Augmenting *nab*-paclitaxel/gemcitabine standard chemotherapy response by merestinib, an inhibitor of c-MET, Axl and DDR signaling pathways, in preclinical pancreatic cancer models

Background and Hypothesis:
Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal malignancies in Western countries. *Nab*-paclitaxel (NPT) plus gemcitabine (Gem) is the standard of care for PDAC leading to a dismal 8.5 months median survival. Aberrant signaling of c-MET, Axl and DDR have been reported in a variety of human cancers including PDAC. Merestinib (Mer) is a potent, small-molecule inhibitor of these pathways. We evaluated the therapeutic efficacy of merestinib to enhance the antitumor response of standard chemotherapy in preclinical models of PDAC.

Project Methods:
Cell proliferation of PDAC-associated cells (AsPC-1, PANC-1 and fibroblasts) were evaluated by colorimetric WST-1 assay. Protein expression was determined by Western blot analysis. Tumor progression studies were performed in NOD/SCID mice.

Results:
In vitro studies demonstrated that both *nab*-paclitaxel plus gemcitabine and merestinib suppressed cell proliferation of PDAC epithelial cells and stromal cells. Importantly, the combination treatment demonstrated additive inhibitory effects. In AsPC-1 cells, at the medium dose level, NPT+Gem, Mer and NPT+Gem+Mer treatments inhibited cell proliferation by 53.9%, 13.5%, and 81.61%, respectively. In PANC-1 cells, at the highest dose level, inhibition in cell proliferation by NPT+Gem, Mer and NPT+Gem+Mer treatments was 53.6%, 3.7%, and 72.8%. In the PDAC-associated fibroblasts, at the medium dose level, NPT+Gem, Mer and NPT+Gem+Mer treatments inhibited growth by 55.3%, 58.0%, and 91.6%. Immunoblot analysis revealed that merestinib caused a decrease in the PI-3K-AKT signaling proteins and an increase in apoptosis-related proteins cleaved PARP-1 or cleaved caspase-3 in PDAC cells either alone or in combination with *nab*-paclitaxel and gemcitabine. *In vivo* study to evaluate tumor growth inhibition effects of merestinib in a subcutaneous PDAC xenograft is currently ongoing.

Conclusion:
The antitumor effect of standard chemotherapy regimen can be significantly enhanced by the c-MET/Axl/DDR pathway inhibitor merestinib, which may lead to clinically relevant therapeutic strategy to increased survival in PDAC patients.