Exploring the Clinical Translation of Synthetic Lethality, PRMT5 Inhibitors in MTAP Depleted Cancers: A Scoping Review

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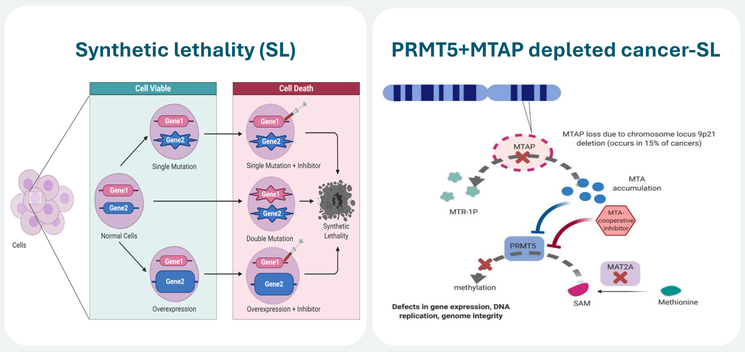
INTRODUCTION

- Targeting the PRMT5/MTAP pathway exploits synthetic lethality, enhancing the susceptibility of MTAP-deficient tumors to PRMT5 inhibition, thus providing a strategic approach for cancer treatment.
- MTAP deficiency leads to elevated levels of methylthioadenosine (MTA), which inhibit PRMT5 through the formation of a PRMT5-MTA complex, thereby increasing the vulnerability of MTAP-depleted tumors to PRMT5 inhibitors.
- This review examines the current translational research landscape and the future potential of PRMT5 inhibition as a therapeutic strategy for cancers characterized by MTAP deficiency.



Abbreviations – MAT2A: Methionine adenosyltransferase 2A, MTA: Methylthioadenosine; MTAP: Methylthioadenosine phosphorylase; PRMT-5: Protein arginine methyltransferase 5; SAM: S-adenosylmethionine; SL: Synthetic lethality

OBJECTIVE

- To synthesize current evidence (preclinical and clinical) on PRMT5 and MTAP Synthetic Lethality combination.
- To provide detailed Challenges For Clinical Translation of Synthetic Lethality, PRMT5 Inhibitors in MTAP Depleted Cancers.

METHOD

Literature Search
- Databases: PubMed, Google Scholar, clinicaltrials.gov
- Keywords & MeSH terms based on PCC format
- Machine assisted expedited search with support of MAIA Evidence module

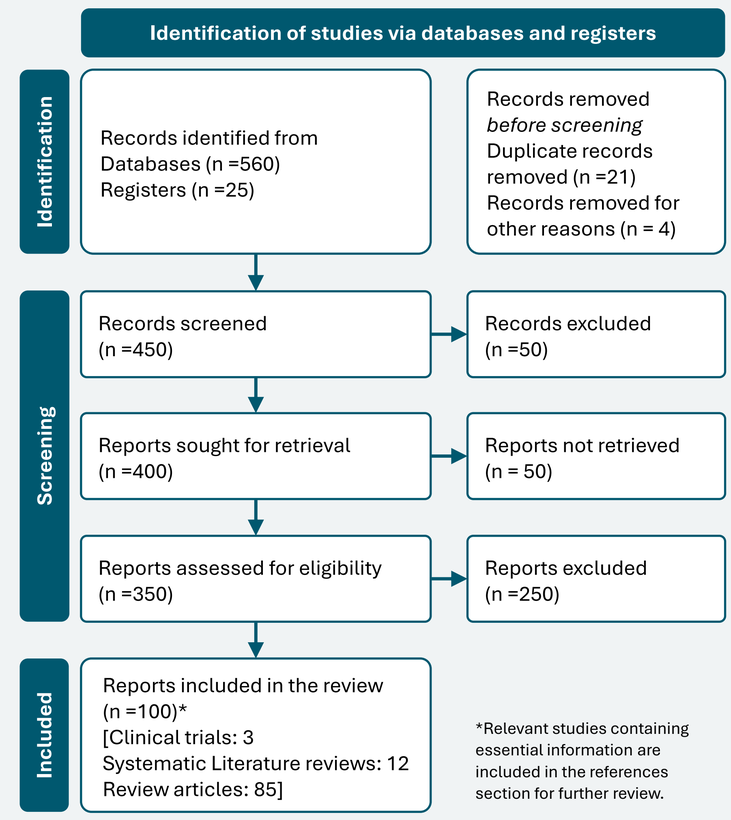
Inclusion Criteria
- Studies: Clinical trials, observational studies, reviews, meta-analyses & Timeframe: Last 10 years (up to April 30, 2024)
- Focus: PRMT5 inhibitors in MTAP-deleted cancer cells

Method
- Adherence to JBI guidelines
- PRISMA-ScR checklist compliance

Data Charting
- Tool: Microsoft Excel (JBI ScR template)
- Elements: In vitro/preclinical data (IC50, cytotoxicity, etc.), clinical trial info (molecule, tumor type, phase, NCT number), and conclusions/remarks

Figure 1.

PRISMA Diagram



*Relevant studies containing essential information are included in the references section for further review.

RESULTS

Clinical Studies

AMG193
MTA-cooperative PRMT5 inhibitor

-Strong preclinical efficacy across various tumor types.

Phase I Trial

- Safety: The most common treatment-related adverse events were nausea (48.8%), fatigue (31.3%), and vomiting (30.0%).

- PK profile: Half-life 13 hours; once-daily dosing.

- Efficacy: Complete intratumoral PRMT5 inhibition was confirmed in paired MTAP-deleted tumor biopsies, and molecular responses (circulating tumor DNA clearance) were observed.

Phase I study in patients with advanced CDKN2A-deleted and/or MTAP-deleted solid tumors

GSK3368715
Type 1 PRMT inhibitor

↑ MMA
↓ ADMA
↑ SDMA
Anti-tumor activity

Phase I Trial

- Safety: Higher rate of thromboembolic Events than expected.

PK profile: C_{max} reached within 1 hour of dosing; high PK variability.

- PD effect: Modest and variable target engagement in tumor.

- Efficacy: Lack of observed clinical benefit; MTAP loss only analysed retrospectively.

Risk/benefit analysis led to early study termination

TNG908
Binds to PRMT5-MTA complex; inhibits PRMT

- Strong preclinical efficacy across various histologies.
- Effective in MTAP-null GBM xenograft models, supporting histology-agnostic clinical development in MTAP-deleted solid tumors.

Recruiting Phase

Phase I planned: To determine the maximum tolerated dose (MTD) and dosing schedule of TNG908 for 28 days.

Phase II planned: To assess anti-neoplastic activity of TNG908 in patients with MTAP-deleted advanced solid tumors by RECIST or mRECIST v1.1 or modified RANO criteria for16 weeks.

Challenges For Clinical Translation of Synthetic Lethality, PRMT5 Inhibitors in MTAP Depleted Cancers

Tumor heterogeneity | Drug resistance | Unexplored relationship between DNA damage and synthetic lethality | Off-target side effects | Risk of secondary malignancies

Table 1:

Oncology drug molecules under pre-clinical development

Inhibitor	Mechanism of action	Tumor model/ In-vitro cell line	Key findings	Source
MRTX-1719	Selectively inhibited PRMT5 in the presence of MTA Inhibition of PRMT5-dependent SDMA modification in MTAP del tumors	Human colorectal cancer HCT116 cell line Lung tumor xenografts	• Differentiated binding mode leverages the elevated MTA in MTAP del cancers • Dose-dependent antitumor activity and inhibition of PRMT5-dependent SDMA modification in MTAP del tumors	Engstrom, Lars D., et al 2023
AG-270	Reduced protein arginine methyltransferase 5 (PRMT5) activity and splicing perturbations	Patient-derived xenograft models	• Potent reduction in intracellular SAM MTAP selective antiproliferative activity • Treats tumors with homozygous MTAP deletion	Kalev, Peter, et al 2021 Konteatis, Zenon, et al 2021
AMI	Down-regulation of eIF4E and targeting PRMT5 Reduce the symmetric demethylation expressions of PRMT5, eIF4E, histone 3, and histone 4	Lung cancer cells	• Apoptosis of lung cancer cells. Down-regulation of eIF4E and targeting PRMT5	Chen, Yingqing, et al 2021
LLY-238	Binds in the SAM pocket of PRMT5 in breast, gastric, and hematological tissues	Mouse xenografts	• Highly potent and cell-permeable with well-defined PK characteristics	Bonday, Zahid Q., et al 2018
HLCL-61	Increased expression of miR-29b and consequent suppression of Sp1 and FLT3	In-vitro activities, yet to start	• Potent and selective PRMT5 inhibitor for treatment of AML	Tarighat, Somayeh S., et al 2016
EPZ015666	Binds selectively to the SAM-PRMT5 complex via a cation-pi molecular interaction	Panel 64 cell lines	• Growth inhibition upon pharmacologic inhibition of PRMT5 with EPZ015666 was not selective for the MTAP−/− genetic background	Marjon, Katya, et al. 2016

Abbreviations- AML: Acute myeloid leukemia; HCT116: Human colorectal carcinoma cell line; MTA: Methylthioadenosine; MTAP: Methylthioadenosine phosphorylase; PK: Pharmacokinetics; PRMT-5: Protein arginine methyltransferase 5; SAM: S-adenosylmethionine; SDMA: Symmetric dimethylarginine.

CONCLUSIONS

01 Strong evidence supports early drug development targeting PRMT5 in MTAP-deleted cancers

02 A deeper understanding of molecular changes post-inhibition is crucial for identifying patients who will benefit from MAT2A/PRMT5 inhibitors

03 Combining PRMT5 and MTAP synthetic lethality strategies with chemotherapy can enhance DNA damage, increasing cancer cell sensitivity and overcoming drug resistance

04 Further research is needed to clarify molecular mechanisms and enhance the clinical viability of this synthetic lethality combination

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