Clinical Foundations for Factor VIIIa Mimetics

What is hemophilia A?

- Hemophilia A is a hereditary bleeding disorder caused by a deficiency of the clotting protein factor VIII (FVIII), leading to impaired blood clotting.[1]
- People with hemophilia A are at risk of spontaneous or prolonged bleeding, which can lead to progressive joint damage over time.[1]

The role of factor VIII:

FVIII replacement has improved outcomes for people with hemophilia.[2,3,4]

What are factor VIIIa mimetics?:

They are specially engineered antibodies that mimic the function of activated factor VIIIa (FVIIIa), which has important functions in maintaining the body's ability to form blood clots and stop bleeding.[5,6]

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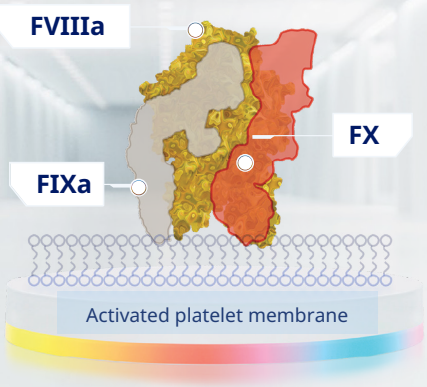
Mimicking the function of natural FVIIIa

Natural FVIIIa binds to activated FIX and FX, forming a complex

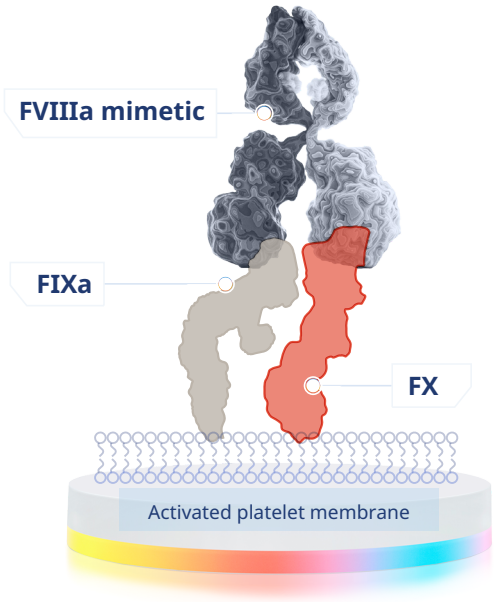


- Following injury, natural FVIII is activated by other clotting factors and localizes to the surface of platelets at the site of damage, where it plays a critical role in supporting clot formation.[2,6]
- Once activated, FVIIIa acts as a scaffold, bringing together two key clotting proteins—factor IXa (FIXa) and factor X (FX)—to form a complex.[2,6]
- The assembly of these clotting factors allows FX to be converted to its active form (FXa), which initiates thrombin generation—a key step in forming a stable clot to stop bleeding.[2,6]

FVIIIa mimetics: Designed to mimic the function of natural FVIIIa

- FVIIIa mimetics have two distinct arms—one arm is designed to bind to FIXa and the other to FX.[7,8]
- FVIIIa mimetics bind to FIXa and FX simultaneously, bringing these two clotting factors together, thereby mimicking the function of natural FVIIIa in the body.[8]
- Connecting these two clotting factors allows FX to be converted to its active form (FXa), which is a key step in producing a stable clot to stop bleeding.[2,6]

FVIIIa mimetics are able to bind FIXa and FX to form a complex



What is mimetic optimization?

- While FVIIIa mimetics support effective clotting, they do not yet work as efficiently as natural FVIIIa.[5] Ongoing efforts to enhance their performance—known as "mimetic optimization"—aim to further improve their function in forming a stable blood clot.[9]
- Small structural adjustments to regions of the antibody can have a substantial impact on the function of an antibody.[10–12] This iterative process of refining the antibody structure is central to help "optimize" the molecule.

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Optimizing FVIIIa mimetics

FVIIIa mimetics can be modified in several ways to optimize their function

1 Where it binds
EPITOPE BINDING

- The ability of FVIIIa mimetics to bind specific sites (epitopes) on their targets is determined by their molecular structure.[13]
- Even small changes in where the antibody binds can substantially influence how it works in the body.[12,13]

2 How strongly it binds
BINDING AFFINITY

- Binding affinity refers to how strongly a treatment attaches to its target.[14]
- For FVIIIa mimetics, this binding affinity needs to fall within a "sweet spot"—not too weak and not too strong.[7,14]
- If binding is too weak, the antibody may not perform its function efficiently. If binding is too strong, the antibody could reduce its own effectiveness through self-inhibition.[7,14]

3 What happens when it binds
COFACTOR ACTIVITY

- When an antibody attaches to its target, it can trigger a structural change to alter how that target functions.[10]
- Natural FVIIIa is a cofactor, designed to boost the activity of FIXa by changing its shape, making FIXa more effective at converting FX to its active form (FXa).[6,7]

PHARMACOKINETICS

- Small changes to a molecule's structure can affect how it behaves in the body—this is known as its pharmacokinetic (PK) profile.[9]
- Factors such as how much of the antibody is absorbed, how long it stays in circulation (half-life), and how quickly it is cleared can influence dosing frequency and route of administration.[15]
- Some antibodies are highly targeted and can be given as fixed doses instead of dosing based on body weight.[16]

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In summary...

There is potential to optimize FVIIIa mimetics by fine tuning their cofactor activity and their binding characteristics to more closely mimic the actions of natural FVIIIa in the clot formation process.

For more details on mimetics visit
www.optimizingmimetics.com

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