GlycoMimetics, Inc.

GLYCOMIMETICS GMI-1271

MECHANISM OF ACTION BACKGROUNDER

E-selectin/E-selectin Ligand as Prognostic Biomarkers and Therapeutic Targets in Cancer

GMI-1271, is a mimic of the E-selectin ligand and as such, an antagonist of E-selectin. As described below, E-selectin functions to facilitate cancer metastasis, activation of cancer survival pathways, and chemo-resistance. Numerous publications demonstrate that higher levels of E-selectin ligand are associated with worse outcomes in cancer patients and with more aggressive, more chemo-resistant disease. Thus, targeting E-selectin may be an attractive potential cancer therapy, in particular in patients with higher of E-selectin ligand on their tumors.

The E-selectin ligand was initially discovered as the cancer biomarker known as CA19-9. It is the basis of an FDA-approved diagnostic that has been used routinely for monitoring the progression of pancreatic cancer for the last 15 years (1). CA19-9 was discovered as a tumor cell surface carbohydrate structure (sialyl Le^a) using monoclonal antibody technology and thereby determined to be tumor-associated through the eyes of the immune system (2).

Almost 10 years after the discovery and use of CA19-9 as a pancreatic cancer diagnostic biomarker, researchers demonstrated that a domain (sialyl $Le^{a/x}$) within this carbohydrate structure binds to an adhesion protein known as E-selectin (3). E-selectin is expressed on endothelial cells lining the blood vessels during an inflammatory response and functions by binding to the E-selectin ligand expressed on the surfaces of inflammatory leukocytes. By recognizing this carbohydrate structure (i.e., E-selectin ligand) expressed on the surfaces of these cells, E-selectin functions to pull these cells out of circulation and to cause them to adhere and roll on the blood vessel walls as an initial step in the process of leukocytes leaving the bloodstream during an inflammatory response (Figure 1). In a similar way, cancer cells have been shown to bind E-selectin when they leave the bloodstream to metastasize.

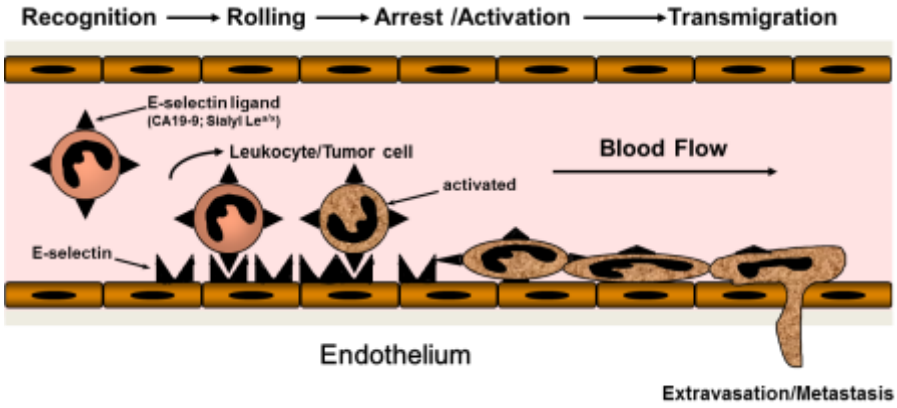

Figure 1. *E-selectin functions to bind cells expressing the E-selectin ligand to blood vessel walls and activate these cells as an initial step in the process of extravasation from the bloodstream.*

Thus, the E-selectin ligand (CA19-9; sialyl $Le^{a/x}$) is a functional biomarker for cancer. Those cancer cells expressing high levels of the E-selectin ligand on their surfaces readily bind to E-selectin on the vascular walls, thereby highjacking the inflammatory pathway for cells to leave the bloodstream, promoting metastasis and infiltrative disease.

More recently, researchers have discovered that cancer cells that bind E-selectin also become activated through the NF-κB pathway, which promotes survival and chemoresistance in these bound cancer cells. In particular, the bone marrow vasculature constitutively expresses low levels of E-selectin that bind and sequester leukemic cells (AML) in these protective niches where they become activated and chemoresistant (4).

The E-selectin antagonist, GMI-1271, not only mobilizes leukemic cells out of these protective niches but preclinical studies have shown that it also blocks NF-κB activation and prevents this E-selectin-mediated chemoresistance, thereby enhancing the therapeutic effects of standard chemotherapy (Figure 2).

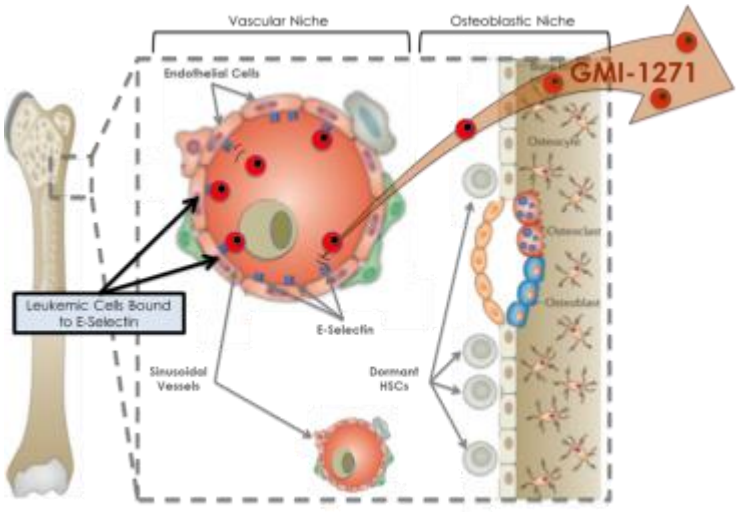

Figure 2. *Leukemic Cells (AML) expressing the E-selectin ligand bind to E-selectin on endothelial cells in the bone marrow microvasculature and become activated and chemoresistant. GMI 1271 mobilizes AML cells out of these protective niches and breaks E-selectin-mediated chemoresistance.*

The E-selectin ligand (sialyl $Le^{a/x}$) is expressed on many different cancers in both solid and liquid tumors, and it is well established that the ligand is associated with poor patient outcomes. In a recent meta-analysis of over 3,000 different types of cancer patients reported in 29 publications, over expression of the E-selectin ligand significantly correlated with lymphatic invasion, venous invasion, deep invasion, lymph node metastasis, distant metastasis, tumor stage, tumor recurrence and low overall survival (5). This mechanism of tumor progression is widespread throughout different cancer indications and represents a clear untapped target in cancer therapy. GMI-1271 as a rationally designed and potent E-selectin antagonist, represents a unique potential drug to counter this mechanism and may have particular relevance where the E-selectin ligand is overexpressed.

References

1. Bast RC, Gold P, Chu TM and Magnani JL (2013) Clinical Chemistry 59(1): 22-31
2. Magnani JL, Nilsson B, Brockhaus M, Zopf DA et. al. (1982) J. Biol. Chem. 257: 14365-14369
3. Berg EL, Robinson M, Mansson O, Butcher EC, Magnani JL (1991) J Biol. Chem. 266: 14869-72
4. Winkler IG, Barbier B, Ward M, Tallack M, Lowe J, et. al. (2016) Blood 128: 2823
5. Liang J, Liang Y, and Gao W (2016) OncoTargets and Therapy 9: 3113-3125