TNG908 is an MTAP\textsuperscript{null}-selective PRMT5 inhibitor that drives tumor regression in MTAP-deleted xenograft models across histologies

Kimberly J Briggs*, Kevin M Cottrell*, Matthew R Tonini, Erik W Wilker, Lina Gu, Charles B Davis, Doug Whittington, Deepali Gotur, Haris Jahic, Matthew J Goldstein, Alan Huang, and John P Maxwell

Tango Therapeutics
100 Binney Street, Suite 700
Cambridge, MA 02142
+1-857-320-4900
info@tangotx.com
PRMT5 is a selective dependency in MTAP<sup>null</sup> cells

Figure 1. MTAP-deletion is a common genetic event in human cancer. (A) Schematic of chromosome 9p21-22 demonstrating close proximity of MTAP to CDKN2A, which encodes the tumor suppressor p16. MTAP is co-deleted with CDKN2A in ~10-15% of all human cancer. (B) MTAP deletion frequency in a subset of human cancers (Cerami et al 2012; Gao et al 2013; Lee et al 2014).

Figure 2. PRMT5 is a selective dependency in MTAP<sup>null</sup> cells. (A) Project DRIVE (Novartis) RNAi data identifying PRMT5 as a selective dependency in MTAP<sup>null</sup> cancer cell lines. (B) Biological rationale for sensitivity of MTAP<sup>null</sup> cells to PRMT5 perturbation. (C) Schematic demonstrating differentiating strategy of Tango MTA-cooperative PRMT5 inhibitors.
MTA-cooperative PRMT5 inhibitors are MTAP<sup>null</sup>-selective

Figure 4. TNG PRMT5 inhibitors are MTAP<sup>null</sup>-selective and differentiated from existing clinical PRMT5 inhibitors. (A and B) Antiproliferative activity of TNG-0240105 (A) and existing clinical PRMT5 inhibitors (B) in the HAP1 MTAP<sup>null</sup>-isogenic cell line pair (Horizon Discovery) in a 7-day CellTiter-Glo assay. The data are presented as mean ± SD. (C and D) Pharmacodynamic activity of TNG-0240105 (C) and existing clinical PRMT5 inhibitors (D) in the HAP1 MTAP<sup>null</sup>-isogenic cell line pair. The data are normalized to a DMSO control for each cell line, and presented as mean ± SD.
TNG908 is MTAPnull-selective across cancer histologies

Figure 5. TNG908 is 15x MTAPnull-selective. Antiproliferative activity of TNG908 in MTAP-isogenic cell lines representing multiple lineages. Data are represented as mean ± SD.

Figure 6. TNG908 drives dose-dependent, MTAPnull-selective antitumor activity in vivo. (A and B) Antitumor activity in HCT116 MTAP-isogenic xenograft models with TNG908 dosed as indicated. n=8 mice per group. Data are represented as mean ± SEM. (C) Terminal pharmacodynamic analysis of HCT116 MTAP-isogenic xenograft models dosed with TNG908 from panels (A and B). A single SDMA-modified substrate was quantified and normalized to a loading control from tumors processed 8 hrs post-last dose. n=4 tumors per group. Data are represented as mean ± SEM.

Figure 7. TNG908 is highly selective for MTAPnull cells in a multi-lineage cell line panel. 199 cancer cell lines representing multiple cancer lineages including NSCLC, PDAC, bladder, CNS and heme malignancies were profiled with either TNG908 (A) or GSK3326595 (B) in a 7-day CellTiter-Glo assay. The maximum effect at 1 µM for each cell line is reported for each compound, and the cell line are colored by MTAP status.
TNG908 drives dose-dependent antitumor activity and tumor regression in MTAP\textsuperscript{null} xenograft models

Figure 8. TNG908 treatment results in dose-dependent and on-target antitumor activity. (A) 21-day efficacy experiment using the LN18 MTAP\textsuperscript{null} xenograft model. TNG908 was dosed as indicated. The 60 mpk BID group was dosed at 90 mpk BID for the first 3 days. N=8 mice per group, data are presented as mean ± SEM. (B) 7-day PK/PD study using the LN18 MTAP\textsuperscript{null} xenograft model. TNG908 was dosed as indicated, and PK and tumor samples were harvested at the indicated timepoints. N=4 tumors per group, and data are presented as mean ± SEM.

Figure 9. TNG908 treatment drives tumor regression in MTAP\textsuperscript{null} xenograft models representing multiple cancer lineages. TNG908 was dosed as indicated in MTAP\textsuperscript{null} models representing the indicated cancer histologies. n=3 mice per group, and data are presented as mean ± SEM.
MTAP<sub>null</sub>-selective PRMT5 inhibitors are efficacious in heterogeneous cell populations

Figure 10. MTA is in flux across cellular membrane. (A and B) LC-MS/MS-based quantification of intracellular (A) and extracellular (B) MTA in HAP1 MTAP-isogenic cell line pair at the indicated timepoints. (C) Cartoon demonstrating MTA secretion by MTAP<sub>null</sub> cells. (D) Intracellular MTA levels in HAP1 MTAP<sub>null</sub> cells. MTAP<sub>null</sub> cells were treated with 10 µM d3-MTA. An approximate equilibrium is drawn for visualization. (E) Cartoon demonstrating bidirectional MTA flux. (F) Intracellular MTA levels in HAP1 MTAP WT cells. MTAP WT cells were treated with 10 µM d3-MTA. (G) Cartoon demonstrating MTA metabolism by MTAP WT cells.

Figure 11. MTAP<sub>null</sub>-selective PRMT5 inhibitors selectively target MTAP<sub>null</sub> cells in heterogeneous cell populations. (A) Experimental schematic. In brief, HAP1 MTAP WT cells with stable RFP expression were mixed at various ratios with HAP1 MTAP<sub>null</sub> cells that have stable GFP expression. The admixtures were cultured in the presence or absence of an MTAP<sub>null</sub>-selective PRMT5 inhibitor for 7 days and then the ratio of RFP to GFP was determined by flow cytometry. (B) Flow cytometry analysis of the results from experiment denoted in (A). n=2 replicates, and data are presented as mean ± SD.
MTAP<sup>null</sup>-selective PRMT5 inhibitors maintain selective viability effects in cells with minimal MTA elevation

**Conclusions**

- MTA-cooperative PRMT5 inhibitors are selective for MTAP<sup>null</sup> cells
- TNG908 demonstrates 15X selectivity for MTAP<sup>null</sup> cells in multiple MTAP-isogenic cell lines representing multiple cancer lineages
- TNG908 treatment drives MTAP<sup>null</sup>-selective antitumor activity in vivo, and tumor regression in xenograft models across histologies
- MTAP<sup>null</sup>-selective PRMT5 inhibitors target MTAP<sup>null</sup> cells even in heterogeneous cell populations
- MTAP<sup>null</sup>-selective PRMT5 inhibitors are MTAP<sup>null</sup>-selective and efficacious when intracellular MTA levels are 2-5x elevated relative to endogenous intracellular MTA levels in MTAP WT cells
- TNG908 is currently undergoing IND-enabling studies for clinical entry in 1H2022

**References**


Thank you!

Contact information

- Tango Therapeutics: info@tangotx.com