PRMT5 is a Novel Therapeutic Target that Sensitizes Pancreatic Cancer to Gemcitabine in a Murine Model

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Objectives: Pancreatic cancer (PDAC) is the third leading cause of cancer-related death in the US. First-line chemotherapy regimens include FOLFIRINOX or gemcitabine +/– paclitaxel, however 5-year survival remains poor. An in vivo genetic knockout CRISPR screen revealed protein arginine methyltransferase 5 (PRMT5) to be a potential therapeutic target in combination with gemcitabine. This finding required confirmation.

Materials and Methods: PRMT5 wild-type (WT) and knockout (KO) mPanc96 PDAC cells were injected bilaterally into the flanks of 40 athymic nude mice. Mice were randomized and treated with gemcitabine (control, 25 mg/kg, 50 mg/kg, 100 mg/kg). In the next experiment, PRMT5 WT mPanc96 cells were injected bilaterally into the flanks of 45 athymic nude mice. Mice were randomized and treated with control, 50 mg/kg or 200 mg/kg of PRMT5-inhibitor (EPZ 015666), with and without gemcitabine.

Results: In the genetic KO experiment, PRMT5 KO tumor volumes were significantly smaller across each treatment group as compared to WT tumors (Figure 1, $p<0.05$). Gemcitabine significantly inhibited tumor growth in dose-dependent fashion in the PRMT5 KO tumors (58% decrease in 100 mg/kg vs. control, $p<0.0001$). In the PRMT5-inhibitor experiment, mice treated with PRMT5-inhibitor demonstrated significantly smaller tumor volumes in a dose-dependent fashion (Figure 1; 67% decrease in 200 mg/kg PRMT5-inhibitor + gemcitabine vs. control, $p=0.0001$).

Conclusions: PRMT5 inhibition greatly improves response to gemcitabine in a murine model of PDAC. PRMT5 is a novel therapeutic target in combination with gemcitabine for pancreatic cancer treatment that necessitates further investigation in preclinical models.

Figure 1. PRMT5 wild-type (WT) vs. knockout (KO) and PRMT5-inhibited tumors in combination with gemcitabine at end of experiments.