Enhanced Delivery of a TLR9 Type C Agonist SD-101 to Liver Tumors in the Oncopig using Pressure Enabled Drug Delivery (PEDD) Versus a Standard Endhole Catheter

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Purpose:

Purpose: SD-101 is a synthetic oligonucleotide class C TLR9 agonist which activates the innate and adaptive immune responses needed for cancer immunotherapy. This includes promotion of anti-tumor CD8+ T cell function (Kawarada et al. 2001) and elimination of myeloid derived suppressor cell populations (Ghosh 2022). Liver tumors are often resistant to therapy due to high interstitial fluid pressure and solid stresses that restrict perfusion and therapeutic uptake (Sheth et al. 2013). Pressure enabled drug delivery (PEDD) may enable enhanced therapeutic concentrations in liver tumors. PEDD has been shown to reduce normal tissue exposure to therapeutic agents while increasing intra-tumoral concentrations (Titano et al. 2019). This study was designed to test the hypothesis that PEDD using a TriNav device would result in superior intra-arterial delivery of fluorescently labeled SD-101 to pig liver tumors when compared to a conventional catheter.

Materials:

The study was conducted in transgenic pigs (oncopigs) 40-70kg in weight. Oncogene expression was induced in liver tissue ex vivo and injected back into the liver at 4 locations to induce tumor formation. An artery supplying the liver lobe with the induced tumor was infused with a fixed dosage of fluorescently labeled SD-101 + 4 mg unlabeled SD-101 in 10ml of saline via PEDD with TriNav or an endhole catheter. Liver tissue was collected for analysis 1 hour post-infusion. Quantification of SD-101 was performed by nearIR fluorescence imaging on 1 cm thick liver sections. NearIR images were overlaid on color images, tumor border delineated, and the mean fluorescent SD-101 signal calculated in concentric rings from the tumor border.

Results:

Statistically significant increases in SD-101 signal intensity were observed at 1mm into tumor and at 1, 3, 5 and 7mm away from the outer edge of tumor with the TriNav device when compared to the endhole device ($p \leq 0.05$). The sum of the mean signal intensities from 5mm into the tumor to 5mm away from the outer edge of tumor were also significantly greater in the TriNav dosed group when compared to the endhole dosed group ($p \leq 0.05$). To further assess delivery of SD-101 to tumor tissue vs normal liver tissue, the data was normalized to the mean fluorescent signal in normal tissue that was greater than 30mm away from the edge of tumor. When the mean intensity of SD-101 signal was normalized to remote normal tissue signal, PEDD resulted in statistically significant increases in SD-101 delivery from 15mm into tumor to 20mm away and at 30mm away from the outer edge of the tumor ($p \leq 0.05$). The sum of mean SD-101 signal intensity from 20mm into tumor to 30mm away from tumor with PEDD was also significantly increased when compared to endhole delivery ($p \leq 0.01$).

Conclusions:

This study demonstrates that intra-arterial delivery of SD-101 to liver tumors in the oncopig via PEDD is superior to an endhole catheter. Importantly, TriNav concentrated delivery near the rapidly growing margin of the tumors while maintaining delivery to more distal regions of the tumors as well. These data support study of SD-101 delivered via PEDD in two ongoing clinical trials for metastatic and primary liver tumors (NCT04935229 and NCT05220722).

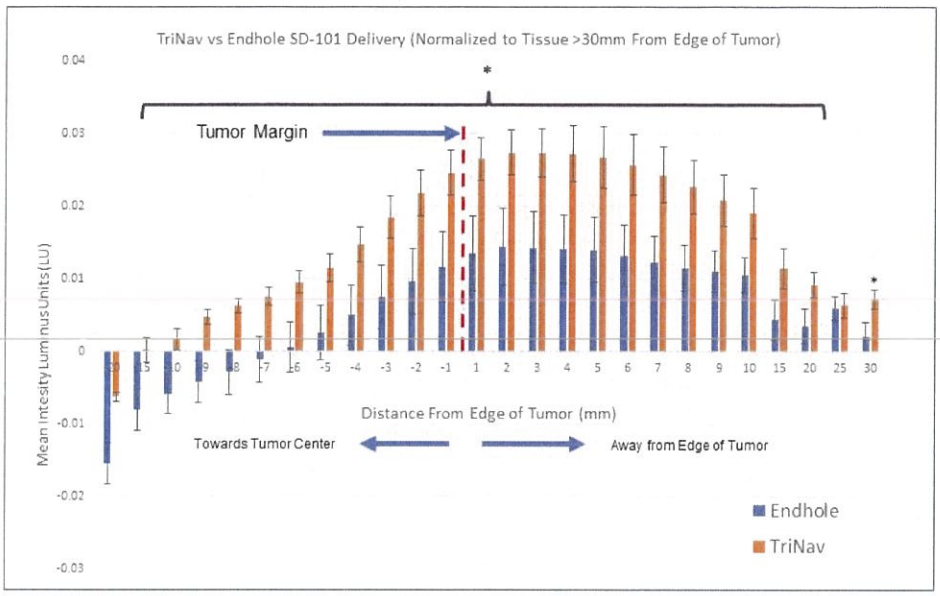
Category:

Industry*

File

Figure 1

A



B

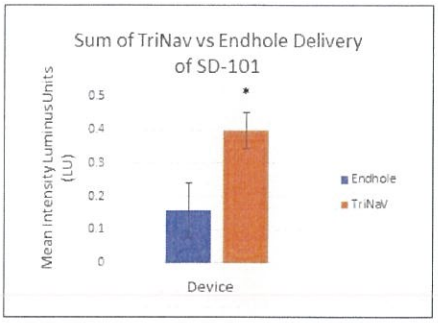


Figure 1: A) Shown are SD-101 fluorescence intensity means and standard errors for TriNav (N=9) and Endhole (N=9) intra arterial delivery of SD-101 when normalized to normal remote tissue signal. 1 tailed t-test . * = $p \leq 0.05$. B) Shown are the sum of means and standard errors for SD-101 fluorescence intensity from 30mm outside to 20mm inside of tumor for TriNav (N=9) and Endhole (N=9) intra arterial delivery of SD-101. 1 tailed t-test . * = $p \leq 0.01$

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