

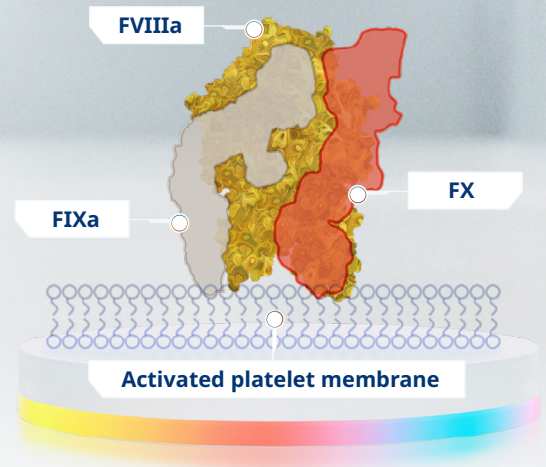
Mimetic optimization: the future of FVIIIa mimetics

Mimicking the hemostatic function of natural FVIIIa

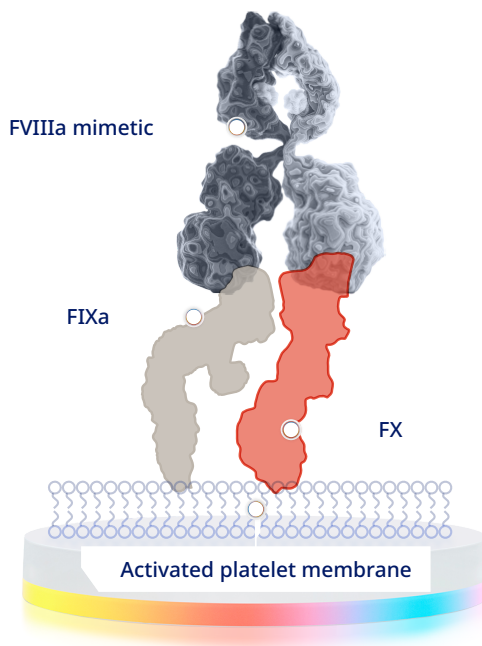
Natural FVIIIa has **several critical actions**:^{1,2}

- FVIII is **activated at the site of injury** by FXa or thrombin, leading to binding to the **activated platelet membrane**²⁻⁵
- FVIIIa **binds FIXa and FX simultaneously**, forming a membrane-bound complex and causing **conformational changes** in the FIXa molecule, increasing its **proteolytic activity**^{1,2,4-8}
- FVIIIa is a **critical cofactor for FIXa activation of FX** and therefore for **thrombin generation**⁴⁻⁶

Complex formation with natural FVIIIa



Complex formation with FVIIIa mimetic



Bispecific antibodies as FVIIIa mimetics

- BsAb are well suited to the task of mimicking natural FVIIIa activity:^{9,10}
- A BsAb, has **two arms** that are engineered to bind to **two different target sites**^{6,9-11}
- BsAbs have been developed that bind FIXa with one arm and FX with the other, and are able to **mimic the functions of FVIIIa**^{6,9-11}
- Although these initial FVIIIa mimetics can form a complex with FIXa and FX, causing FX activation and in turn thrombin generation, they **do not have the same level of activity as natural FVIIIa**^{1,12-15}
- This means that there is **room for BsAb improvement**, and the potential for even greater advancement in FVIIIa mimetics

? What is mimetic optimization?

Optimization is the process of engineering changes in the structure of a therapeutic Ab with the purpose of "enhancing their safety, efficacy and developability"

(Wang, 2021)¹⁶

- Biotechnology can be used to **make changes in the antibody molecule**, and the resultant effects on function can be **assessed by specific assays**^{9,16-20}
- Even **small changes** in molecular structure can have **important implications** for the function of the molecule^{9,16-21}
- The results can **guide further refinements** of the structure and function in an **ongoing process** of molecular optimization^{16,17}

How can FVIIIa mimetics benefit from mimetic optimization?

Optimization of BsAbs may have the potential to develop FVIIIa mimetics that can more closely mimic the multiple functions of natural FVIIIa in the maintenance of hemostasis^{1,2,16,17}

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

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