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

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PRMT5 is a selective dependency in MTAP^{null} cells

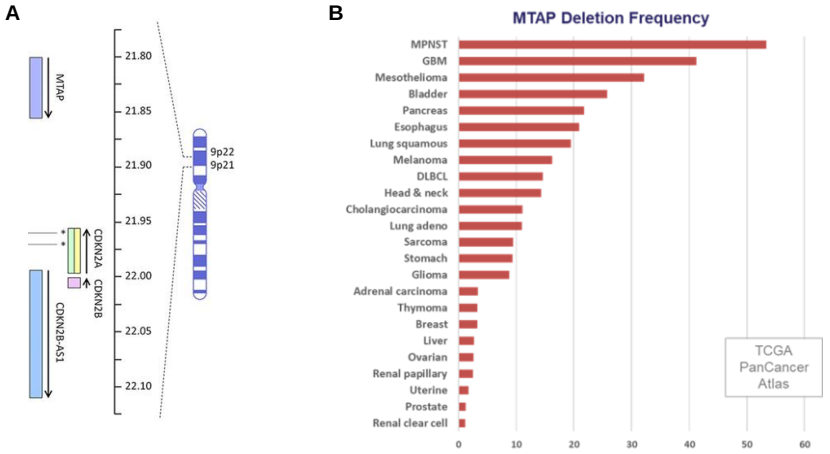


Figure 1. ***MTAP*-deletion is a common genetic event in human cancer.** (A) Schematic of chromosome 9p21-22 demonstrating close proximity of *MTAP* to *CDKN2A*, which encodes the tumor suppressor p16. *MTAP* is co-deleted with *CDKN2A* in ~10-15% of all human cancer. (B) *MTAP* deletion frequency in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

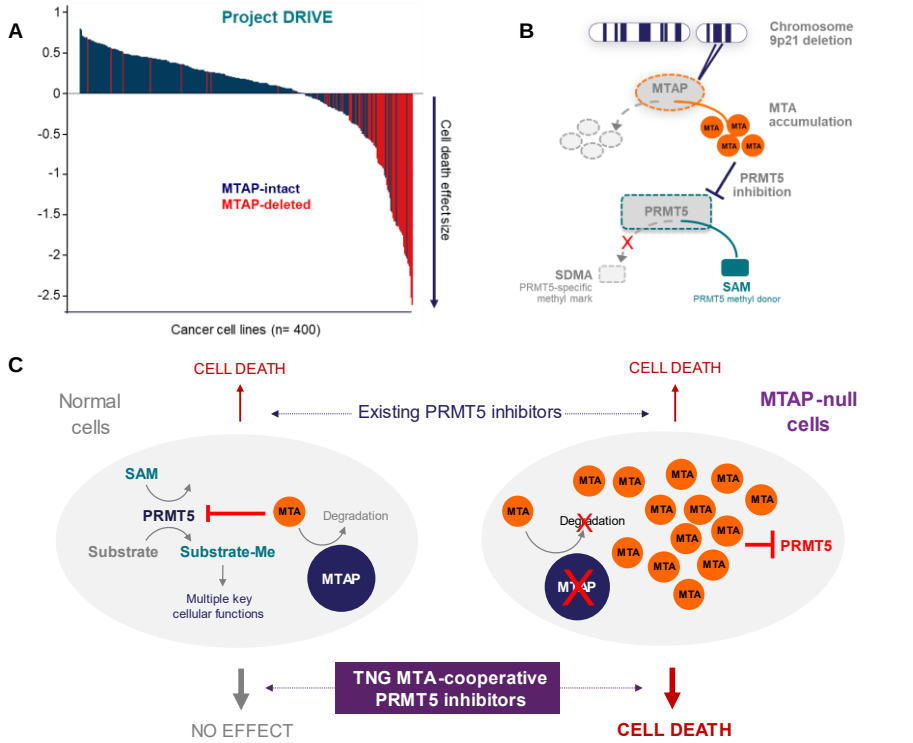


Figure 2. PRMT5 is a selective dependency in MTAP^{null} cells. (A) Project DRIVE (Novartis) RNAi data identifying PRMT5 as a selective dependency in MTAP^{null} cancer cell lines. (B) Biological rationale for sensitivity of MTAP^{null} cells to PRMT5 perturbation. (C) Schematic demonstrating differentiating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

MTA-cooperative PRMT5 inhibitors are MTAP^{null}-selective

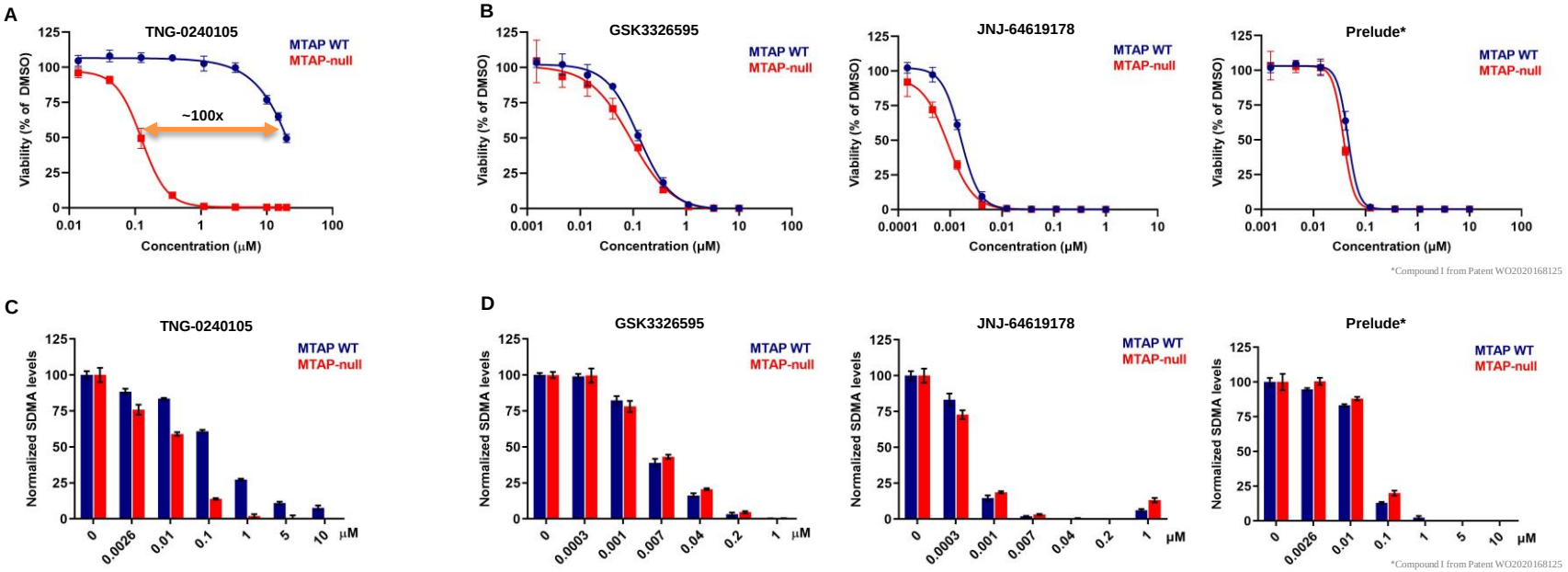
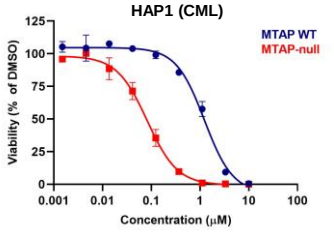
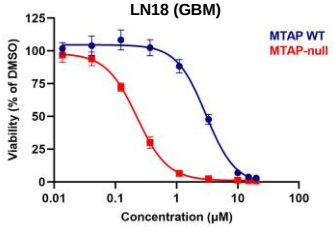


Figure 4. TNG PRMT5 inhibitors are MTAP^{null}-selective and differentiated from existing clinical PRMT5 inhibitors. (A and B) Antiproliferative activity of TNG-0240105 (A) and existing clinical PRMT5 inhibitors (B) in the HAP1 MTAP-isogenic cell line pair (Horizon Discovery) in a 7-day CellTiter-Glo 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-isogenic cell line pair. The data are normalized to a DMSO control for each cell line, and presented as mean± SD.

TNG908 is MTAP^{null}-selective across cancer histologies





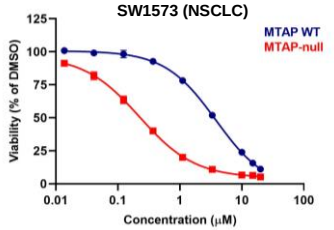


Figure 5. TNG908 is 15x MTAP^{null}-selective. Antiproliferative activity of TNG908 in MTAP-isogenic cell lines representing multiple lineages. Data are represented as mean ± SD.

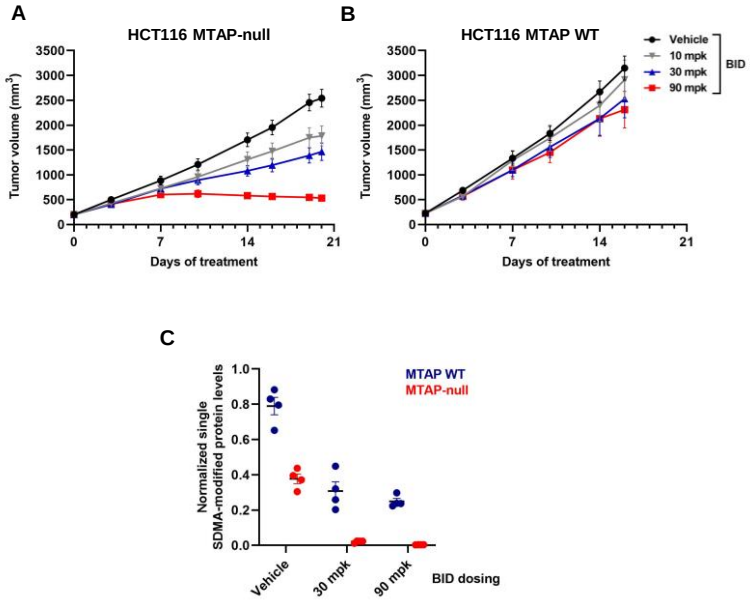


Figure 6. TNG908 drives dose-dependent, MTAP^{null}-selective antitumor activity in vivo. (A and B) Antitumor activity in HCT116 MTAP-isogenic xenograft models with TNG908 dosed as indicated. n=8 mice per group. Data are represented as mean ± SEM. (C) Terminal pharmacodynamic analysis of HCT116 MTAP-isogenic 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.

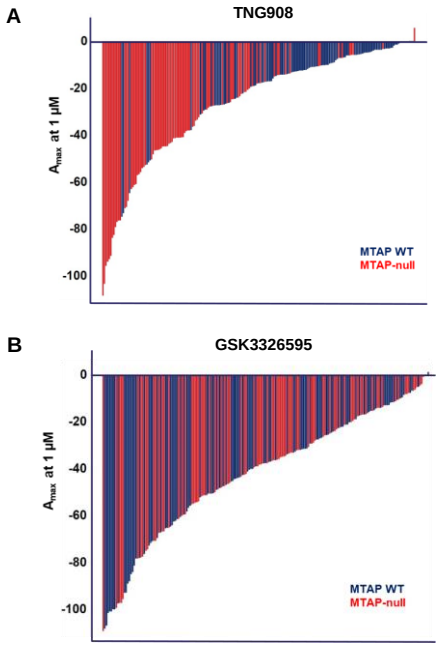


Figure 7. TNG908 is highly selective for MTAP^{null} cells in a multi-lineage cell line panel. 199 cancer cell lines representing multiple cancer lineages including NSCLC, PDAC, bladder, CNS and heme malignancies were profiled with either TNG908 (A) or GSK3326595 (B) in a 7-day CellTiter-Glo assay. The 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^{null} xenograft models

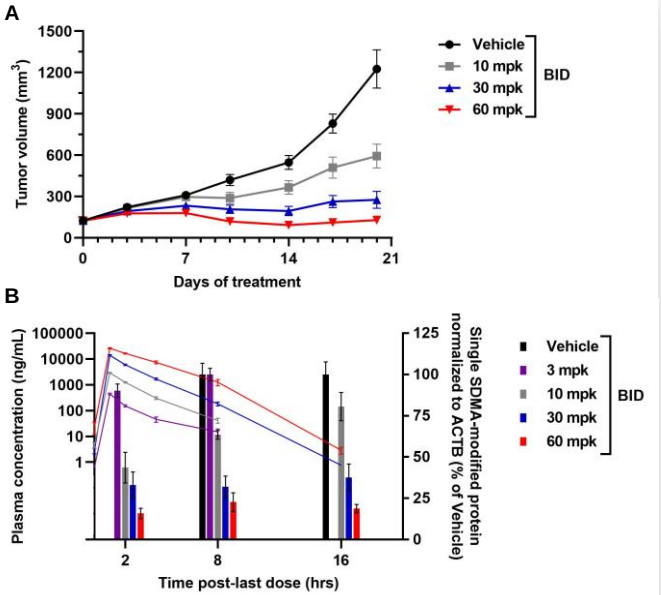


Figure 8. TNG908 treatment results in dose-dependent and on-target antitumor activity. (A) 21-day efficacy experiment using the LN18 MTAP^{null} xenograft model. TNG908 was dosed as indicated. The 60 mpk BID group was dosed at 90 mpk BID for the first 3 days. N=8 mice per group, data are presented as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

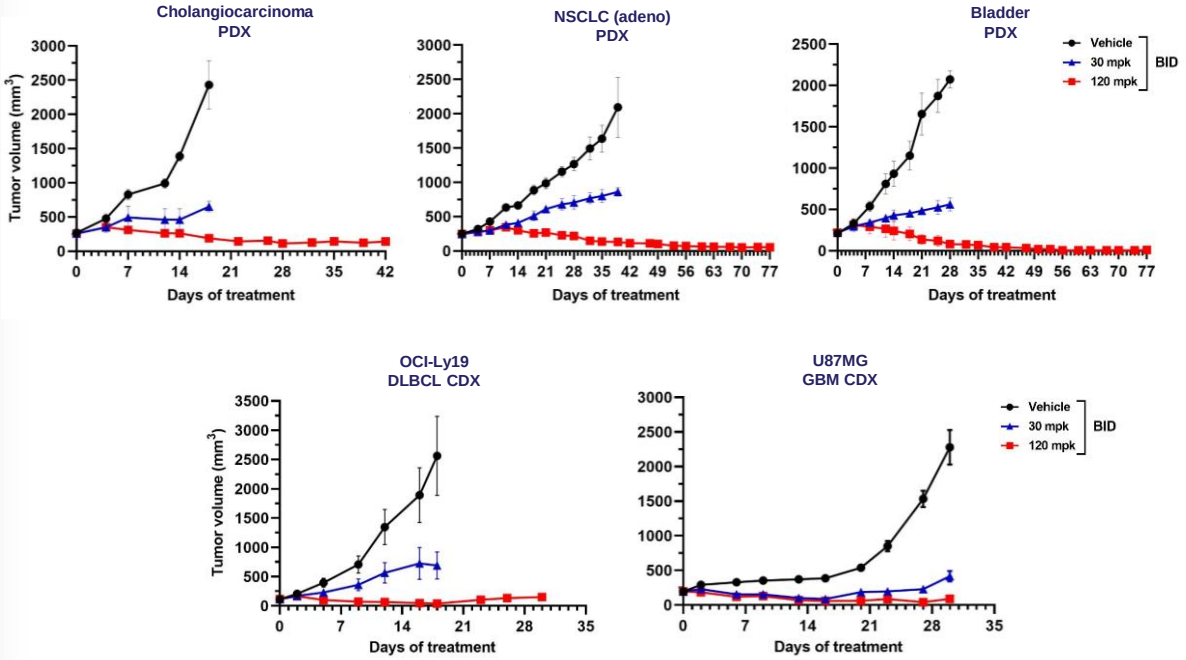


Figure 9. TNG908 treatment drives tumor regression in MTAP^{null} xenograft models representing multiple cancer lineages. TNG908 was dosed as indicated in MTAP^{null} models representing the indicated cancer histologies. n=3 mice per group, and data are presented as mean ± SEM.

MTAP^{null}-selective PRMT5 inhibitors are efficacious in heterogeneous cell populations

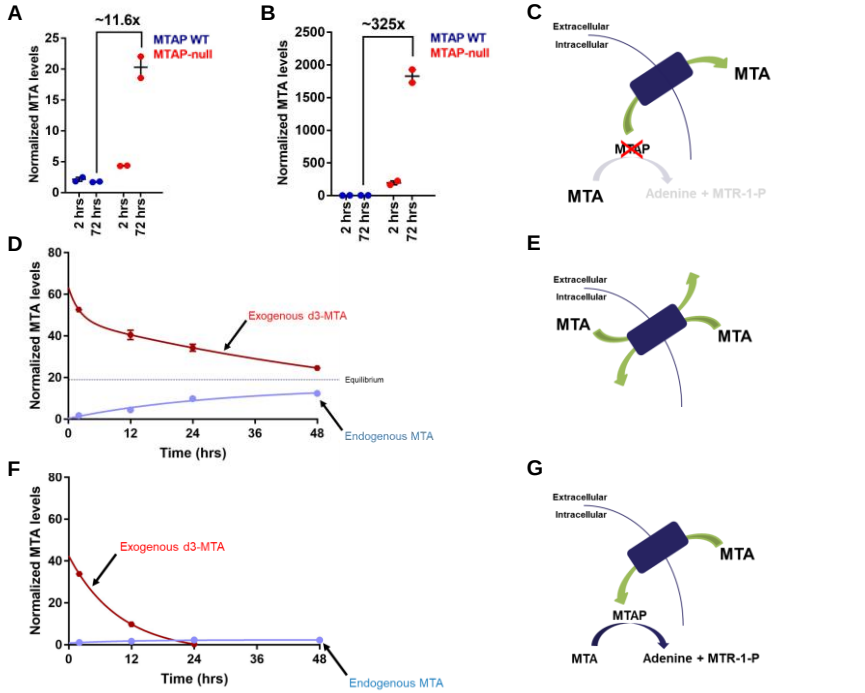


Figure 10. MTA is in flux across cellular membrane. (A and B) LC-MS/MS-based quantification of intracellular (A) and extracellular (B) MTA in HAP1 MTAP-isogenic cell line pair at the indicated timepoints. (C) Cartoon demonstrating MTA secretion by MTAP^{null} cells. (D) Intracellular MTA levels in HAP1 MTAP^{null} cells. MTAP^{null} 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.

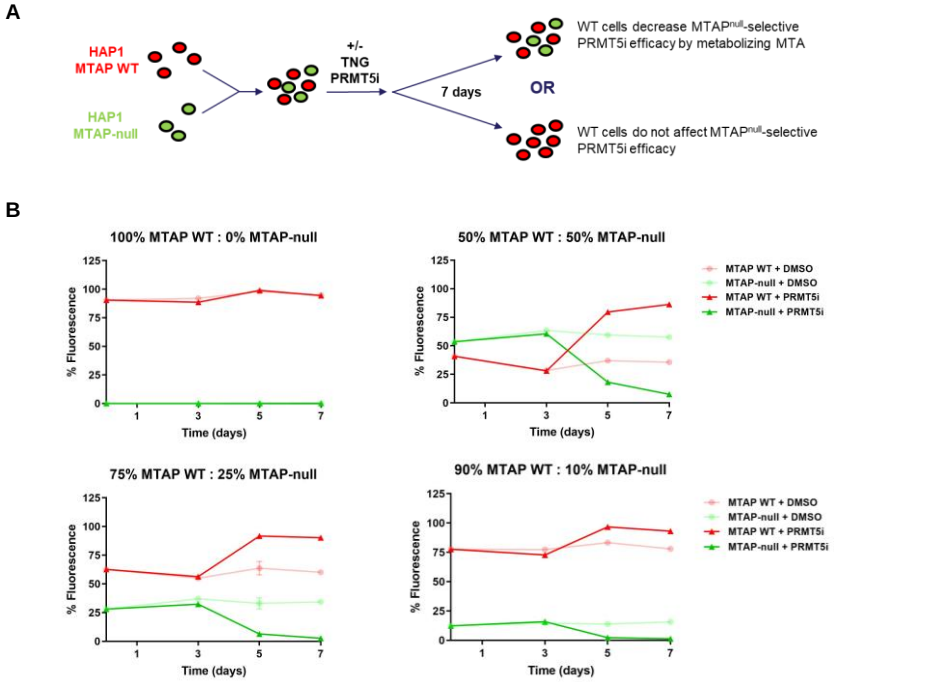


Figure 11. MTAP^{null}-selective PRMT5 inhibitors selectively target MTAP^{null} cells in heterogeneous cell populations. (A) Experimental schematic. In brief, HAP1 MTAP WT cells with stable RFP expression were mixed at various ratios with HAP1 MTAP^{null} cells that have stable GFP expression. The admixtures were cultured in the presence or absence of an MTAPnull-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^{null}-selective PRMT5 inhibitors maintain selective viability effects in cells with minimal MTA elevation

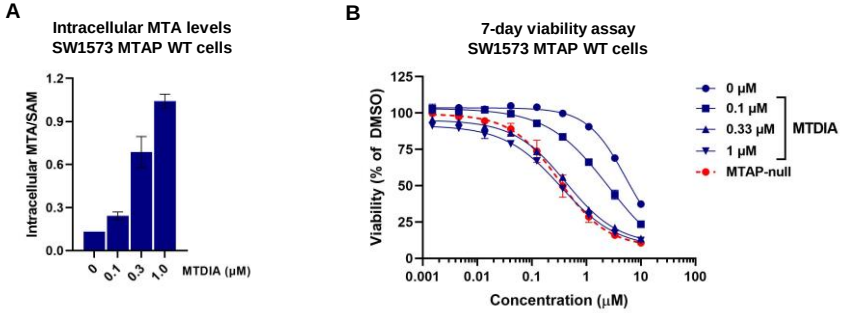


Figure 12. MTAP^{null}-selective PRMT5 inhibitors are efficacious and selective in cells with reduced MTA levels. (A) LC-MS/MS-based quantification of intracellular MTA in SW1573 MTAP WT cell line when treated for 48 hrs with the indicated concentration of MTDIA, an MTAP inhibitor. (B) 7-day CellTiter-Glo viability assay demonstrating that MTAP^{null}-selectivity and efficacy are maintained when MTA levels are increased ~2x, and maximal when MTA levels are increased 5x relative to untreated MTAP WT cell line.

Conclusions

- **MTA-cooperative PRMT5 inhibitors are selective for MTAP^{null} cells**
- **TNG908 demonstrates 15X selectivity for MTAP^{null} cells in multiple MTAP-isogenic cell lines representing multiple cancer lineages**
- **TNG908 treatment drives MTAP^{null}-selective antitumor activity *in vivo*, and tumor regression in xenograft models across histologies**
- **MTAP^{null}-selective PRMT5 inhibitors target MTAP^{null} cells even in heterogeneous cell populations**
- **MTAP^{null}-selective PRMT5 inhibitors are MTAP^{null}-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**

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Thank you!

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