Understanding FVIIIa Mimetics

Factor VIII (FVIII) therapy has improved outcomes for people with hemophilia A[1]. Despite advances and ongoing challenges, efforts continue to refine treatment approaches, including exploring alternative delivery methods for activated FVIII (FVIIIa)[1].

Natural FVIIIa supports hemostatic balance by activating only on platelets at sites of injury[2–4], bridging factor IXa (FIXa) and factor X (FX) to form the Xase complex[2–5], and enhancing the activation of FX by FIXa to drive thrombin generation[3,5–7].

Therapeutic antibodies, with their high binding specificity, are promising candidates for mimicking FVIIIa functions[1,5,8,9]. Lacking structural similarity to natural FVIIIa, they are unaffected by FVIIIa inhibitors[9–11].

FVIIIa mimetics form complexes with FIXa and FX[12–15]. However, their binding and function fall short compared with natural FVIIIa, leaving room for improvement to enhance FX activation[14–16].

? What is Mimetic Optimization?

Optimization involves engineering changes in the structure of a therapeutic antibody (Ab) for enhancing their function.

Biotechnology can be used to modify the antibody molecule, and the effects on function can be assessed using specific assays[9,16–20].

Even small changes in molecular structure can significantly impact the function of the molecule[10,17–22].

The results can guide further refinements of the structure and function in an ongoing process of molecular optimization[14,17].

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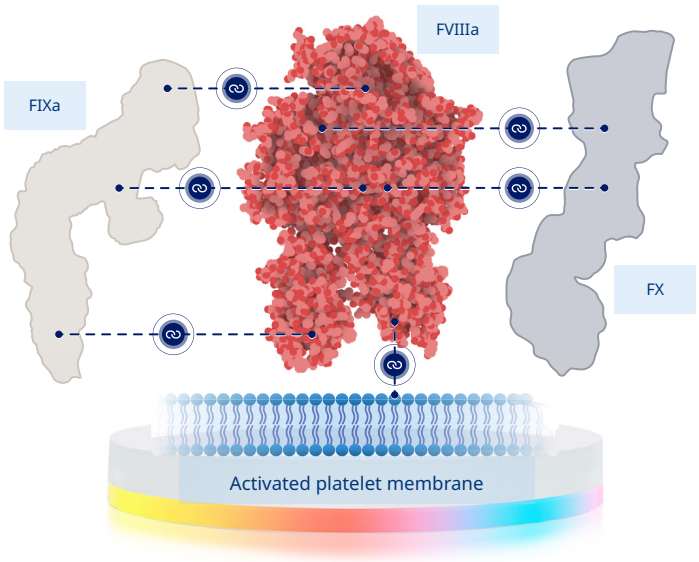
FVIIIa Mimetics as a Class of Molecules

Mimicking the hemostatic function of natural FVIIIa

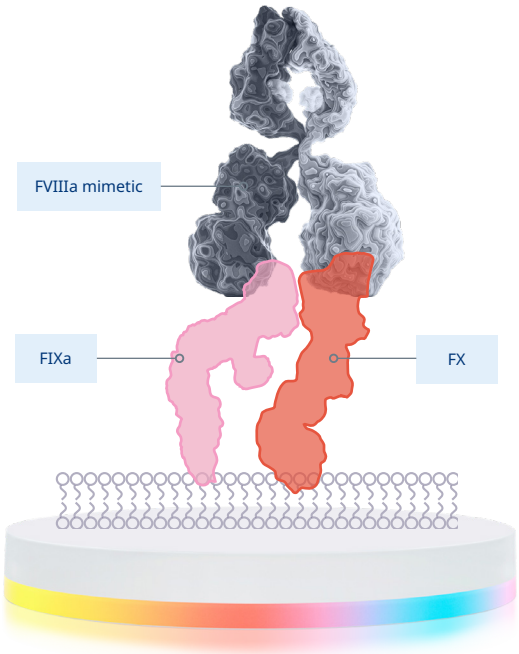
Natural FVIIIa performs several critical functions[1,2]:

- FVIII is activated at the injury site by FXa or thrombin, leading to binding to the activated platelet membrane[2–4,14].
- FVIIIa binds FIXa and FX simultaneously, forming a membrane-bound complex and causing conformational changes in increasing its proteolytic activity[3–8,14].
- FVIIIa is a critical cofactor for FIXa activation of FX and therefore for thrombin generation[3,4].

Complex formation with natural FVIIIa[3-8,14]



Complex formation with FVIIIa mimetics[3-8,14]



Bispecific antibodies (BsAbs) as FVIIIa mimetics

- BsAbs are well suited to mimic natural FVIIIa activity[9,10].
- FVIIIa mimetics provide a critical function by bridging two molecular components essential for coagulation[5,10,11].
- BsAbs have been developed to bind FIXa with one arm and FX with the other, mimicking FVIIIa functions[9,10].
- Although these initial FVIIIa mimetics can form a complex with FIXa and FX, causing FX activation and in turn thrombin generation, they do not match the activity level of natural FVIIIa[12–16].
- This indicates room for BsAb improvements and the potential for even greater advancements in FVIIIa mimetics[9].

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Optimizing FVIIIa Mimetics

1

Where it binds:

EPITOPE BINDING

The ability to bind specific sites (epitopes) on the target is determined by the molecular structure of a BsAb[10,17–21]. Changing the epitope's location—even by a few amino acids[10]—or the affinity of the binding process, can alter the behavior and effect of the BsAb[17,18].

2

How strongly it binds:

BINDING AFFINITY

Binding affinity describes the strength of the interaction between a biological molecule and its ligand[18,22]. Ideally, it should be in the "sweet spot" between too low (inefficient binding) or too high (self-inhibition)[5,14,18,22].

3

What happens when it binds:

COFACTOR ACTIVITY

Upon binding to its target, an antibody can induce conformational changes in the 3D structure of the target molecule, known as the allosteric effect[18,22]. Natural FVIIIa enhances the proteolytic activity of FIXa via allosteric activation, which is crucial for FX activation[8,14,22]. This is a critical aspect of FVIIIa's ability in maintaining hemostasis and makes FVIIIa a powerful cofactor for FIXa[8,14].

PHARMACOKINETIC (PK) PROPERTIES

Changes to the structure of a molecule can affect its PK profile[17]. Bioavailability impacts dosing regimens and administration route[17,23–24]. Half-life and clearance rate control dosing intervals. The highly targeted action of therapeutic antibodies may allow for fixed rather than mg/kg dosing[25].

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Scientific Advances in the Optimization of Factor VIIIa Mimetics

Precision engineering of BsAbs has the potential to develop optimized FVIIIa mimetics that can more closely mimic the multiple actions of natural FVIIIa in the maintenance of hemostasis

For more details on mimetics, visit
optimizingmimetics.com

BsAb, bispecific antibody; FIXa, activated factor IX; FX, factor X; FVIII, factor VIII; FVIIIa, activated factor VIII; PK, pharmacokinetics.

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