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Review

Emerging roles of protein arginine methyltransferase in multiple myeloma

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Multiple myeloma (MM) is a cancer of plasma cells characterized by the clonal expansion of abnormal plasma cells in the bone marrow. These malignant cells overcrowd the bone marrow, disrupt normal hematopoiesis, and produce excessive amounts of immunoglobulins, leading to severe clinical manifestations. Despite significant advancements in treatment, relapsed/refractory MM remains incurable. Protein arginine methylation, catalyzed by protein arginine methyltransferases (PRMTs), is a critical post-translational modification involved in regulating various cellular processes. Aberrant expression of PRMTs has been strongly linked to poor prognosis in many cancers, including MM. Among the PRMT family, PRMT1, PRMT4 (CARM1), and PRMT5 have emerged as potential therapeutic targets for MM. This review will first explore the expression patterns of PRMTs in MM and assess their association with disease prognosis. We will then provide a comprehensive overview of the functions of these PRMTs in MM pathology, discuss the development of PRMT inhibitors currently being evaluated in clinical trials, and offer insights into the potential of targeting PRMTs for MM treatment in clinical settings.

INTRODUCTION

Multiple myeloma (MM) is a cancer of plasma cells initiated by mutations in germinal center (GC) B cells, often involving hypodiploidy and chromosomal translocations in the immunoglobulin heavy chain (IgH) locus (14q32) or light chain loci (κ at 2p12 or λ at 22q11).[1,2] During immune responses, naive B cells undergo rapid proliferation and genetic modifications in the GC, including somatic hypermutation, affinity maturation, and class-switch recombination to enhance antigen specificity.[3] MM typically involves more than 400 somatic mutations per patient, broadly categorized into primary abnormalities (such as trisomies and IgH translocations) and secondary abnormalities (including gain(1q), del(1p), del(17p), del(13), RAS mutations, and MYC translocations). Approximately 40% of MM patients have hyperdiploidy, marked by trisomies of specific chromosomes (e.g., 3, 5, 7, 9, 11, 15, 19, and 21), while around 30% exhibit translocations involving the IgH locus on chromosome 14q32, including t(4; 14), t(11; 14), t(14; 16), t(6; 14), and t(14; 20). A small proportion of patients display both trisomies and IgH translocations. These cytogenetic abnormalities vary across MM progression stages, impacting disease course, treatment response, and prognosis.[4–6] MM cells from patients secrete both whole immunoglobulins (52% immunoglobulin G and 21% immunoglobulin A and free lambda or kappa light chains (16%). Non-class-switched immunoglobulin forms are rare (2% immunoglobulin D and 0.5% immunoglobulin M).[7]

MM progresses through three stages. (1) Monoclonal gammopathy of undetermined significance (MGUS)[8–10]: a premalignant stage with asymptomatic plasma cell dyscrasia, occurring in about 3% of individuals over 50 and 5% of those over 70. MGUS progresses to symptomatic MM at a rate of 1%–2% per year, with an 18% cumulative risk over 20 years. Primary chromosomal abnormalities often arise in MGUS. (2) Smoldering multiple myeloma (SMM)[11,12]: an intermediate, asymptomatic stage with a high progression risk (approximately 10% per year) to active MM. Early intervention is recommended for high-risk SMM patients, as this stage is considered optimal for therapeutic strategies targeting MM evolution. Cytogenetic abnormalities, such as t(4; 14), del(17p), and gain(1q), increase progression risk from MGUS or SMM to MM. (3) Active MM is characterized by uncontrolled plasma cell proliferation, causing symptomatic disease. High-risk MM is identified by specific genetic alterations, including del(17p), t(4; 14), t(14; 16), t(14; 20), gain(1q), and p53 mutations, which are linked to poorer prognosis and increased disease aggressiveness.[5]

Protein arginine methyltransferases (PRMTs) catalyze the methylation of arginine (R) residues on both histone and non-histone proteins.[13] This process involves adding methyl groups to the terminal nitrogen atoms of the guanidino group. The PRMT family consists of nine members, divided into three types: type I (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6, and PRMT8), type II (PRMT5 and PRMT9), and type III (PRMT7). While all PRMTs mediate monomethylation of R, only type I and II enzymes catalyze dimethylation. Type I PRMTs produce asymmetric dimethylarginine (ADMA), while type II enzymes generate symmetric dimethylarginine (SDMA) (Figure 1).

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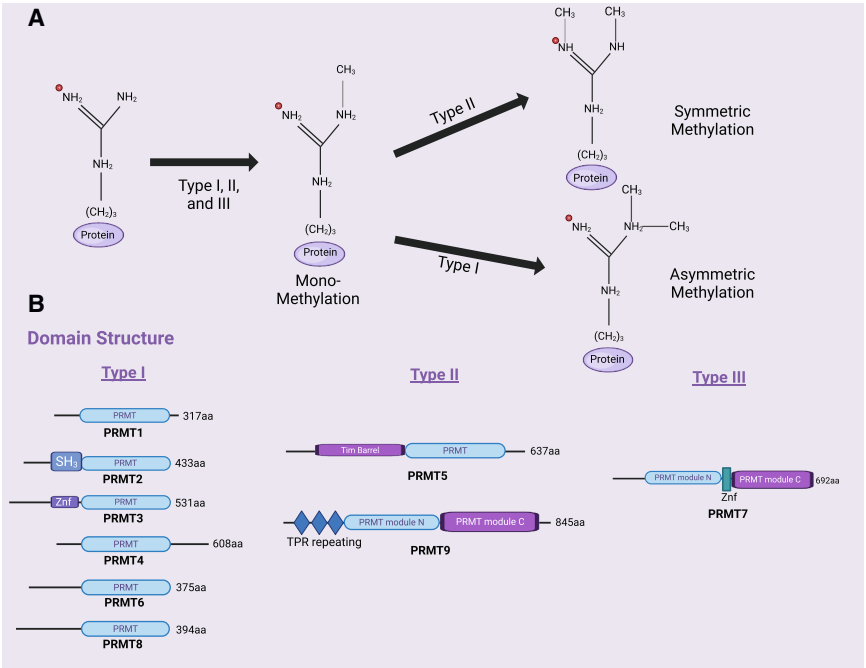

Figure 1. Overview about the PRMT family

(A) Mono-arginine methylation is catalyzed by PRMT type I, II, and III. Only type II and type II can generate di-arginine methylations. Symmetric di-arginine methylation (SDMA) and asymmetric di-arginine methylation (ADMA) are generated by PRMT type II and type I, respectively. (B) Domain structure of individual PRMT members. Znf, zinc-finger domain; SH3, SRC Homology 3 domain; TPR repeating, tetratricopeptide repeat domain.

PRMT-mediated R methylation plays a critical role in cellular processes such as transcription regulation, RNA splicing, DNA repair, and signal transduction.[14,15] Aberrant PRMT expression is linked to various cancers, positioning them as promising therapeutic targets. Their potential in cancer therapy has been thoroughly reviewed.[16,17] However, no comprehensive review has focused specifically on the role of PRMTs in MM.

This review provides an overview of PRMT expression in MM and explores their association with prognosis. We also summarize current literature on the functional roles of individual PRMTs in MM pathology. Given the emerging evidence of PRMTs' involvement in MM, particularly in relapsed/refractory (RR) cases, this review highlights their potential as therapeutic targets for MM treatment.

PRMTs REGULATE GENE EXPRESSION

PRMTs exert their cellular functions primarily through substrate-specific methylation. Type I PRMTs, except PRMT4 (CARM1), predominantly target glycine/arginine-rich (GAR) motifs, while type II PRMTs methylate both individual arginine residues and GAR motifs. This substrate diversity enables PRMTs to regulate gene expression at various levels, including transcription, post-transcription, translation, and post-translation.[18]

In transcriptional regulation, PRMTs methylate both histone and non-histone proteins. Histone H4 serves as a common substrate for PRMT1 and PRMT5. PRMT1-mediated H4R3me2a facilitates gene activation by promoting H3 and H4 acetylation.[19] Conversely, PRMT5-mediated H4R3me2s suppresses gene expression by recruiting the PHF1/CRL4B repressor complex.[20] PRMT5 can also enhance transcription through symmetric dimethylation of H3R2 (H3R2me2s), which promotes H3K4me3 accumulation via the WDR5/MLL (WD Repeat Domain 5/Mix Lineage Leukemia) complex,[21] facilitating the euchromatin conformation. On the other hand, PRMT6-mediated H3R2me2a inhibits WDR5/MLL binding to H3K4, leading to gene repression.[22] Additional histone arginine methylations, including PRMT2-H3R8me2a[23–25] and CARM1-H3R17me2a/H3R26me2a,[26,27] have been implicated in gene activation and cancer progression.

PRMTs also regulate transcription through non-histone protein methylation. CARM1, for example, methylates the transcription co-activator CBP (CREBP binding protein) at R742, promoting GRIP-1 (glutamate receptor-interacting protein 1) and steroid hormone-induced gene activation.[28,29] PRMT1 and PRMT5 further facilitate transcriptional elongation by methylating SPT5, enhancing its interaction with RNA polymerase II.[30]

Post-transcriptionally, PRMTs influence RNA processing by methylating RNA-binding proteins (RBPs) and splicing factors. PRMT1 modifies RBPs like Sam68,[31] hnRNP A2,[32] FUS,[33] and hnRNP A1,[34] altering their localization and function. In contrast, PRMT5 methylates Sm proteins in the cytoplasm, a crucial step in small nuclear ribonucleoprotein (snRNP) maturation and splicing fidelity.[35,36] Additionally, PRMT5-mediated SRSF1 methylation regulates pre-mRNA binding and protein interactions.[37] CARM1[38] and PRMT9[38,39] also influence splicing through their interactions with splicing factors.

In translation regulation, PRMTs play a significant role by methylating ribosomal RBPs. PRMT1 promotes MLL translation in T cell acute lymphoblastic leukemia through Aven methylation.[40] PRMT3 modifies ribosomal protein S2, which is essential for 40S ribosomal subunit assembly.[41–43] Similarly, PRMT5 methylates hnRNP A1 to enhance IRES-dependent translation[44] and ribosomal protein S10 to facilitate its incorporation into the ribosome.[45]

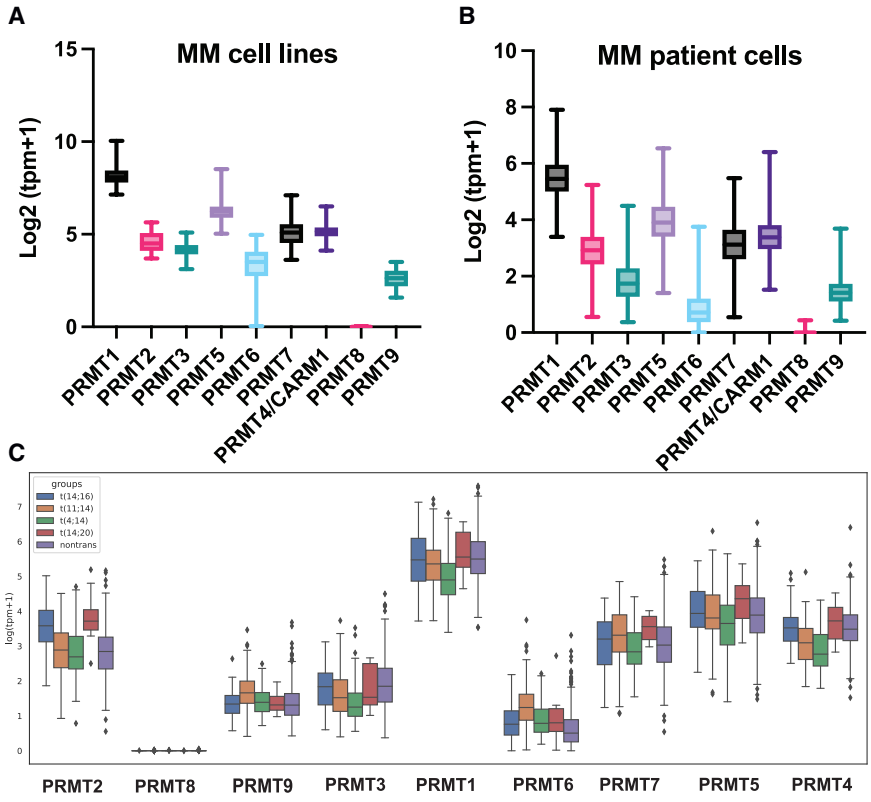

Figure 2. Expression of PRMT family in MM cells
Expression of PRMT family in MM cell lines (A) and patient-derived cells (B). (C) Expression of PRMT family in different genetic subgroups of MM patients (indicated translocations and non-translocation).

Overall, PRMT-mediated arginine methylation directly impacts protein stability, expression, and activity, influencing a range of cellular processes. Their roles in normal development, disease progression, and cancer have been extensively reviewed.[14,15,46–48]

EXPRESSION OF THE PRMT FAMILY IN MM CELLS

While novel treatments have improved progression-free survival (PFS), RR MM remains incurable. Our group focuses on dissecting the role of PRMTs in MM pathology. By analyzing publicly available transcriptomic datasets, we found that PRMT1, PRMT4 (CARM1), and PRMT5 are highly expressed in both MM cell lines (Cancer Cell Line Encyclopedia, Figure 2A; Table S1) and patient samples (dataset from Multiple Myeloma Research Foundation, Figure 2B). Patients with elevated expression of these PRMTs were strongly associated with poor overall survival (OS) and PFS. Additionally, RR MM patients showed markedly higher PRMT expression compared to those with newly diagnosed MM.[49–51] Our previous studies, along with others, have demonstrated that these genes are critical for MM cell pathology through various mechanisms that will be discussed in detail in the following.

We further examined the expression of PRMTs across different genetic subgroups of MM and observed that PRMT1, CARM1, and PRMT5 are consistently overexpressed across all subgroups (Figure 2C). To evaluate the prognostic significance of these PRMTs, we performed multivariate Cox proportional hazards regression. High-risk MM subtypes, defined by biallelic deletion of TP53 (bi-TP53), amplification or gain of chromosome 1q (Amp 1q and gain 1q), and translocations t(4; 14) and t(14; 16), align with the International Staging System 3.

Our analysis revealed that elevated PRMT1 expression is significantly associated with high-risk MM, in terms of both OS and PFS. CARM1 expression is also linked to high-risk stages, albeit to a lesser extent than PRMT1. Of the three, PRMT5 shows the weakest association with high-risk disease (Figure 3).

FUNCTIONS OF PRMTs IN MM PATHOLOGY

PRMT1

PRMT1 is the most predominant type I PRMT, accounting for over 80% of ADMA formation.[52] PRMT1 regulates numerous cellular processes, including transcriptional control, signal transduction, and DNA damage repair, by methylating both histone and non-histone substrates.[53] The structure, isoforms, and fundamental functions of PRMT1 have been thoroughly reviewed.[54,55] Aberrant expression of PRMT1 is associated with poor prognosis in various cancers.

Our group was the first to demonstrate that PRMT1 is essential for the survival of MM cells.[51] We found that elevated PRMT1 expression correlates strongly with poor survival and relapse in refractory MM patients. Disrupting PRMT1, by either deletion or inhibition of its enzymatic activity, impaired MM cell viability by inducing cell-cycle arrest and apoptosis. *In vivo*, our xenograft model confirmed the anti-MM effects of PRMT1 inhibition. Notably, we also observed that PRMT1 modulates T cell activation in co-culture assays, suggesting that PRMT1 inhibition could enhance immunotherapy. Consistent with our findings, Liu et al. reported that PRMT1 methylates cGAS, preventing its dimerization and suppressing the cGAS/STING pathway. Inhibition of PRMT1 increases tumor-infiltrating lymphocytes in a cGAS-dependent manner and enhances PD-L1 expression in tumor cells, potentiating antitumor effects when combined with anti-PD-1 therapy.[56] Emerging evidence highlights the significant role of PRMT1 in T cell function and immunotherapy. PRMT1 is crucial for Th17 cell differentiation by promoting STAT3 expression, which replaces the inhibitory STAT5 at the interleukin-17 locus.[57] Notably, targeting PRMT1 has been shown to

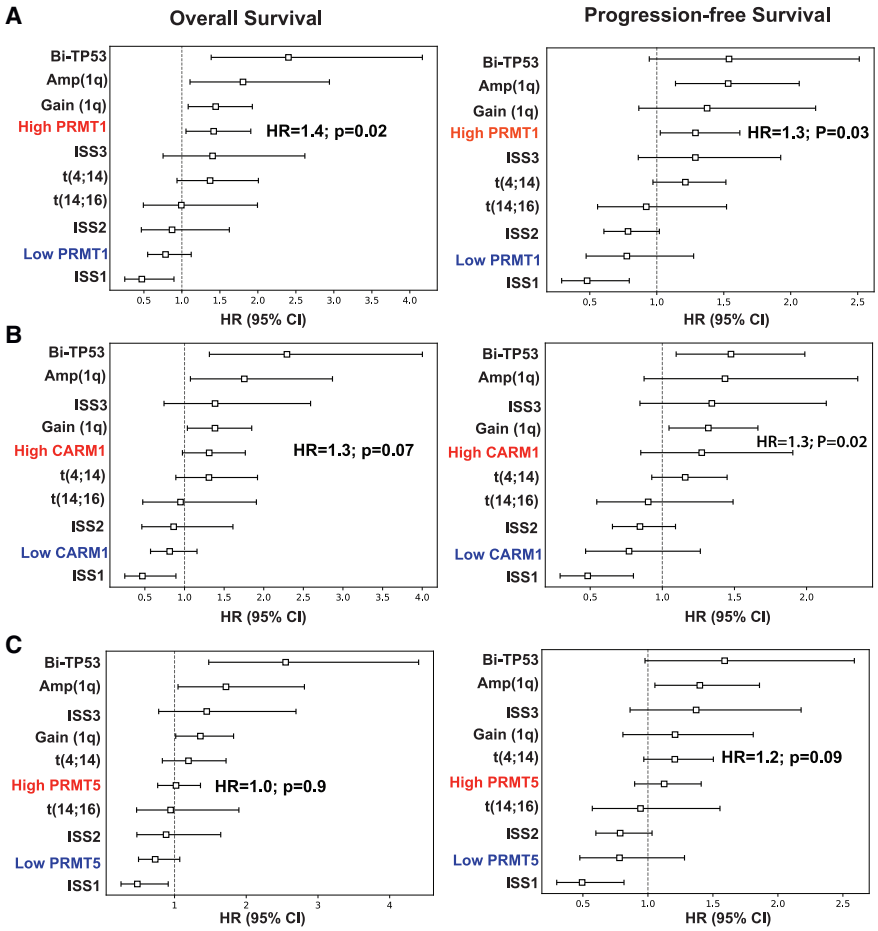

Figure 3. Risk factors of PRMT family in MM

Multivariate Cox proportional hazard regression analysis for PRMT1 (A), PRMT4/CARM1 (B), and PRMT5 (C). HR, hazard ratio. *p* values (p) were indicated. HR > 1 is associated with poor prognosis. High and Low represent high and low expression of genes in patients, respectively.

effectively prevent chronic graft-versus-host disease by reducing Th17 cells.[58] Several studies further reported that PRMT1 inhibition enhances the efficacy of anti-PD1 therapy by modulating T cell functions. Analysis of data from The Cancer Genome Atlas Program revealed that elevated PRMT1 expression is associated with poor survival and reduced immune infiltration in melanoma patients.[59] Additionally, PRMT1 suppresses interferon gamma-induced major histocompatibility complex class I expression, thereby reducing CD8+ T cell-mediated cytotoxicity in human melanoma models.[60] Consistent with these findings, other studies have shown that PRMT1 inhibition activates the interferon pathway by facilitating the formation of double-stranded RNA from endogenous retroviral elements (ERVs). Mechanistically, PRMT1 mediates H4R3me2a, leading to increased H3K27ac at enhancer regions of DNMT1. Consequently, PRMT1 suppression downregulates DNMT1 expression, promoting ERV transcription and subsequent interferon signaling.[61]

PRMT1 also regulates m6A RNA modifications by methylating METTL14 and WTAP in both cancer[62] and stem cells.[63] In MM cells, Jia et al. found that knockdown of PRMT1 reduces oxidative phosphorylation stress by downregulating NDUFS6 expression, which was identified as a novel m6A target of WTAP.[50] PRMT1 regulates the m6A writer complex (METTL3-METTL14-WRAP) by methylating WTAP[50] and METTL14,[62,63] thereby increasing the mRNA levels of NDUFS6.

The role of m6A methylation in MM pathology has been previously explored. IDH2 regulates global m6A methylation by activating the RNA demethylase FTO, which decreases m6A levels on WNT7B transcripts, leading to increased WNT7B expression and activation of the Wnt signaling pathway.[64] Additionally, the RNA demethylase ALKBH5 has been shown to be critical for MM tumorigenesis.[65] ALKBH5 enhances the stability of TRAF1 transcripts by reducing m6A abundance in the 3′-untranslated region, which in turn activates nuclear factor κB (NF-kB) and mitogen-activated protein kinase signaling, promoting MM progression.

CARM1 (PRMT4)

CARM1, a type I PRMT, is responsible for methylating over 300 substrates and plays a critical role in diverse cellular processes, including cell-cycle regulation, differentiation, RNA processing, and transcriptional activation.[66–71] Unlike PRMT1, which preferentially methylates the GGRGG motif, CARM1's substrates contain proline-rich sequences rather than RGG motifs.[68] Elevated CARM1 expression is linked to poor prognosis in several cancers,[72–76] and its role in tumorigenesis is multifaceted.[69,77,78] In alignment with our findings, CARM1 is highly expressed in MM cells and is associated with poor survival outcomes.[79]

The potential of targeting CARM1 for MM treatment was first demonstrated in 2017 with the development of a specific CARM1 inhibitor, EZM2302, which suppressed MM growth in a subcutaneous mouse model. Tumor cell ADMA levels were significantly reduced in a dose-dependent manner.[80] Another potent CARM1 inhibitor, TP-064, was developed and showed strong suppression of CARM1 enzymatic activity at nanomolar concentrations.[81] This inhibitor induced G1 cell-cycle arrest in MM cell lines. Additionally, deletion of CARM1 in MM cells downregulated genes involved in cell-cycle regulation and upregulated pro-apoptotic genes via the activation

of the p53 signaling pathway. Notably, CARM1 sensitized MM cells to bortezomib, highlighting its potential in combination therapy for MM[79].

Further research is required to elucidate the precise mechanisms by which CARM1 influences MM pathology. Importantly, the therapeutic potential of targeting CARM1 should be validated using more clinically relevant patient-derived xenograft (PDX) models.

PRMT5

PRMT5 is a predominant type II PRMT responsible for the majority of SDMA in mammals. It forms a hetero-octameric complex with methylosome protein 50 (MEP50), enabling the SDMA of various substrates, including histones and non-histone proteins.[82] The methylation of histone proteins (H3R2, H3R8, and H4R3) affects chromatin accessibility, thereby regulating gene transcription.[83,84] PRMT5 plays a critical role in several cellular processes, such as cell signaling, differentiation, DNA repair, RNA splicing, and cell-cycle control,[18,85–91] by methylating a wide range of non-histone proteins.[92] Elevated PRMT5 expression is strongly associated with various cancers and poor survival outcomes. The role of PRMT5 in tumorigenesis and its potential as a therapeutic target in cancer have been extensively reviewed.[46,92–98]

The first evidence indicating PRMT5 as a potential therapeutic target for MM was reported in 2017.[49] Consistent with our findings, the study revealed that PRMT5 is highly expressed in MM patient cells and is associated with poor prognosis. Disrupting PRMT5, through either genetic knockdown or pharmacological inhibition, significantly reduced MM cell growth both *in vitro* and *in vivo*. Targeting PRMT5 also suppressed NF-κB signaling, a key pathological pathway in MM cells. Mechanistically, PRMT5 interacts with and methylates TRIM21, an E3 ubiquitin ligase. Notably, PRMT5-mediated methylation of TRIM21 prevents the autophagic degradation of IKKB, facilitating NF-κB activation.

Pyroptosis, a highly inflammatory form of lytic programmed cell death often associated with infection responses, has been increasingly recognized for its role in tumor development. A comprehensive review explored how pyroptosis could be leveraged as a potential cancer therapy.[99] In MM cells, PRMT5 was shown to regulate pyroptosis.[100] Knockdown of PRMT5 induced pyroptosis, but not conventional caspase 3-mediated apoptosis. Overexpression of CASP1 reduced MM cell viability by inducing pyroptosis. The study also found that H4R3me2s (SDMA of H4R3) was enriched in the promoter of CASP1, suppressing its transcription. Inhibition of PRMT5 decreased H4R3me2s levels at the CASP1 promoter, while CASP1 knockdown partially rescued MM cells from PRMT5 inhibition-induced growth suppression. Additionally, transcriptomic analysis of MM cells treated with a PRMT5 inhibitor suggested that PRMT5 regulates other key biological pathways in MM, including DNA repair, alternative splicing, nonsense-mediated decay, and the PI3K/mTOR pathway.[101]

PRMT INHIBITORS IN CLINICAL TRIALS

Aberrant PRMT expression is strongly associated with poor prognosis in many cancers, making the development of specific PRMT inhibitors crucial for both treatment and understanding PRMT-related disease mechanisms. Solid preclinical studies have paved the way for translating findings on PRMT5 and type I PRMTs into clinical trials. Since 2019, many PRMT inhibitors have been patented, with nine (primarily targeting PRMT5 and type I PRMTs) tested in clinical trials.[97,102,103]

GSK3326595, a selective PRMT5 inhibitor, was the first to enter clinical testing: a phase 1 trial (NCT02783300) in RR solid tumors and non-Hodgkin's lymphoma. The trial was completed, and outcomes showed promising responses, particularly in bladder cancer and adenoid cystic carcinoma, with adverse effects including nausea, anemia, and fatigue (METEOR-1 trial). A phase 1/2 study (NCT03614728) in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia was terminated due to limited clinical activity despite robust target engagement.[104] A phase 2 breast cancer trial (NCT04676516) is complete, but results remain unreported.

Three other PRMT5 inhibitors, including JNJ-64619178, PF-06939999, and PRT543, are in phase 1 trials. JNJ-64619178 (NCT03573310, active, but not recruiting) showed dose-dependent toxicity and preliminary antitumor activity, with intermittent dosing sustaining target inhibition.[105] PF-06939999 (NCT03854227, terminated) demonstrated a tolerable safety profile and clinical responses in a subset of patients, validating PRMT5 as a viable cancer target. PRT543 (NCT03886831, completed) was tolerable, though efficacy in advanced adenoid cystic carcinoma was limited.[106]

The type I PRMT inhibitor GSK3368715 showed striking preclinical efficacy, particularly in MTAP-null tumors,[107] but its phase 1 trial in diffuse large B cell lymphoma and selected solid tumors (NCT03666988) was terminated due to thromboembolic events and lack of efficacy.[108]

MAT2A inhibitors, which target PRMT5 activity, are also under investigation. AG-270, a MAT2A inhibitor, showed promising pharmacokinetics but significant toxicity in a phase 1 trial (NCT03435250, terminated).[109] Ongoing trials are evaluating its combination with taxane-based therapies for lung and pancreatic cancers. AMG 193, a CNS-penetrant methylthioadenosine-cooperative PRMT5 inhibitor, was tested in the phase 1 trial (NCT05094336, active and recruiting) for MTAP-deleted solid tumors. The dose exploration data reported a favorable safety profile without clinically significant myelosuppression. Promising antitumor activity was also observed.[110] Several PRMT5 inhibitors of this kind (CNS-penetrant, MTAP-deleted tumors) are currently being tested in different phase 1 trials (NCT05732831, NCT04089449, NCT05275478, and NCT05245500). There are two active NCI-sponsored phase 1/2 clinical trials to study the efficacy of PRMT5 inhibitor (AZD3470) in patients with MTAP-deficient advanced/metastatic solid tumor (NCT06130553) and RR hematologic malignancies (NCT06137144).

While these early trials show promise, challenges remain in improving safety, optimizing dosing strategies, and identifying effective combination therapies. Developing biomarkers to select patients likely to respond to PRMT inhibitors will be critical for future trials.

PERSPECTIVE IN TARGETING PRMT FAMILY FOR MM TREATMENT

PRMTs play a pivotal role in several key cellular processes, many of which are targets of cancer cells to drive tumor growth and survival. Aberrant expression of PRMTs, particularly PRMT1, PRMT4 (CARM1), and PRMT5, has been strongly associated with poor prognosis and survival in MM. These findings make PRMTs attractive therapeutic targets, especially since they are implicated in multiple pathways crucial to MM cell survival. While the first clinical trial using PRMT inhibitors for cancer treatment started a decade ago, there is no current trial using PRMT inhibitors for MM treatment.

Despite preliminary preclinical success of targeting PRMTs for MM treatment, several challenges remain. (1) All the current published preclinical data showing the *in vivo* efficacy of targeting PRMTs were done in xenograft models using MM cell lines. Testing the antitumor efficacy of PRMT inhibitors using MM PDX models is crucial to demonstrate the potential of these inhibitors as therapeutic options for MM patients. (2) PRMTs have a wide range of biological functions in normal cells, so inhibiting them could lead to toxicity or off-target effects. Thus, MM-specific targeting is crucial to enhance the efficacy and mitigate the toxicity. Nanoparticles or extracellular vesicles conjugated with antibodies or aptamers targeting MM cells specifically are promising delivery platforms to achieve the MM-specific targeting. (3) MM is a heterogeneous disease, and not all patients may respond equally well to PRMT-targeted therapies. Biomarker development is critical to identify which patients would benefit most from PRMT inhibition. For examples, cells harboring splicing factor mutations (SRSF2, U2AF1, and SF3B1) are highly sensitive to PRMT1 and PRMT5 inhibitor, while EZH2-null cells are significantly more resistant.[111] (4) Like many targeted therapies, resistance to PRMT inhibitors may develop over time. Understanding the mechanisms of resistance and identifying strategies to overcome them will be crucial for the long-term success of PRMT inhibitors in MM.

Future directions for PRMT-targeted therapies in MM include precision medicine approaches to stratify patients based on PRMT expression levels or specific mutations and exploring combination therapies to enhance efficacy. Given the immune-related functions of some PRMTs, their inhibitors may also modulate the immune environment, improving responses to immunotherapy. Overall, targeting PRMTs represents a promising therapeutic strategy for MM, with strong biological rationale and encouraging preclinical evidence. However, clinical success will depend on overcoming challenges such as toxicity, resistance, and patient selection. With further research and careful clinical development, PRMT inhibitors could become an important addition to the MM treatment arsenal, especially for patients with relapsed or refractory disease.

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AUTHOR CONTRIBUTIONS

N.T.T. conceived the project. N.T.T. and S.F.Q. designed, reviewed, interpreted, and wrote the manuscript. E.L. and B.A.W. analyzed the data related to the expression and risk factors of PRMTs.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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