

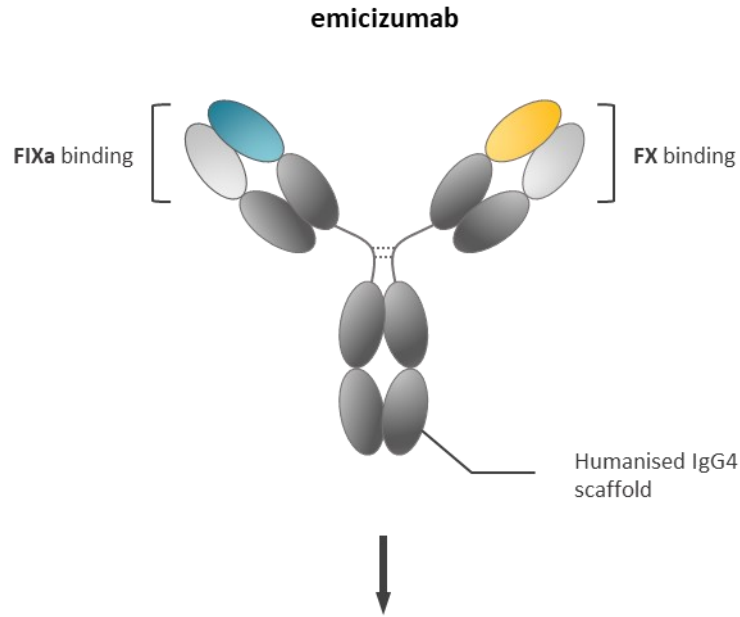


American Society of Hematology
Helping hematologists conquer blood diseases worldwide

A FVIII-mimetic bispecific antibody with an embedded self-regulation mechanism reduces the risk of prothrombotic events for the treatment of haemophilia A

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Emicizumab : a bispecific Ab with FVIII mimetic activity



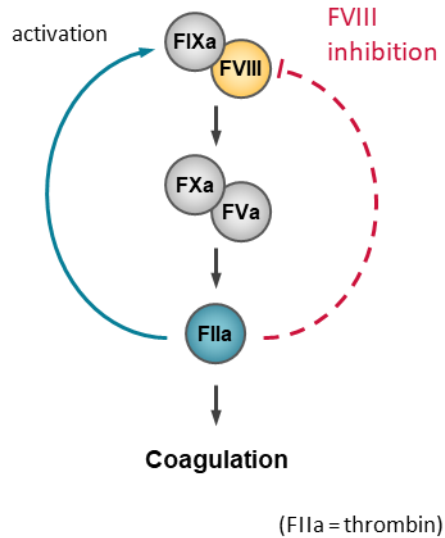
Fully humanised IgG4 bispecific antibody targeting
coagulation FIX/FIXa and FX/FXa

- Bypass FVIII deficiency and restore the coagulation cascade
 - Long half-life and prophylaxis achieved with fortnightly subcutaneous injections
 - Efficient for the treatment of patients with and without inhibitors
- ⇒ **Emicizumab has transformed our approach to the treatment of haemophilia A**

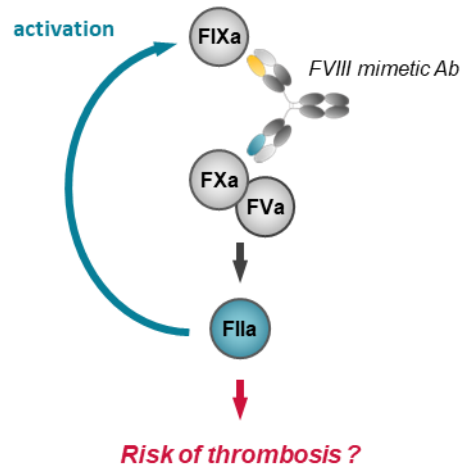
Functional differences between FVIII and emicizumab

	Clinical dev.	Post-approval
Thrombotic microangiopathy	3	1
Thrombosis	4	19

Physiological condition



FVIII mimetic antibody



Factor VIII

- Heavily regulated molecule with a short half-life
- Requires both activation and inactivation

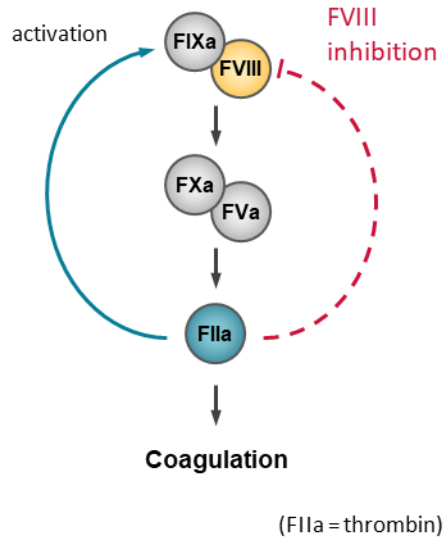
FVIII mimetic antibody

- In excess in circulation with a long half-life
- **Not sensitive physiologic inhibition pathways**

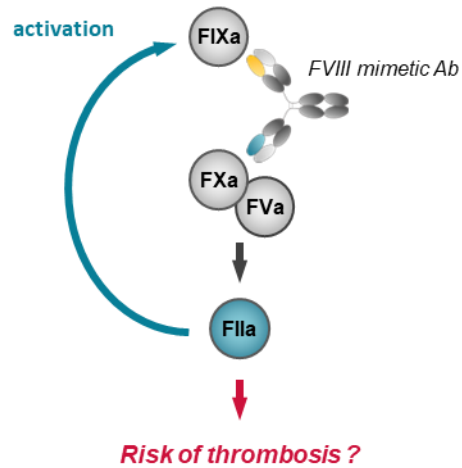
Self-regulation to control the coagulation cascade

⇒ **Thrombin mediated self-regulation** will restore the coagulation balance and reduce the risk of thrombosis

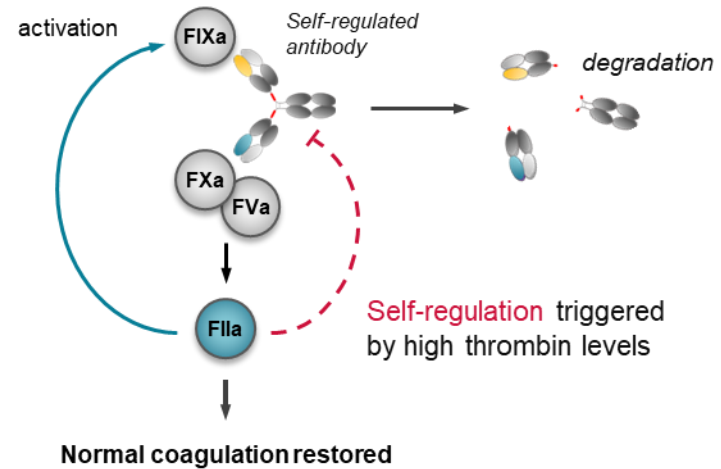
Physiological condition



FVIII mimetic antibody

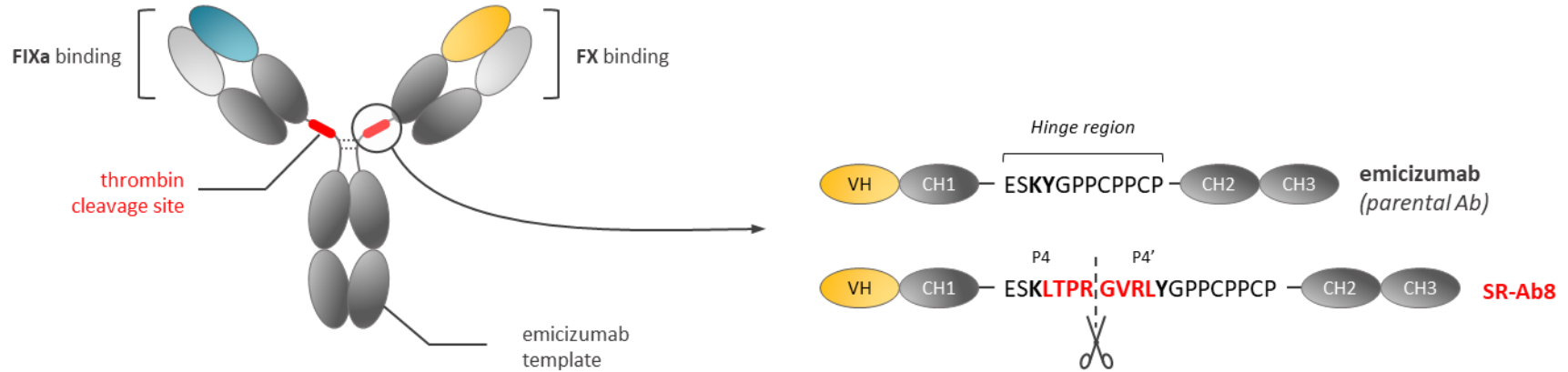


Self-regulated FVIII mimetic antibody



SR-Ab8 : a prototype of self-regulated antibody

SR-Ab8 (*thrombin cleavable bsAb*)

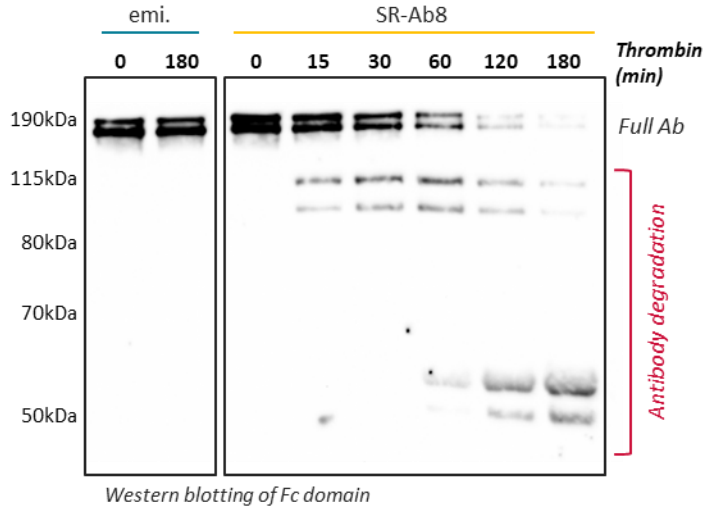


- Prototype designed using the backbone of emicizumab
- Several thrombin cleavable peptides were tested before selecting the **LTPRGVRL** synthetic sequence⁽¹⁾
- The peptide is inserted in the hinge region to achieve deficient inactivation of the antibody

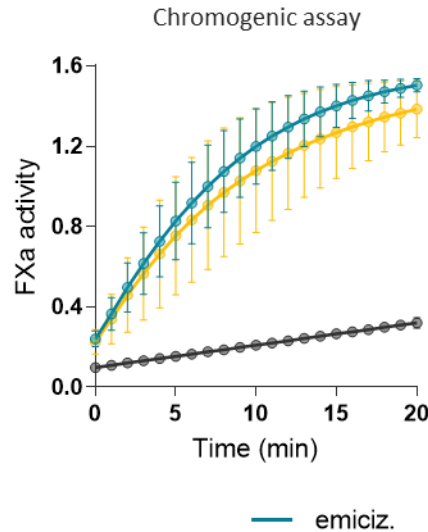
Physiochemical properties of SR-Ab8 *in vitro*

- ⇒ SR-Ab8 can be **inactivated by thrombin** but shows **uncompromised FVIII mimetic potential** in an *in vitro* FXa activation assay
- ⇒ Self-regulation **reduces abnormal thrombin** generation associated with FVIII mimetic antibodies in presence of aPCC

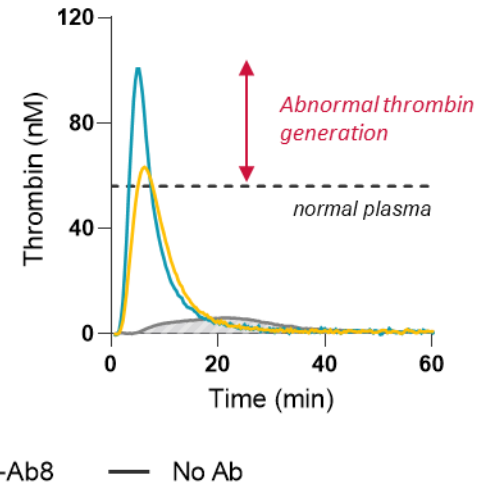
In vitro thrombin cleavage assay



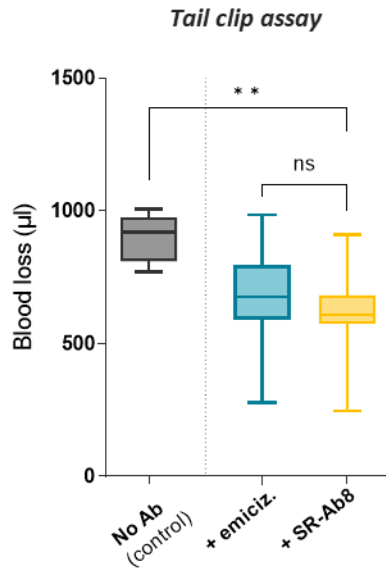
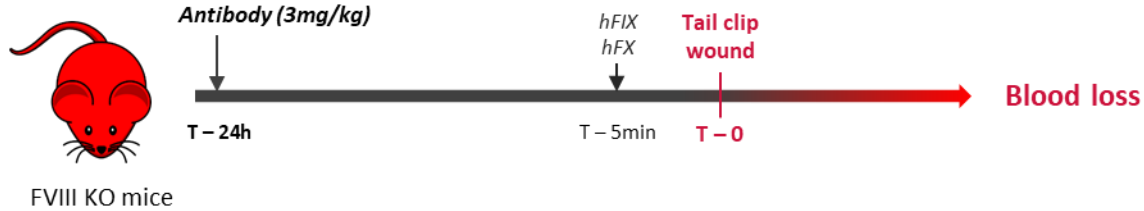
In vitro activity assay



Thrombin generation assay + aPCC⁽¹⁾

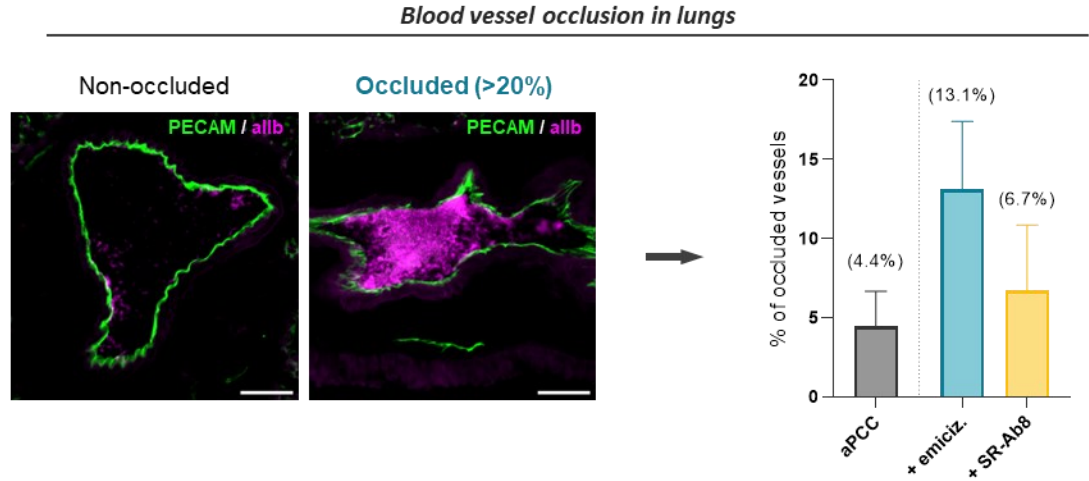
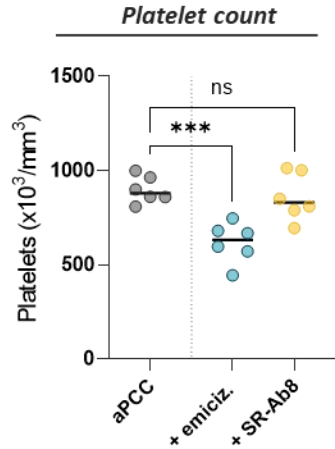
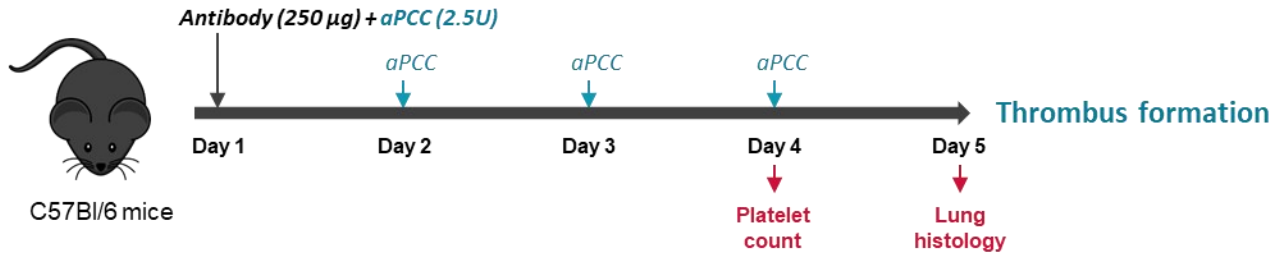


SR-Ab8 shows uncompromised efficacy *in vivo*



- ⇒ Both bispecific antibodies partially correct the bleeding tendency in HA mice
- ⇒ SR-Ab8 is undistinguishable from the parental antibody
- ⇒ Insertion of a thrombin cleavable peptides does not compromise SR-Ab8 efficacy

Self-regulation reduces prothrombotic outcomes *in vivo*



⇒ Reduced thrombocytopenia and blood vessel occlusion associated with FVIII mimetic antibodies combined with aPCC

Conclusion

- ⇒ SR-Ab8 is a **self-regulated FVIII mimetic antibody** designed with a thrombin cleavable peptide
- ⇒ SR-Ab8 **FVIII mimetic potential is uncompromised** both *in vitro* and *in vivo*
- ⇒ Self-regulation **reduces the excessive thrombin generation** in presence of aPCC *in vitro* (TGA)
- ⇒ Self-regulation **reduces the prothrombotic outcome** of FVIII mimetic antibodies when combined with aPCC *in vivo*



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