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#4503 A Small Molecule Glycomimetic Antagonist of E-selectin (GMI-1271) Prevents Pancreatic Tumor Metastasis and Offers Improved Efficacy of Chemotherapy

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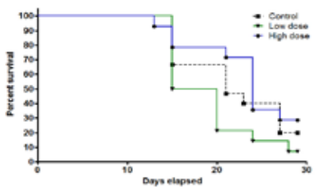
ABSTRACT

The processes of intra- and extravasation of tumor cells into and out of the blood and lymphatic systems are crucial steps during metastasis to distant organ sites. These processes are tightly regulated by the initial binding of sialyl Lewis^a and sialyl Lewis^x (sialyl Le$^{a/x}$) carbohydrate moieties found on tumor cells to the adhesion protein E-selectin expressed on the activated endothelium. GMI-1271 is a small molecule glycomimetic rationally designed based on the bioactive conformation of sialyl Le$^{a/x}$ and is a potent and specific antagonist of E-selectin. In vitro treatment of human lymphatic endothelial cells with GMI-1271 resulted in a decrease in the number of sialyl Lewis^a-expressing pancreatic cancer cells (S2.013 and BxPC-3) binding to the endothelium in a dose-dependent manner. GMI-1271 treatment also inhibited the transendothelial migration of S2.013 and BxPC-3 cells through a lymphatic cell monolayer.

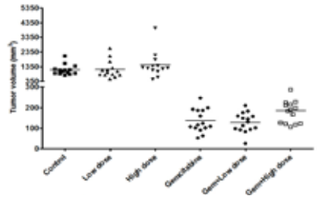
We evaluated the in vivo efficacy of GMI-1271 following orthotopic implantation of pancreatic tumor cell line S2.013, which expresses high levels of sialyl Lewis^a (CA19-9), into nude mice. Following 2 weeks of tumor growth, mice were treated by intraperitoneal injections for 4 weeks with either PBS once daily, once daily with 40mg/kg GMI-1271 (low dose), twice daily with 40mg/kg GMI-1271 (high dose), twice a week with 60mg/kg gemcitabine injections, combination low dose GMI-1271 and gemcitabine injections, or combination high dose GMI-1271 and gemcitabine injections. Co-treatment of either low or high dose GMI-1271 with gemcitabine resulted in a significant decrease in the number of metastasis to the lymph nodes (p=0.02 low dose; p=0.04 high dose). In addition, compared with gemcitabine alone, low dose GMI-1271 plus gemcitabine was found to be effective at reducing the number of metastatic lesions (per histological section) in the liver (p=0.001), lung (p=0.026) and diaphragm (p=0.01). Based on the significant effects of combination therapy on tumor metastasis, the small molecule glycomimetic antagonist to E-selectin, GMI-1271, offers great promise in preventing pancreatic tumor cell entry into the blood and lymphatic systems and offers a novel treatment for the improved efficacy of standard chemotherapy.

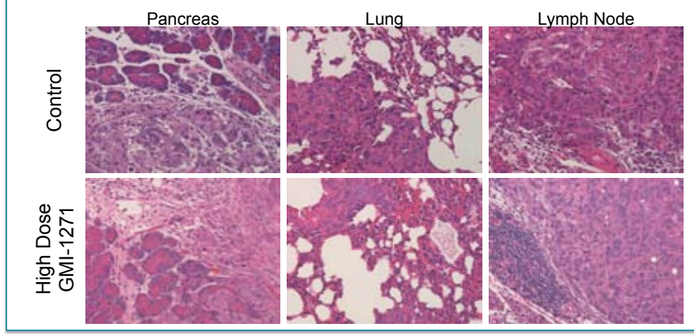
In Vivo Orthotopic Pancreas Implantation & GMI-1271 Treatment

Survival

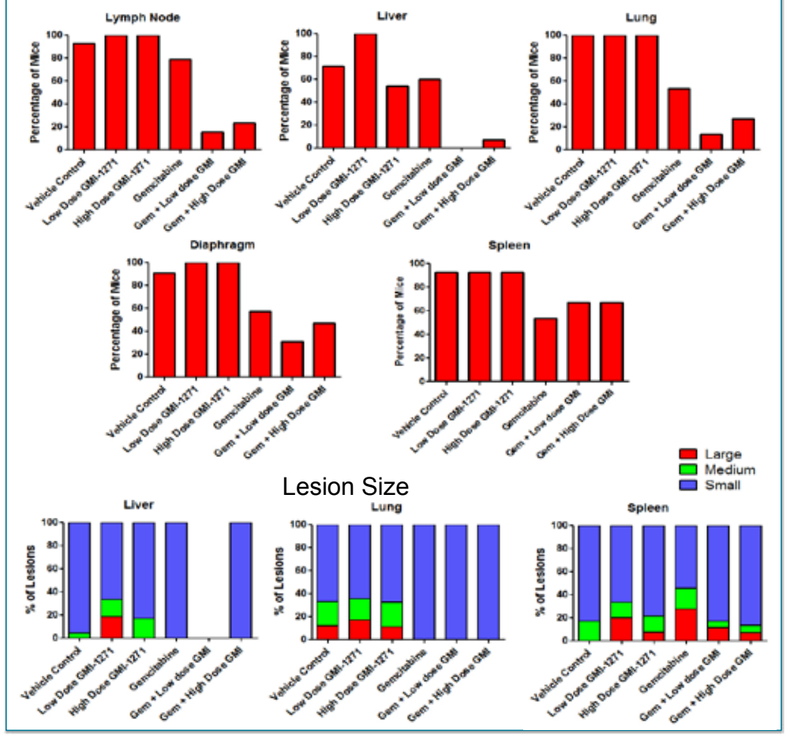


Tumor Volume

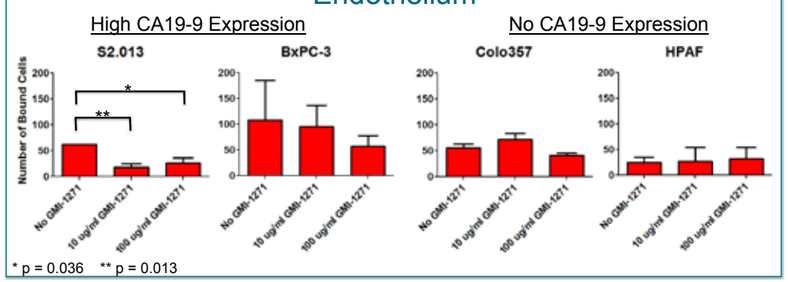




In Vivo Orthotopic Pancreas Implantation & GMI-1271 Treatment - Metastases

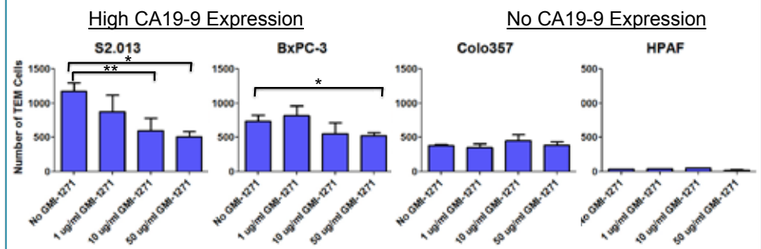


GMI-1271 Inhibits PDAC Cell Binding to the Lymphatic Endothelium



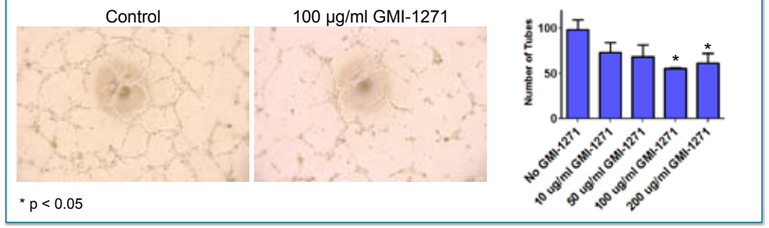
* p = 0.036 ** p = 0.013

GMI-1271 Inhibits PDAC Transendothelial Migration



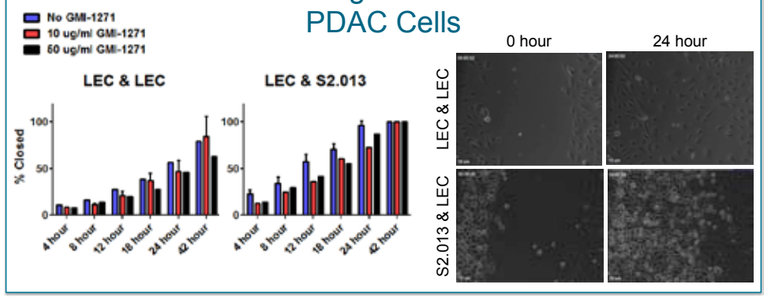
* p < 0.05 ** p < 0.005

GMI-1271Reduces *In Vitro* Tubulogenesis



* p < 0.05

GMI-1271 Reduces Migration between hLECs and PDAC Cells



Conclusions

- In combination with gemcitabine, the E-selectin small molecule inhibitor, GMI-1271, significantly decreases pancreatic ductal adenocarcinoma metastases, but does not alter primary tumor size.
- GMI-1271 decreases the binding of CA19-9 PDAC cells to the endothelium and also reduces these cells' ability to undergo transendothelial migration in a dose dependent manner.
- GMI-1271 significantly inhibits matrigel-induced tubulogenesis *in vitro*.
- GMI-1271 reduces co-culture migration that occurs between hLECs and PDAC cells populations.

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