# PERIO-01: Enabling tumor microenvironment reprogramming by a TLR9 agonist using Pressure-Enabled Drug Delivery™ (PEDD™) to address intrahepatic immunosuppression and drug delivery barriers

Sapna P. Patel[1], Steven C. Katz[2,3,4], Rahul A. Sheth[1], Ravi Murthy[1], Virginia Honaker[1], Chantell M. Farinas[1], Mara L. Casteneda[1], Laura Timciuc[1], Tarin Hennegan[1], Cara Haymaker[1], Victor G. Prieto[1], Bryan Cox[2], Ann-Marie Hulstine[2], Jason LaPorte[2], Ashley Moody[2], Marlana Orloff[5], Richard D. Carvajal[6]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]TriSalus Life Sciences, Westminster, CO, [3]Department of Surgery, Brown University, Providence, RI, [4]Lifespan Health System, Providence, RI, [5]Thomas Jefferson University, Philadelphia, PA, [6]Columbia University Medical Center, New York, NY

Contact: SPPatel@mdanderson.org

Abstract #158628

## Background

- Liver tumors are resistant to immune infiltration in part due to a highly tolerogenic tumor microenvironment (TME) that includes the presence of myeloid-derived suppressor cells (MDSCs).
- This results in low responses to checkpoint inhibitors in patients with liver metastasis (LM).
- Toll-like receptor agonists have been studied in combination with checkpoint inhibitors, with little success in patients with liver tumors when delivered by needle injection.
- Overcoming the pressure gradient as well as immunosuppression are keys to successful immune responses in the liver.

## Methods

- PERIO-01 is an open-label first-in human Phase 1 trial of the TLR9 agonists SD-101 given by hepatic arterial infusion (HAI) using Pressure-Enabled Drug Delivery™ (PEDD™) in metastatic uveal melanoma (MUM) (NCT04935229).
- SD-101 is delivered over 2 cycles, with 3 weekly doses per cycle.
- Plasma was analyzed for SD-101 levels by LC-MS and cytokine levels by Luminex.
- NanoString was used to analyze gene expression levels within PBMCs, LM, and normal liver tissue and nSolver advanced analysis was performed to score for cell types and pathways.

## Results

**Figure 1. PEDD™ of SD-101 via HAI increases plasma levels of IFNγ and TNFα for LM-bearing MUM patients**

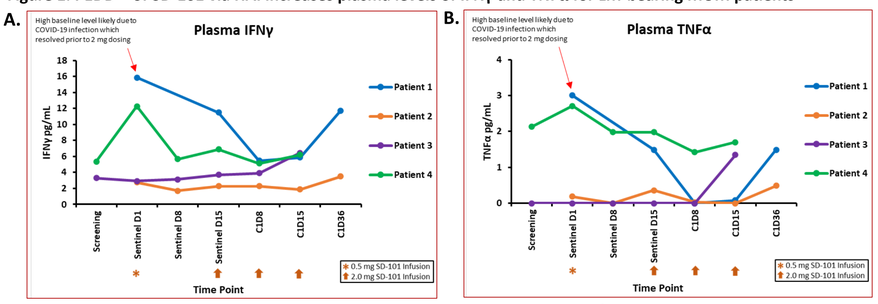


**Figure 1**. Plasma was collected at the indicated time points, either between infusion days or pre-infusion. Plasma cytokines were analyzed for **A.** IFNγ and **B.** TNFα using Luminex.

## Summary

- Plasma levels of IFNγ and TNFα trended up following SD-101 cycle 1, with only transient serum drug levels (<137 ng/mL, <4 hours).
- NanoString analysis of gene expression levels in LM one month following SD-101 cycle 1 revealed increases in ISG15, IL-9, IFNα, and IL-2 transcripts, with increased scores for macrophages, exhausted CD8 T cells, Th1 cells, and Th1 activation.
- Within normal liver tissue, there was a decrease in scores for exhausted CD8 T cells, Th1 cells, and total T cells.
- Gene expression analysis of PBMCs revealed instances of increased scores for NK , B , and Th1 cells despite low serum drug levels.
- Expression of genes associates with MDSC, including ARG1, IDO1, CSF2 (GM-CSF), and NOS2 decreased within LM.

## Conclusions

SD-101 HAI via PEDD™ has been well tolerated at the 2 mg dose level with demonstration of SD-101 activity within the LM TME in MUM patients. Reciprocal changes in genes in normal liver suggests migration of immune cells into LM . The TME reprogramming demonstrated thus far, including reduction in MDSC-associated genes, may support better immune checkpoint inhibitor performance in MUM and other intrahepatic indications presently under study.

**Figure 2. Plasma levels of SD-101 are transient and remain low following PEDD™**

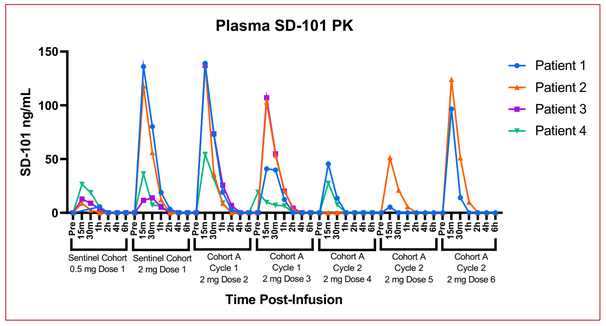


**Figure 2**. Plasma was collected on infusion days at the indicated time points and analyzed for SD-101 levels by LC-MS.

**Figure 3. SD-101 treatment produces a favorable shift in gene expression patterns**

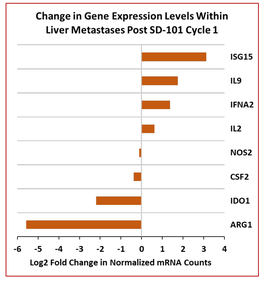


**Figure 3**. NanoString analysis of LM at baseline and post-cycle 1.

**Figure 4. PEDD™ of SD-101 via HAI creates a shift in the immune microenvironment in both LM and normal liver tissue**

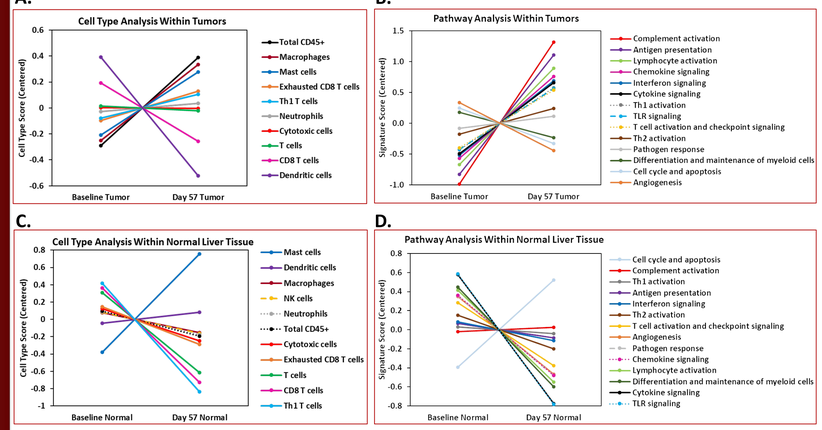


**Figure 4**. Cell type and pathway scoring determined by advanced analysis of NanoString gene expression data of LM and normal liver tissue at baseline and following SD-101 cycle 1 (Day 57). Scores were generated for cell types within tumors (**A.**) and normal liver tissue (**C.**), and pathways within tumors (**B.**) and normal liver tissue (**D.**).

**Figure 5. PEDD™ of SD-101 via HAI leads to increases in circulating NK cells, CD56dim NK cells, B cells, and Th1 T cells in some subjects.**

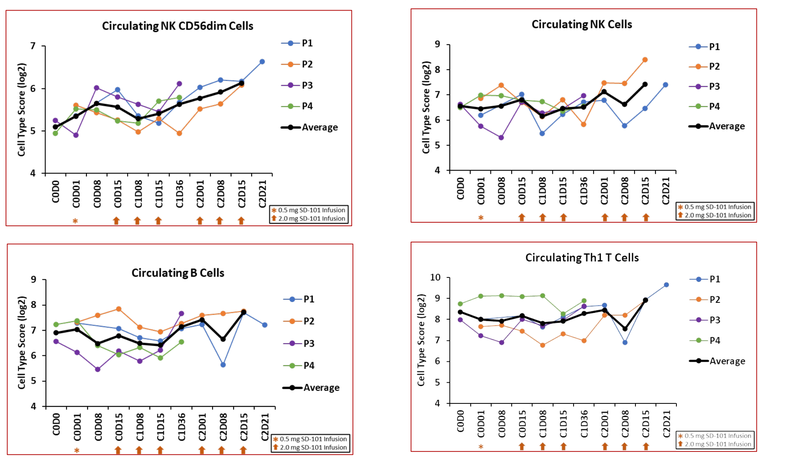


**Figure 5**. Cell type scoring determined by advanced analysis of NanoString gene expression data of PBMCs collected at the indicated time points. Scores were generated for NK CD56dim cells (**A.**), NK cells (**B.**), B cells (**C.**), and Th1 T cells (**D.**).

View the Clinicaltrials.gov site for the PERIO-01 trial:

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