M402, a novel heparan sulfate mimetic, inhibits pancreatic tumor growth and desmoplasia potentially via Shh signaling in an orthotopic mouse model

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Abstract # 1524

BACKGROUND

- One of the striking hallmarks of pancreatic adenocarcinoma (PDAC) is the presence and abundance of the fibrous tumor stroma (desmoplasia) which prevents uptake of standard care chemotherapeutics (such as gemcitabine).
- The pancreatic tumor stroma is composed of tumor cells, activated fibroblasts (such as pancreatic stellate cells), inflammatory cells and extensive acellular ECM.
- The desmoplastic response involves the complex interplay between these cell types and key soluble heparin-binding growth factors which include sonic hedgehog (shh), EGF, HB-EGF, TGFs, PDGF and FGFs.
- In particular, dysregulation of shh has been implicated in pancreatic cancer pathogenesis.

Hypothesis: M402 is a rationally engineered heparan sulfate mimetic with reduced anticoagulant activity. M402 has been previously shown in preclinical studies to reduce metastatic invasion and tumor angiogenesis through disruption of multiple key heparin-binding growth factor-mediated pathways (for example, FGF2, VEGF, SDF1α, P-Selectin). Sonic hedgehog signaling has also been shown to be dependent on heparan sulfate/heparin.

M402 was shown to be a potential candidate for primary tumor treatment and to potentially modulate tumor-stroma interactions in pancreatic ductal adenocarcinoma (PDAC).

GOAL: We evaluated M402 treatment alone or in combination with gemcitabine in the Capan-2 orthotopic human pancreatic ductal adenocarcinoma model (that has a strong desmoplastic response).

MATERIALS & METHODS

- M402 Uptake in Capan-2 Primary Tumors
- Histology of Capan-2 Primary Tumors
- M402 Therapeutic Study Design – cont’d
- M402 Uptake in Capan-2 Primary Tumors
- M402 Uptake in Capan-2 Primary Tumors
- Localization and mRNA of Shh & Gli1 in Capan-2 Tumors

RESULTS

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CONCLUSIONS

- The Capan-2 pancreatic cancer model shows extensive fibrosis, adhesions around the primary tumors and invasion into the adjacent organs. The tumors metastasized at a low rate to more distant sites (intestinal regions), particularly to the colon and mesentry as well as the peritoneal wall.
- There is also a dose-dependent reduction in primary tumor weight, tumor take frequency and metastatic lesions with gemcitabine treatment.
- Combination treatment with M402 and gemcitabine (45 mg/kg) showed comparable reduction in primary tumor weight as gemcitabine treatment alone at 60 mg/kg.
- M402 monotherapy also showed a dose-dependent reduction in primary tumor weight.
- M402 can modulate tumor-stroma interactions involved in the desmoplastic response in this orthotopic murine model of pancreatic cancer.
- These results provide further rationale for the clinical investigation of M402 as a potential anti-desmoplastic agent in pancreatic adenocarcinoma patients.

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