Exploration of a potent E-selectin antagonist (GMI-1271) as a potential therapeutic for treating breast cancer metastasis to the lung and bone

Mark Esposito1, Neil Campbell2, Yong Wei3, Qiong Qiu1, John L. Magnani3, Yibin Kang1
1 Princeton University, Princeton, NJ; 2 CINJ, New Brunswick, NJ; 3 GlycoMimetics, Gaithersburg, MD

Abstract
The propensity of breast cancer to metastasize to the lung and bone with high frequency presents an attractive opportunity for specific therapeutic intervention. Targeting the initial steps of metastasis, such as survival in circulation, arrest, and extravasation, may constitute a more effective approach than treatment during the later steps. E-Selectin has been implicated as a pro-metastatic endothelial receptor which mediates the initial stages of tumor cell arrest and extravasation to the lung, liver and bone. We examined the ability of the potent E-selectin antagonist GMI-1271 (Kᵦ = 0.54 μM) to inhibit E-selectin binding to lung and bone metastatic cells. Flow cytometry analysis was used to evaluate the effects of GMI-1271 in vitro while treatment of bone and lung metastasis with GMI-1271 during the initial stages of metastatic seeding were used in xenograft models. Results demonstrated that metastatic breast cancer cells express carbohydrates ligands recognized by E-selectin as determined by interaction with E-selectin-Fc chimeric protein and the antibody HECA-452. GMI-1271 could significantly reduce metastatic breast cancer cell binding to E-selectin in vitro. Treatment of mice following intracardiac injection resulted in a significant reduction of mortality (H.R. = 0.29, p = 0.044) while treatment following tail vein injection demonstrated a directional increase in survival (p = 0.061 and p = 0.055). These results designate GMI-1271 as a potential therapeutic for treatment of late stage breast cancer.

Objectives
Here we evaluate the potential therapeutic value of E-selectin inhibition during lung or bone metastasis.

We sought to answer three questions:
1. Does E-selectin bind to highly metastatic cells in vitro?
2. Does treatment with GMI-1271 or GMI-1303 during the initial stages of metastatic seeding extend survival?
3. Does GMI-1271 enhance the effects of chemotherapy in treating lung metastases?

Results

Conclusions
Here we show that:
1. Highly metastatic cells bind E-selectin in vitro, this can be inhibited by GMI-1271
2. GMI-1271 is an effective therapeutic for treatment of mice with lung or bone metastasis
3. Combination therapy with chemotherapy and GMI-1271 shows significant improvement over either treatment alone.
4. GMI-1271 shows potential for clinical treatment of breast cancer patients with advanced disease.