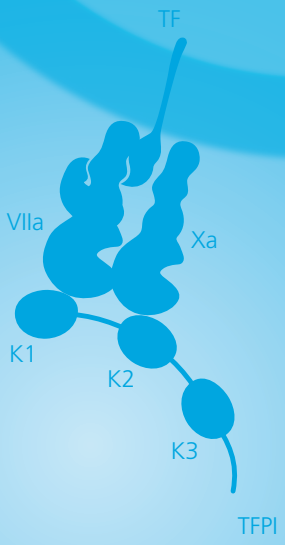
Emerging non-factor therapies for hemophilia

and their mechanisms of action



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Emerging non-factor therapies for hemophilia

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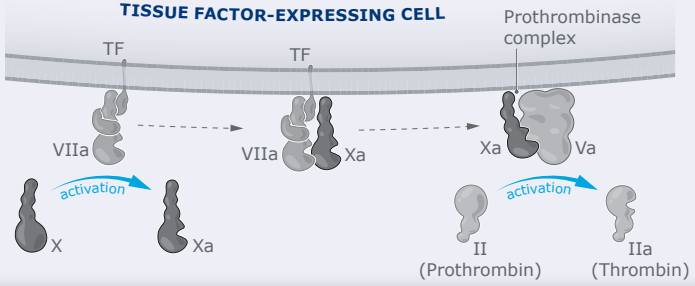
Replacement therapies using either plasma-derived or recombinant FVIII or FIX have been the foundation for restoring hemostasis in people with hemophilia.[1–3]

Novel therapeutic options are being investigated to reduce the burden of disease and treatment.[2]

- **In hemophilia A, FVIII is deficient. In hemophilia B, FIX is deficient.[1]**
- **These defects impair coagulation, leading to hemorrhage.[1]**

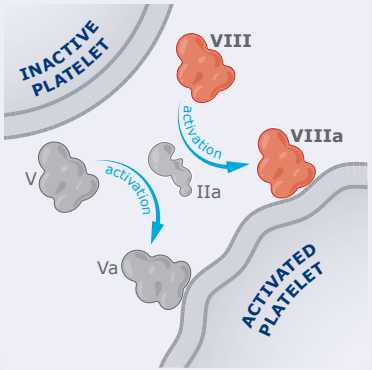
Initiation

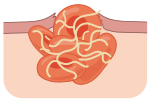
Following injury, tissue factor and FVIIa form a complex, which generates FXa. Together with FVa, FXa forms the prothrombinase complex, leading to minute amounts of thrombin generation.[2,4]



Amplification

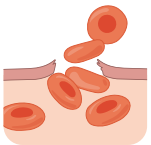
Thrombin activates platelets and multiple coagulation factors, including FV and FVIII.[2,4]





Clot formation

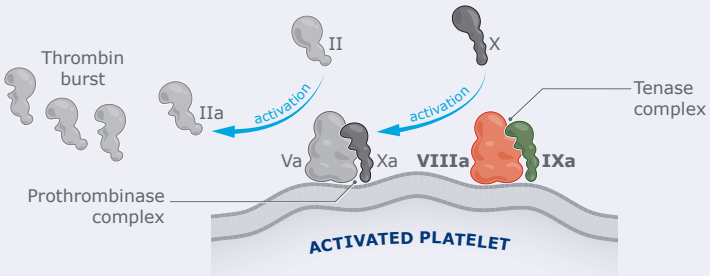
Normal coagulation



In hemophilia, factor deficiency impedes stable clot formation.[1]

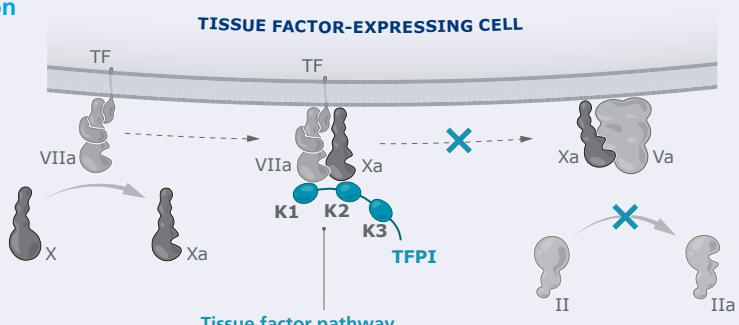
Propagation

Sequential formation of the tenase (FVIIIa/FIXa) and prothrombinase (FXa/FVa) complexes on the surface of the activated platelet drives a thrombin burst, leading to fibrinogen cleavage to fibrin, further platelet activation, and ultimately clot formation.[2–4]



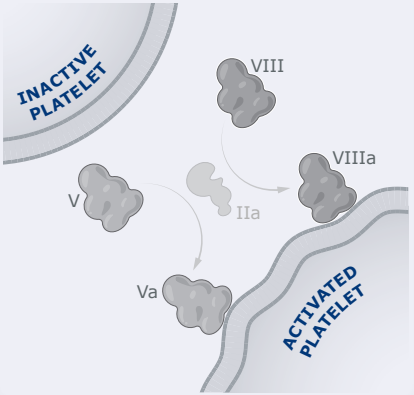
- **In normal hemostasis, a complex system allows regulation of coagulation to prevent thrombosis.[2,5]**
- **The physiological anticoagulants involved in this system are potential targets for relieving the natural inhibition of coagulation to promote clot formation and limit bleeding in people with hemophilia.[2,5]**

Initiation

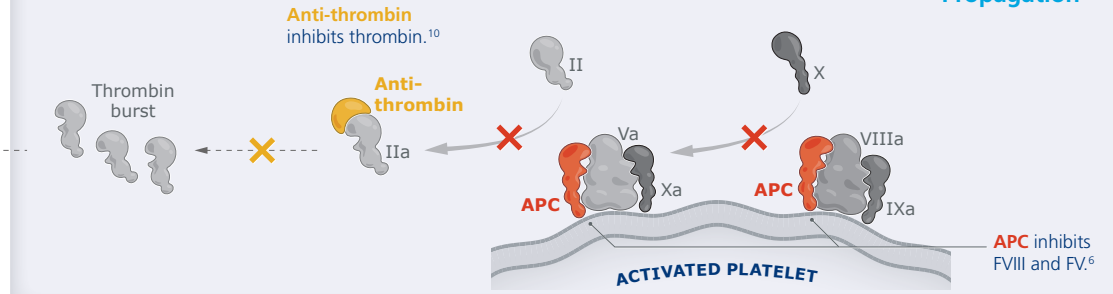


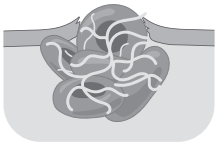
Tissue factor pathway inhibitor controls the initiation phase by regulating the activity of FXa and the TF/FVIIa complex.[2,5]

Amplification



Propagation

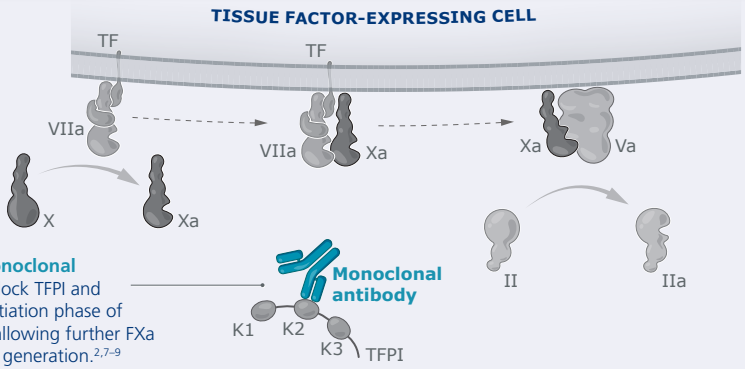




Clot formation downregulated in normal hemostasis and hemophilia

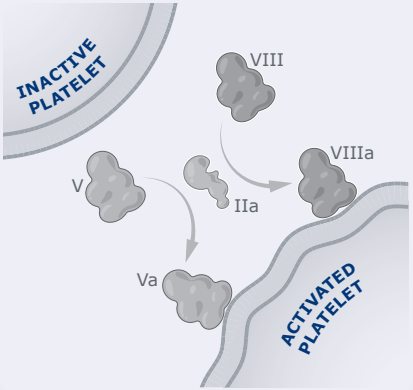
- **Emerging non-factor therapies are being developed to block the natural inhibitors of coagulation or mimic the procoagulant activity of a missing clotting factor.[2,3]**
- **These therapies target various points of the coagulation cascade to restore thrombin generation despite FVIII or FIX deficiency.[2,3,5]**

Initiation

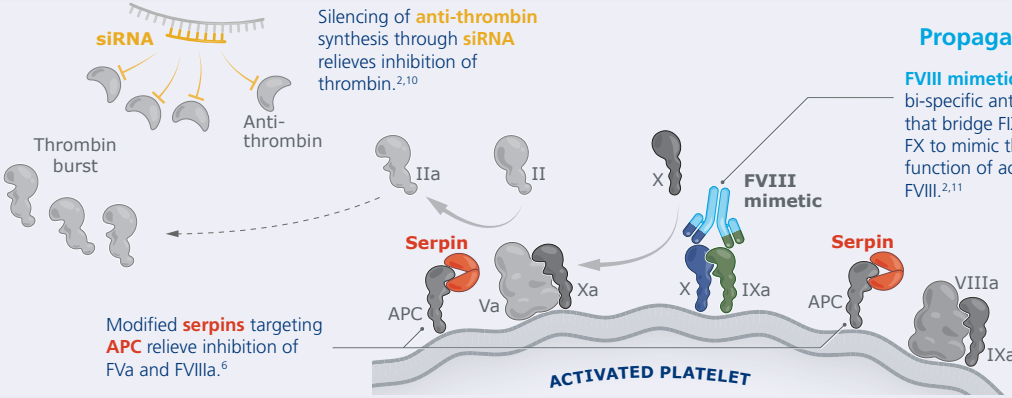


Anti-TFPI monoclonal antibodies block TFPI and extend the initiation phase of coagulation, allowing further FXa and thrombin generation.[2,7–9]

Amplification



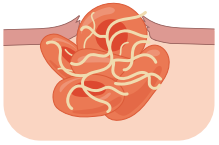
Propagation



Silencing of **anti-thrombin** synthesis through **siRNA** relieves inhibition of thrombin.[2,10]

FVIII mimetics are bi-specific antibodies that bridge FIXa and FX to mimic the function of activated FVIII.[2,11]

Modified **serpins** targeting **APC** relieve inhibition of FVa and FVIIIa.[6]



Clot formation

APC, activated protein C; **FII**, factor II; **FIIa**, activated factor II; **FIX**, factor IX; **FIXa**, activated factor IX; **FV**, factor V; **FVa**, activated factor V; **FVII**, factor VII; **FVIIa**, activated factor VII; **FVIII**, factor VIII; **FVIIIa**, activated factor VIII; **FX**, factor X; **FXa**, activated factor X; **II**, factor II; **IIa**, activated factor II; **IX**, factor IX; **IXa**, activated factor IX; **K1**, Kunitz 1; **K2**, Kunitz 2; **K3**, Kunitz 3; **siRNA**, short interfering RNA; **TF**, tissue factor; **TFPI**, tissue factor pathway inhibitor; **V**, factor V; **Va**, activated factor V; **VII**, factor VII; **VIIa**, activated factor VII; **VIII**, factor VIII; **VIIIa**, activated factor VIII; **X**, factor X; **Xa**, activated factor X.

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Illustrations of coagulation regulation in healthy subjects and patients with hemophilia are simplified, and do not claim to be exhaustive.

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