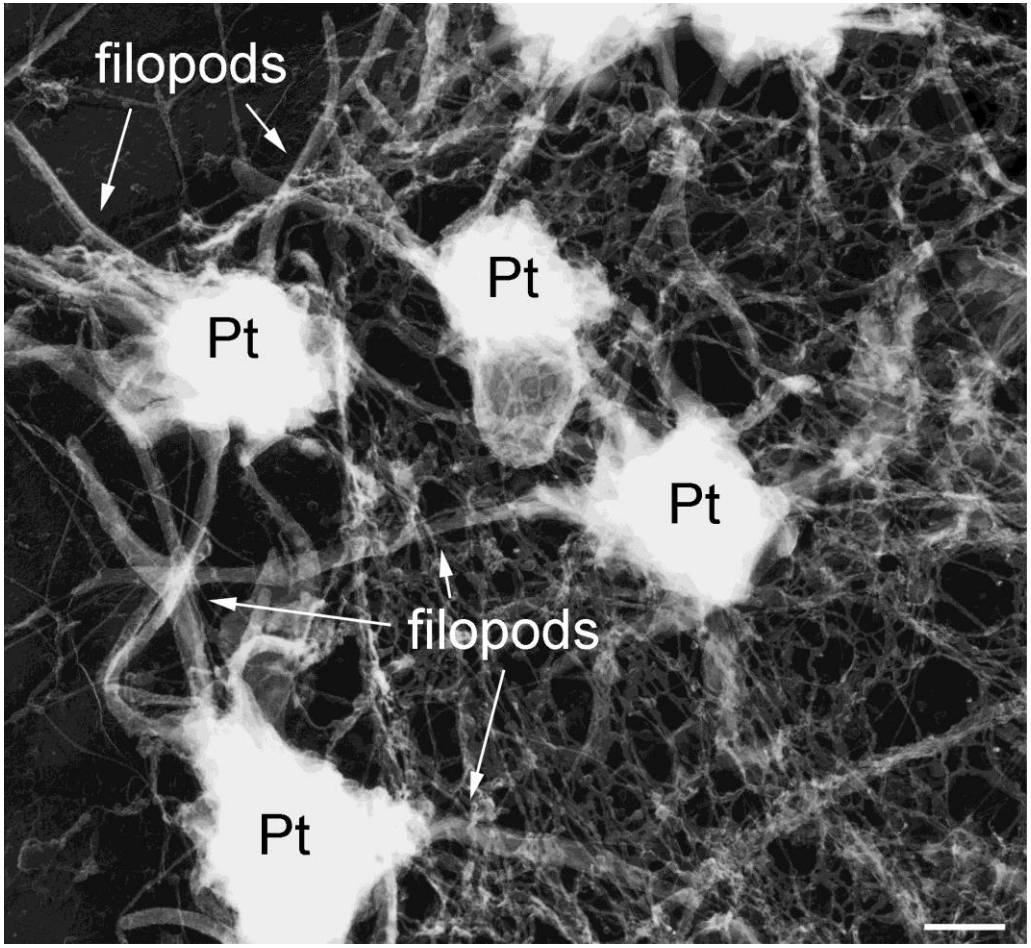


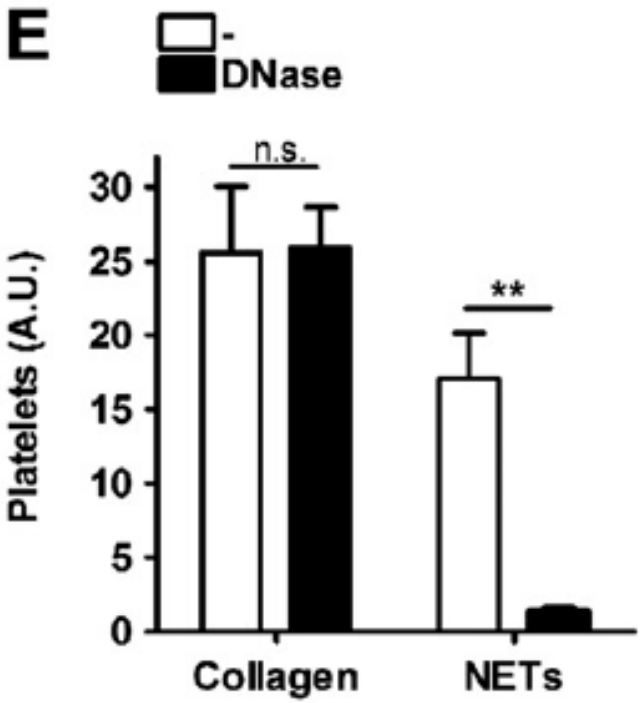
- **Matrice adhésive**

- **Concentration léthales en protéines anti-microbiennes (Elastase, MPO, cathepsine G, alpha-désensines, histones...)**

Les NETs: une matrice favorisant l'adhésion

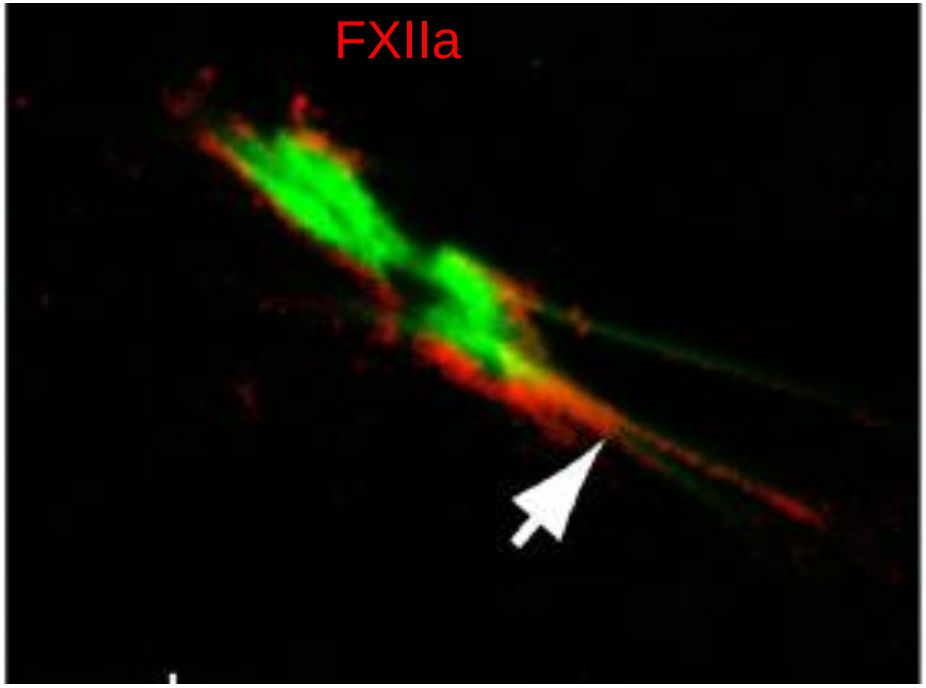
Une matrice pour les plaquettes, une surface thrombogène:





Importance des NETs dans la thrombogenèse

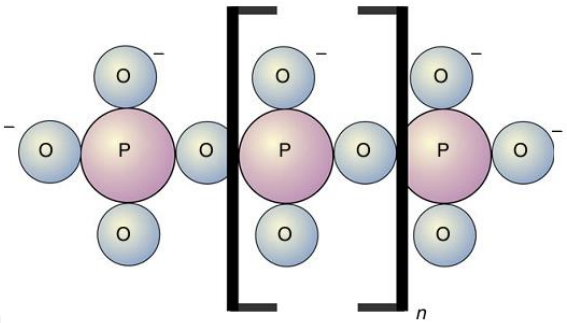
NETs (sytox)



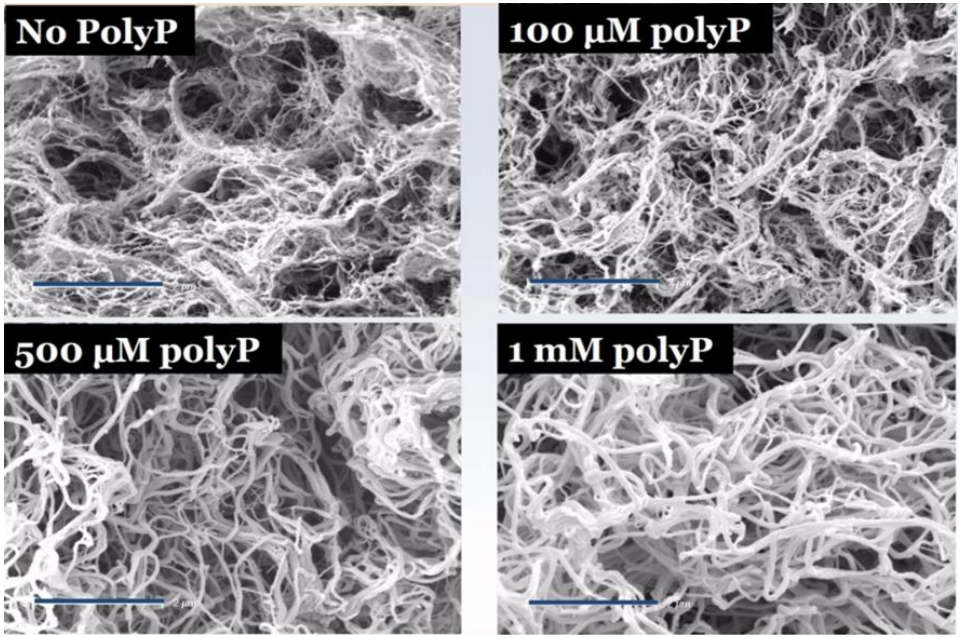
von Brühl *et al*., J Exp Med 2012

- Importance dans l'activation du facteur XII
- Exposition de Facteur Tissulaire, PDI

Polyphosphates

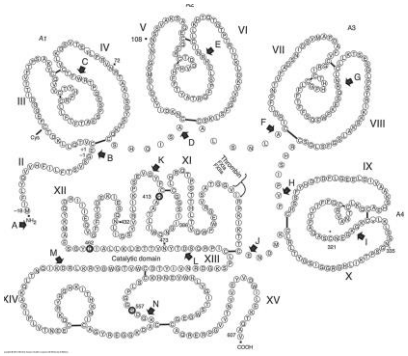


- Polymères linéaires d'orthophosphates de taille variable
- Présents de façon ubiquitaire dans de nombreuses bactéries comme dans plusieurs organelles cellulaires des mammifères.
- Présents dans les granules denses plaquettaires et sont sécrétés lors de l'activation plaquettaire.



Smith and Morrissey Blood 2008

La coagulation en 2016



1 Tissue Injury
Platelet Activation
Inflammation
Stasis
Hypoxia

2 Polyphosphate
Nucleic Acid Polymers
Basement Membranes
Artificial Surfaces

Thrombin Generation

IX
VIIa
TF
Ca^{2+}
PL
IXa
VIIIa
X
Xa
Va
Prothrombin
Thrombin

XIa
XI

Contact Activation
(Kallikrein-Kinin System)

XII
HKa
BK+AMPs
HK
α-Kal
XIIa
PK
HK

3 Platelet Activation
Fibrin Formation
TAFI Activation

4 Fibrin Stabilization

5 Effects on Blood Vessels

Thrombosis

FXI-ASO
Efficacité

Critère primaire d'Efficacité : TV symptomatique ou attestée par veinographie bilatérale (8-12 jours après chirurgie)

Outcome	FXI-ASO, 200 mg (N=134)	FXI-ASO, 300 mg (N=71)	Enoxaparin, 40 mg (N=69)
Efficacy			
Primary efficacy outcome: total venous thromboembolism — no. (% [95% CI])†	36 (27 [20 to 35])	3 (4 [1 to 12])	21 (30 [20 to 43])
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 90% CI)	−4 (5)	−26 (−18)	—
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 95% CI)	−4 (8)	−26 (−16)	—
P value for superiority of FXI-ASO to enoxaparin	0.59	<0.001	—
Secondary efficacy outcomes: components of the primary efficacy outcome — no. (%)			
Symptomatic venous thromboembolism	2 (1)	0	1 (1)
Asymptomatic deep-vein thrombosis	34 (25)	3 (4)	20 (29)
Proximal deep-vein thrombosis	7 (5)	1 (1)	4 (6)
Distal deep-vein thrombosis	29 (22)	2 (3)	17 (25)

Buller – NEJM-2014

FXI-ASO
Sécurité

Outcome	FXI-ASO, 200 mg (N=144)	FXI-ASO, 300 mg (N=77)	Enoxaparin, 40 mg (N=72)
Safety§			
Principal safety outcome: major or clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	2 (3 [<1 to 9])	6 (8 [3 to 17])
Risk difference, FXI-ASO vs. enoxaparin — % (95% CI)	−6 (−12 to 1)	−6 (−13 to 2)	
P value by Fisher's exact test, FXI-ASO vs. enoxaparin	0.09	0.16	
Major bleeding — no. (% [95% CI])¶	0 [0 to 2.5]	1 (1 [<1 to 7])	0 [0 to 5.0]
Clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	1 (1 [<1 to 7])	6 (8 [3 to 17])
Receipt of blood transfusion — no. (%)	55 (38)	22 (29)	23 (32)
Adverse events — no. of patients (%)			
≥1 adverse event	114 (79)	62 (81)	47 (65)
Serious adverse event‖	3 (2)	1 (1)	0
Any adverse event resulting in permanent discontinuation of study drug**	1 (1)	1 (1)	0
Injection-site–related adverse event††	32	25	2

Buller – NEJM-2014