

# 3273 Pan-Selectin Antagonist, GMI-1070 Decreases Venous Thrombosis in a Mouse Model

Program: Hemostasis and Thrombosis

Session: Vascular Wall Biology, Endothelial Progenitor Cells and Platelet Adhesion

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**Introduction:** E- and P-selectin have structural similarities and both facilitate white blood cell tethering on vascular endothelium. The beneficial effect of combined E- and P-selectin inhibition in decreasing venous thrombosis (VT) by gene deletion in a mouse model of VT has been demonstrated. GMI-1070 is a pan-selectin inhibitor designed to mimic the bioactive conformation of the sialyl-Le<sup>x</sup> carbohydrate binding domain of E-selectin and the sulfate interactions of P- and L-selectins. GMI-1070 has primary activity against E-selectin, with second and tertiary activity against P- and L-selectin. It has passed Phase I clinical trials showing no serious adverse events, and has a serum half-life in humans of 7 to 8 hours. In this study, the effect of pan-selectin inhibition by GMI-1070 on reducing VT was evaluated.

**Methods:** Male C57BL/6J mice (20-25grams) underwent our electrolytic IVC model (EIM) to produce a non-occlusive thrombosis via electrical free radical stimulation (250  $\mu$ Amp) for 15 minutes. Experimental groups included the following: GMI-1070 delivered continuously by mini osmotic pump (300 mg/ml), and mice administered saline via the same protocol served as controls (SAL CTR). Continuous delivery of GMI-1070, or saline, began one day pre-thrombus induction. Mice were euthanized 2 and 6 days post-thrombosis for tissue harvest and blood collection for the following evaluations: thrombus weight (grams); plasma soluble E- and P-selectin (ng/mg total protein); vein wall E- and P-selectin protein by ELISA (pg/mg total protein); and vein wall inflammatory cell counts per high powered field.

**Results:** Continuous GMI-1070 administration significantly decreased venous thrombus weight (WT) two days post thrombosis ( $78 \pm 8$  vs.  $216 \pm 97 \times 10^{-4}$  grams,  $P < 0.01$ ), and also significantly decreased TW six days post thrombosis versus saline controls ( $85 \pm 8$  vs.  $170 \pm 48 \times 10^{-4}$  grams,  $P \leq 0.05$ ) [Figure 1]. Circulating E-selectin protein was decreased significantly at both day 2 ( $21700 \pm 2014$  vs.  $56360 \pm 4284$  pg/mg total protein,  $P < 0.01$ ), and day 6 ( $33070 \pm 3586$  vs.  $67310 \pm 2833$  pg/mg total protein,  $P < 0.01$ ) post VT compared to respective saline controls. GMI-1070 significantly decreased vein wall E-selectin protein versus saline controls 6 days post

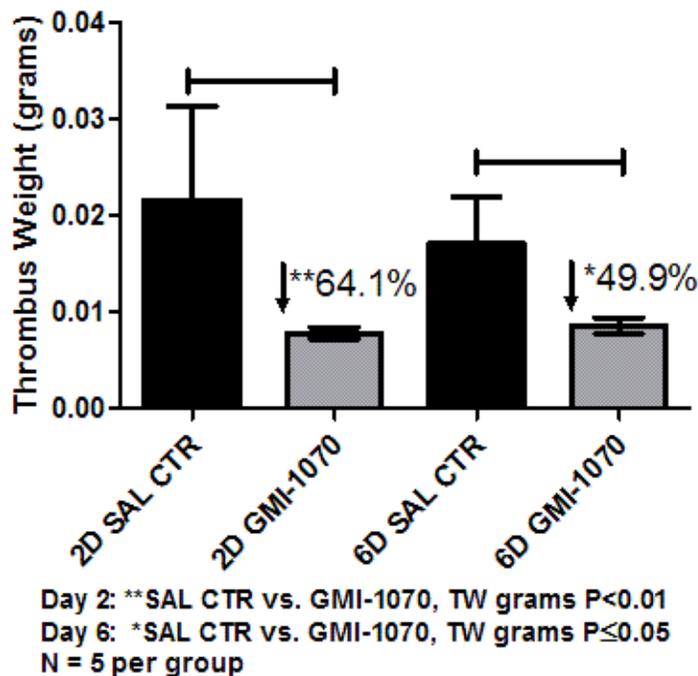
thrombosis (281±36 vs. 676±102 pg/mg total protein, P<0.02). No effect on vein wall P-selectin protein was noted. Vein wall inflammatory cell evaluation showed neutrophils peaking at day 2, then significantly decreasing by day 6 in these mice (23±5 vs. 7±1 Cells/5HPFs, P<0.01).

Conversely, vein wall monocytes were found in significant numbers 6 days post thrombosis in mice receiving GMI-1070 versus saline controls (P<0.01). Both neutrophils and monocytes showed trends of increased vein wall extravasation versus saline groups.

Conclusions: GMI-1070 therapy significantly decreased venous thrombus formation. This pan-selectin inhibitor modulated circulating E- and P-selectin and vein wall E- selectin levels thus decreasing systemic and local inflammatory effects of both adhesion molecules. GMI-1070 therapy significantly increased vein wall monocytes and these mice had the greatest VT resolution. GMI-1070 has a high therapeutic potential for decreasing thrombosis and selectin related events.

Figure 1:

### The Effect of GMI-1070 on Thrombus Weight



**Disclosures:** **Patton:** *GlycoMimetics, Inc.:* Employment, Equity Ownership. **Magnani:** *GlycoMimetics, Inc.:* Employment, Equity Ownership.