Le indagini di laboratorio nella diagnosi delle malattie ematologiche
quando il medico e il laboratorista parlano la stessa lingu
Sabato 16 Dicembre 2017 - Aula Magna, Nuovo Arcispedale S. Ann

TERAPIA ANTICOAGULANTE:
PASSATO, PRESENTE, FUTURO

Dott. Stefano Morate
Dipartimento Medicine Specialistic
Fisiopatologia della Coagulazio

Azienda Ospedaliero - Universitaria
Ferrara

Società Medico Ch
di Ferra

TERAPIA ANTICOAGULANTE

DIFETTO "CONTROLLATO" indotto nel SISTEMA DELL'EMOSTASI fisiologica

FFICACIA:

PREVENZIONE - TRATTAMENTO DEGLI EVENTI TROMBOTICI

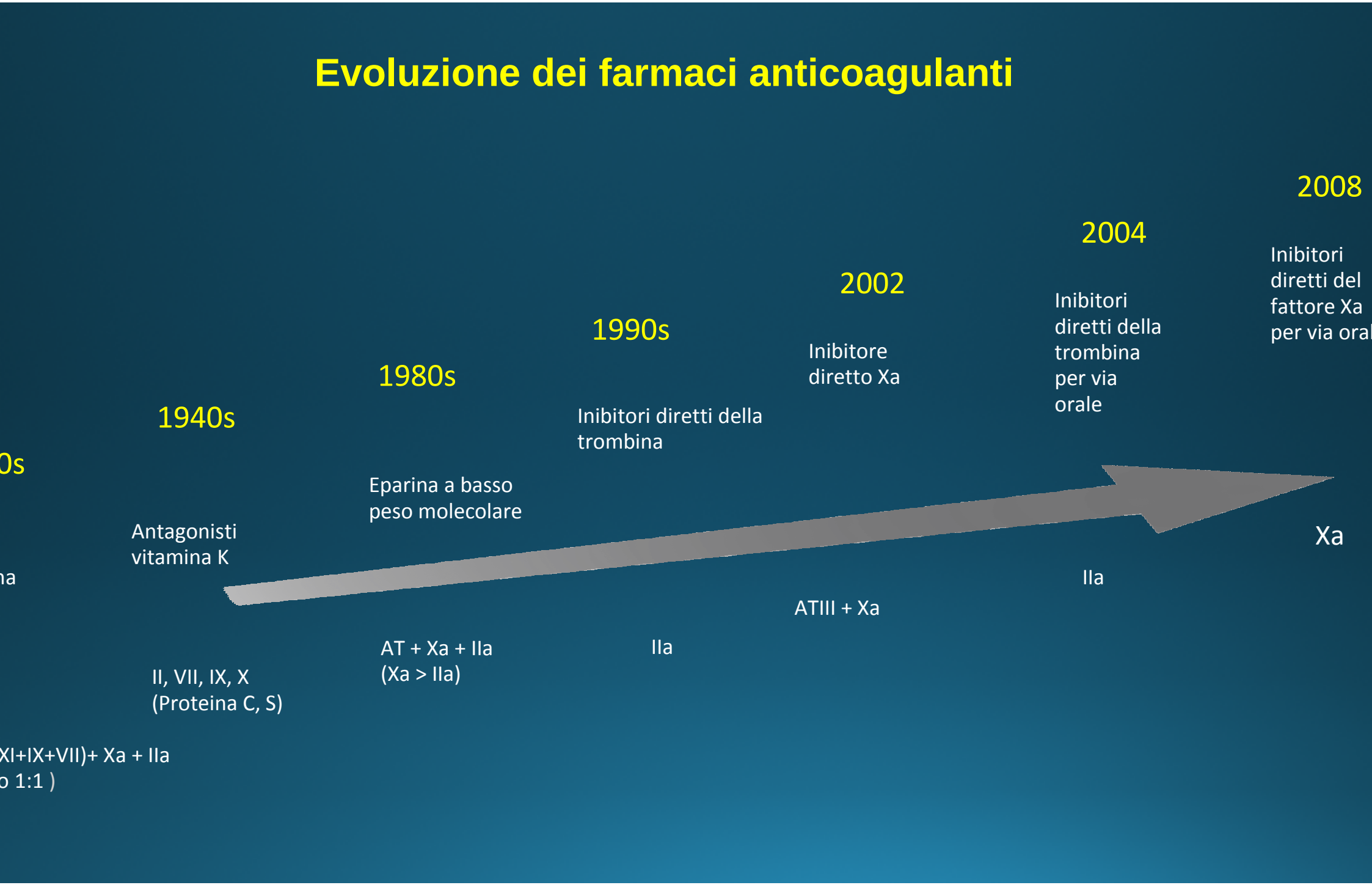
CUREZZA:

RISCHIO EMORRAGICO che deriva dal suo impiego

STUDI CLINICI

Verifica e confronto di efficacia e sicurezza: nuovi farmaci vs farmaco di riferimento

Evoluzione dei farmaci anticoagulanti



Terapia anticoagulante: indicazioni **(RCP)**

arina non frazionata (ENF o UFH) p.m.m. ~ 15.000

- Profilassi e terapia della malattia tromboembolica venosa e arteriosa
- Gestione iniziale della SCA
- Cardiochirurgia e chirurgia vascolare

arina a basso peso molecolare (EBPM o LMWH) p.m.m. 3.600 – 6.500; attività Anti-Xa:IIa 1,9:1,0 -

- Profilassi e trattamento della TVP con o senza EP
- UA e NSTEMI in associazione con acido acetilsalicilico
- Prevenzione della coagulazione in corso di emodialisi

bitori Indiretti del Fattore Xa (fondaparinux) p.m. 1.728 per singola molecola; attivo solo su FX

- Profilassi e trattamento della TVP con o senza EP
- UA, NSTEMI e STEMI

bitori della Trombina (argatroban, bivalirudina)

- Anticoagulazione in pz adulti con HIT che richiedono una terapia parenterale
- PCI

arfarin e acenocumarolo

- Profilassi e terapia della EP, TVP
- Profilassi della tromboembolia arteriosa associata a FA, protesi valvolari meccaniche o biologiche, trombosi murale intracardiaca e IMA
- Profilassi del reinfarto

… e i DOA ?

DOA: IL "FUTURO SEMPLICE"

FIBRILLAZIONE ATRIALE

- Dabigatran PRADAXA®: RE-LY
- Rivaroxaban XARELTO®: ROCKET – AF
- Apixaban ELIQUIS®: AVERROES - ARISTOTLE
- Edoxaban LIXIANA®: ENGAGE AF – TIMI 48

TEV/EP

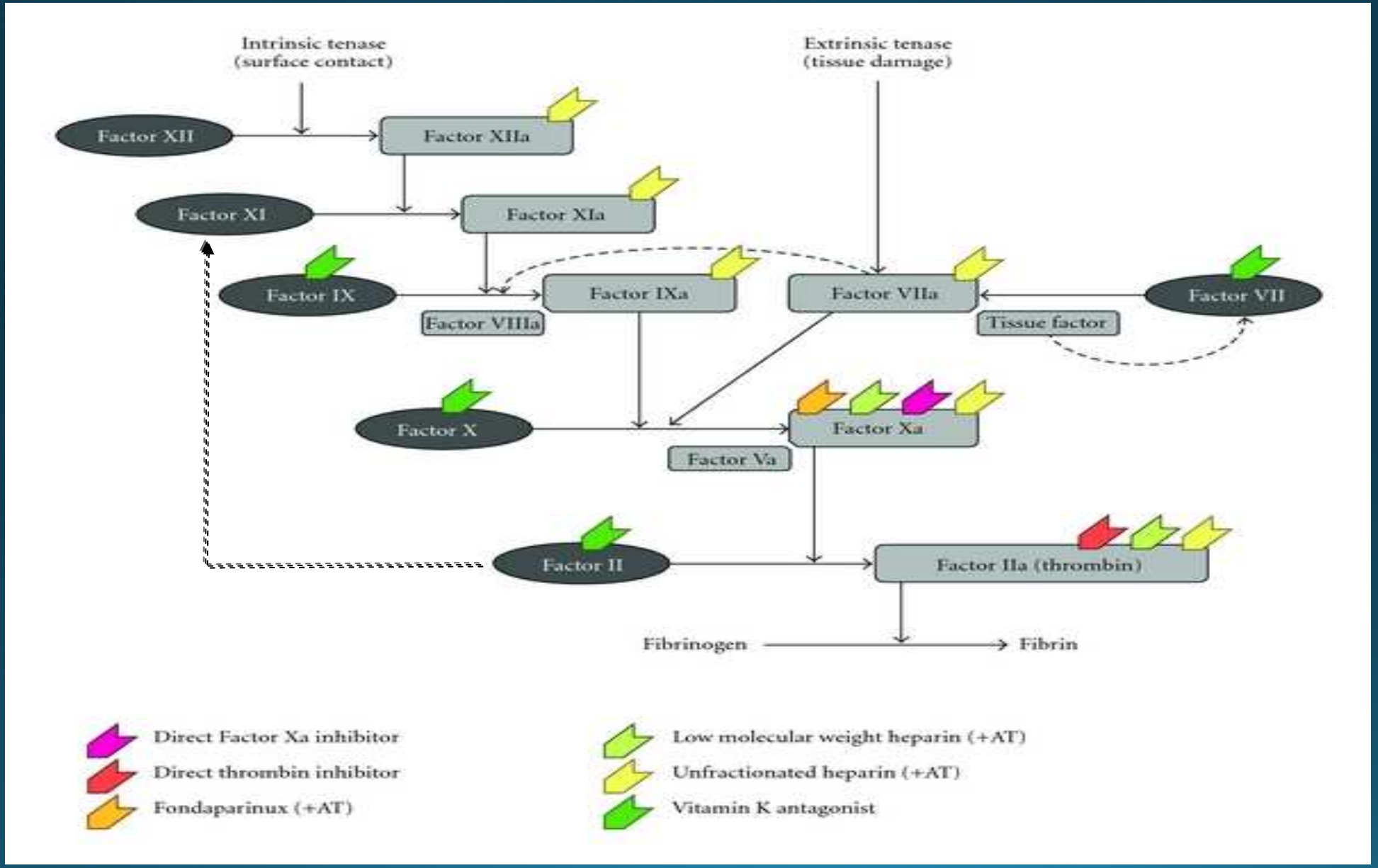
- Rivaroxaban XARELTO®: RECORD 1,2,3,4 EINSTEIN-DVT EINSTEIN-PE
  EINSTEIN-EXTENSION
- Apixaban ELIQUIS®: ADVANCE 1,2,3 BOTTICELLI -DVT AMPLIFY
  AMPLIFY-EXT
- Dabigatran PRADAXA®: RE-COVER
- Edoxaban LIXIANA®: HOKUSAI - VTE

… decine di migliaia di pazienti

DOA trials registrativi

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
V lassi in ortopedia tamento lassi paziente medico	•RE-MOBILIZE •RE-NOVATE I-II •RE-MODEL •RE-COVER I-II •RE-MEDY •RE-SONATE	•RECORD I-IV •EINSTEIN DVT •EINSTEIN PE •EINSTEIN EXSTENSION •*MAGELLAN*	•ADVANCE I-III •AMPLIFY •AMPLIFY EXSTENSION •*ADOPT*	•HOKUSAI
	•RE-LY	•ROCKET-AF	•ARISTOTLE •AVERROES	•ENGAGE-AF
A		•*ATLAS ACS 2-TIMI 51*	•*APPRAISE II*	•*ENTRUST-AF*

apia anticoagulante: **IL PASSATO SEMPRE PRESENTE E IL PRESENTE INDICAT**



IL “SISTEMA” HA ANCHE TEMPI E MODI DIVERSI…

Terapia anticoagulante: **IL FUTURO PRESENTE**

Original Article

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

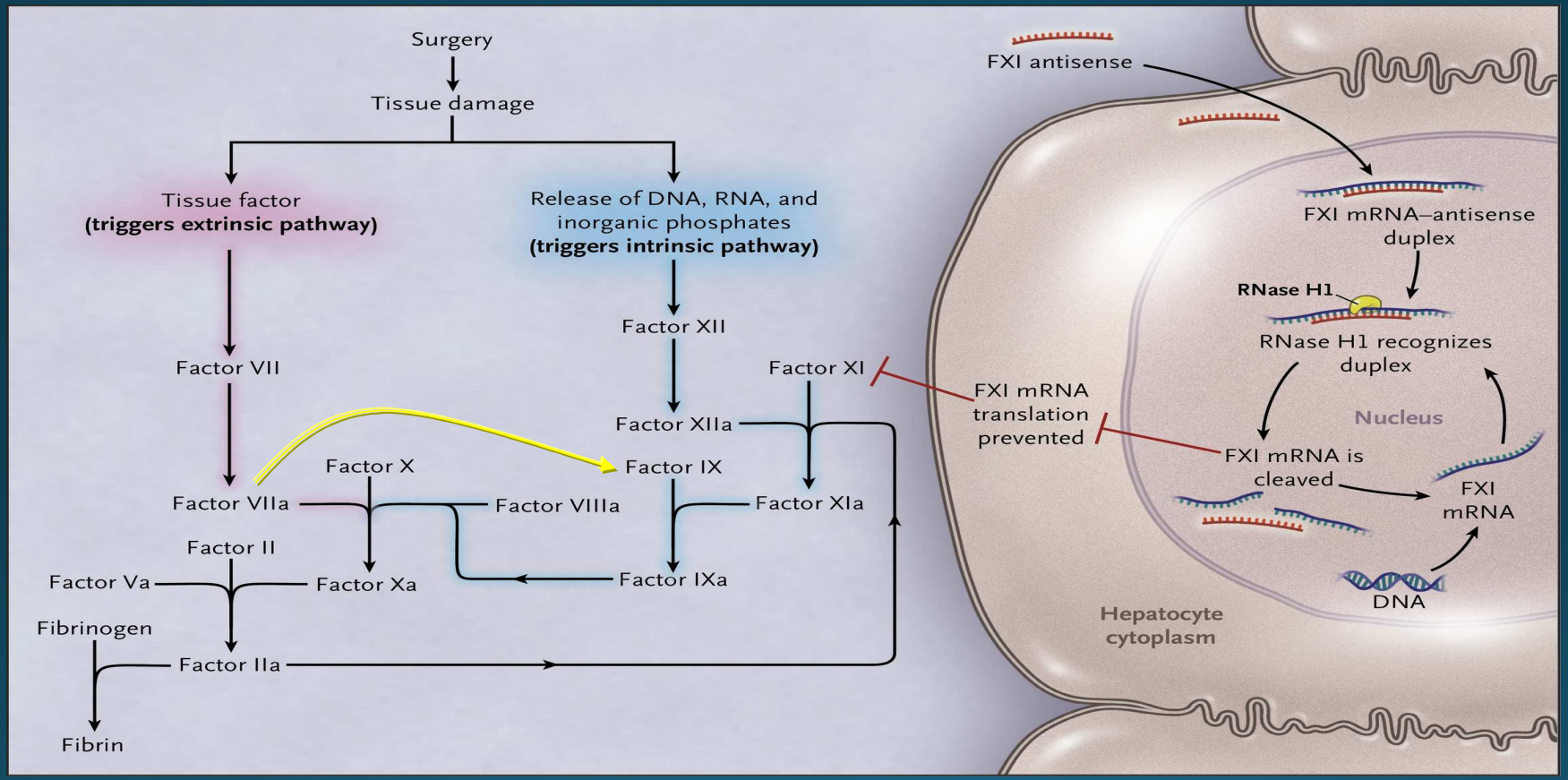
Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators

N Engl J Med
Volume 372(3):232-240
January 15, 2015

The NEW ENGLAND JOURNAL of MEDICI

SOs – OLIGONUCLEOTIDI ANTISENSO

Effect of FXI-ASO on the Coagulation System.



Büller HR et al. N Engl J Med 2015;372:232-240

Study Overview

- Enoxaparin is used to prevent deep-vein thrombosis in patients undergoing total knee arthroplasty.

- In this study, an antisense oligonucleotide against factor XI was more effective than enoxaparin in preventing deep-vein thrombosis and caused less bleeding.

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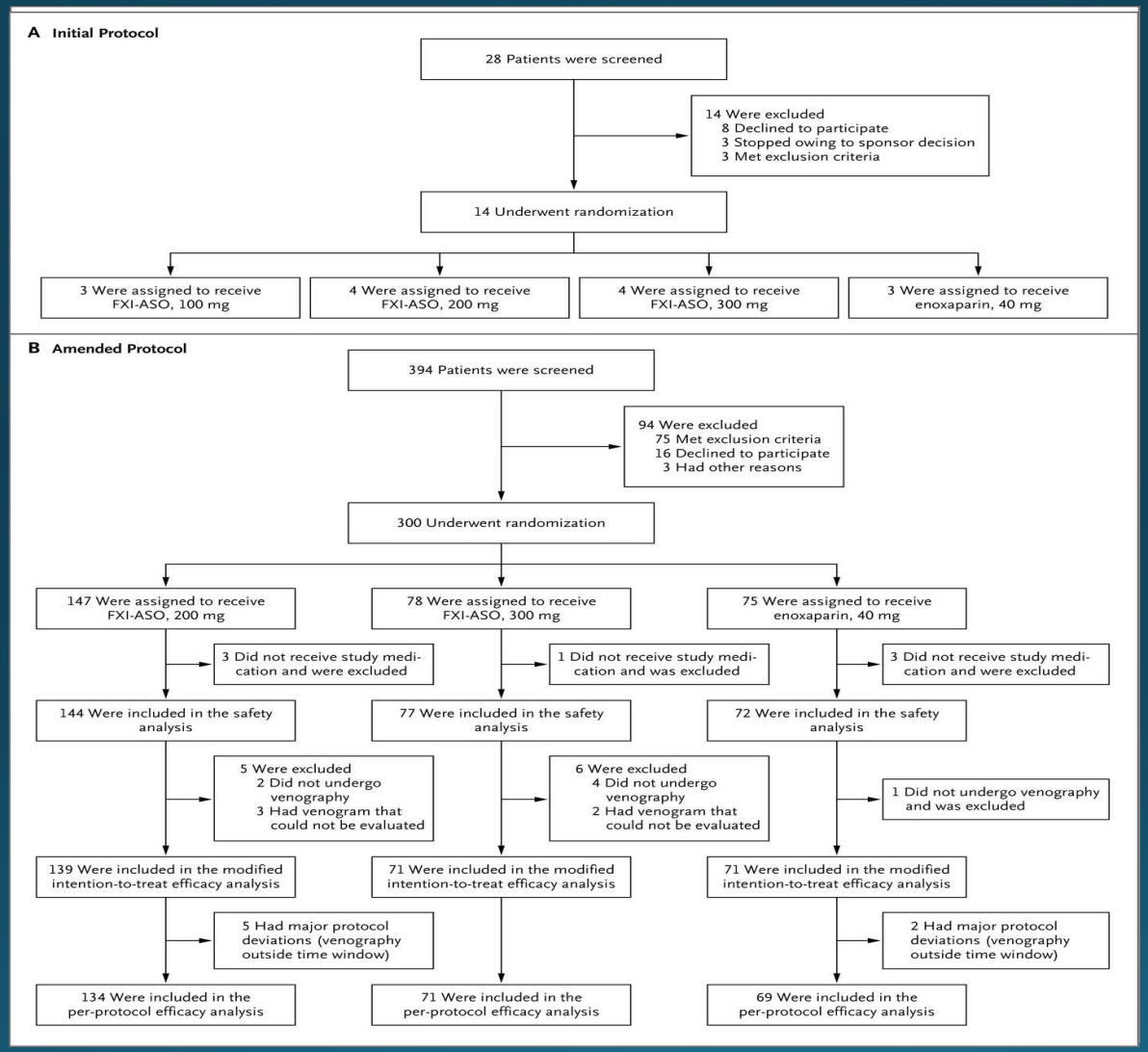
Enrollment, Randomization, and Populations for Analysis.



Büller HR et al. N Engl J Med 2015;372:232-240

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Demographic and Clinical Characteristics of the Patients.

able 1. Demographic and Clinical Characteristics of the Patients.*

haracteristic	FXI-ASO, 200 mg (N=144)	FXI-ASO, 300 mg (N=77)	Enoxaparin, 40 mg (N=72)
ge — yr	63±9	63±8	64±9
emale sex — no. (%)	118 (82)	60 (78)	60 (83)
Veight — kg			
Mean	89	90	87
Range	52–124	52–130	52–132
reatinine clearance — ml/min	112±31	116±30	111±30
Duration of surgery — hr	1.8±0.7	1.9±0.8	1.9±0.8
ime to ambulation — hr	35±19	39±21	39±20
ength of hospital stay — days	15±5	14±5	16±5
ype of anesthesia received — no. of patients†			
General	138	72	64
Spinal	4	1	7
ctivated partial-thromboplastin time ratio	0.97±0.11	0.95±0.09	0.95±0.11
actor XI activity — units/ml	1.20±0.20	1.16 ±0.22	1.23±0.21
Duration of enoxaparin treatment — days			
Median	—	—	10
Interquartile range			10–10
roportion of prescribed injections of FXI-ASO received — %	97	92	—

lus–minus values are means ±SD. The characteristics listed here were assessed in the safety population, which included all patients who eceived at least one dose of study medication. There were no clinically important differences among the treatment groups in any of the listed haracteristics. There were also no statistically significant between-group differences, with the exception of the type of anesthesia received, with nore patients in the enoxaparin group than in the FXI-ASO groups receiving spinal anesthesia (P=0.02).
lot all patients in the safety population underwent surgery.

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Efficacy and Safety Outcom

ficacy and Safety Outcomes.*

	FXI-ASO, 200 mg (N=134)	FXI-ASO, 300 mg (N=71)	Enoxaparin, 40 mg (N=69)
icacy outcome: total venous thromboembolism — no. (% [95% CI])†	36 (27 [20 to 35])	3 (4 [1 to 12])	21 (30 [20 to 43])
fference, FXI-ASO vs. enoxaparin — % (upper limit of 90% CI)	−4 (5)	−26 (−18)	—
fference, FXI-ASO vs. enoxaparin — % (upper limit of 95% CI)	−4 (8)	−26 (−16)	—
for superiority of FXI-ASO to enoxaparin	0.59	<0.001	—
efficacy outcomes: components of the primary efficacy outcome — no. (%)			
omatic venous thromboembolism	2 (1)	0	1 (1)
tomatic deep-vein thrombosis	34 (25)	3 (4)	20 (29)
al deep-vein thrombosis	7 (5)	1 (1)	4 (6)
deep-vein thrombosis	29 (22)	2 (3)	17 (25)
y efficacy outcome: extent of venous thrombosis on venography			
s with deep-vein thrombosis — no. (%)	36 (27)	3 (4)	21 (30)
of deep-vein thrombosis — no.			
teral‡	2	0	2
nfluent distal into proximal	6	0	2
lated proximal			
Large: ≥10 cm	0	0	1
Small: <10 cm	0	1	0
lated distal			
Extensive: ≥2 veins	16	0	7
Limited: <2 veins	12	2	9
afety 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])
fference, FXI-ASO vs. enoxaparin — % (95% CI)	−6 (−12 to 1)	−6 (−13 to 2)	
by Fisher's exact test, FXI-ASO vs. enoxaparin	0.09	0.16	
bleeding — no. (% [95% CI])¶	0 [0 to 2.5]	1 (1 [<1 to 7])	0 [0 to 5.0]
lly relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	1 (1 [<1 to 7])	6 (8 [3 to 17])
blood transfusion — no. (%)	55 (38)	22 (29)	23 (32)
ents — no. of patients (%)			
erse event	114 (79)	62 (81)	47 (65)
s adverse event‖	3 (2)	1 (1)	0
verse event resulting in permanent discontinuation of study drug**	1 (1)	1 (1)	0
ite–related adverse event††	32	25	2

utcomes were assessed in the per-protocol efficacy population, which comprised all patients who received at least one dose of edication and who could be evaluated for the primary efficacy outcome, with the exclusion of patients with major protocol violations. tcomes were assessed in the safety population, which included all patients who received at least one dose of study medication.
es confidence interval.
ous thromboembolism was a composite of asymptomatic deep-vein thrombosis (detected by mandatory bilateral venography), ob- confirmed symptomatic venous thromboembolism, fatal pulmonary embolism, or unexplained death for which pulmonary embolism t be ruled out. None of the patients had a pulmonary embolism.
0-mg FXI-ASO group, one patient had bilateral distal deep-vein thrombosis and one patient had distal deep-vein thrombosis con- the popliteal vein in the right leg and distal deep-vein thrombosis alone in the left leg; in the enoxaparin group, one patient had distal deep-vein thrombosis and one patient had bilateral distal deep-vein thrombosis confluent to the proximal veins.
y outcomes reported here include data from the first administration of the study drug to study day 136 (end of the study). The ion period in the FXI-ASO groups was longer than that with enoxaparin because the FXI-ASO injections were started on day 1 (36 ore surgery) and continued to day 39 (3 days after surgery), and patients in the 300-mg group received two injections per dosing. oxaparin group, the injections started on the day of surgery or the day before.
ode of surgical-site hematoma requiring drainage occurred in a patient in the 300-mg FXI-ASO group.
0-mg FXI-ASO group, the serious adverse events were transient ischemic attack (in one patient), fistula of the postoperative scar atient), and ligature fistula (in one patient); in the 300-mg FXI-ASO group, one patient had a periprosthetic infection. All these ere considered by the investigators as unlikely to be related or as unrelated to FXI-ASO therapy.
ons for discontinuation were itching and worsening of preexisting arterial hypertension (one patient in the 200-mg FXI-ASO group) ding from the surgical site (one patient in the 300-mg FXI-ASO group).
-site adverse events included one or more of the following: erythema, pain, pruritus, swelling, and hematoma.

R et al. N Engl J Med 2015;372:232-240

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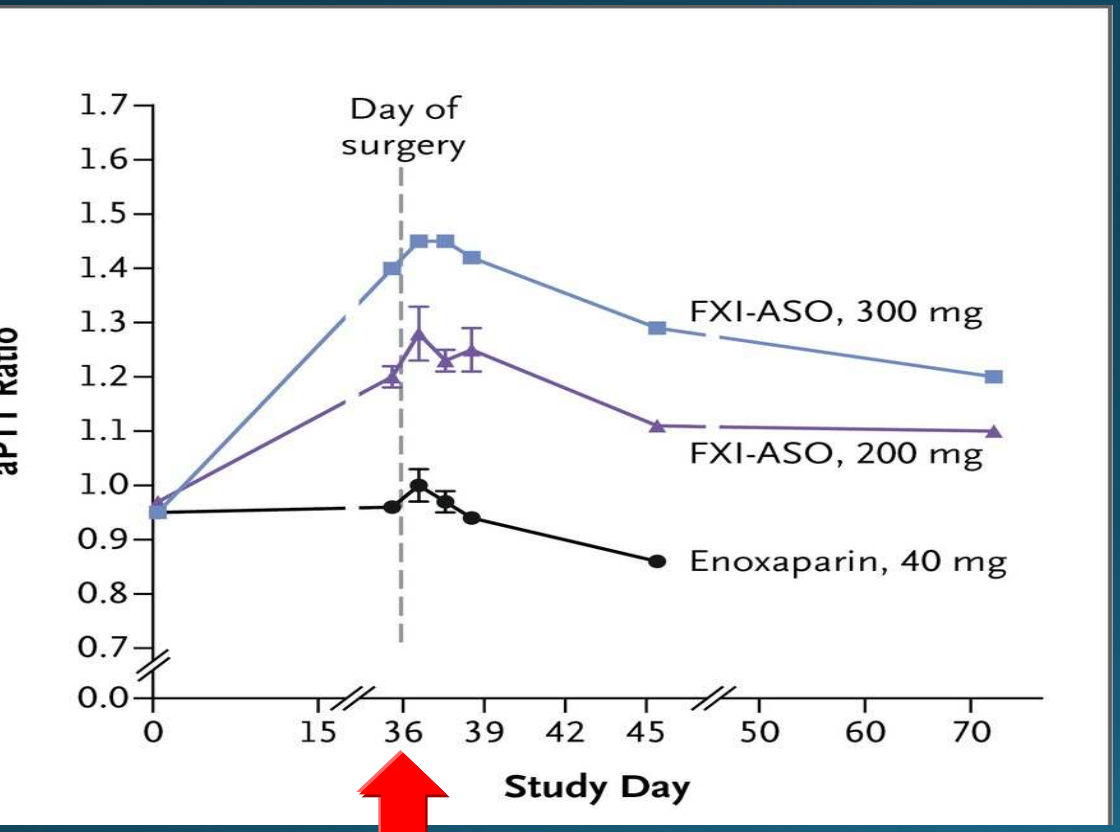
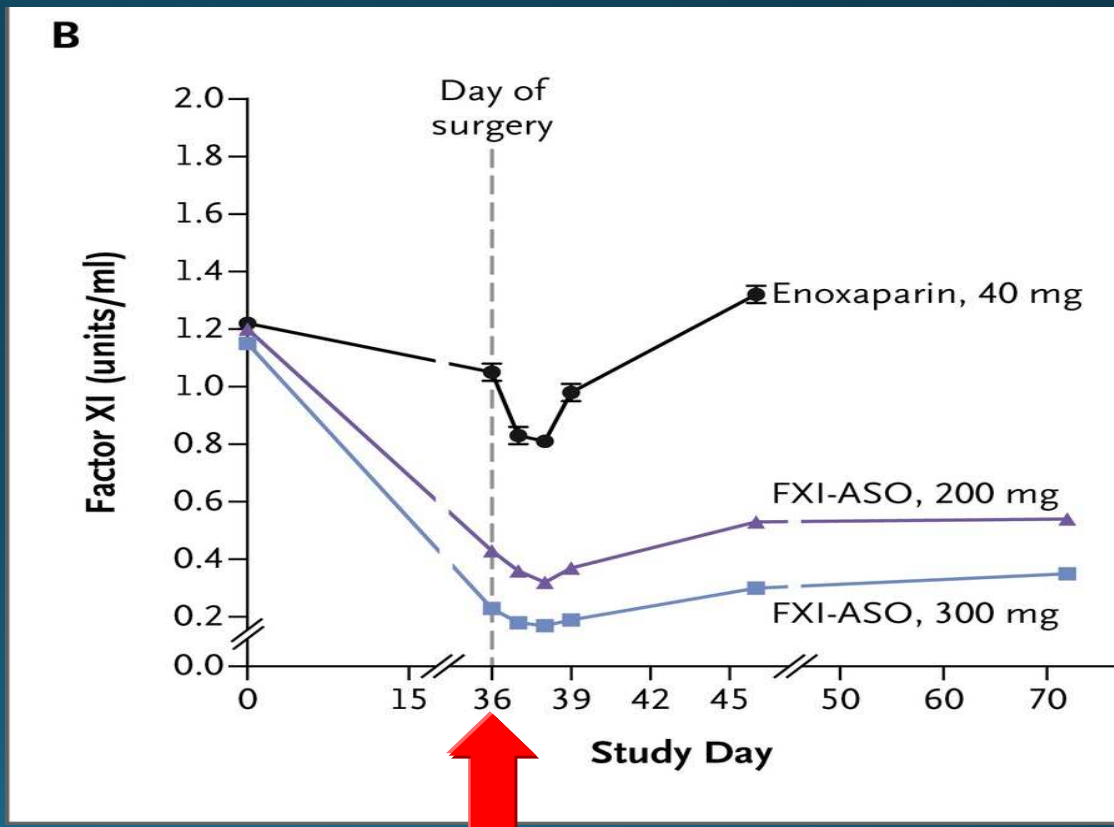
Efficacy and Safety Outcomes.

EFFICACY	ASO 200 mg	ASO 300 mg	Enox. 40 mg
TVP totali	**36/134 = 27%** p = 0,59	**3/71 = 4%** p = 0,001%	**21/69 = 30%** /
sintomatiche	2 = 1%	0	1 = 1%
asintomatiche	34 = 25%	3 = 4%	20 = 29%
prossimali	7 = 5%	1 = 1%	4 = 6%
distali	29 = 22%	2 = 3%	17 = 25%
bilaterali	2 = 1%	0	2 = 2%
Totali TVProfonde	36 = 27%	3 = 4%	21 = 30%
SAFETY			
Major or relevant non major **bleeding**	**4 = 3%**	**2 = 3%**	**6 = 8%**
Blood transf.	55 = 38%	22 = 29%	23 = 32%
Eventi avversi (tutti) prevalenti in sede di iniezione	114 = 79%	62 = 81%	47 = 65%

Activated Partial-Thromboplastin Time **(aPTT) Ratios and Factor XI Levels** before and after Surgery on Day 36





Büller HR et al. N Engl J Med 2015;372:232-24

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Conclusions

This study showed that factor XI contributes to postoperative venous thromboembolism; reducing factor XI levels in patients undergoing elective primary unilateral total knee arthroplasty was an effective method for its prevention and appeared to be safe with respect to the risk of bleeding.

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FXII

FXI

FIX

Perché l’interesse per questi nuovi bersagli terapeutici ?

Bersagli terapeutici

- **FXI** a) **il difetto congenito conosciuto da oltre 50 anni ha scarsa rilevanza emorragica**

  b) <u>feedback di attivazione</u> : Trombina → FXI

  Naito K et Al J Biol Chem, 1991

  Colman RW et Al Blood, 1996

  Pedicord DL et Al Proc Natl Acad Sci USA, 2007

  Wielders SJ et Al Arterioscler Thromb Vasc Biol, 2004

  Kravtsov DV et Al Blood, **2009**

  Deficit di FXI: emofilia C sintomi emorragici modesti (chirurgia ORL e urologica)

  1-9:1.000.000

  (8% ebrei Ashkenazy)

- **FVIII** **(Emofilia A) e in particolare** **FIX** **(Emofilia B)**

  il difetto congenito <u>lieve</u> raramente procura gravi emorragie spontanee

  Deficit di FVIII: emofilia A sintomi emorragici (grave, moderata, lieve)

  1:10.000

  Deficit di FIX: emofilia B sintomi emorragici (grave, moderata, lieve)

  1:30.000

- **FXII, PK, HMWK** **deficit anche severi non causano emorragie**

FXI e malattie trombotiche

La <u>rarità del difetto</u> rende difficile collegare studi clinici con l'incidenza di malattie tromboemboliche…

Meijers JC et al "High levels of coagulation FXI as a risk factor for venous thrombosis". N Engl J Med 2000

Berliner JI et al "Elevated levels of FXI are associated with cardiovascular disease in women". Thromb Res 2002

Doggen CJet al "Level of intrinsic coagulation factors and the risk of mycardial infarction among men: opposite and synergistic effects of FXI and FXI 2006

Danis B et al "Procoagulant factors and the risk of myocardial infarction in young women". Eur J Haematol 2006

Merlo C et al "Elevated levels of plasma prekallikrein, high molecular weight kininogen and FXI in coronary heart disease" Atherosclerosis 2002

Yang DT et al "Elevated FXI activity levels are associated with an increased odds ratio for cerebrovascular events". Am J Clin Pathol 2006

Salomon O et al "Reduced incidence of ischemic stroke in patients with severe FXI deficiency". Blood 2008

… <u>studi su modelli animali</u>:

knockout mice carenti di FXI

FXI: modelli animali

Gailani D et al: **“A murine model of FXI deficiency”.** **Blood Coagul Fibrinolysis 1997**

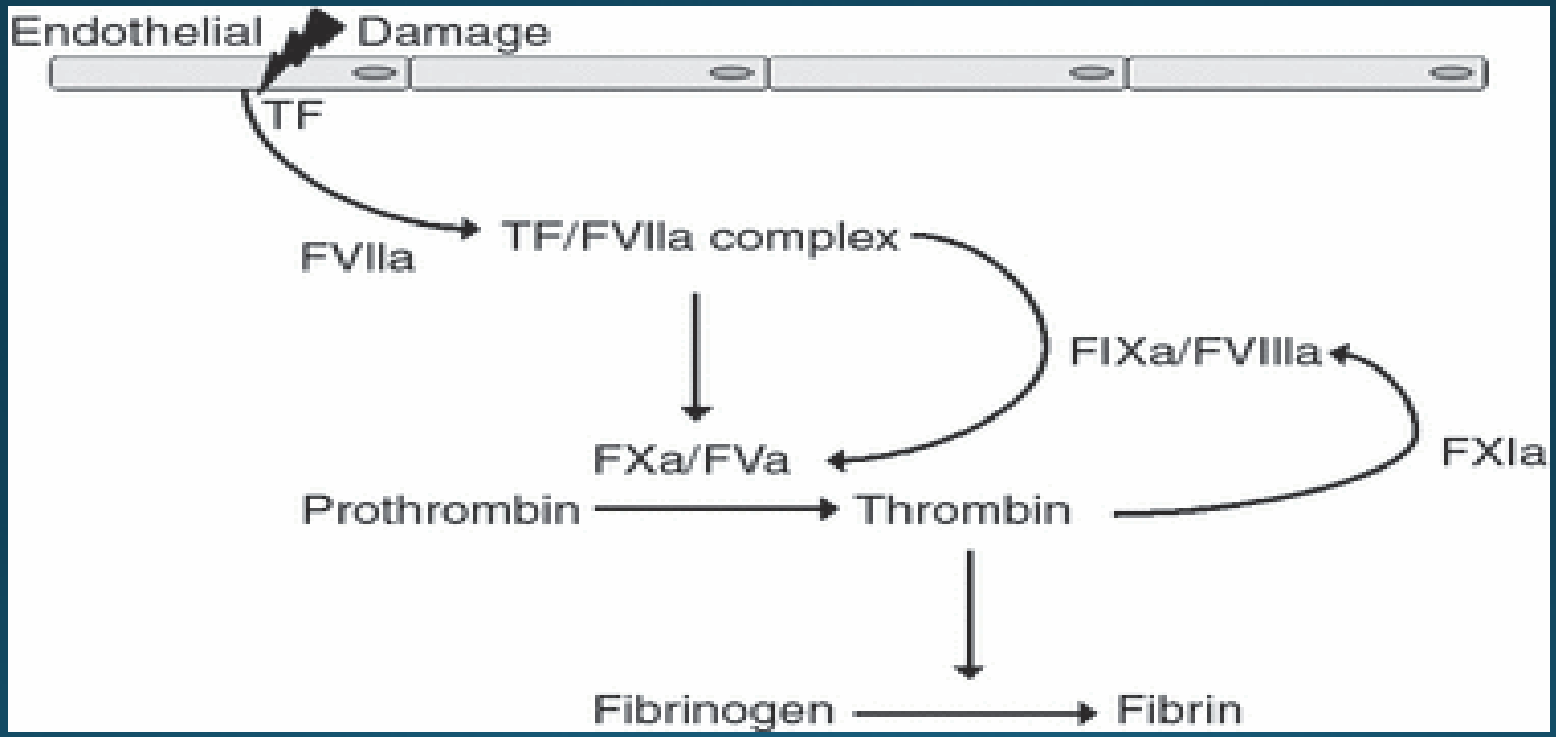
Rosen ED et al ”**FXI** is essential for thrombus formation following FeCl3-induced injury of the carotid artery in the mouse”
Thromb Haemost 2002

Renne T et al “Defective thrombus formation in mice lacking coagulation **FXII**”
J Exp Med 2005

Gruber A et al “FXI-dependence of surface- and tissue factor-initiated thrombus propagation in primates”
Blood 2003

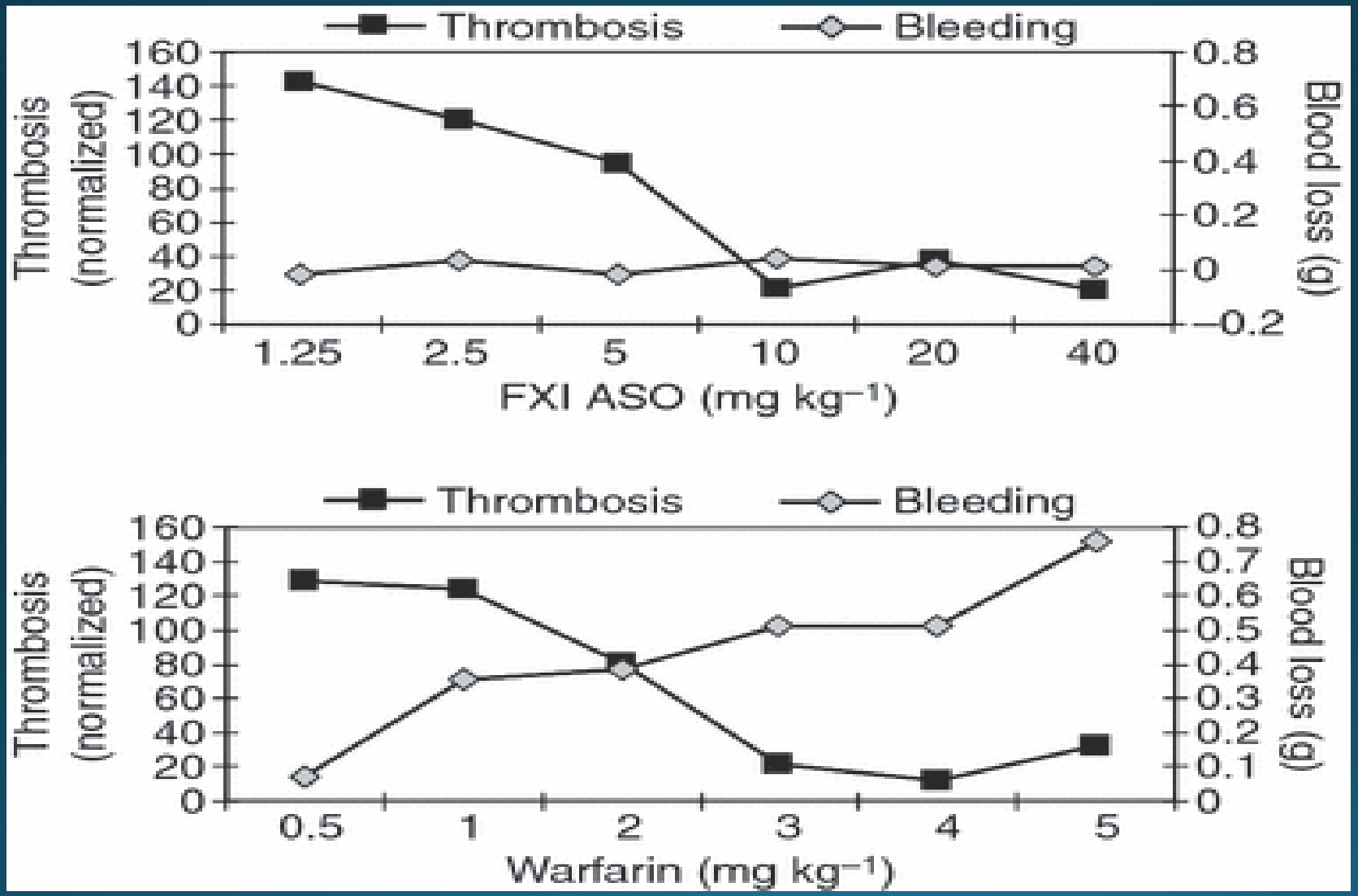
Schumacher WA et al “Antithrombotic and hemostatic effects of a small molecule FXIa inhibitor in rats”
Eur J Pharmacol 2004

Coagulation factor XI as a novel target for antithrombotic treatment



Löwenberg et Al
Journal of Thrombosis and Haemostasis, 2 NOV 2010

ffects of warfarin vs. FXI antisense oligonucleotides (ASO) treatment on thrombosis and bleeding in mice



of Thrombosis and Haemostasis
3, Issue 11, pages 2349-2357, 2 NOV 2010 DOI: 10.1111/j.1538-7836.2010.04031.x
nelibrary.wiley.com/doi/10.1111/j.1538-7836.2010.04031.x/full#f4

Terapia anticoagulante: IL **FUTURO PRESENTE**

RNA aptamers as reversible antagonists of coagulation factor IX

ristopher P. Rusconi, Elizabeth Scardino, Juliana Layzer, George A. Pitoc, Thomas L. Ortel, Dougald Monroe & Bruce A. Sullenger

Nature 419, 90–9405 September, 05 2002

doi:10.1038/nature00963

...futuro remot

Terapia anticoagulante: IL **FUTURO PRESENTE**

First-in-human experience of an antidote-controlled anticoagulant using RNA aptamer technology: a phase 1a pharmacodynamic evaluation of a drug-antidote pair for the controlled regulation of factor IXa activity.

Dyke CK et Al Circulation Oct. 27, 2006

… futuro passato?

Terapia anticoagulante: IL **FUTURO PRESENTE**

A randomized, partially blinded, multicenter, active-controlled, ose-ranging study assessing the safety, efficacy, and harmacodynamics of the REG1 anticoagulation system in patie with acute coronary syndromes: Design and rationale of the RAD Phase IIb trial

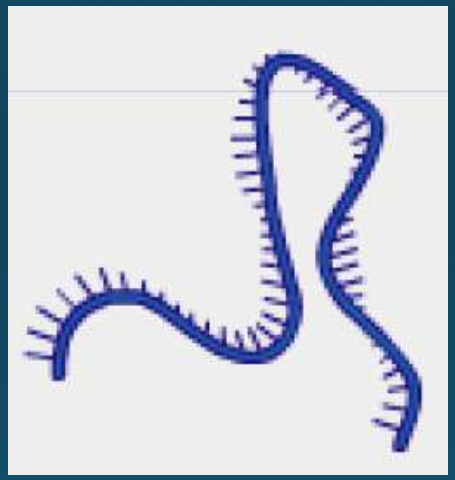
homas J.PovsicMD, PhDalMauricio G.CohenMDblRoxanaMehranMDclChristopher E.BullerMDdlChristophBodeMDelJan CornelMDflJarosław D.KasprzakMDglGillesMontalescotMDhlDianeJosephaWilliam A.WarginPhDiChristopher RusconiPhDjSteven L.ZelenkofskeDOklRichard C.BeckerMDalJohn H.AlexanderMD, MHSal

American Heart Journal Vol 161, Issue 2, February 2011

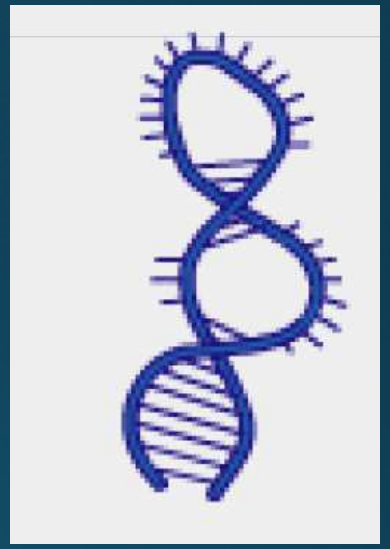
APTAMERI

Acidi nucleici a singolo filamento caratterizzati da una specifica **struttura tridimensionale** che si lega direttamente alla proteina target.

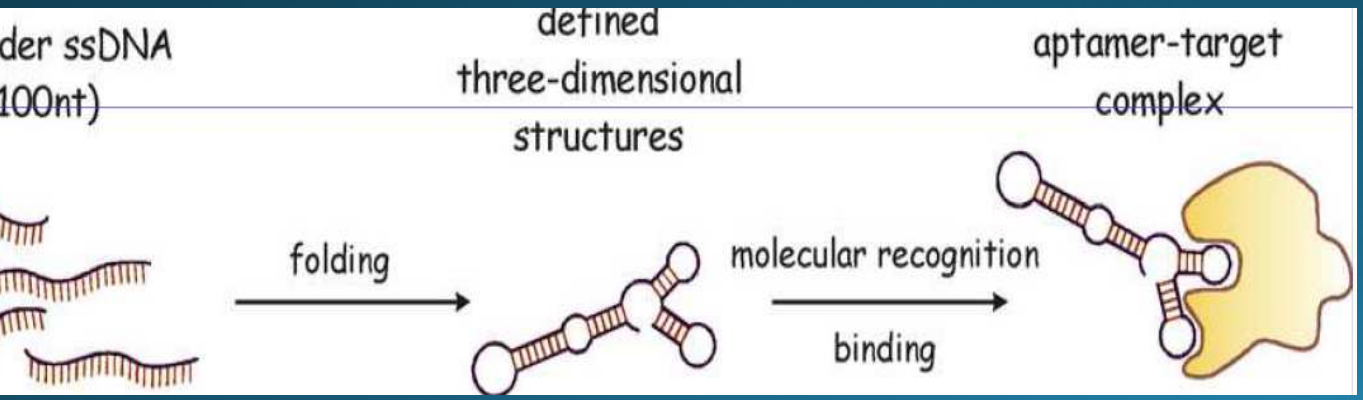
Molecola Lineare



Folding



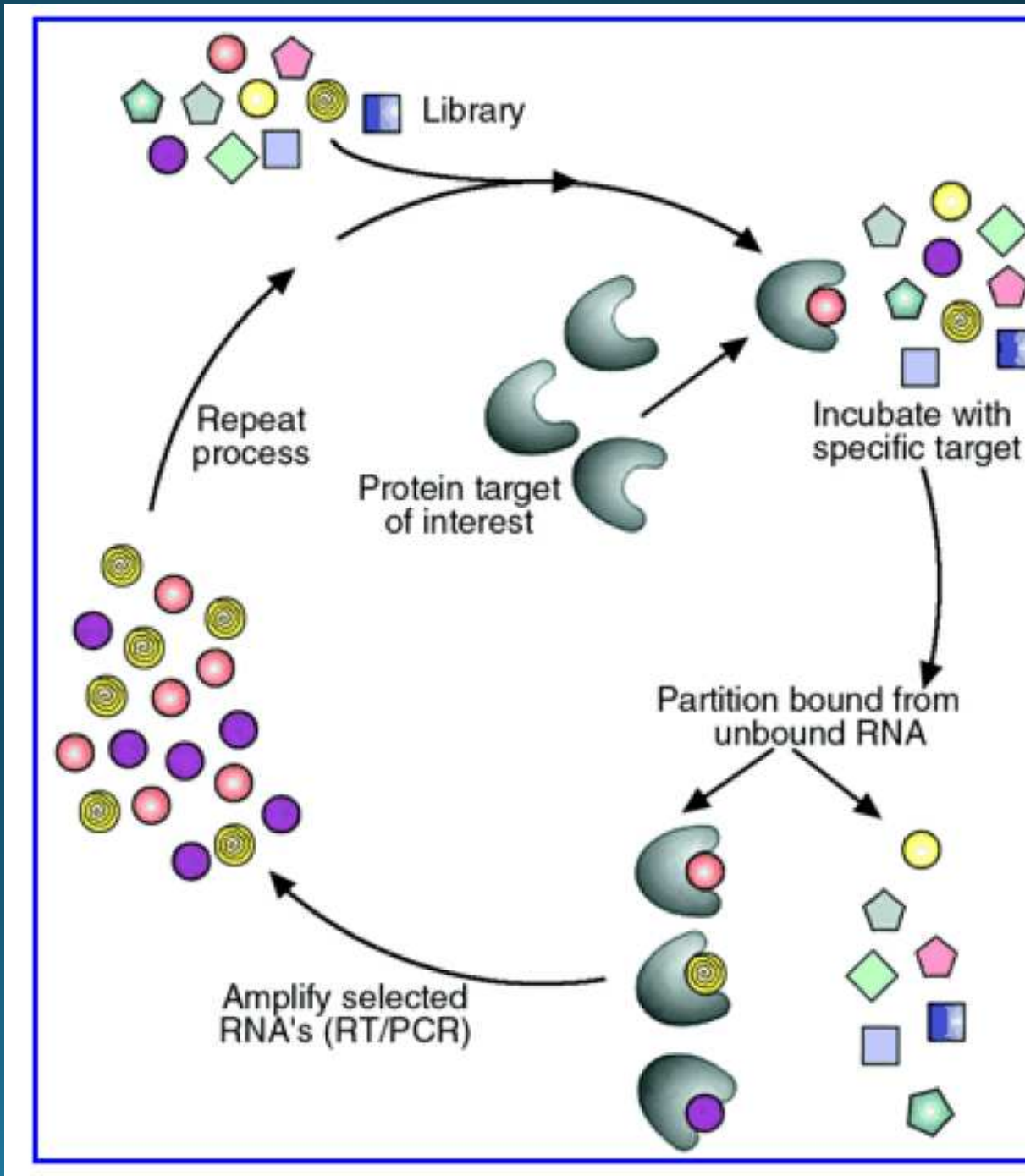
Struttura tridimensionale stabile



Interazione Acido Nucleico/Protein

ezione in vitro degli Aptameri:

LEX (systematic evolution of ligands by
ponent enrichment)



Applicazioni degli aptameri

- RICERCA
- DIAGNOSTICA
- TERAPIA

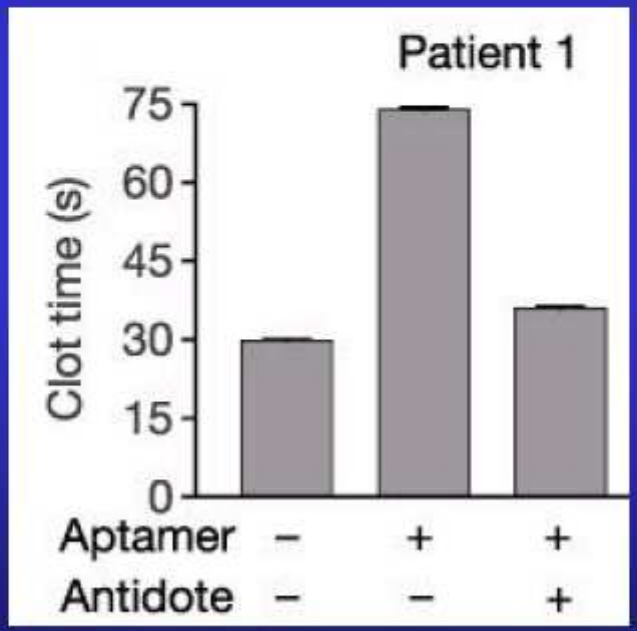
Complesso di attivazione del FX

Aptamero selezionato

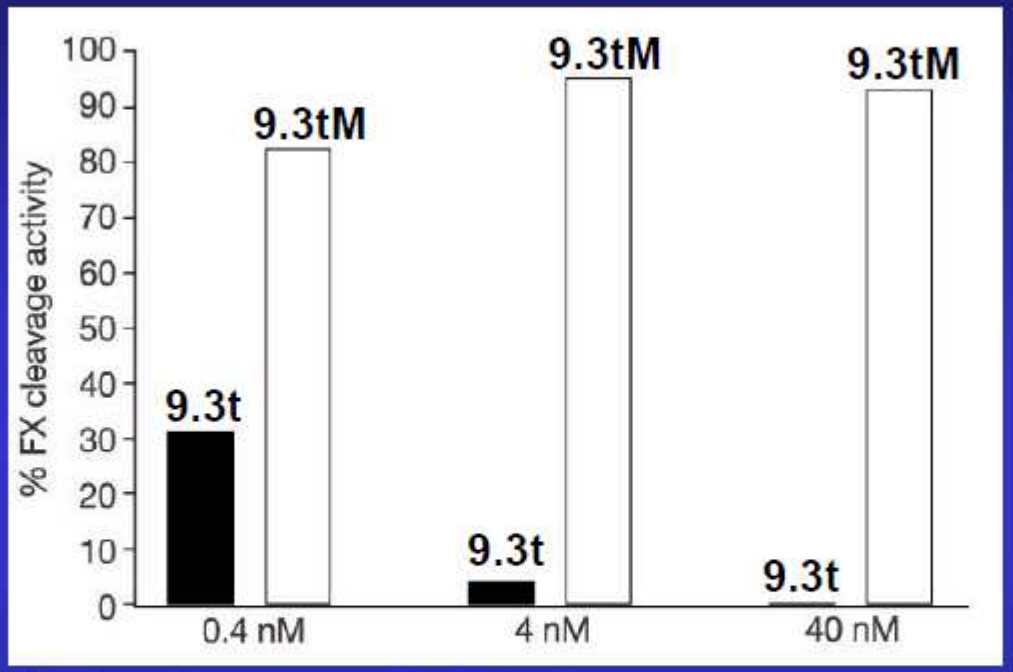
1. Elevata AFFINITA' con il FIXa
2. SPECIFICITA' per il FIXa

Efficacia di aptamero e antidoto su pazienti

6 Pazienti con trombosi → pazienti non sottoponibili ai normali trattamenti anticoagulanti



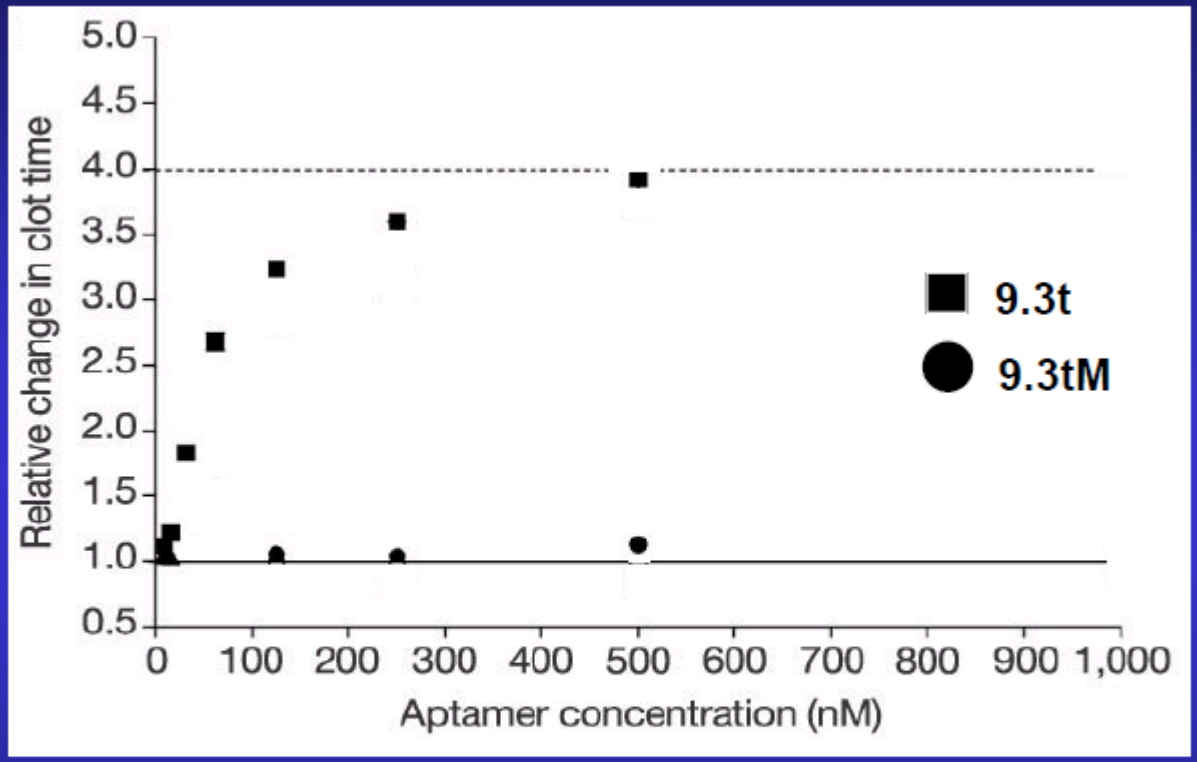
Inibizione IN VITRO dell'attività del FIXa



9.3t: aptamero selezionato
9.3tM: controllo negativo

L'aptamero blocca l'attività del FIXa in vitro

Inibizione IN VIVO dell'attività del FIXa

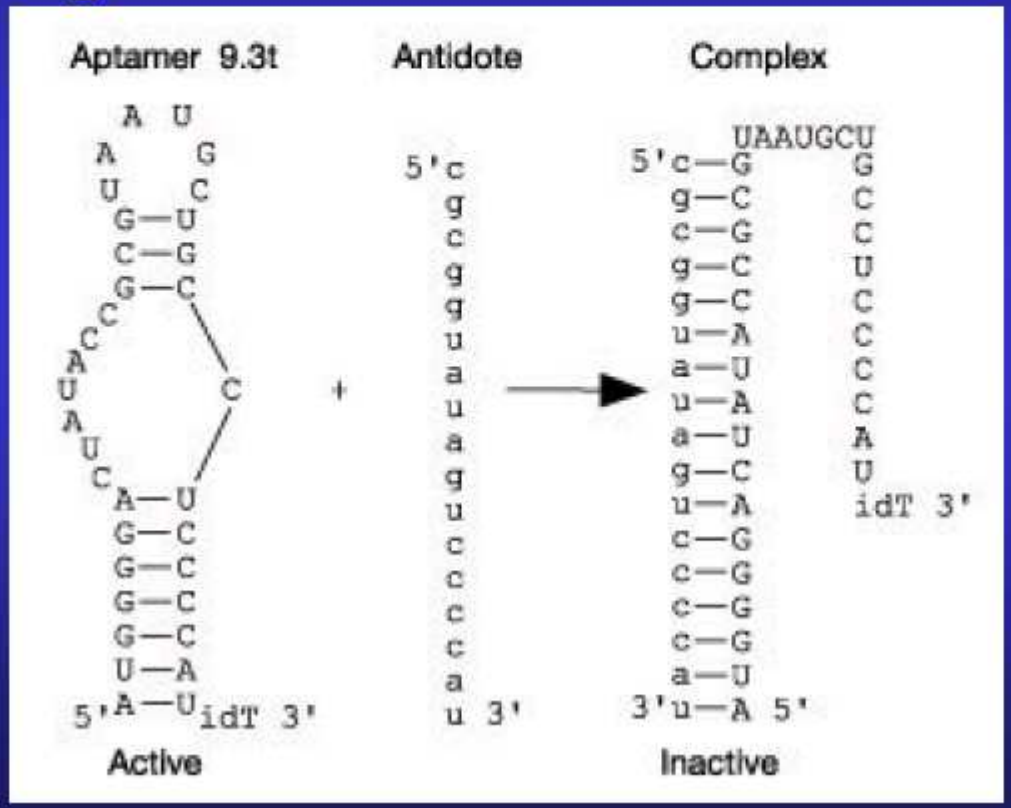


9.3t prolunga il tempo di coagulazione in modo dose-dipendente

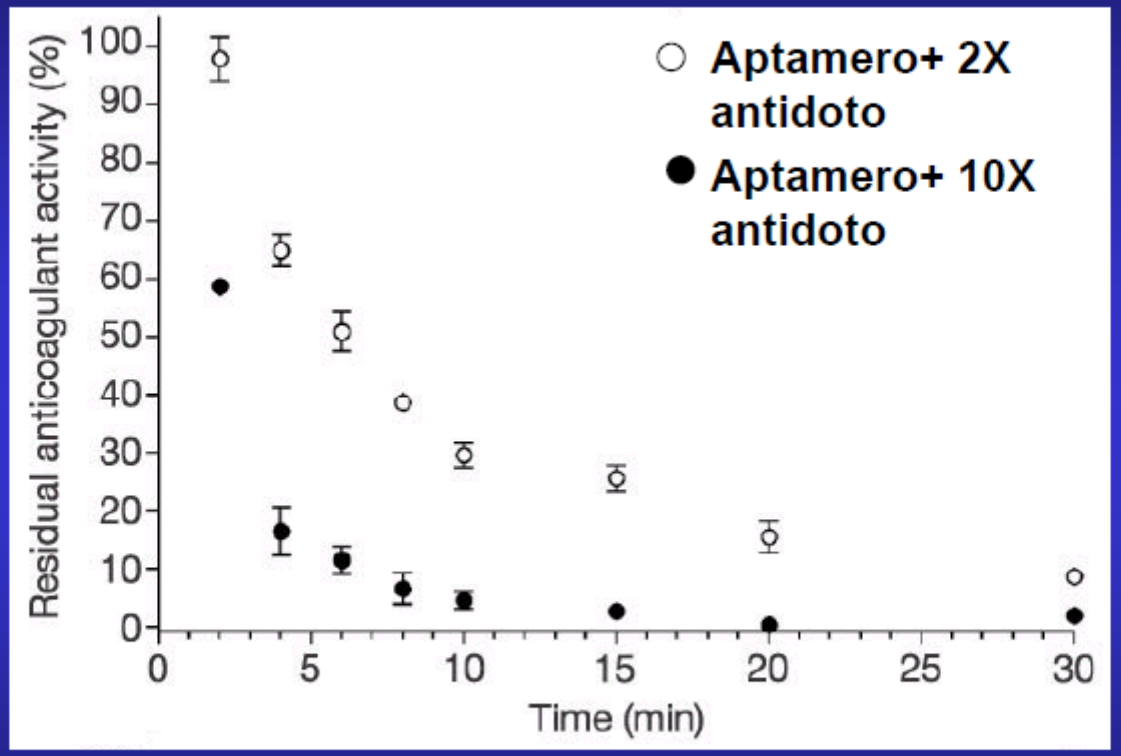
L'aptamero inibisce l'attività del FIXa in vivo

Reversibilità dell'azione dell'aptamero: ANTIDOTO

Antidoto = oligo complementare all'aptamero, in grado di alterare la sua conformazione

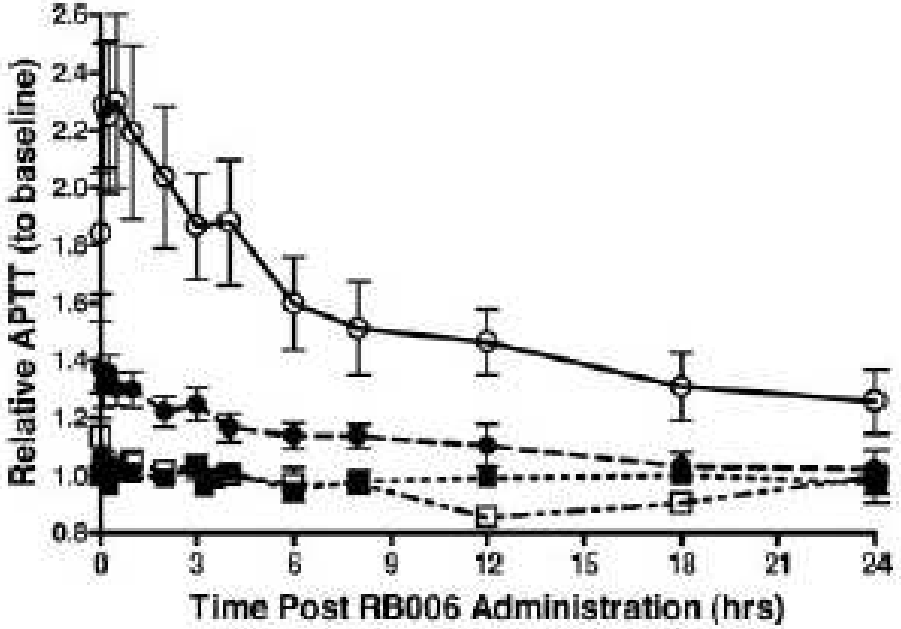


Reversibilità dell'azione dell'aptamero: ANTIDOTO



L'azione dell'antidoto è rapida e dose-dipendente

rmacodinamica: aptamero anti-FIX (RB006) e antidoto (RB007)



ure 5. Pharmacodynamic effects of RB006 at 0 to 24 hours
er administration. The relative increase in APTT over baseline
subjects receiving RB006 followed by placebo (arm 3) is
own vs placebo. Because of the tripping of the prespecified
TT stopping rule, no subjects received a 90-mg dose of
006 followed by placebo. Data represent the mean±SEM for
subjects receiving treatment at each dose level. Lines repre-
nt the best point-to-point fit of the data. ■ Indicates placebo;
15 mg RB006; ●, 30 mg RB006; and ○, 60 mg RB006.

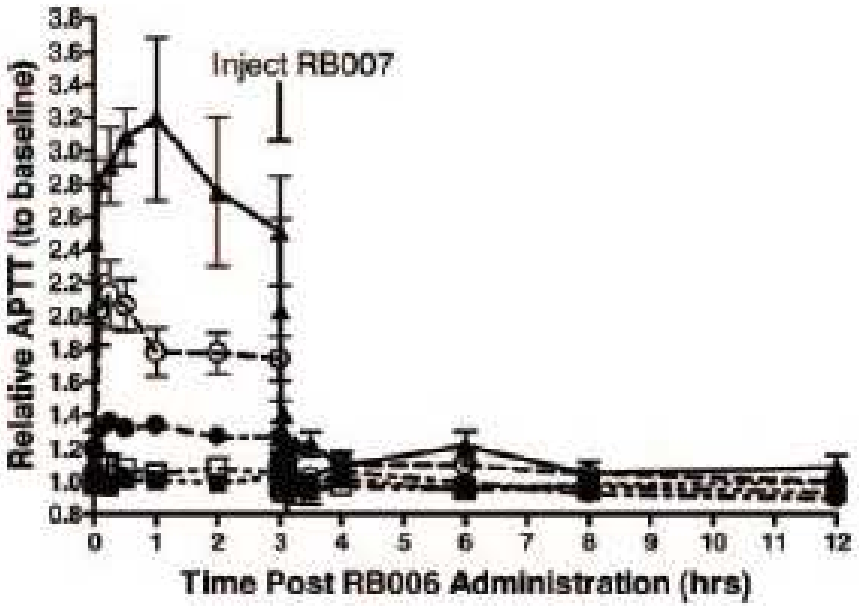


Figure 6. Neutralization of the pharmacodynamic effect of
RB006 by RB007. The relative increase in APTT over basel
for all subjects receiving RB006 followed 3 hours later by R
(arm 2) is shown vs placebo. Data represent the mean±SE
all subjects receiving treatment at each dose level. Lines re
sent the best point-to-point fit. ■ Indicates placebo/placebo
15 mg RB006/30 mg RB007; ●, 30 mg RB006/60 mg RB0
60 mg RB006/120 mg RB007; and ▲, 90 mg RB006/180 m
RB007.

ptamero e CORRELAZIONE CON APTTR

Antidoto e CORRELAZIONE CON APTTR

The Intrinsic Pathway of Coagulation as a Target for Antithrombotic Therapy

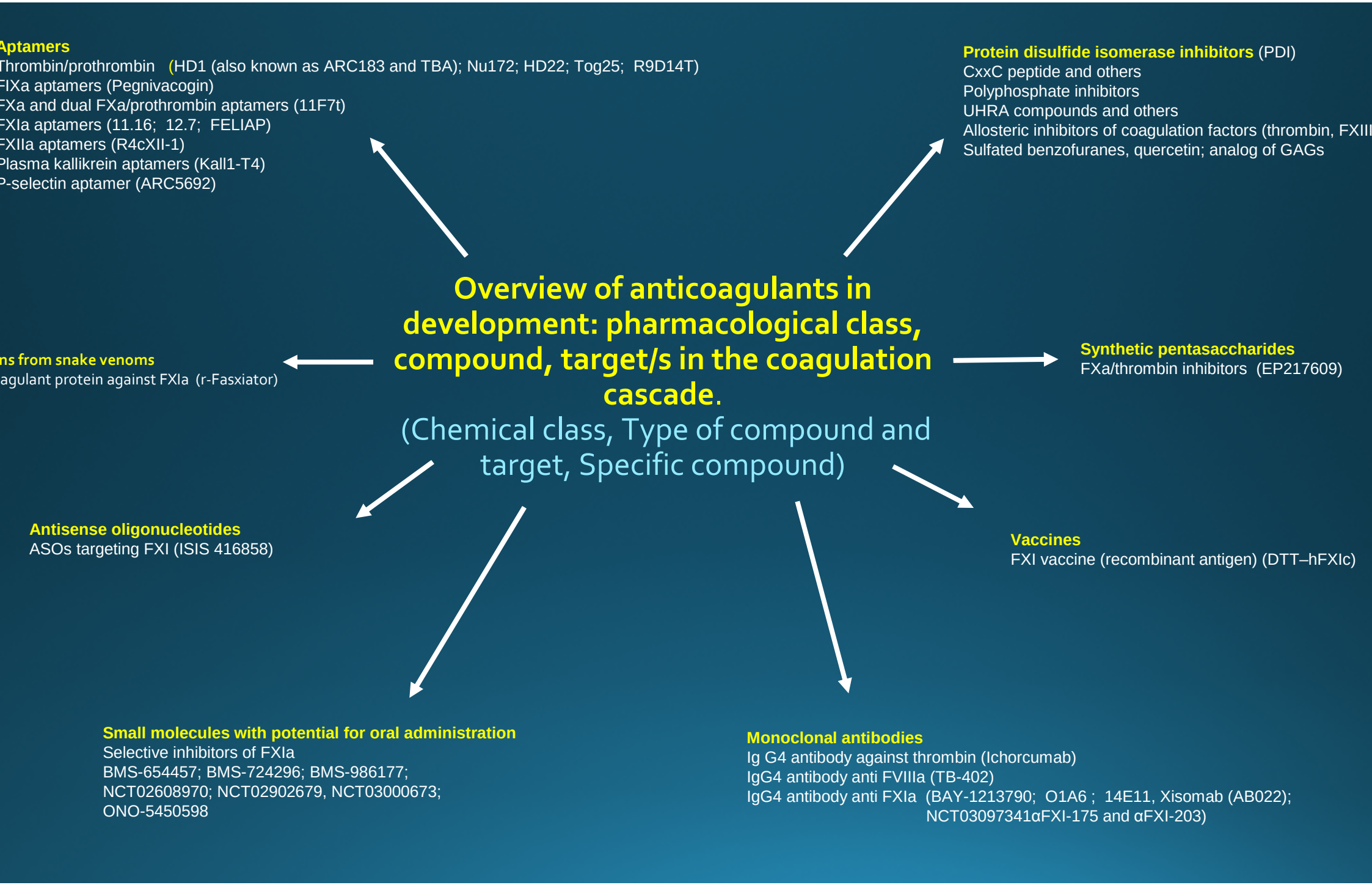
lison P. Wheeler1,2 and **David Gailani**1,3

epartment of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, TN.
epartment of Pediatrics, Vanderbilt University, Nashville, TN.
epartment of Medicine, Vanderbilt University, Nashville, TN.

Hematol Oncol Clin North Am. **2016 October** ; 30(5): 1099–1114. doi:10.1016/j.hoc.2016.05.007

Overview of anticoagulants in development: pharmacological class, compound, target/s in the coagulation cascade.

(Chemical class, Type of compound and target, Specific compound)



Aptamers
Thrombin/prothrombin (HD1 (also known as ARC183 and TBA); Nu172; HD22; Tog25; R9D14T)
FIXa aptamers (Pegnivacogin)
FXa and dual FXa/prothrombin aptamers (11F7t)
FXIa aptamers (11.16; 12.7; FELIAP)
FXIIa aptamers (R4cXII-1)
Plasma kallikrein aptamers (Kall1-T4)
P-selectin aptamer (ARC5692)

Protein disulfide isomerase inhibitors (PDI)
CxxC peptide and others
Polyphosphate inhibitors
UHRA compounds and others
Allosteric inhibitors of coagulation factors (thrombin, FXII
Sulfated benzofuranes, quercetin; analog of GAGs

ns from snake venoms
agulant protein against FXIa (r-Fasxiator)

Synthetic pentasaccharides
FXa/thrombin inhibitors (EP217609)

Antisense oligonucleotides
ASOs targeting FXI (ISIS 416858)

Vaccines
FXI vaccine (recombinant antigen) (DTT–hFXIc)

Small molecules with potential for oral administration
Selective inhibitors of FXIa
BMS-654457; BMS-724296; BMS-986177;
NCT02608970; NCT02902679, NCT03000673;
ONO-5450598

Monoclonal antibodies
Ig G4 antibody against thrombin (Ichorcumab)
IgG4 antibody anti FVIIIa (TB-402)
IgG4 antibody anti FXIa (BAY-1213790; O1A6 ; 14E11, Xisomab (AB022);
NCT03097341αFXI-175 and αFXI-203)

The Intrinsic Pathway of Coagulation as a Target for Antithrombotic Therapy

Attivazione fisiologica dell'Emostasi:

ruolo prevalente del TF

Attivazione patologica dell'Emostasi:

ruolo prevalente della fase di contatto

Key et Al Hemat, 2014

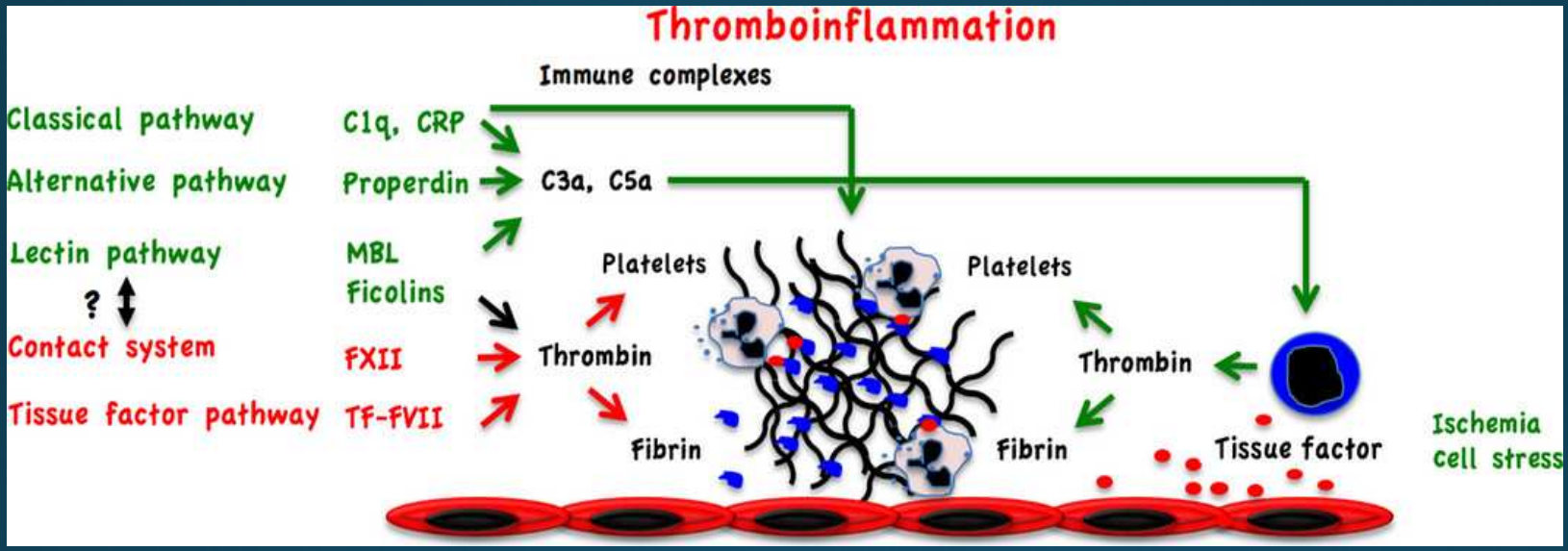
…xxxxx

Chirurgia

Oncologia

I.B.D.

Obesità



atopatie

Diabete

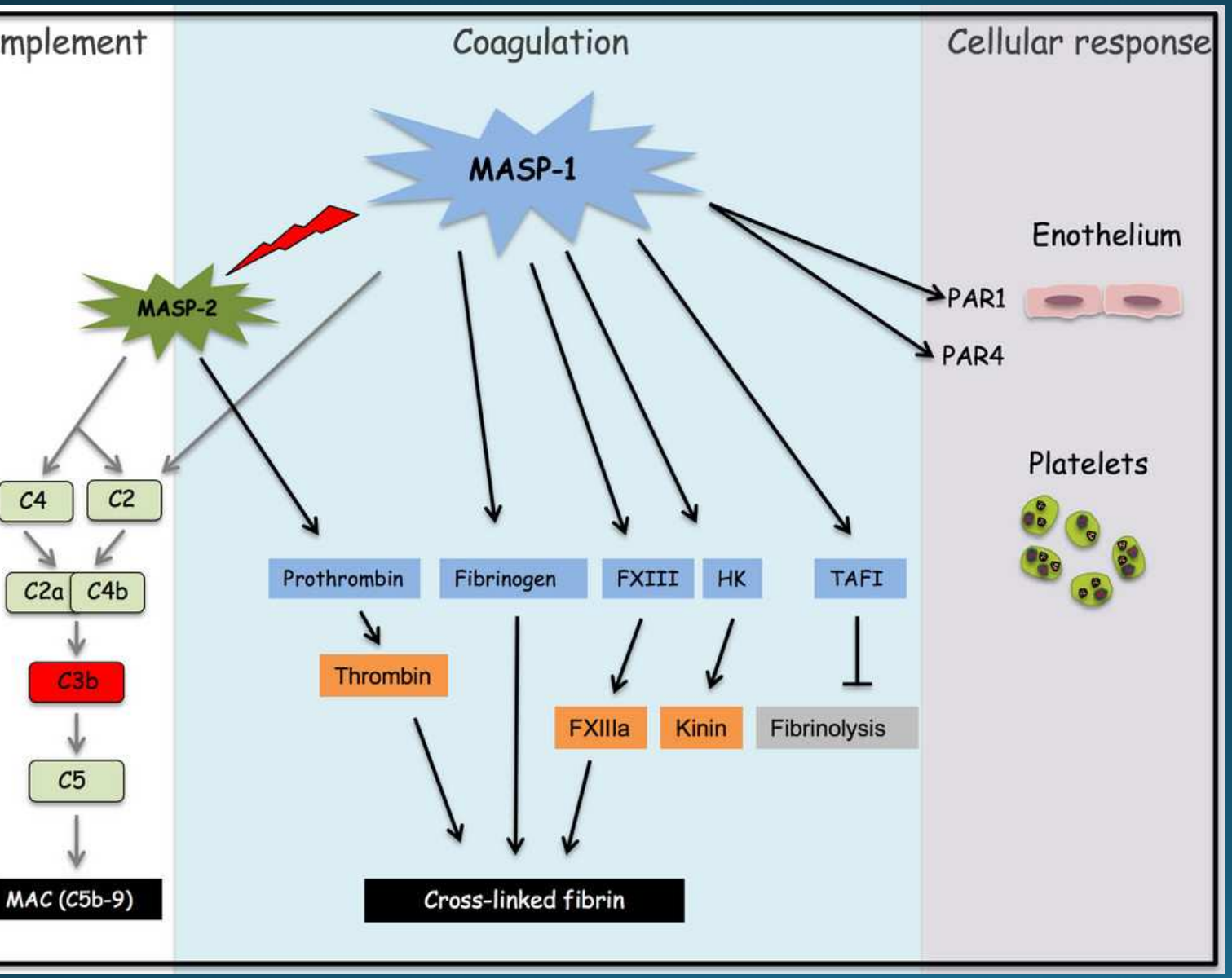
TROMBOINFIAMMAZIONE

Gravidanza

Nefropatie

Malattie reumatologiche

Impianto di biomateriali



ATTIVATORI IN COMUNE....

LA VIA DELLA LECTINA

Le sue proteasi attivano zimogeni di entrambi i sistemi:

- MASP-1: - **thrombin-like substrate specificity:**
  - attiva Fibrinogeno, FXIII, HK, TAFI , PAR-1, PAR-
  - cliva C_2 → amplifica la generazione di C_4bC_2a
  - attiva MASP-2 e MASP-3
- MASP-2: - **Fxa-like substrate specificity:**
  - protrombina
  - cliva C_4 e C_2 → (C_2a/C_4b) → C_3b → C_5 → MAC (C_5

Endo et Al, J. In
Kranp et A
Hess et Al, Hess et

LA VIA INTRINSECA

- Le sue proteasi attivano zimogeni di entrambi i sistemi:

- FXIIa: C_1q, r , s
- FXIa, FXa, FIXa, FIIa: C_3 , C_5
- Plasmina: C_5
- KK: C_3

"... its proteases act as natural C_3 and C_5 convertase"

Amara et Al, J

INIBITORI IN COMUNE….

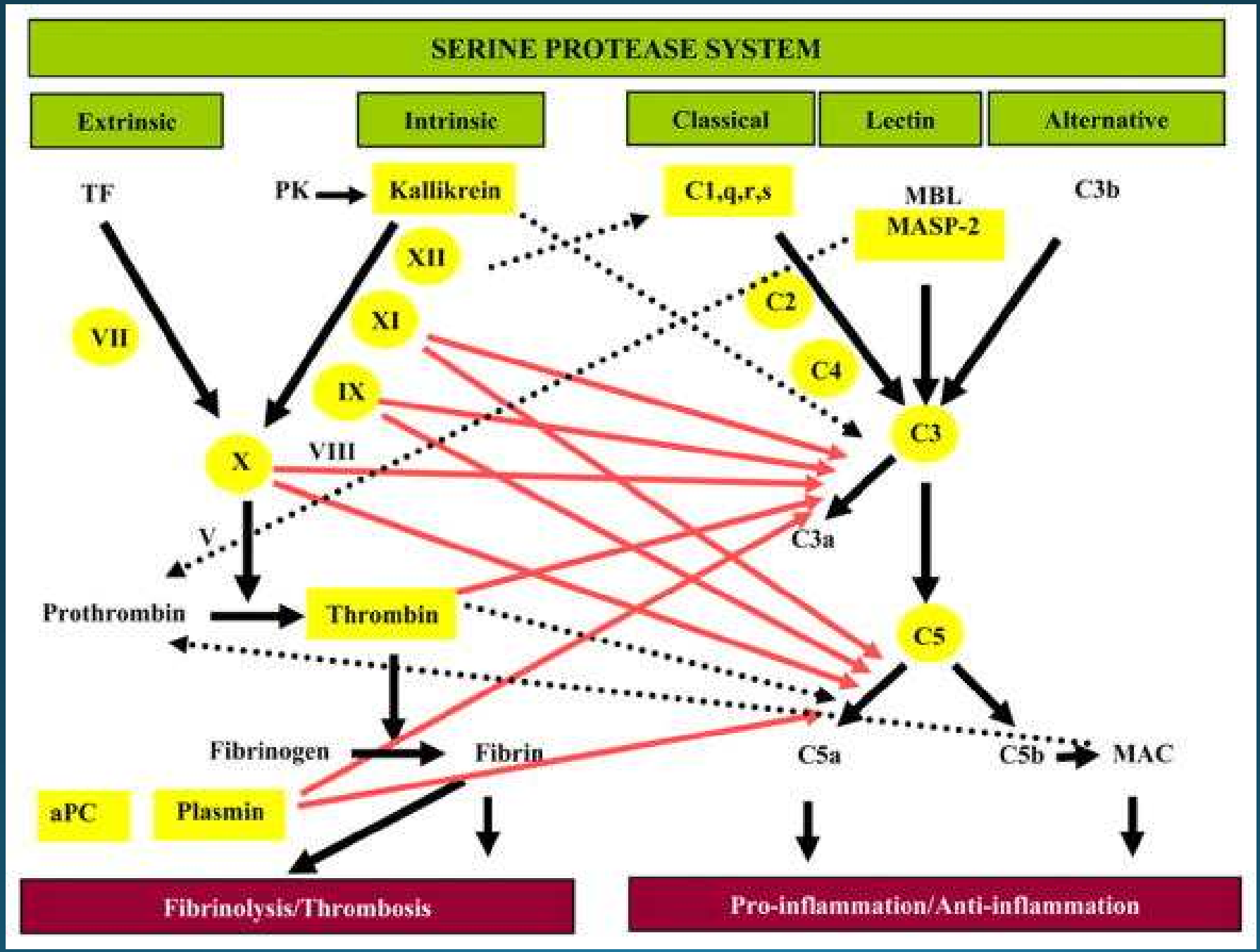
ema del Complemento: controllo e localizzazione.

itori in fase fluida

C1-INH:	MASP-1, MASP-2,	(FXII, FXI, Kallikreina)
C4BP:	CP, LP	(Proteina S)

tema della Coagulazione: controllo e localizzazione.

AT: FXIIa, FXIa, FXa, FIXa, FVIIa, FIIa	(MASP-1, MASP-2, KK)
PC/PS: FVa, FVIIIa, TAFI	(C_3 e C_5)


SERINE PROTEASE SYSTEM
Extrinsic
Intrinsic
Classical
Lectin
Alternative
TF
PK
Kallikrein
C1,q,r,s
MBL
MASP-2
C3b
XII
XI
IX
VII
X
VIII
V
C2
C4
C3
C3a
Prothrombin
Thrombin
C5
Fibrinogen
Fibrin
C5a
C5b
MAC
aPC
Plasmin
Fibrinolysis/Thrombosis
Pro-inflammation/Anti-inflammation