Dianas terapéuticas en la hemostasia

J. Gracia
Especialista en Hematología y Hemoterapia
Especialista en Medicina Intensiva
Medical Manager Biopharma Spain
Madrid, Abril 2018

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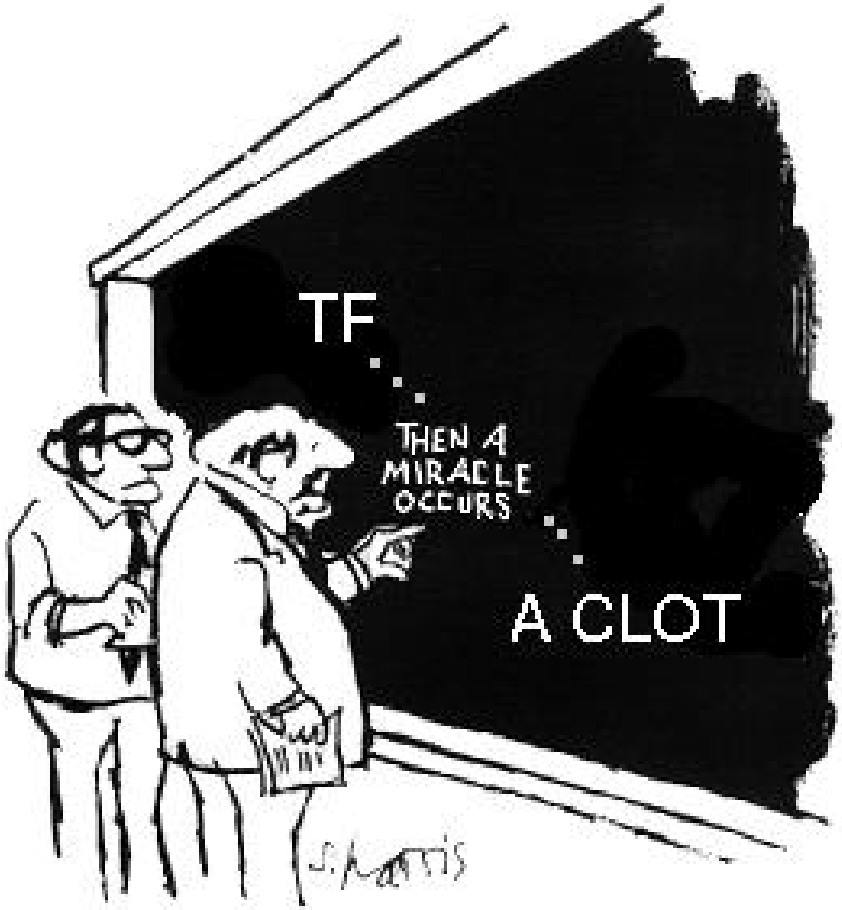
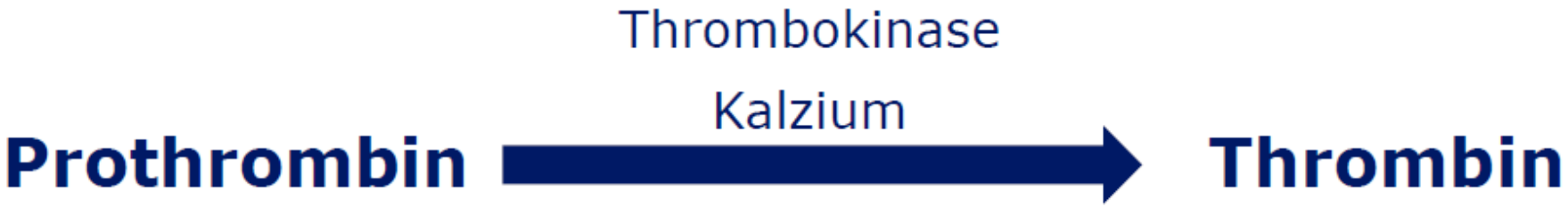


"I think you should be more explicit here in step two."



fibrinogen
prothrombin
accelerator (AC-) globulin
Antihemophiliac Factor
Antihemophilic Factor B
Antihemophilic Globulin (AHG)
Antihemophilic Globulin A
Autoprothrombin I
Autoprothrombin II
Autoprothrombin III
Beta cothromboplastin
Christmas Factor
Contact Factor
Cothromboplastin
Facteur Antihemophilique A
Fibrin Stabilizing Factor
Thromboplastic Plasma Component
Thromboplastinogen
Hageman Factor
Hemophilia A factor
Hemophilia B Factor
Hemophilia C factor
Labile Factor
Laki-Lorand Factor
Pavlovsky Factor
Plasma Thromboplastic Factor
Plasma Thromboplastic Factor A
Plasma Thromboplastin Antecedent (PTA)
Plasma Thromboplastin Component
Plasmakinin
Platelet Cofactor
Proaccelerin
Proconvertin
Prothrombokinase
Protransglutamidase
Prower Factor
Robbins Factor
Serum Factor
Serum Prothrombin Conversion Accelerator (SPCA)
Stable Factor
Stuart Factor
Stuart-Prower Factor

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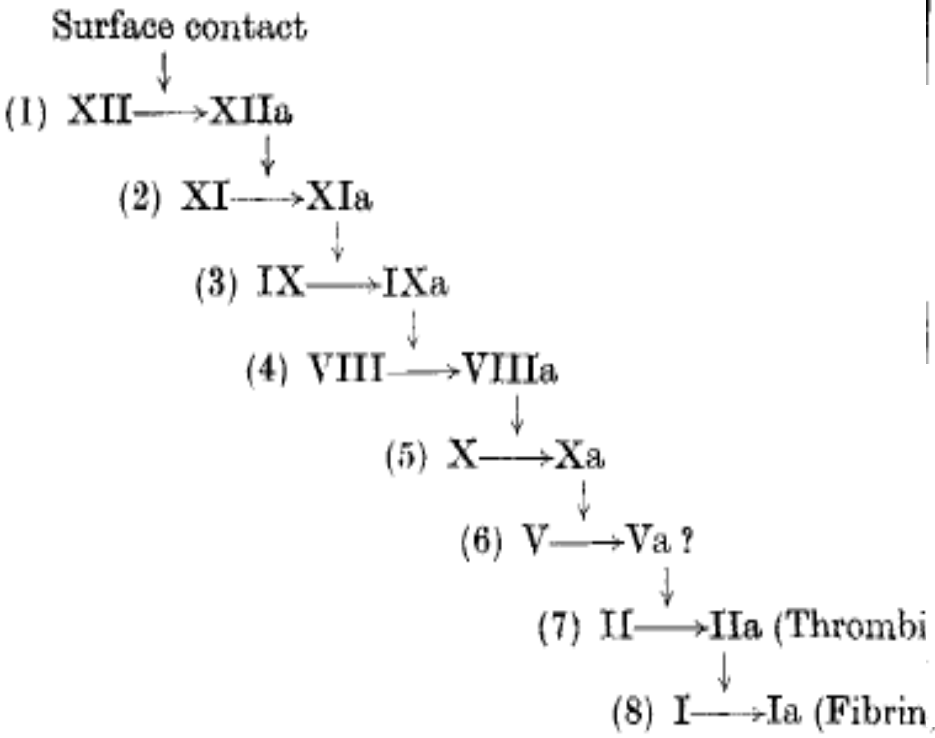
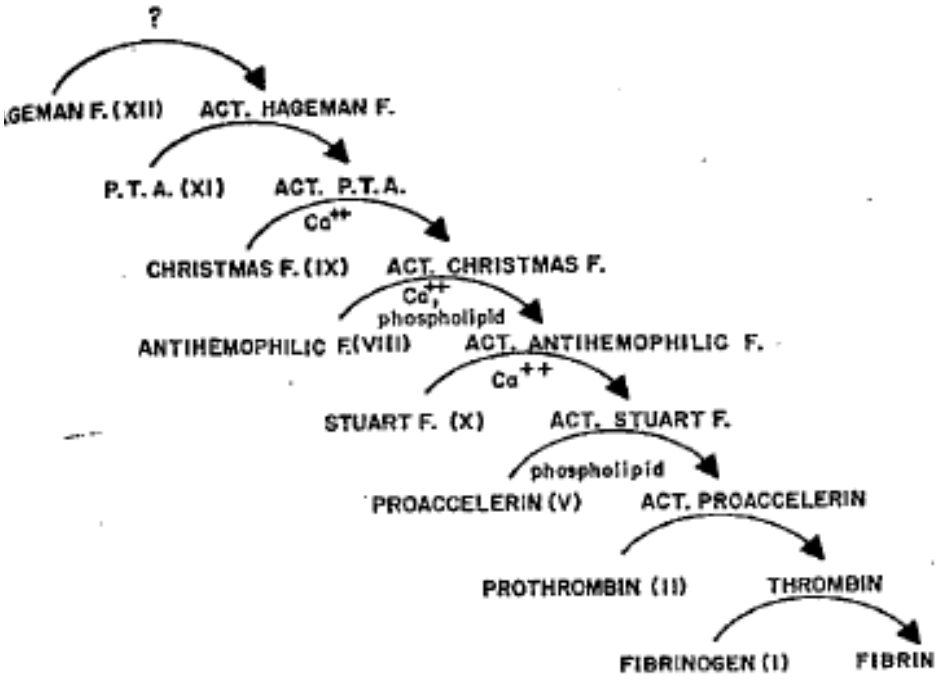


MacFarlane. Nature 1964, Vol 202; 498-499



Davie, Ratnoff. Science 1964, 145:1310-1312

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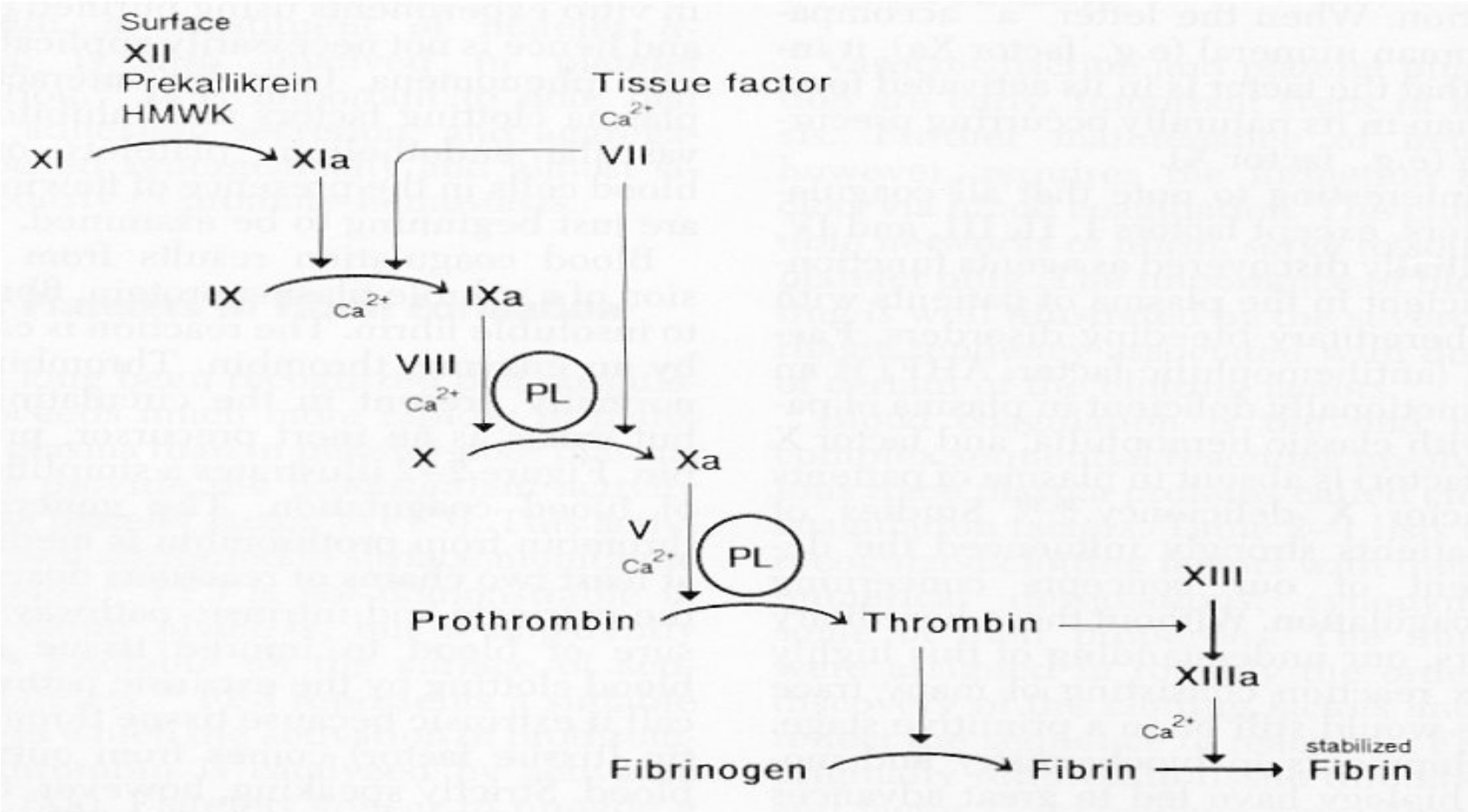

Østerud. Proc Natl Acad Sci, 1977; 74: 5260-64

The coagulation "cascade" model and PT/aPTT tests were developed in tandem

Thus, the **cascade model** is a good reflection of results obtained in these clinical lab tests that detect deficiencies of coagulation **proteins**

However, it isn't such a good model of the more complex situation of hemostasis *in vivo*…

The “cascade” model also doesn’t explain why FVIII or FIX deficiency results in a severe bleeding

Harold R. Roberts, MD

Dougald "Mac" Monroe, PhD

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Thromb Haemost 2001; 85: 958–65

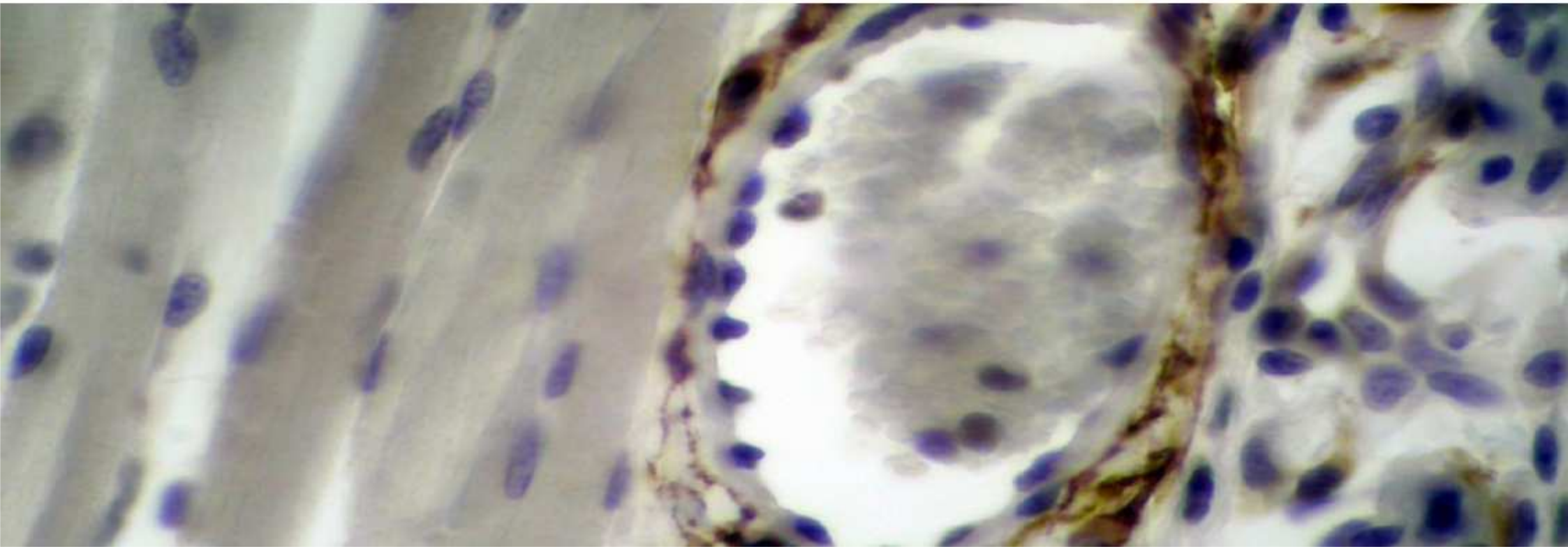
Review Article

A Cell-based Model of Hemostasis

Maureane Hoffman, Dougald M. Monroe III

Pathology and Laboratory Medicine Service, Durham VA and Duke University Medical Centers, Durham, NC, USA, and Division of Hematology/Oncology, Department of Medicine, The University of North Carolina, Chapel Hill, NC, USA

TF-bearing cells form a “hemostatic envelope” around vessels



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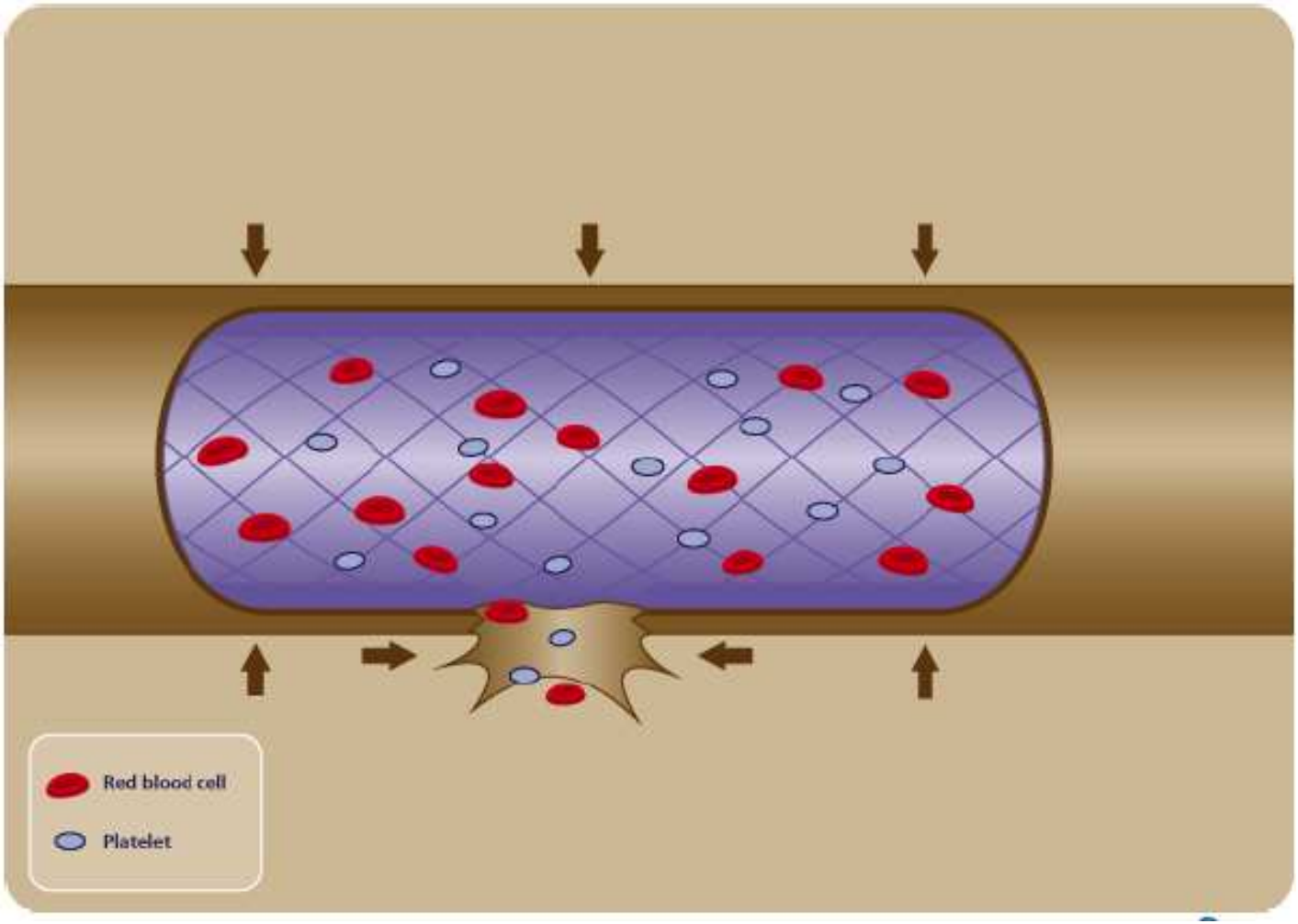
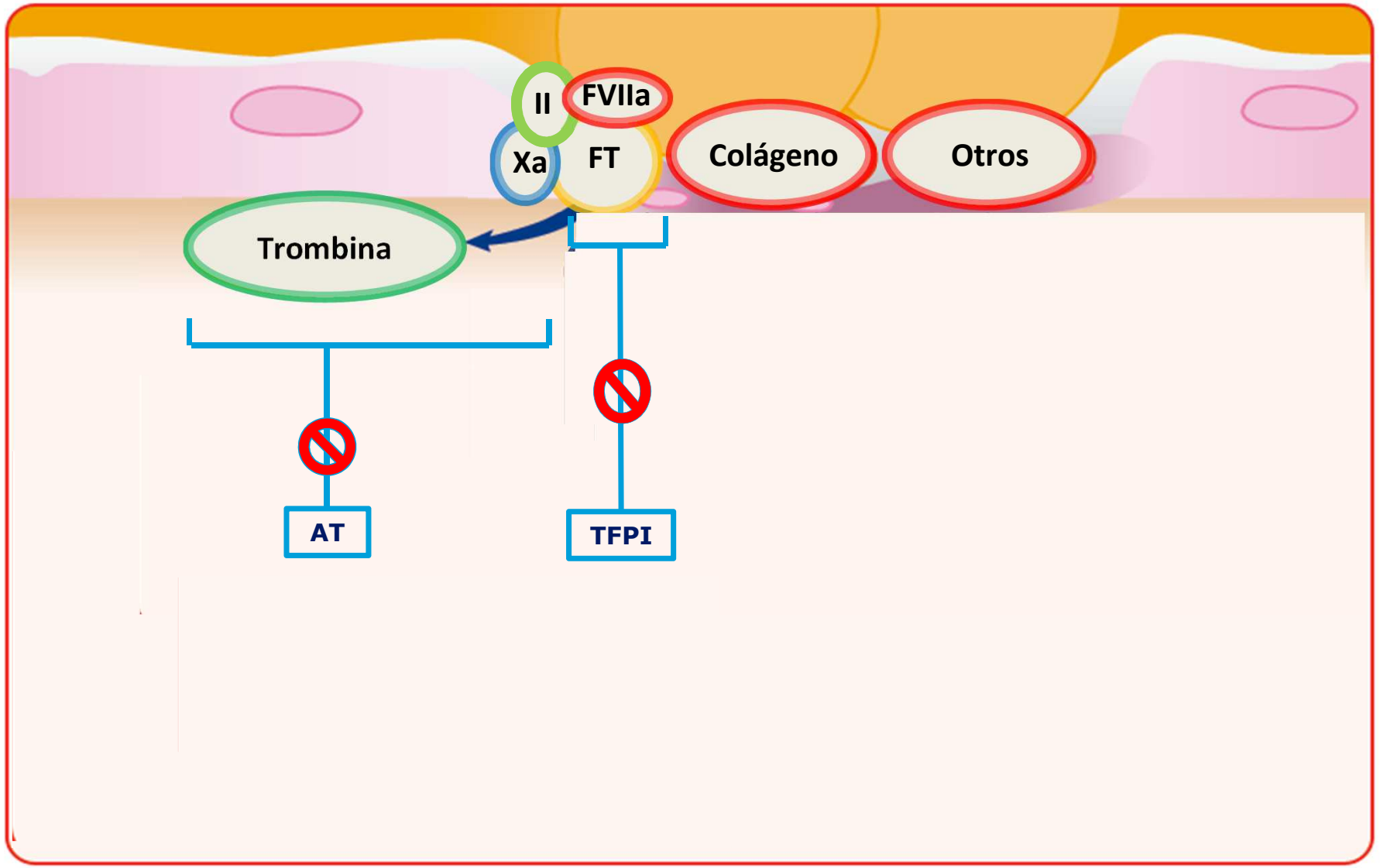
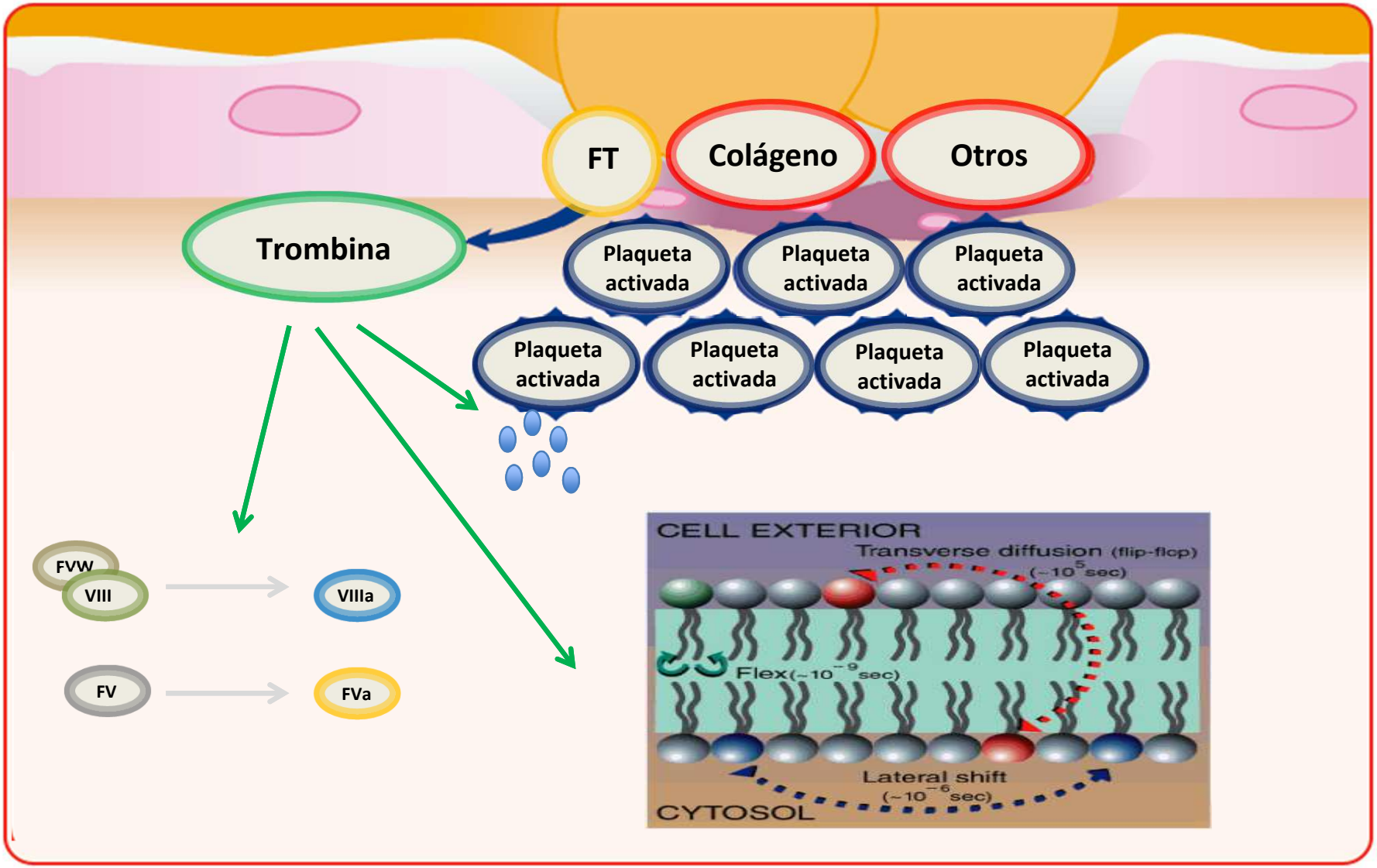
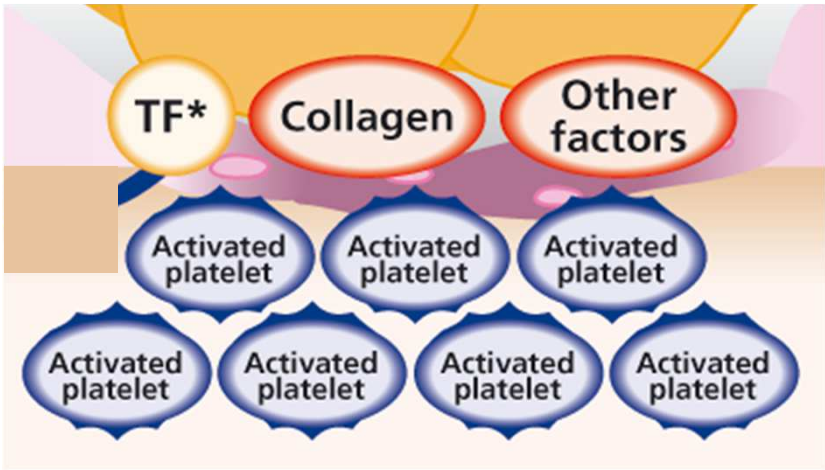



FT
Colágeno
Otros


II
FVIIa
Xa
FT
Colágeno
Otros
Trombina
AT
TFPI

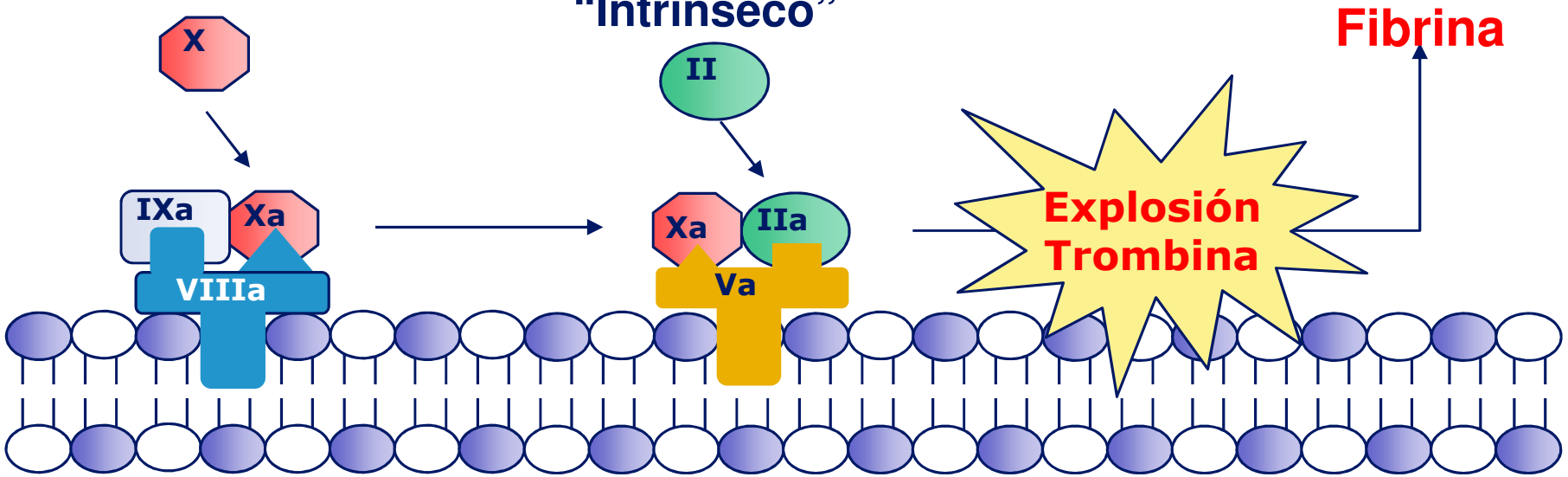

FT
Colágeno
Otros
Trombina
Plaqueta activada
Plaqueta activada
Plaqueta activada
Plaqueta activada
Plaqueta activada
Plaqueta activada
Plaqueta activada
FVW
VIII
VIIIa
FV
FVa
CELL EXTERIOR
Transverse diffusion (flip-flop)
(~10^5 sec)
Flex(~10^-9 sec)
Lateral shift
(~10^-6 sec)
CYTOSOL

Modelo celular coagulación



Complejo Tenasa

Complejo Protrombinasa "Intrínseco"



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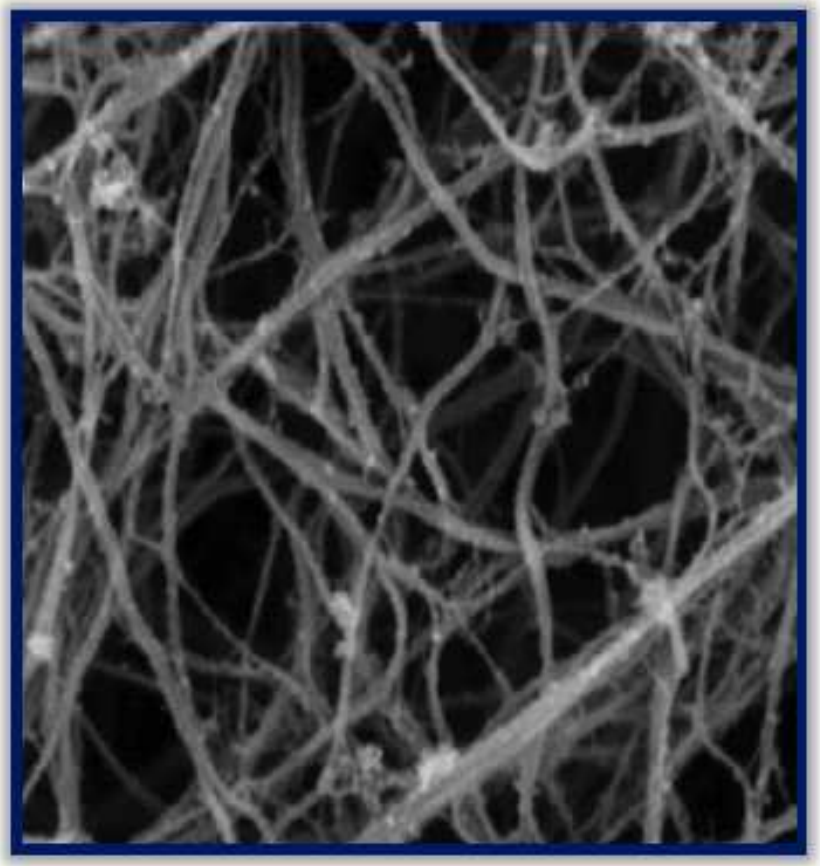
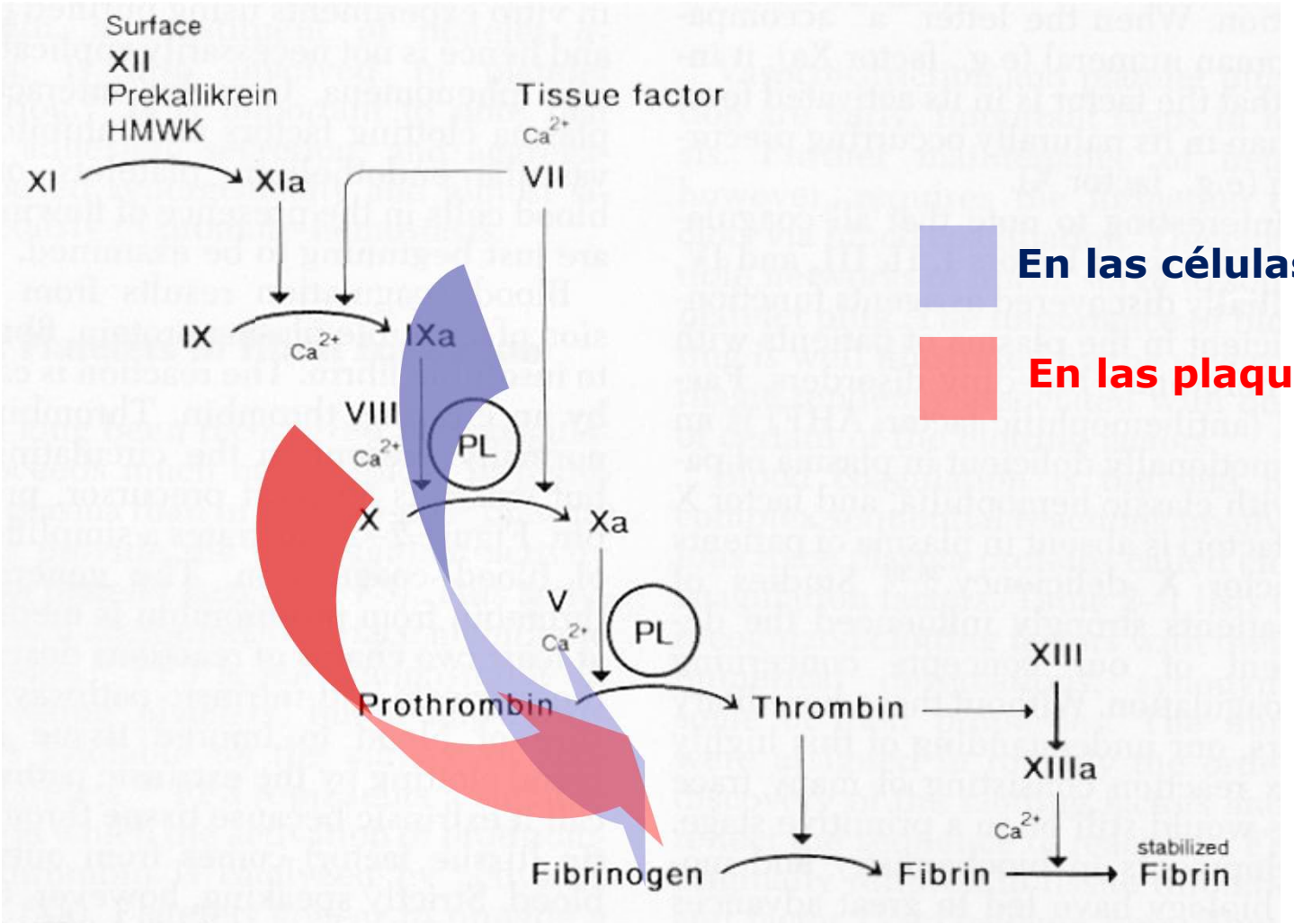
IIa

Fibrinogen





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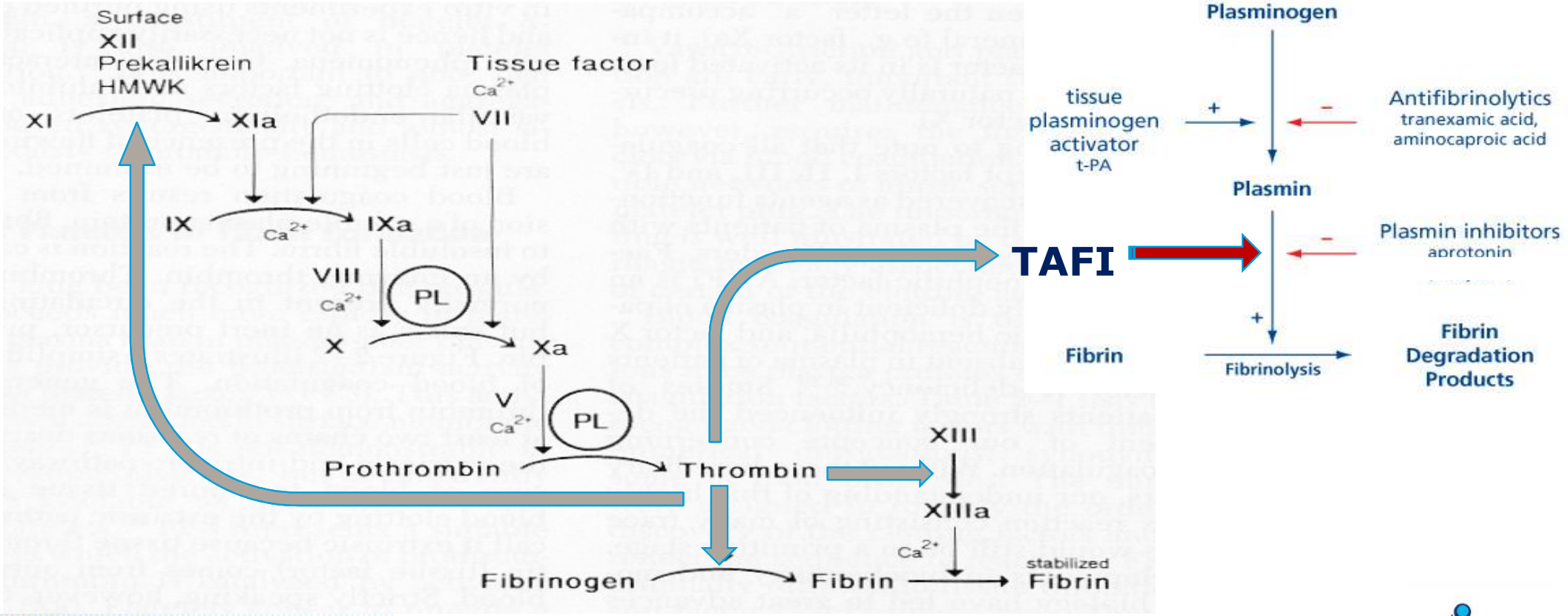

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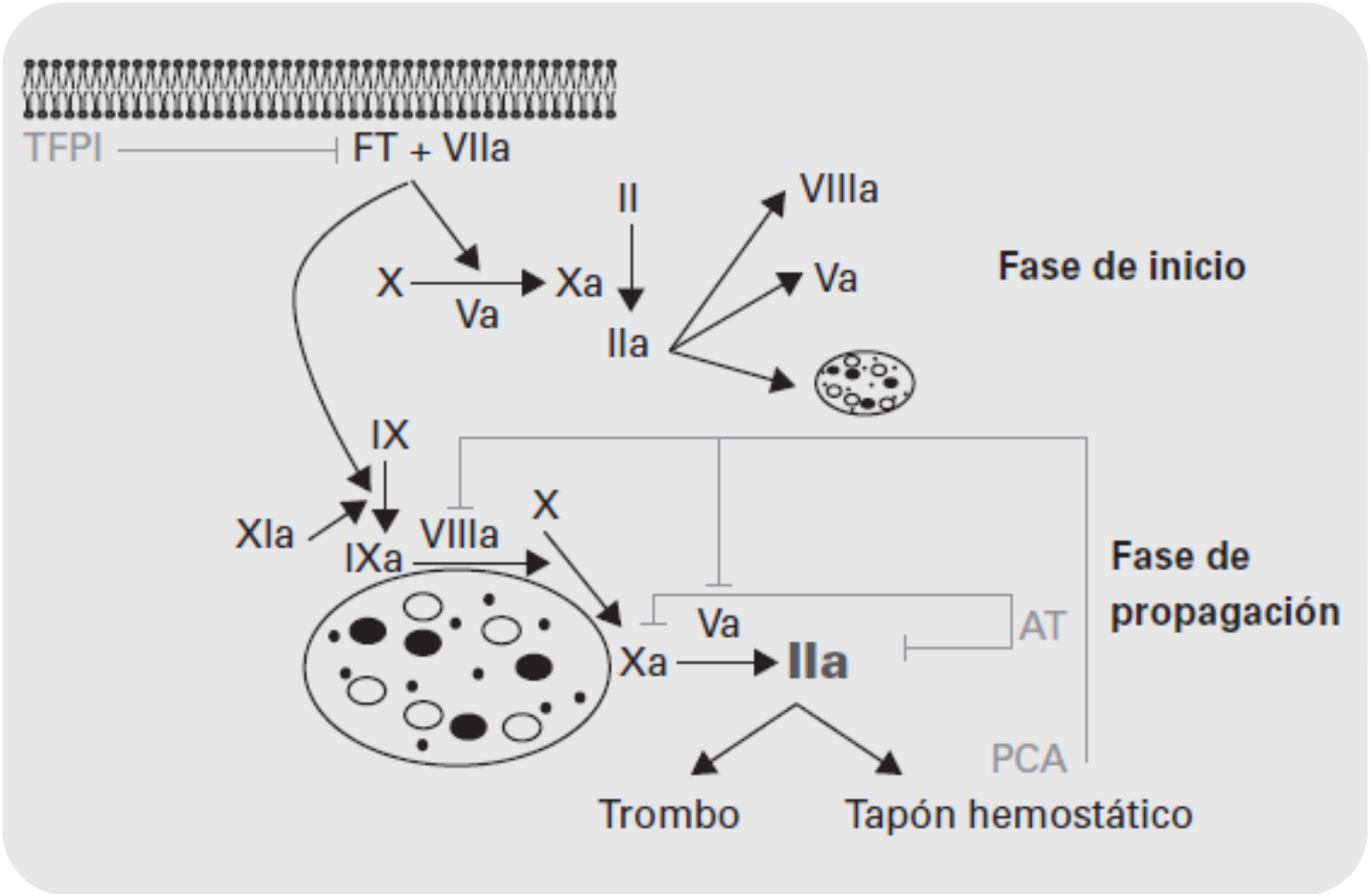
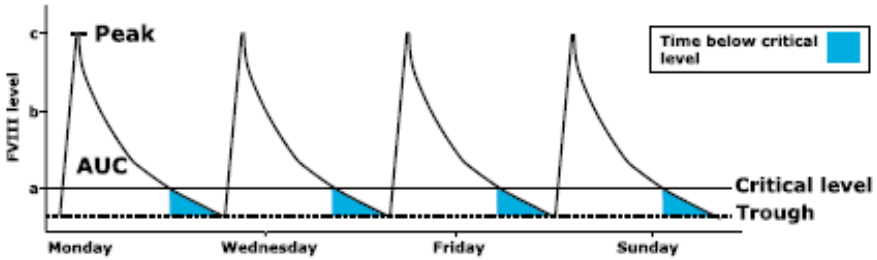
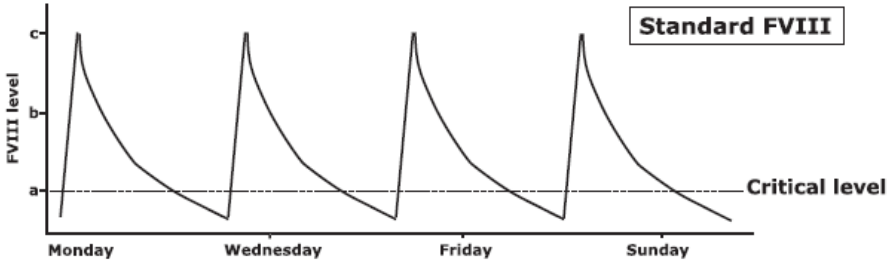
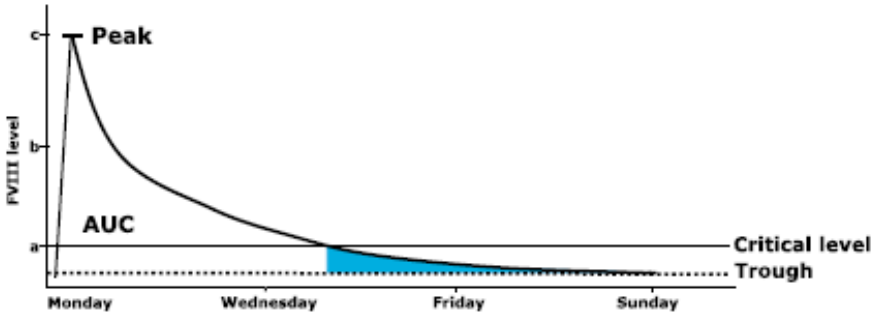


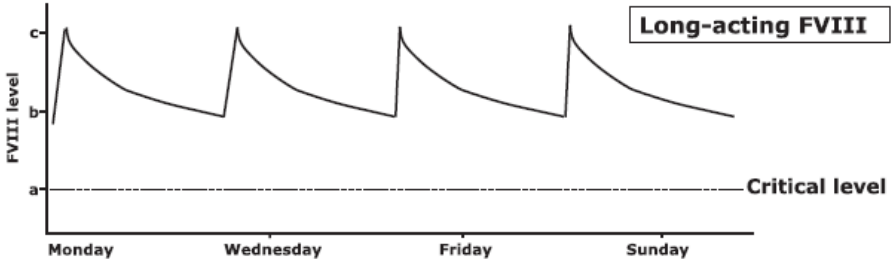
TERAPIA SUSTITUTIVA

- Plasma fresco congelado
- PCC
- Fibrinógeno
- Concentrados de factor









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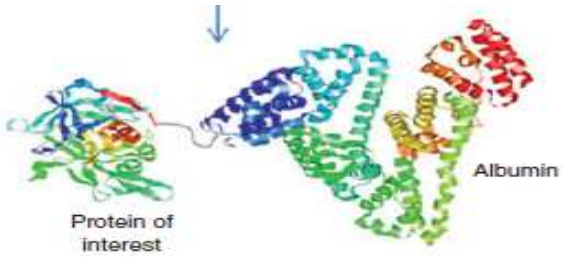
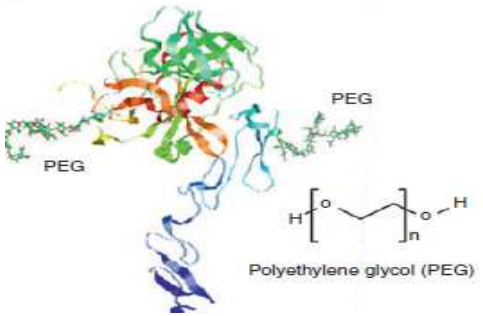
Métodos para prolongar la vida media





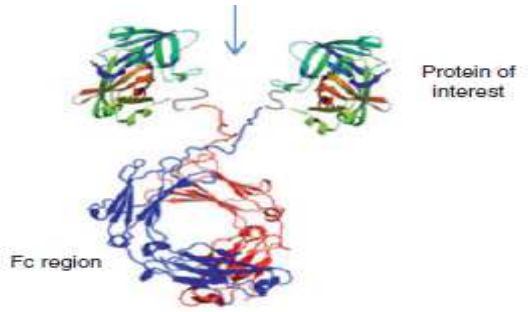
Pegilación

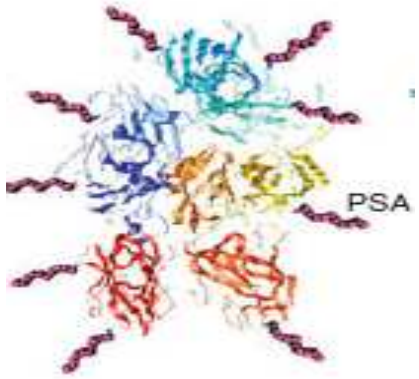
Unión a albúmina

Unión a Fc-IgG1

Unión a Ac. polisiálico

Modificación secuencia proteica





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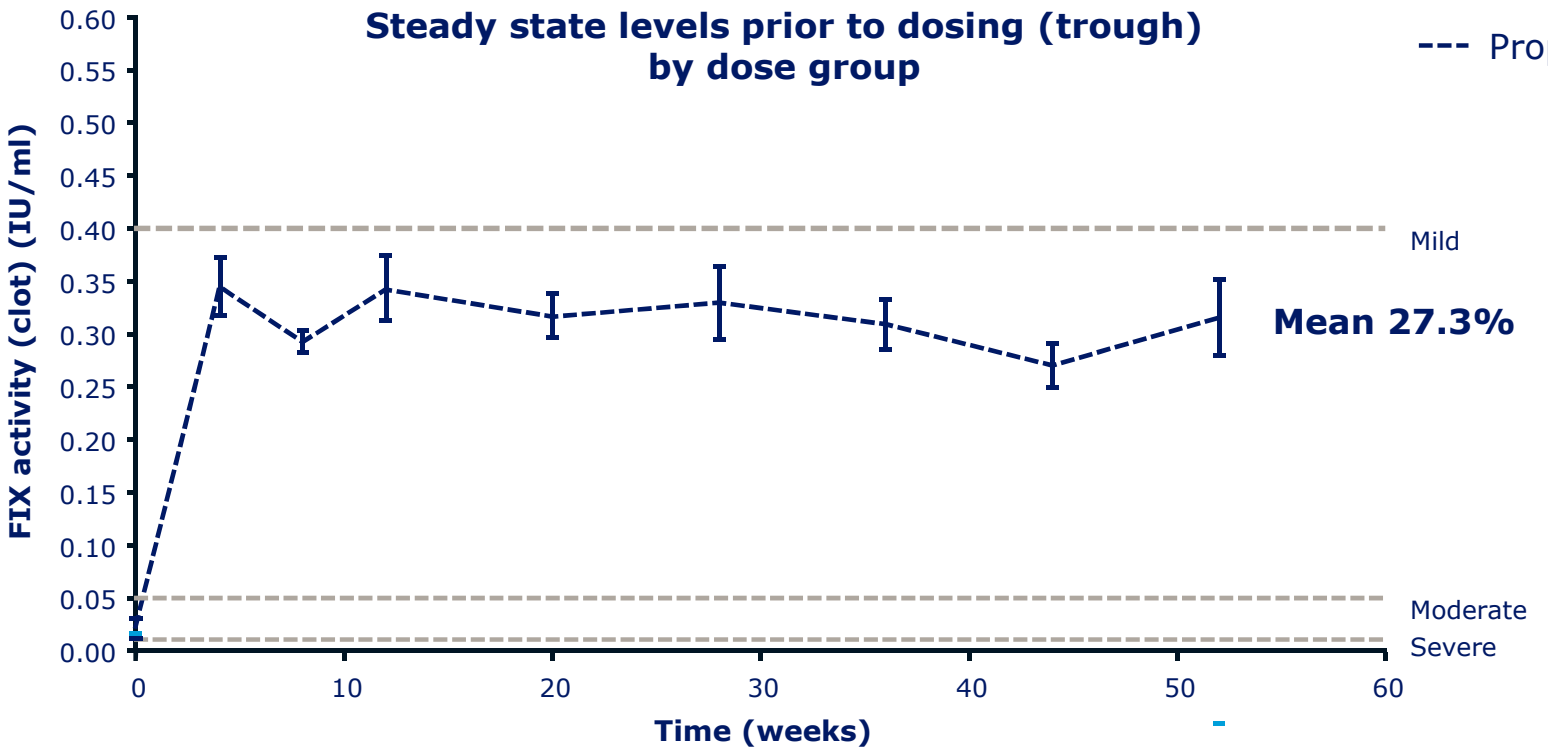
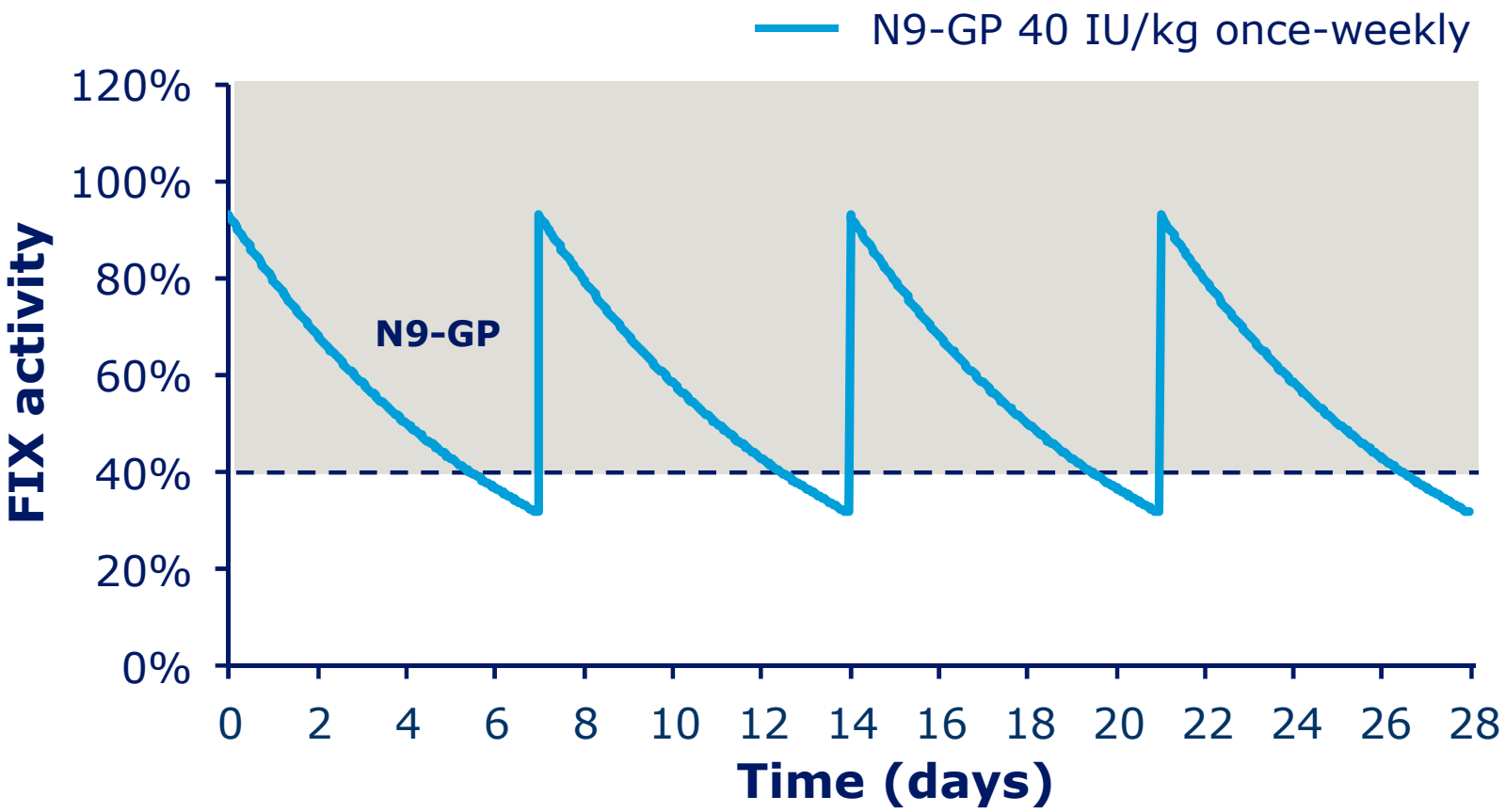

Steady state levels prior to dosing (trough) by dose group
--- Prophylaxis 40 IU/kg
FIX activity (clot) (IU/ml)
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Mild
Mean 27.3%
Moderate
Severe
0
10
20
30
40
50
60
Time (weeks)


N9-GP 40 IU/kg once-weekly
120%
100%
80%
60%
40%
20%
0%
FIX activity
N9-GP
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Time (days)

TERAPIA SUSTITUTIVA

- Plasma fresco congelado
- PCC
- Fibrinógeno
- Concentrados de factor

AGENTES BY-PASS

- rFVIIa
- PCCa
- rpFVIII

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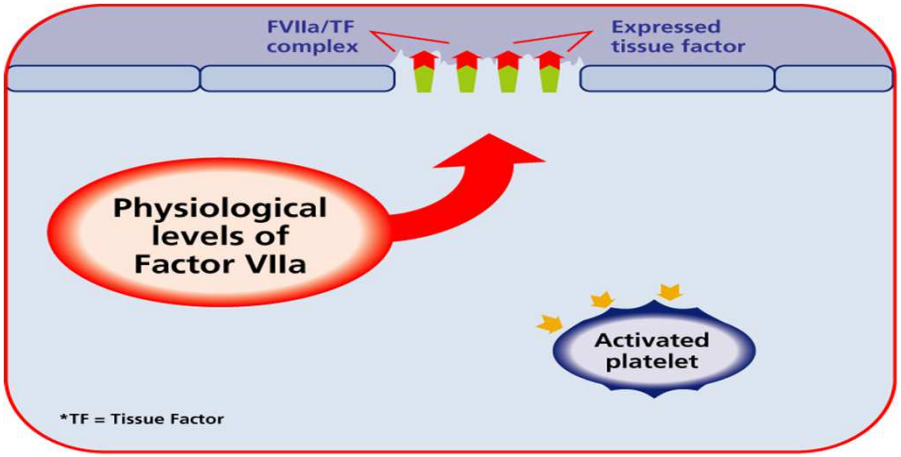
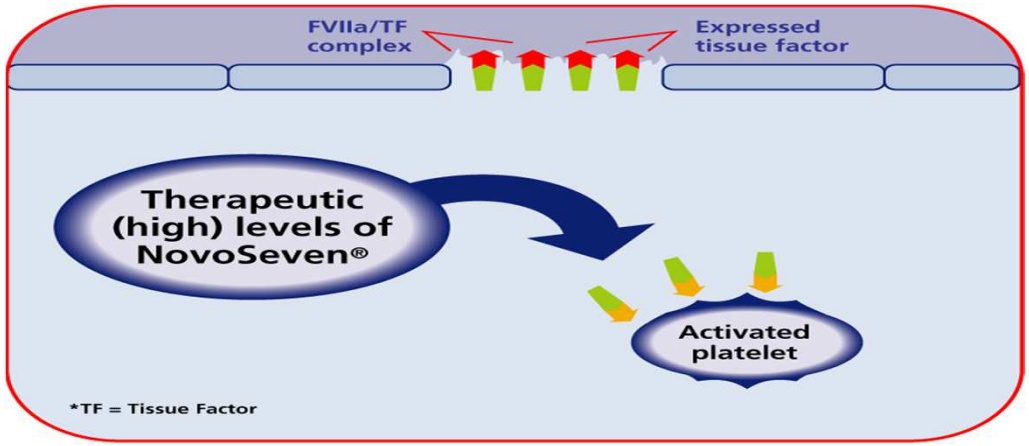
rFVIIa. Mecanismos de acción





- NovoSeven® se une al FT expuesto con gran afinidad.
- Dosis "fisiológicas"
- Mecanismo de acción sustitutivo

- Una concentración mayor activa el complejo protrombinasa intrínseco plaquetario
- Efecto by-pass con dosis "farmacológicas"
- Perfil de seguridad

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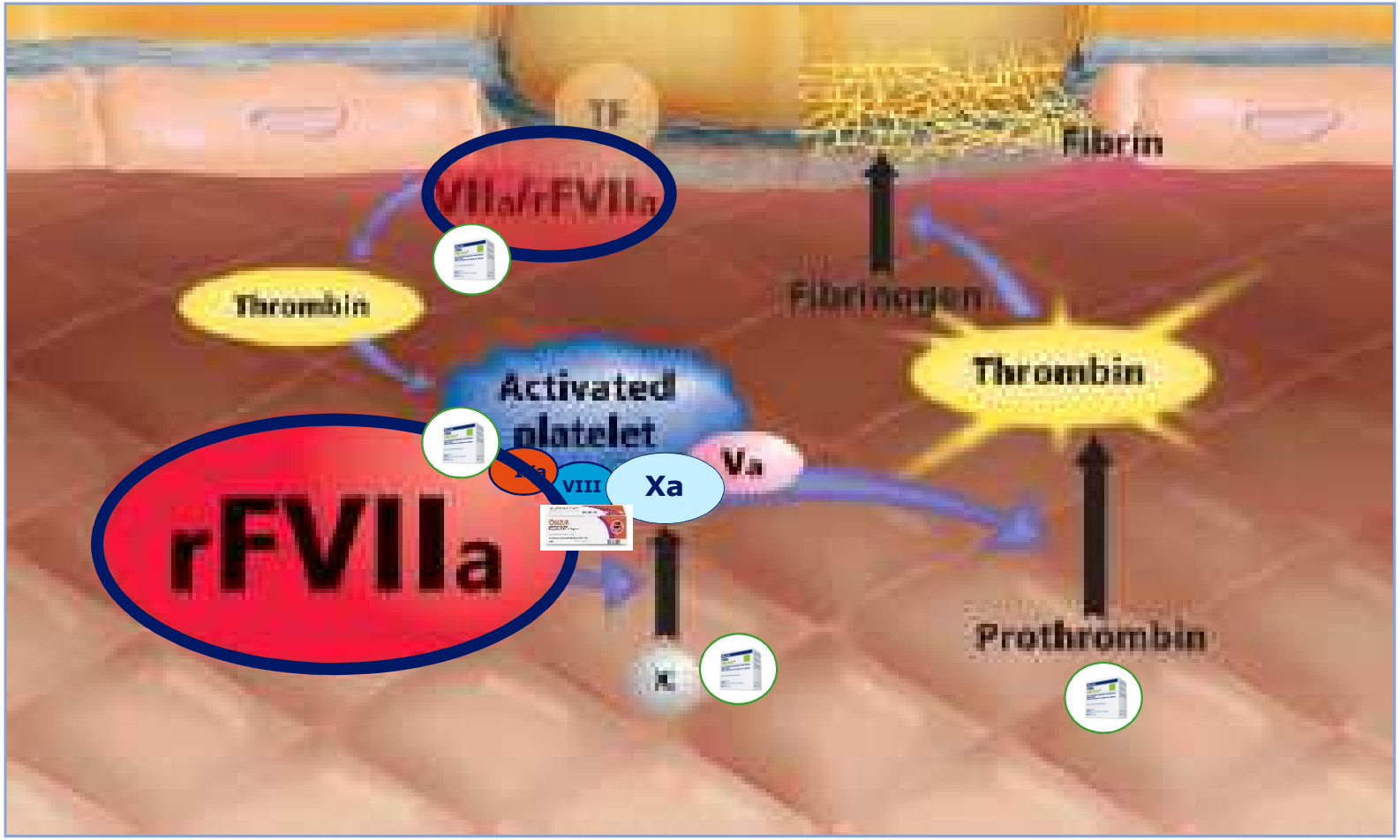

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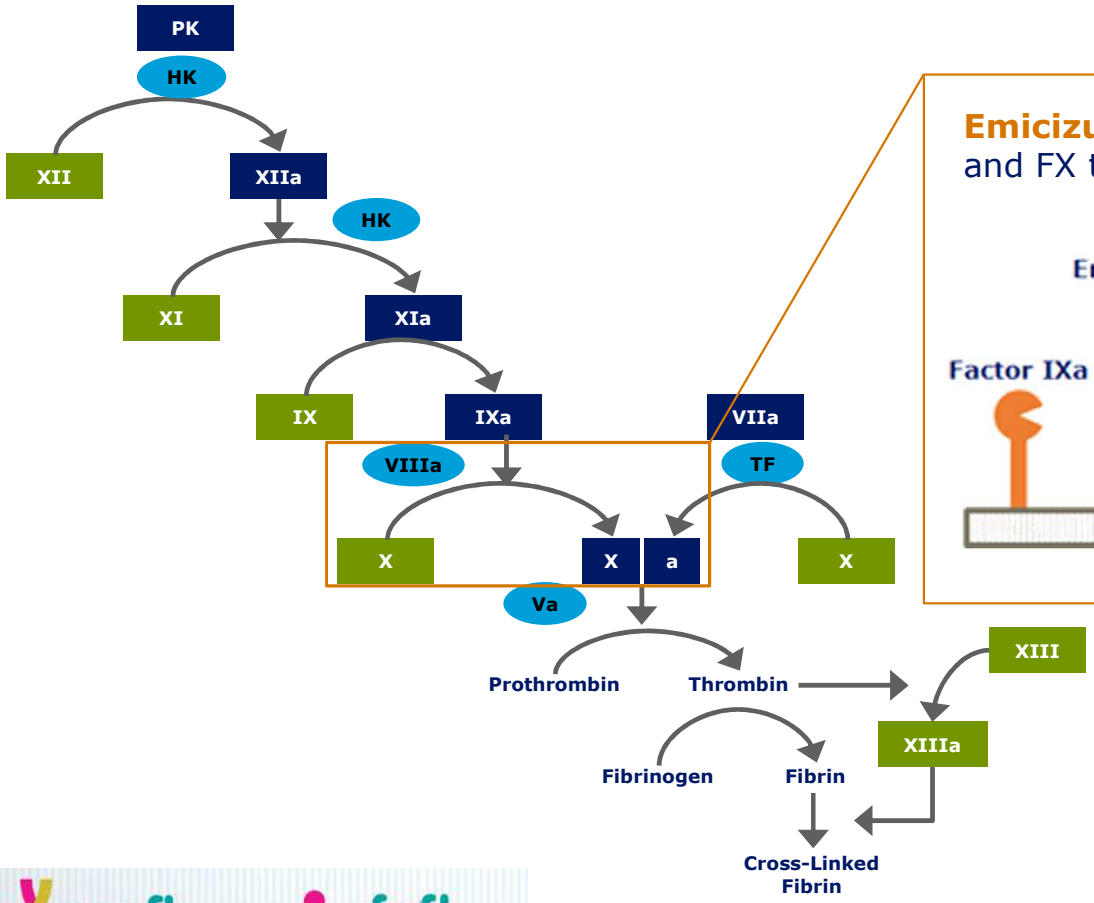
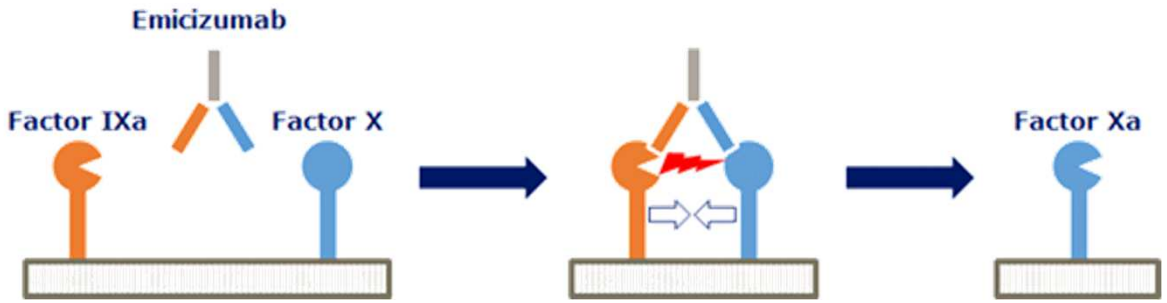
Nuevas dianas terapéuticas

Product	Company	Technology	Stage of development	Main characteristics
rFVIIa-FP	CSL Behring (Marburg, Germany)	Fusion protein with albumin	Phase II/III study ongoing	Prolonged half-life (8.5 h)
ACE910	Chugai Pharmaceuticals/La Roche Hoffman (Tokyo, Japan)	Chimeric bispecific humanized antibody	Phase I study ongoing (interim analysis published)	Prolonged half-life (2 wk) SC weekly administration reduced ABR in hemophiliacs
Concizumab	Novo Nordisk (Bagsvaerd, Denmark)	Humanized monoclonal antibody	Phase I studies (Explorer 1–3)	Prolonged half-life (31.1–74.2 h) SC or IV administration improved thrombin generation and reduced TFPI levels for ≥ 14 d in hemophiliacs
ALN-AT3	Alnylam Pharmaceuticals (Cambridge, MA)	siRNA	Phase I study (interim analysis published)	SC administration improved thrombin generation, whole blood clot formation, and reduced antithrombin levels to 20% in hemophilia patients

Pipeline haemophilia therapies: Emicizumab



Emicizumab mimics the action of FVIIIa by bridging between FIXa and FX to promote the FIXa-catalysed activation of FX.



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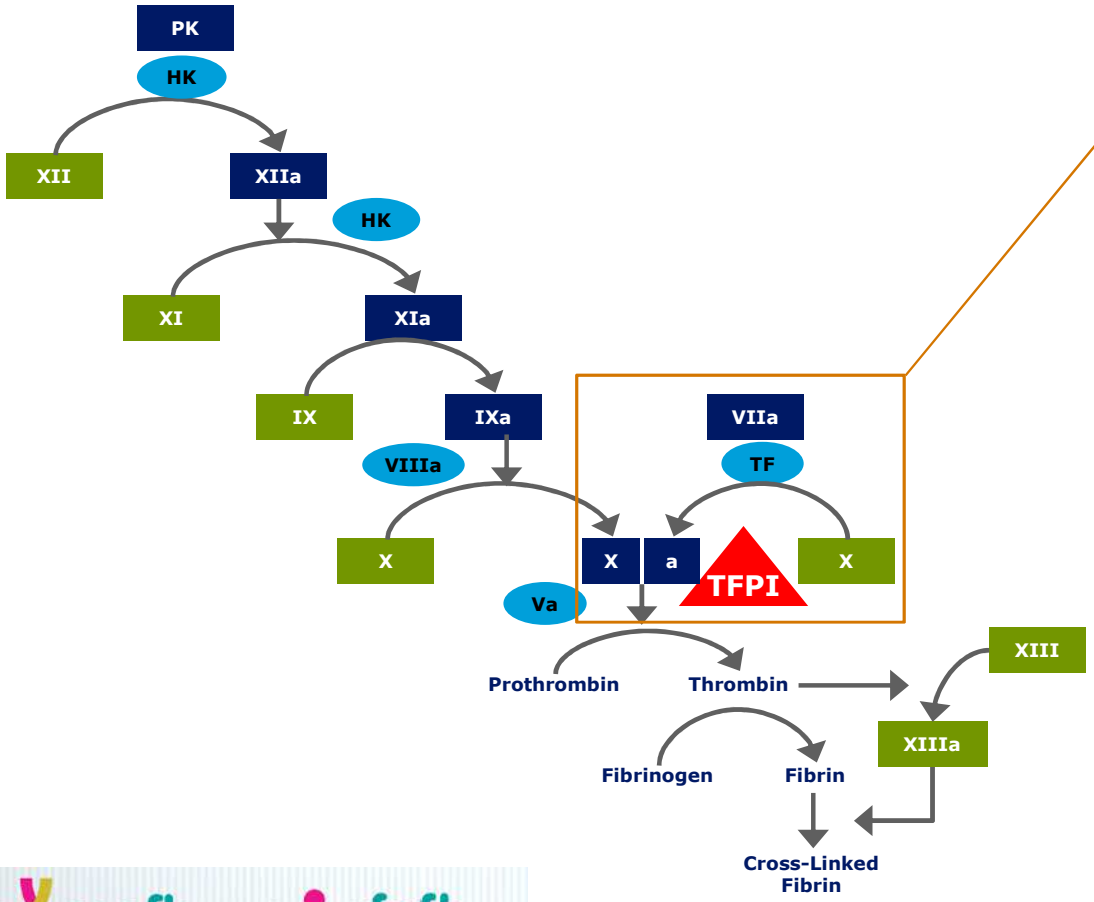
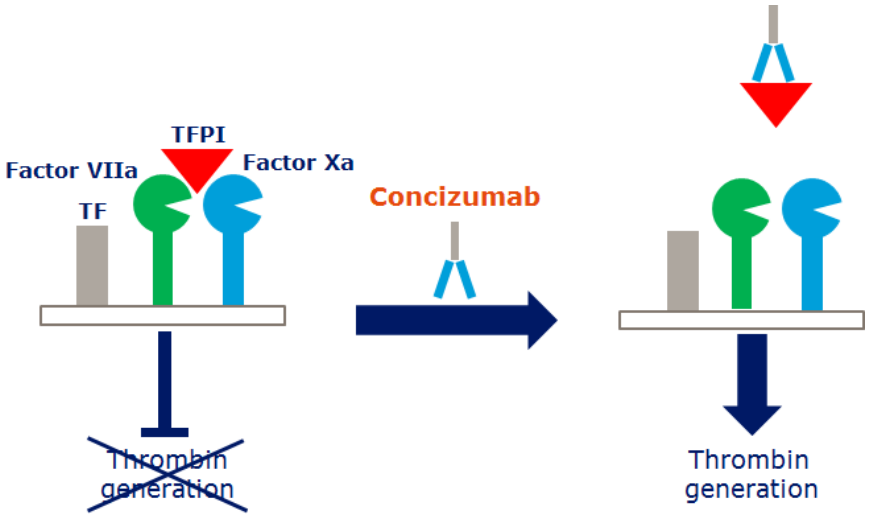
Pipeline haemophilia therapies: Concizumab



Tissue factor pathway inhibitor (TFPI) can reversibly inhibit FXa and subsequently the FVIIa-TF complex.

Concizumab inhibits TFPI, allowing sufficient thrombin generation to overcome a deficit in FVIII or FIX.



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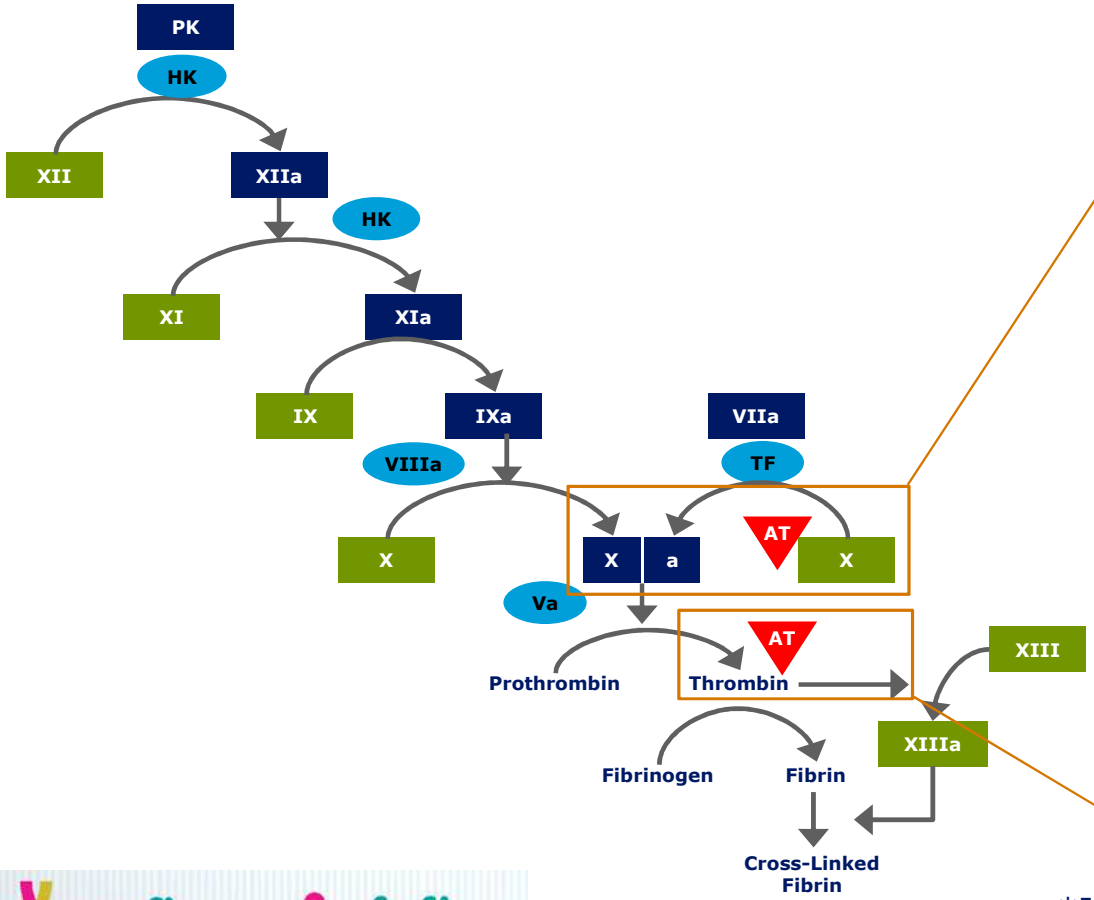
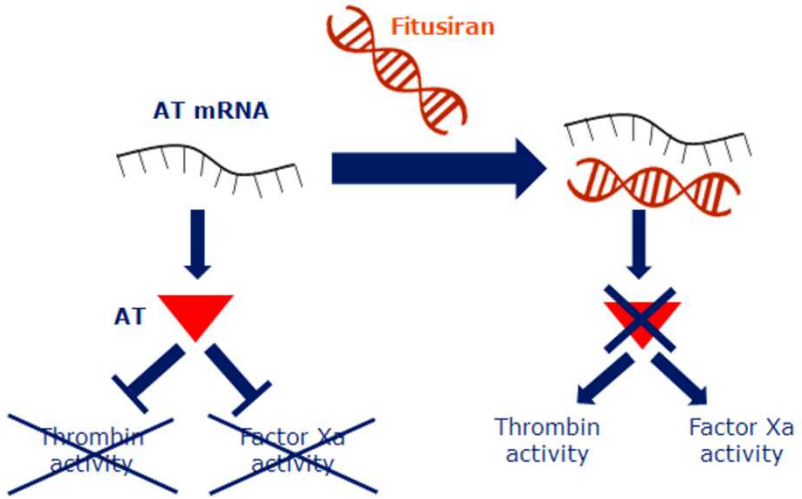
Pipeline haemophilia therapies: Fitusiran*



Antithrombin (AT) inhibits the activity of thrombin and FXa to regulate blood coagulation.

Fitusiran is a small interfering RNA (siRNA) therapeutic that blocks production of AT. Reduced levels of AT promote thrombin generation to restore haemostasis and prevent bleeding.



*In September 2017 the fitusiran clinical development plan was suspended due to a patient suffering a fatal thrombotic event. The suspension was lifted in December 2017.

Nuevas dianas terapéuticas

^{super}FVa	–	Bioengineered FVa variant	Preclinical phase	Increased thrombin generation in acquired hemophilia models Synergistic effect with rFVIIa
FXa^{I16L}	–	Bioengineered zymogen-like FXa variant	Preclinical phase	Longer lasting plasma activity than wild-type FXa (60 min Vs. 1 min) Increased thrombin generation in hemophilia models

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Merry Christmas for Patients with Hemophilia B

Katherine P. Ponder, M.D.

GRACIAS

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