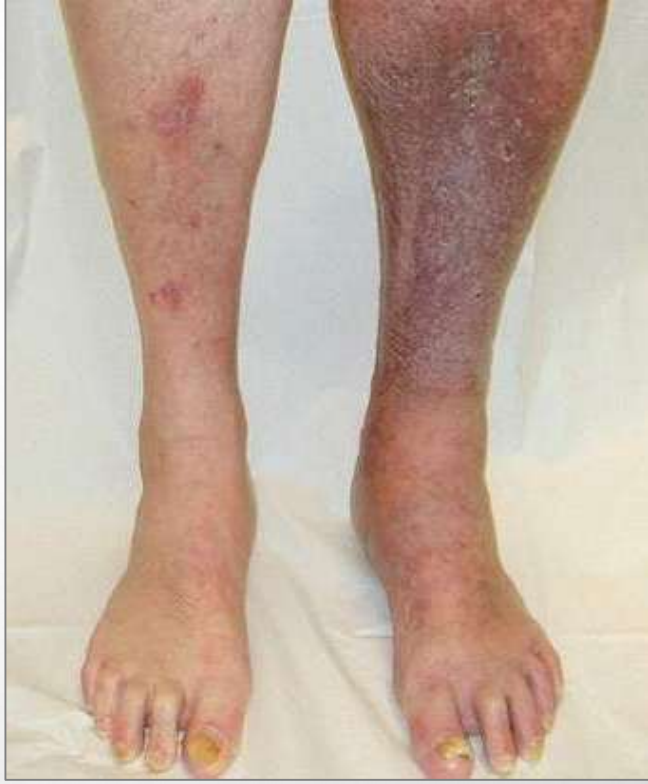
ICTHIC, Bergamo 2018

ALTERNATIVE TARGETS TO TREAT CANCER-INDUCED THROMBOSIS

NICOLA J MUTCH

UNIVERSITY OF ABERDEEN

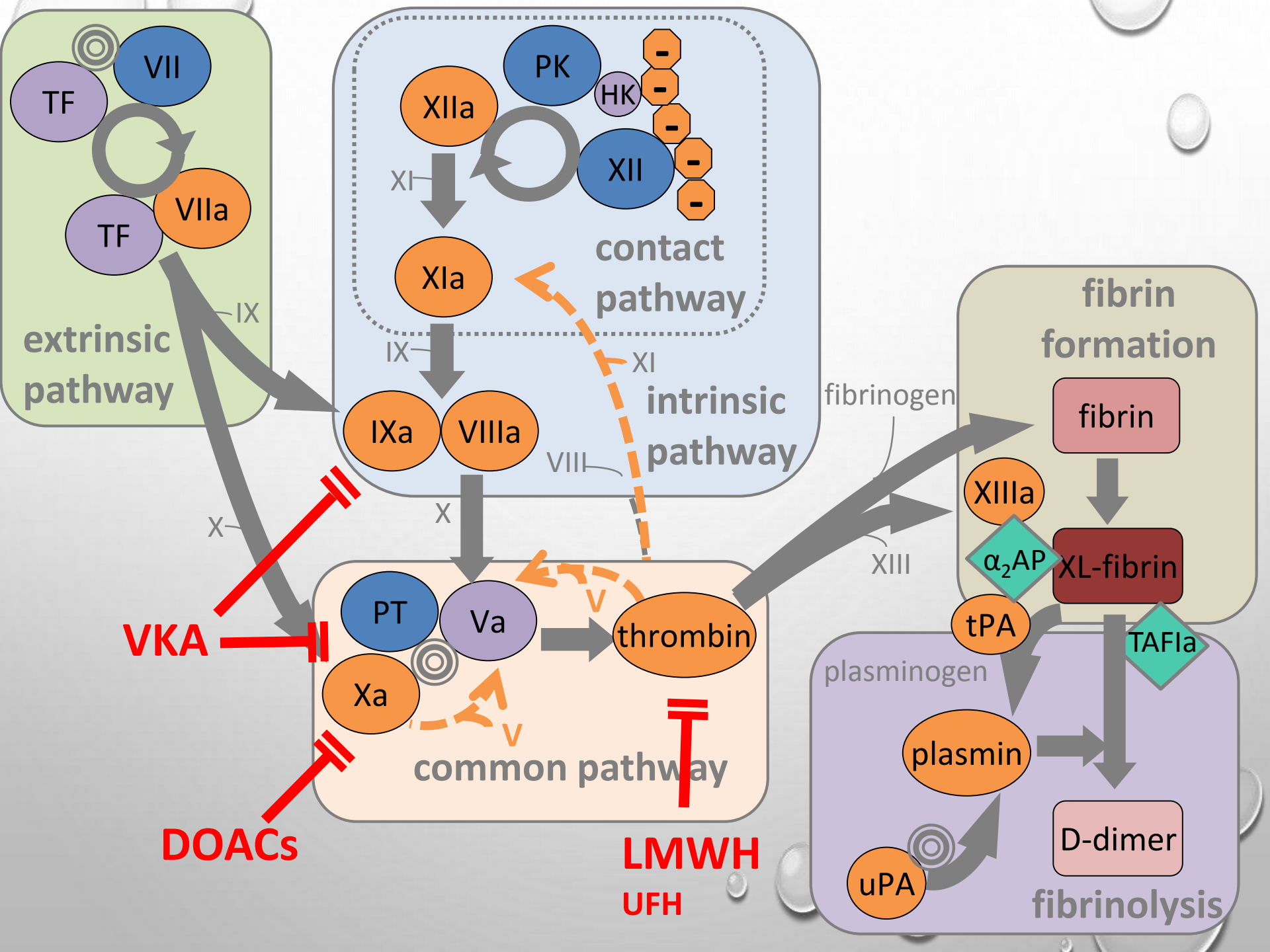


1 IN 4

PEOPLE WORLDWIDE DIE OF CONDITIONS CAUSED BY THROMBOSIS.

IT IS A LEADING CAUSE OF GLOBAL DEATH AND DISABILITY.

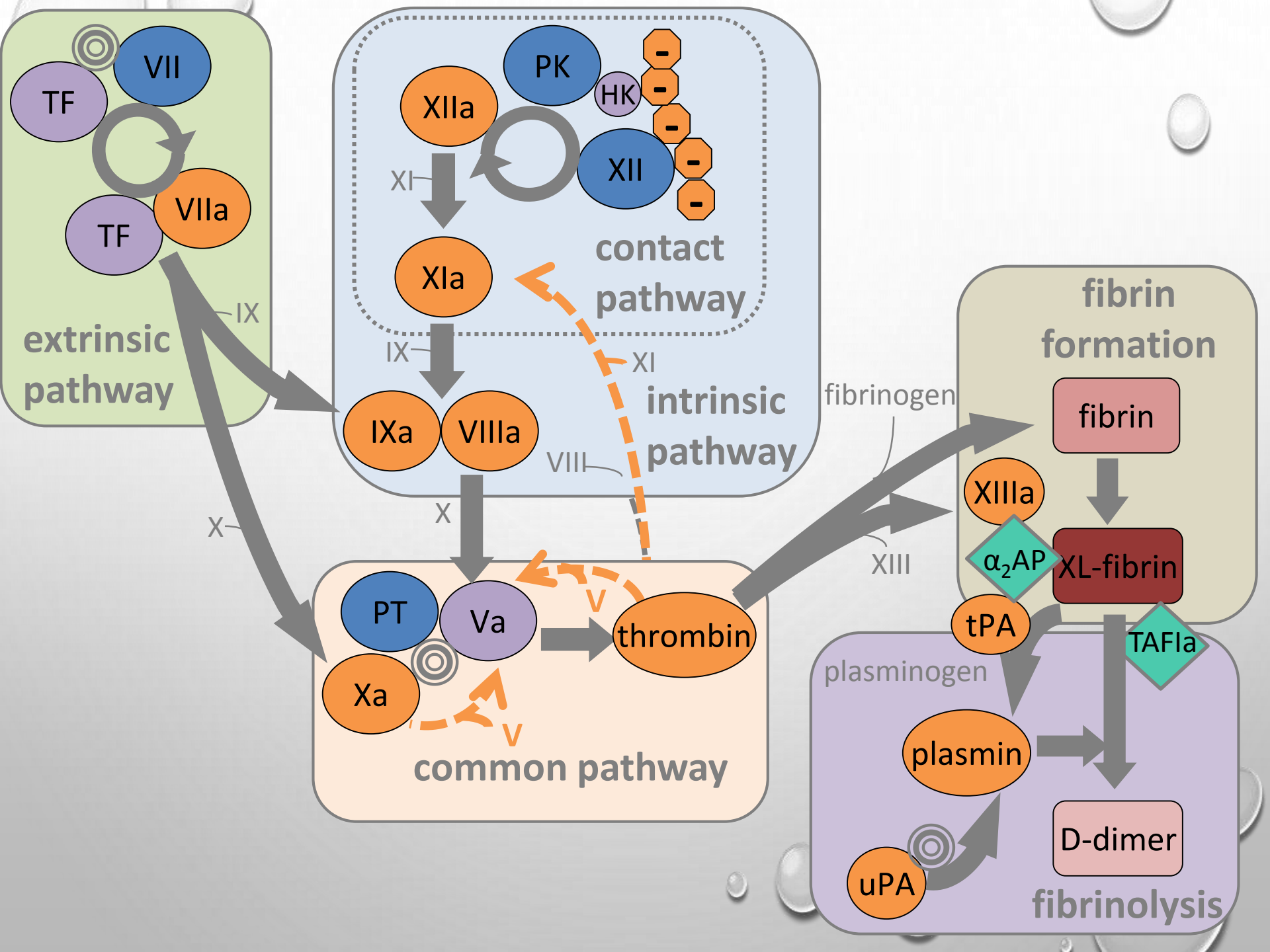
- **Patients with cancer are at a four-fold higher risk of VTE** Horsted *et al*, 2012
- **3-fold higher mortality compared to matched peers without VTE** Sørensen et al, 2000


VII
TF
TF
VIIa
extrinsic pathway
IX
PK
HK
XIIa
XII
XI
contact pathway
XIa
IX
XI
intrinsic pathway
IXa
VIIIa
VIII
X
X
PT
Va
thrombin
V
Xa
V
common pathway
VKA
DOACs
LMWH
UFH
fibrinogen
fibrin formation
fibrin
XIIIa
XIII
α2AP
XL-fibrin
tPA
TAFIa
plasminogen
plasmin
D-dimer
uPA
fibrinolysis

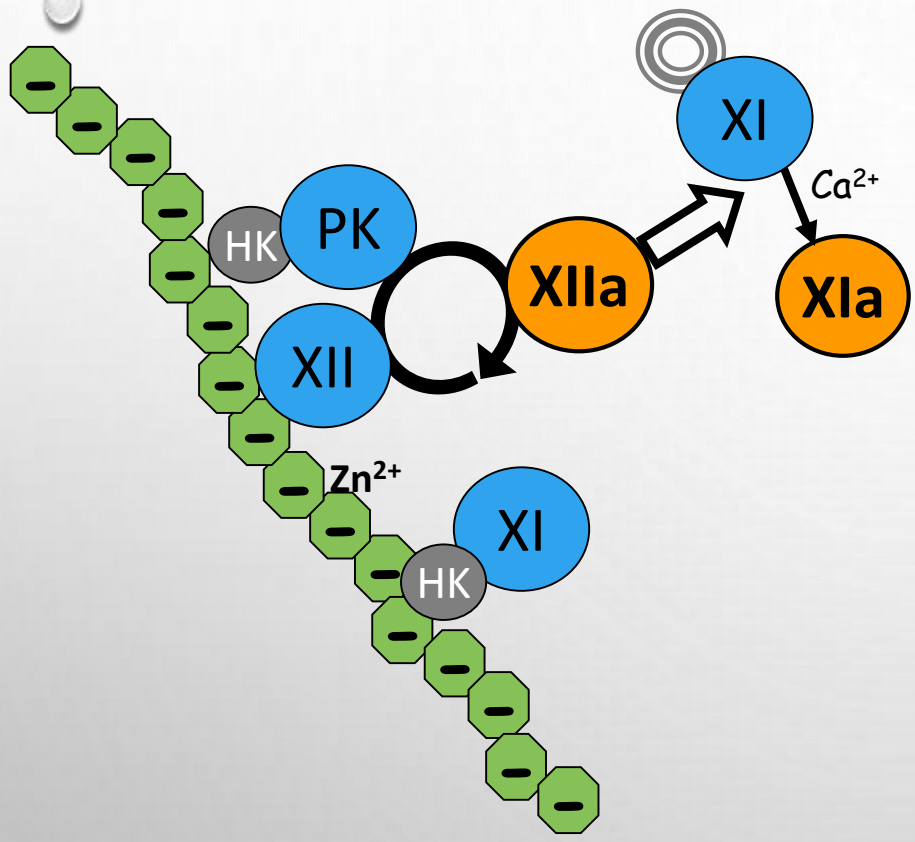
- **In cancer anticoagulation is associated with an increased risk of bleeding**

Holy grail:

An antithrombotic drug that reduces thrombosis with minimal or no bleeding complications


VII
TF
VIIa
TF
extrinsic pathway
IX
X
PK
HK
XIIa
XII
XI
XIa
contact pathway
IX
XI
IXa
VIIIa
VIII
intrinsic pathway
X
PT
Va
V
thrombin
Xa
V
common pathway
fibrinogen
fibrin
fibrin formation
XIII
XIIIa
α2AP
XL-fibrin
tPA
TAFIa
plasminogen
plasmin
D-dimer
uPA
fibrinolysis

Contact pathway activation



Natural surfaces

Polyphosphate
Smith SA*, Mutch NJ* *et al. PNAS; 2006; 103: 903-8*

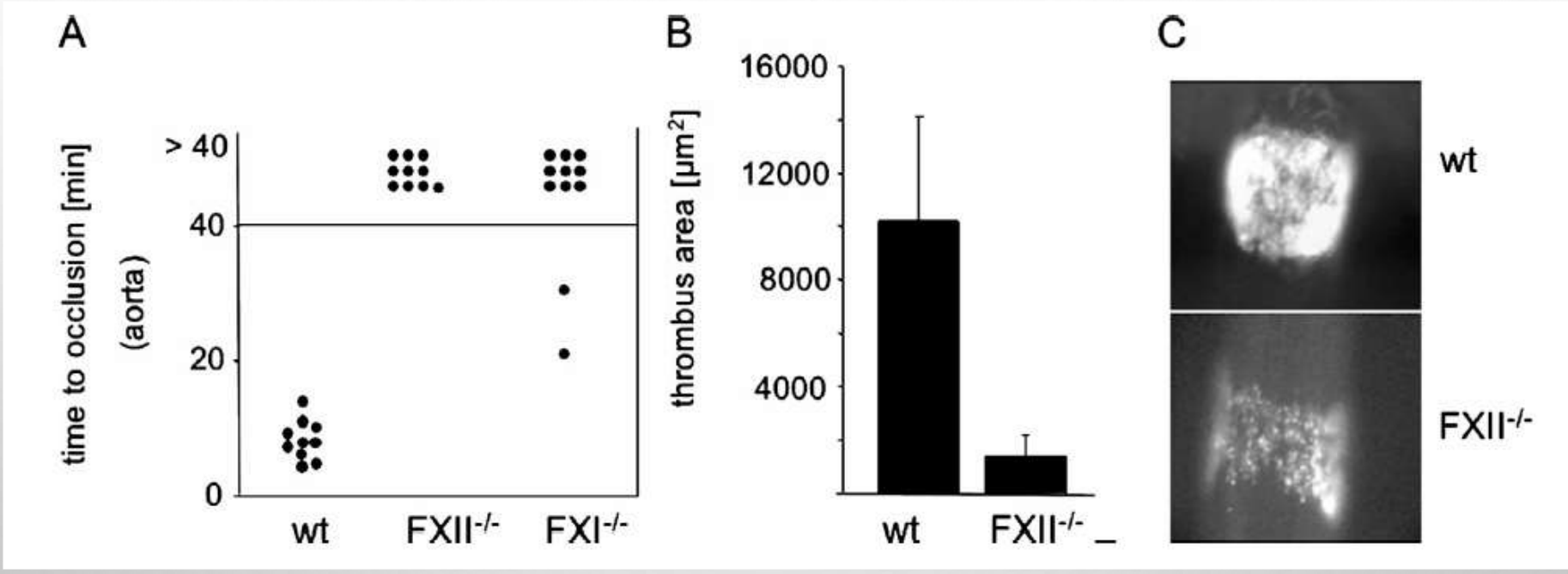
DNA/RNA
Kannemeier C *et al. PNAS; 2007; 104: 6388-93*

Neutrophill extracellular traps (NETs) **Gould TJ et al. ATVB; 2014; 34:1977-84**

Collagen
van der Meijer PE. Blood; 2009; 114:889-90.

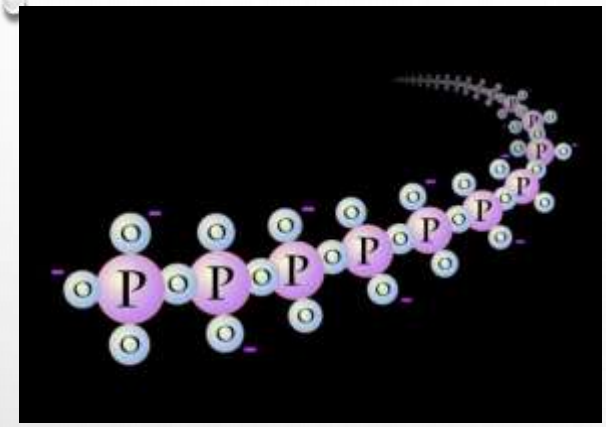
Misfolded proteins
Maas C *et al.* J Clin Invest. 2008 Sep;118(9):3208-18.

FXII deficiency attenuates thrombosis but not haemostasis

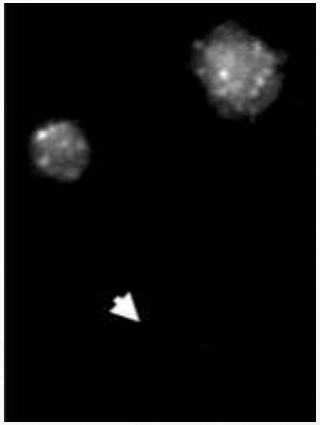


Renné et al, JEM. 2005; 202:271-281

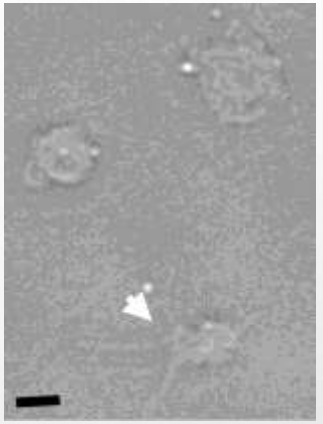
Platelet polyphosphate (polyP)



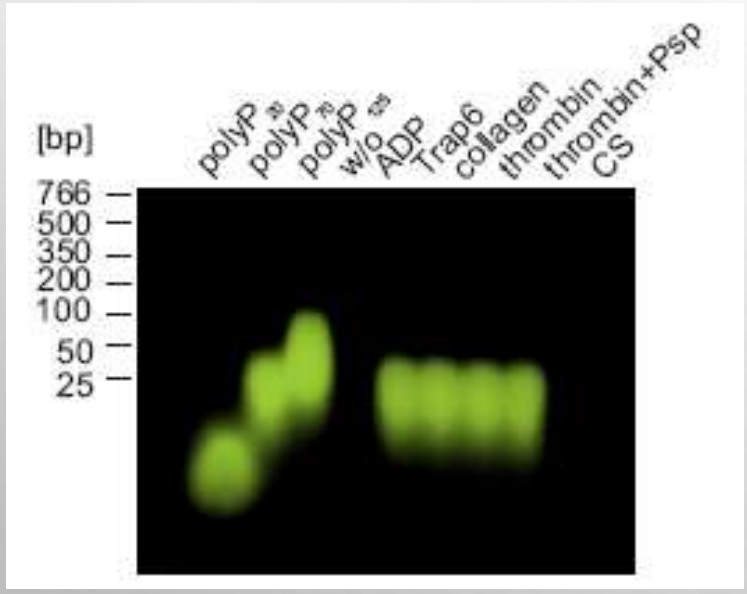
DAPI stain

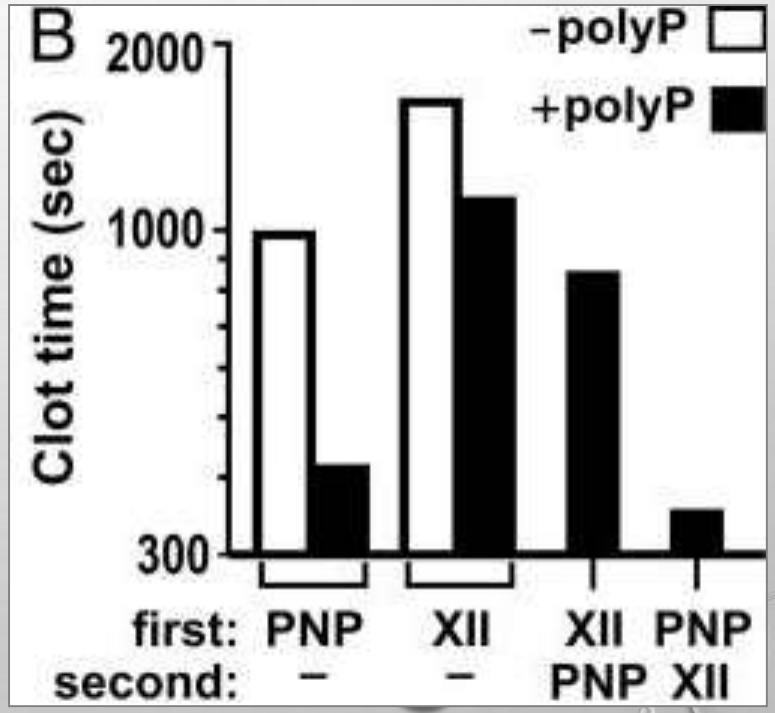


Bright field



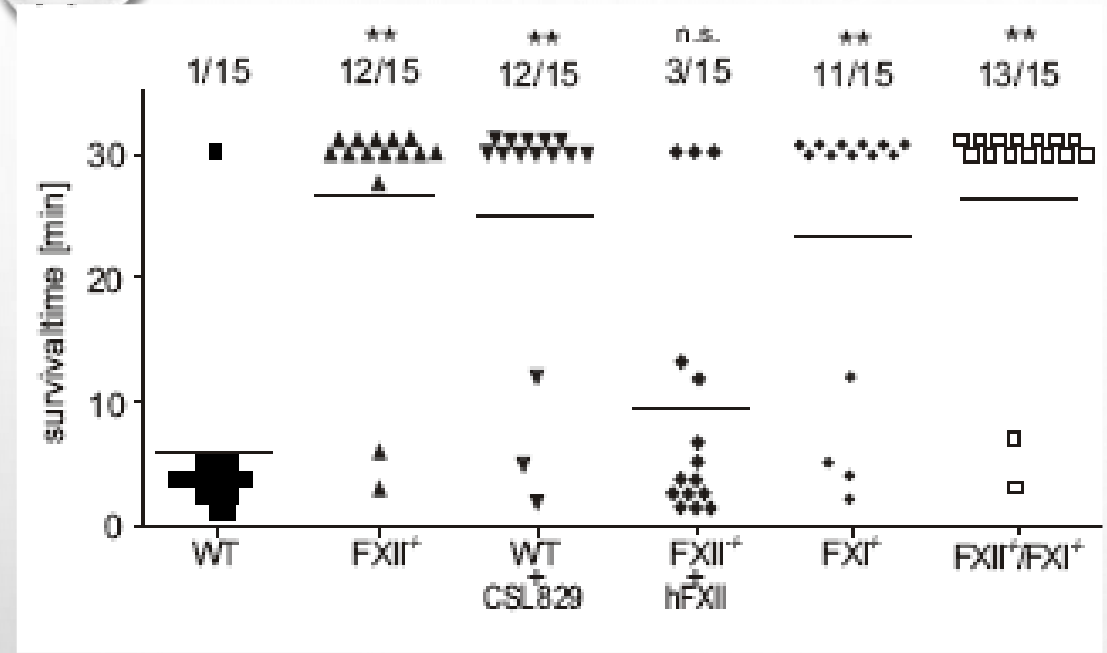
= 10 μm

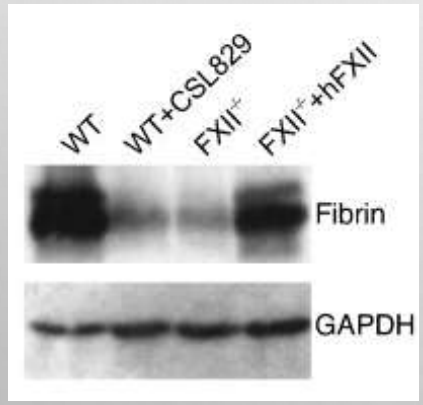


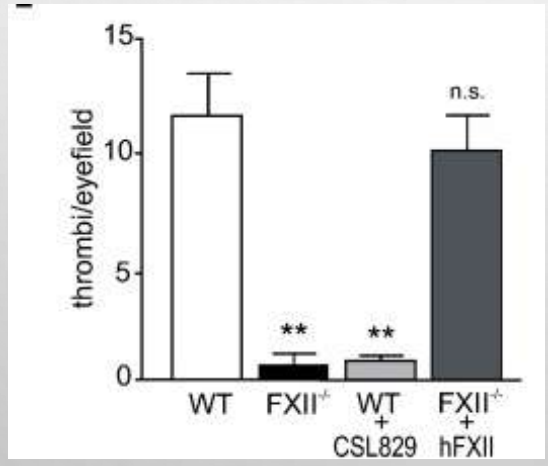


Ruiz, F. A. et al. J. Biol. Chem. 2004; ***279****:44250-44257*
Müller, F, Mutch NJ* et al, Cell. 2009;* ***139****:1143-1156*
Smith SA*, Mutch NJ* et al*. PNAS; 2006;* ***103:*** *903-8.*

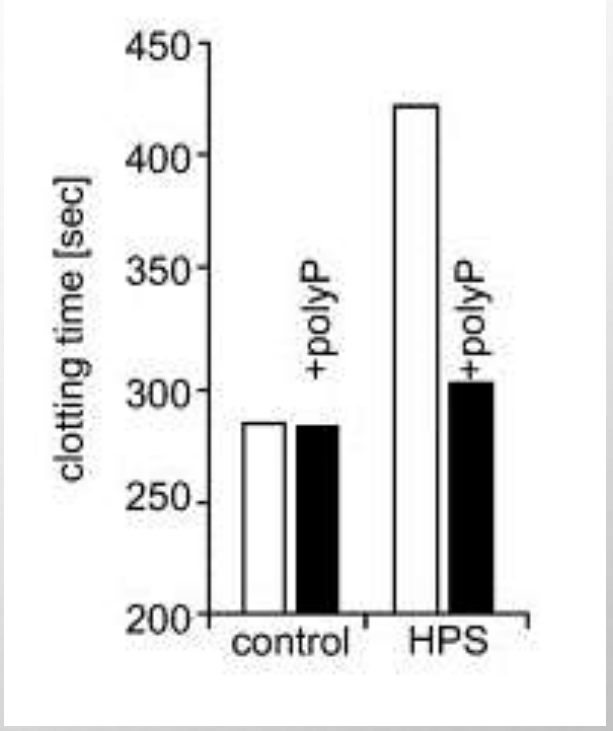
PolyP initiates FXII activation







Hermansky-Pudlak Syndrome



Müller, F, Mutch NJ* et al, Cell. 2009; 139:1143-1156*

FXI/FXII deficiency in humans….

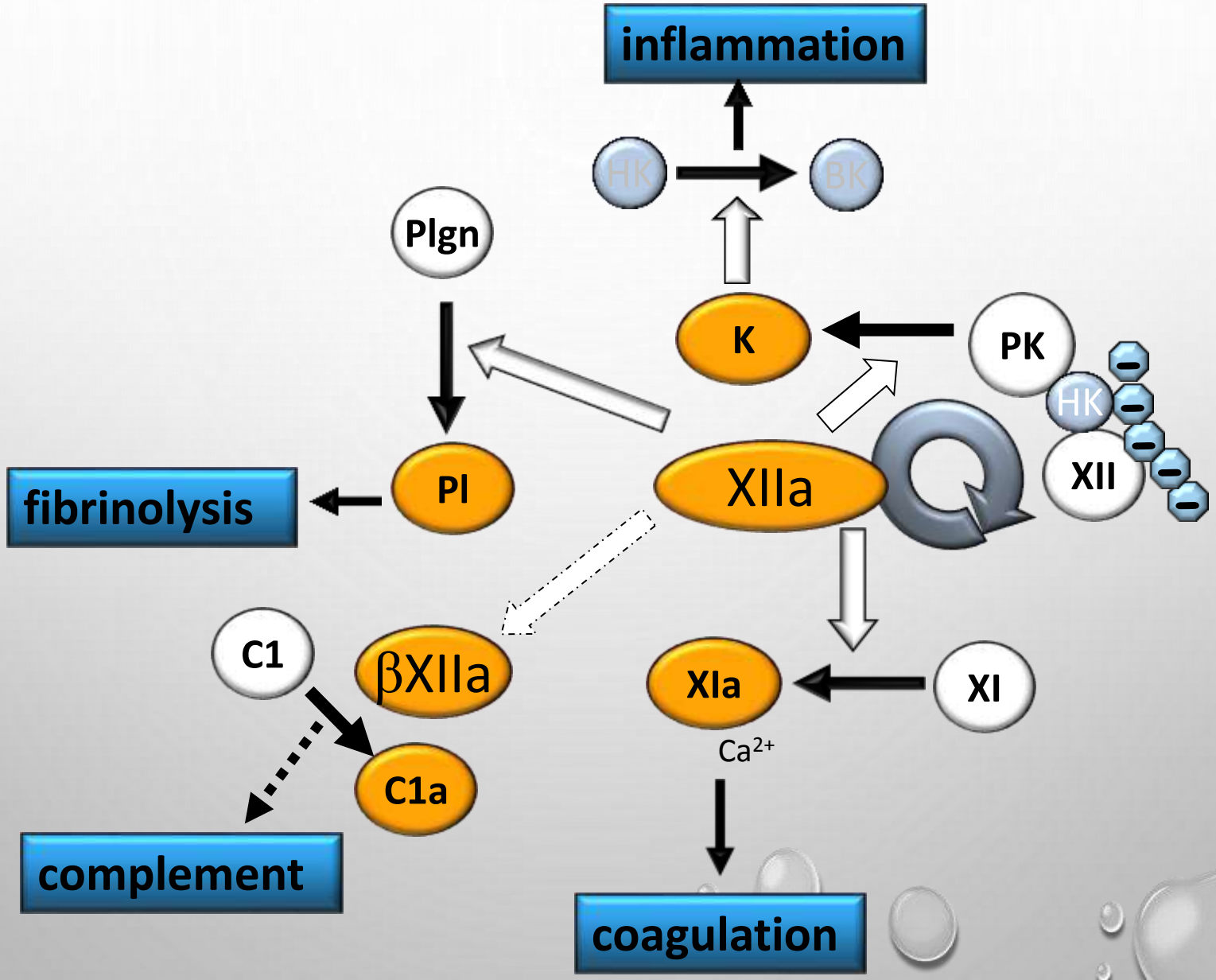
FXI deficiency

- protected from VTE and ischemic stroke
- higher levels associated with increased risk of VTE and ischemic stroke

FXII deficiency

- no differences in VTE or ischemic stroke

The promiscuous contact pathway….



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Table 2. Efficacy and Safety Outcomes.*

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)
Exploratory efficacy outcome: extent of venous thrombosis on venography			
Patients with deep-vein thrombosis — no. (%)	36 (27)	3 (4)	21 (30)

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

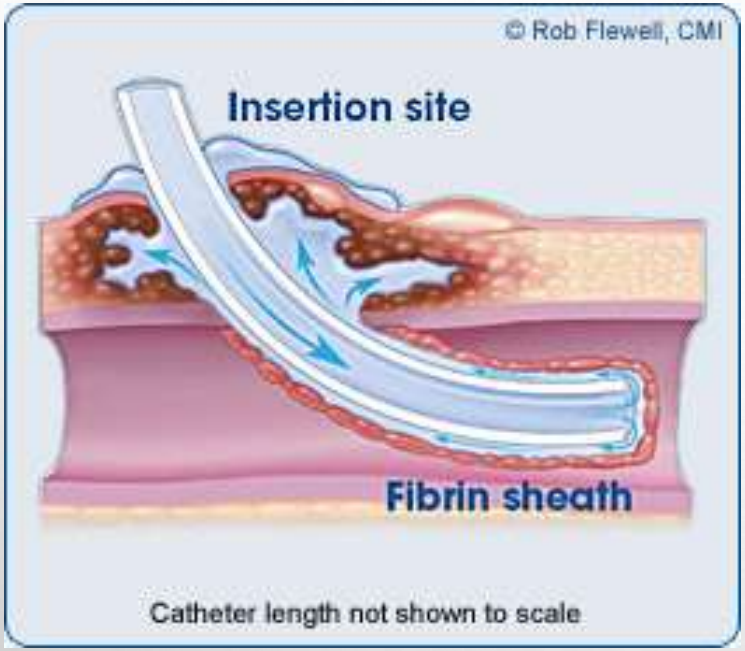
Role for the intrinsic pathway in driving VTE

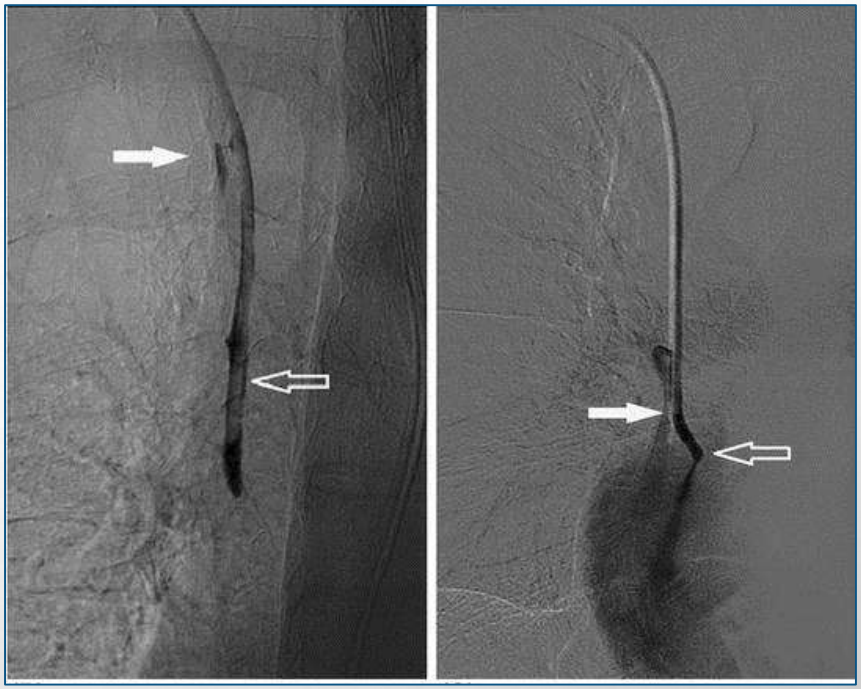
Which is the better target – FXI or FXII?

	FXI	FXII
Epidemiological data	Strong	Weak
Risk of bleeding	Low	None
Evidence for crucial role in thrombosis	Phase 2	Preclinical
Potential for bypassing inhibition	Back activation of FXI by thrombin	None
Potential for off-target effects	Low	May modulate inflammation via BK

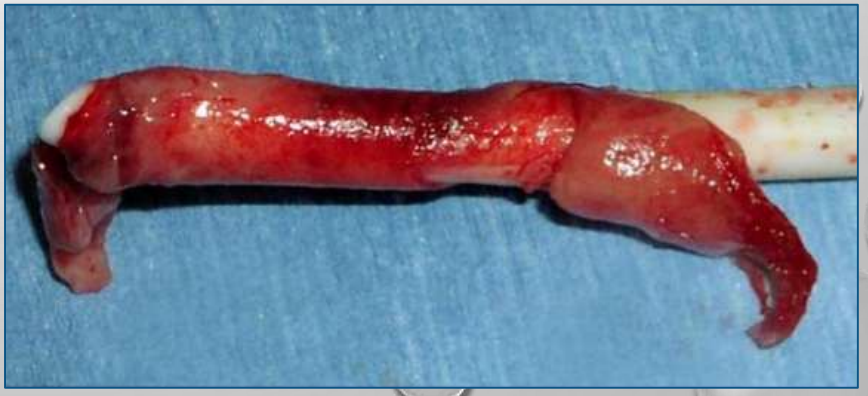
Weitz and Fredenburg, 2017

Catheter-related thrombosis



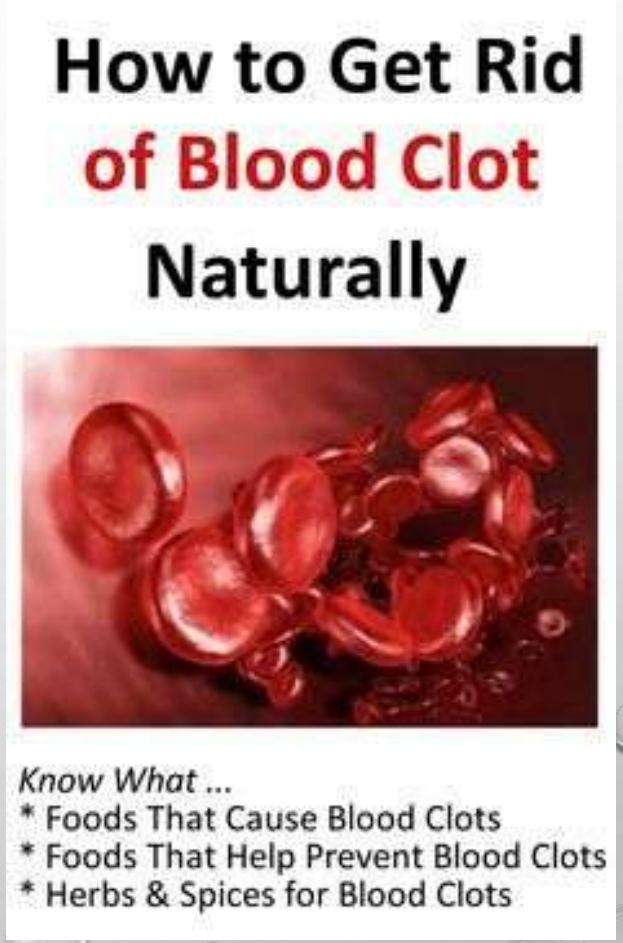


- ~50% catheters due to thrombosis
- FXII-driven thrombosis

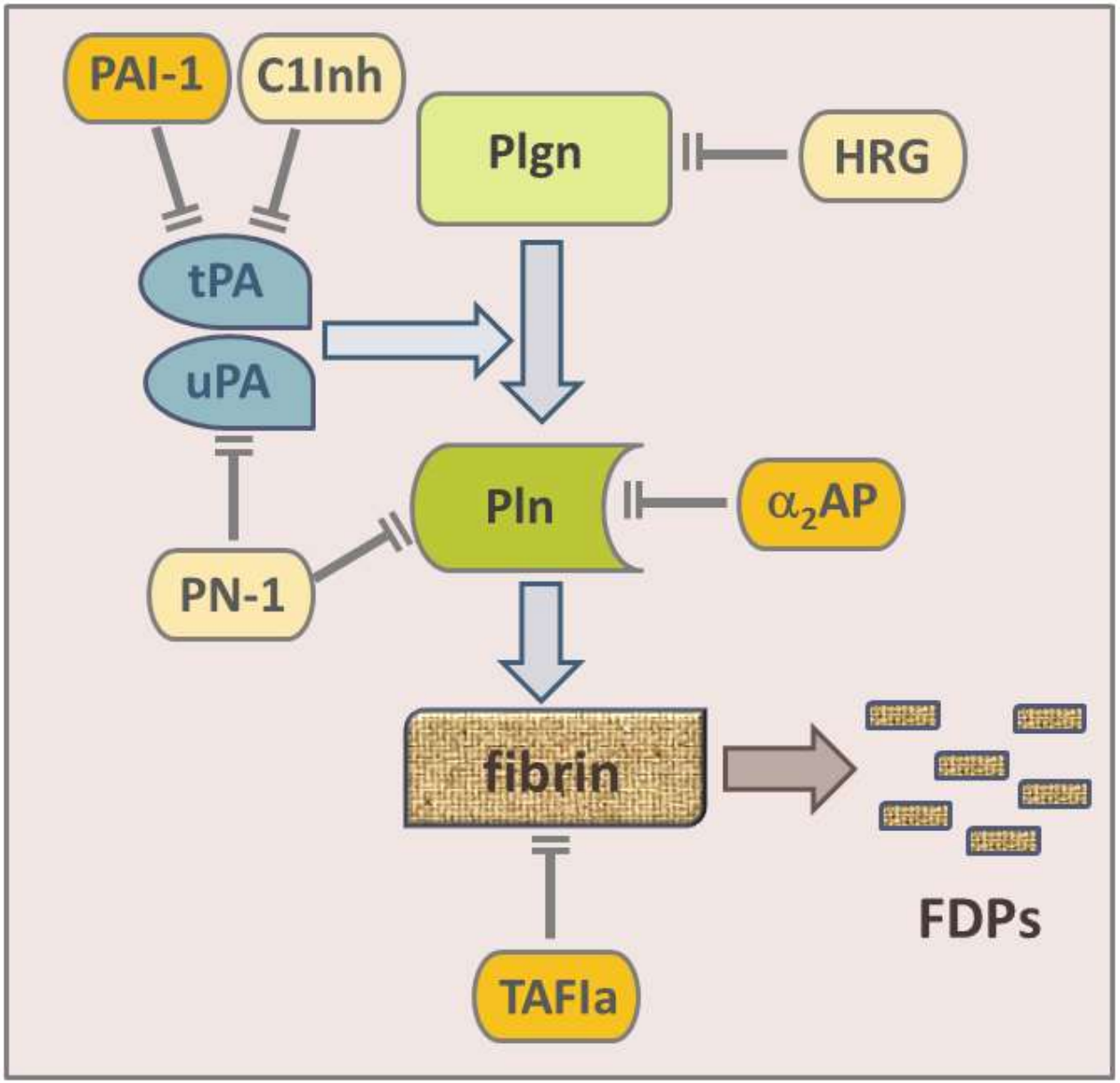


The contact pathway has potential as a safer 'antithrombotic' target?

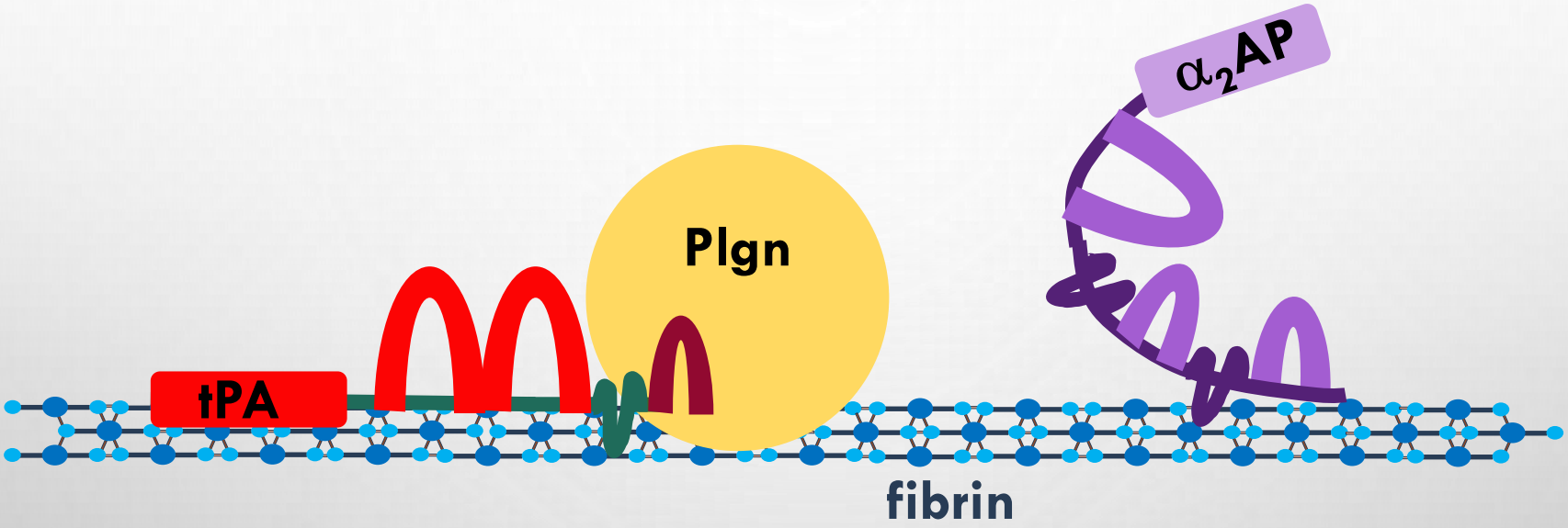
FXII- and FXI-directed anticoagulant strategies are a new era in anticoagulation that will minimise thrombosis with minimal risk of bleeding risk.



Fibrinolysis

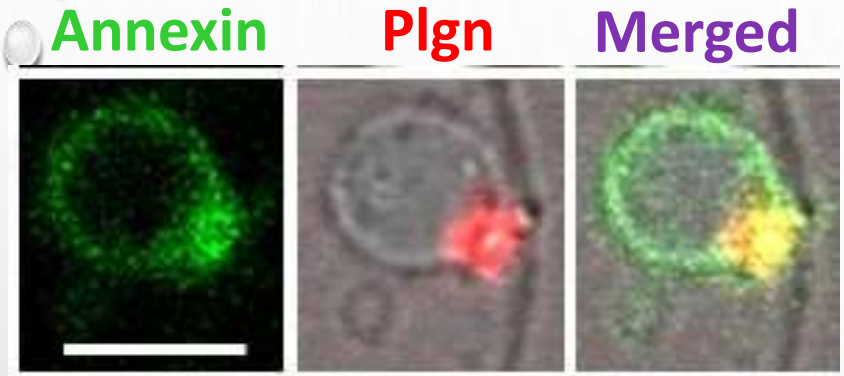


Fibrinolysis is also dramatically enhanced by surfaces



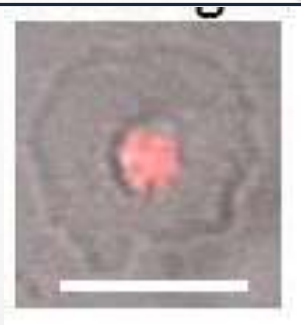
Fibrin stimulates tPA-mediated plasminogen activation 1250-fold i.e. mediates its own destruction

Fibrinolysis – nature's own 'brakes'



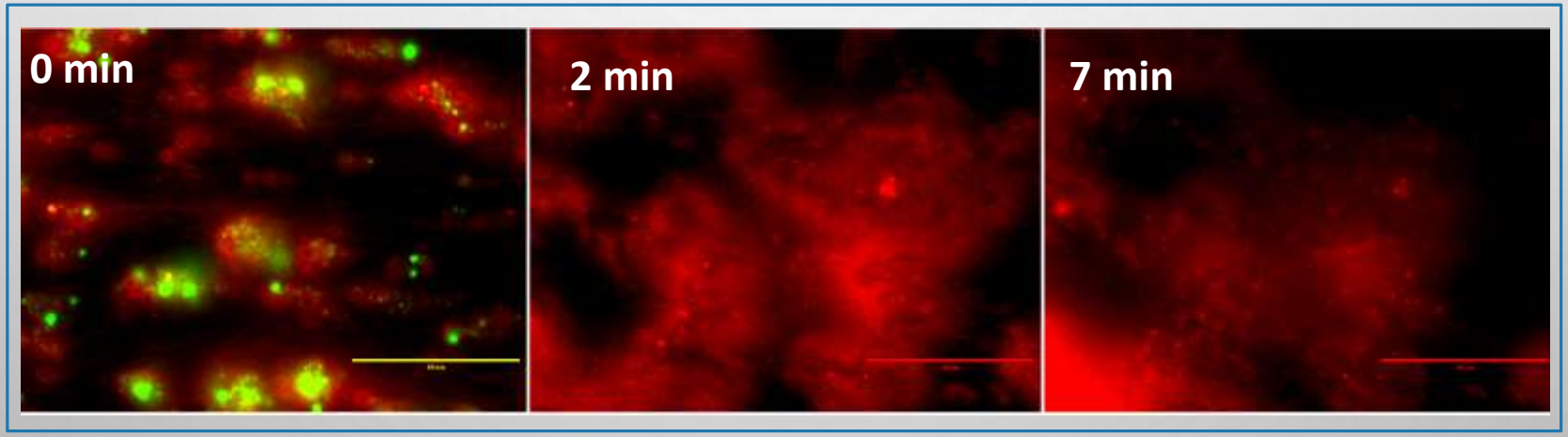
Thrombin/collagen

Plasminogen on procoagulant platelets



Plasminogen on spread platelets

Whyte CS, Swieringa F, van Der Meijden P, Heemskerk J, & Mutch NJ, *Blood 2015; **125**: 2568*



Can we harness nature's own 'brake' service to develop novel antithrombotic drugs?

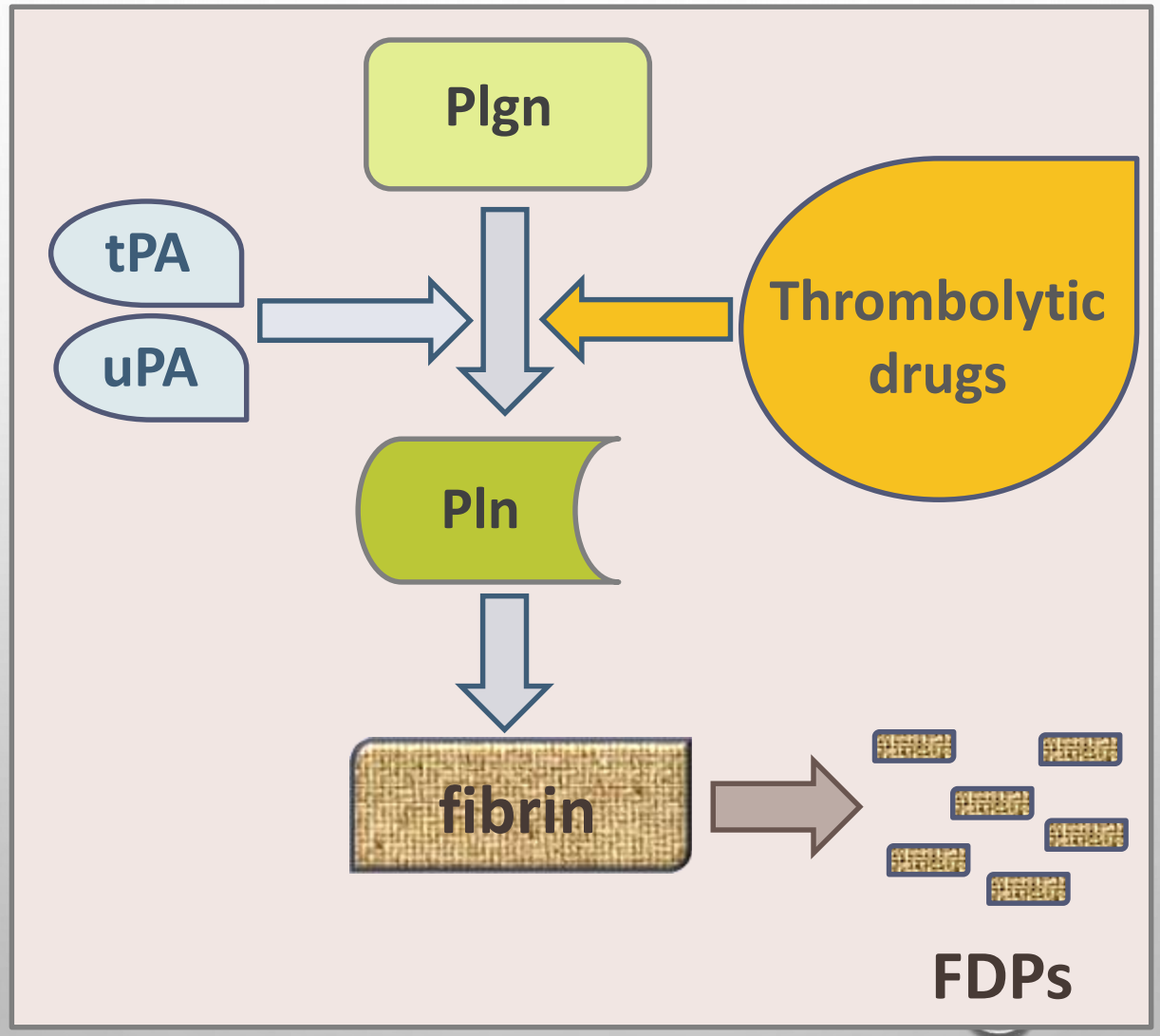
Thrombolytic drugs

Current uses:

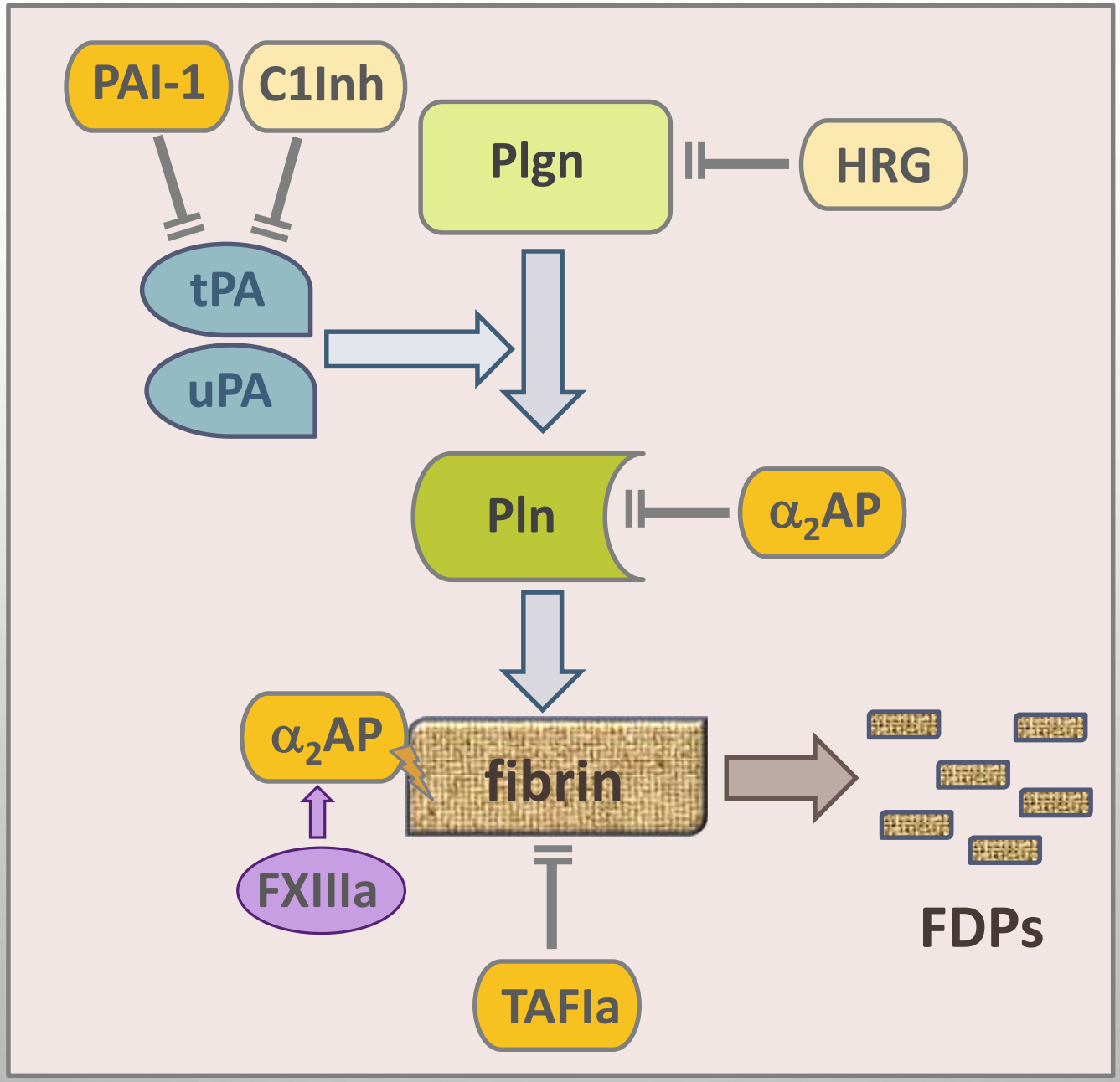
- ✓Acute ischaemic stroke – within 4 h window
- ✓Acute myocardial infarction
- ✓Peripheral arterial thrombosis
- ✓Massive pulmonary embolism & DVT
- ✓Occluded haemodialysis shunts

Based on tPA

Current thrombolytic drugs drive plasminogen activation

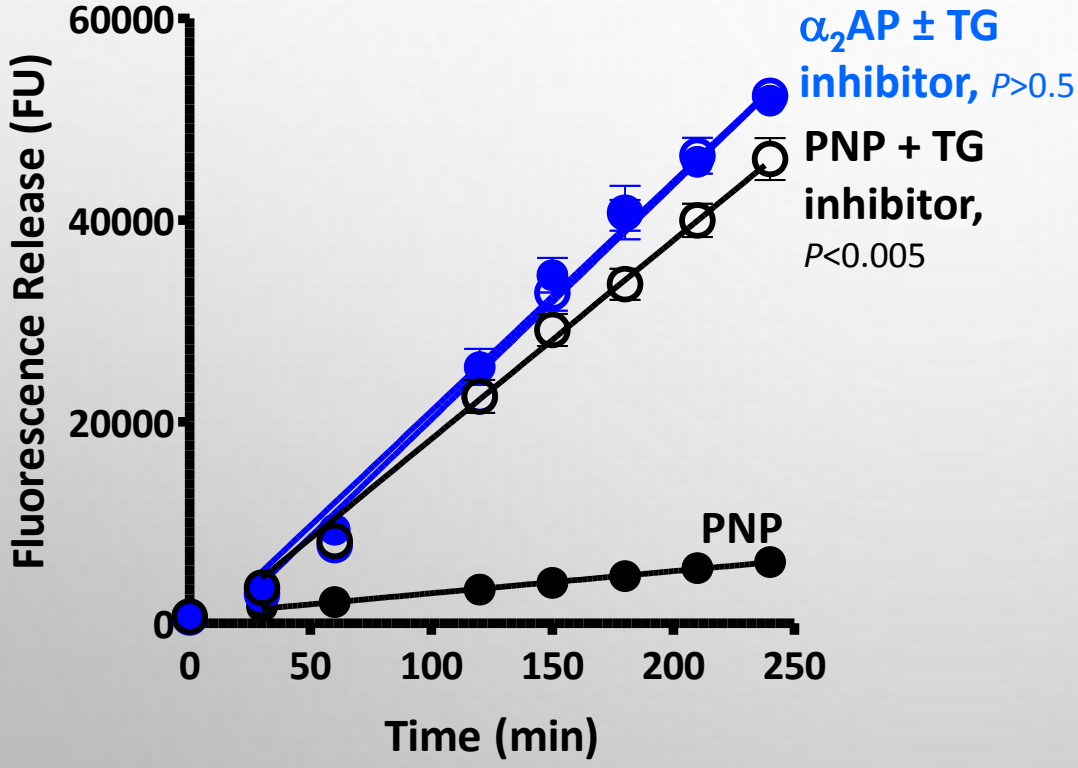


Targeting Inhibitors

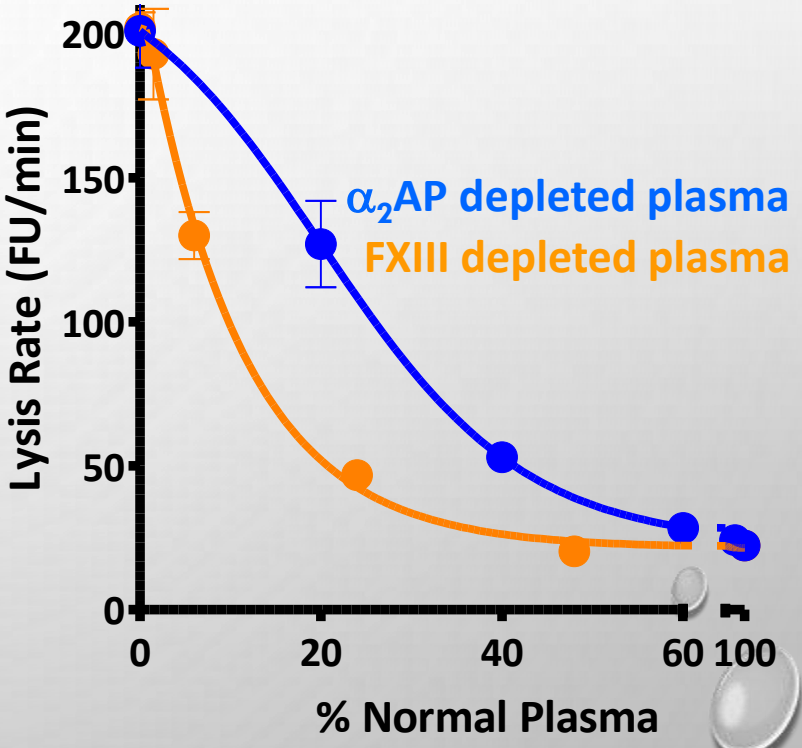


α_2AP & FXIII deficient plasma lyse at strikingly similar rates

TG inhibitor has no impact on lysis of α_2AP-depleted thrombi

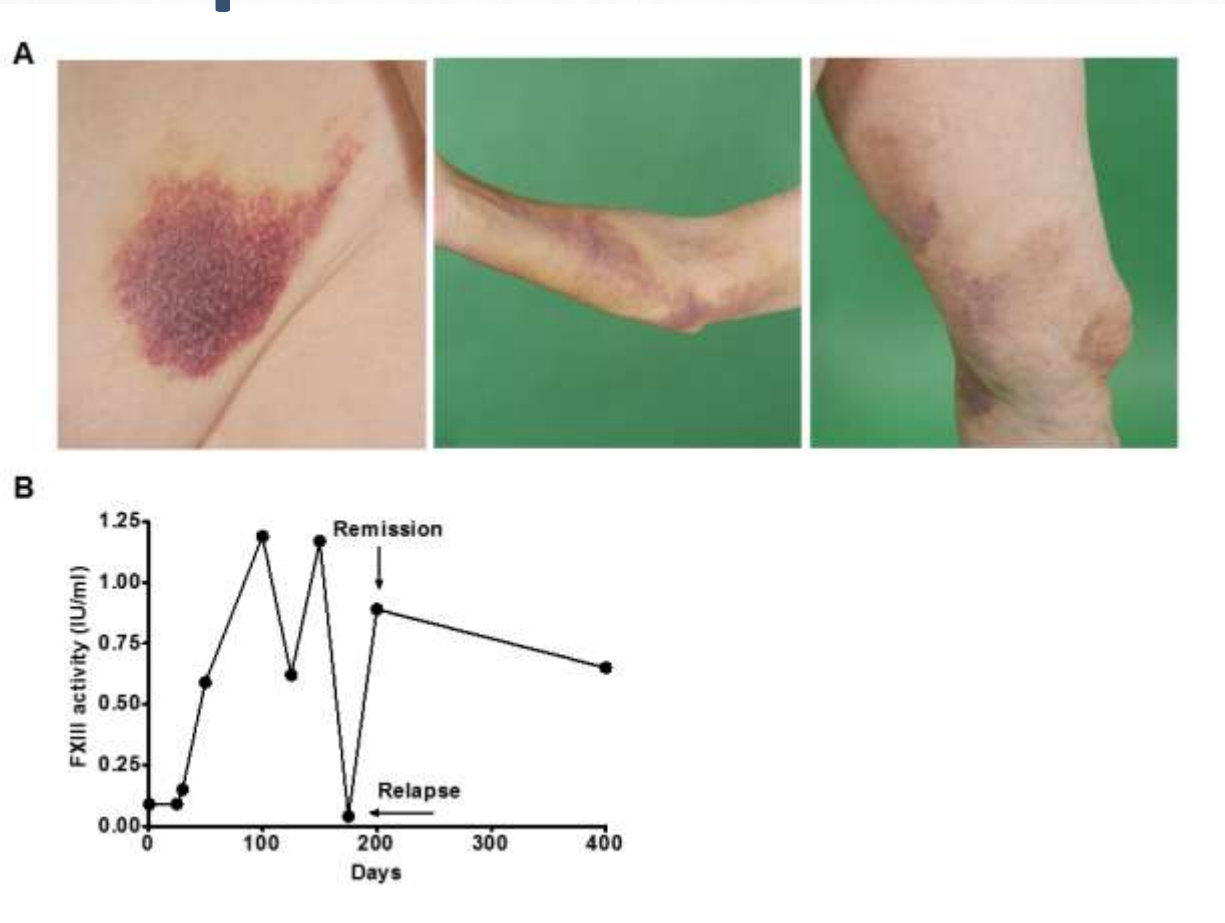


Lysis of FXIII and α_2AP-depleted thrombi is normalized by PNP



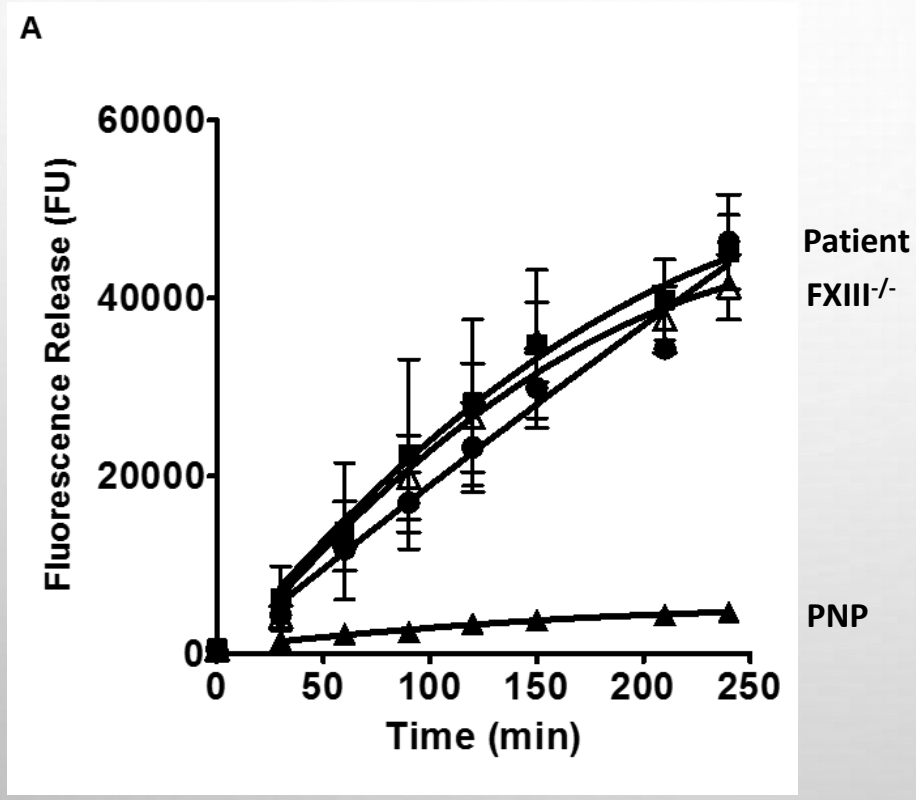
Fraser *et al*, 2011 Blood

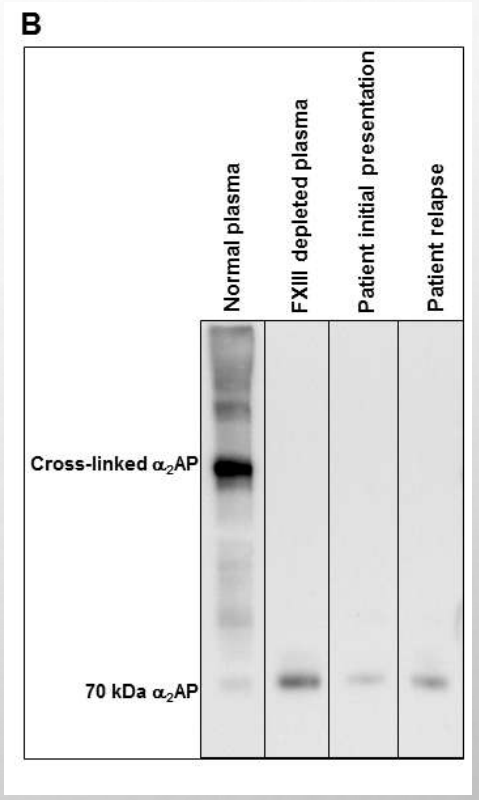
Acquired FXIII deficiency results in spontaneous bleeds



Mitchell JL *et al* Brit J Haematol 2017

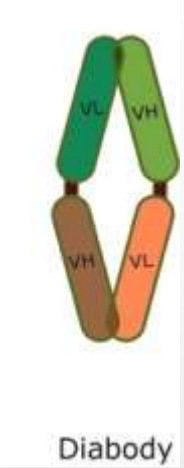
Bleeding in acquired FXIII deficiency is due to defective crosslinking of α_2AP to fibrin





Mitchell JL *et al* Brit J Haematol 2017

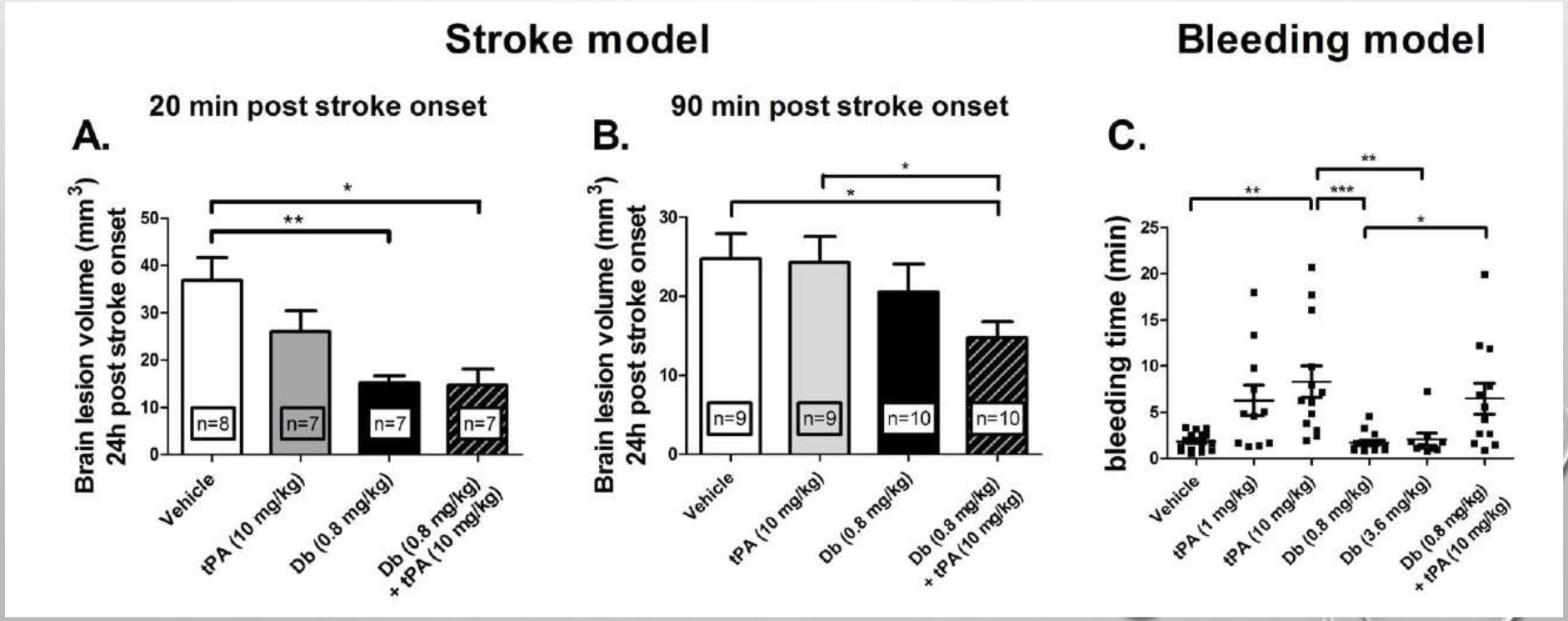
Novel anticoagulants – targeting inhibitors



Diabody approach

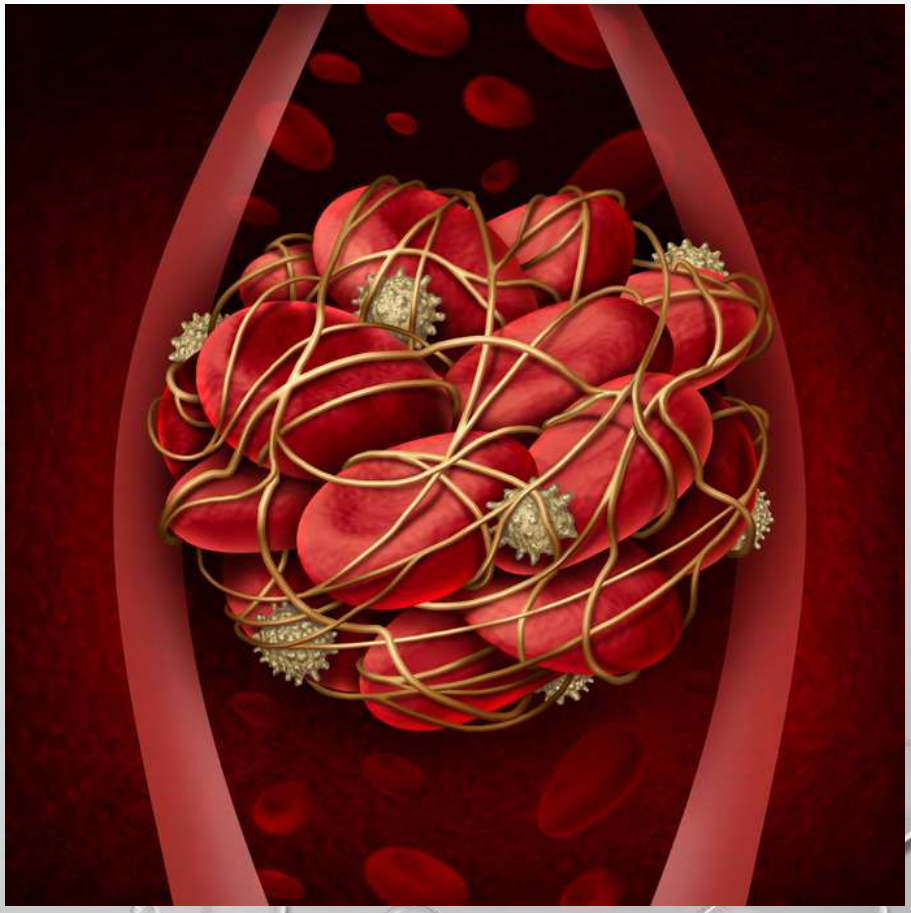
- Targets PAI-1 and TAFIa simultaneously
- Small size allows penetrance into thrombi

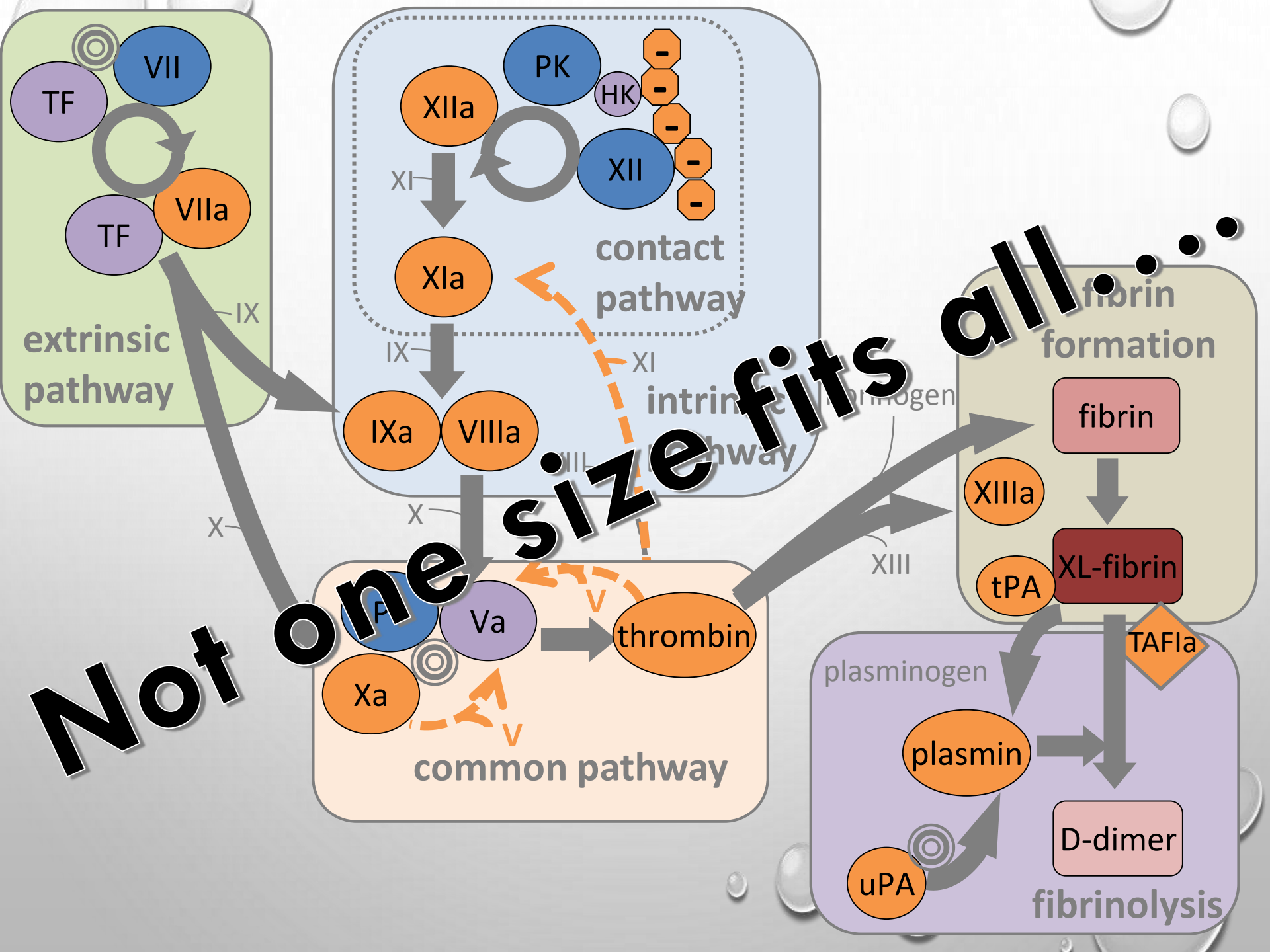
Denorme F et al. Stroke 2016; 47: 2419-22.



Antithrombotics that augment clot breakdown

Drugs targeted toward the fibrinolytic cascade could ‘hijack’ the body’s innate pathways to put the ‘brakes’ on thrombus formation and augment clot dissolution




VII
TF
TF
VIIa
extrinsic pathway
IX
PK
HK
XIIa
XII
XI
XIa
contact pathway
IX
XI
IXa
VIIIa
intrinsic pathway
X
X
P
Va
Xa
thrombin
V
V
common pathway
fibrin formation
fibrin
XIIIa
XL-fibrin
tPA
TAFIa
plasminogen
plasmin
D-dimer
uPA
fibrinolysis
Not one size fits all…

Acknowledgements

British Heart Foundation

British Society for Haemostasis & Thrombosis

1495 University of Aberdeen

- Microscopy and Histology Core Facility
- The Iain Fraser Cytometry Centre

Maastricht University

- Prof Johan Heemskerk
- Frauke Swieringa
- Dr Paola van Der Meijden
- Tom Mastenbroek