

## **GMI-1070: a Small, Glycomimetic, Pan-selectin Antagonist that Improves Blood Flow and Inhibits Blood Cell Adhesion in Sickle Mice**

**J. T. Patton<sup>1</sup>, J. Chang<sup>2</sup>, A. Sarkar<sup>1</sup>, B. Wagner<sup>3</sup>, B. Ernst<sup>3</sup>, P. S. Frenette<sup>2</sup>, J. L. Magnani<sup>1</sup>**

<sup>1</sup> *GlycoMimetics, Inc., 101 Orchard Ridge Dr., Gaithersburg, Maryland, United States*

<sup>2</sup> *Department of Medicine, Mount Sinai School of Medicine, New York, N.Y., United States*

<sup>3</sup> *Institute of Molecular Pharmacology, University of Basel, Basel, Switzerland*

Knowledge of the bioactive conformation of carbohydrates can be used to rationally design glycomimetic molecules with higher affinity and improved pharmacokinetics and bioavailability. In designing more active glycomimetic selectin inhibitors, the low enthalpy ( $\Delta H^0$ ) of the reaction is compensated by pre-forming the bioactive conformation thereby improving the entropy ( $\Delta S^0$ ), known as S/H compensation. Modifications of the molecule that also stabilize the core structure, further improve  $\Delta S^0$  and binding activity. To improve  $\Delta H^0$ , second site interactions were explored. For P and L-selectins, interactions were combined for both carbohydrate and sulfate-binding domains to develop glycomimetic pan-selectin inhibitors, one of which, (GMI-1070) is now in development and scale-up synthesis as a lead compound. GMI-1070 is a potent inhibitor of all three selectins, E, P, and L, *in vitro* and also inhibits leukocyte migration *in vivo*. Sickle cell disease is characterized by endothelial activation, slow blood flow, and enhanced cell adhesion leading to painful episodes of vaso-occlusive crisis and eventually death. The selectins, notably E and P-selectins, appear to play major roles in this disease as determined by transgenic sickle mice studies. Mice genetically engineered to exclusively express human sickle hemoglobin (Hb  $\beta^s$ ) present with inducible vaso-occlusive crisis resulting in early death. Recent reports demonstrate that antibodies against the selectins as well as genetic knockouts of E and P-selectins are protective (1,2). Based on this background information, GMI-1070 was tested for effects on induced vaso-occlusive crisis in sickle mice by using intravital microscopy techniques. Intravenous administration of GMI-1070 display dramatic effects of restoring blood flow to normal levels and virtually eliminating adhesion of sickle red blood cells to leukocytes *in vivo*. Based on these results, we are encouraged to pursue the use of GMI-1070 to prevent or attenuate painful vaso-occlusive crisis and early death of sickle cell patients.

(1) Embury S.H., et al (2004) *Blood* 104: 3378-3385

(2) Turhan A., Weiss L.A., Mohandas N., Collier B.S., and Frenette P.S. (2002) *PNAS* 99: 3047-3051.