Genome-wide drug anchor screens identify CAAP1 and AKAP17A as regulators of PRMT5 inhibitor sensitivity

Abstract #4636

Satoshi Yoda*, Matthew R Tonini*, Hilary E Nicolson, Samuel Poleretzky, Silvia Fenoglio, Steven Lombardo, Lauren Grove, Samuel R Meier, Ashley Choi, Yi Yu, Kevin M Cottrell, John P Maxwell, Teng Teng, Jannik N Andersen, Kimberly J Briggs

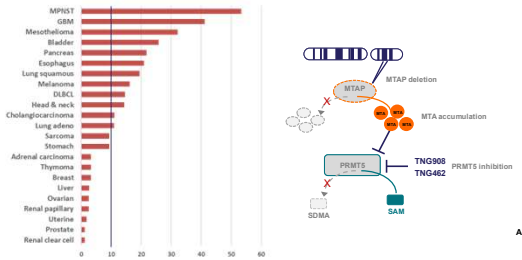
*These presenters contributed equally.

Introduction

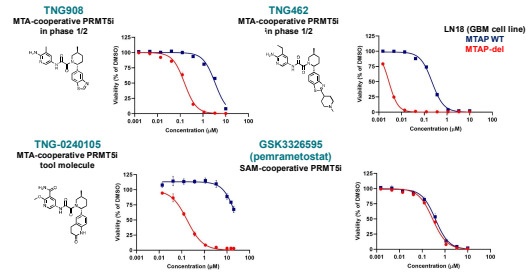
MTA-cooperative PRMT5 inhibitors are an emerging treatment option for patients with one of the 10-15% of all human cancers harboring MTAP homozygous deletion. To identify potential regulators of sensitivity to PRMT5 inhibitors, we performed genome-wide CRISPR knockout screens in the presence and absence of an MTA-cooperative PRMT5 inhibitor. Knockout of CAAP1 and AKAP17A were among the strongest sensitizing hits across multiple MTAP-deleted cancer cell lines representing different histologies. Strikingly, the CAAP1 gene co-localizes with MTAP and CDKN2A on chromosome 9p21. Co-deletion of CAAP1 is reported in 20 percent of MTAP-deleted cancers in the TCGA PanCancer Atlas. CAAP1 or AKAP17A knockout in MTAP-deleted cancer cell lines sensitized the cells to PRMT5 inhibitors including the clinical-stage MTA-cooperative inhibitors, TNG908 and TNG462, and the non-MTA-cooperative inhibitor, GSK3326595. Moreover, we discovered that CAAP1 and AKAP17A protein levels are interdependent, as knockout of either gene caused decreased protein levels for the other. Consistent with this finding, CAAP1 reconstitution in CAAP1-deleted cell lines led to increased AKAP17A levels. Endogenous CAAP1 and AKAP17A protein levels are positively correlated across a panel of cancer cell lines and MTAP-deleted patient-derived xenograft models. Consistent with a previous report (Ni et al., 2023), exogenous CAAP1 and AKAP17A co-immunoprecipitation studies suggest that the proteins form a protein complex. AKAP17A and CAAP1 are not well-characterized proteins, but PRMT5 inhibitors induce global alternative splicing events (ASEs) in cancer cells, and based on preliminary studies a possible function for the CAAP1/AKAP17A complex could be to mitigate ASEs induced by PRMT5 inhibition. Collectively, these data indicate that CAAP1 and AKAP17A exist interdependently and mediate sensitivity to PRMT5 inhibitors. The colocalization and 20 percent incidence of CAAP1 deletion in the setting of MTAP deletion may suggest that such patients will have improved responses to PRMT5-targeted therapy.

MTA-cooperative PRMT5 inhibitors are synthetic lethal with MTAP deletion

Homozygous MTAP deletion frequency

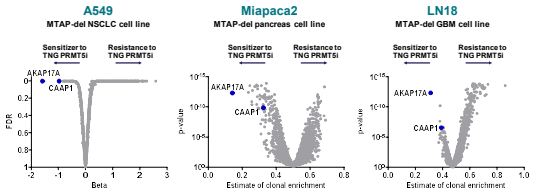


Tango PRMT5 inhibitors are selective for MTAP-deleted cancer cells



CAAP1 and AKAP17A identified as potential sensitizers to PRMT5 inhibition

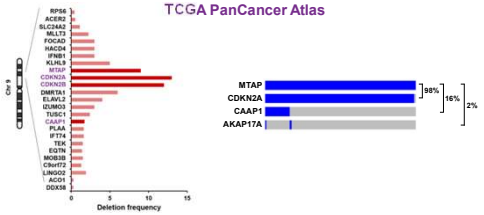
CRISPR knockout in vitro anchor screens



CAAP1 and AKAP17A among top dropout hits across multiple histologies

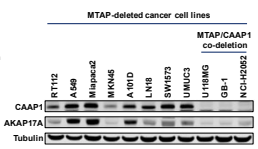
CAAP1 can be co-deleted with MTAP and CDKN2A

TCGA PanCancer Atlas

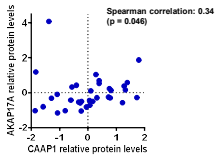


CAAP1 and AKAP17A form a protein complex and are functionally co-dependent

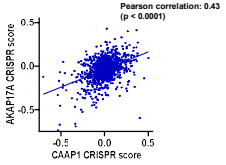
Protein level correlation in vitro



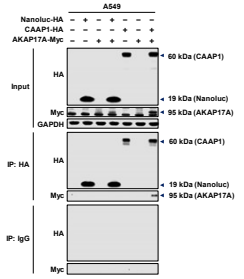
Protein level correlation in vivo



Functional co-dependency

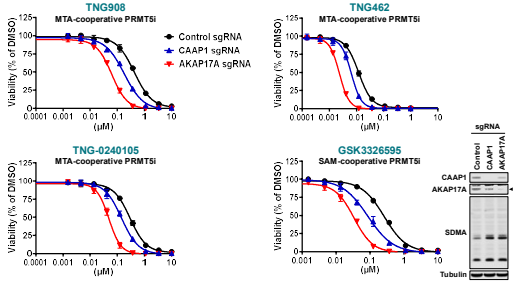


Co-immunoprecipitation



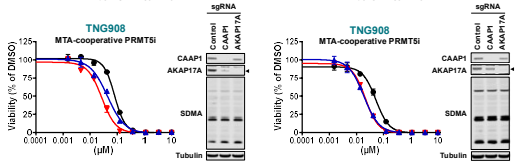
CAAP1 or AKAP17A knockout can sensitize cells to PRMT5 inhibitors

Miapaca2
MTAP-del pancreas cell line



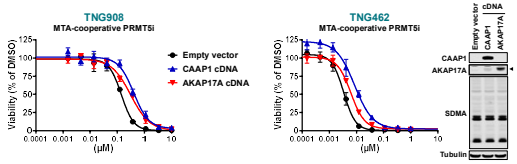
A549
MTAP-del NSCLC cell line

LN18
MTAP-del GBM cell line



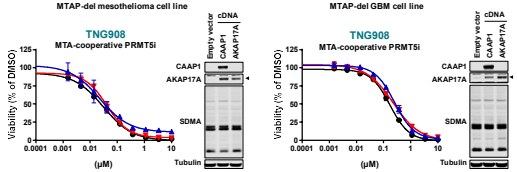
CAAP1 reconstitution can reduce sensitivity to PRMT5 inhibitors

U118MG
MTAP-del GBM cell line



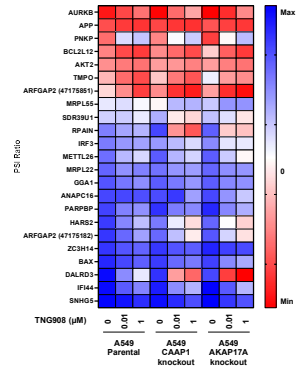
NCI-H2052
MTAP-del mesothelioma cell line

GB1
MTAP-del GBM cell line



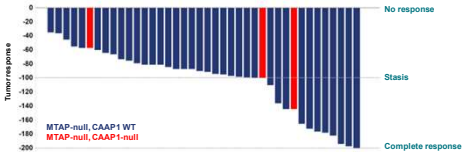
CAAP1 or AKAP17A knockout alters PRMT5i-mediated alternative splicing events

Alternative splicing events measured by PCR



CAAP1 deletion is not necessary for response to TNG908

In vivo tumor response to TNG908 and CAAP1 gDNA status



Summary

- CAAP1 and AKAP17A knockout can sensitize cells to MTA-cooperative and SAM-cooperative PRMT5 inhibitors in vitro
- CAAP1 and AKAP17A can form a complex in vitro and may mitigate global alternative splicing events caused by PRMT5 inhibition
- CAAP1 deletion is not necessary for response to TNG908
- Currently, these data do not support prospective selection for CAAP1 co-deleted tumors for enrollment in MTA-cooperative PRMT5 inhibitor clinical trials including NCT05275478 and NCT05732831

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References

Ni et al., Proteomic analysis reveals CAAP1 negatively correlates with platinum resistance in ovarian cancer. J Proteomics. 2023.

Cerami et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discov. 2012.

Gao et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci. Signal. 2013.

Lee et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nature Genet. 2014.