Development of Thrombospondin-1 as a clinical pharmacodynamic biomarker for VT1021, a first-in-class therapeutic agent that reprograms the tumor microenvironment

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The authors have no conflicts of interest to disclose

Background

VT1021 is a first-in-class therapeutic agent tested in a Phase I clinical study in solid tumors (NCT03364400). *In vivo* preclinical studies demonstrated that VT1021 inhibited tumor growth via stimulation of p53 and Thrombospondin-1 (TSP-1) in myeloid derived suppressor cells (MDSCs) (Kang et al, 2009; Catena et al. 2013; Wang et al. 2016). Moreover, induction of TSP-1 reprogrammed the tumor microenvironment and induced apoptosis in tumor cells via its cell surface receptors CD36 and CD47 (Kaur et al. 2010; Zhang et al. 2009). Here, the utility of TSP-1 as a pharmacodynamic biomarker for VT1021 and its correlation with clinical response is reported.

MOA: VT1021 induces Thrombospondin-1, a tumor suppressor protein

VT1021: Binds to MDSCs and Induces TSP-1 Expression

VT1021: a 5-amino acid cyclic peptide

What is known about Prosaposin (Psap)

- Precursor of Saposin A,B,C, and D
- Functions as lipid hydrolase activators
- Full-length Psap can be shunted into ER and secreted

What we discovered

- Binds to receptor on **myeloid-derived suppressor cells (MDSCs),** which are found to be accumulated in the TME
- Induces signal transduction cascade to increase production of Thrombospondin-1 (TSP-1) in the TME

Kang et al. PNAS 2009; 106 (29); pp 12115-20
Catena et al. Cancer Discov. 2013; 5 (578-589)
Wang et al. Science Trans Med 2016; 8 (329-334)

TSP-1: A Multi-faceted Tumor Suppressor Protein*

By binding to CD36, CD47 and other cell surface molecules, TSP-1:

- Induces apoptosis in tumor & endothelial cells
- Regulates cell adhesion, migration, invasion, and proliferation
- Modulates immune and inflammatory responses

*TRENDS in Molecular Medicine

Contact

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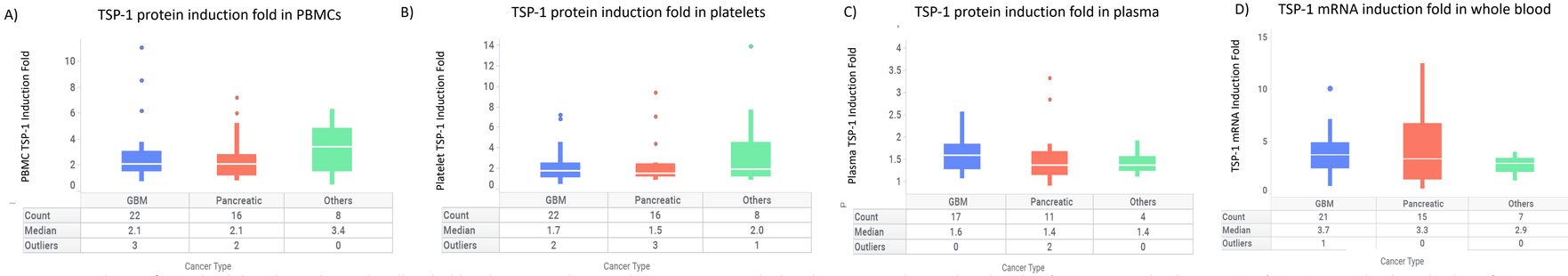
TSP-1 induction as a potential pharmacodynamic biomarker for VT1021 in various tumor types



	GBM	Pancreatic	Others
Count	22	16	8
Median	2.1	2.1	3.4
Outliers	3	2	0

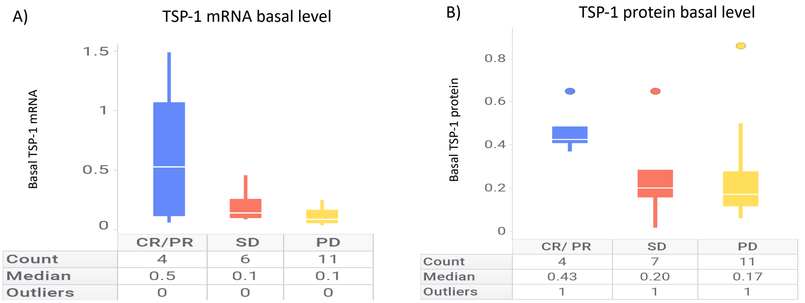
	GBM	Pancreatic	Others
Count	22	16	8
Median	1.7	1.5	2.0
Outliers	2	3	1

	GBM	Pancreatic	Others
Count	17	11	4
Median	1.6	1.4	1.4
Outliers	0	2	0

	GBM	Pancreatic	Others
Count	21	15	7
Median	3.7	3.3	2.9
Outliers	1	0	0

Figure 1. Up-regulation of TSP-1 levels have been observed in all evaluable subjects post-dosing with VT1021 across multiple indications in a phase 1 clinical study. A) TSP-1 protein levels in PBMCs. B) TSP-1 protein levels in platelets. C) TSP-1 protein levels in plasma samples. D)) TSP-1 mRNA levels from whole blood. Count refers to the number of subjects available for the analysis. Fewer plasma samples were analyzed due to sample deviation. Median refers to median TSP-1 induction fold. GBM: Glioblastoma cohort. Pancreatic: Pancreatic cancer cohort. Others include cancer types other than GBM and pancreatic cancer.

Glioblastoma: Basal TSP-1 level as a potential predictive biomarker

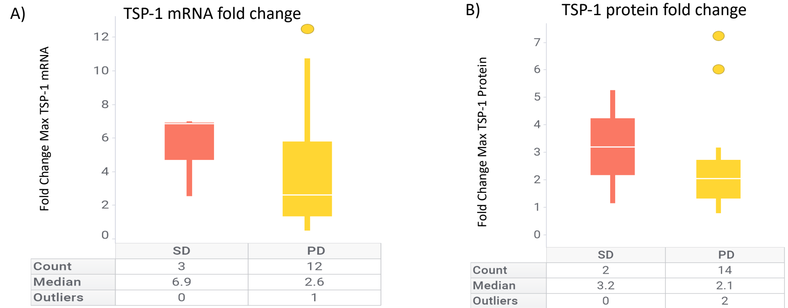


	CR/PR	SD	PD
Count	4	6	11
Median	0.5	0.1	0.1
Outliers	0	0	0

	CR/ PR	SD	PD
Count	4	7	11
Median	0.43	0.20	0.17
Outliers	1	1	1

Figure 2. Higher basal TSP-1 in PBMCs has been observed in CR/PR subjects compared to SD or PD subjects. A) Basal TSP-1 mRNA levels in GBM subjects. B) Basal TSP-1 protein levels in GBM subjects. CR: complete response. PR: partial response. SD: stable disease. PD: progressive disease.

Pancreatic cancer: TSP-1 induction as a potential prognostic biomarker

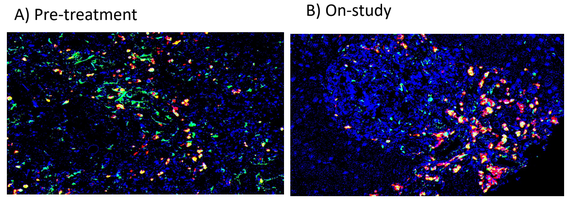


	SD	PD
Count	3	12
Median	6.9	2.6
Outliers	0	1

	SD	PD
Count	2	14
Median	3.2	2.1
Outliers	0	2

Figure 3. Higher TSP-1 induction fold in PBMCs has been observed in SD subjects compared to PD subjects. A) Induction fold of TSP-1 mRNA in pancreatic cancer subjects post-VT1021. B) Induction fold of TSP-1 protein in pancreatic cancer subjects post-VT1021. SD: stable disease. PD: progressive disease.

TSP-1 expression in the TME



See poster 369 for more results

Figure 4. Increased colocalization of TSP-1 and CD11b (MDSCs) was observed in the tumor microenvironment in tumor biopsy samples from a subject with pancreatic cancer post-dosing with VT1021. A) Pre-treatment biopsy sample. B) On-study biopsy sample. Pseudo-color images from liver metastasis samples shown with Hematoxylin (bule), TSP-1 (green) and CD11b (pink) and colocalization of TSP-1 and CD11b (yellow).

Conclusions

- Based on both protein and mRNA levels, TSP-1 induction has the potential to be a useful pharmacodynamic biomarker for VT1021 in various tumor types.
- For subjects with GBM, basal TSP-1 levels in PBMCs is a potential predictive biomarker.
- For subjects with pancreatic cancer, TSP-1 induction in PBMCs is a potential prognostic biomarker.
- In tumor biopsy samples from subjects with pancreatic cancer, increased colocalization of TSP-1 and CD11b was observed in on-study samples, supporting a role of TSP-1 in reprogramming the tumor microenvironment.
- The predictive/prognostic utility coupled with the ability to measure levels in peripheral blood makes TSP-1 a powerful biomarker to assess and predict clinical response to VT1021.

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Clinical trial information: NCT03364400