Pressure-Enabled Drug Delivery (PEDD™) of a class C TLR9 agonist in combination with checkpoint inhibitor therapy in a murine pancreatic cancer model

Abstract #394276

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Abstract

Background: Despite advances in other solid organ tumors, immunotherapy has had at best modest results in pancreatic ductal adenocarcinoma (PDAC). This is thought to be due to a desmoplastic, immunosuppressive tumor micro-environment (TME). Recent pre-clinical cancer models and early-phase clinical trials have demonstrated the efficacy of toll-like receptor 9 agonists (TLR9A), including the synthetic CpG oligonucleotide SD101, to stimulate innate and adaptive immune cells and eliminate suppressive myeloid cells. We hypothesized that Pressure Enabled Drug Delivery (PEDD™) via Pancreatic Retrograde Venous Infusion (PRVI™) of a TLR9a would improve responsiveness to systemic anti-programmed death receptor-1 (PD-1) checkpoint inhibitor therapy in a murine orthotopic PDAC model.

Methods: Murine PDAC (KPC4580P) tumors were implanted into the pancreatic tails of C57BL/6J mice and treated 8 days after implantation. Mice were assigned to PRVI saline (pSAL, n=9), systemic anti-PD1 100 mcg/mouse on Day 0, 2 and 4 (sAPD1, n = 6), 30mcg PRVI TLR9A (pTLR9A, n=9), 30mcg systemic TLR9a (sTLR9a, n=7) on Day 0, and combination 30mcg PRVI TLR9a on Day 0 and systemic anti-PD1 100 mcg/mouse on Day 0, 2 and 4 (COMBO, n =9). Fluorescently-labeled TLR9A (radiant efficiency [RE]) was measured on day 1. Blood and tumors were collected at necropsy 10 days after infusion.

Results:

All mice survived to necropsy. Site of tumor fluorescence measurements revealed higher intensity fluorescence in pTLR9A compared to sTLR9a (7.5x10^5 vs. 2.4x10^5 RE, p= 0.048). Flow cytometry demonstrated significantly lower MDSCs in the COMBO vs. pSAL. Tumor weights were significantly lower in the COMBO group compared to pSAL (400 vs. 964 mg, p=0.003), and were also lower, although not significantly, than in the pTLR9A (400 vs. 518mg, p=0.5), and sAPD1 (400 vs. 645 mg, p = 0.7) groups.

Conclusion:

PEDD of TLR9A by PRVI with systemic anti-PD-1 demonstrated improved PDAC tumor control in murine model.

Figure 1. Pancreatic Venous Isolation via PRVI

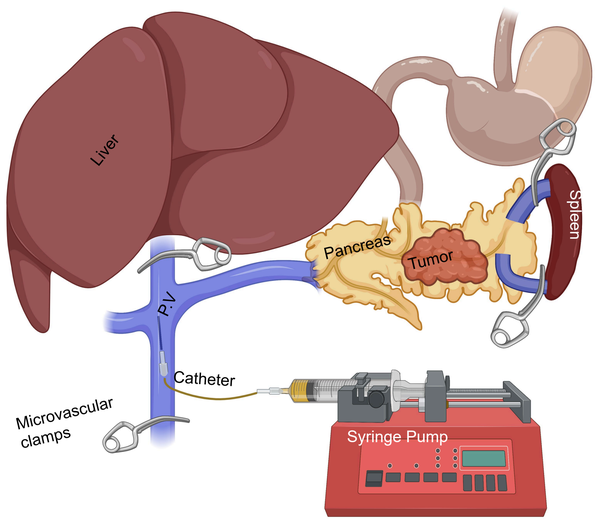

Figure 1A: Development of novel murine PRVI model with pancreatic venous isolation PRVI.

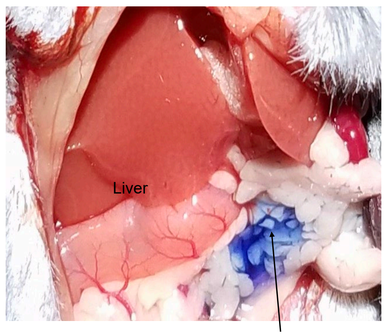

Figure 1B: Proof-of-concept study showing feasibility of infusing the pancreas via PRVI. Localized blue dye delivered to the murine pancreas .

Figure 2: In Vivo Fluorescence

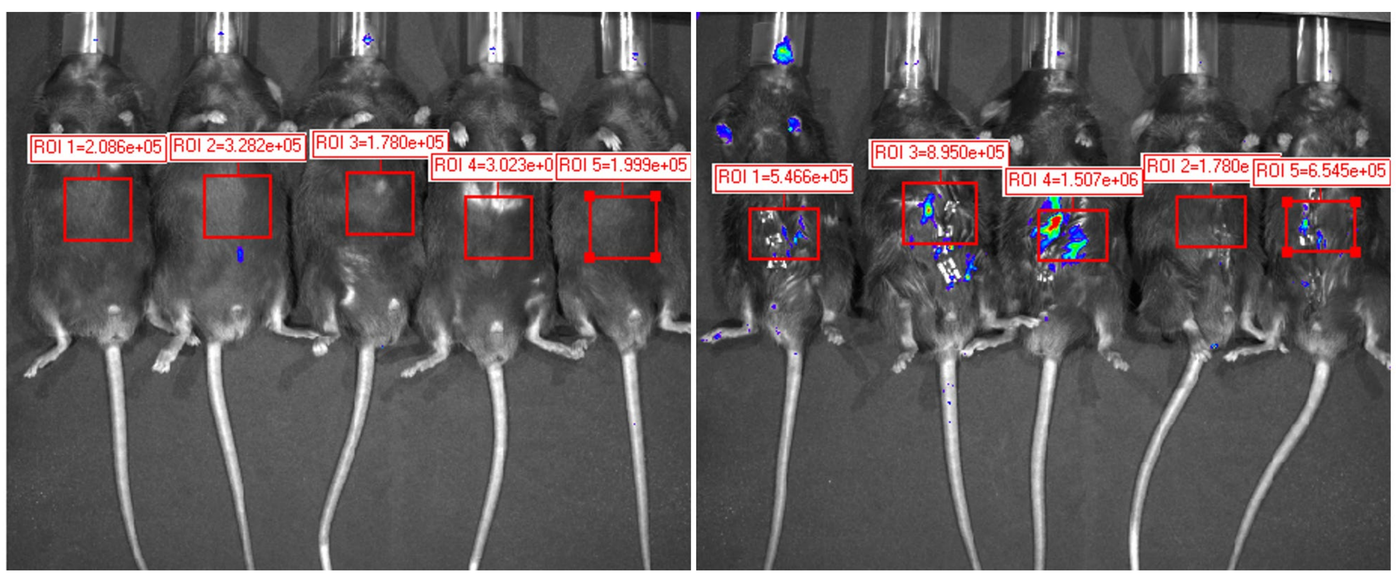

Figure 2: Radiant efficiency of fluorescently labeled TLR9A (SD-101-Alexa660) in systemic delivery vs PRVI measured at region of interest (ROI) of pancreatic tail tumor.

Figure 3. Tumor Weights

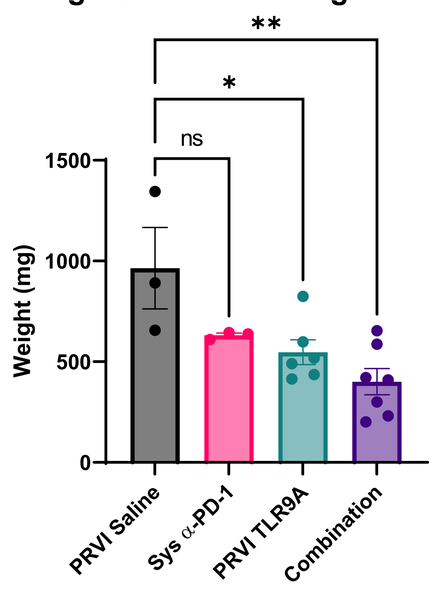

Figure 3: Tumor weights evaluated on day 10 post-treatment.

Summary

- Our group has previously shown feasibility of isolating the pancreatic venous drainage and pressurizing this system in order to target therapeutics to pancreatic cancer in a retrograde fashion, as referenced below.
- This study demonstrates an increased localized concentration of TLR9A in the area of the target murine PDAC lesion when delivered via PRVI to the pancreas compared with systemic delivery per our immunofluorescence data.
- The addition of anti-PD-1 to TLR9A shows improvement in murine PDAC tumor response rates as measured by gross tumor weight.
- This novel delivery modality may be key in overcoming the physical and immunological boundaries which make PDAC treatment resistant.
- Given prior efficacy of intratumoral injection of TLR9A and checkpoint inhibition therapies, comparing intratumoral injection with PRVI may be an area of interest.
- The promising results of checkpoint inhibition therapy and TLR9A in the treatment of PDAC should prompt continued study.

References: Shankara Narayanan JS, Vicente DA, Ray P, Chai LF, Erdem S, Carr MJ, Capacio BA, Cox BF, Jaroch DB, Katz SC, White RR. Pressure-enabled delivery of gemcitabine in an orthotopic pancreatic cancer mouse model. Surgery. 2020 Sep;168(3):448-456. doi: 10.1016/j.surg.2020.04.059. Epub 2020 Jun 30. PMID: 32620306.

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