*Supplemental Data*

**Improved coagulation and hemostasis in hemophilia with inhibitors by combinations of $^{super}$Factor Va and Factor VIIa**

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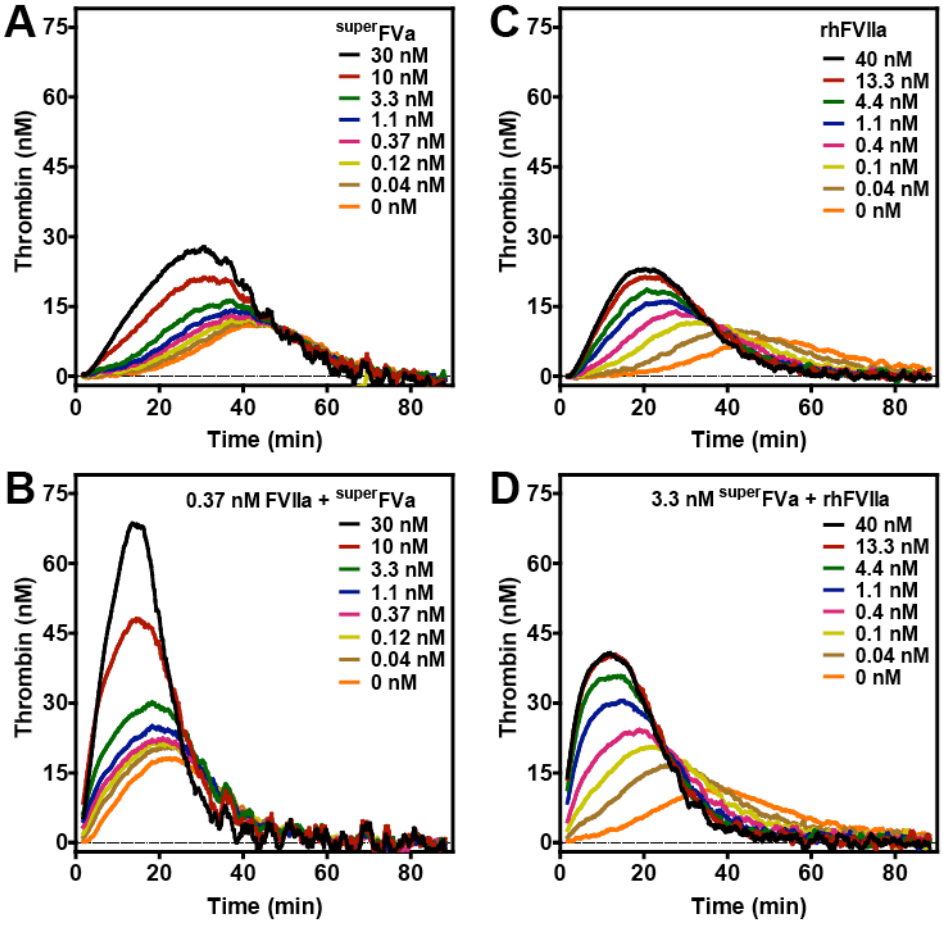
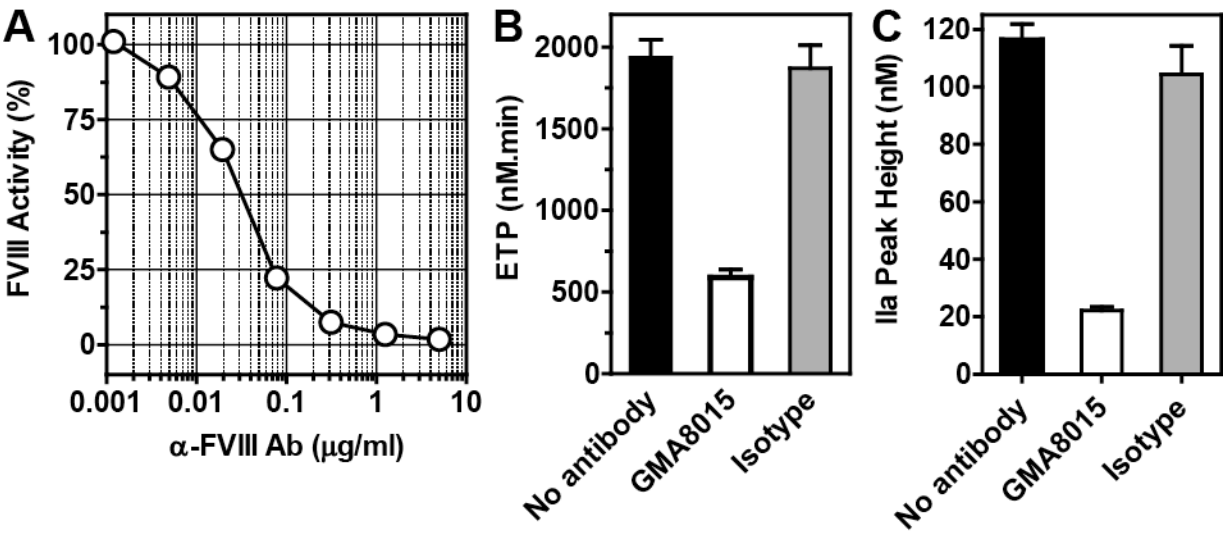
## Supplemental Figure 1




**Supplemental Figure 1. Cooperative effects of FVIIa and $^{super}$FVa on thrombin generation in FVIII deficient plasma**

Representative examples of thrombin generation profiles in the presence of increasing concentrations of $^{super}$FVa in the absence (**A**, top panels) or presence (**B**, bottom panel) of 0.37 nM rhFVIIa and thrombin generation profiles for increasing concentrations of rhFVIIa in the absence (**C**, top panel) or presence (**D**, bottom panel) of 3.3 nM $^{super}$FVa.

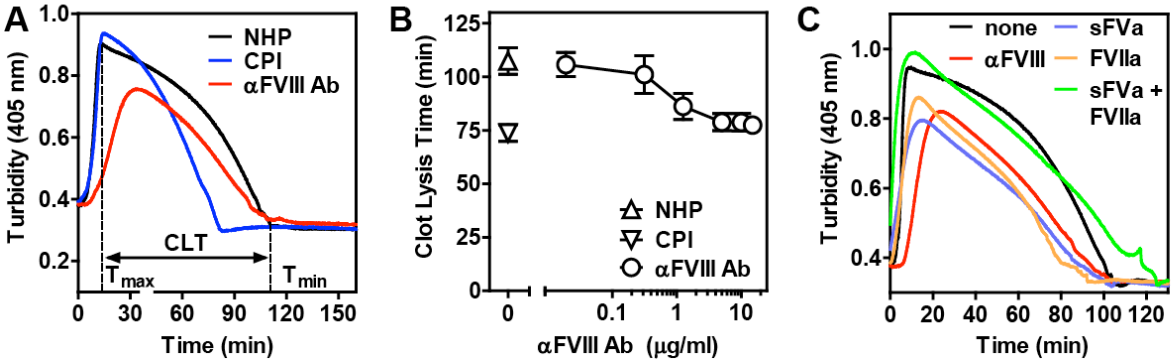
## Supplemental Figure 2




**Supplemental Figure 2. Characterization of the GMA8015 anti-FVIII antibody**

**A**) Residual FVIII activity in normal human plasma determined by APTT assays using the Nijmegen Bethesda assay after adding increasing concentrations of GMA8015 anti-FVIII antibody. The BU titer for GMA8015 was calculated to be 32,000/mg from this curve. **B**) Endogenous Thrombin Potential (ETP) and **C**) peak height of thrombin (IIa) generation in normal human plasma in absence and presence of 1.25 µg/mL GMA-8015 inhibitory anti-FVIII antibody at (40 BU) or GMA-650 isotype ($IgG_{2a}$) control antibody. Error bars indicate SEM (n≥3).

## Supplemental Figure 3



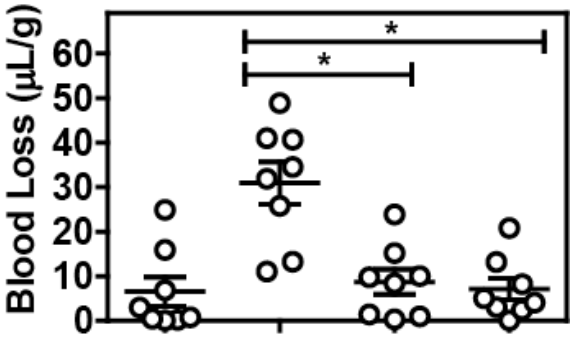

**Supplemental Figure 3. Effects of the inhibitory anti-FVIII antibody (GMA8015) on the clot lysis time of NHP**

(**A**) Representative examples of clot lysis times of NHP with and without the GMA-8015 anti-FVIII antibody or CPI. $T_{max}$ is the time to maximum coagulation and $T_{min}$ is the time to maximum fibrinolysis. (**B**) Clot lysis times ($T_{min}$ - $T_{max}$) as determined for NHP (triangle), for NHP with CPI (inverted triangle), or for NHP with increasing concentrations of anti-FVIII antibody (open circles). (**C**) Representative clot lysis profiles of NHP (black line), NHP + 10 µg/ml αFVIII antibody (red line), and NHP + 10 µg/ml αFVIII antibody supplemented with either 0.37 nM $^{super}$FVa (sFVa, blue line), 4.4 nM rhFVIIa (orange line), or the combination thereof (green line). NHP denotes normal human plasma and CPI, carboxypeptidase inhibitor from potato tubers. Error bars indicate SEM (n≥3).

| Minimal concentration for CLT normalization | NHP with α-FVIII Ab | | | |
|---|---|---|---|---|
| | $^{super}$FVa (nM) | | rhFVIIa (nM) | |
| | 0 | 0.37 | 0 | 0.37 |
| rhFVIIa (nM) | 40 | 0.04 | - | - |
| $^{super}$FVa (nM) | - | - | 3.33 | 0.37 |

**Supplemental Table 1. Minimum concentrations of rhFVIIa alone, $^{super}$FVa alone, or their combination required to correct the clot lysis time of NHP spiked with inhibitory anti-FVIII antibody.** The mean clot lysis time (CLT) of NHP was ~105 min without anti-FVIII antibody and ~76 min in the presence of the GMA-8015 inhibitory anti-FVIII antibody (10 µg/ml; 320 BU). Values are within +/- 10% and are derived from the curves in Figure 5.

# Supplemental Figure 4




| | | | | |
|---|---|---|---|---|
| Saline | + | + | - | - |
| FVIII-Ab | - | + | + | + |
| mFVIIa (µg/kg) | - | - | 90 | - |
| rhFVIIa (mg/kg) | - | - | - | 3 |

**Supplemental Figure 4**. **Bleed correction efficacy of rhFVIIa versus mFVIIa in wt-BalbC mice injected with an inhibitory anti-FVIII antibody.**

BalbC mice were injected intravenously with the inhibitory GMA-8015 antibody against FVIII (0.25 mg/kg; 35BU). Two hours later mice were treated intravenously with saline, mFVIIa (90 µg/kg), or rhFVIIa (3 mg/kg). Blood loss was determined at 20 min after tail clip and was expressed as µl blood loss per gram mouse weight. Error bars indicate mean ± SEM (n=8), * indicates $p < 0.05$.