TNG917 is a clinical-grade, potent and selective inhibitor of EHMT1/2 for the treatment of immune cold tumors

Abstract #3242

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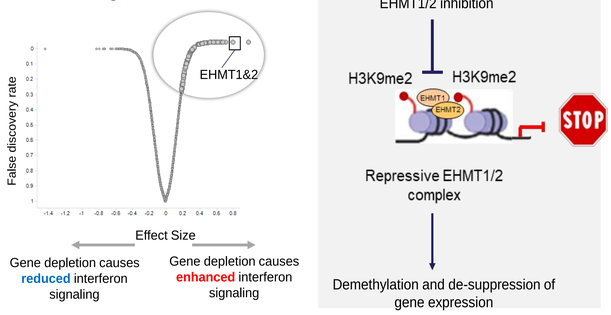
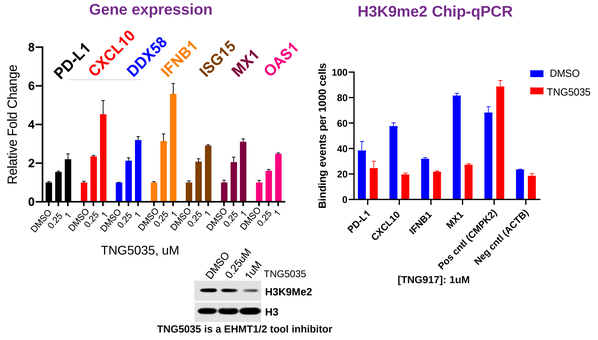
Introduction

CRISPR-based functional genomics screening can be designed to identify novel cancer cell intrinsic targets that increase tumor immunogenicity. Using a FACS-based CRISPR sorting screen for PD-L1 expression, we identified Euchromatic histone-lysine-*N*-methyltransferase 1 and 2 (EHMT1/2) as negative modulators of the interferon signaling pathways. EHMT1 and EHMT2 are histone methyltransferases that mono- and di-methylate lysine 9 of histone H3 to repress gene transcription of defined target genes. Gene knockout or pharmacological inhibition of EHMT1/2 in cancer cells resulted in de-repression of gene promoters, upregulation of interferon-stimulated genes (ISGs), and secretion of pro-inflammatory cytokines. Here, we present the preclinical characterization of TNG917 - an oral and highly selective EHMT1/2 inhibitor with low nanomolar cellular potency, and favorable pharmacodynamic and pharmacokinetic properties. In humanized and syngeneic mouse models, treatment with TNG917 in combination with anti-PD1 promoted a T-cell-infiltrated tumor microenvironment, led to significant anti-tumor activity, and resulted in survival benefit. In summary, our in vitro and in vivo studies provide a rationale for the clinical development path of TNG917, in combination with checkpoint inhibition, in patients with immune cold tumors.

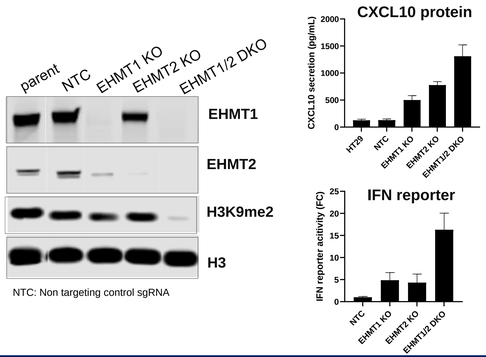
EHMT1/2 were identified as suppressors of interferon signaling based on CRISPR screens



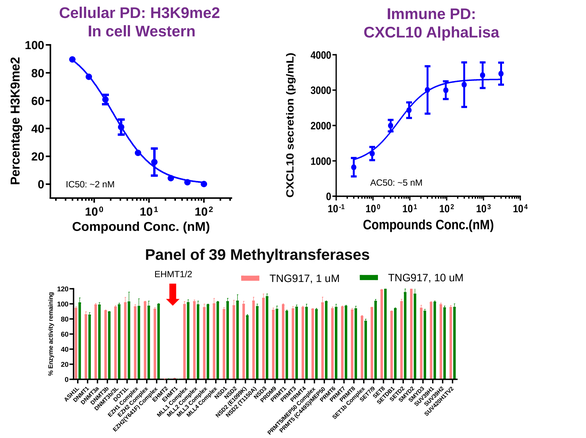
EHMT1/2 inhibition induces interferon signaling by directly regulating H3K9me2 promoter methylation of a set of interferon-stimulated genes (ISG)



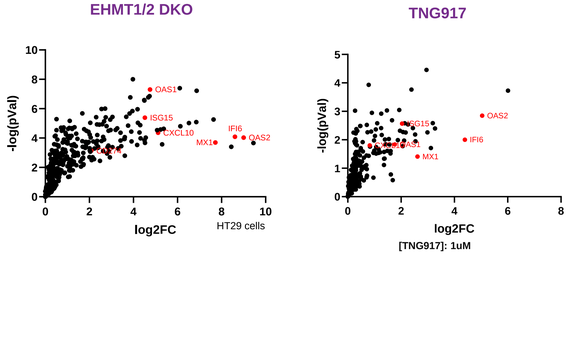
Double knockout (DKO) of EHMT1 and EHMT2 is superior at inducing CXCL10 expression and IFN signaling



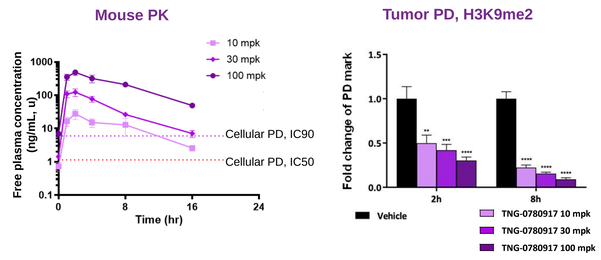
TNG917 is a potent and selective inhibitor of EHMT1/2 both in vitro and in cells



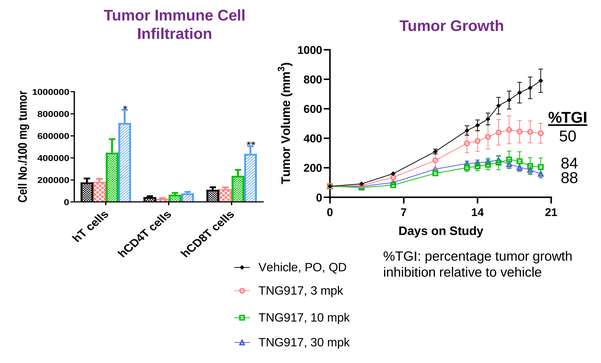
TNG917 treatment phenocopies EHMT1/2 knockout in inducing ISG expression



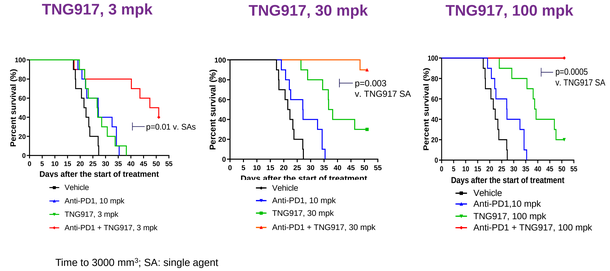
TNG917 demonstrates dose-dependent in vivo PK/PD in MC38 model



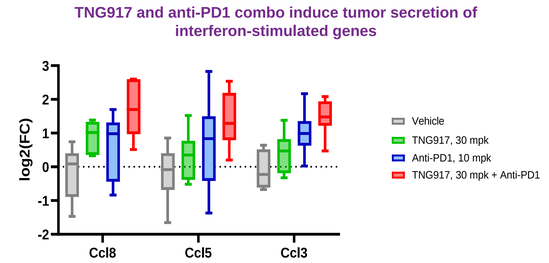
TNG917 demonstrates significant immune-based efficacy in immune competent, humanized CRC tumor model



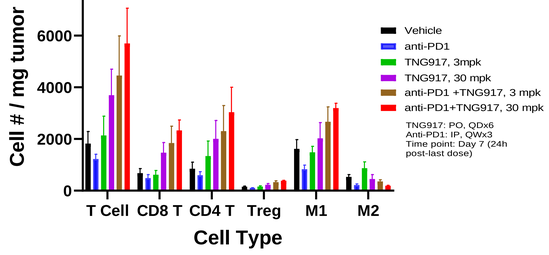
TNG917 extends survival in combination with anti-PD1 in CT26 syngeneic tumors



Combination of TNG917 and anti-PD1 significantly increases ISGs and tumor immune cell infiltration in CT26 model



TNG917 and anti-PD1 combo induce intratumoral T cells and M1 cells, and decrease in M2 cells



Summary and prospective

- EHMT1/2 was identified as a novel tumor intrinsic immune evasion target using a FACS-based CRISPR screen
- Genetic or pharmacological inhibition of EHMT1/2 reverses tumor immune invasion through de-repression of key cytokines (ie, PDL1, CXCL10)
- TNG917 is a potent and selective EHMT1/2 inhibitor that exhibits low nanomolar potency in reducing H3K9me2 levels and inducing expression of chemotactic cytokines in cells
- TNG917 demonstrates strong in vivo efficacy in combination with anti-PD1 in immune cold models, with consistent ISG induction and tumor immune cell infiltration in mechanistic studies
- TNG917 is a clinical development candidate with favorable ADME properties and safety profile. The in vivo efficacy and mechanism of action studies support the clinical development path of TNG917
- Suitable patient population for TNG917 treatment includes up to 85% of immune-cold colorectal cancers
- TNG917 is open to licensing opportunities due to project prioritization

Acknowledgements

CRO partners: Wuxi Apptec Co., Ltd.; Actif Motif Inc., ChemPartner; Biortus, Reaction Biology, Enamine