Evidence for synergy between TNG908, an MTAPnull-selective PRMT5 inhibitor, and sotorasib in an MTAPnull/KRASG12C xenograft model

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ABSTRACT

MTAP deletion is one of the most common genetic alterations in human cancer, occurring in more than 10% of lung and pancreatic adenocarcinomas. PRMT5 dependence in cells with *MTAP* deletions is a strong and prevalent synthetic lethal interaction. TNG908 has a novel MTA-cooperative binding mechanism that drives synthetic lethality with *MTAP* deletion, unlike PRMT5 inhibitors currently in clinical development, and is 15X selective for MTAP^{null} over MTAP^{WT} cells. Approximately 30% of MTAP^{null} lung adenocarcinomas and 85% of MTAP^{null} pancreatic adenocarcinomas are also KRAS-mutant. *In vitro* studies in MTAP^{null}/KRAS-mutant cancer cell lines demonstrate that combination of MTAP^{null}-selective PRMT5 inhibitors with MAPK pathway inhibitors, including agents that inhibit ERK, MEK or KRAS, drive a synergistic combination benefit. Approximately 15% of MTAP^{null} lung adenocarcinomas are also KRAS^{G12C}-mutant. In an MTAP^{null}/KRAS^{G12C}-mutant lung adenocarcinoma xenograft model, combination of TNG908 and sotorasib at clinically relevant doses drove tumor regressions, which outperformed exposure-matched single agent activity for either compound, demonstrating a strong *in vivo* combination benefit. These data suggest that treatment of KRAS^{G12C}-mutant lung adenocarcinoma with TNG908 and a KRAS^{G12C} inhibitor may be of clinical benefit in lung cancers with concurrent *MTAP* deletion and KRAS^{G12C} mutation.

MTAP deletion is a common genetic alteration in cancer

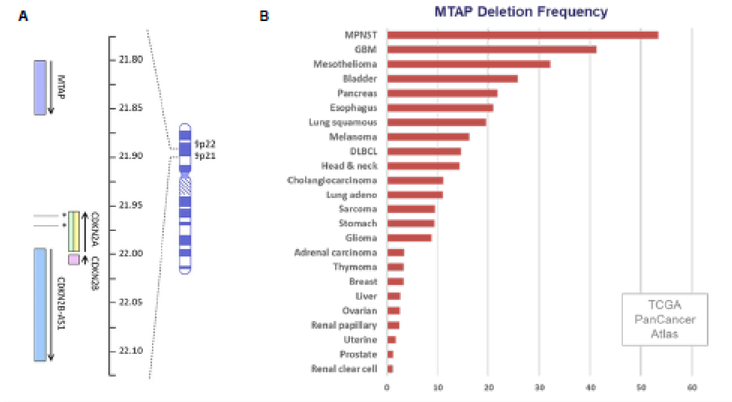

Figure 1: *MTAP*-deletion is a common genetic event in human cancer. (A) Schematic of chromosome 9p21-22 demonstrating close proximity of *MTAP* to *CDKN2A*, which encodes the tumor suppressor p16. *MTAP* is co-deleted with *CDKN2A* in ~10-15% of all human cancer. (B) *MTAP* deletion frequency in a subset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

MTAP deletion frequently co-occurs with KRAS mutation

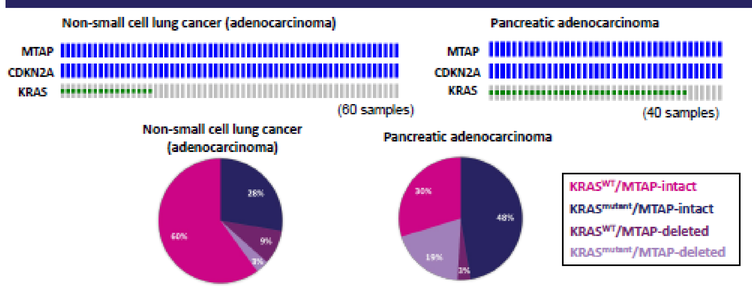

Figure 2. *MTAP* deletion co-occurs with KRAS mutation. Frequency of *MTAP* and *KRAS* genetic alterations in non-small cell lung cancer (adenocarcinoma) and pancreatic adenocarcinoma (Cerami et al 2012; Gao et al 2013). The NSCLC (adenocarcinoma) analysis includes 507 patient samples, and the pancreatic adenocarcinoma analysis includes 175 patient samples. KRAS mutation analysis is restricted to driver mutations.

PRMT5 is a MTAP^{null}-selective dependency

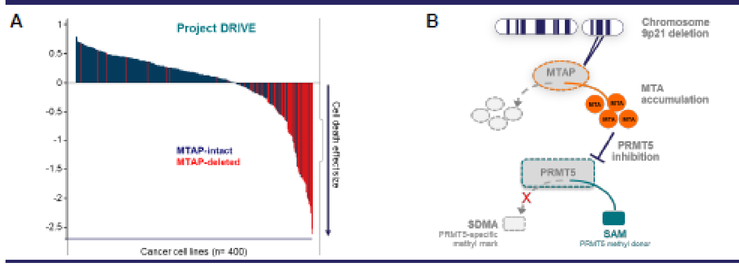

Figure 3: PRMT5 is a selective dependency in MTAP^{null} cells. (A) Project DRIVE (Novartis) RNAi data identifying PRMT5 as a selective dependency in MTAP^{null} cancer cell lines. (B) Biological rationale for sensitivity of MTAP^{null} cells to PRMT5 perturbation.

TNG908 is an MTAP^{null}-selective PRMT5 inhibitor

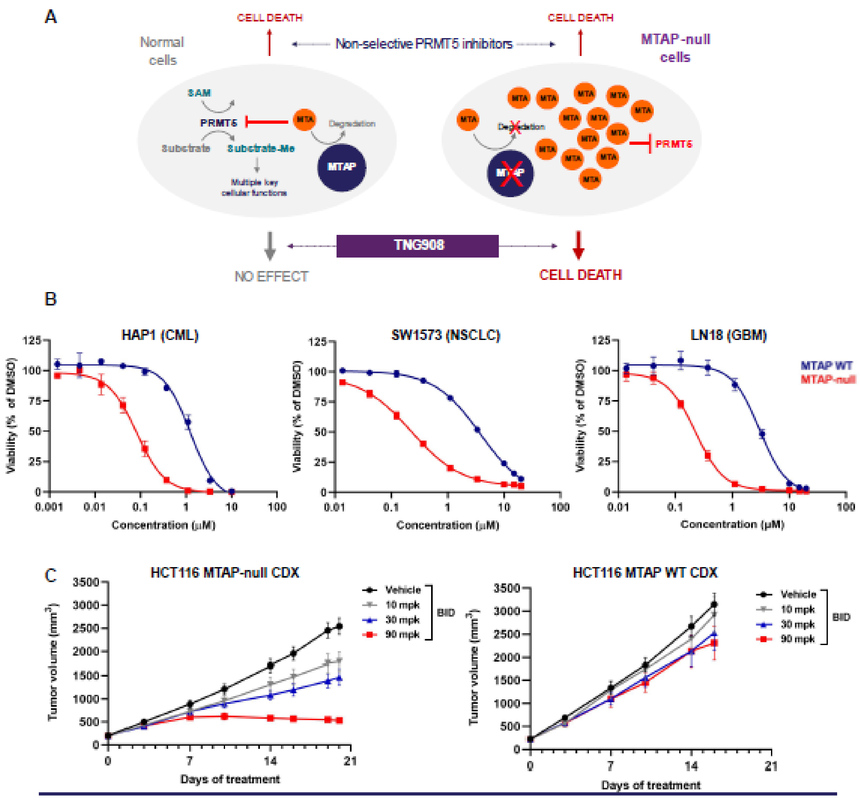

Figure 4: TNG908 is MTAP^{null}-selective in vitro and in vivo. (A) Schematic demonstrating differentiating therapeutic strategy for TNG908. B) Antiproliferative activity of TNG908 in MTAP-isogenic cell lines representing multiple lineages. Data are represented as mean ± SD. C) Antitumor activity in HCT116 MTAP-isogenic xenograft models with TNG908 dosed as indicated. n=8 mice per group. Data are represented as mean ± SEM.

MTAP^{null}-selective PRMT5 and MAPK pathway inhibition provide a therapeutic benefit in vitro

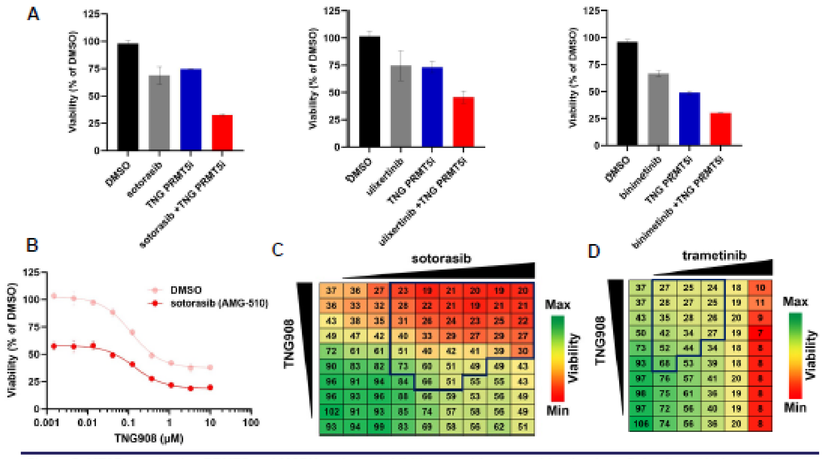

Figure 5: MTAP^{null}-selective PRMT5 and MAPK pathway inhibition provides a combination benefit in vitro. (A) Antiproliferative activity of an MTA-cooperative PRMT5 tool inhibitor in combination with the indicated MAPK pathway inhibitors. Data are represented as mean ± SD. (B) Antiproliferative activity of TNG908 in combination with sotorasib. Data are represented as mean ± SD. (C and D) Synergy analysis of the antiproliferative effect of TNG908 in combination with either sotorasib (C) or trametinib (D) in the LU99 MTAP-null/KRAS^{G12C} NSCLC (adenocarcinoma) cell line. Region of HSA synergy outlined in blue.

Combination benefit is not due to enhanced PRMT5 or MAPK pathway inhibition in vitro

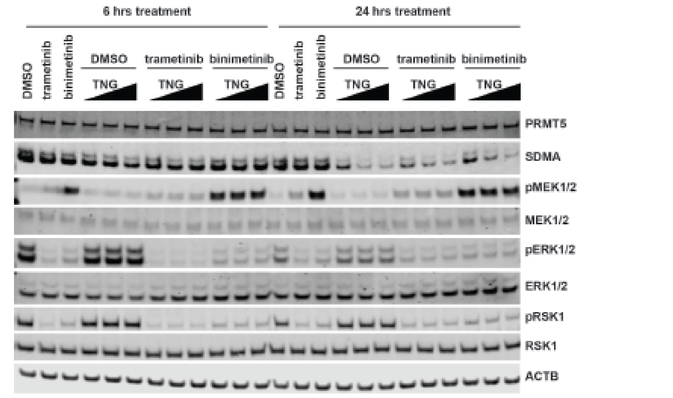

Figure 6: PRMT5 and MAPK pathway inhibition is not enhanced by the combination treatment of an MTAP^{null}-selective PRMT5 inhibitor and MEK inhibitors in the SW1573 cancer cell line. Immunoblot of lysates harvested from the SW1573 MTAP-null/KRAS^{G12C} NSCLC (adenocarcinoma) cell line treated for the indicated timepoints with the indicated inhibitors. TNG, an MTAP^{null}-selective PRMT5 inhibitor tool compound.

TNG908 and KRAS^{G12C} inhibitor combination treatment drives tumor regression in vivo

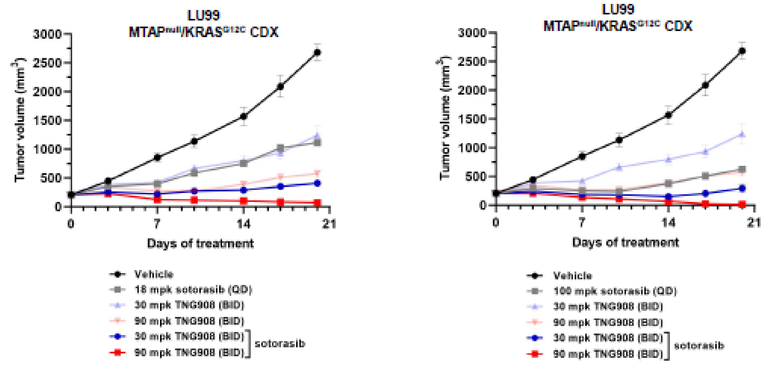

Figure 7: TNG908 and sotorasib combination treatment in an MTAP-null/KRAS^{G12C} NSCLC xenograft model drives tumor regression . The LU99 MTAP-null/KRAS^{G12C} mutant NSCLC xenograft model was treated for 21 days with single agent TNG908 or sotorasib, or a combination of TNG908 and sotorasib. Strong single agent TNG908 activity is driven in the LU99 model at 30-120 mpk BID. Sotorasib doses were chosen to be clinically relevant, and were adjusted in combination with TNG908 to deliver equivalent exposures to single agent. n=8 mice per group, and data are presented as mean ± SEM.

SUMMARY

- 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
- KRAS mutation frequently co-occurs with *MTAP* deletion in NSCLC and pancreatic adenocarcinoma
- PRMT5 and KRAS inhibition in MTAP^{null}/KRAS^{mutant} cancer cell lines provides a combination benefit in vitro, and drives tumor regression at clinically relevant doses in an MTAP^{null}/KRAS^{mutant} xenograft model
- Treatment of KRAS^{G12C}-mutant lung adenocarcinoma with TNG908 and a KRAS^{G12C} inhibitor may be of clinical benefit in lung cancers with concurrent *MTAP* deletion and KRAS^{G12C} mutation