Biochemical characterization of TNG908 as a novel, potent MTA-cooperative PRMT5 inhibitor for the treatment of MTAP-deleted cancers


ABSTRACT

TNG908 is a clinical stage MTA-cooperative PRMT5 inhibitor that leverages the synthetic lethal interaction between PRMT5 inhibition and MTA loss-of-function to target MTAP-deleted cancers. TNG908 cooperatively binds to PRMT5 and selectively kills MTAP-deleted cancer cells compared to MTAP WT cells. Here we present biochemical and orthogonal binding assay data to demonstrate that TNG908 is a potent, small molecules that exhibit MTA-cooperative PRMT5 binding and selectively kill MTAP-deleted cancer cells compared to MTAP WT cells. PRMT5 is an intrinsic inhibitor of PRMT5 when bound to a PRMT5-substrate protein complex. MTA is rapidly metabolized by MTAP in normal cells and functions as an inhibitor of PRMT5 when bound to a PRMT5-substrate protein complex. MTA is structurally similar to SAM but lacks the amino-carboxy terminus, therefore functions as an intrinsic inhibitor of PRMT5 when bound to a PRMT5-substrate protein complex. MTA is structurally similar to SAM but lacks the amino-carboxy terminus, therefore functions as an inhibitor of PRMT5 when bound to a PRMT5-substrate protein complex.

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

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