

CONGRÈS  
d'FRANÇAIS  
d'HÉMOSTASE

Instituts  
thématiques



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PARIS-SACLAY

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MAI  
2023



Palais des Congrès

SAINT-MALO

Le Grand Large



**SFTH**

SOCIÉTÉ FRANÇAISE  
DE THROMBOSE  
ET D'HÉMOSTASE

**HiTh**

INSERM UMR 1176

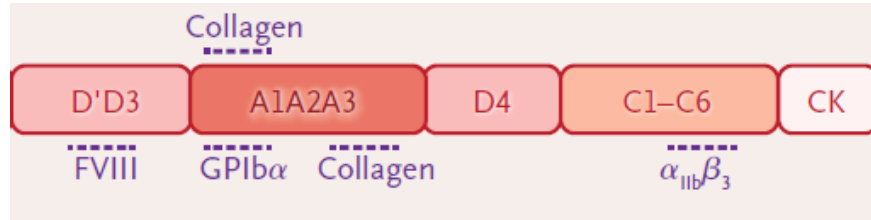
Hémostase

Inflammation - Thrombose

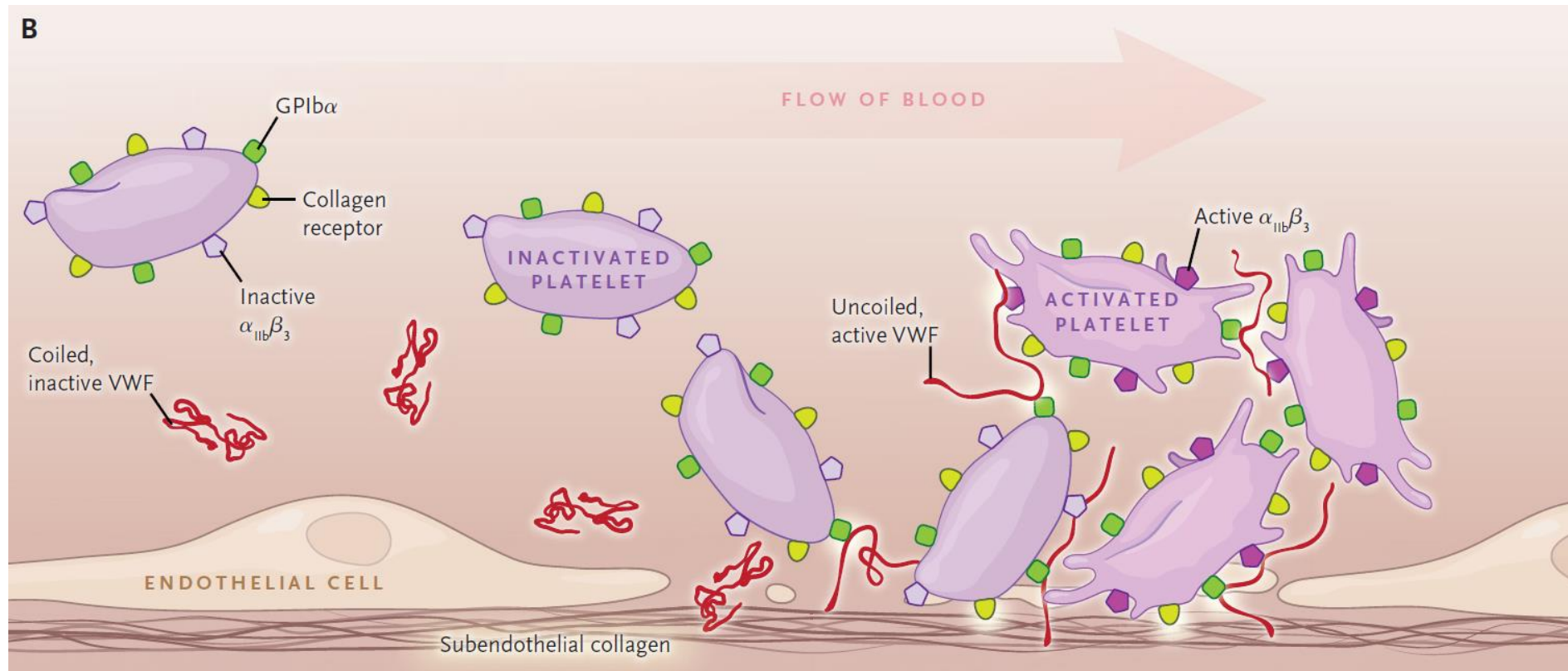
*KB-V13A12, a novel nanobody-based  
therapeutic molecule  
for the treatment of von Willebrand disease*

Ivan Peyron, Caterina Casari, Olivier D. Christophe, Peter J. Lenting and Cécile V. Denis

# Von Willebrand Factor (VWF)



A multimeric plasma glycoprotein involved in platelet plug formation after vascular injury



# Von Willebrand Disease (VWD): a congenital bleeding disorder

Hemophilia A	VWD
Coagulation factor VIII	Von Willebrand factor
Men (mostly)	Men and women
1 male birth / 5000	From 0.1 to 1% of the population
6000 patients in France	7000-8000 symptomatic patients in France mostly with a partial quantitative deficiency
2500 patients with a severe form in France	50 to 100 patients with a severe form in France
Bleeding in muscles and in the joints leading to severe joint damage and arthropathy	Mucocutaneous bleedings: GI tract, nose, mouth, gynecological
Numerous treatments available. Constant innovation	Treatments unchanged for the past 30 years

## Recurrent theme in Quality of Life-studies:

- Severe/moderate VWD patients have clinically and statistically significant reductions in nearly all health related-QoL domains, both for the physical and mental aspects
- In particular, women express considerable morbidity in emotion and pain

## Recent study on depression and anxiety (US study)

Rate of depression was found to be 64% in VWD patients!

⇒ Need to develop new treatments also for moderate VWD

**Idea:** To develop a simple and easily administrable treatment aiming to increase half-life of endogenous VWF in order to:

- increase its plasma concentration
- decrease bleeding symptoms

# Albumin and FcRn



## Major Types:

### ■ Albumin (60%)

Major component of osmotic pressure of plasma

### ■ Globulins (35%)

Antibodies (immunoglobulin) and transport proteins

### ■ Fibrinogens (4%)

Functions in blood clotting

### ■ Other (<1%)

Various roles ( $\alpha$ -1-antitrypsin, coagulation factors, etc.)

Half-life : 21 days!

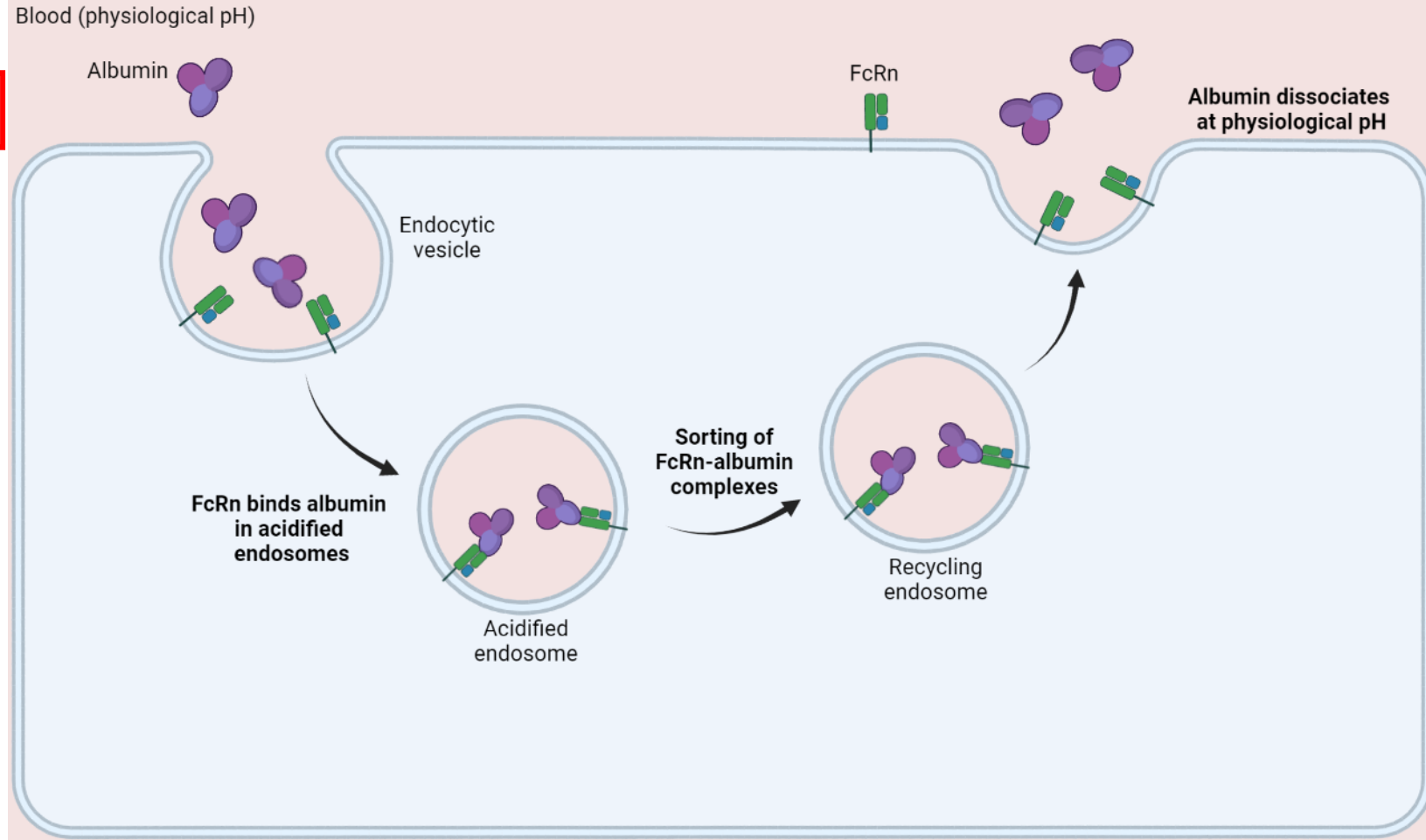
# Albumin and FcRn



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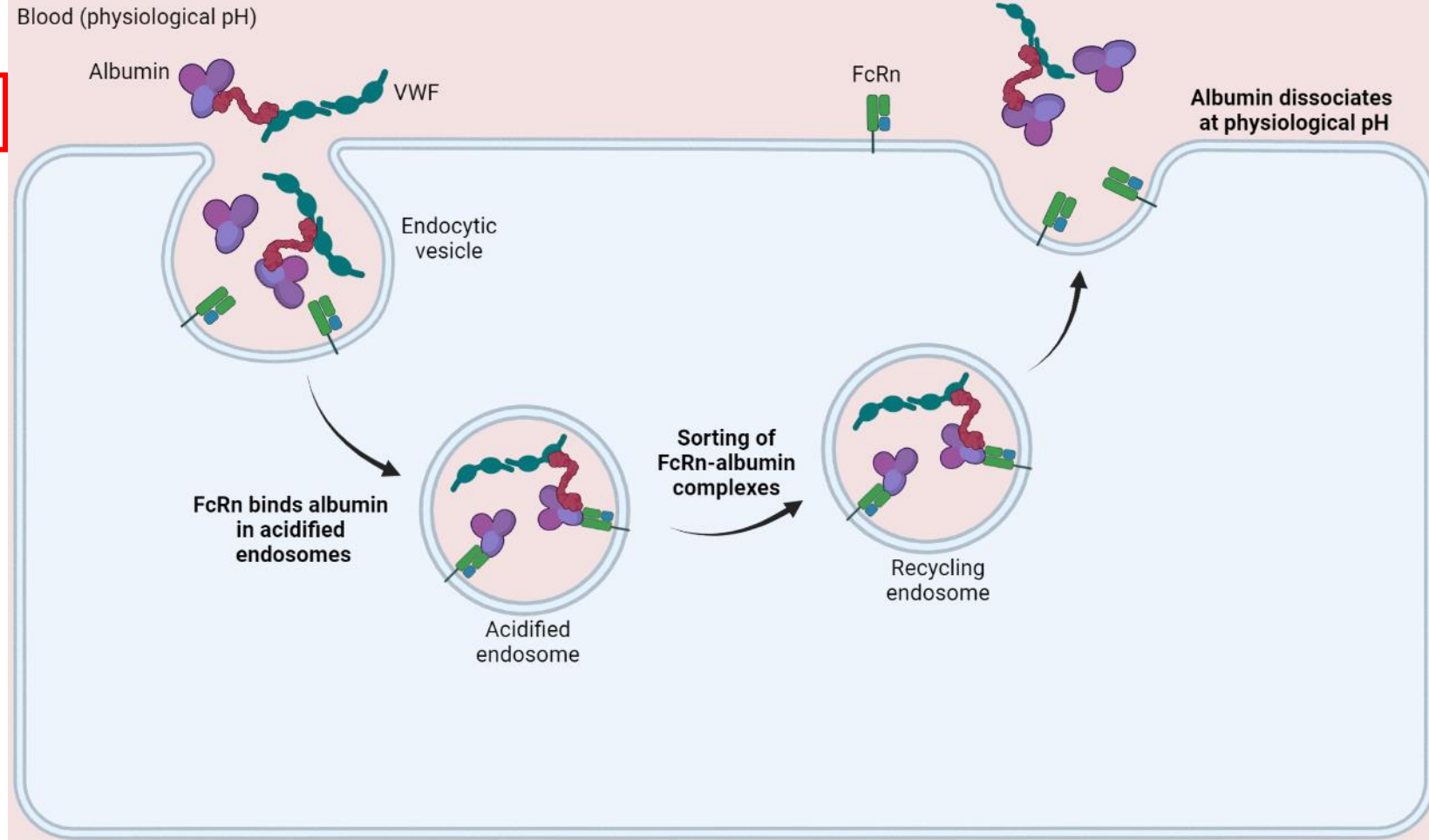
# Albumin and FcRn



## Major Types:

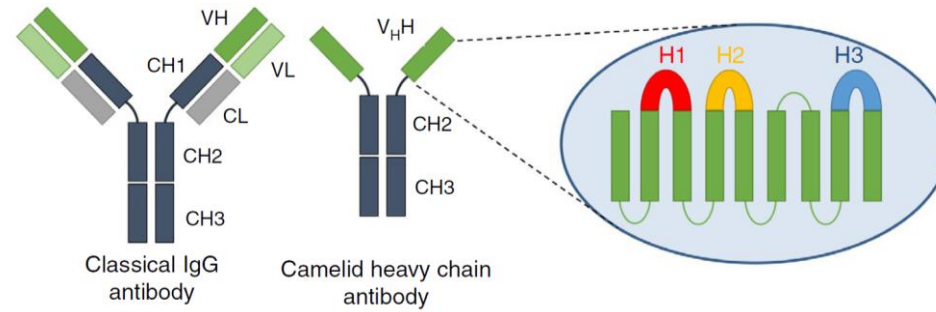
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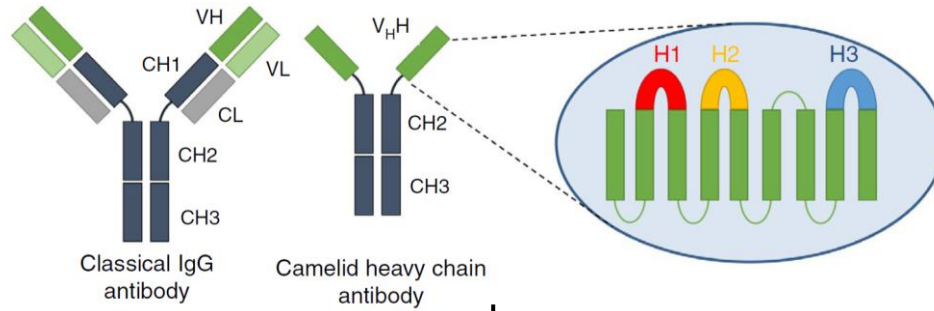
**Aim: develop a molecule that creates a bridge between VWF and albumin**

# Generation of KB-V13A12

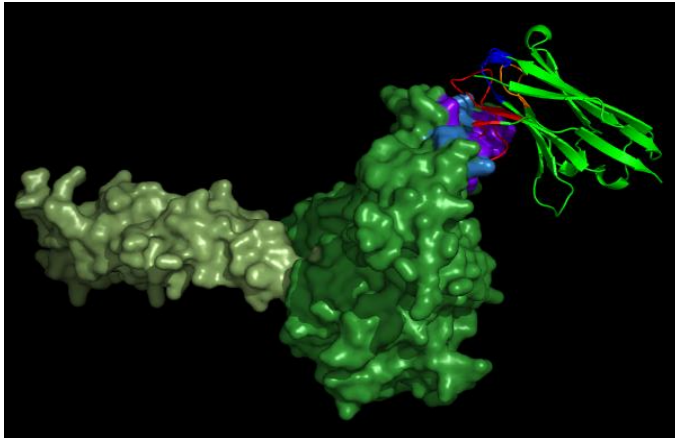




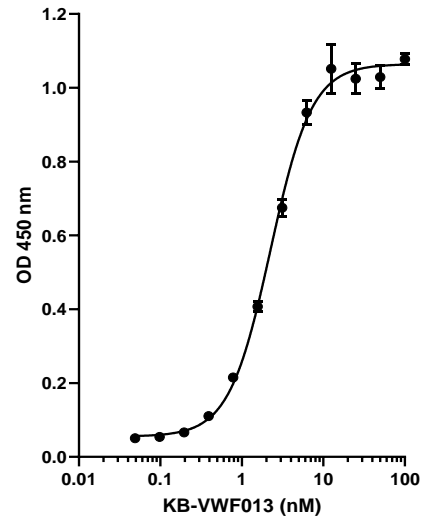
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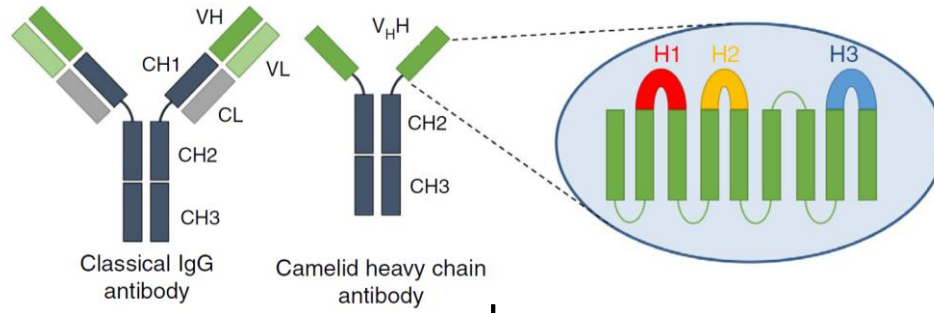
KB-VWF013 (V13)



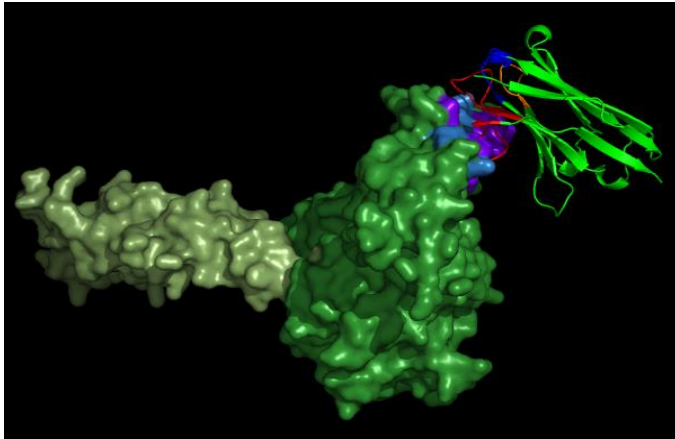
VWF binding



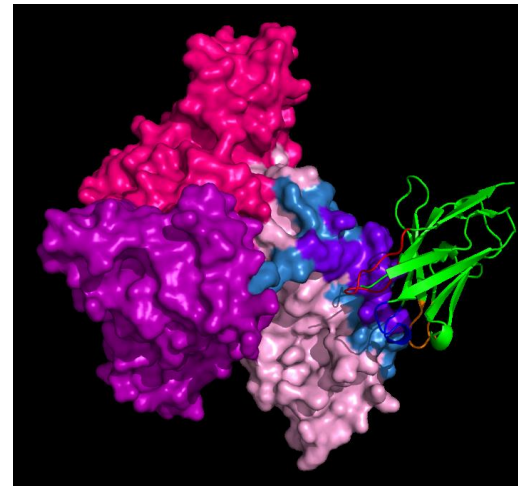
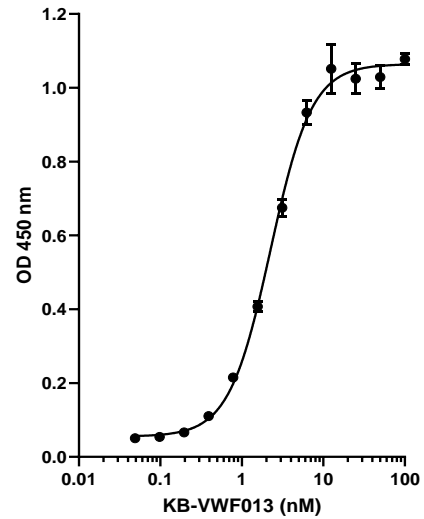
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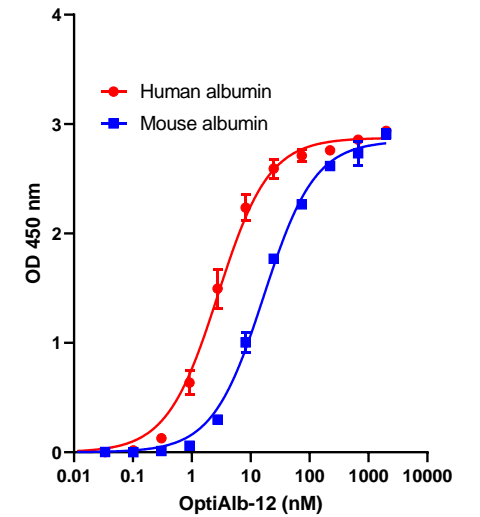
## KB-VWF013 (V13)



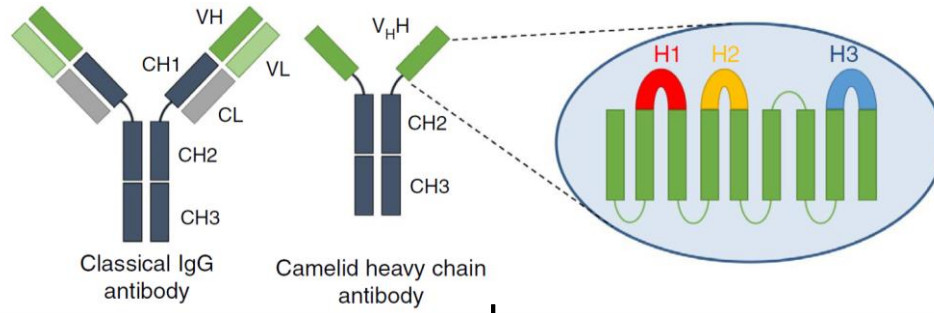
### VWF binding



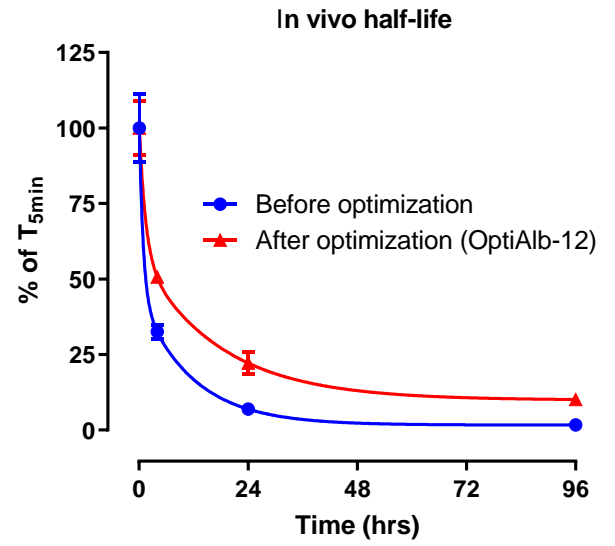
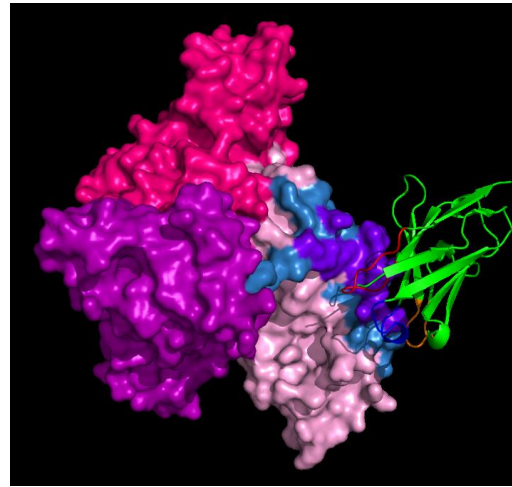
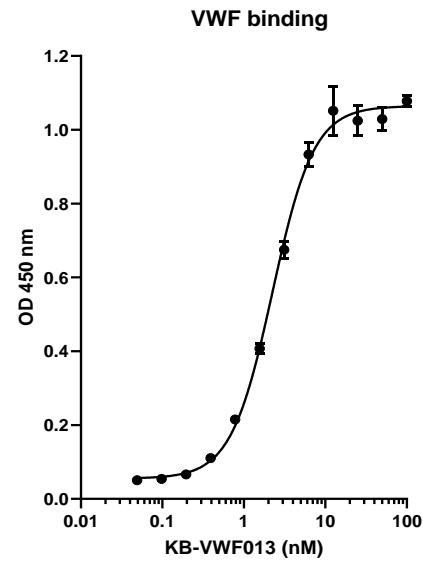
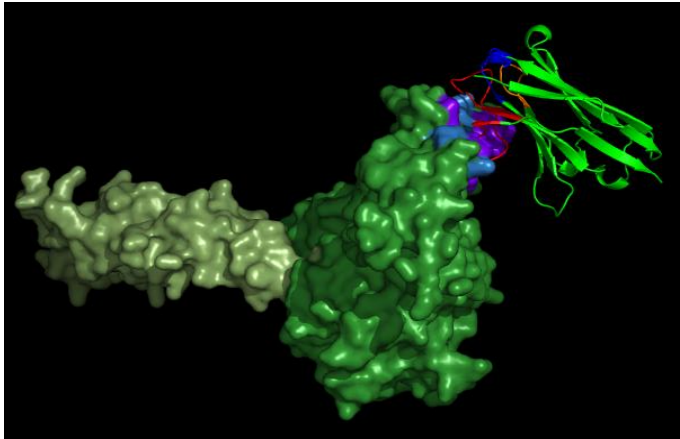
### Albumin binding



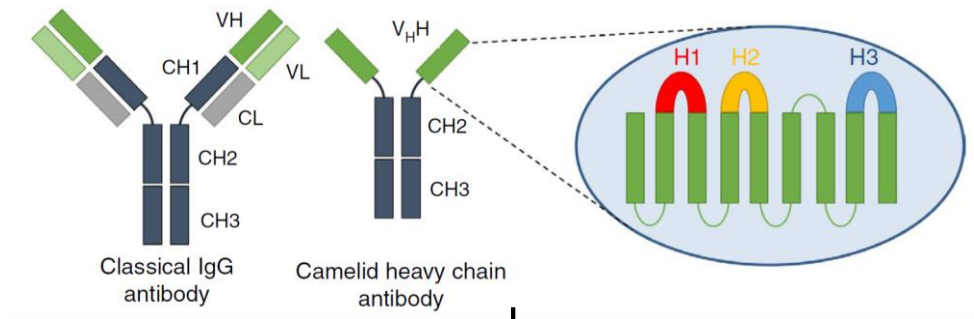
# Generation of KB-V13A12



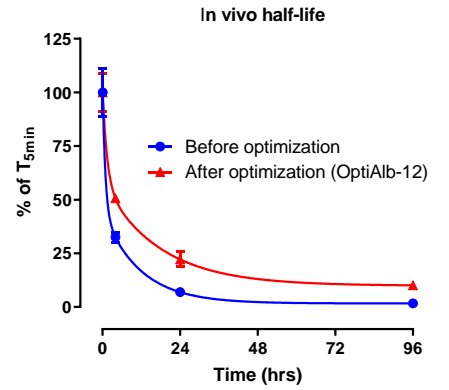
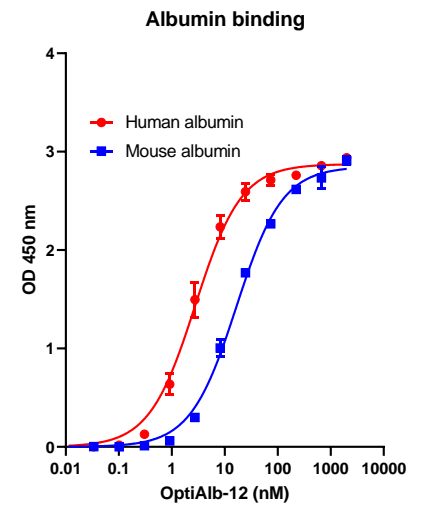
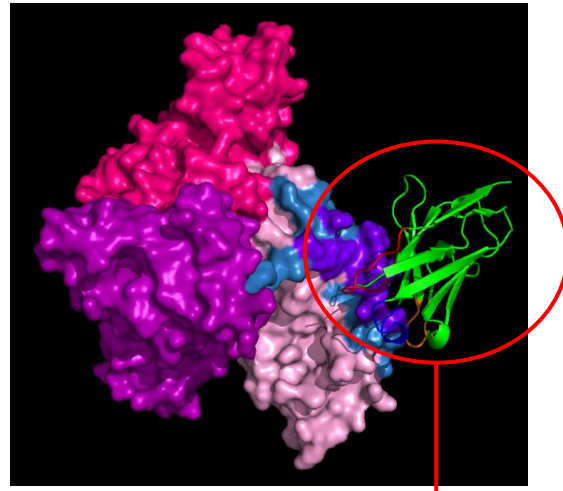
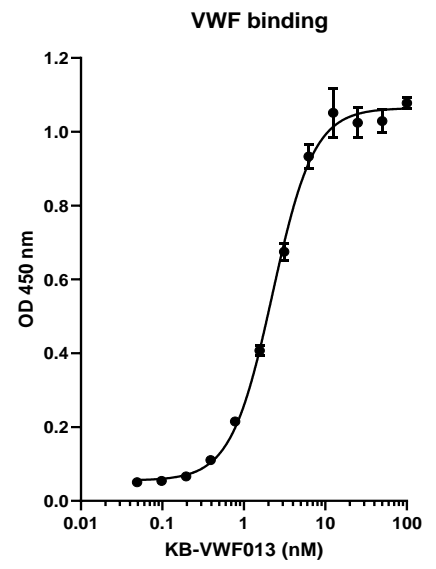
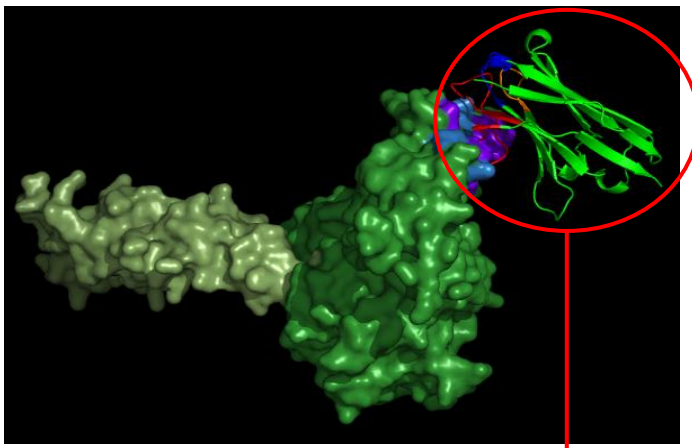
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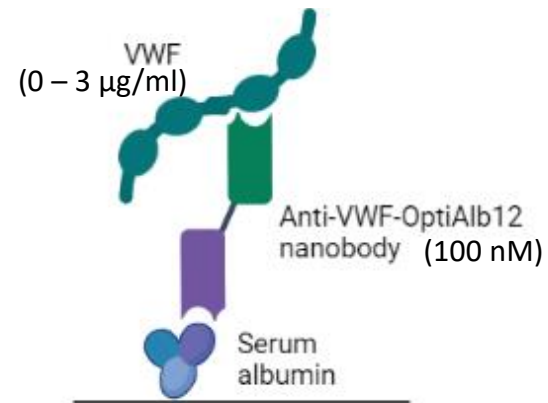
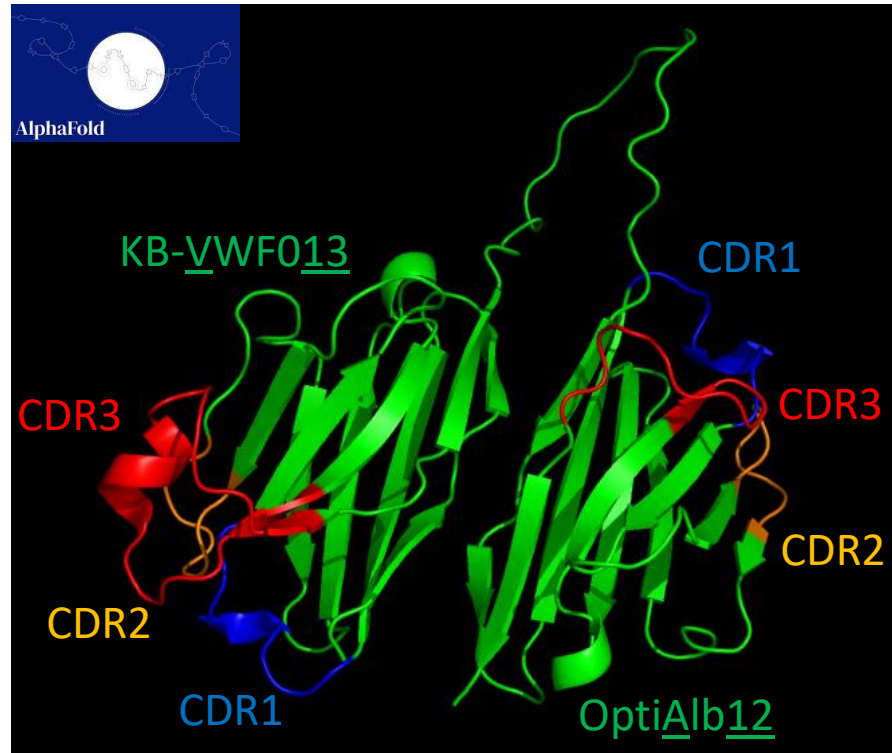
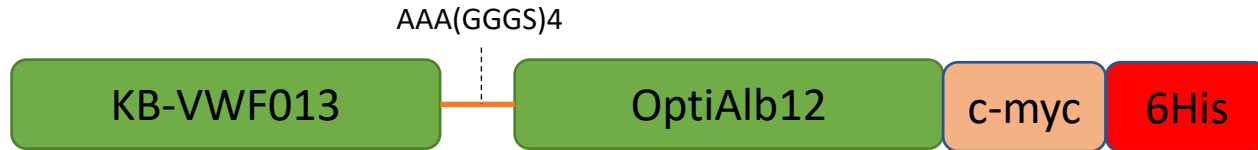


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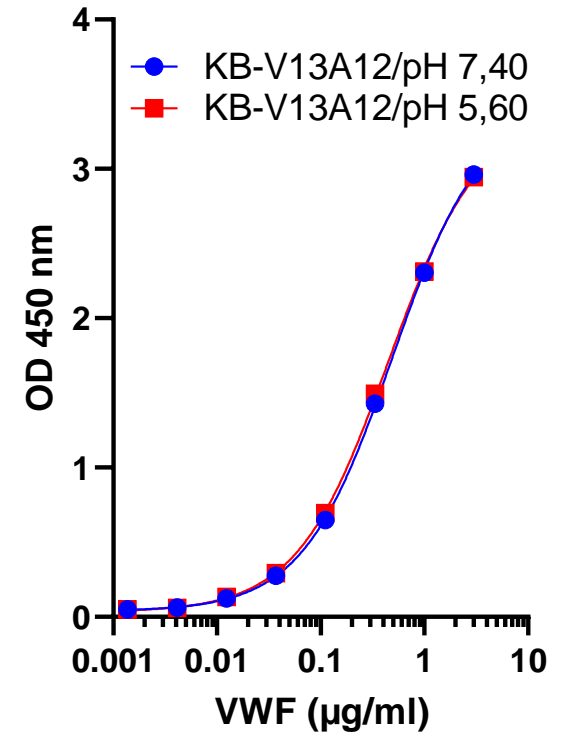
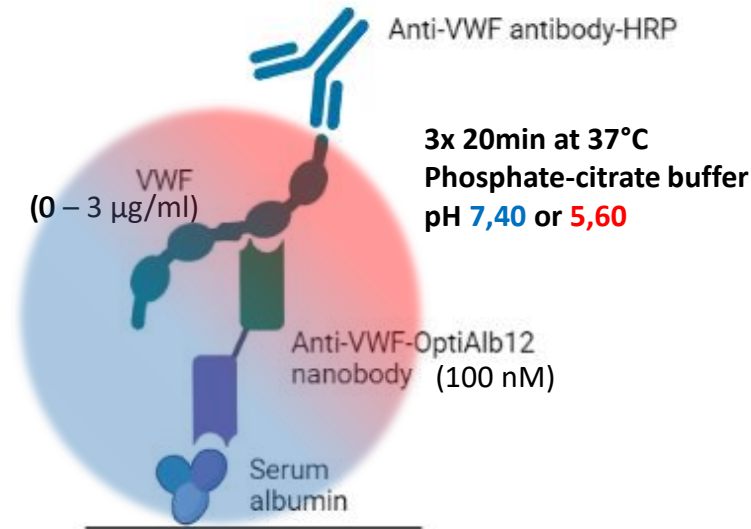
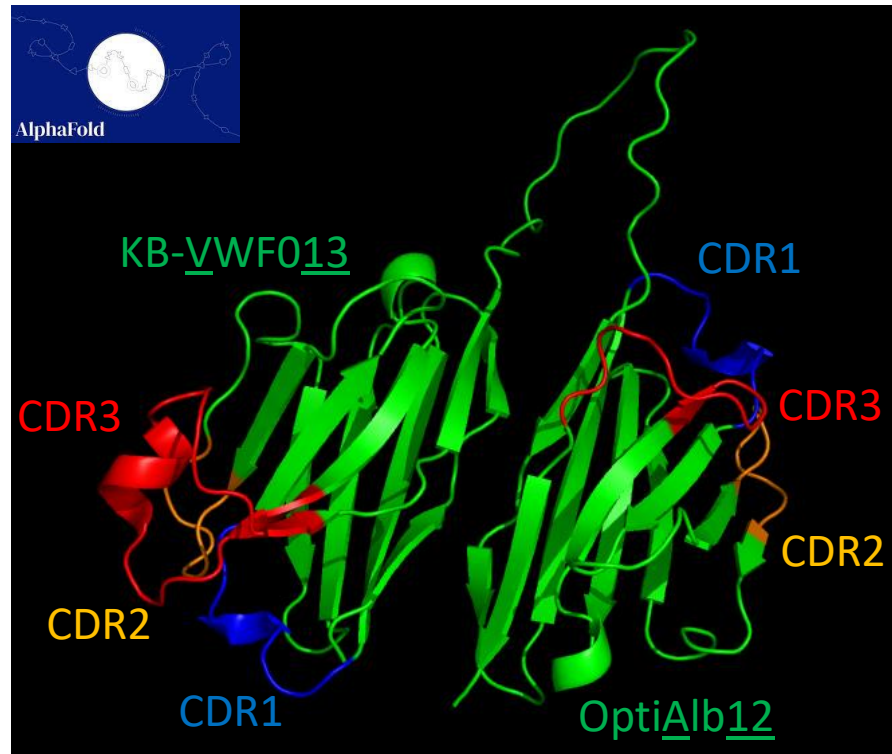
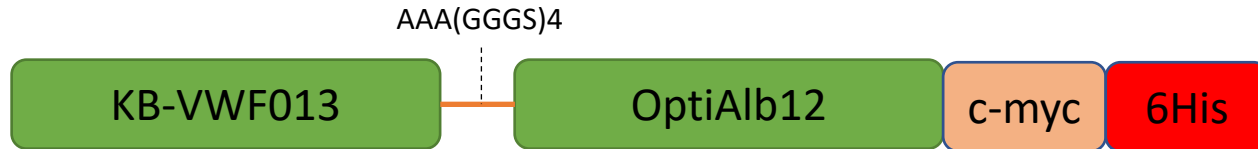


**KB-V13A12**

# Characterization of KB-V13A12 *in vitro*



# Characterization of KB-V13A12 *in vitro*



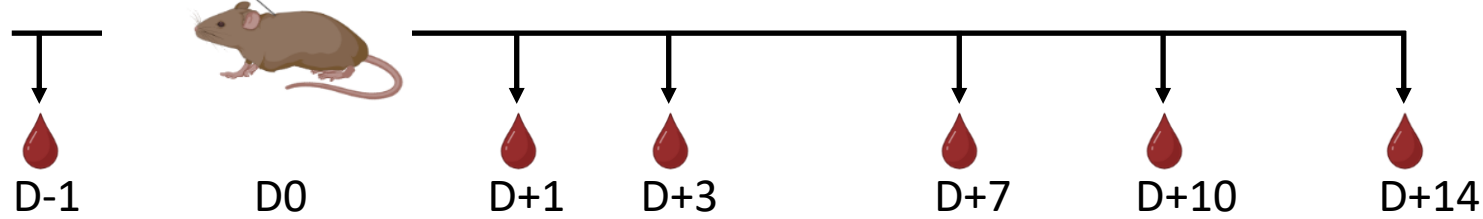
- KB-V13A12 binds albumin and VWF simultaneously
- The [albumin]-[KB-V13A12]-[VWF] complex is stable at lysosomal pH

# Effect of KB-V13A12 *in vivo*

## Modulation of VWF levels

KB-V13A12  
5 mg/kg  
s.c. injection

Mouse model  
expressing 10% hVWF:  
Type 1 VWD

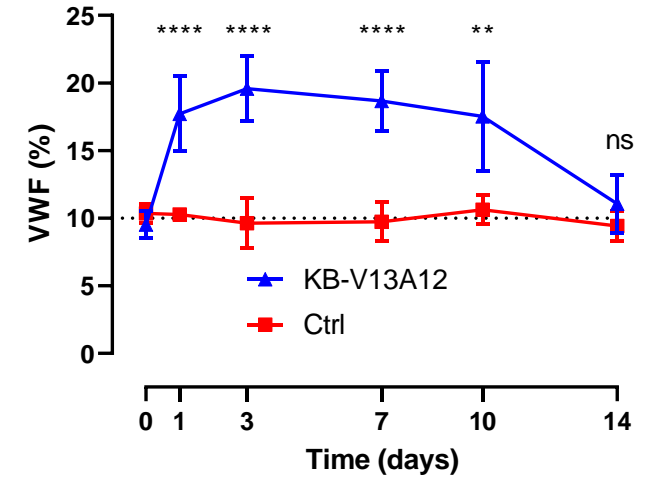
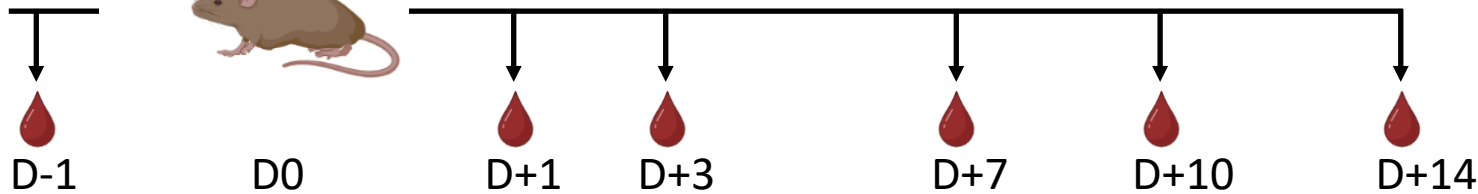


# Effect of KB-V13A12 *in vivo*

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One-way ANOVA

**A single subcutaneous injection of KB-V13A12 elevates VWF levels for up to 10 days**

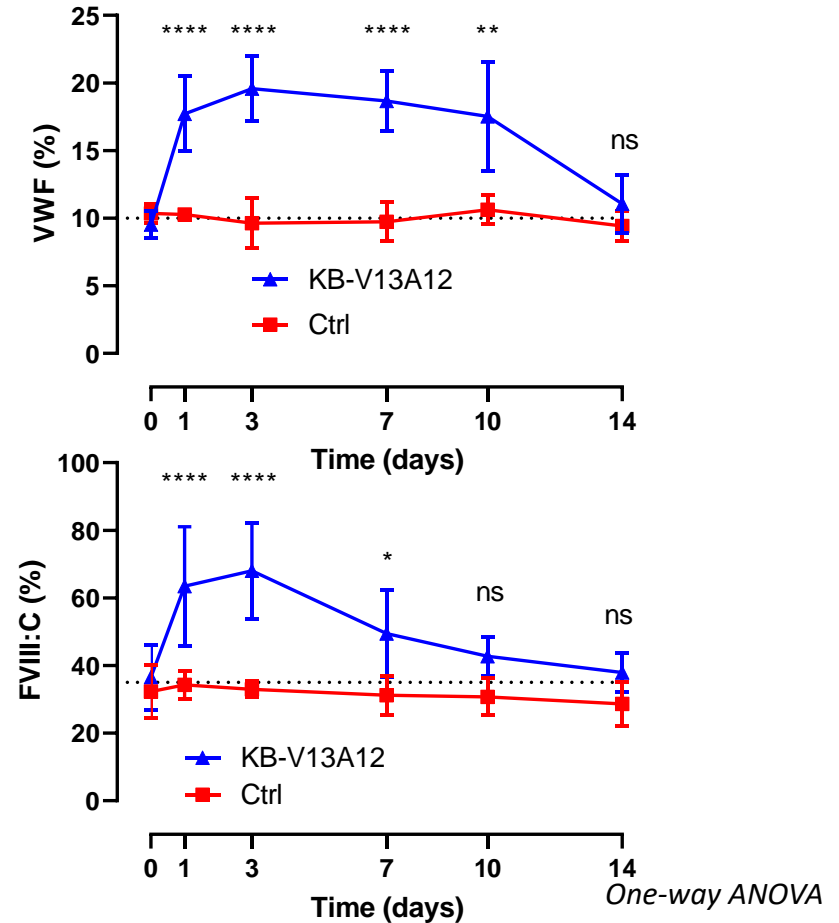
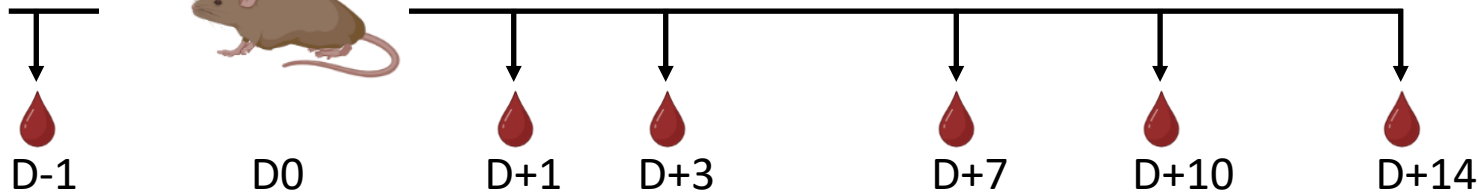


# Effect of KB-V13A12 *in vivo*

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Mouse model  
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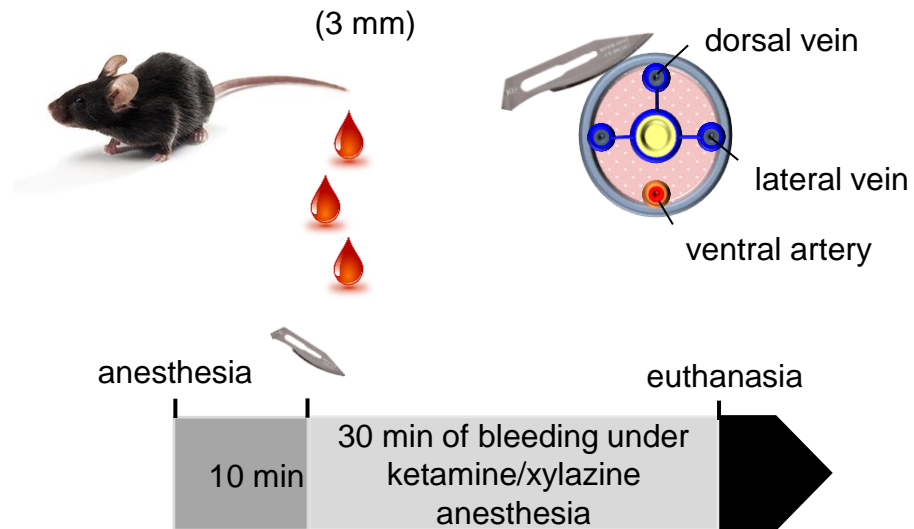
**A single subcutaneous injection of KB-V13A12 elevates VWF levels for up to 10 days**  
**The rise in VWF level is accompanied by a rise in FVIII levels**

# Functional effect of KB-V13A12 *in vivo*

## Effect on bleeding

WT mice or mouse  
model expressing 10%  
hVWF: Type 1 VWD

### Tail clip bleeding model

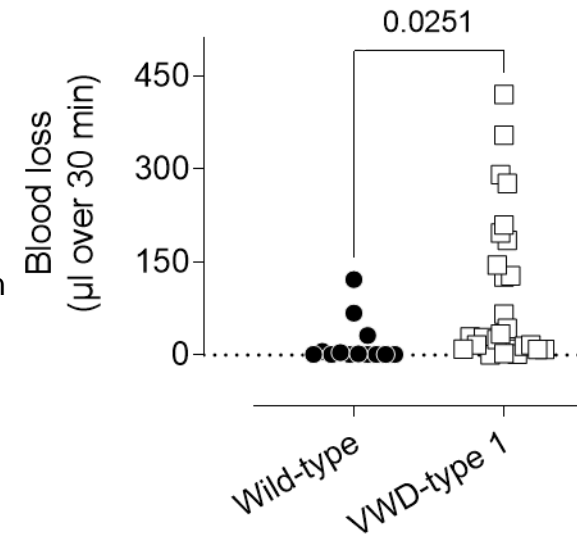
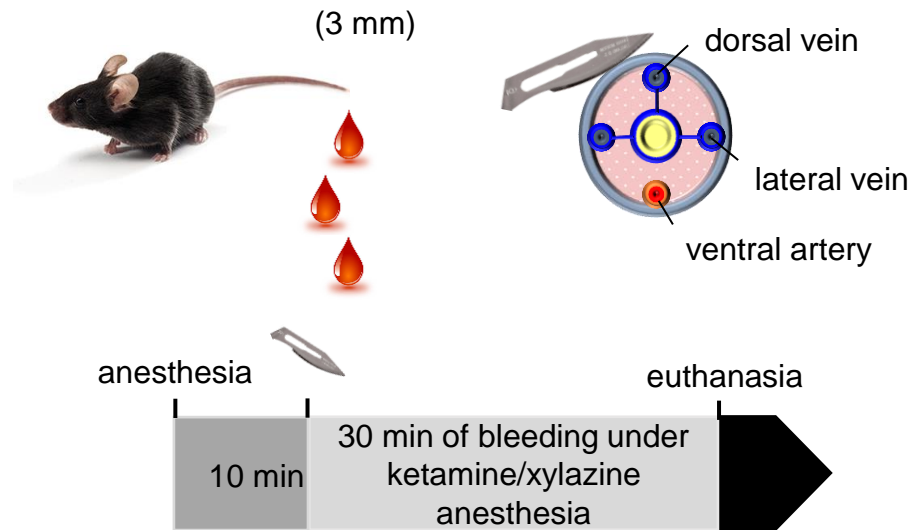


# Functional effect of KB-V13A12 *in vivo*

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WT mice or mouse model expressing 10% hVWF: Type 1 VWD

### Tail clip bleeding model



One-way ANOVA

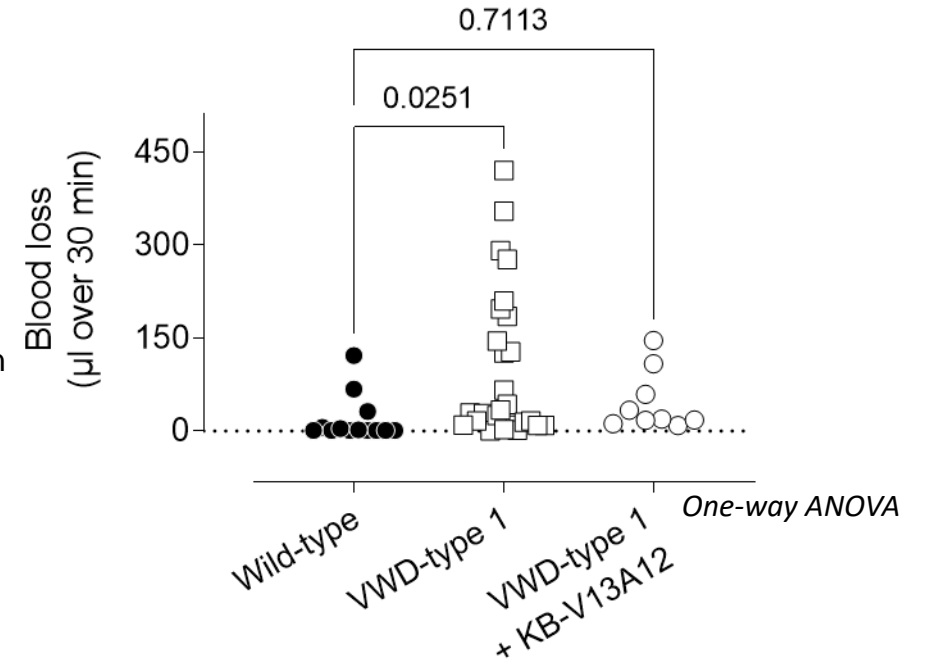
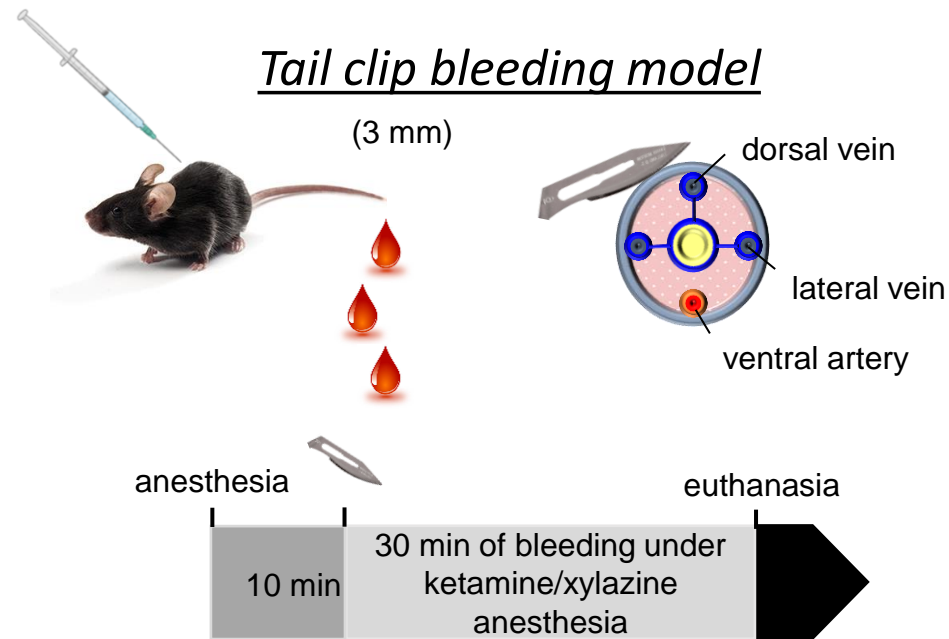
**- VWD type 1 mice lose more blood compared to wild-type mice**

# Functional effect of KB-V13A12 *in vivo*

## Effect on bleeding

KB-V13A12 (5 mg/kg)  
 s.c. injection  
 3 days before procedure

WT mice or mouse  
 model expressing 10%  
 hVWF: Type 1 VWD



- VWD type 1 mice lose more blood compared to wild-type mice
- KB-V13A12 restores functional hemostasis in VWD type 1 mice

# Merci de votre attention

