

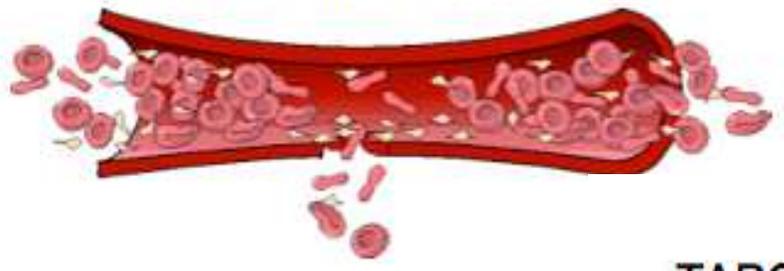
Dianas terapéuticas en la hemostasia

Juan Gracia

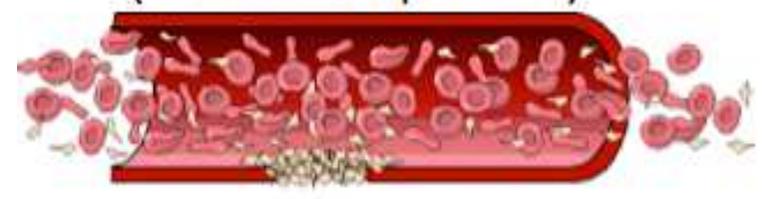
Madrid, 14 Marzo 2017



ESPASMO VASCULAR



TAPON PLAQUETARIO (Hemostasia primaria)

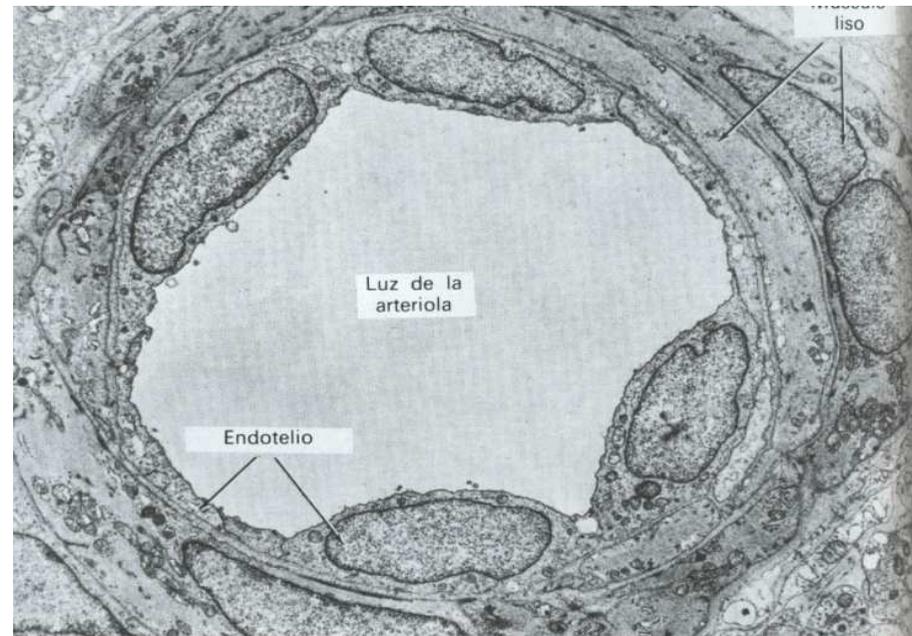


FIBRINOLISIS

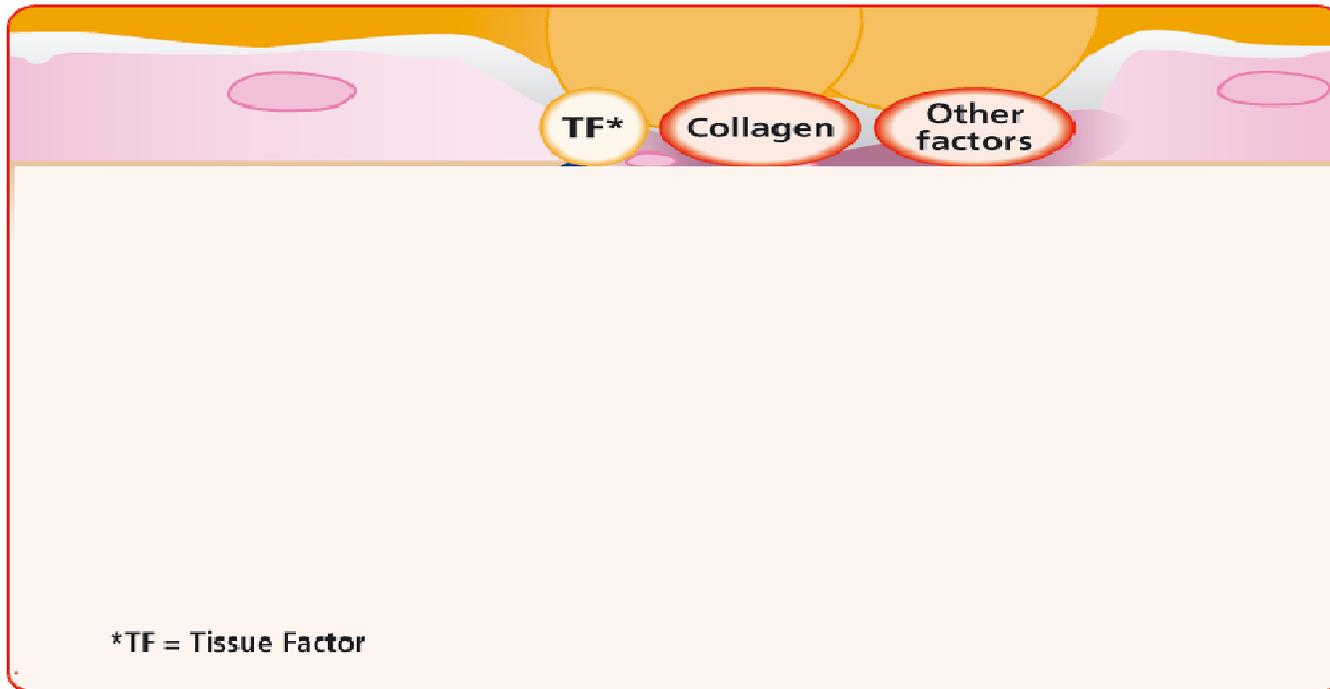


El endotelio: envoltura anti-hemostática

- Mecanismo físico
 - Carga eléctrica negativa
- Mecanismos químicos
 - Sustancias antiagregantes: prostaciclina, ON, ADPasa
 - Sustancias anticoagulantes: heparán sulfato, PC, TFPI
 - Profibrinolíticos: t-PA

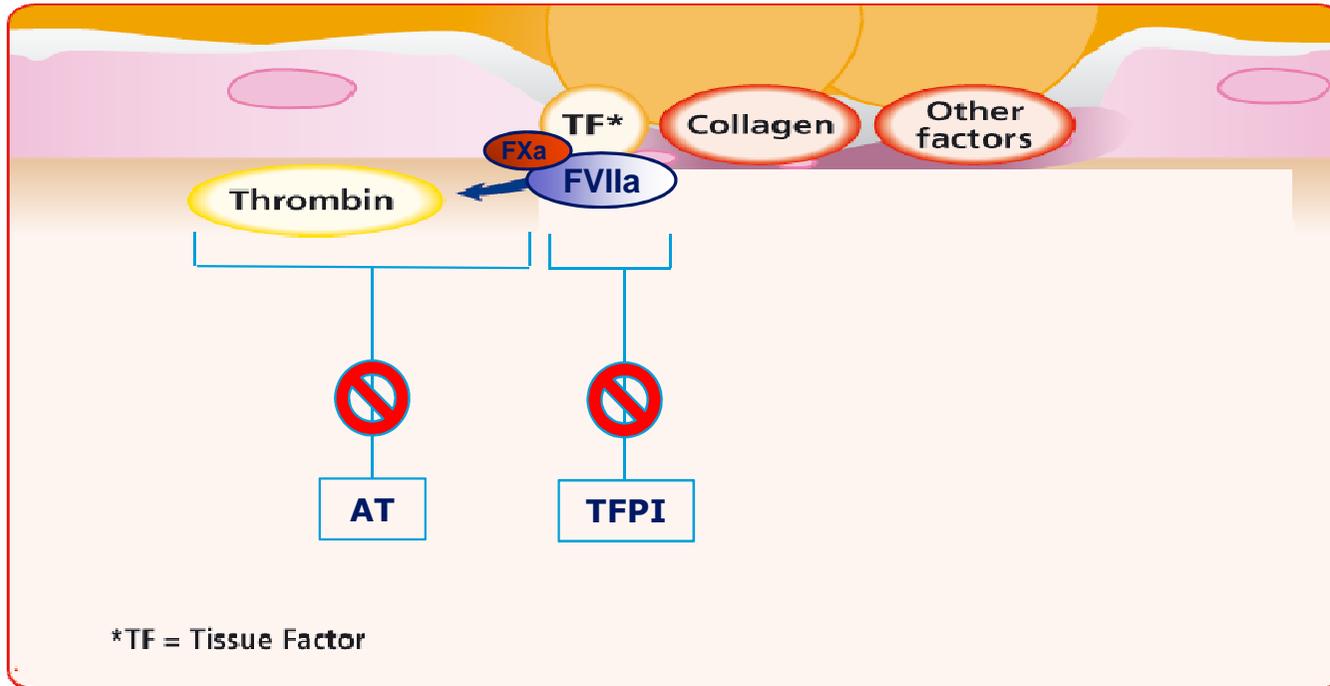


El subendotelio garantiza la hemostasia local



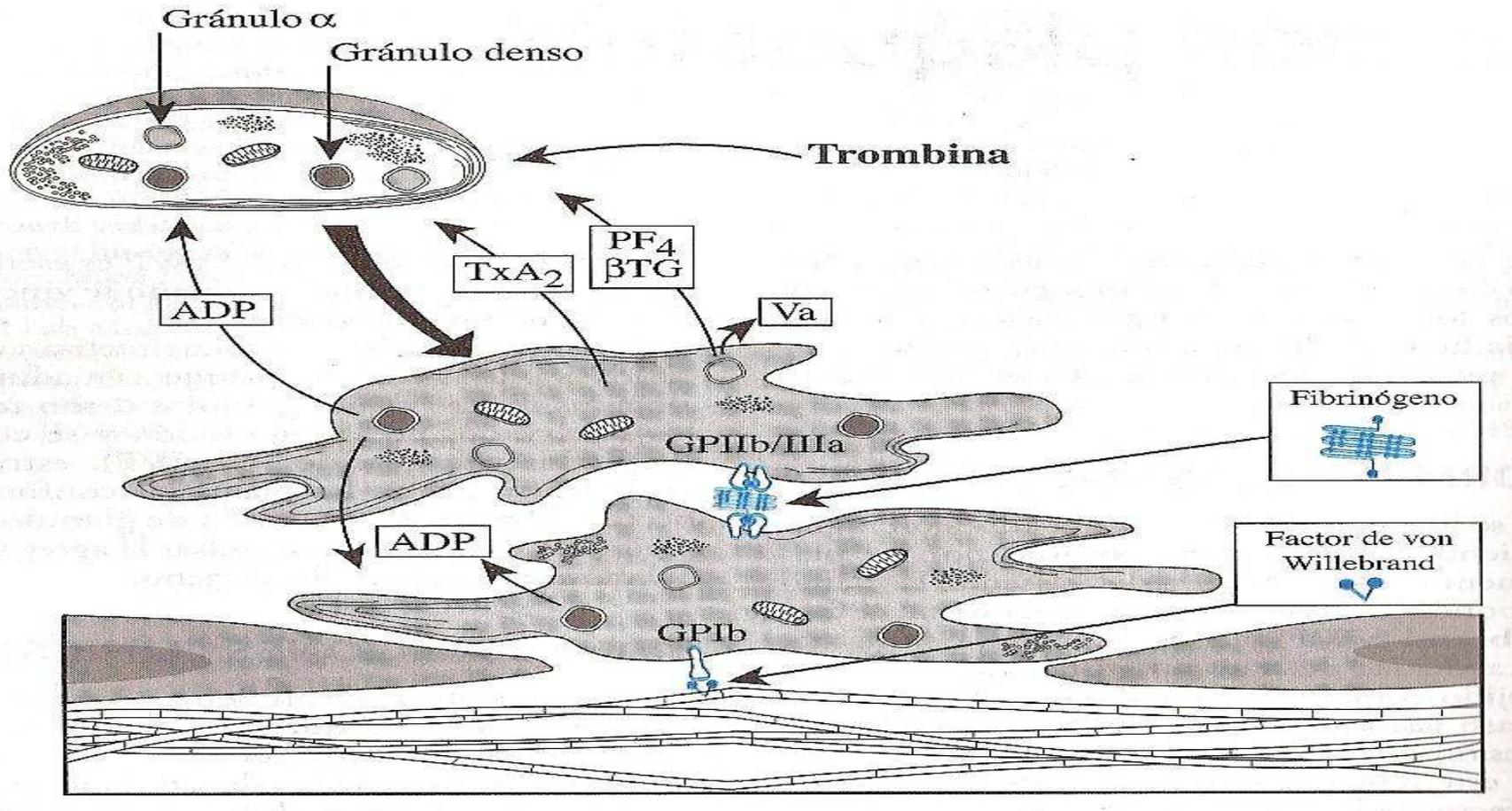
- El subendotelio es expuesto a la circulación

El subendotelio garantiza la hemostasia local

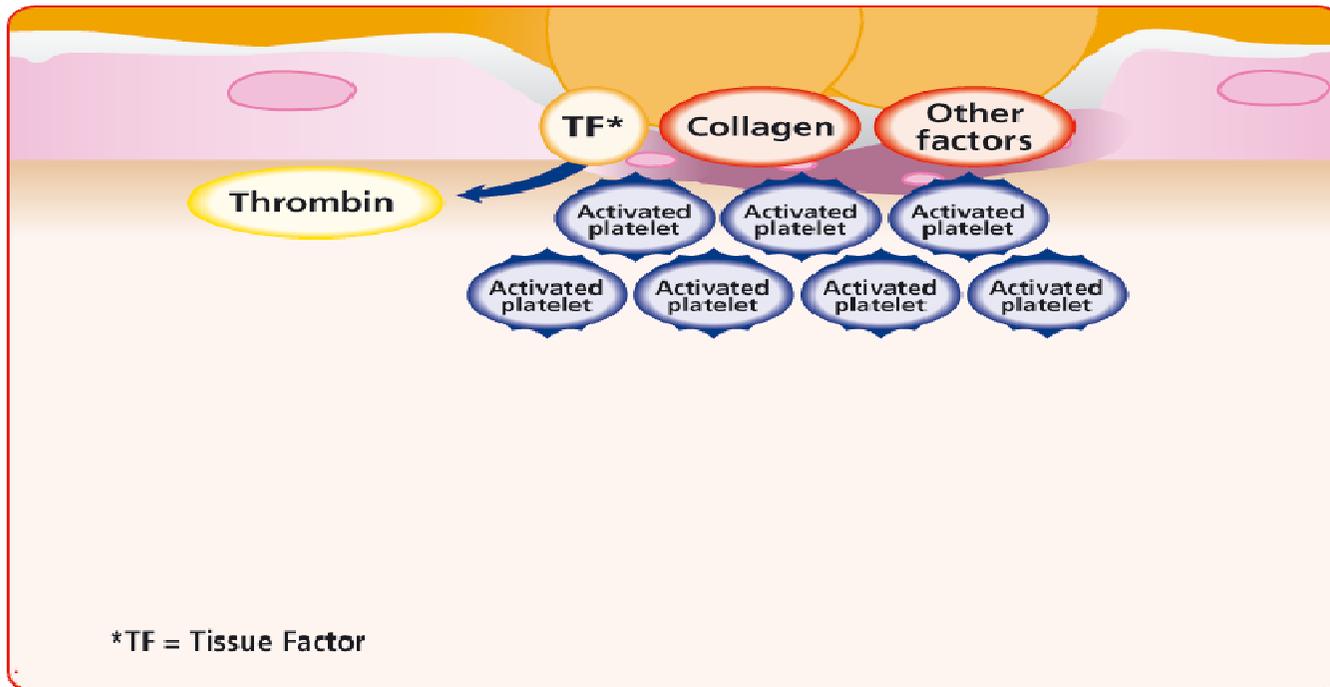


- El subendotelio es expuesto a la circulación
- Trombina

Activación plaquetar

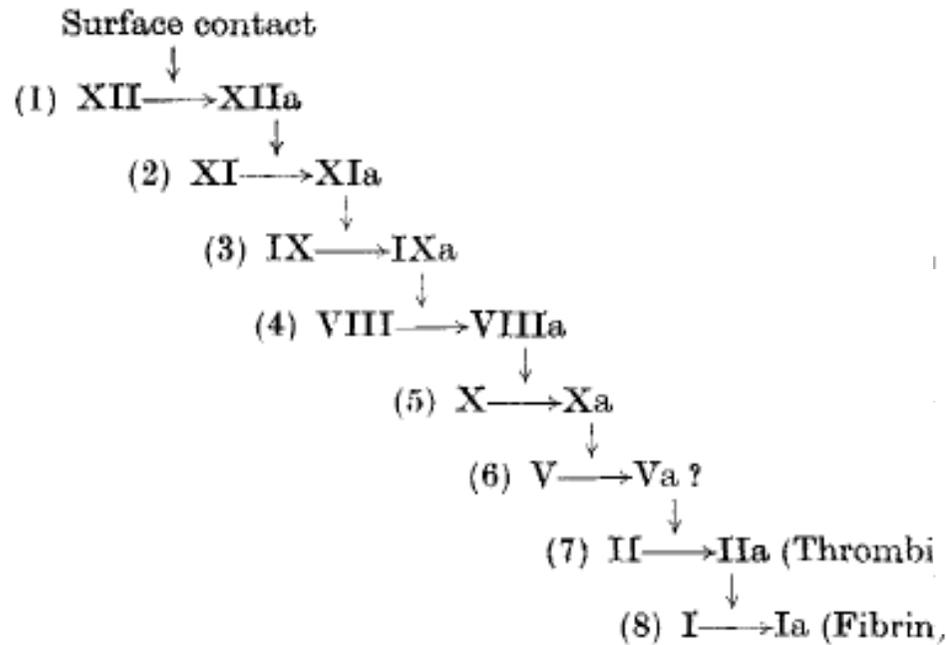


Hemostasia primaria

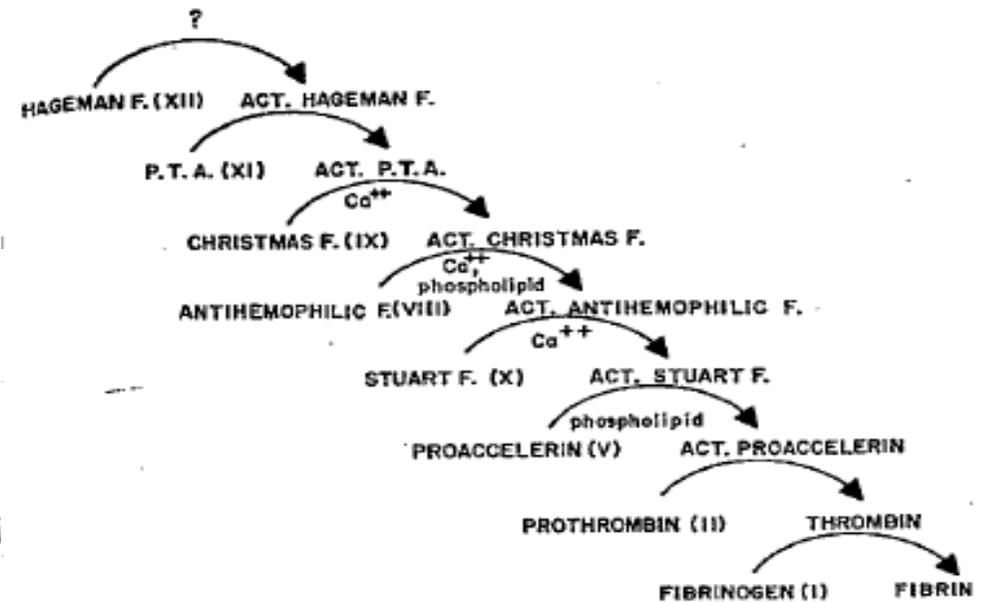


- El subendotelio es expuesto a la circulación
- Las plaquetas se adhieren al lugar de la lesión
- Las plaquetas se agregan para formar un trombo plaquetario

“Cascade, Waterfall Model of Coagulation”



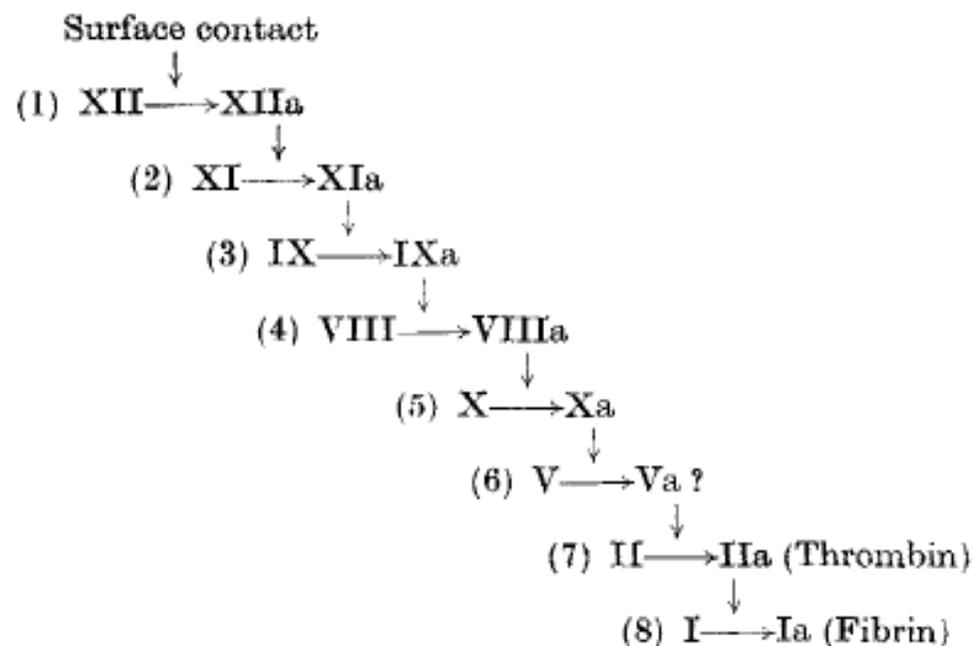
MacFarlane. *Nature* 1964, Vol 202; 498-499



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



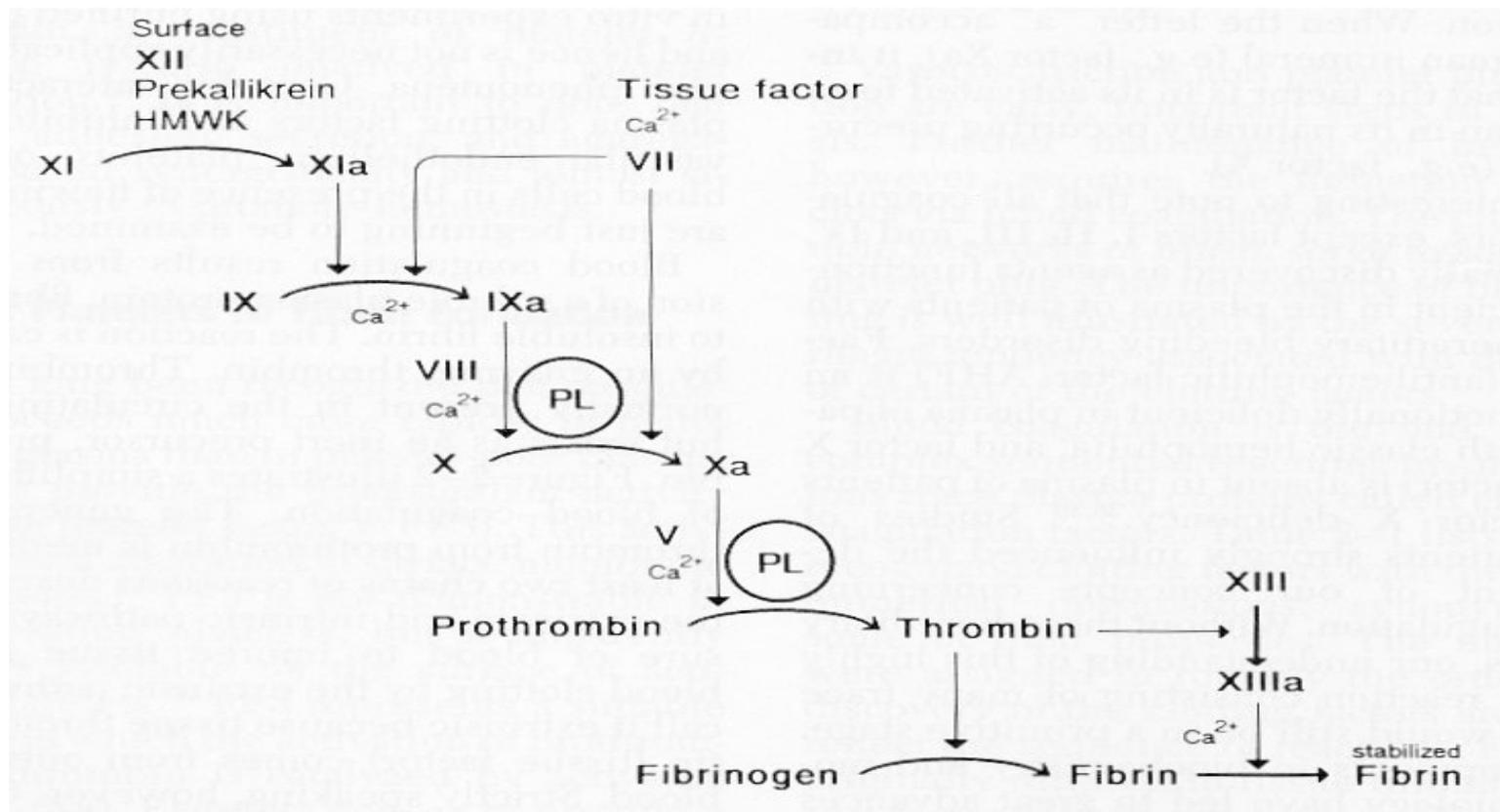
“Cascade, Waterfall Model of Coagulation”



“but the puzzle remained”

- Los pacientes con déficit de sistema de contacto no sangran
- Los pacientes con déficit de FVII sangran
- El FT juega un papel predominante en el inicio de la coagulación
- El complejo VIIa/FT es un potente activador del X
- Entonces ¿por qué sangran los hemofílicos?

“Cascade, Waterfall Model of Coagulation”



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

Modelo celular de la coagulación

Thromb Haemost 2001; 85: 958-65

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Review Article

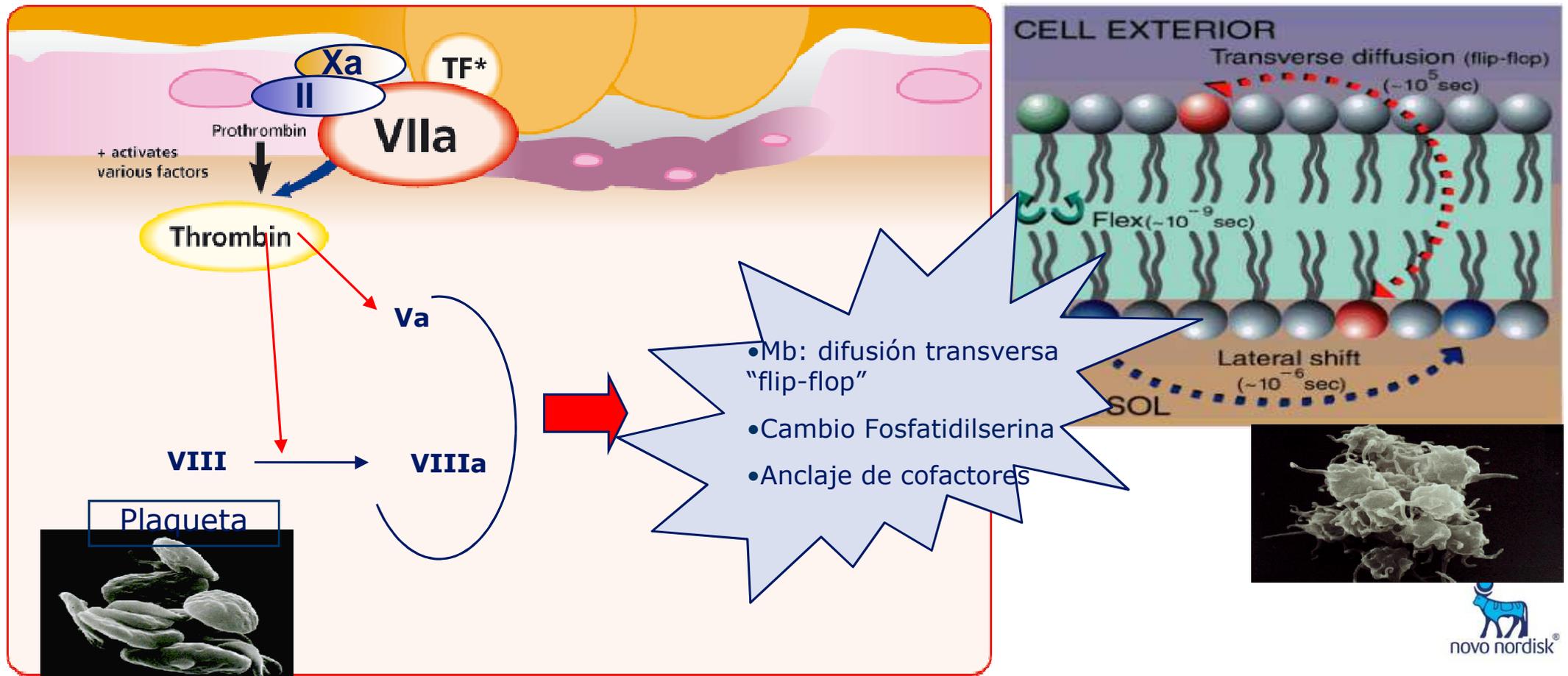
A Cell-based Model of Hemostasis

Maureane Hoffman, Dougald M. Monroe III

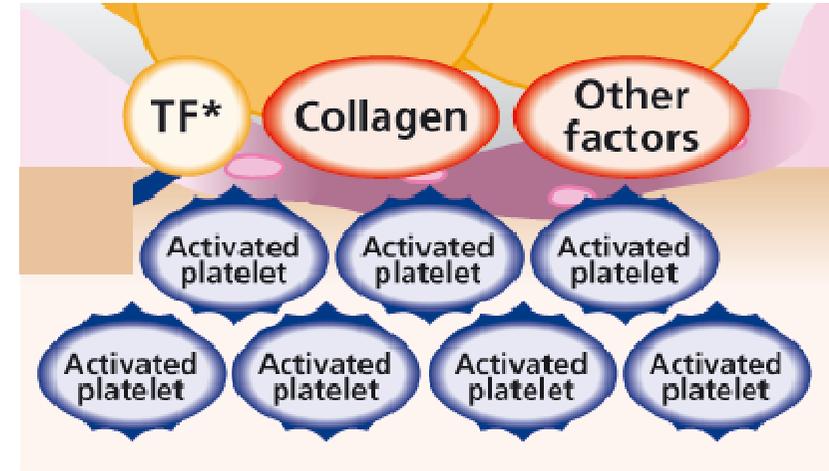
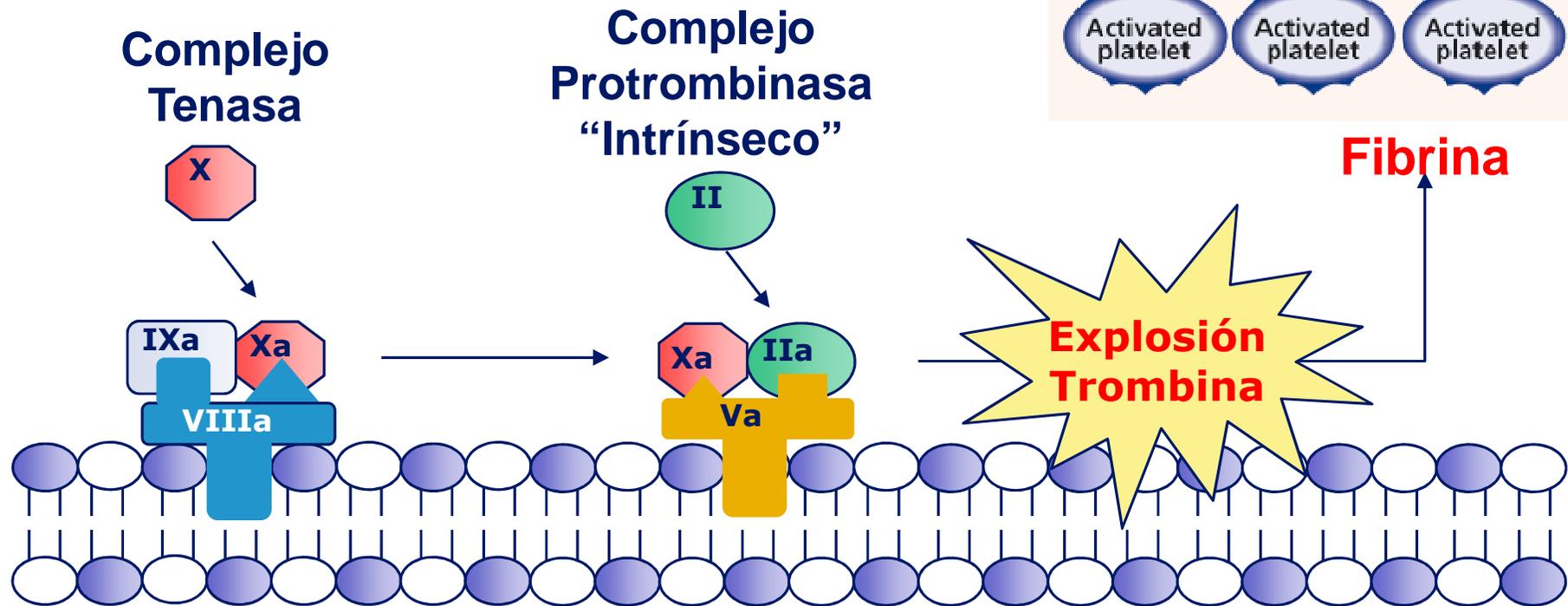
Pathology and Laboratory Medicine Service, Durham VA and Duke University Medical Centers,
Durham, NC, USA, and Division of Hematology/Oncology, Department of Medicine,
The University of North Carolina, Chapel Hill, NC, USA

- Complejo factor tisular-VIIa
- Superficies celulares

Modelo celular de la coagulación



Modelo celular coagulación



2 ideas importantes



Seminars in
HEMATOLOGY



Platelet Tissue Factor: How Did It Get There and Is It Important?

Nigel S. Key

Recently, the presence of functionally active tissue factor (TF) in platelets has been reported by several groups. In this location, TF is postulated to play an important role in the propagation phase of thrombus formation. Although the existence of platelet TF still remains controversial to some extent, a review of the current literature proposes at least three distinct sources of "platelet-associated TF" in those laboratories that have reported its presence: (1) TF that is taken up in the form of circulating microparticles, usually derived from monocytes; (2) TF stored in the α -granules of platelets that may have been taken up and/or endogenously synthesized; and (3) TF that is synthesized and expressed on the plasma membrane of mature platelets. These pathways are not mutually exclusive, and the dominant mechanism may depend on the state of platelet activation and, possibly, on other host factors that differ in physiological hemostasis versus pathological thrombosis. This brief review will summarize the state-of-the-art understanding on the origins and possible role of platelet TF.

Semin Hematol 45(suppl 1):S16-S20 © 2008 Elsevier Inc. All rights reserved.

Otras acciones de la trombina

Journal of Thrombosis and Haemostasis, 1: 1504–1514

REVIEW ARTICLE

What is all that thrombin for?

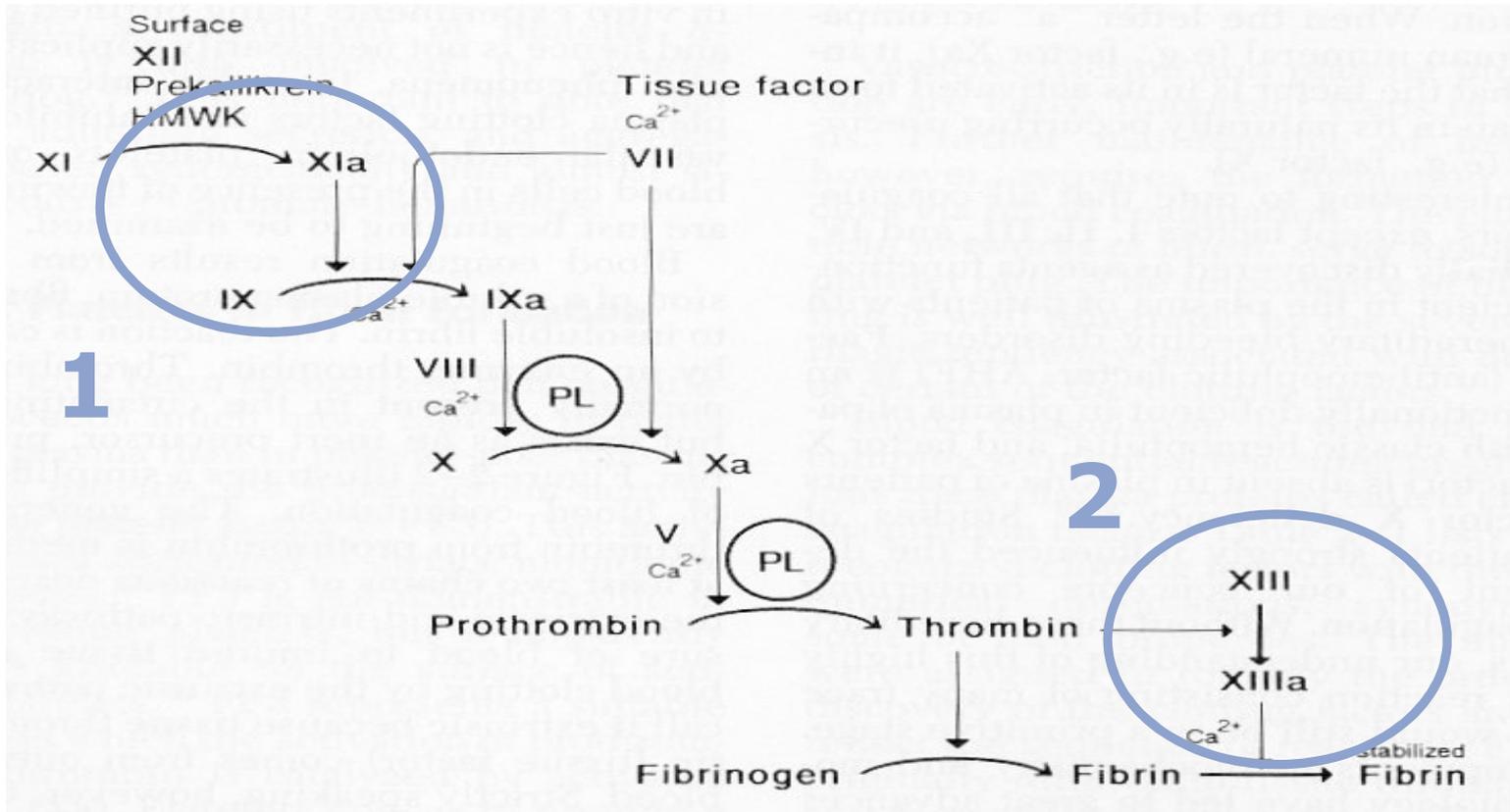
K. G. MANN, K. BRUMMEL and S. BUTENAS

Department of Biochemistry, University of Vermont, College of Medicine, Burlington, VT, USA

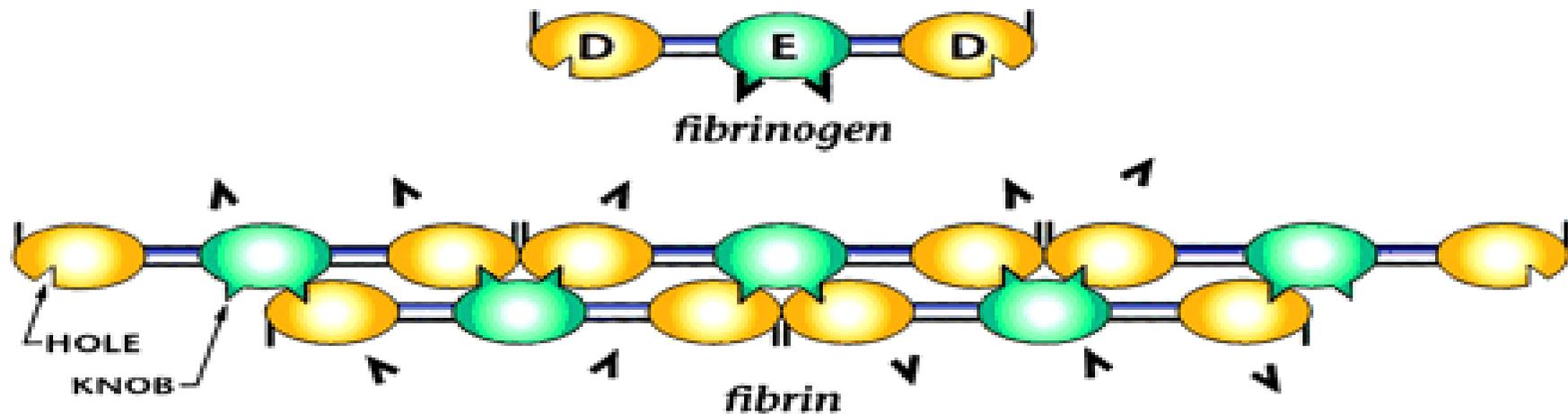
To cite this article: Mann KG, Brummel K, Butenas S. What is all that thrombin for? *J Thromb Haemost* 2003; 1: 1504–14.

- La formación de fibrina ocurre al inicio de la fase de propagación, cuando la explosión de trombina en la superficie plaquetaria está tan solo empezando
- >95% de la trombina se genera tras la formación del coágulo
- La trombina tiene otras acciones

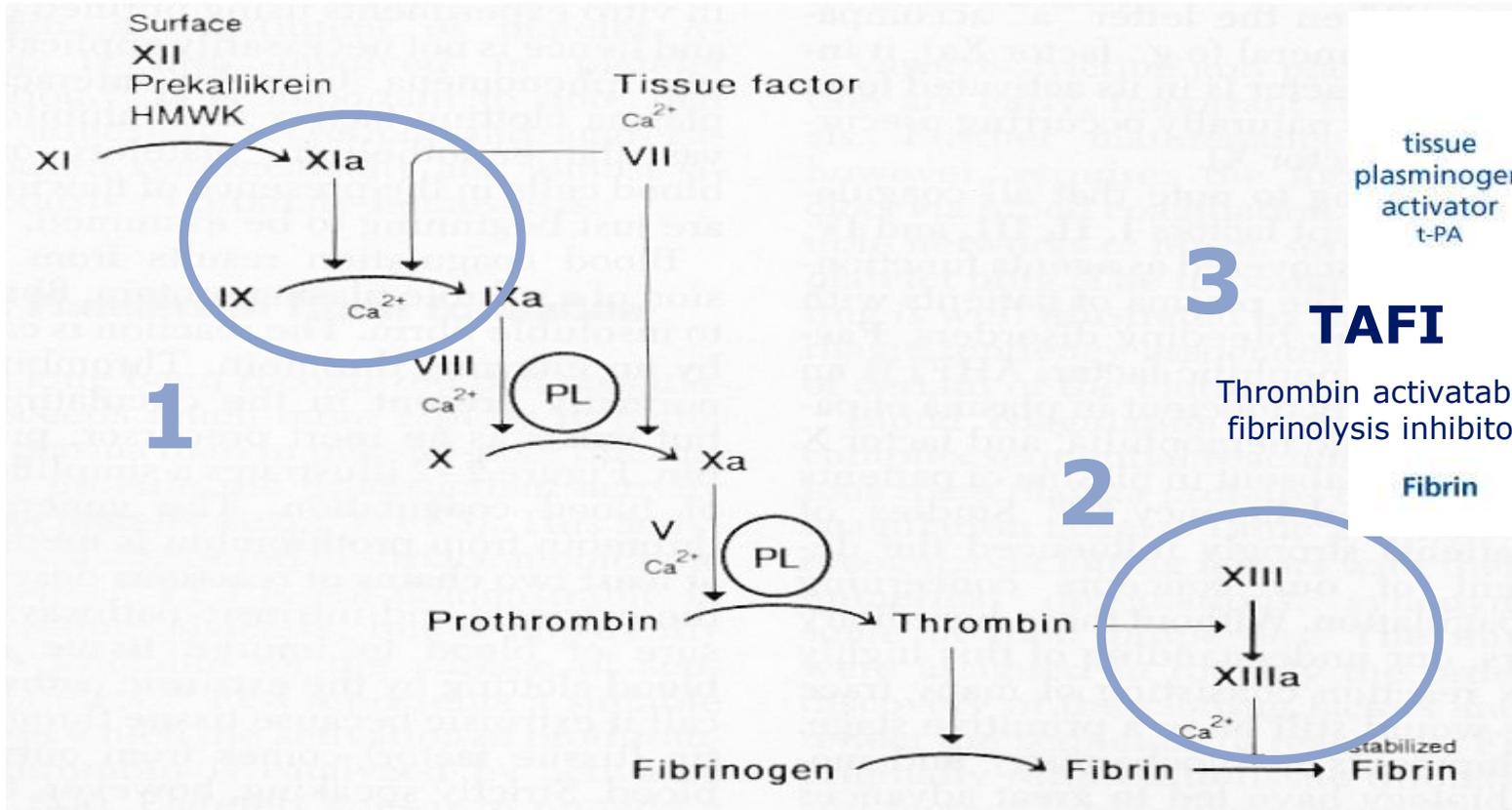
Modelo celular de la coagulación



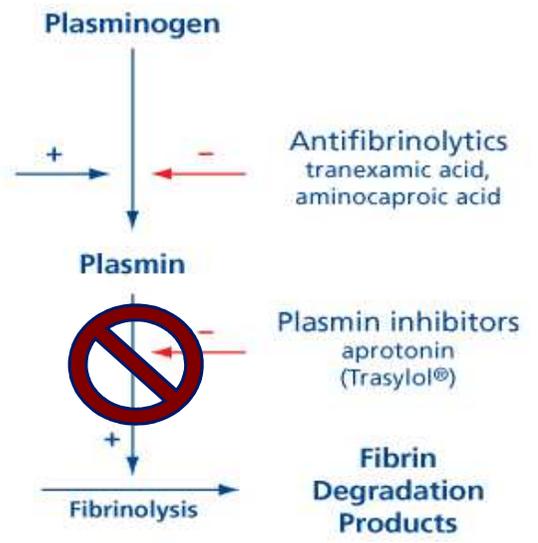
FXIII: Estabilizador de fibrina



Modelo celular de la coagulación



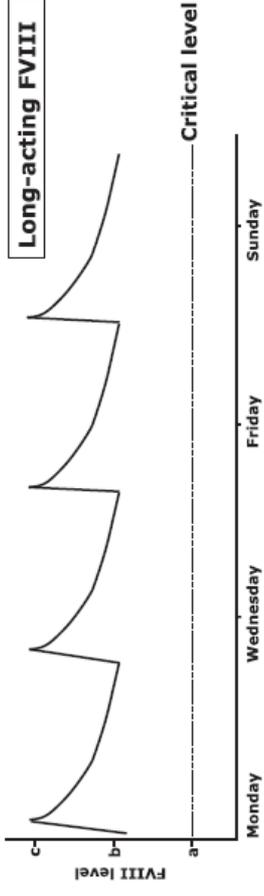
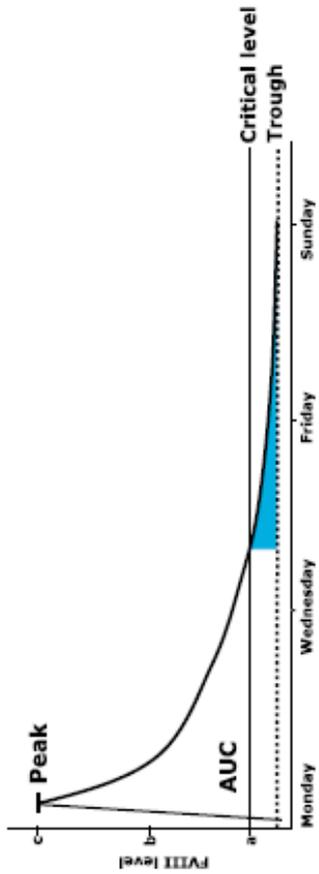
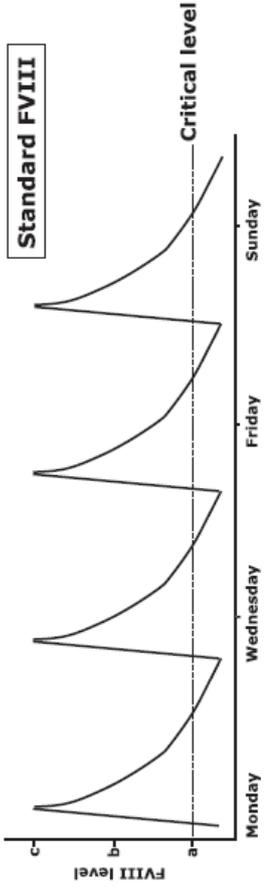
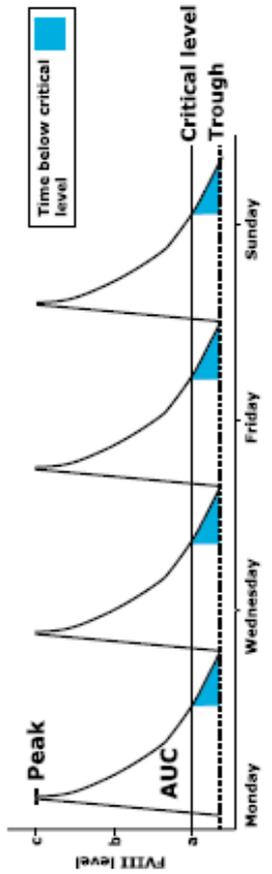
3
TAFI
Thrombin activatable
fibrinolysis inhibitor





TERAPIA SUSTITUTIVA

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



Métodos para prolongar la vida media

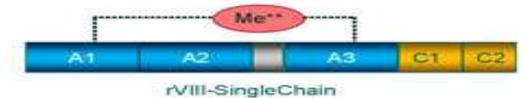
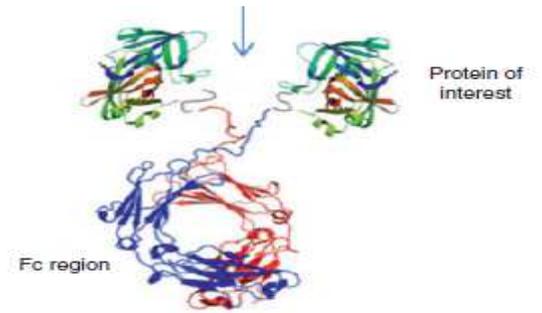
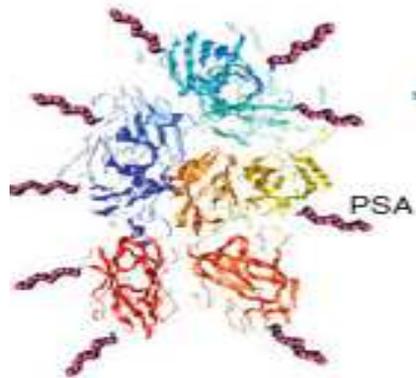
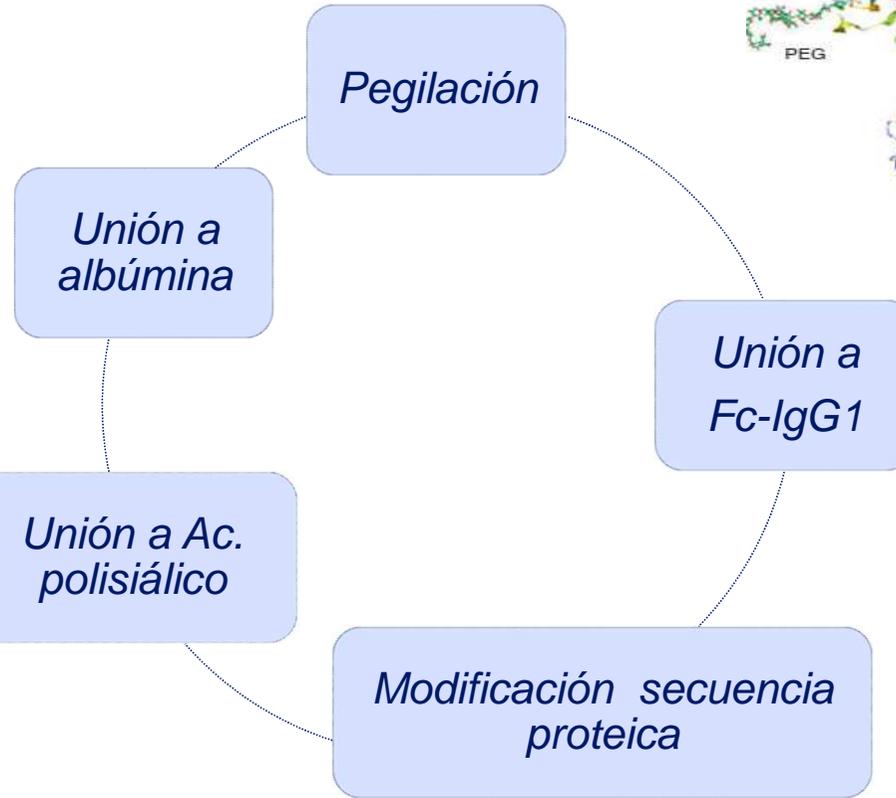
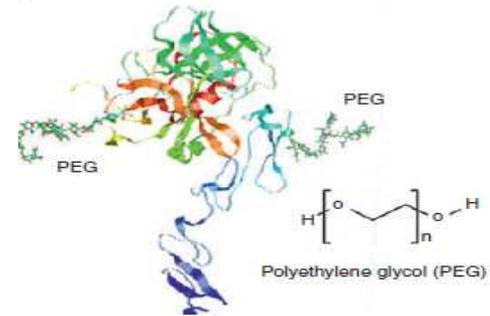
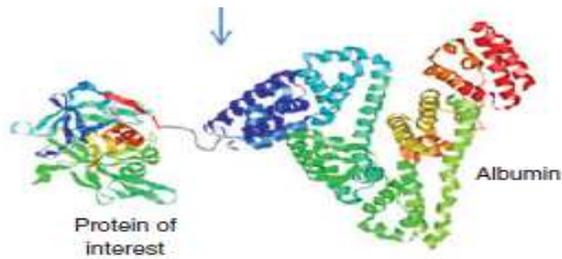


Table 1. New recombinant factor VIII concentrates.

Name	Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Kowaltry®	Bay 81-8973	Bayer	FVIII full length	Hemophilia A	Approved by the FDA and EMA	Cofactor of FX activation
Iblia®		CSL Behring	FVIII full length	Hemophilia A	Approved by the FDA and EMA	Cofactor of FX activation
NovoEight®	Turoctocog alfa	NovoNordisk (Bagsværd, Denmark)	BD truncated	Hemophilia A	Approved by the FDA and EMA	Cofactor of FX activation
Nuwiq®	Simoctocog alfa	Octapharma (Lachen, Switzerland)	BD deleted	Hemophilia A	Approved by EMA	Cofactor of FX activation
NovoEight-GP®	Turoctocog alfa pegol	NovoNordisk	BD truncated, site-directed glycopegylation with 40-kDa PEG	Hemophilia A	Phase III completed	Cofactor of FX activation
BAY94-9027	Damoctocog alfa pegol	Bayer	BDD rFVIII, site-specific glycopegylation with 60-kDa PEG	Hemophilia A	Phase III completed	Cofactor of FX activation
Adynovate® (BAX855)	Octocog alfa pegol	Baxalta (Bannockburn, IL, USA)	Full-length rFVIII-controlled-pegylation with branched-chain PEG	Hemophilia A	Approved by the FDA 2015	Cofactor of FX activation
rVIII-SingleChain	lonoctocog alfa	CSL Behring	Single-chain rFVIII compound, B-domain truncated, light and heavy chains covalently linked	Hemophilia A	Phase III completed	Cofactor of FX activation
Eloctate®	Efralococog alfa	Biogen (Cambridge, MA, USA)/ SOBI (Stockholm, Sweden)	BDD, Fc fusion	Hemophilia A	Approved by the FDA and EMA	Cofactor of FX activation

FDA: Food and Drug Administration; BD: B-domain; BDD: B-domain deleted; EMA: European Medicines Agency; PEG: PolyEthylene Glycol .

Table 2. New recombinant factor IX concentrates.

Name	Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Rixubis [®]	Nonacog gamma	Baxalta	Nonacog alfa	Hemophilia B	Approved by the FDA and EMA	Precursor of FIXa
IXinity [®]	Trenonacog alfa	Cangene (Winnipeg, Canada)	Nonacog alfa	Hemophilia B	Approved by the FDA	Precursor of FIXa
Innofactor [®]	Nonacog alfa	Stragen Pharma SA (Geneva, Switzerland)	Nonacog alfa	Hemophilia B	Approved in Russia	Precursor of FIXa
Idelvion [®]	Albutrepenonacog alfa	CSL-Behring	rFIX, albumin fusion	Hemophilia B	Approved by the FDA and EMA	Precursor of FIXa
Alprolix [®]	Eftrenonacog alfa	Biogen/SOBI	rFIX, Fc fusion	Hemophilia B	Approved by the FDA and EMA	Precursor of FIXa
NovoNine GP [®]	Nonacog beta pegol	Novo Nordisk	rFIX, pegylation	Hemophilia B	Phase III completed	Precursor of FIXa

FDA: Food and Drug Administration; EMA: European Medicines Agency.



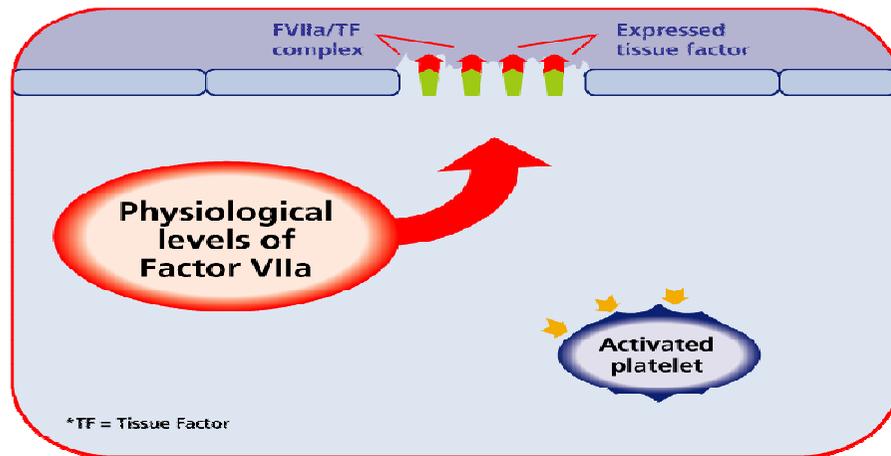
TERAPIA SUSTITUTIVA

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

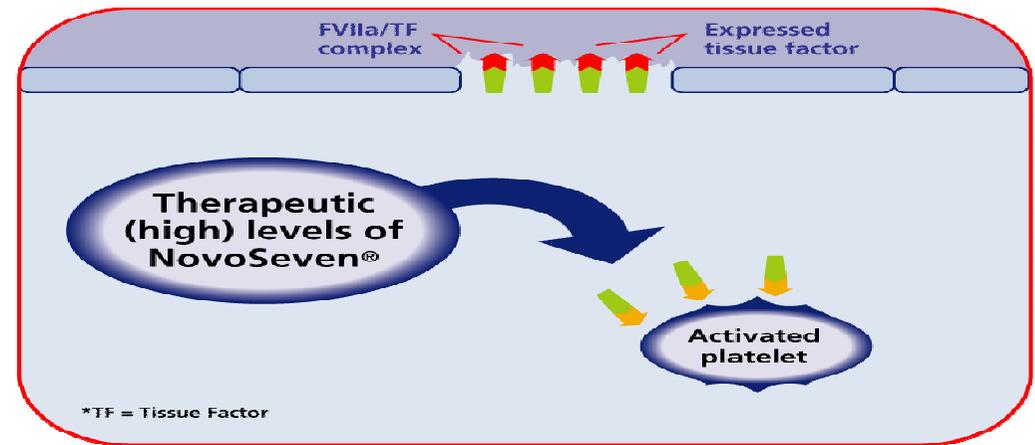
AGENTES BY-PASS

- rFVIIa
- PCCa
- rpFVIII

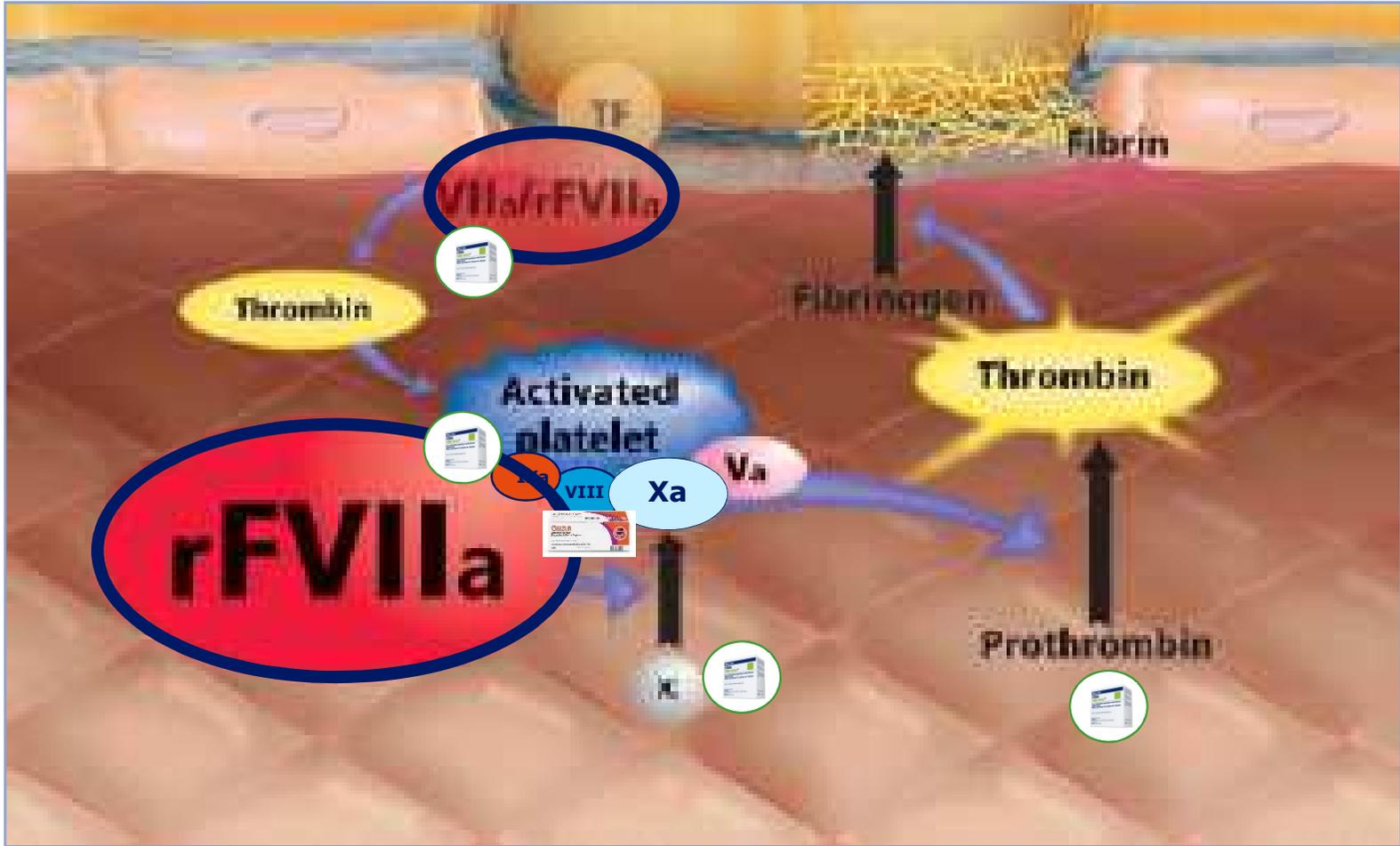
rFVIIa. Mecanismos de acción



- 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



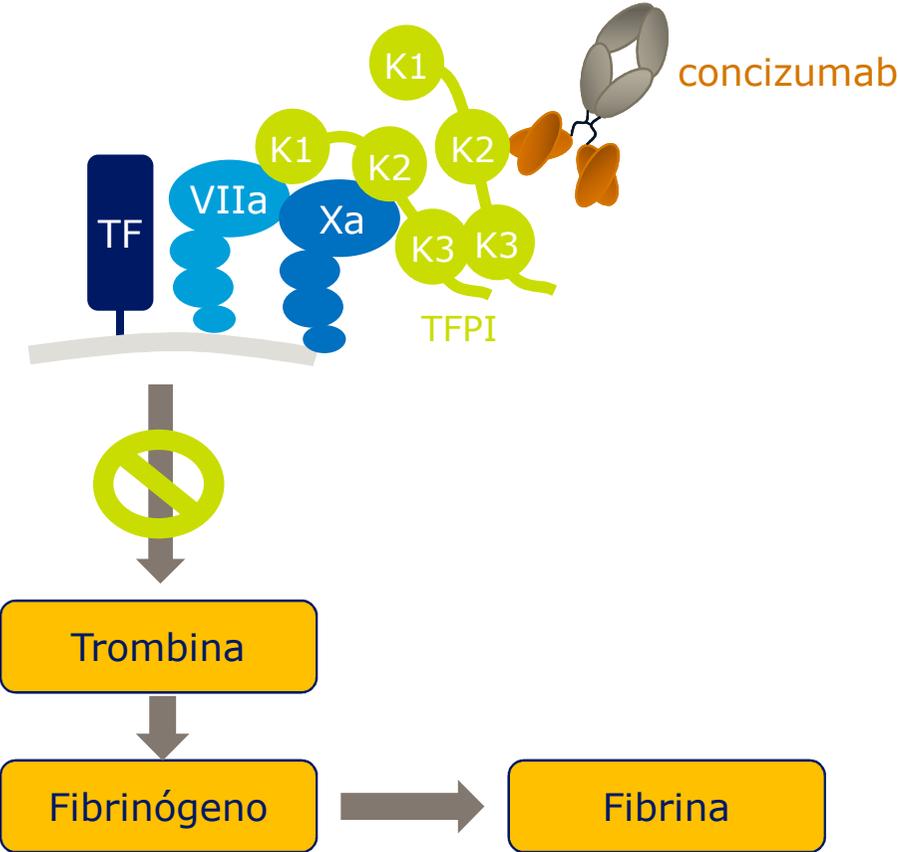
rpFVIII (susoctocog alfa)

- Celulas BHK, medio sin proteínas animales
- Nanofiltración y solvente-detergente
- Monitorización por método coagulativo
- PK. Vida media similar al FVIII. Recuperaciones erráticas
- Reactividad cruzada 33 – 56%
- Inmunogenicidad
- Dosis altas, envases pequeños.

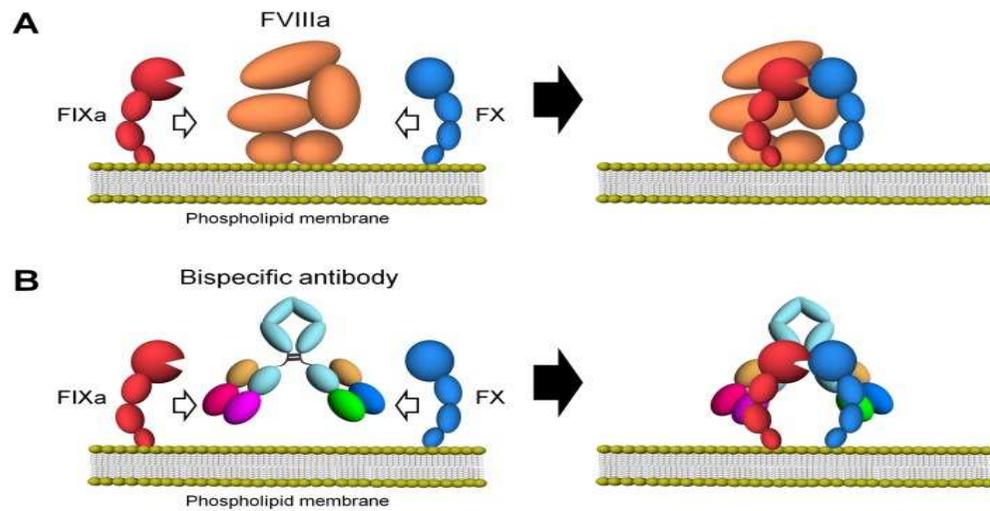
Nuevas dianas terapéuticas

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	Alynham 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

Concizumab

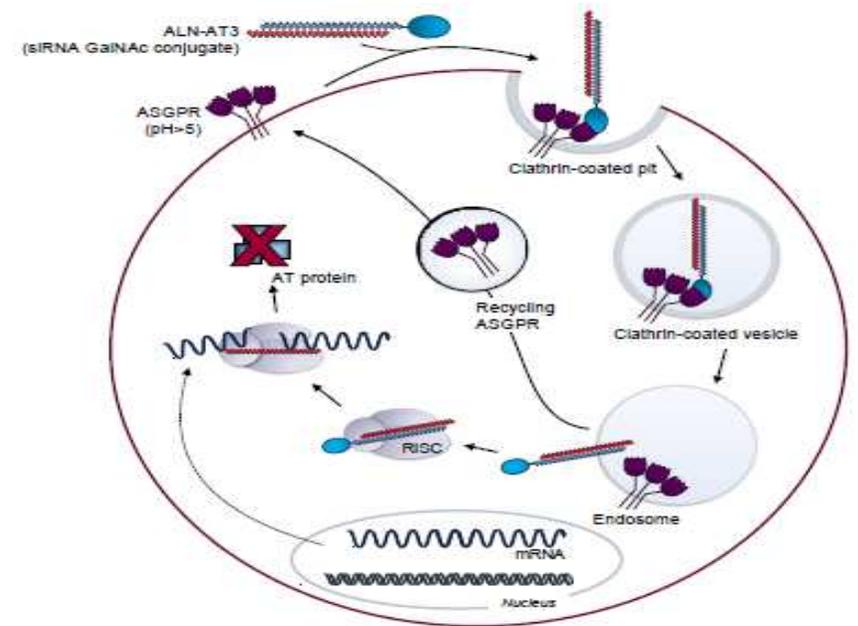


Emicizumab



...mimicking FVIII function...

Fitusiran



...silencing Antithrombin gene...

2 grandes ventajas de las nuevas moléculas

- Prolongación de la vida media
- Administración subcutánea



Nuevas dianas terapéuticas

^{super} FXa	–	Bioengineered FXa variant	Preclinical phase	Increased thrombin generation in acquired hemophilia models Synergistic effect with rFVIIa
FXa ^{116L}	–	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
FXIII	CSL Behring (Marburg, Germany)	Plasma-derived product	Preclinical phase	Long half-life (9 d) Improve clot stability alone or in association with rFVIIa

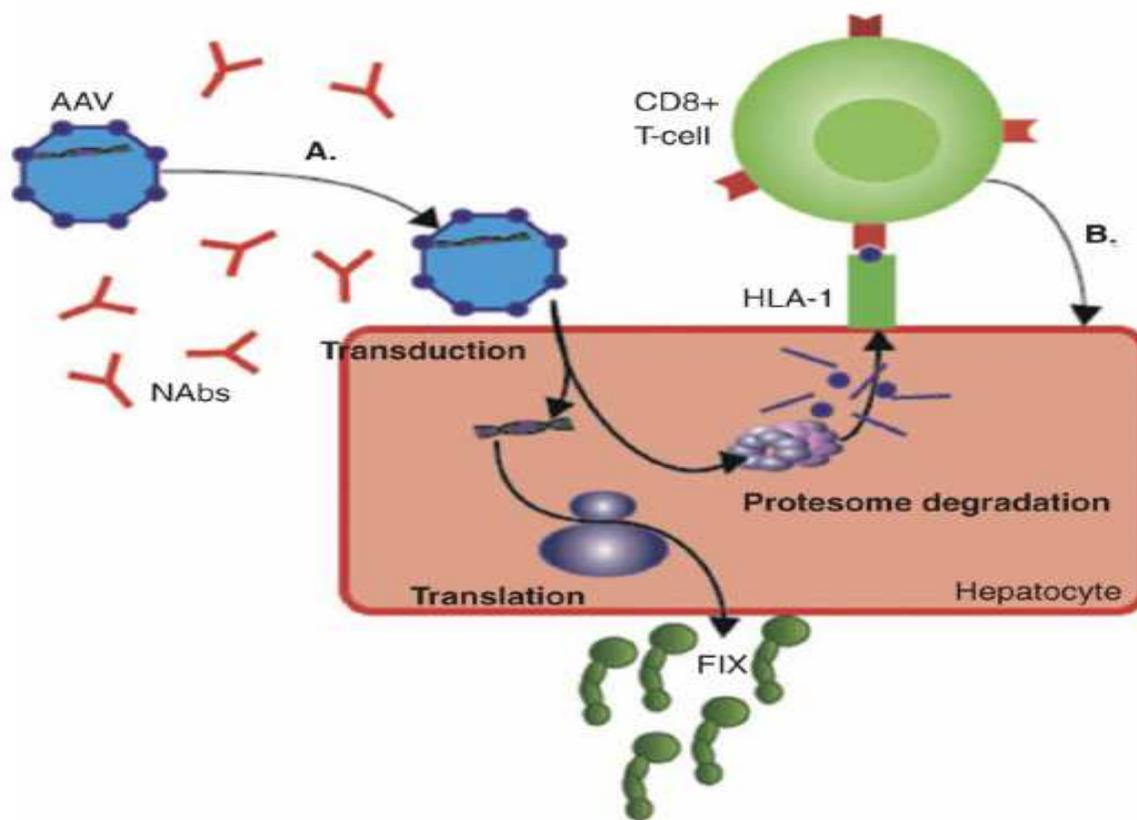
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL



Merry Christmas for Patients with Hemophilia B

Katherine P. Ponder, M.D.



GRACIAS