HMB-001 | A Novel Bispecific Antibody Accumulating and Targeting Endogenous FVIIa to Activated Platelets for Subcutaneous Prophylaxis in Multiple Bleeding Disorders Including Glanzmann Thrombasthenia

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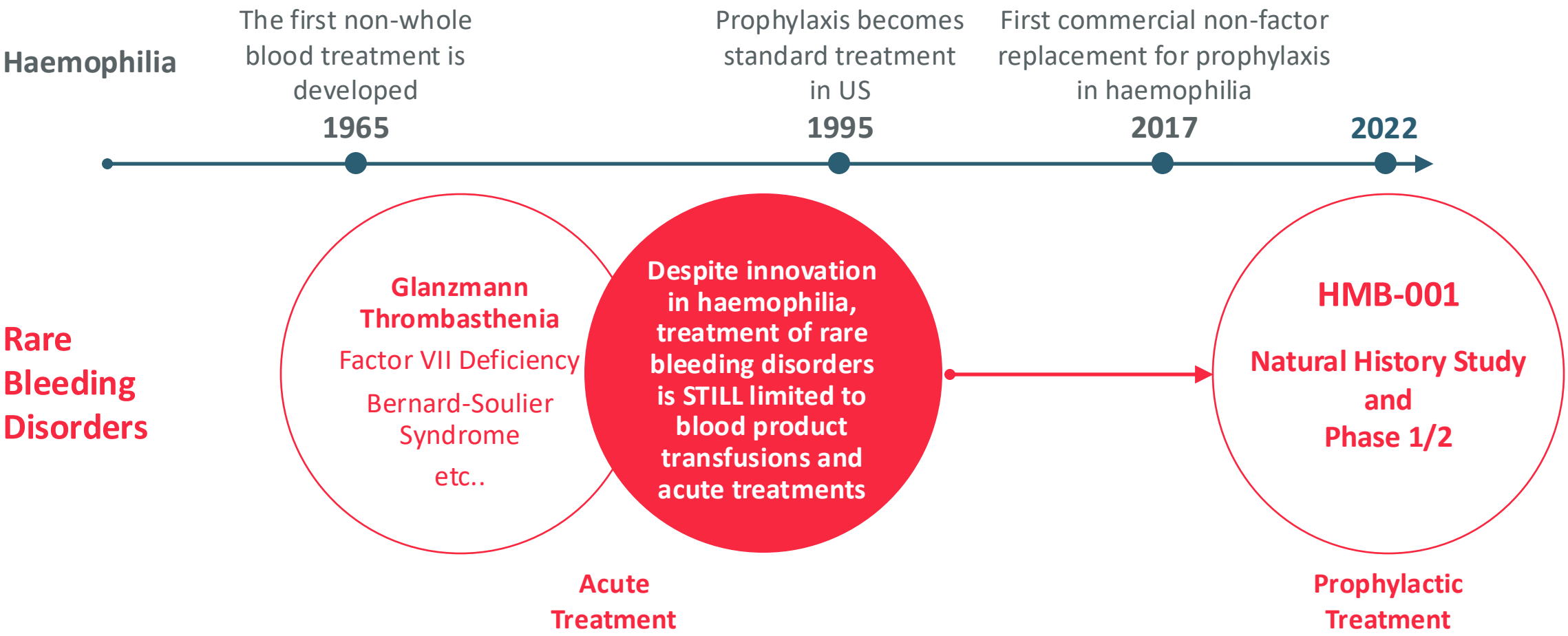
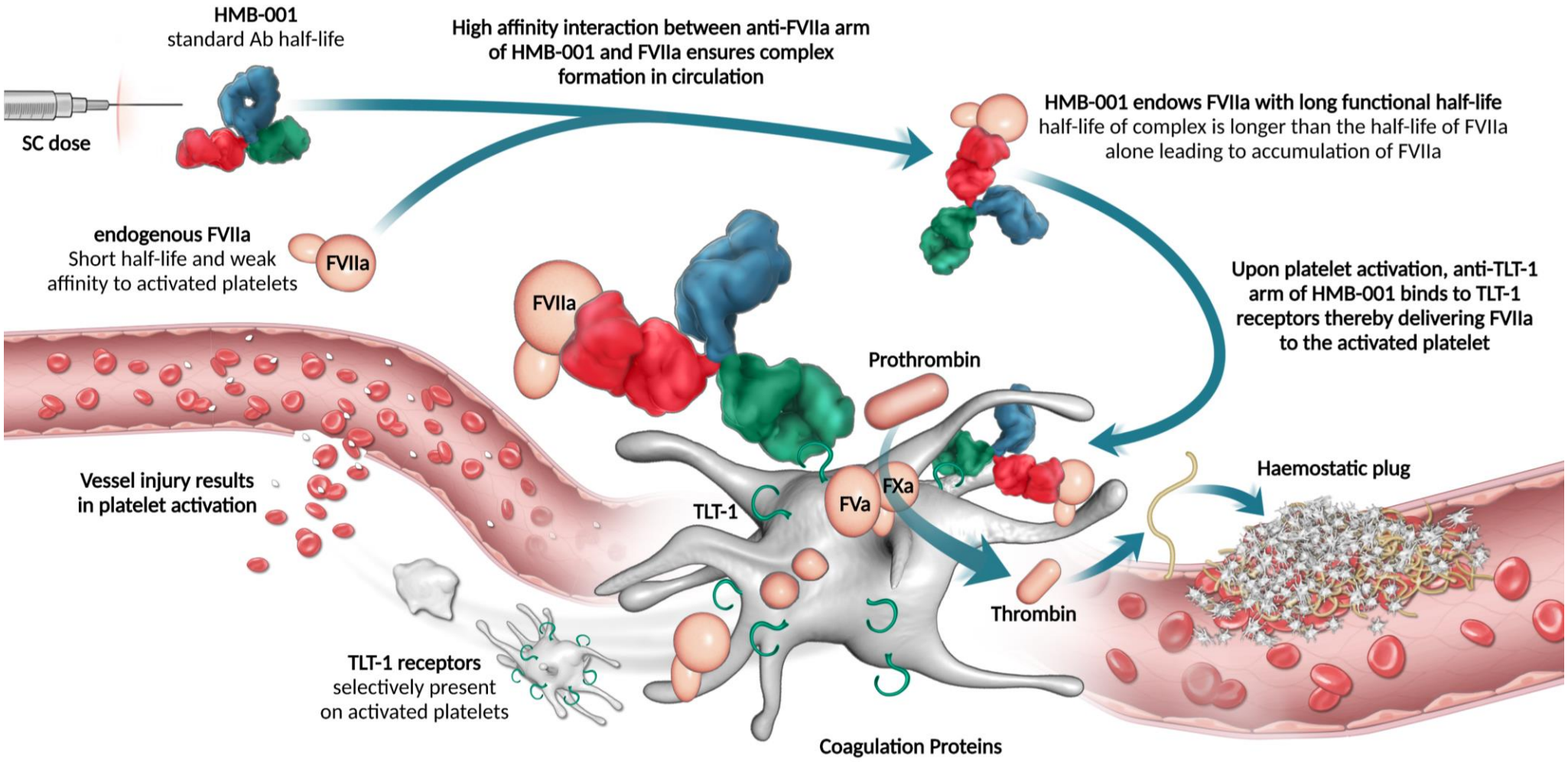
Prophylaxis is not readily available for people with Rare Bleeding Disorders



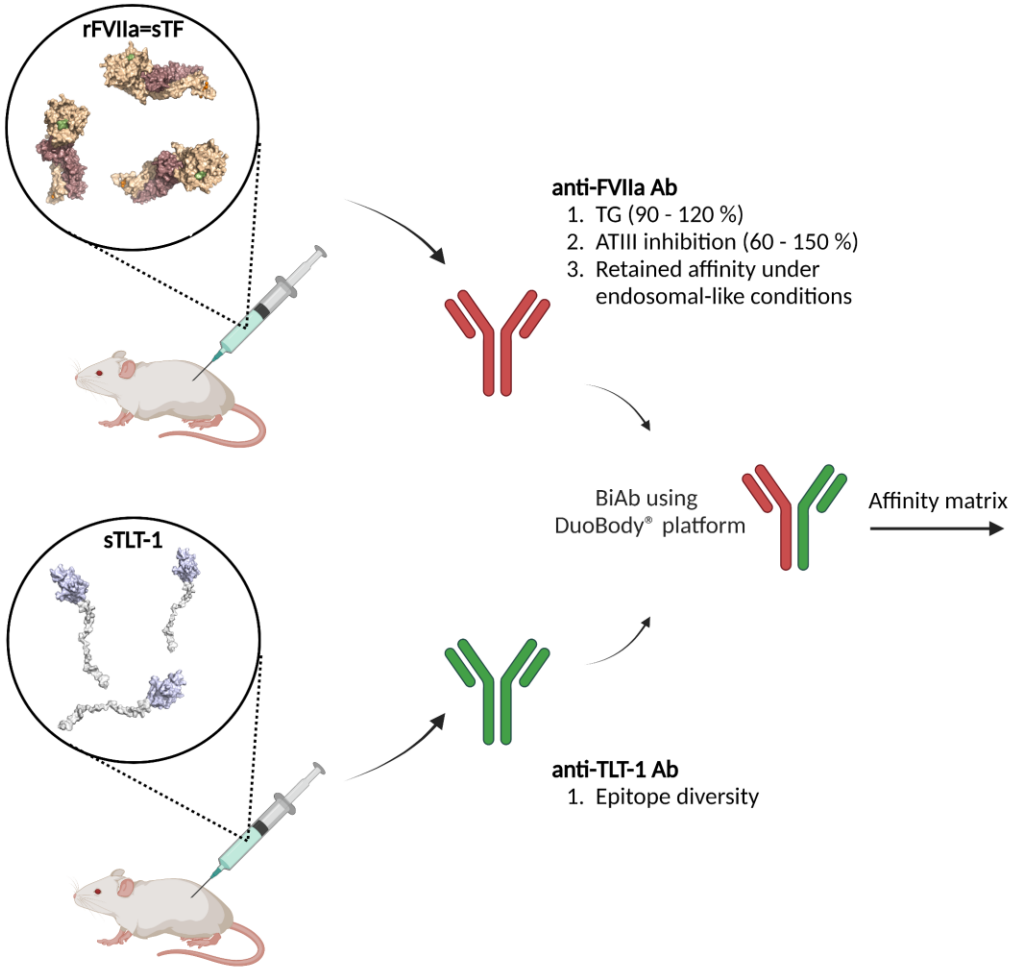
HMB-001 | A novel bispecific antibody targeting FVIIa & TLT-1

HMB-001 binds and accumulates endogenous FVIIa and, following vessel lesion, localizes FVIIa to the surface of activated platelets



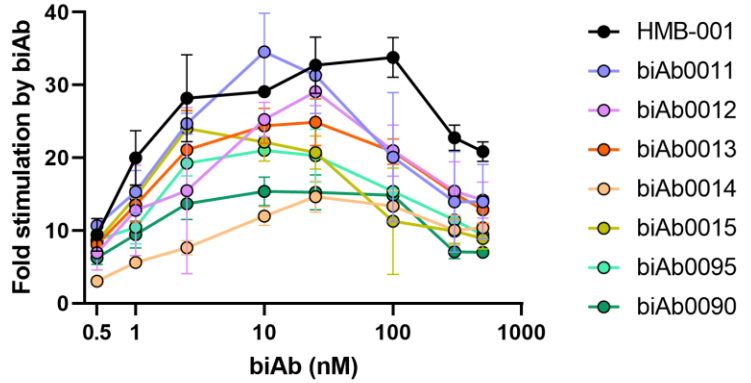
HMB-001 | Engineered for optimal affinity towards FVIIa and TLT-1

HMB-001 discovery strategy



Optimal target affinity identified using FXa generation assay, HMB-001 provides most stimulation

BiAb	$K_{D,FVIIa}$, nM	$K_{D,sTLT-1}$, nM	Fold stimulation @ 100 nM biAb
HMB-001	0.06	2.9	33.8 ± 2.8
biAb0011	0.28	2.9	20.1 ± 8.9
biAb0012	2.2	2.9	21.0 ± 3.5
biAb0013	16.2	2.9	20.8 ± 1.8
biAb0014	600	2.9	13.3 ± 2.1
biAb0015	0.06	19	11.3 ± 7.3
biAb0095	0.06	75	14.8 ± 1.0
biAb0090	0.06	320	15.4 ± 0.8

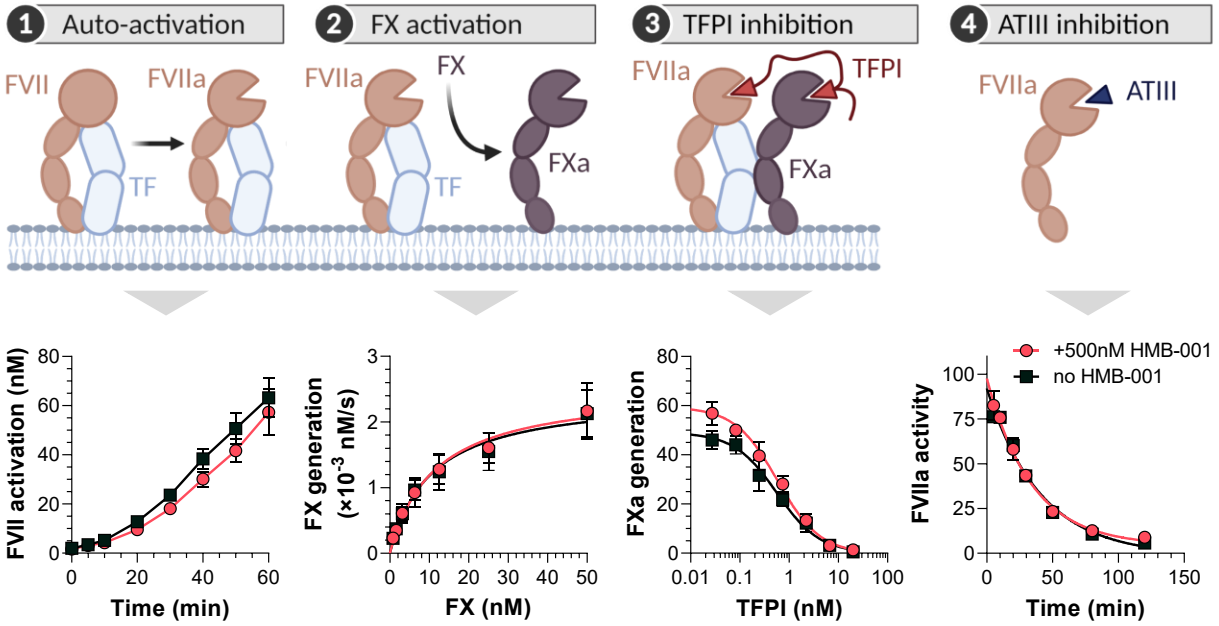


***In vitro* study design**

- Affinity measured using SPR. Fold stimulation measured using FXa generation assay (mean ± SD, n = 3)
- FXa generation measured in presence of 4 nM rTLT-1 in PS:PC (25:75) vesicles, 2.5 nM rFVIIa, biAb (0 to 500 nM). 150 nM pdFX activated for 20 min. The generated FXa is quantified by hydrolysis of 1 mM S-2765.

HMB-001 | Neutral binding to FVII(a) and activated platelets

HMB-001 binding does not affect key physiological functions of FVII(a)



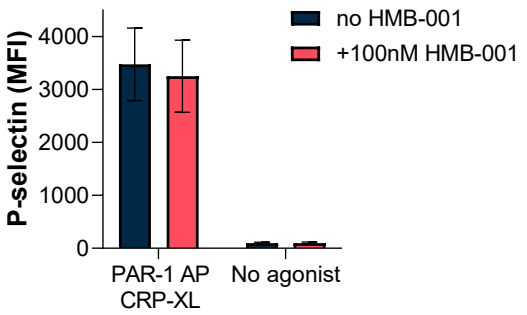
***In vitro* study design**

1. 2pM TF:FVIIa and 145nM FVII ± 500nM HMB-001
2. 2pM TF:FVIIa and 0-50nM FX ± 500nM HMB-001
3. 2pM TF:FVIIa, 50nM FX and 0-20nM TFPI ± 500nM HMB-001
4. 40nM FVIIa, 5µM ATIII, 12µM LMW Heparin ± 500nM HMB-001

HMB-001 does not affect platelet activation and aggregation

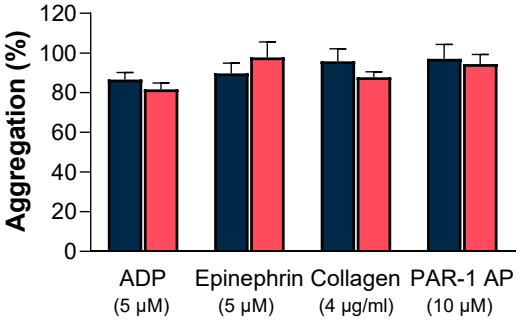
1 Platelet activation

- Exposure of normal whole blood to platelet activator ± 100nM HMB-001
- After 20 min, P-selectin exposure was quantified by FACS (mean ± SD, n = 3)



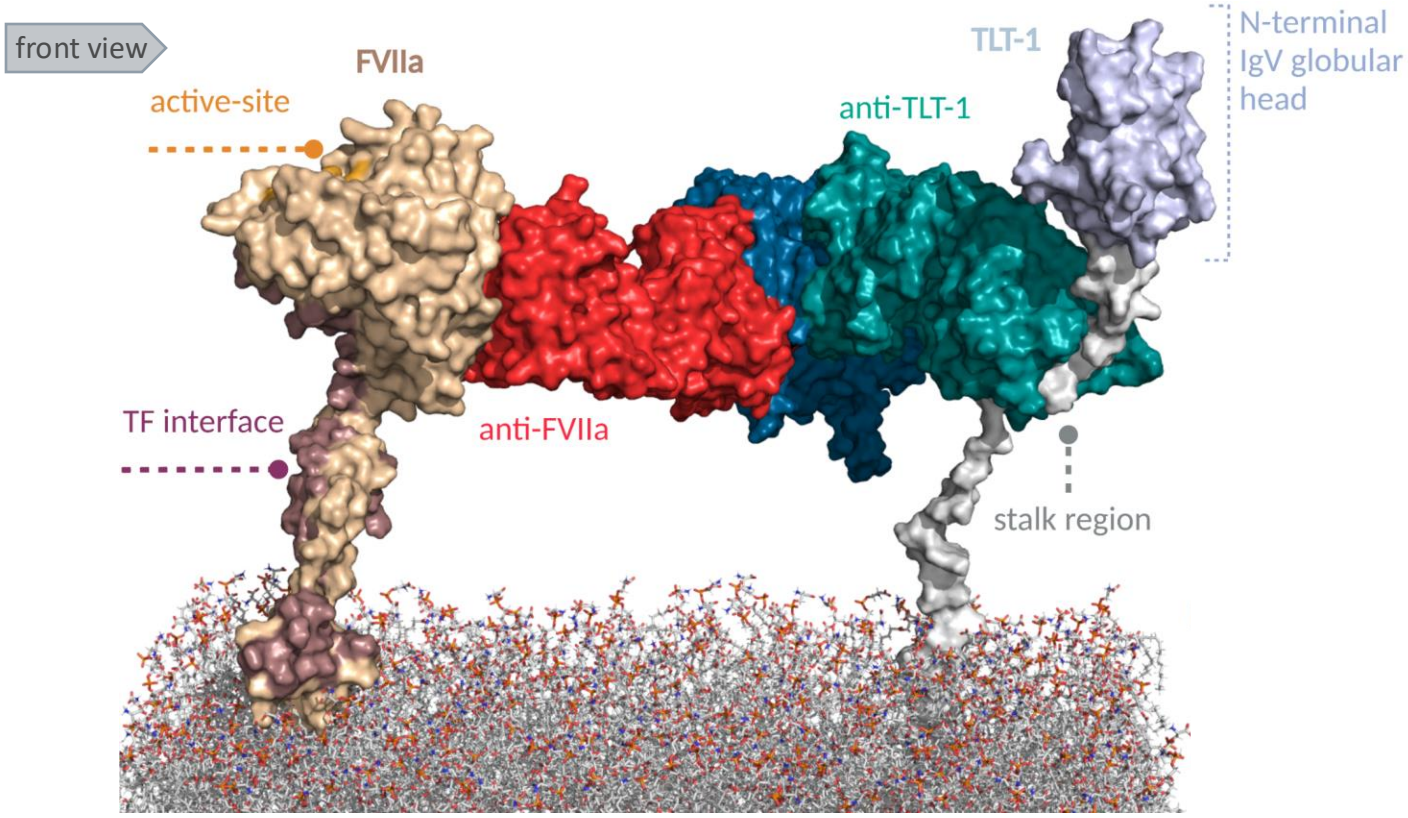
2 Platelet aggregation

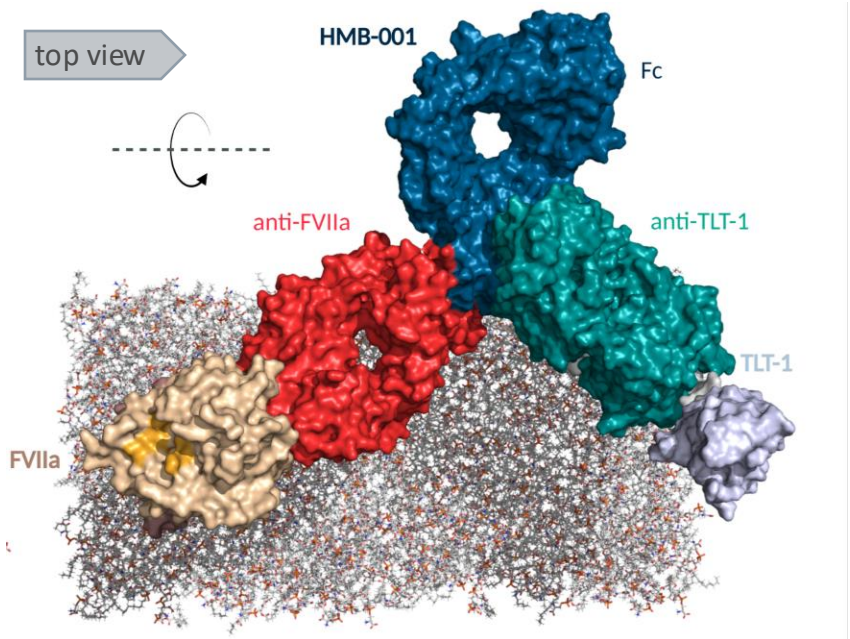
- Aggregation of platelet rich plasma in presence of platelet activator ± 100nM HMB-001
- Max amplitude at 1 hr (mean ± SD, n = 3)



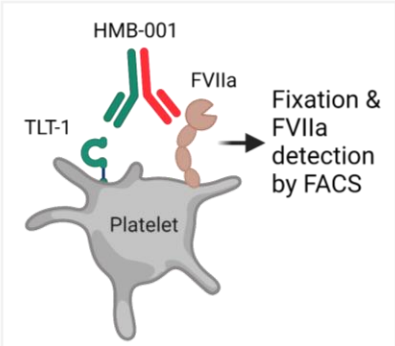
HMB-001 | Productive assembly with FVIIa and TLT-1 as predicted by X-ray crystallography and modelling

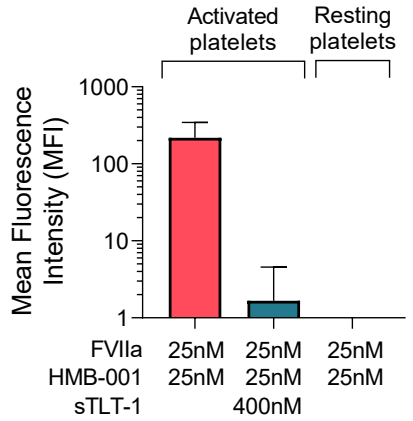
Complex structure	Resolution
HMB-001 anti-FVIIa Fab:FVIIa:sTF	3.5 Å
HMB-001 anti-TLT-1 Fab:TLT-1 stalk peptide	1.5 Å





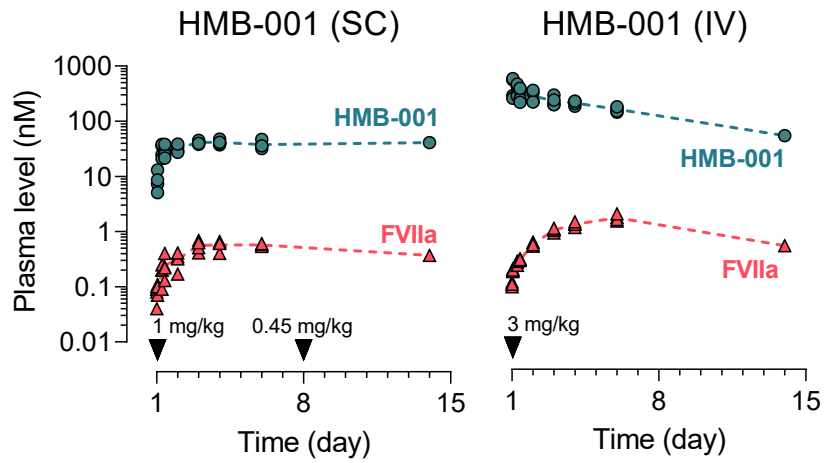
Activated platelet delivery of FVIIa by HMB-001

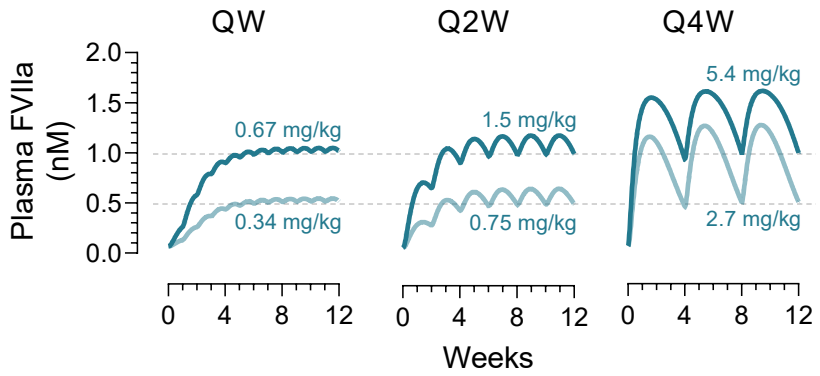




HMB-001 | Accumulation of endogenous FVIIa and ~10-fold potentiation of FVIIa activity via TLT-1 targeting

HMB-001 administration results in the accumulation of endogenous FVIIa





PK in cynomolgus monkey

Study design

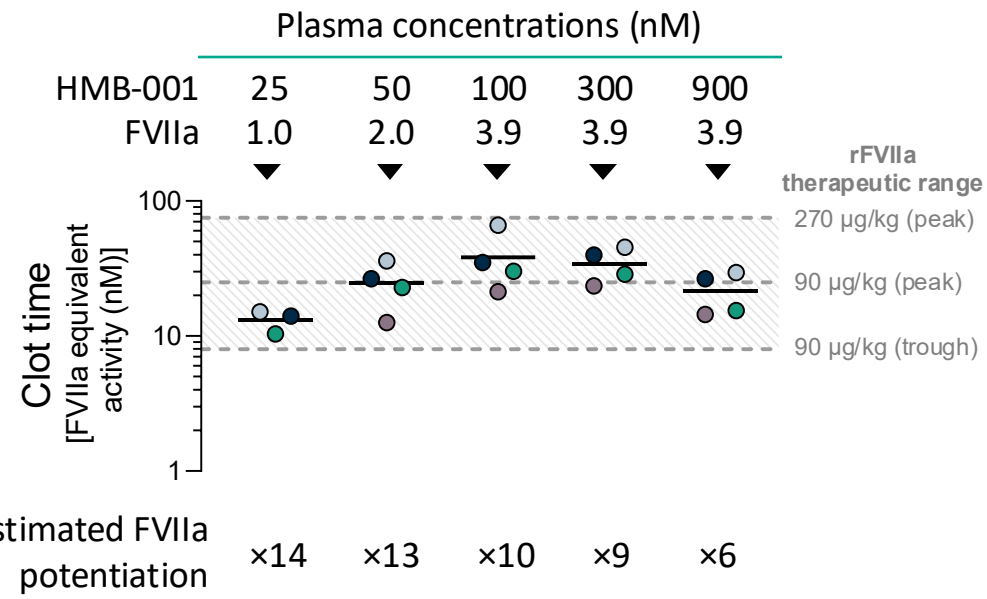
- Study in healthy NHP (cynomolgus monkey)
- SC/IV administration of HMB-001 (n = 4)
- Measurement of HMB-001 (ELISA) and FVIIa (FVIIa:clot assay)

Predicted PK in humans

Study design

- Population PK/PD model describing HMB-001 and FVIIa based on PK in NHP
- Allometric scaling applied to simulate multiple-dose scenarios in the human setting

HMB-001 raises activity of FVIIa to therapeutic levels in Haemophilia A whole blood



Study design

- Clot-formation monitored by thromboelastography (TEG) in HA-like (FVIII inhibited) whole blood from 3-4 healthy donors supplemented with FVIIa, FVII and HMB-001
- Measured clot (R) times were converted to 'FVIIa equivalent activity' by comparison to standard curve with rFVIIa

Glanzmann Thrombasthenia | Definition

Cause

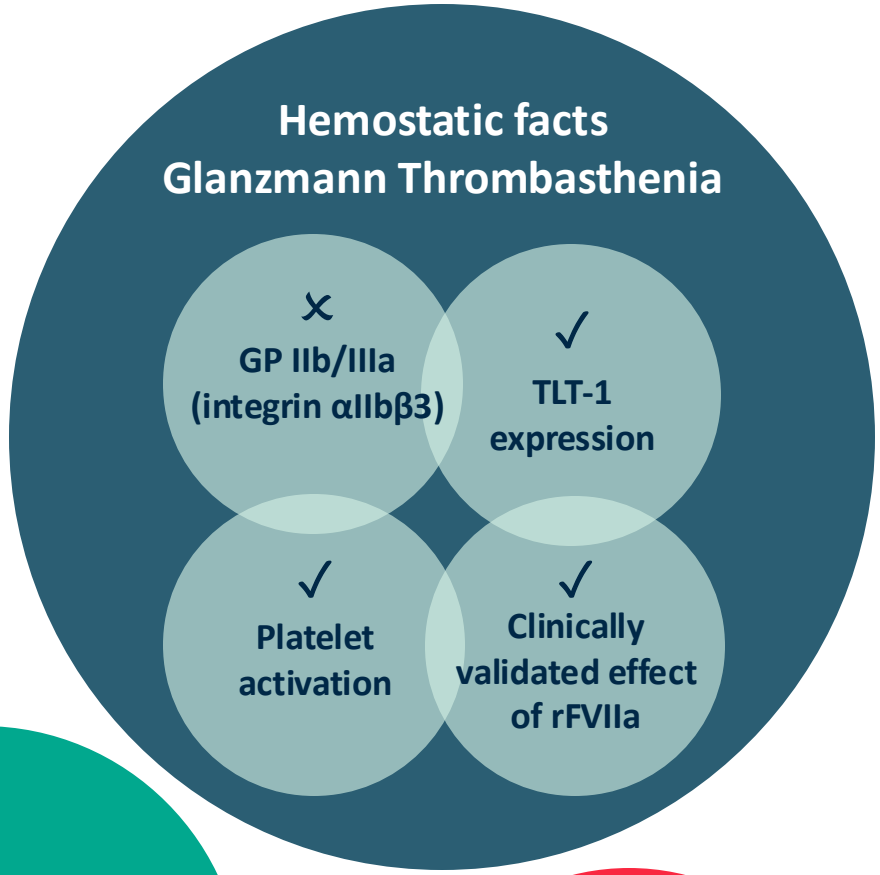
- Deficiency of Glycoprotein IIb/IIIa (integrin αIIbβ3) – the major fibrinogen receptor on platelets
  - → abnormal platelet aggregation
  - → recurring bleeding events

Affected Population

- Autosomal recessive rare bleeding disorder
- All ages and gender

Standard of Care

- Blood product transfusions – platelets and red cells as required
- Recombinant factor VIIa (rFVIIa)
- Antifibrinolytics
- Bone marrow transplantation



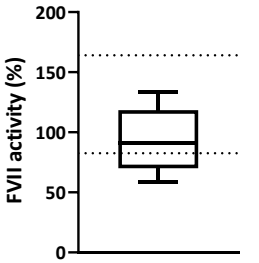
No prophylactic treatment available to prevent spontaneous bleed events

Median Prevalence
1:400,000
Approximately
18,500
patients worldwide

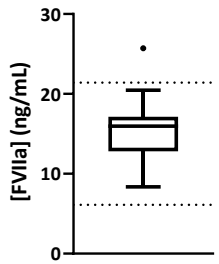
HMB-001 | 10-fold potentiation of FVIIa activity in *ex vivo* platelet aggregation model of Glanzmann Thrombasthenia (GT)

Retained FVII activity, FVIIa levels and TLT-1 in GT

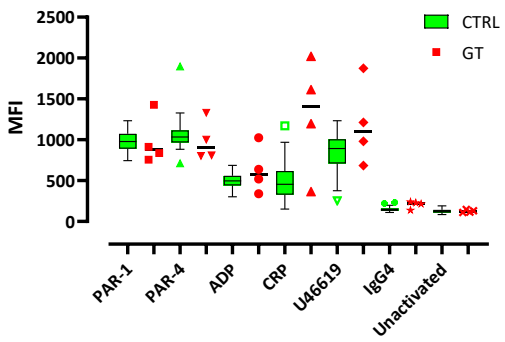
Total FVII activity



FVIIa levels

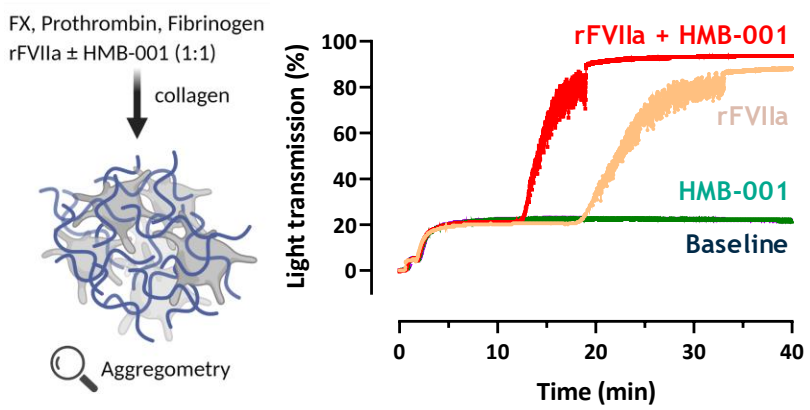


TLT-1 expression

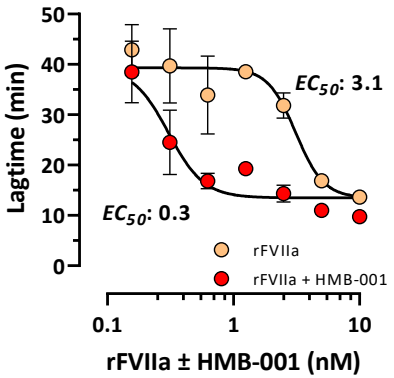


HMB-001 potentiates FVIIa activity in platelet aggregation assay in GT platelets and potentiation is TLT-1 dependent

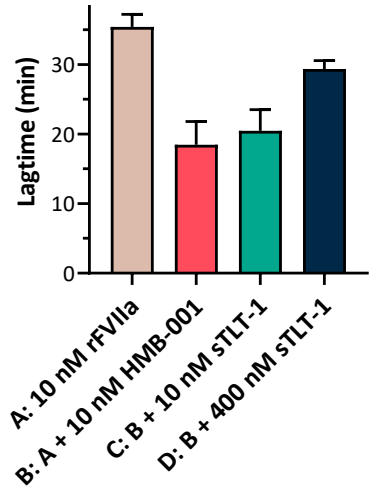
Aggregation of GT platelets



Concentration-response



HMB-001 potentiation is TLT-1 dependent



Study design

- Plasma FVII activity and plasma FVIIa levels in GT blood samples (n = 13)
- TLT-1 expression upon platelet activation using FACS (n = 4)

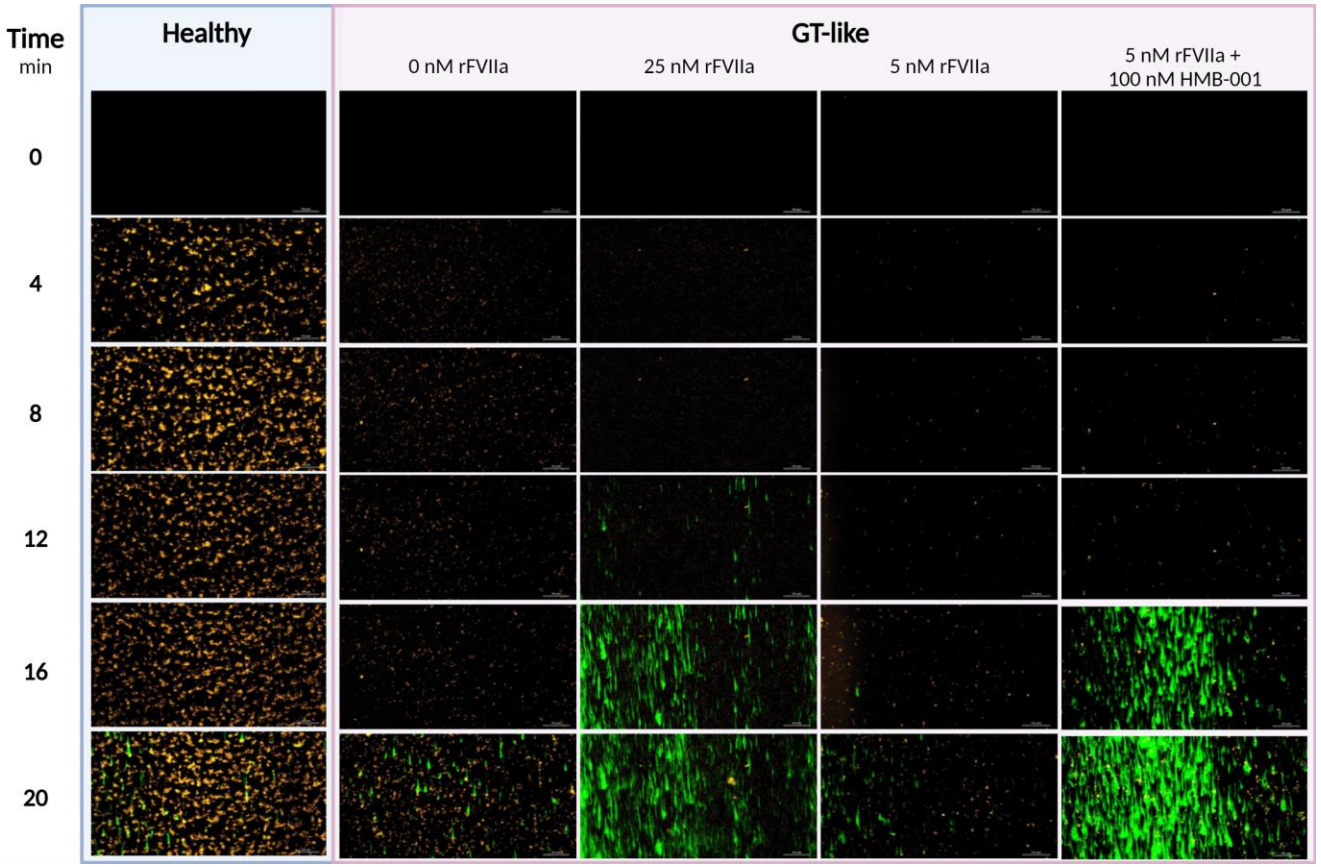
Study design

- GT platelets for platelet aggregation assay. GT-like platelets for dose-response and TLT-1 effect assay. GT-like: GPIIb/IIIa-inhibited (RGDW) normal human platelets
- Platelet activation by collagen in presence of FX, Prothrombin, Fibrinogen and rFVIIa ± HMB-001 (equimolar concentration)
- Aggregation monitored by light transmission aggregometry. Reported as lag-time = time to half maximum aggregation (mean ± SD, n = 3)

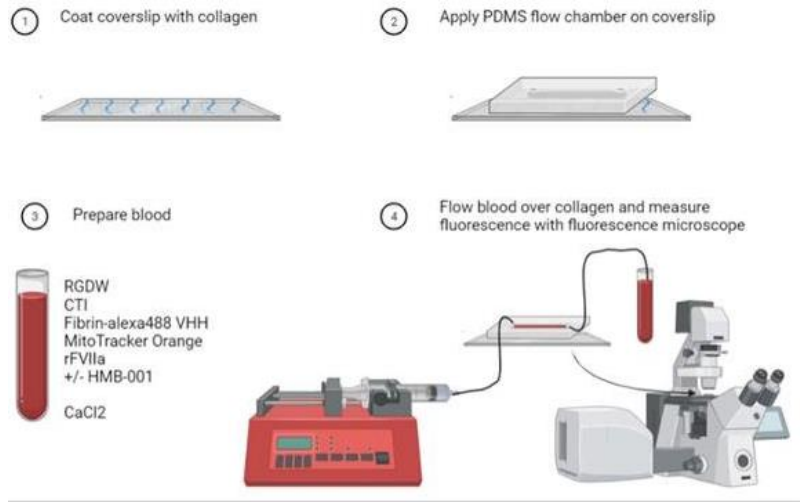
Ref: Lisman et. al., *Blood*, 2004

HMB-001 | Potentiation of FVIIa-mediated fibrin formation in *ex vivo* flow model of Glanzmann Thrombasthenia (GT)

HMB-001 potentiates FVIIa-mediated fibrin formation in flow model using human whole blood and GT-like platelets



Flow model assay setup



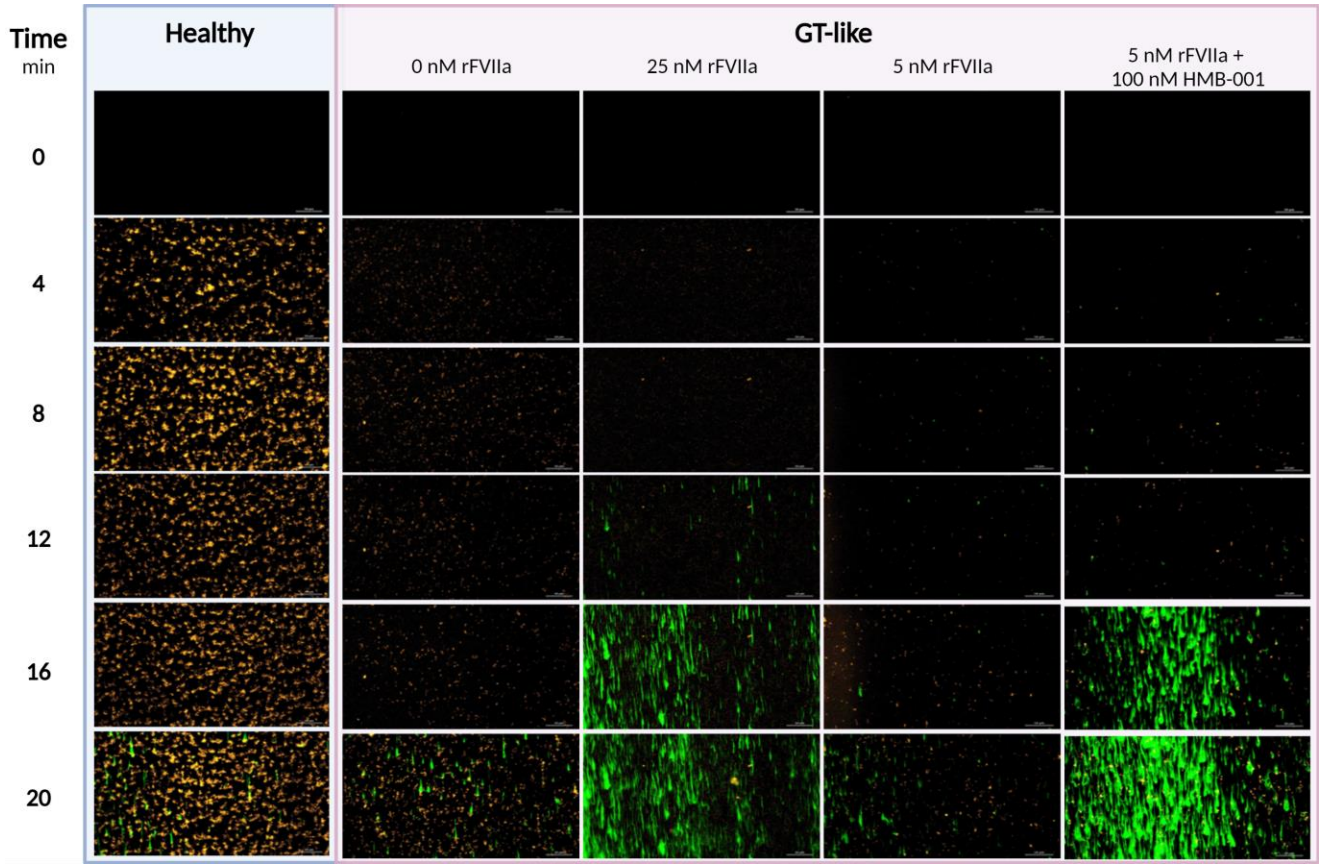
***Ex vivo flow model* study design**

- Coverslips coated with bovine type I collagen. Polydimethylsiloxane (PDMS) parallel plate microfluidic device washed and blocked with 1% BSA. Coverslips attached to the PDMS device and mounted in a confocal microscope.
- Platelets labelled with MitoTracker™ Orange. Human citrated whole blood, supplemented with AF488-conjugated anti-fibrin, CTI ± 0 – 25 nM rFVIIa or 0 – 100 nM HMB-001 and recalcified. For GT-like, αIIbβ3 blocked with 500 µM D-RGDW and blood pulled through the flow chamber with a syringe pump at a shear rate of 300 s^{-1}.
- Snap shots taken at 20x magnification with an interval of 20 seconds to monitor platelet adhesion and fibrin formation in real time for 20 minutes.

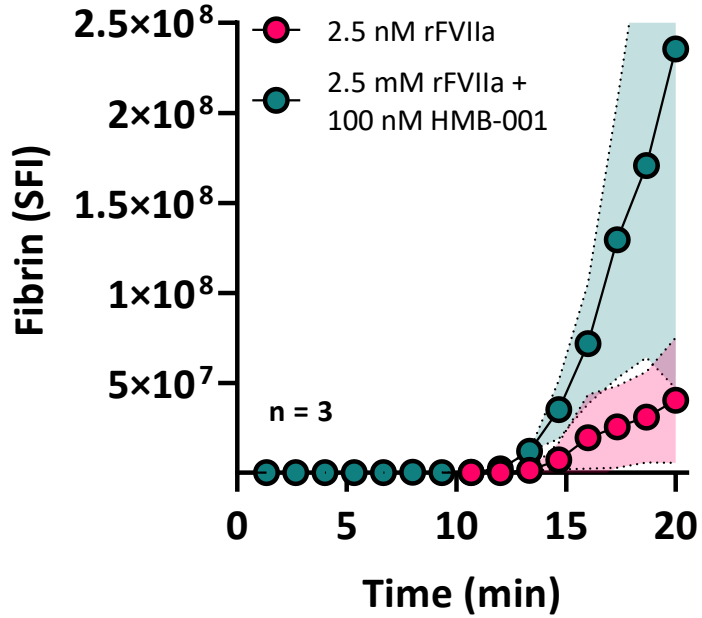
Ref: Neeves KB et. al., *JTH* 2008

HMB-001 | Potentiation of FVIIa-mediated fibrin formation in *ex vivo* flow model of Glanzmann Thrombasthenia (GT)

HMB-001 potentiates FVIIa-mediated fibrin formation in flow model using human whole blood and GT-like platelets



Potentiation confirmed using whole blood from GT patients



Conclusions

HMB-001 - A novel bispecific antibody that binds endogenous FVIIa and TLT-1 on activated platelets

- Accumulates FVIIa in circulation
- Targets FVIIa to the activated platelet → enhance FX activation and thrombin generation and restore clot formation

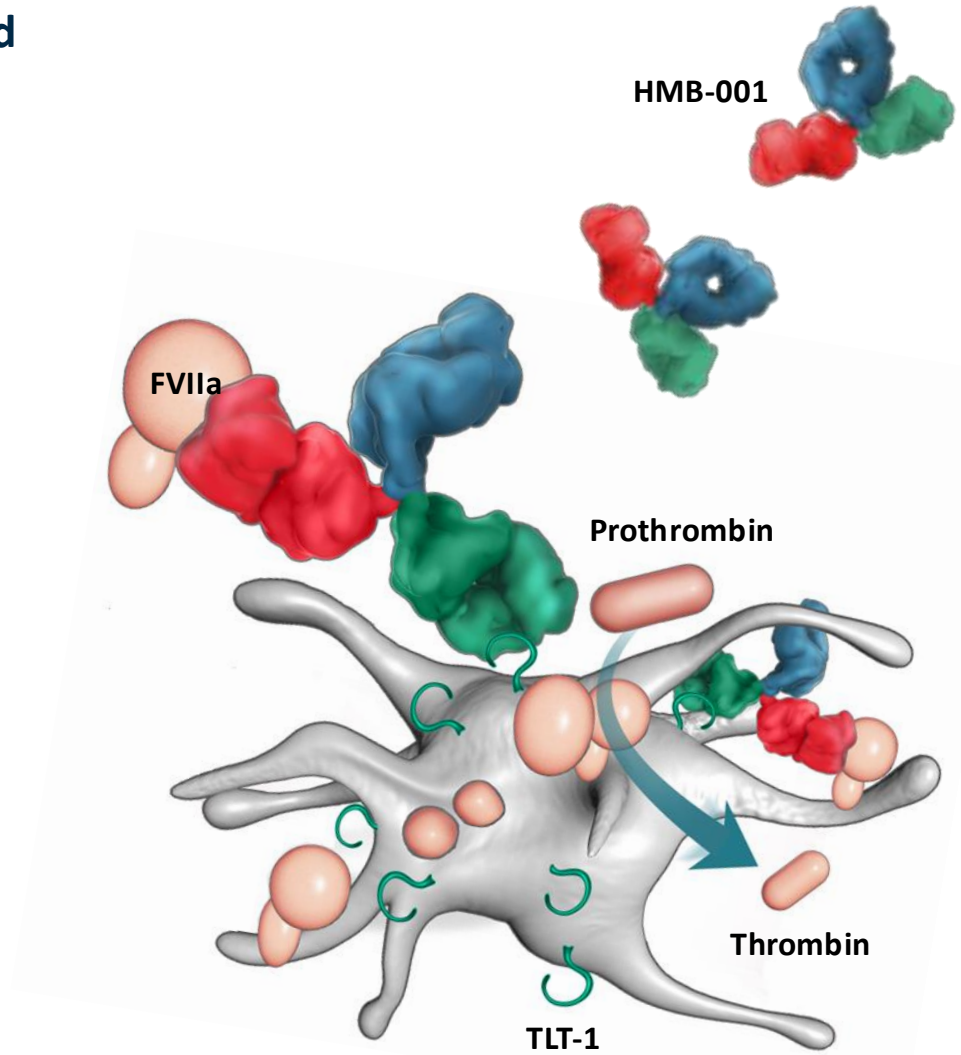
***In vivo* and *ex vivo* experimental models demonstrate**

- A dose-dependent accumulation of endogenous FVIIa up to 40-fold above baseline
- An about 10-fold potentiation of FVIIa activity

  → *together bringing the activity into the therapeutic range based on experience with rFVIIa*

HMB-001 is in CTA/IND enabling development

- On-going phase 1/2 in GT patients in London, UK
- On-going Natural History Studies in GT
- Contact Dr. Catherine Rea, Email: catherine@hemab.com

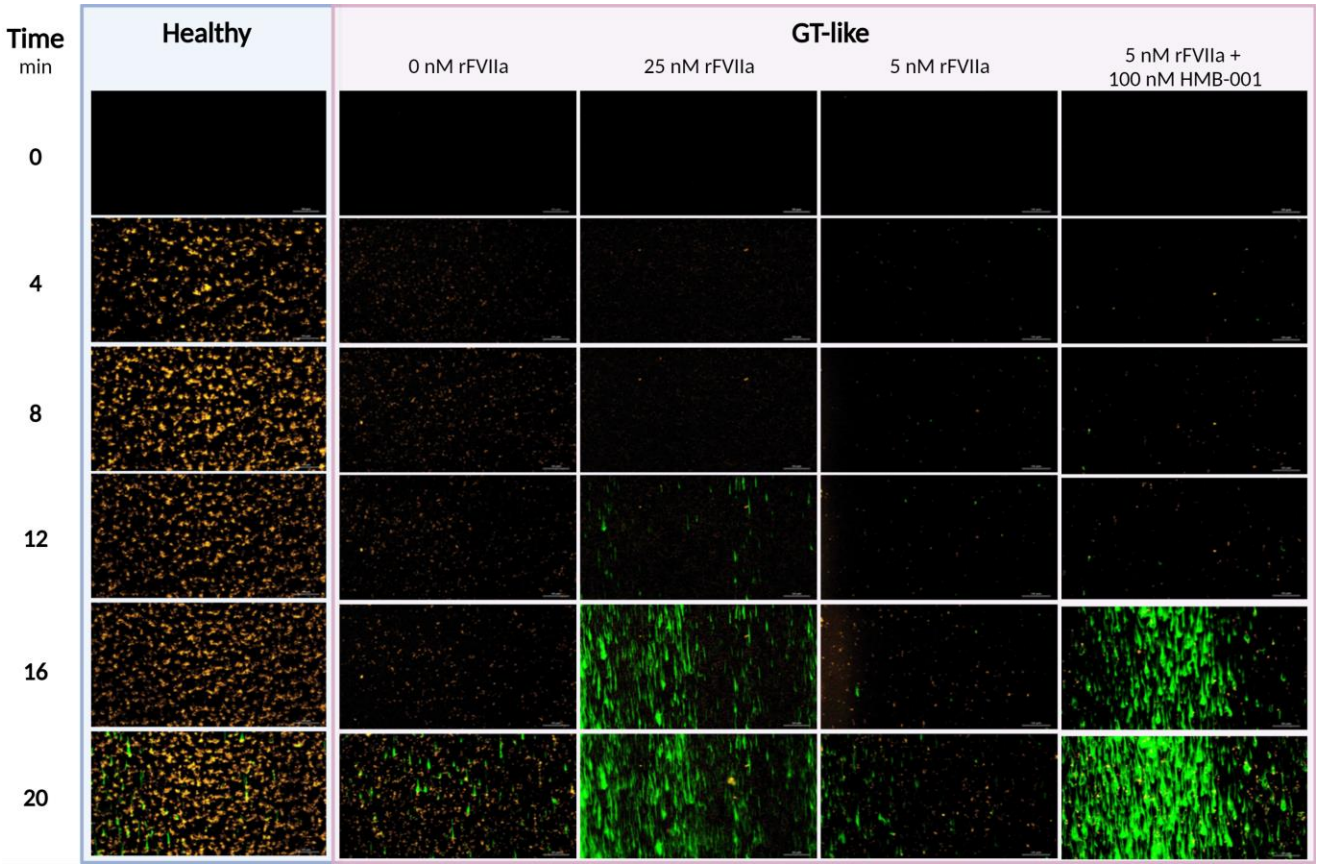


Disclosures for Prafull S. Gandhi

Research Support/P.I.	**No relevant conflicts of interest to declare**
Employee	**Hemab Therapeutics**
Consultant	**No relevant conflicts of interest to declare**
Major Stockholder	**Hemab Therapeutics**
Speakers Bureau	**No relevant conflicts of interest to declare**
Honoraria	**No relevant conflicts of interest to declare**
Scientific Advisory Board	**No relevant conflicts of interest to declare**

HMB-001 | Potentiation of FVIIa-mediated fibrin formation in *ex vivo* flow model of Glanzmann Thrombasthenia (GT)

HMB-001 potentiates FVIIa-mediated fibrin formation in flow model using GT-like platelets



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