HMB-001 – a novel bispecific antibody accumulating and targeting endogenous FVIIa to activated platelets supports enhanced haemostatic responses in models of Glanzmann's thrombasthenia

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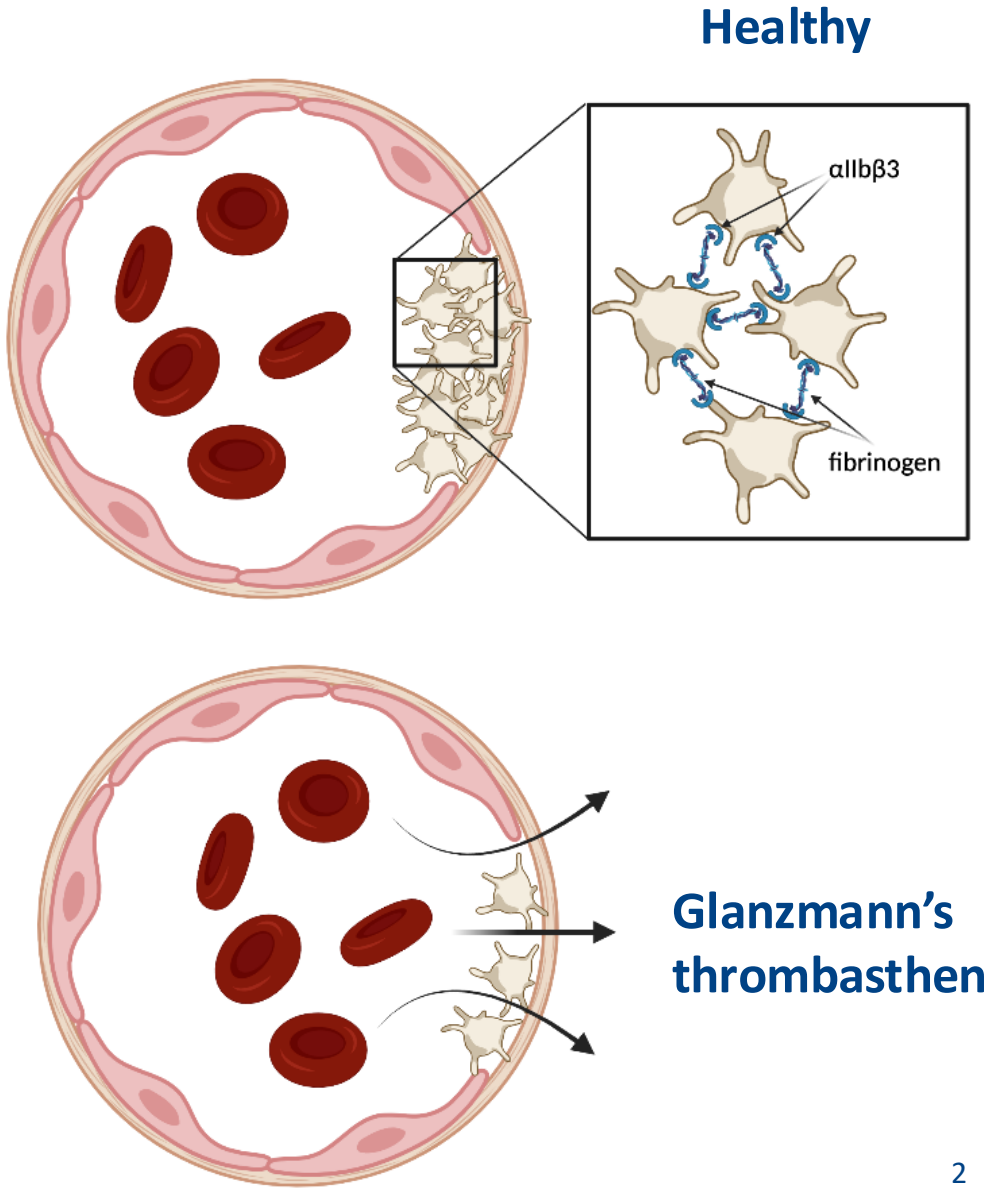
Glanzmann’s thrombasthenia (GT)

Rare autosomal recessive bleeding disorder

- Prevalence 1:450,000
- Mutations in ITGA2B or ITGB3
- Deficiency or loss of function of the platelet fibrinogen receptor αIIbβ3

- Limited prophylactic treatment options



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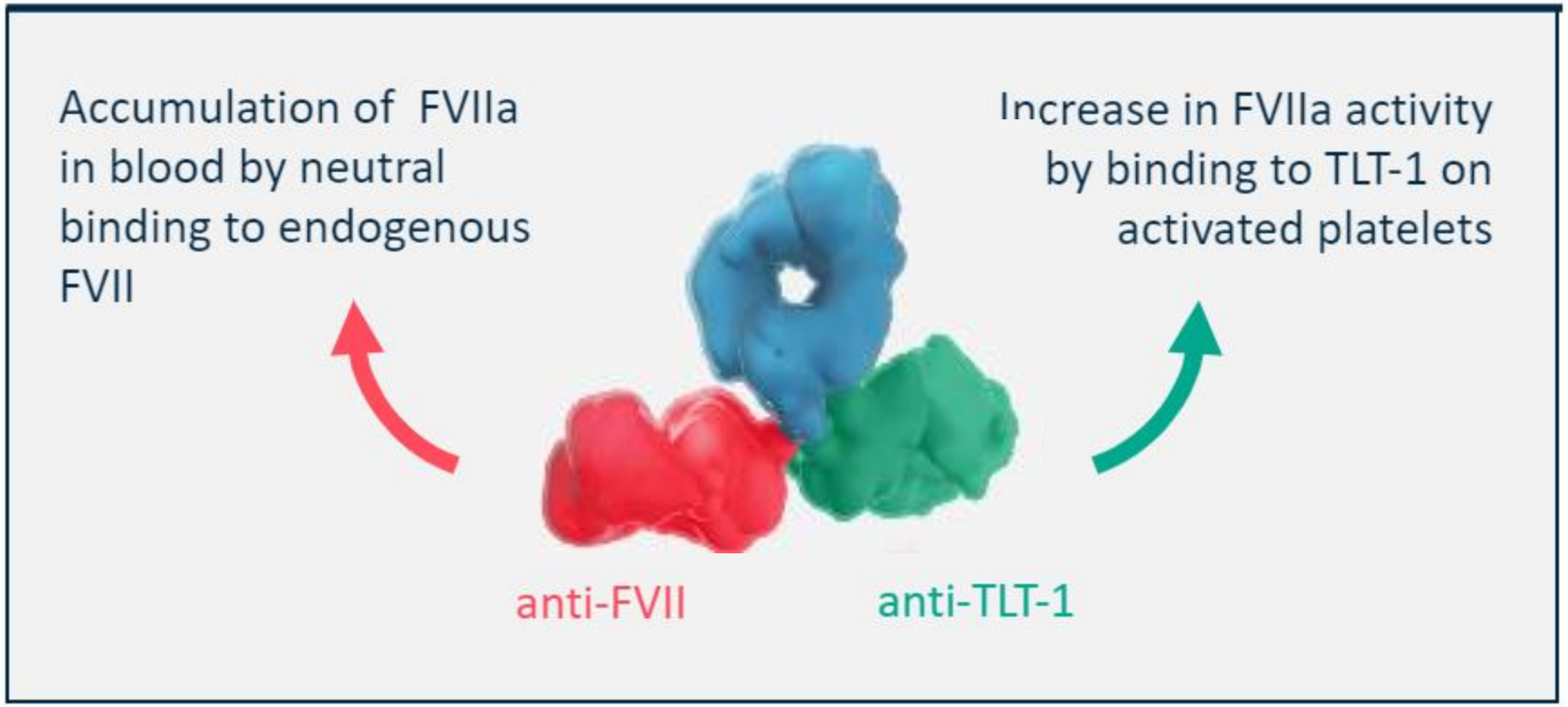
HMB-001 – A novel therapy for prophylaxis treatment of Glanzmann's thrombasthenia

Bispecific therapeutic antibody



Engineered at NovoNordisk®, leveraging Genmab Duobody® platform

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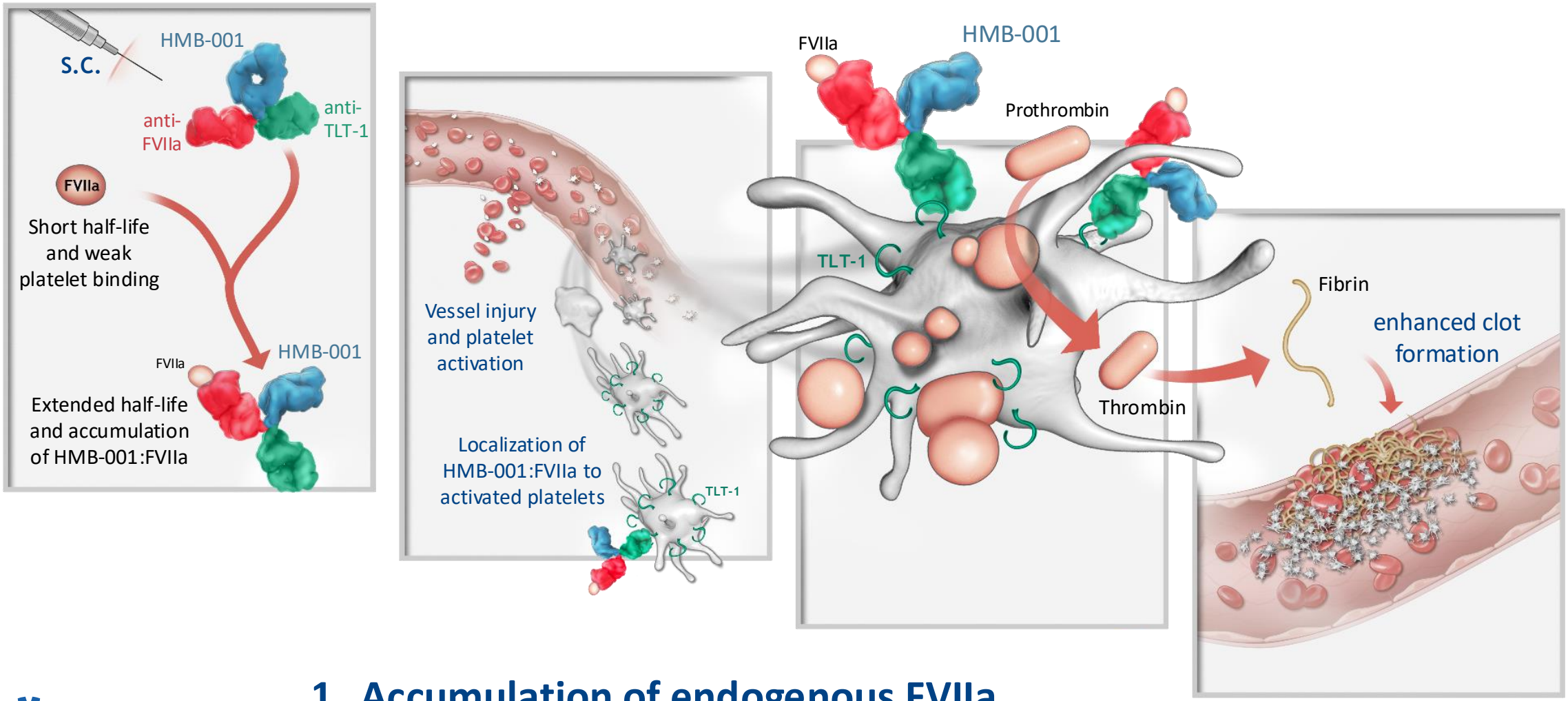
HMB-001 – Targeting FVIIa to platelets



1. **Accumulation of endogenous FVIIa**
2. **Targeting of FVIIa to the platelet surface**

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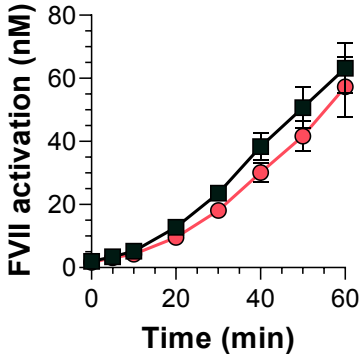
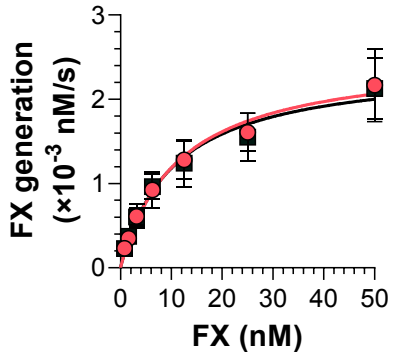
HMB-001 does not interfere with physiological functions of FVIIa

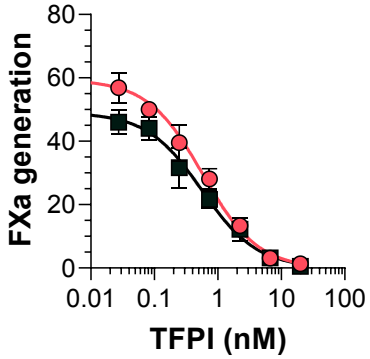
FVIIa auto-activation



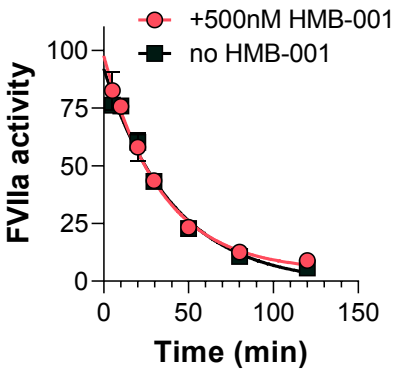
FX activation

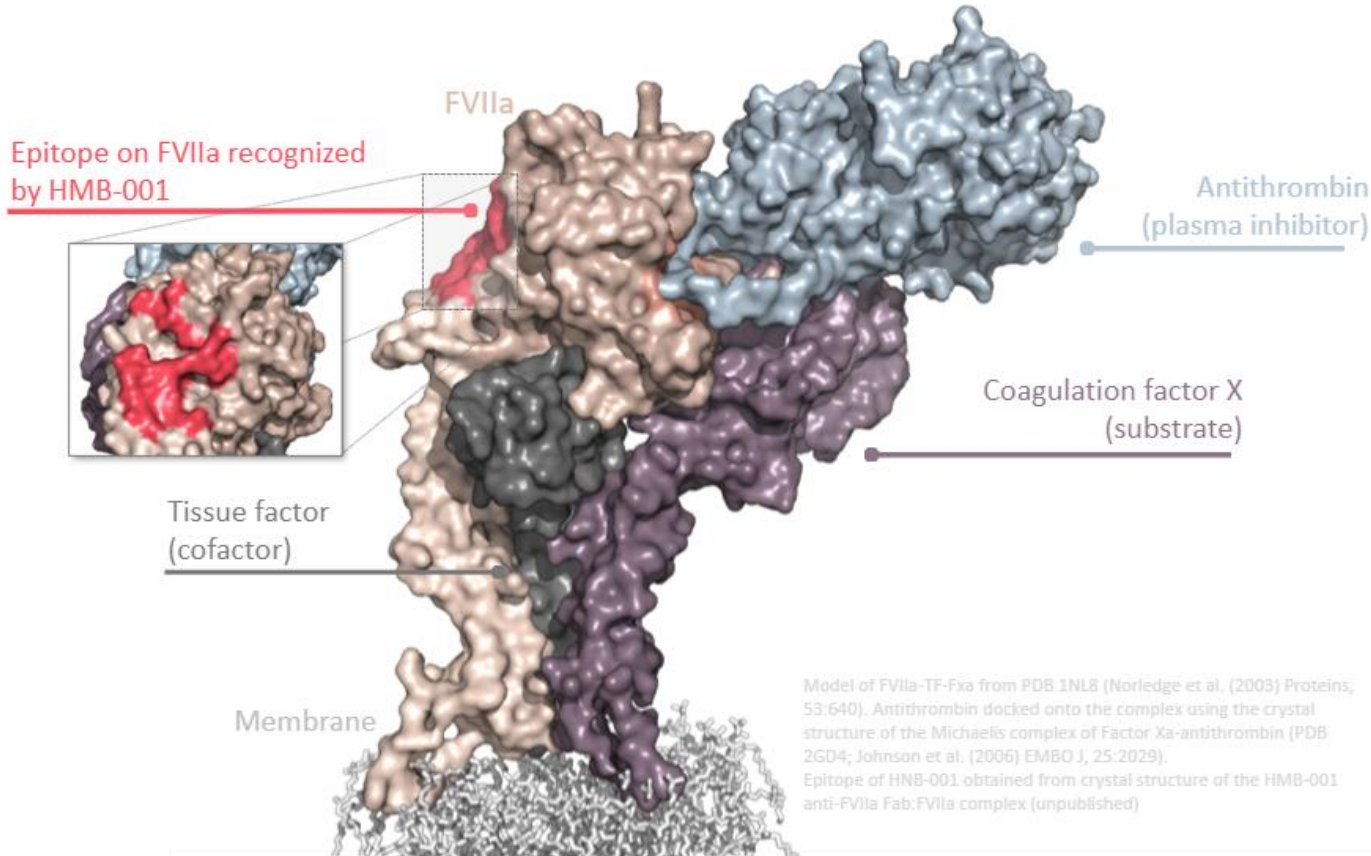


TFPI inhibition FXa



ATIII inhibition





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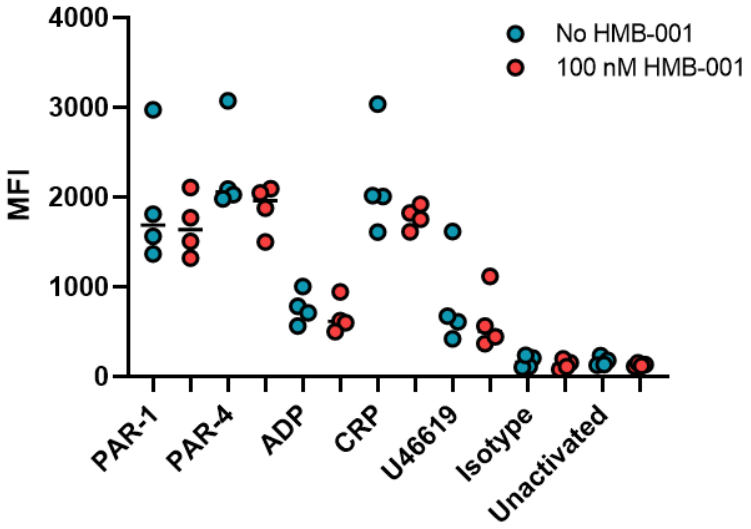
HMB-001 does not interfere with platelet function

P-selectin expression



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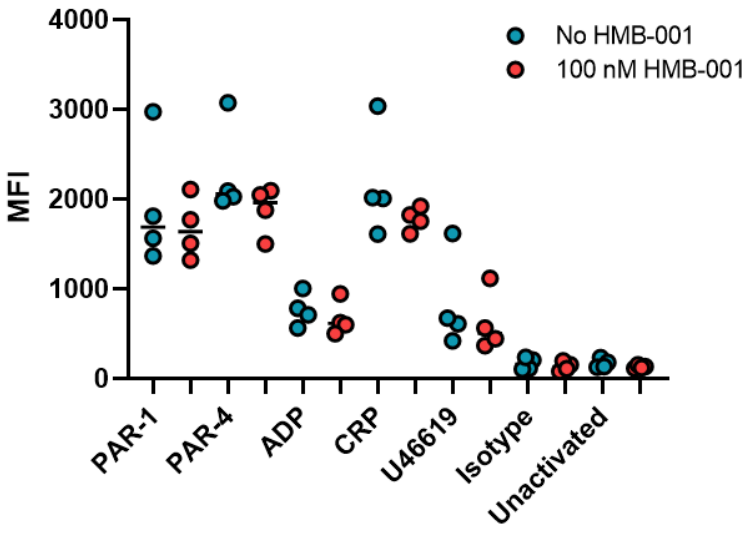
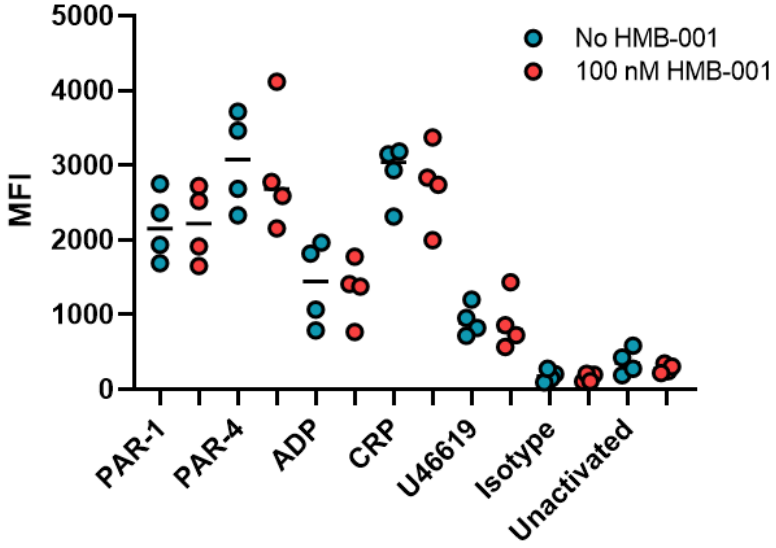
HMB-001 does not interfere with platelet function

P-selectin expression



Fibrinogen binding



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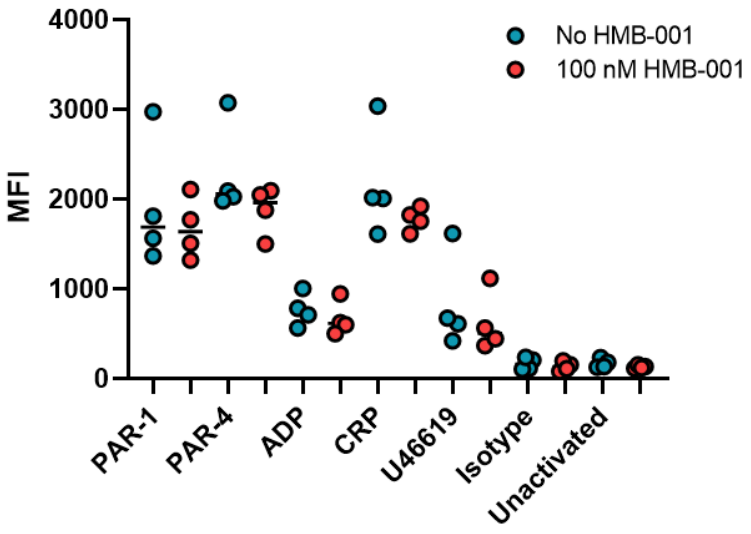
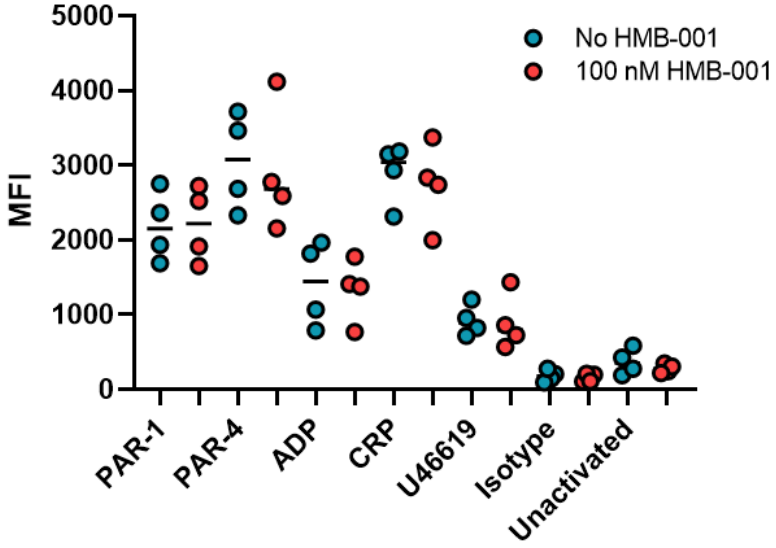
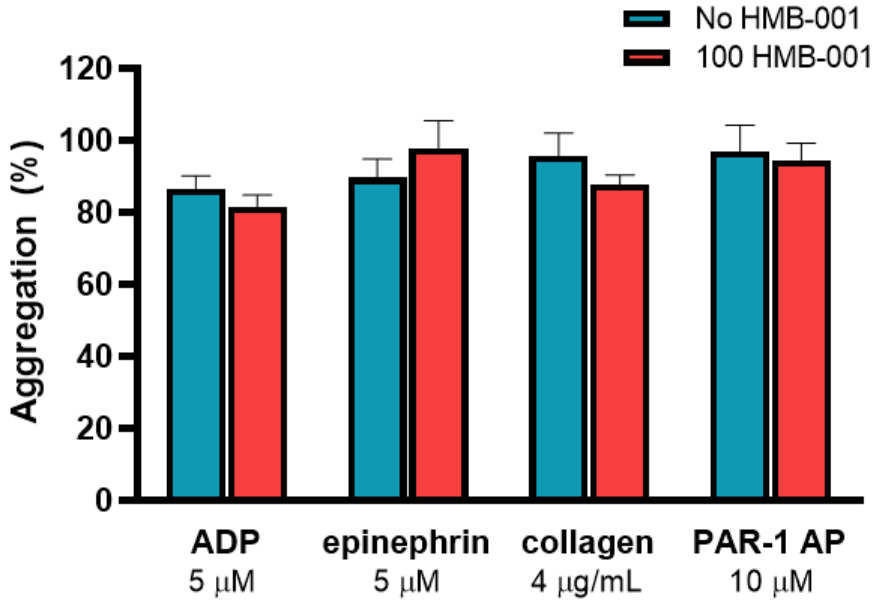
P-selectin expression



Fibrinogen binding



Aggregation



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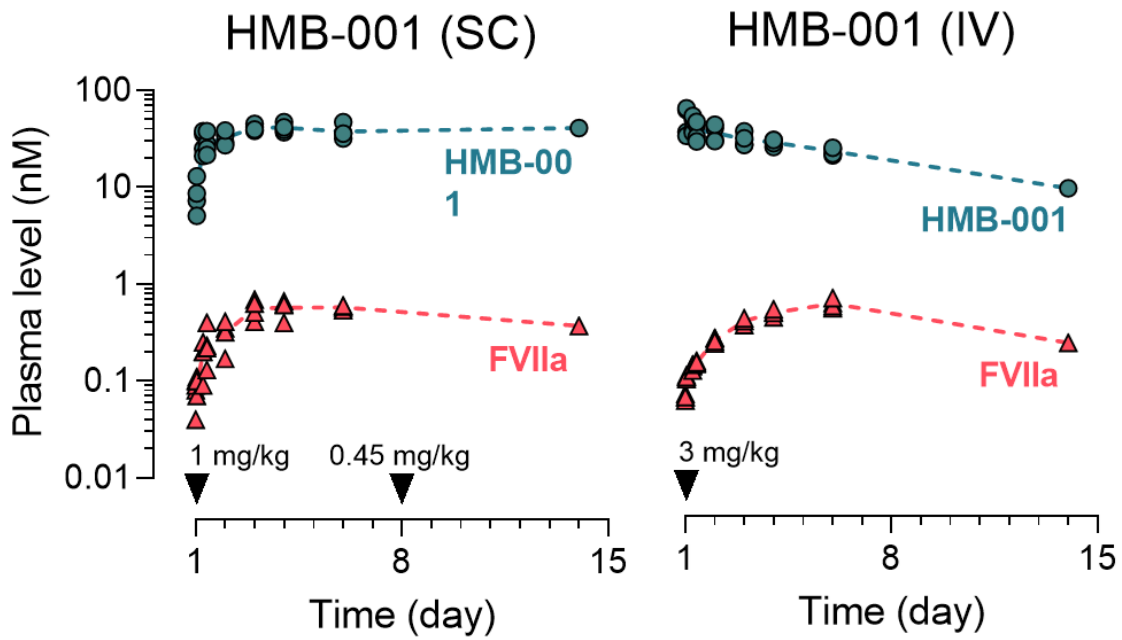
Accumulation of endogenous FVIIa in cynomolgus monkeys

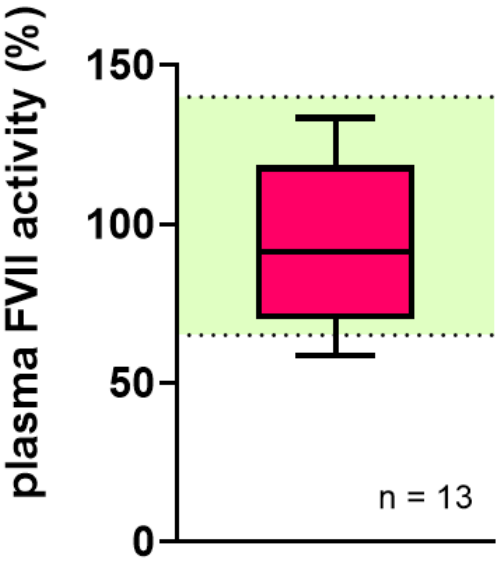


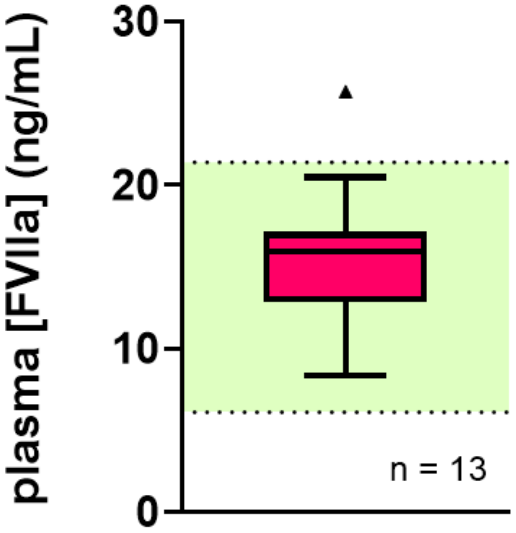
n = 4

Are FVII(a) levels and TLT-1 expression normal in GT patients?

FVII(a) levels and TLT-1 expression are normal in GT patients

FVII(a) levels





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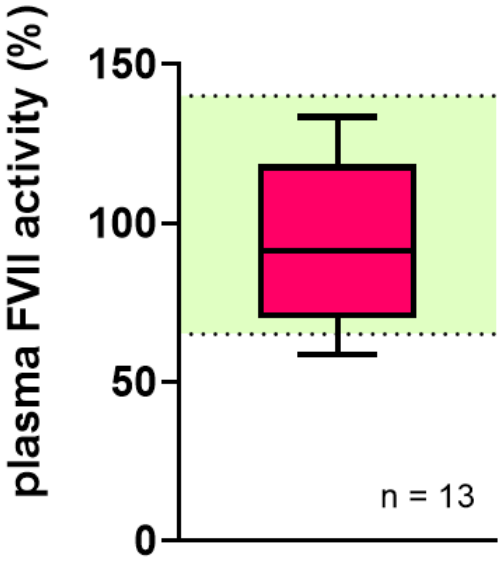
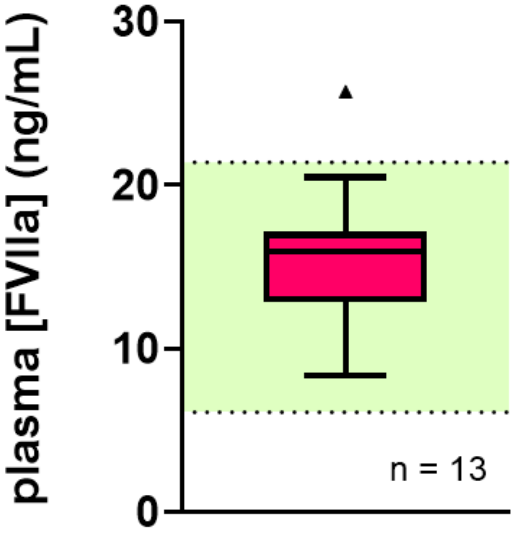
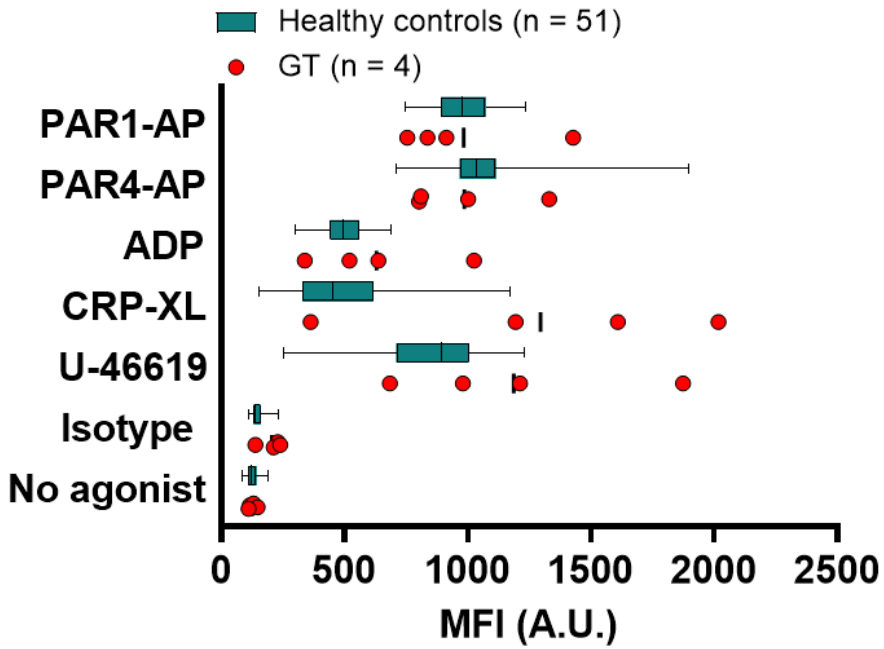
FVII(a) levels and TLT-1 expression are normal in GT patients

FVII(a) levels





TLT-1 expression



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Can we measure the effect of HMB-001 *ex vivo*?

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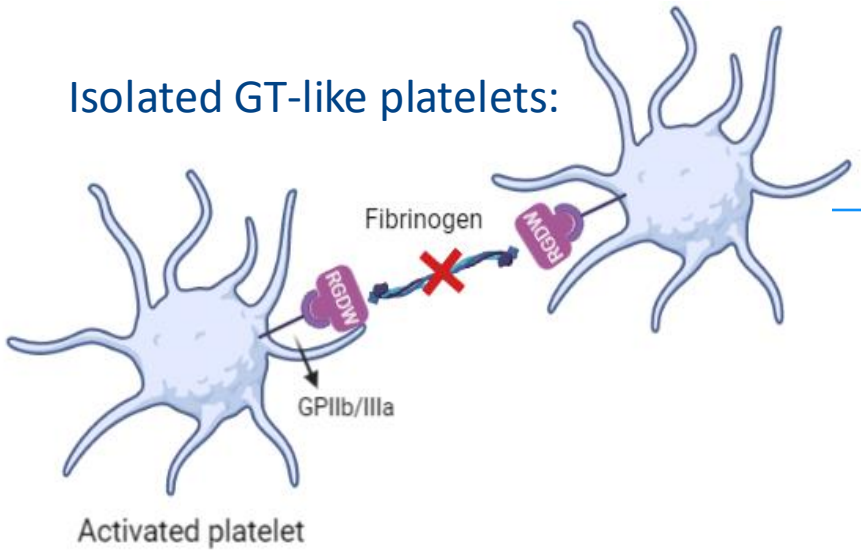
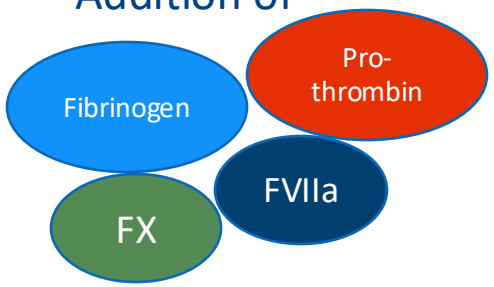
Fibrin-dependent aggregation in GT-like platelets

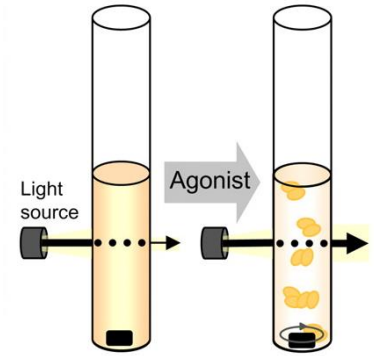
Isolated GT-like platelets:

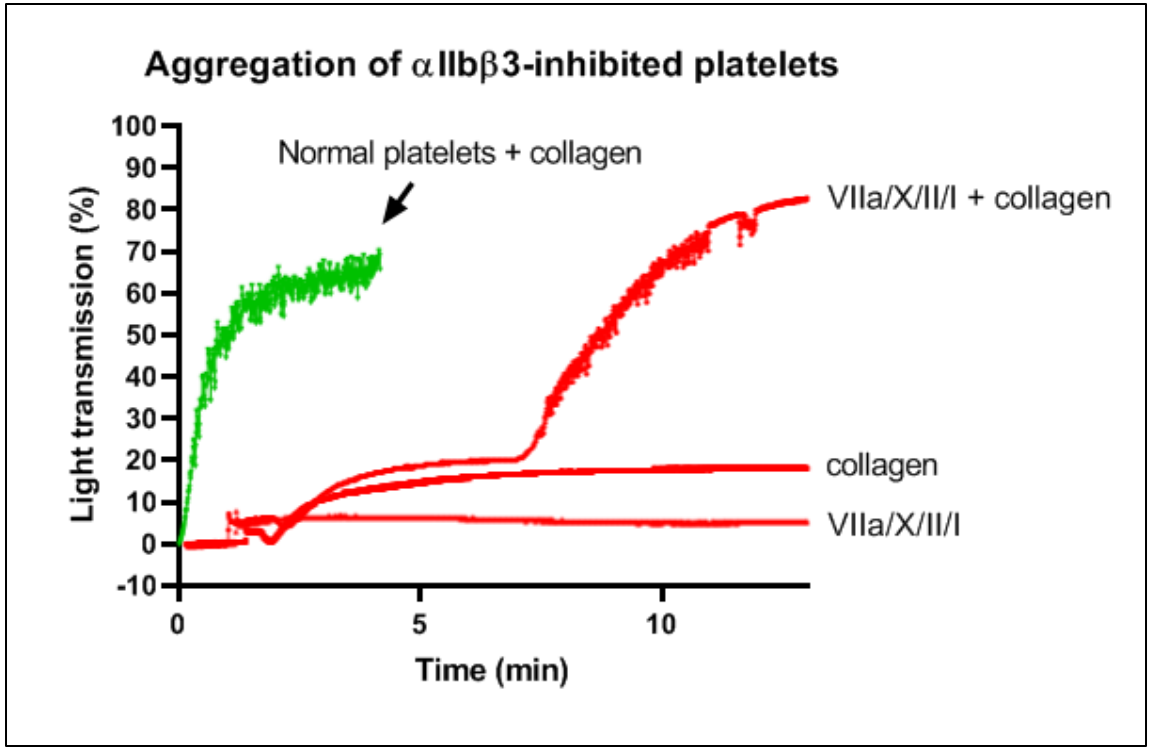


Addition of



Fibrin-dependent aggregation





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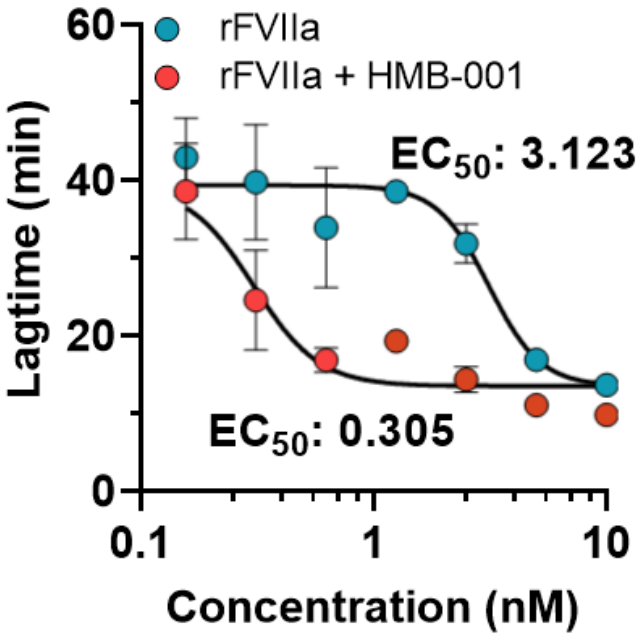
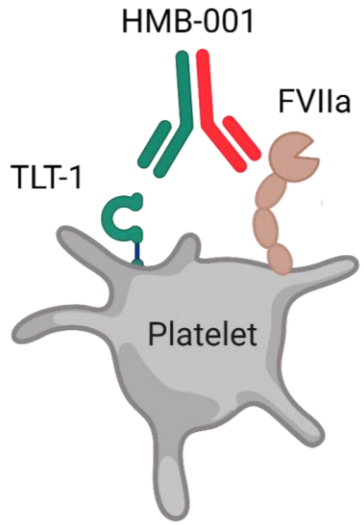
HMB-001 enhances rFVIIa efficacy 10-fold

GT-like platelets





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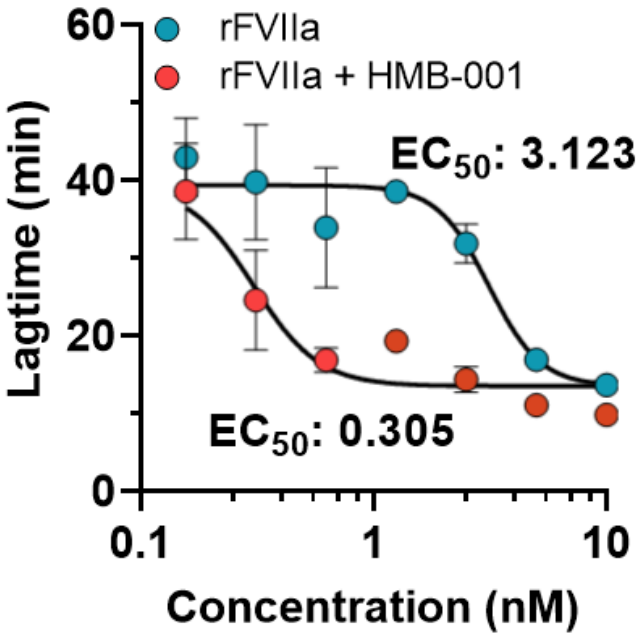
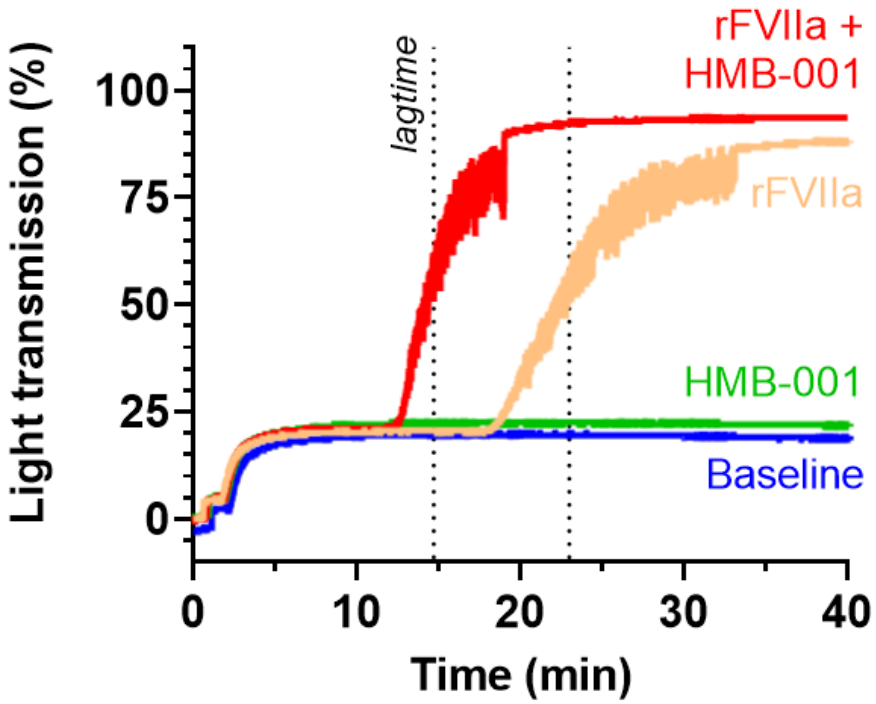
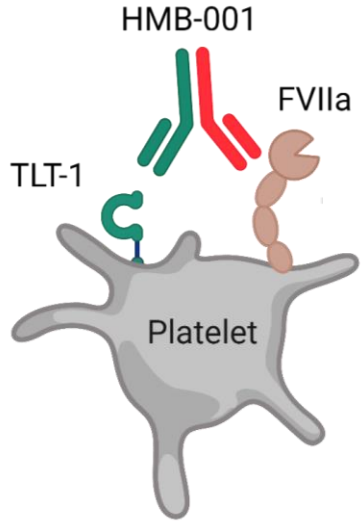


GT platelets





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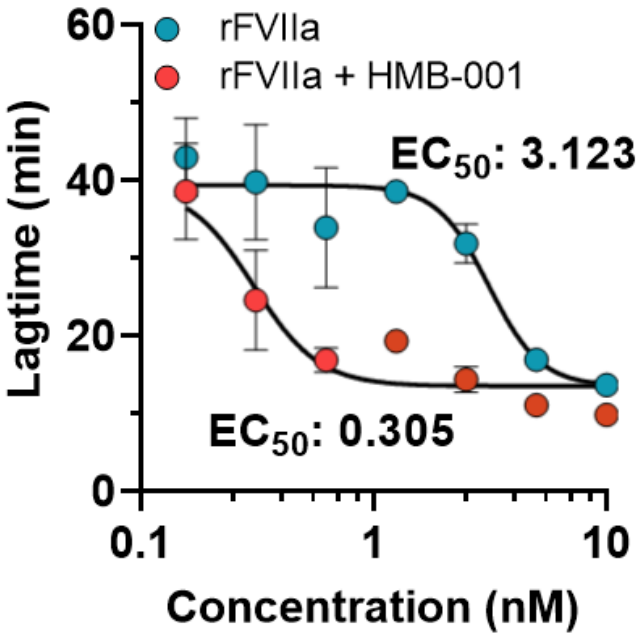
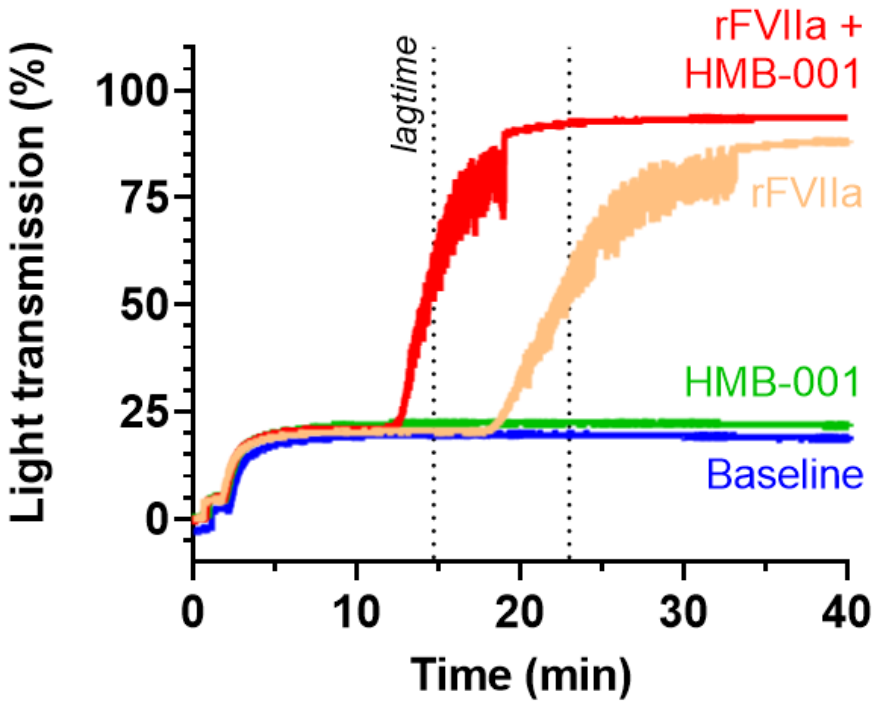
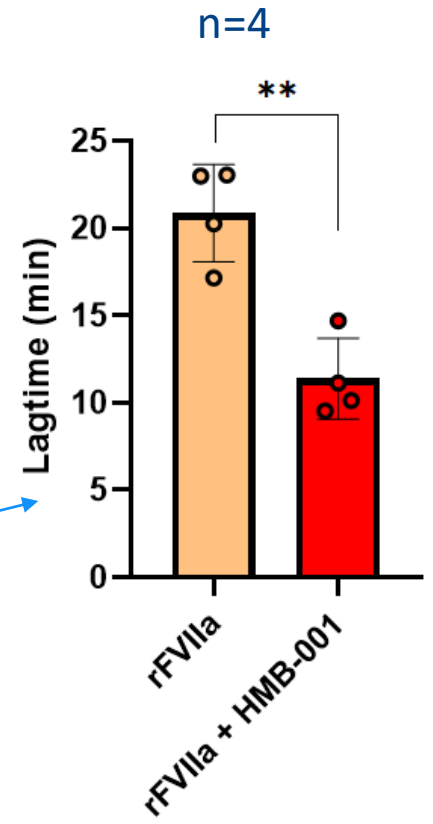
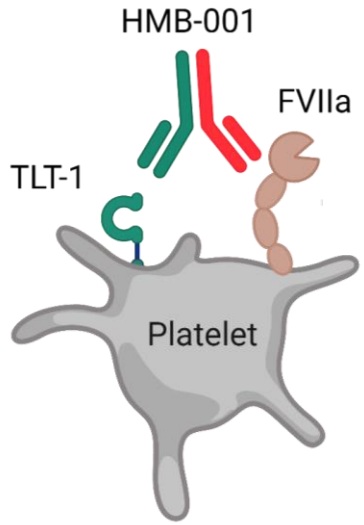
GT-like platelets



GT platelets







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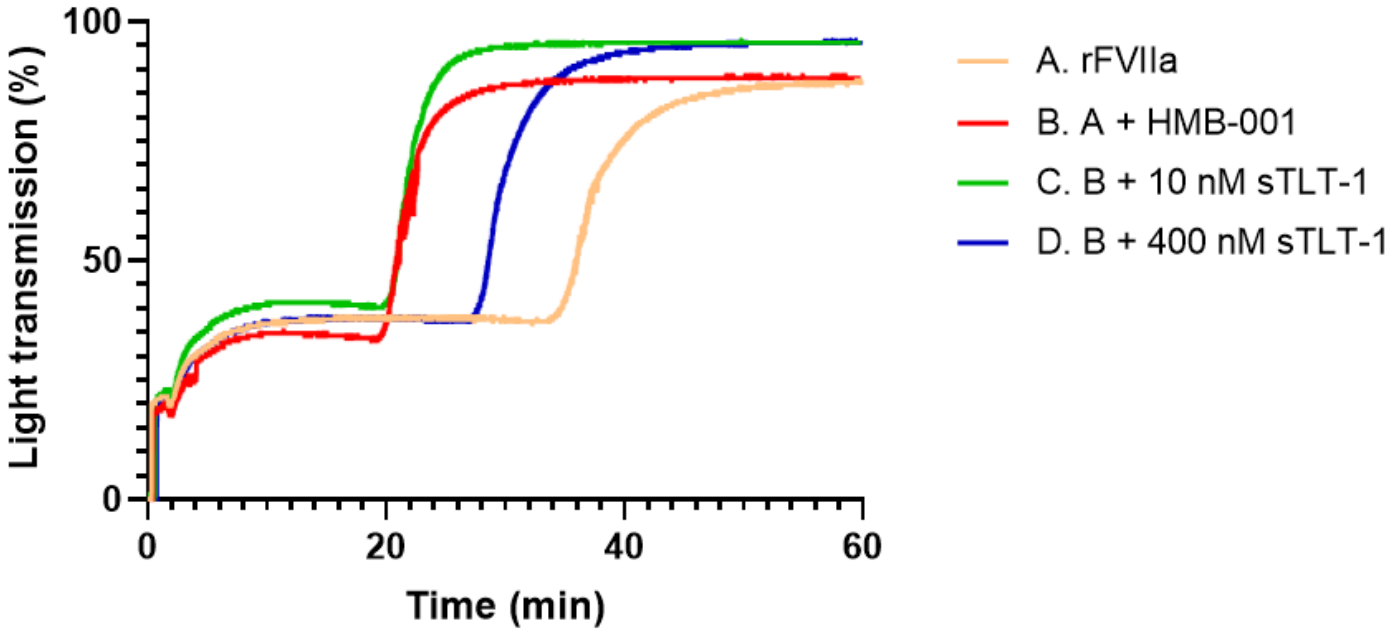
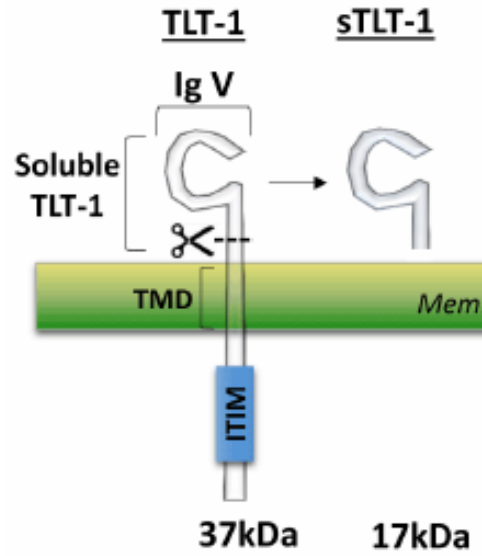
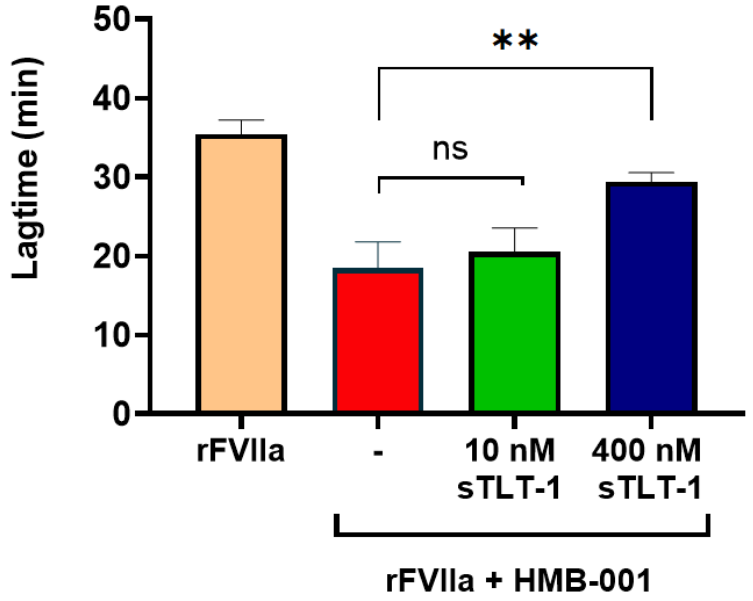
Effect of soluble TLT-1 (sTLT-1) on HMB-001





Plasma levels ~100 pM



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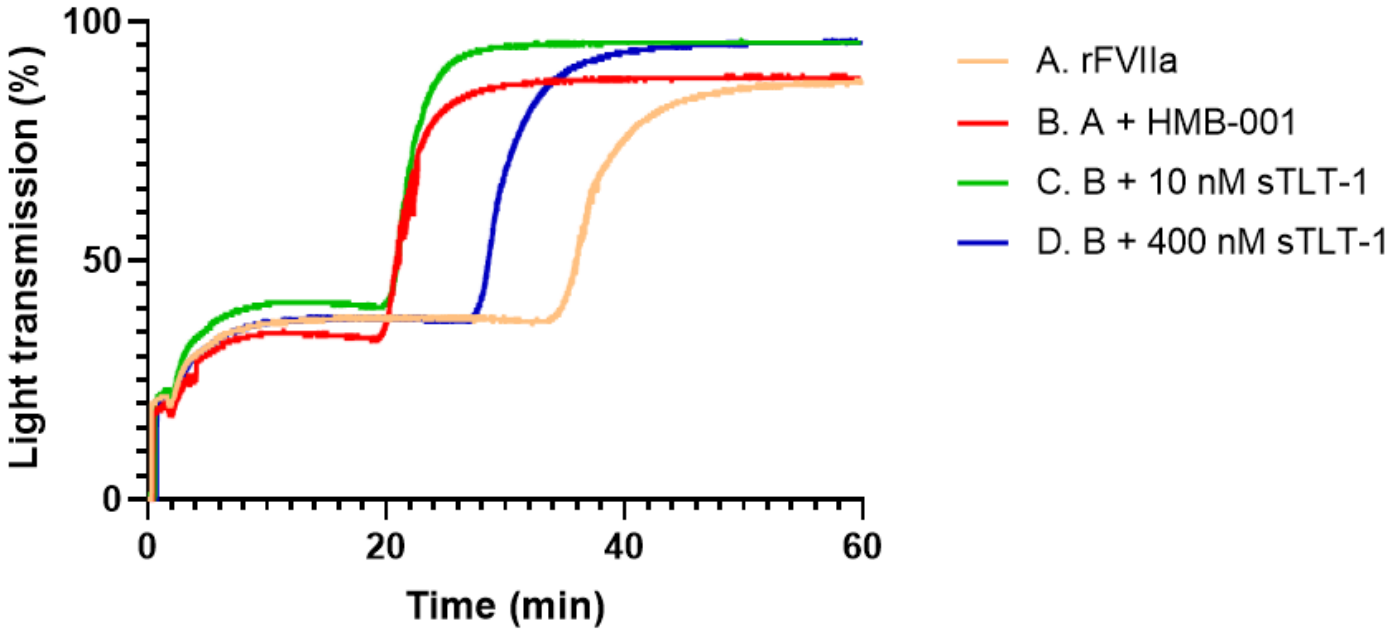
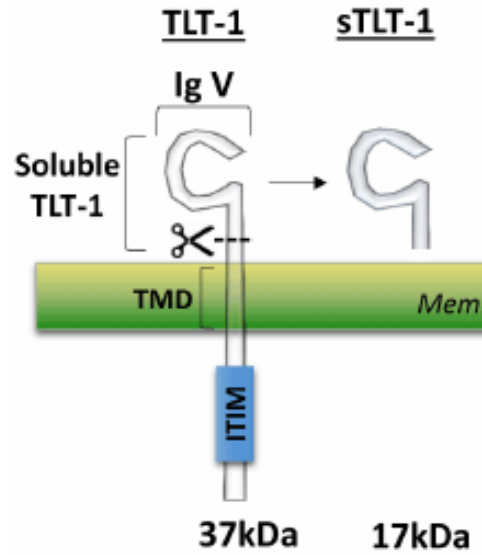
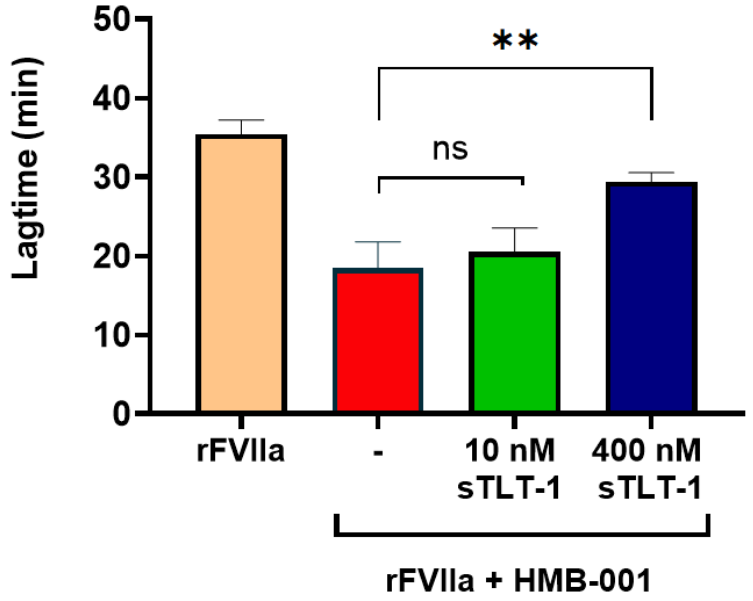
Effect of soluble TLT-1 (sTLT-1) on HMB-001





Plasma levels ~100 pM



1. **Plasma sTLT does not inhibit HMB-001 (<10 nM)**

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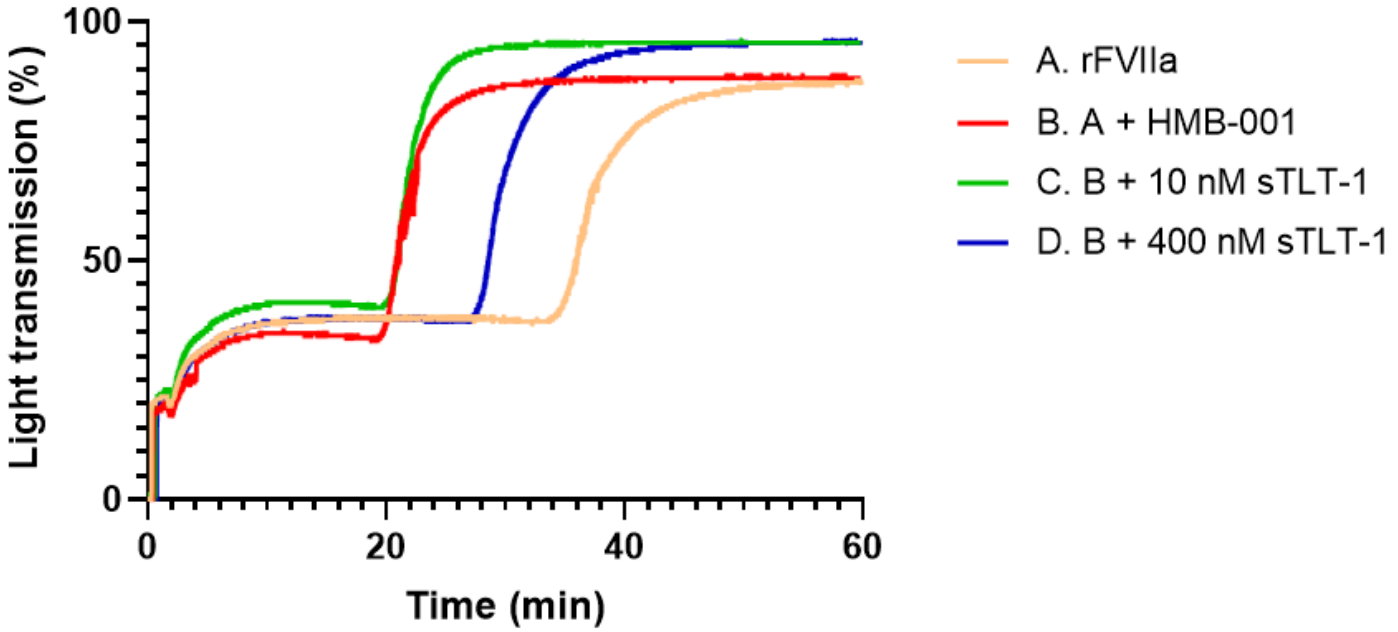
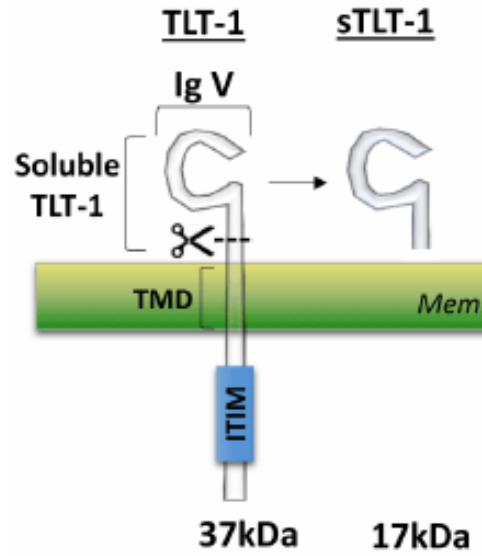
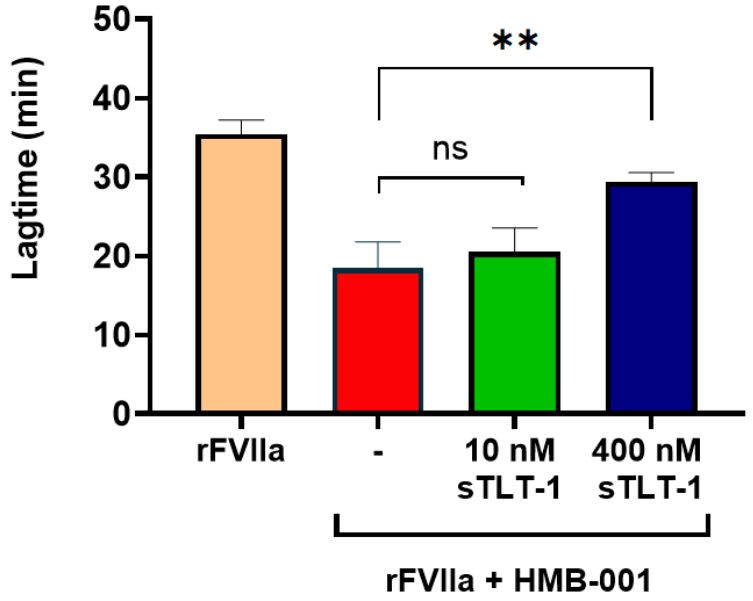
Effect of soluble TLT-1 (sTLT-1) on HMB-001





Plasma levels ~100 pM



1. **Plasma sTLT does not inhibit HMB-001 (<10 nM)**
2. **HMB-001 is TLT-1 dependent**

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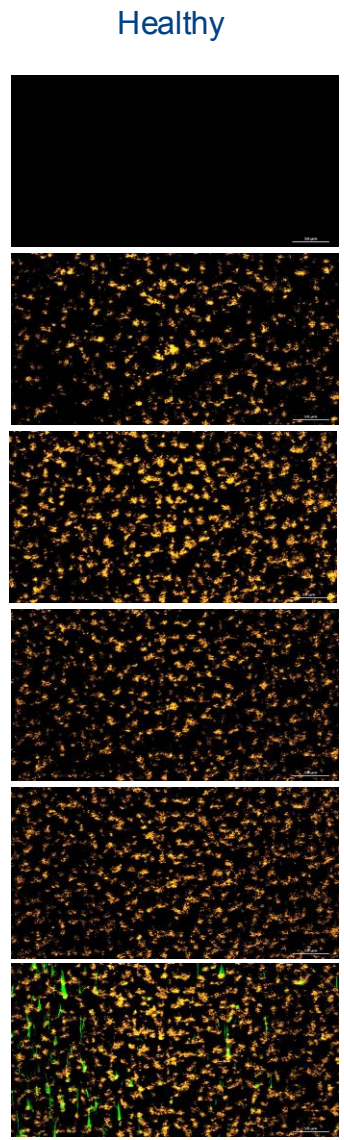
Flow study on collagen surface (300 s^{-1})



Platelets

Fibrin

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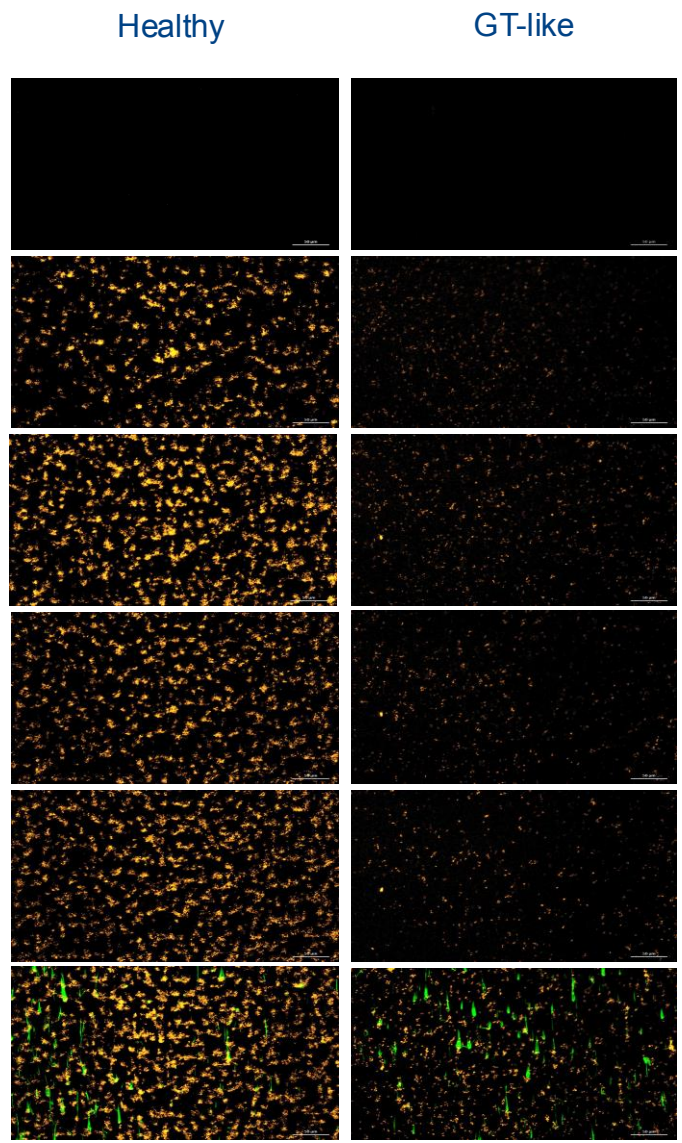
Flow study on collagen surface (300 s^{-1})



Platelets

Fibrin

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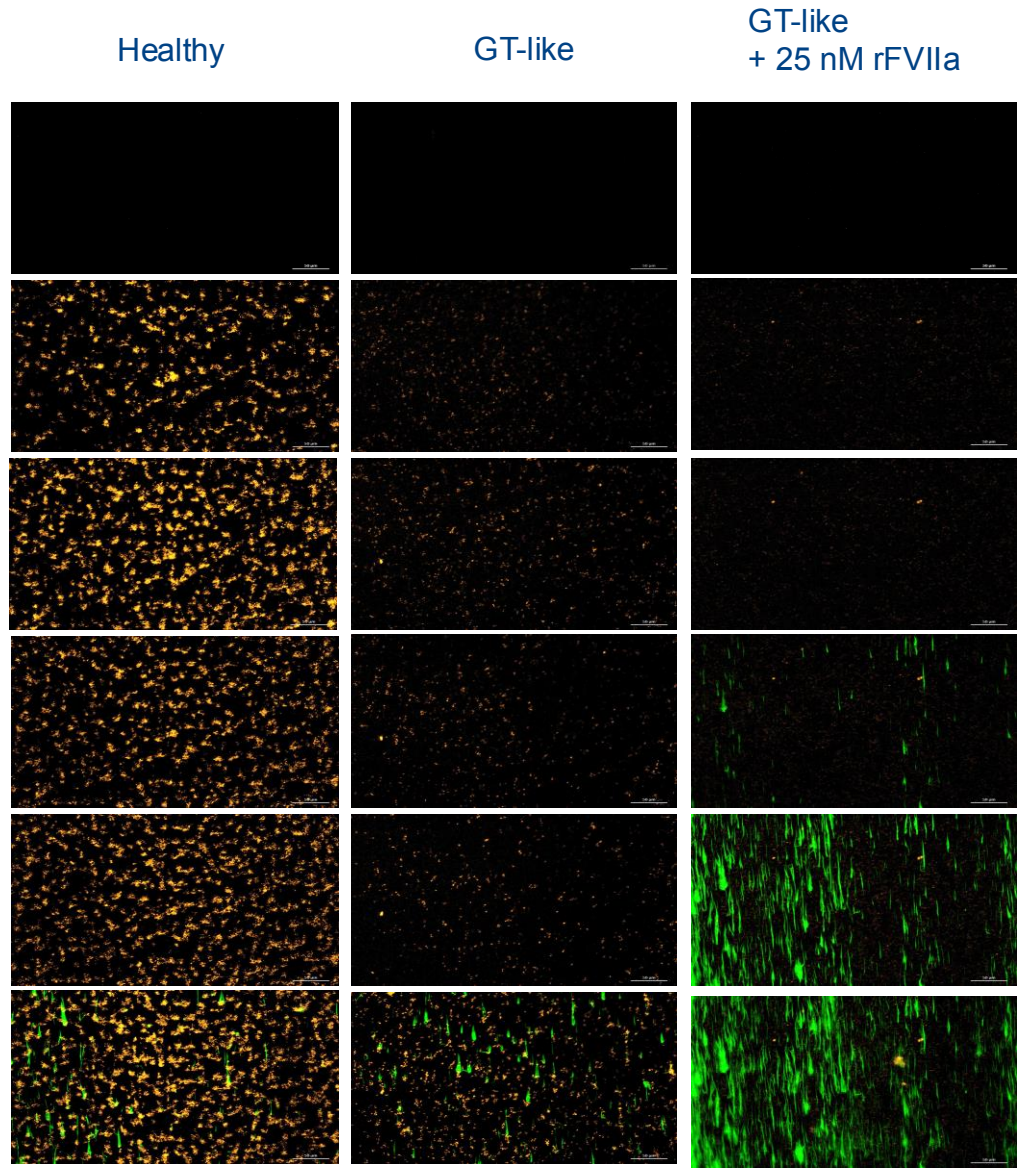
Flow study on collagen surface (300 s^{-1})



Platelets

Fibrin

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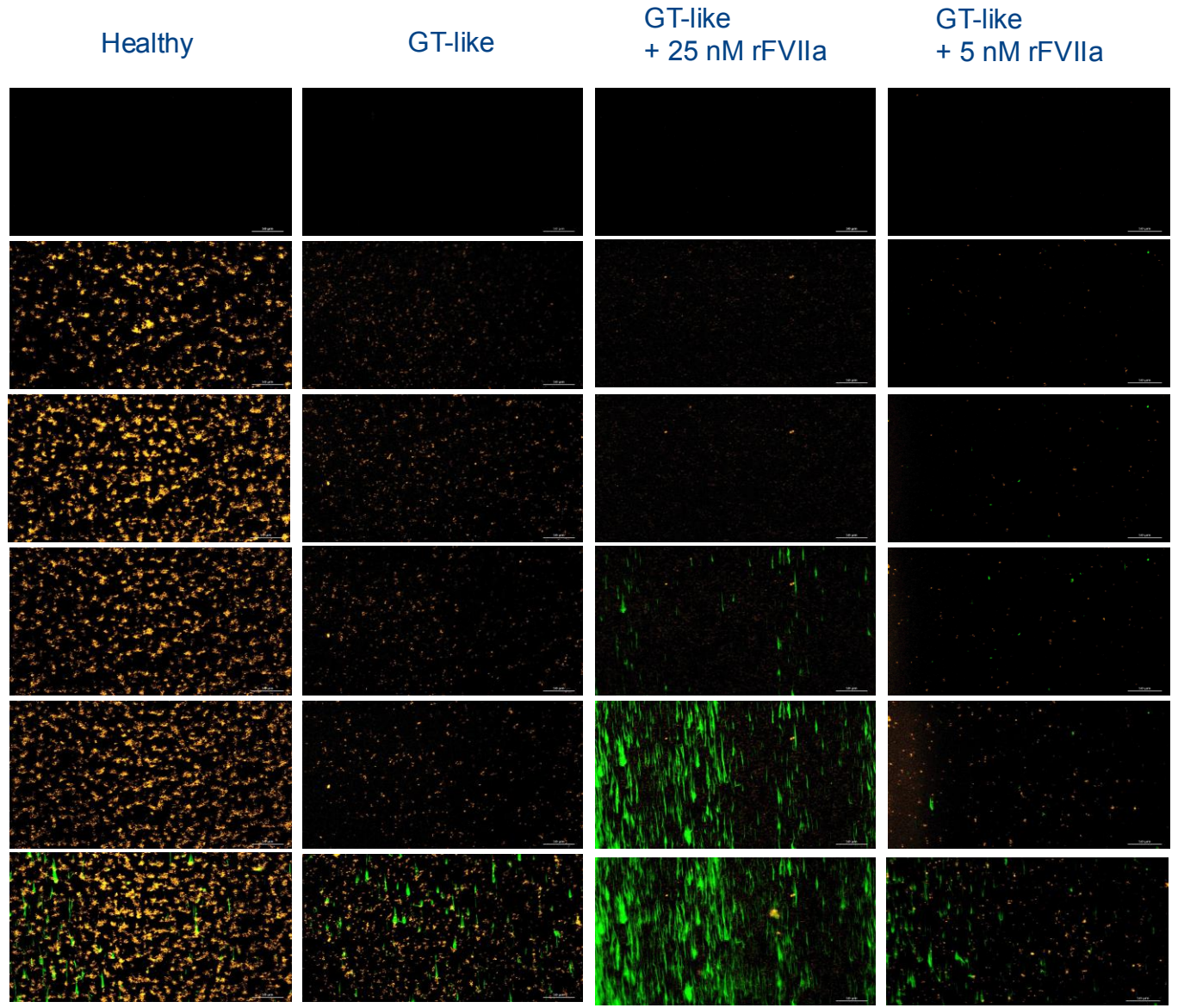
Flow study on collagen surface (300 s^{-1})



Platelets

Fibrin

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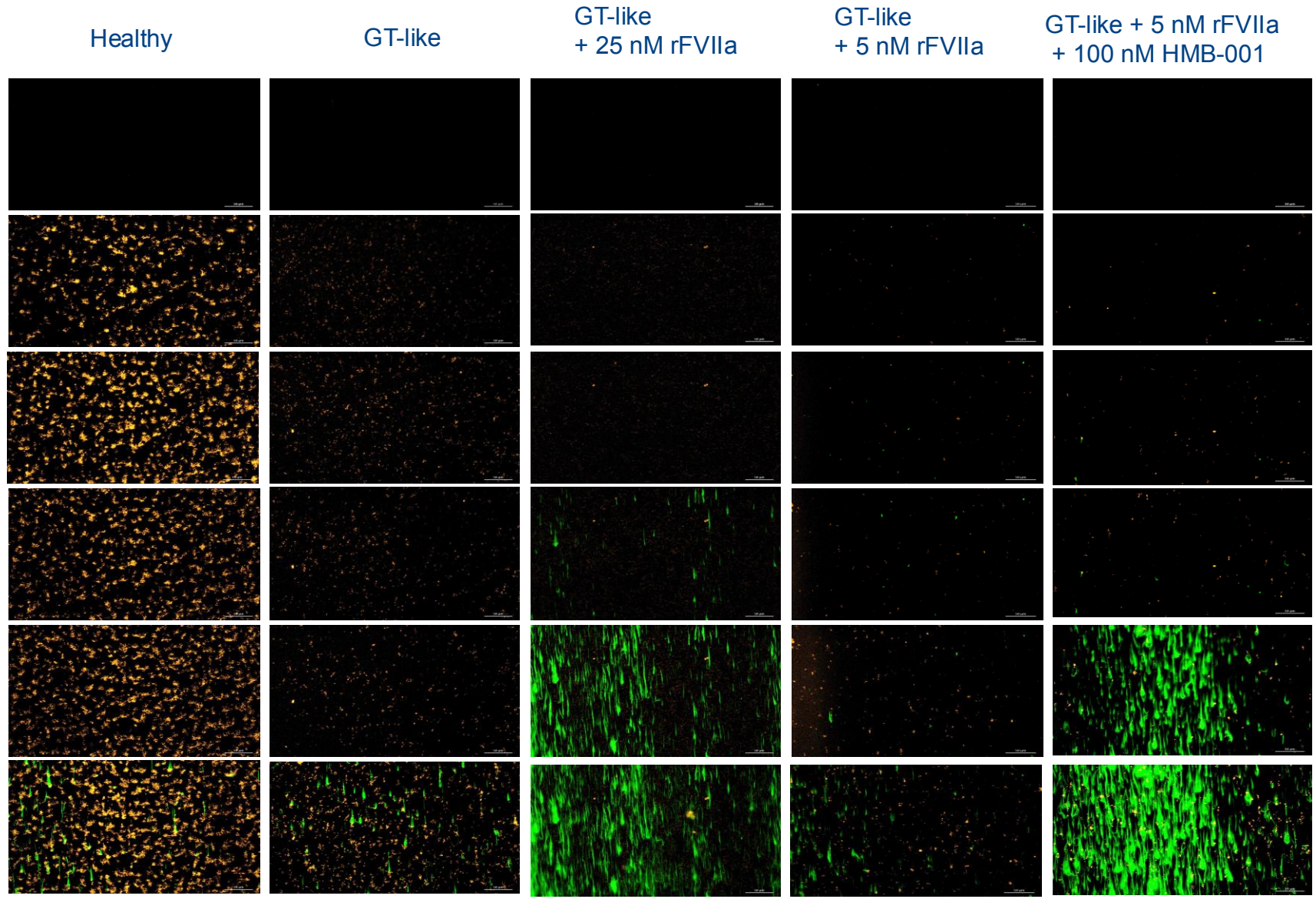
Flow study on collagen surface (300 s^{-1})



Platelets

Fibrin

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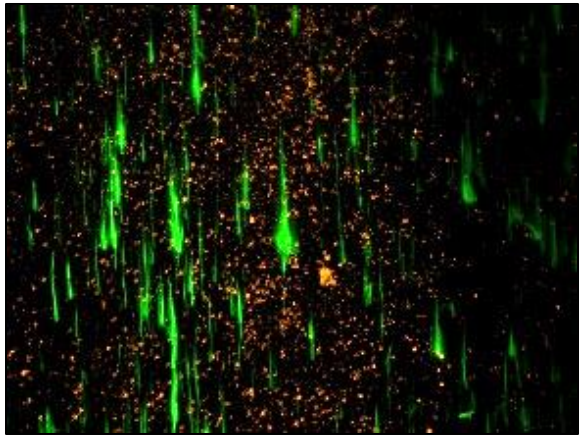
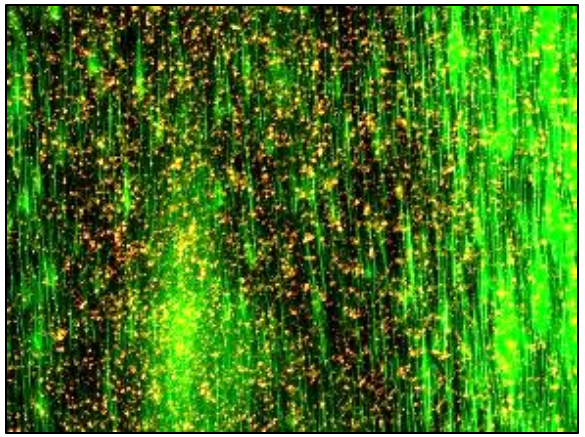
HMB-001 is effective under flow in GT whole blood

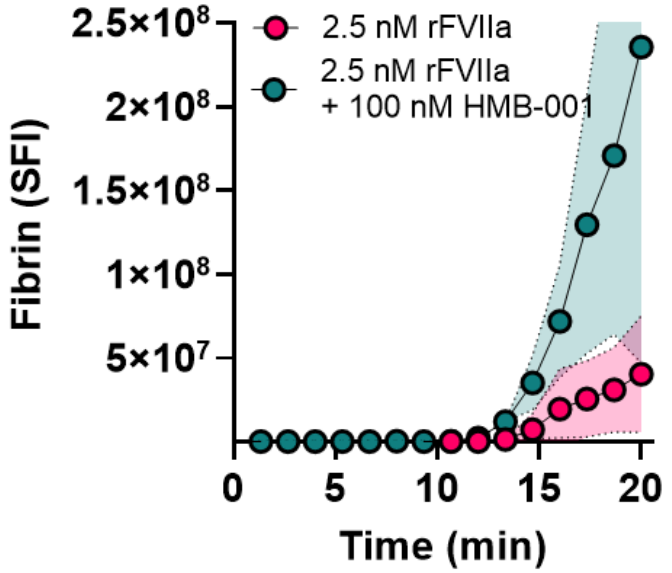
No HMB-001
t=20 min



100 nM HMB-001
t=20 min



Fibrin formation over time in GT patients (n=3)



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Summary

1. HMB-001 is a bispecific antibody with a FVIIa arm and TLT-1 arm
    - Based on monkey studies accumulation of endogenous FVIIa
    - Based on *ex vivo* studies 10 fold-potentiation of FVIIa efficacy
2. HMB-001 does not interfere with normal platelet function
3. FVII(a) levels and TLT-1 expression on activated platelets are normal in GT patients
4. HMB-001 enhances FVIIa efficacy by
    - Enhancing fibrin-dependent platelet aggregation
    - Enhancing fibrin formation under flow on adhered platelets

Acknowledgements

Center for Benign Haematology, Van Creveldkliniek, UMC Utrecht
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Dr. Henrik Østergaard
Dr. Johan Faber
Dr. Søren Bjørn
Dr. Amalie Bonde
Dr. Catherine Rea
Dr. Benny Sørensen

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HEMAB Therapeutics