

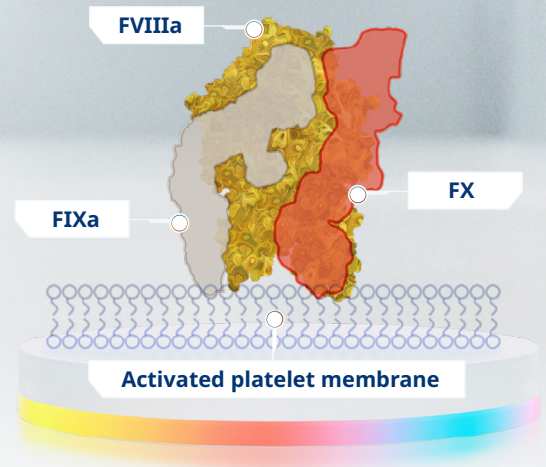
# Mimetic optimization: the future of FVIIIa mimetics

## Mimicking the hemostatic function of natural FVIIIa

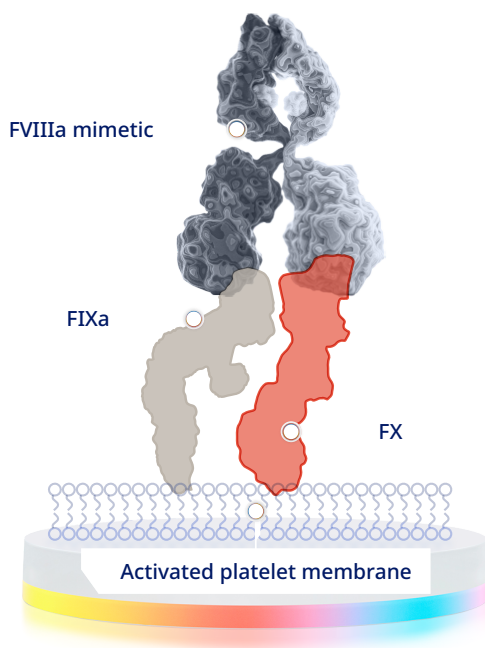
Natural FVIIIa has **several critical actions**:<sup>1,2</sup>

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

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:<sup>9,10</sup>
- A BsAb, has **two arms** that are engineered to bind to **two different target sites**<sup>6,9-11</sup>
- BsAbs have been developed that bind FIXa with one arm and FX with the other, and are able to **mimic the functions of FVIIIa**<sup>6,9-11</sup>
- 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**<sup>1,12-15</sup>
- 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)<sup>16</sup>

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

# 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<sup>1,2,16,17</sup>*

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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