

# LY2109761

Melisi et al. hypothesized that targeting TbetaRI/II kinase activity with the novel inhibitor LY2109761 would suppress pancreatic cancer metastatic processes. The effect of LY2109761 has been evaluated on soft agar growth, migration, invasion using a fibroblast coculture model, and detachment-induced apoptosis (anoikis) by Annexin V flow cytometric analysis. The efficacy of LY2109761 on tumor growth, survival, and reduction of spontaneous metastasis have been evaluated in an orthotopic murine model of metastatic pancreatic cancer expressing both luciferase and green fluorescence proteins (L3.6pl/GLT). To determine whether pancreatic cancer cells or the cells in the liver microenvironment were involved in LY2109761-mediated reduction of liver metastasis, we used a model of experimental liver metastasis. LY2109761 significantly inhibited the L3.6pl/GLT soft agar growth, suppressed both basal and TGF-beta1-induced cell migration and invasion, and induced anoikis. In vivo, LY2109761, in combination with gemcitabine, significantly reduced the tumor burden, prolonged survival, and reduced spontaneous abdominal metastases. Results from the experimental liver metastasis models indicate an important role for targeting TbetaRI/II kinase activity on tumor and liver microenvironment cells in suppressing liver metastasis. Targeting TbetaRI/II kinase activity on pancreatic cancer cells or the cells of the liver microenvironment represents a novel therapeutic approach to prevent pancreatic cancer metastasis <sup>1)</sup>.

1)

Melisi D, Ishiyama S, Sclabas GM, Fleming JB, Xia Q, Tortora G, Abbruzzese JL, Chiao PJ. LY2109761, a novel transforming growth factor beta receptor type I and type II dual inhibitor, as a therapeutic approach to suppressing pancreatic cancer metastasis. *Mol Cancer Ther*. 2008 Apr;7(4):829-40. doi: 10.1158/1535-7163.MCT-07-0337. PubMed PMID: 18413796; PubMed Central PMCID: PMC3088432.

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