Enhancing cytotoxic chemotherapy response through targeted BET bromodomain inhibition in preclinical pancreatic cancer models

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Background and Hypothesis:
Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis and the standard of care regimen, nab-paclitaxel (NPT) plus gemcitabine (Gem), leads to a dismal 8.5 months median survival. Targeted inhibition of Bromodomain and Extra-Terminal (BET) protein is currently under investigation for several cancers. We hypothesize that BET protein pathway inhibition by iBet-762 will enhance cytotoxic chemotherapy response in PDAC.

Experimental Design:
In vitro cell proliferation assays were performed using WST-1 reagent. Protein expressions were determined by Western Blot analysis. *In vivo* animal survival and tumor growth experiments were performed in NOD-SCID mice.

Results:
Inhibition in cell proliferation in human PDAC cells at 1 μM concentration in NPT+Gem, iBET-762, and NPT+Gem+iBet762 was 64%, 27%, 76% in AsPC-1; 43%, 13%, 69% in Panc-1; and 42%, 51%, 75% in MIA PaCa cells. iBET-762 decreased oncogenic proteins c-Myc, β-catenin, Vimentin, and P-AKT while apoptosis related proteins such as cleaved PARP-1 and cleaved caspase-3 and cell cycle inhibitors proteins P21 & P27 were increased. In a peritoneal dissemination model, median animal survival compared to control (21 days) was increased after therapy with NPT+Gem (33 days, a 57% increase), iBet-762 (30 days, a 43% increase) and NPT+Gem+iBET-762 (44 days, a 110% increase). Effect of iBET-762 in combination with chemotherapy on local tumor growth is currently underway.

Conclusion and Potential Impact:
These findings suggest that the effects of standard chemotherapy can be enhanced through specific inhibition of BET proteins activity, and supports the clinical application of iBET-762 in combination with standard chemotherapy in PDAC patients.