

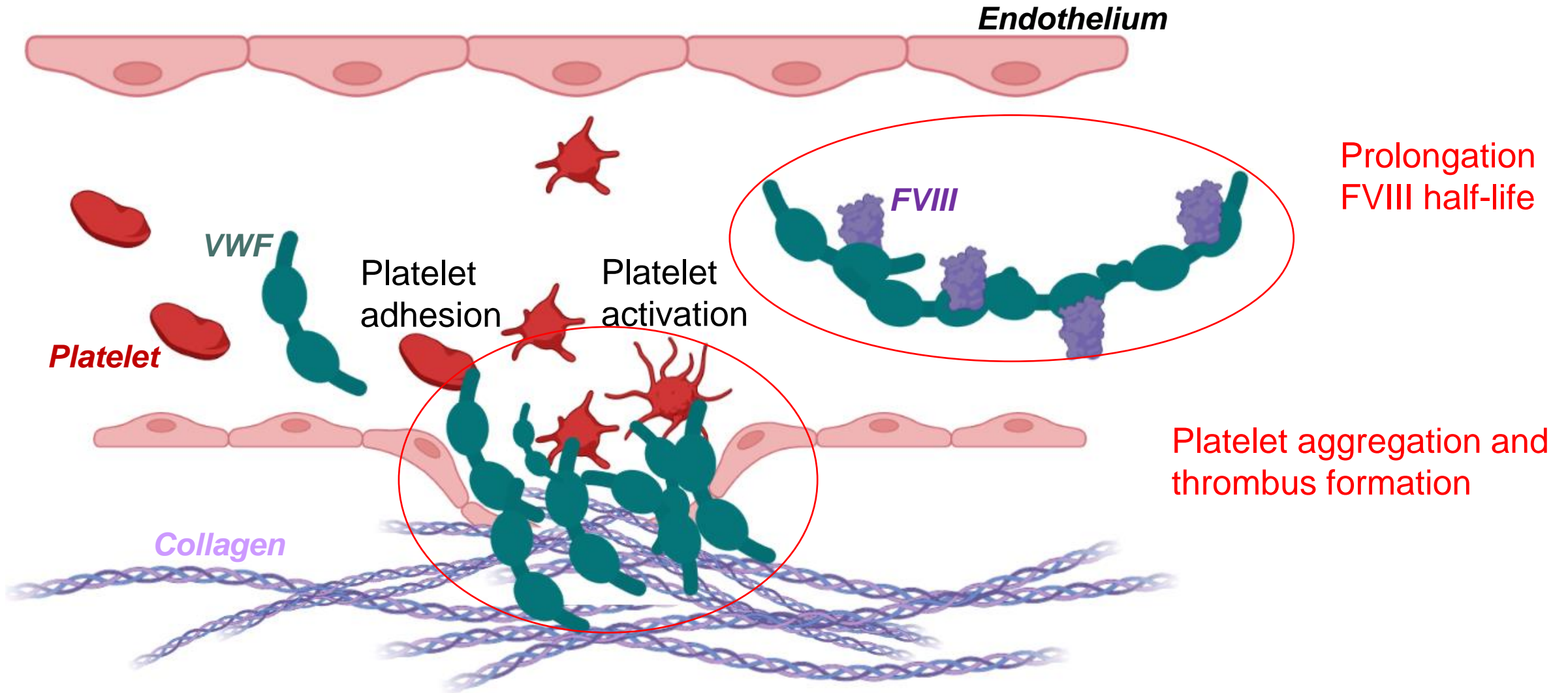
Emicizumab ameliorates hemostasis in a von Willebrand Disease-type 3 murine model

Geneviève McCluskey, PhD

CFH St Malo, 12 mai 2023

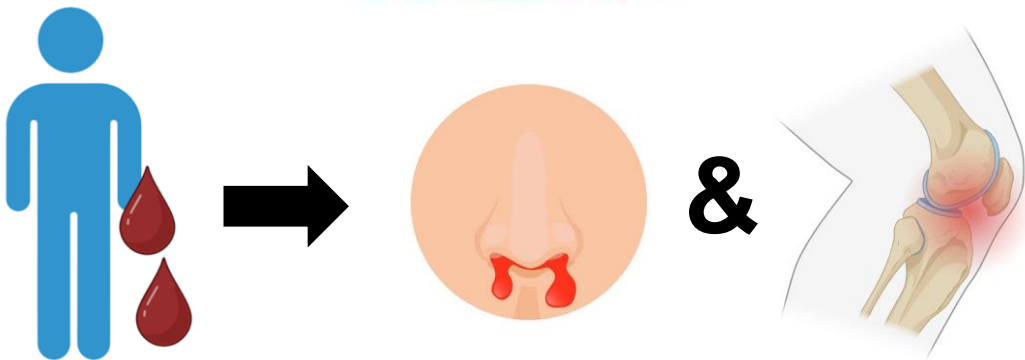
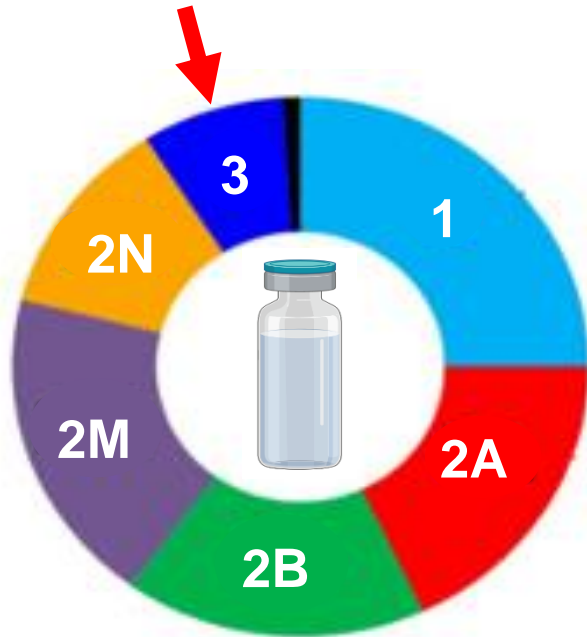


The roles of von Willebrand Factor



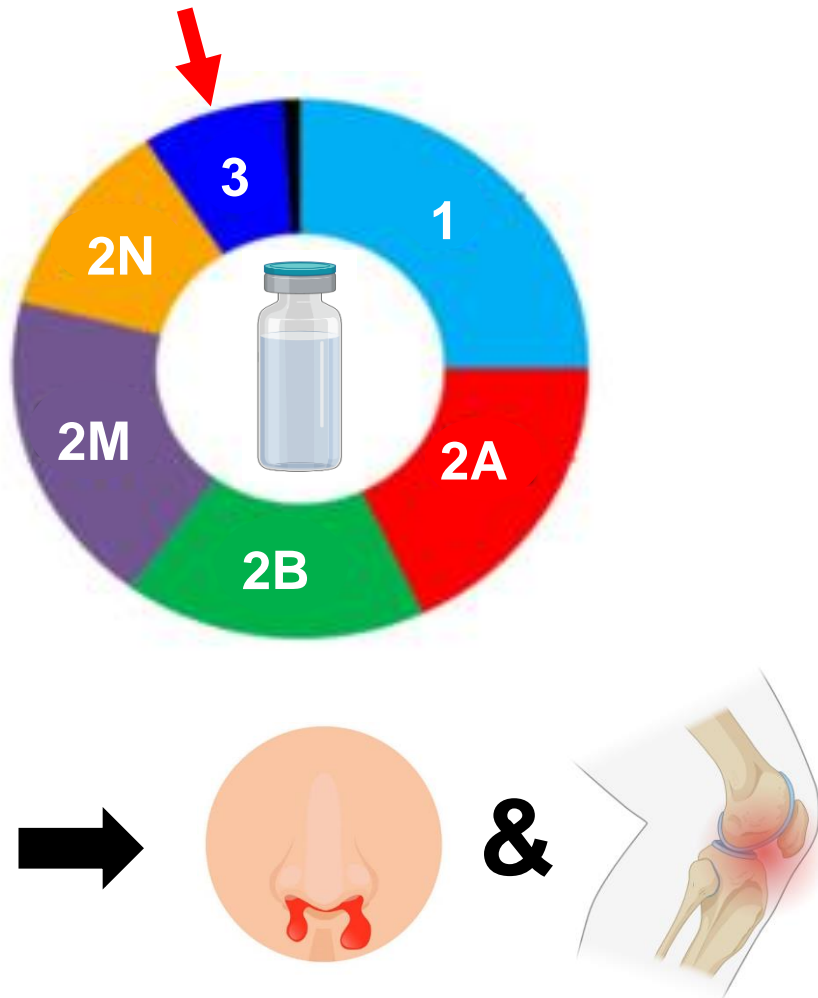
Von Willebrand Disease-type 3: a double deficiency

The most severe and rarest form, with quantitative defect <5%

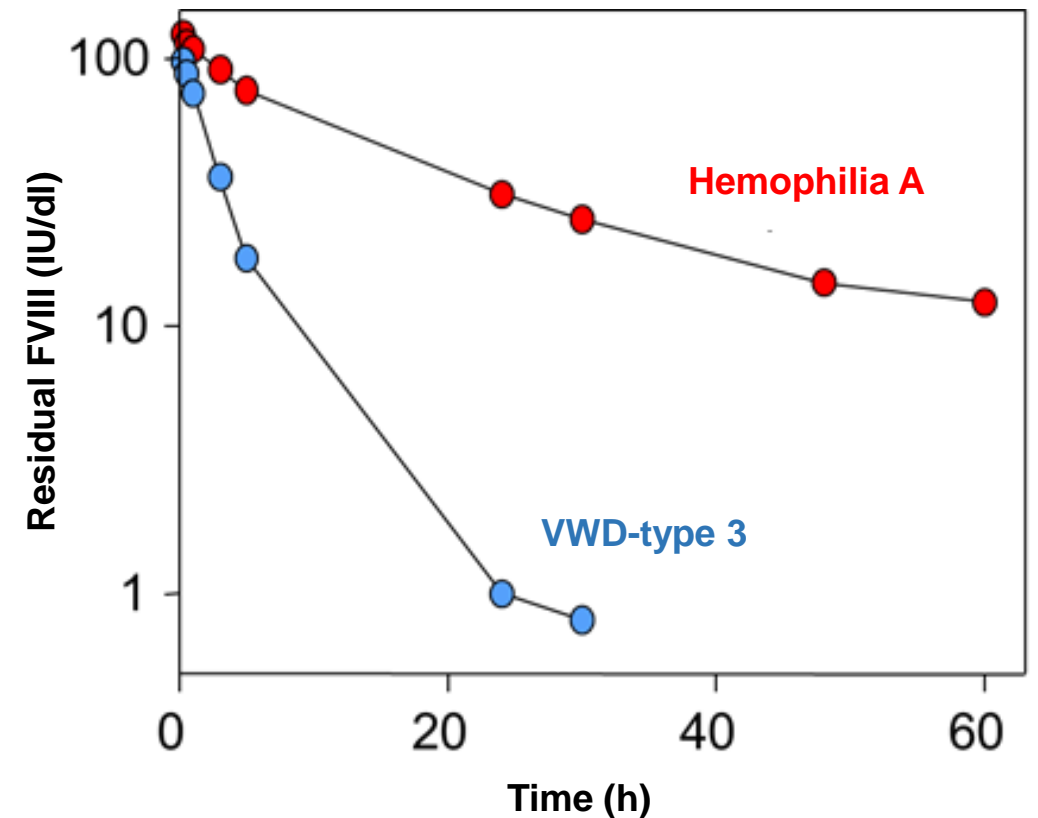


Von Willebrand Disease-type 3: a double deficiency

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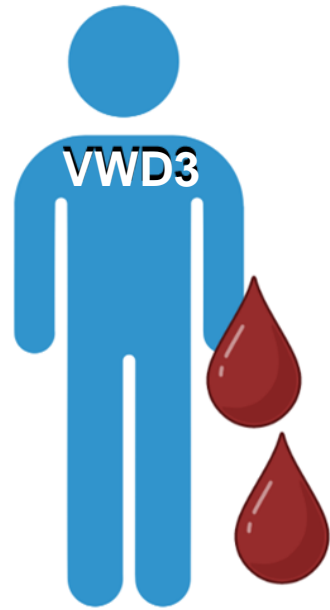


Decay of exogenous FVIII in circulation in VWD-type 3 & Hemophilia A patients



Can improvement of FVIII activity correct bleeding in VWD-type3?

FVIII in VWD-type 3: clinical cases



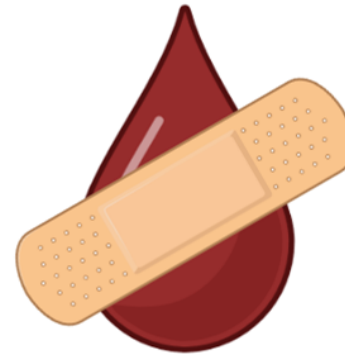
X5 clinical cases

+

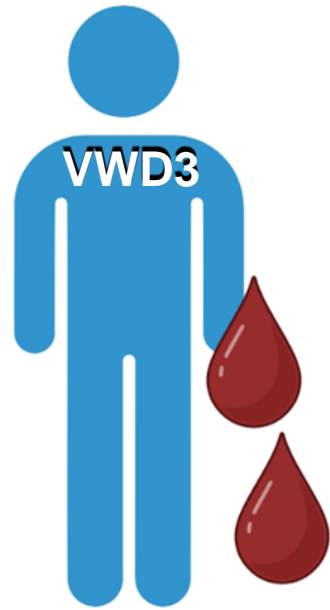
FVIII



=



FVIII in VWD-type 3: clinical cases



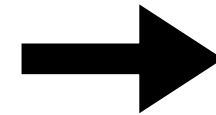
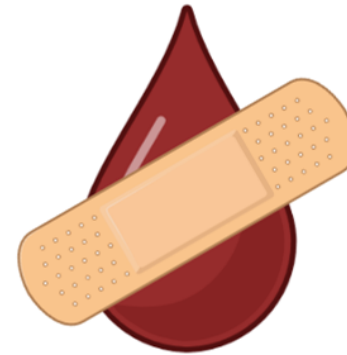
X5 clinical cases

+

FVIII

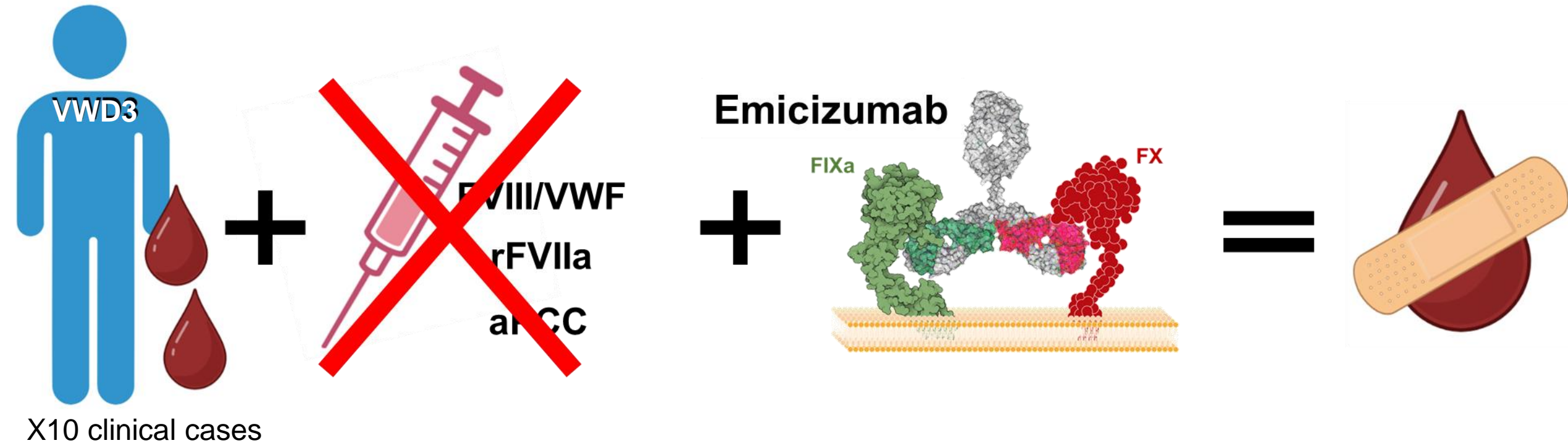


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FVIII short half life

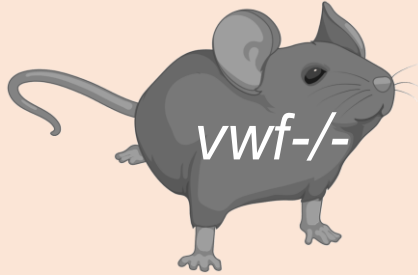
Emicizumab in VWD-type 3: clinical cases



Aim:

To assess the effects of emicizumab on haemostasis parameters in a VWD-type 3 mouse model

VWD-type 3 model: VWF *Knock-out* mouse



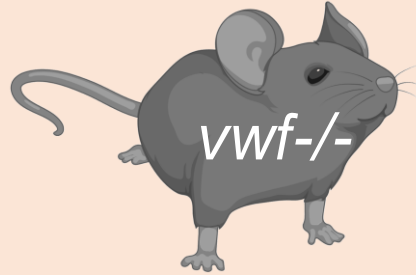
➤ **VWF:Ag** = not detectable

➤ **FVIII:C** = $4.2 \pm 1.1\%$

➤ Severe bleeding phenotype upon challenge

➤ No spontaneous bleeding

VWD-type 3 model: VWF *Knock-out* mouse



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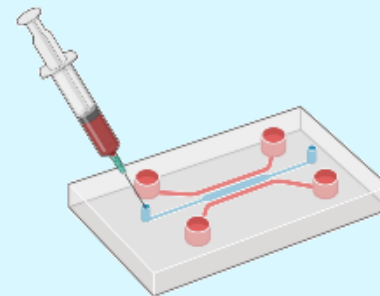
➤ No spontaneous bleeding

Denis et al, PNAS 1998

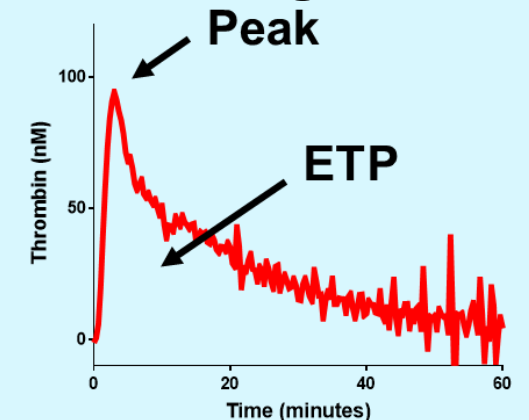
**EMICIZUMAB's
impact on
haemostasis?**



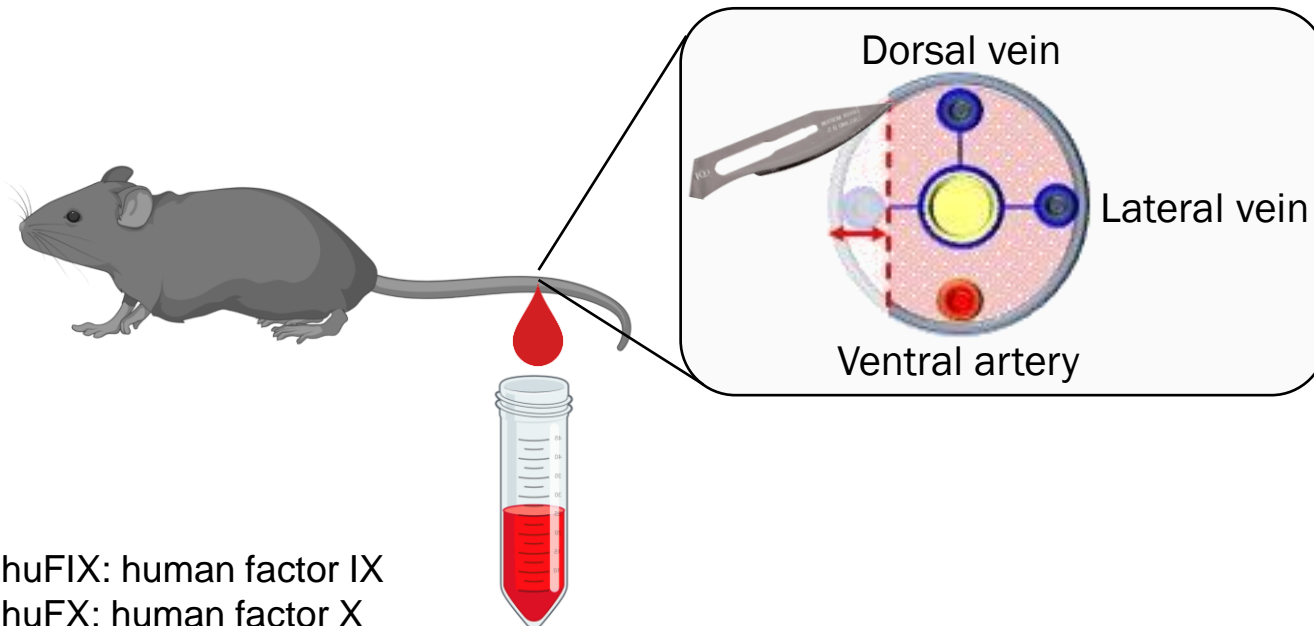
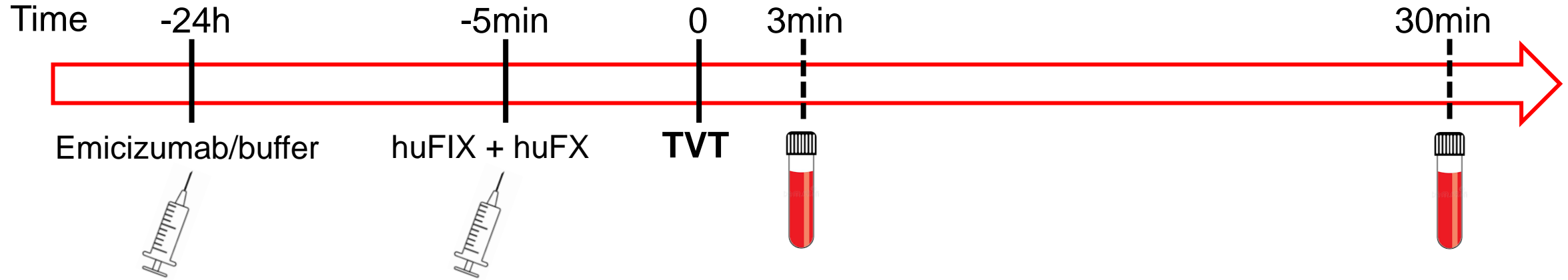
... on clot formation?



... on coagulation?



Impact on haemostasis: The *tail-vein-transection assay*



Read-out:

- **Time to first arrest (*seconds*)**
- **Total amount of blood shed (μl)**

Impact on thrombus formation: the perfusion chamber

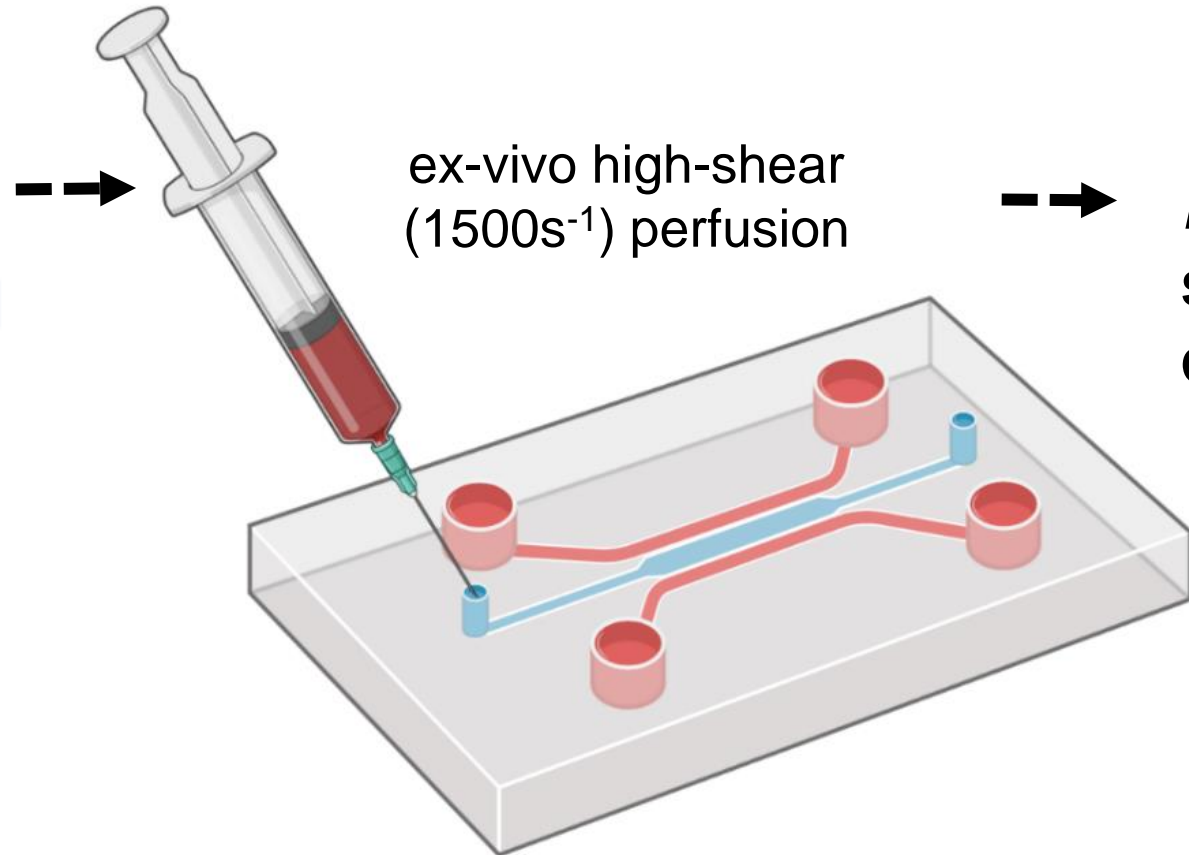
VWD-type 3 blood



+ Buffer (Vehicle)

OR

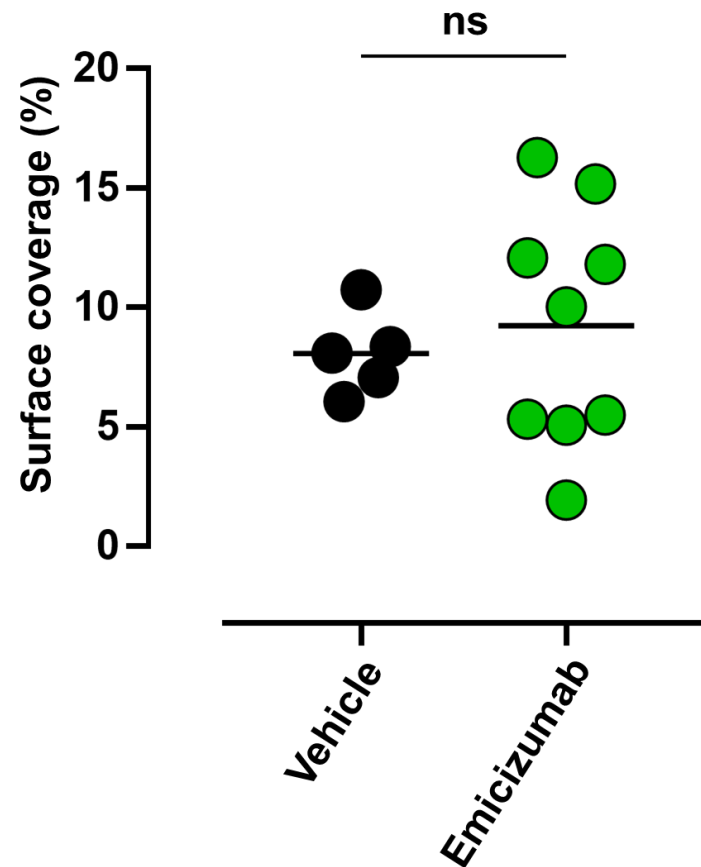
+ Emicizumab, FIX, FX



ex-vivo high-shear
(1500s^{-1}) perfusion

Read-out:
**surface
coverage**

How does Emicizumab affect thrombus formation?



- VWD-type 3 blood treated with emicizumab has higher surface coverage
- Emicizumab seems to **improve thrombus formation** in VWD-type 3 murine blood

Impact on coagulation: the thrombin generation test (TGT)

VWF KO mouse
plasma



+ Buffer (Vehicle)

OR

+ Emicizumab
+ FIX
+ FX

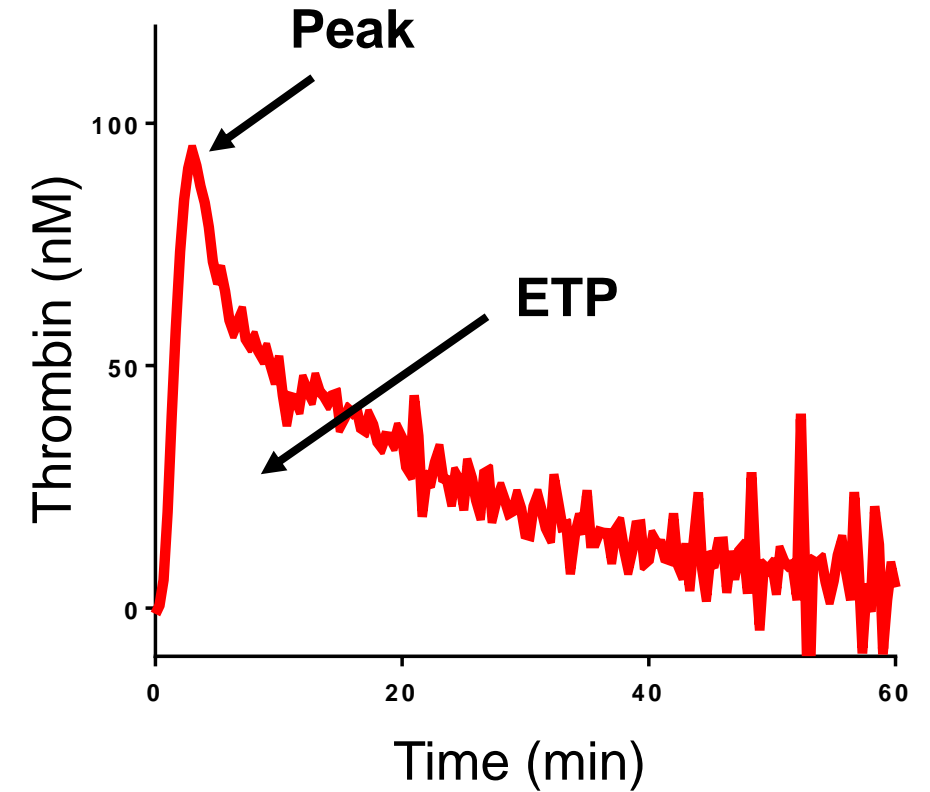
OR

+ FVIII

WT plasma



+ activated FXI
+ Phospholipids

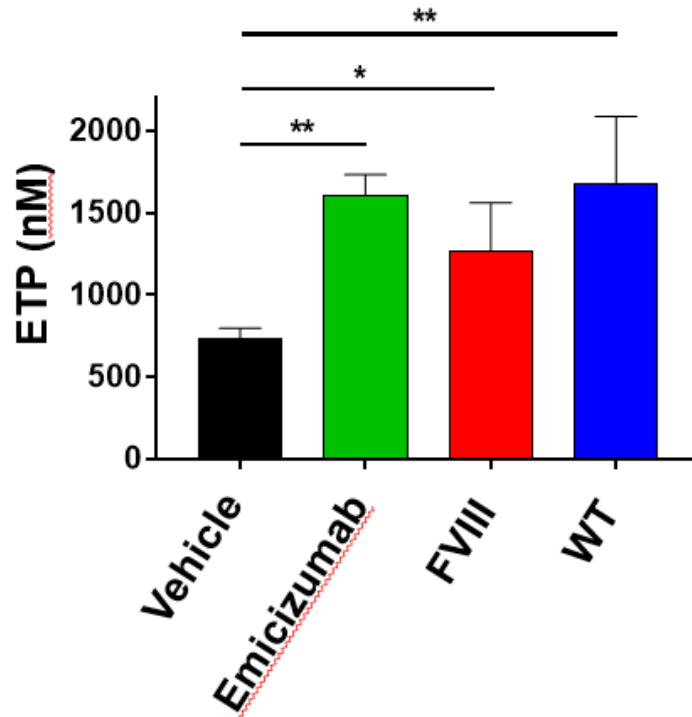


Human factor IX
Human factor X

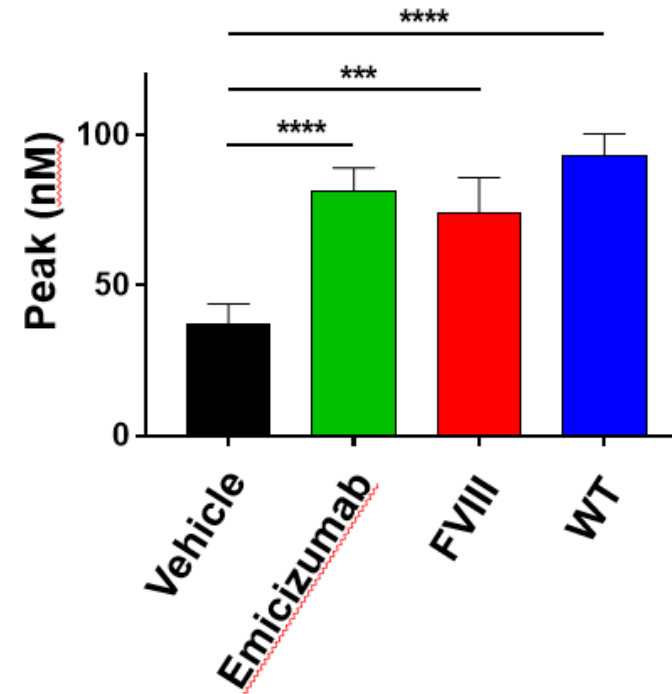
ETP: endogenous thrombin potential

How does Emicizumab affect coagulation in VWD-type 3 mice?

Endogenous thrombin potential



Peak thrombin



FVIII=0,1IU/ml

- Addition of emicizumab to VWD-type 3 plasma increases endogenous thrombin potential and peak thrombin
- Emicizumab **promotes coagulation** in VWD-type 3 mice

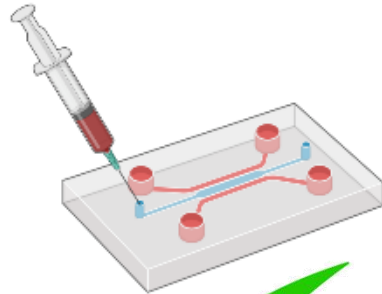
Conclusions

Emicizumab in VWD-type 3 mouse models enhances...

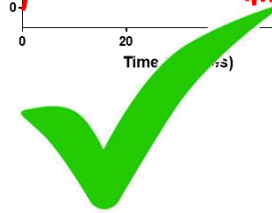
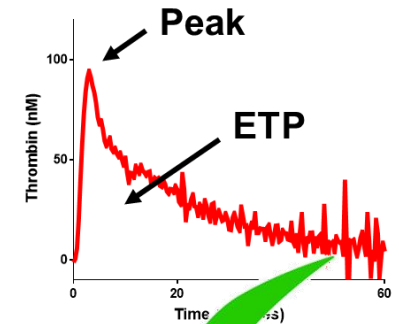
... haemostasis



... clot formation



... coagulation

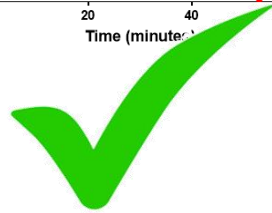
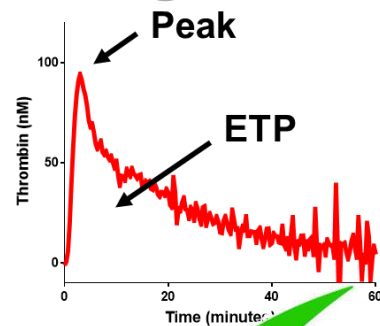


Emicizumab in VWD-type 3 mouse models enhances...

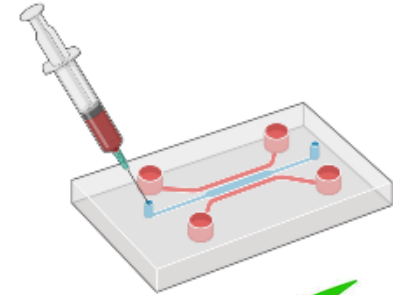
... haemostasis



... coagulation



... clot formation



→ Impact of emicizumab in murine models confirms what was observed in patients: could it be considered for clinical trials?

→ What would be the impact of emicizumab in other VWD models?

MERCI!

Acknowledgments:

Caterina Casari
Cécile Denis
Peter Lenting
Olivier Christophe
Thibaud Sefiane
Emilie Bocquet

U1176

HIT_h



VWD-type 3 patients receiving emicizumab: case reports

	7 yrs ♂	48 yrs ♀	2 yrs, ♂	9 yrs ♂	6 yrs ♀	11 yrs ♀
Allo-antibodies anti-VWF	✓	✓	✓	x	✓	x
Joints swelling/bleeding	✓	✓	✓	✓	not reported	not reported
Mucocutaneous bleeding	✓	not reported	✓	not reported	✓	✓
Other symptoms		Arthropathy		Arthropathy	Thrombocytopenia	Anemia
Emicizumab (sc)	3mg/kg/w (4x) 1.5mg/kg/w (9months) 3mg/kg/EOW	3mg/kg/w (4x) 1.5mg/kg/w	3mg/kg/w (4x) 1.5mg/kg/w	3mg/kg/w (4x) 1.5mg/kg/w (+1 dose HaemateP)	3mg/kg/w (4x) 3mg/kg/EOW	3mg/kg/month
Hemostatic improvement	Yes	Yes	Yes	Yes	Yes	Yes
Treatment follow-up	9 months	1 month	12 months	11 months	6 months	8 months
References	Weyand et al. Blood Advances 2019	Sigaud et al. ISTH abstract 2020	Cefalo et al. Haemophilia et al 2020	Barg et al. Blood Cells Molecules and Diseases 2021	Shanmukhaiah et al. Haemophilia 2022	Shanmukhaiah et al. Haemophilia 2022