TNG456 is a next-generation, brain-penetrant, MTA-cooperative PRMT5 inhibitor for the treatment of solid tumors with MTAP loss

Poster #462

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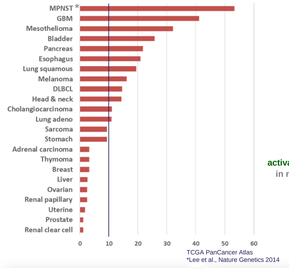
Abstract

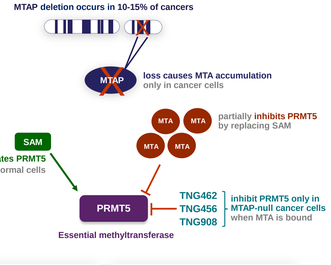
MTAP deletions occur in 10-15% of all human cancers, providing one of the largest precision oncology patient populations. MTA-cooperative PRMT5 inhibitors leverage the well-characterized synthetic lethal relationship between PRMT5 inhibition and MTAP deletion. TNG908, TNG462, AMG 193, BMS-986504, and AZD3470 are clinical-stage MTA-cooperative PRMT5 inhibitors for the treatment of solid tumors with MTAP loss, though only TNG908 and AMG 193 are reported to be brain-penetrant. TNG456 is a next-generation, highly potent and selective MTA-cooperative PRMT5 inhibitor designed for patients with MTAP-null cancers including gliomas and other tumors which frequently metastasize to the brain, such as NSCLC. In vitro, TNG456 is 55X selective for MTAP-null cancer cell lines over isogenic MTAP WT cell lines (compared to 15X for TNG908) and has marked selectivity for MTAP-null cancer cell lines independent of lineage in a large, diverse cell line panel. TNG456 is brain-penetrant in preclinical species with a Kpuu range of 0.5-1.1 in non-human primates and dogs. Oral administration of TNG456 drives dose-dependent antitumor activity including durable tumor regressions and complete responses in multiple cell line- and patient-derived xenograft models. With enhanced potency and selectivity for MTAP-null cancer cells, and strong preclinical evidence of brain-penetrance, TNG456 has the potential for broad clinical activity in MTAP-null solid tumors including gliomas and CNS metastases.

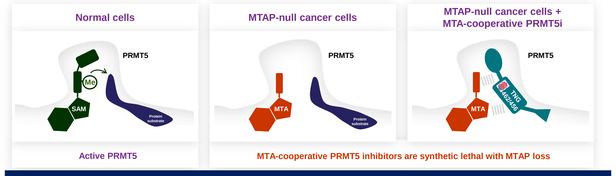
MTA-cooperative PRMT5 inhibitors are synthetic lethal with *MTAP* deletion

Homozygous MTAP deletion frequency

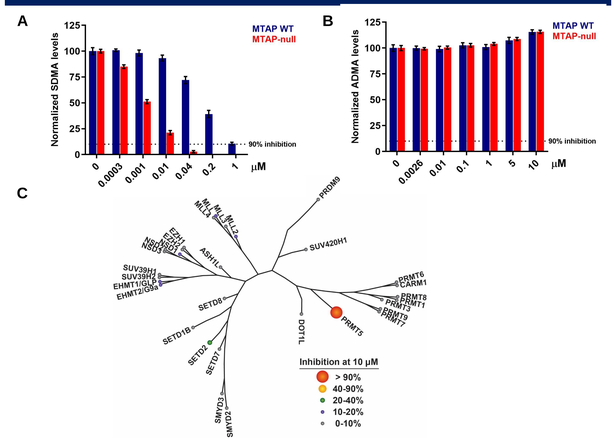


Biological rationale for synthetic lethality

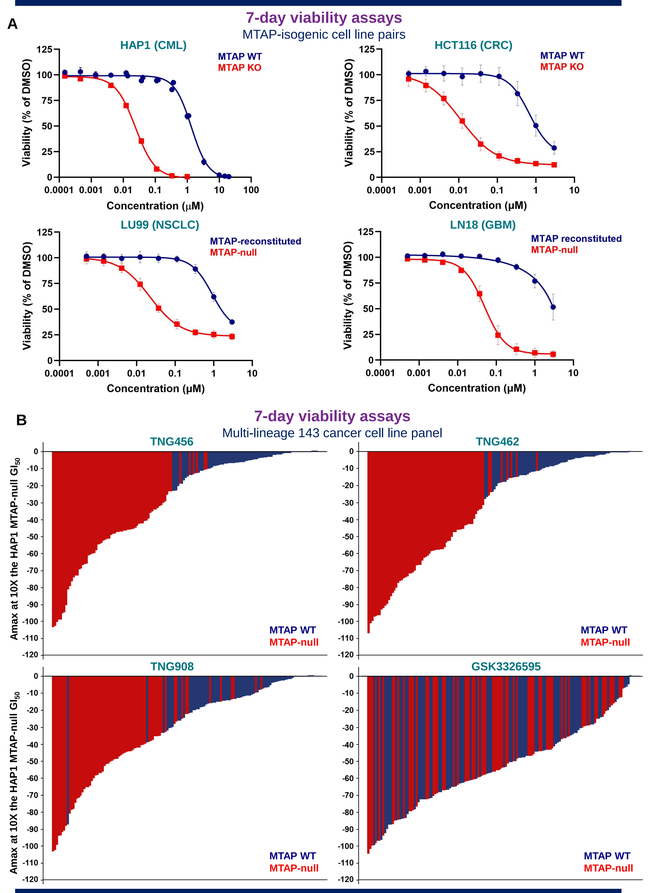




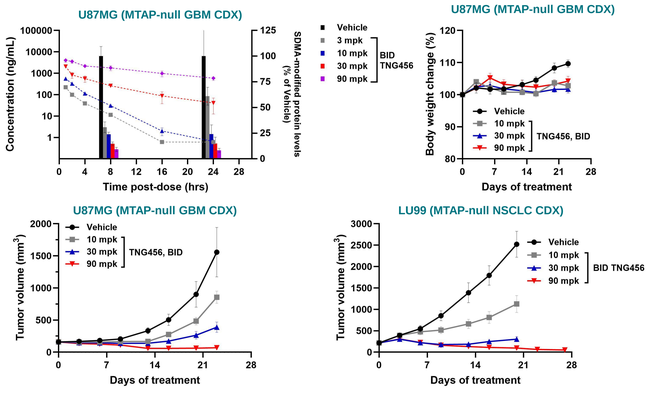
PD modulation is on-target and selective for MTAP-null cells



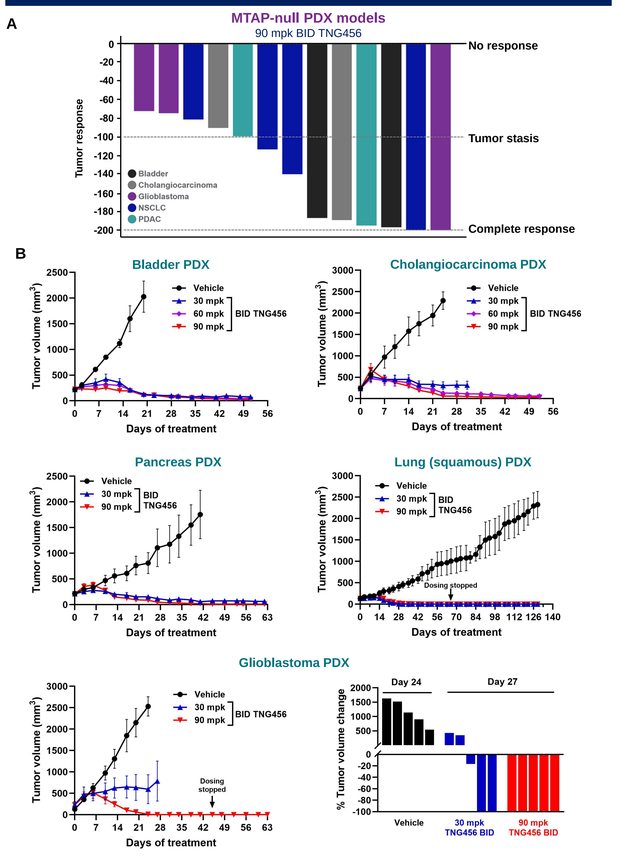
TNG456 antiproliferative activity is potent and 55X selective for MTAP-null cancer cells



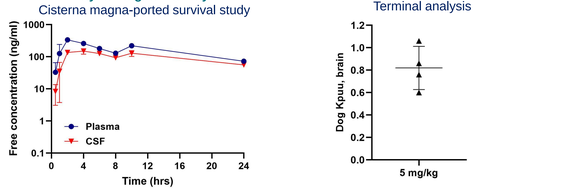
TNG456 efficacy is on-target and dose-dependent



TNG456 drives tumor regressions across histologies



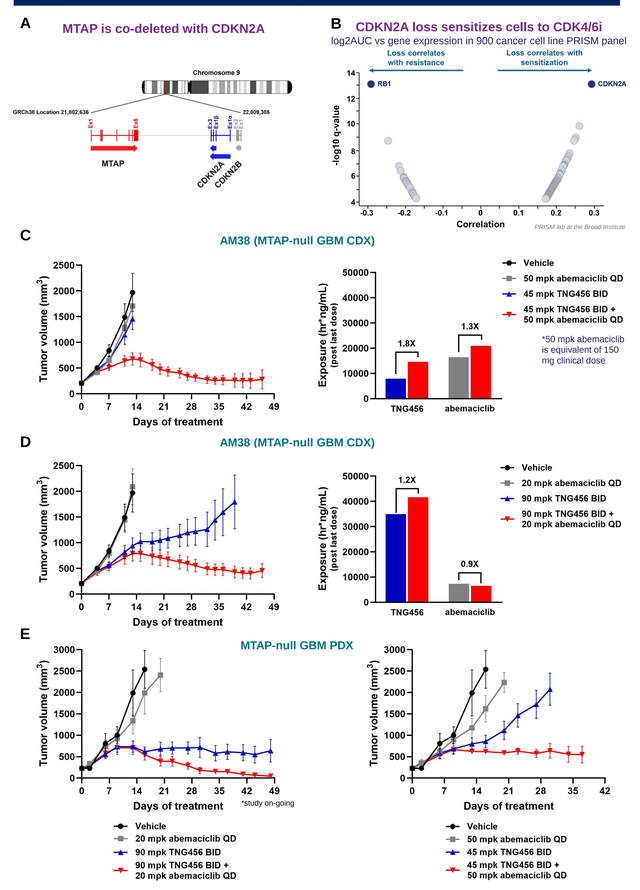
TNG456 is brain penetrant in preclinical species



TNG PRMT5 inhibitor profiles

	Potency	MTAP selectivity	Clinical CNS exposure
TNG456	20 nM	55X	0.5-1X plasma (predicted)
TNG462	4 nM	45X	-
TNG908	110 nM	15X	0.3X plasma (observed)

TNG456 + abemaciclib drives a significant combination benefit in aggressive MTAP-deleted xenograft models



Summary

- MTAP is deleted in 10-15% of all human cancer and frequently deleted in CNS malignancies (>40% glioblastomas) and tumors that metastasize to the brain (15% NSCLC and 16% melanoma)
- TNG456 is potent and 55X selective for MTAP-null cells
- Efficacy is on-target and observed across MTAP-null histologies
- Predicted clinical brain exposure is well above efficacy threshold
- Significant combination benefit observed with abemaciclib in aggressive preclinical models supports clinical combination strategy
- TNG456 monotherapy is currently enrolling patients in a Phase 1/2 clinical trial (NCT06810544)

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