

PRMT7 at the crossroads of cancer progression and therapeutic targeting (Review)

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Abstract. Protein arginine methyltransferase 7 (PRMT7), the sole type III PRMT family member, catalyzes arginine monomethylation and has recently emerged as an important regulator of cancer biology. Increasing evidence indicates that PRMT7 participates in tumor initiation and progression through epigenetic regulation, transcriptional control, RNA processing and signaling pathway modulation. Dysregulated PRMT7 expression has been reported in diverse malignancies, including leukemia, breast cancer, lung cancer, renal cell carcinoma, hepatocellular carcinoma, prostate cancer and gastric cancer. Functionally, PRMT7 has been implicated in epithelial-mesenchymal transition, cancer stemness, metastasis and immune modulation, although its effects may vary depending on cellular and tumor context. The present review summarizes the structural and biochemical features of PRMT7, its mechanistic roles across different cancer types, and its potential as a therapeutic target. Recent progress in PRMT inhibitor development was also discussed, with particular emphasis on PRMT7-selective compounds such as SGC3027, SGC8158 and JS1310, as well as the key challenges that remain for clinical translation. Elucidating the context-specific functions and targetable vulnerabilities of PRMT7 may provide new opportunities for precision cancer therapy.

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1. Introduction

Protein arginine methylation is a fundamental post-translational modification that contributes to the regulation of gene expression, RNA metabolism and intracellular signaling (1,2). Catalyzed by the protein arginine methyltransferase (PRMT) family, this modification alters the steric and hydrogen-bonding properties of arginine residues while preserving their overall positive charge, thereby reshaping molecular interactions and cellular responses (1-3). Accumulating evidence indicates that aberrant arginine methylation is closely linked to the development and progression of human diseases, especially cancer (4,5).

The mammalian PRMT family consists of nine enzymes that are classified into three types according to their catalytic products, with additional differences in structural organization and substrate preference across family members (1,6,7) (Table I). Type I PRMTs catalyze the formation of monomethyl-arginine (MMA) and asymmetric dimethylarginine, whereas type II PRMTs generate MMA and symmetric dimethylarginine (1,6,7). PRMT7 is the only type III PRMT identified in mammals and is uniquely restricted to MMA formation (7-9). This catalytic property is supported by its distinctive structural architecture, including a tandem double-module organization and a zinc-finger-containing region, which distinguish PRMT7 from type I and type II PRMTs (7-9). Such structural divergence not only underlies its unique enzymatic behavior but also contributes to its distinct regulatory functions within the arginine methylation network. Beyond its role as a monomethyl-transferase, PRMT7 may also function as a regulatory component within the broader arginine methylation network. Because MMA represents a common intermediate in arginine dimethylation reactions, PRMT7-mediated monomethylation can serve

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Abbreviations: PRMT7, protein arginine methyltransferase 7; MMA, monomethyl-arginine; T-ALL, T-cell acute lymphoblastic leukemia; CML, chronic myeloid leukemia; EMT, epithelial-mesenchymal transition; NSCLC, non-small-cell lung cancer; HCC, hepatocellular carcinoma

Key words: PRMT7, arginine monomethylation, epigenetics, cancer progression, tumor immunity, PRMT inhibitors

as a ‘priming’ event that enables subsequent methylation by other PRMT family members in specific contexts. A representative example is the PRMT7-PRMT5 methylation relay, in which PRMT7-catalyzed H4R17 monomethylation enhances PRMT5-dependent H4R3 symmetric dimethylation (H4R3me₂s) through an allosteric mechanism (10). This finding highlights that PRMT7-mediated MMA formation is not merely a terminal modification but can also function as an upstream regulatory event controlling broader arginine methylation dynamics. These unique properties also provide a rationale for selective inhibitor development.

Early mechanistic studies of PRMTs focused on histone arginine methylation and transcriptional regulation (5). More recent biochemical and proteomic studies have markedly expanded the known substrate spectrum to include diverse non-histone proteins (11-13). Depending on the PRMT and substrate involved, non-histone methylation can regulate protein stability, subcellular localization, molecular interactions, RNA processing, translation, metabolism and signal transduction (5,11,14). Certain PRMT family members may also converge on shared substrates, or influence one another through sequential or cooperative methylation events, such as the PRMT7-PRMT5 histone methylation relay (10,13). In addition, the functions of certain PRMTs extend beyond the nucleus, with cytoplasmic and mitochondrial substrates linking arginine methylation to translational stress responses, protein homeostasis, and cellular metabolism (14-16). This broad regulatory scope is reflected in the frequent dysregulation of PRMT expression and activity across numerous cancers (5,17). Within this family, PRMT7 has recently emerged as an important functional regulator because of its context-dependent functions. PRMT7 is implicated in the progression of a broad spectrum of malignancies, including leukemia, breast cancer (BC), lung cancer (LC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), prostate cancer (PC) and gastric cancer (GC) (5,17,18). In most settings, PRMT7 exhibits tumor-promoting activity by facilitating epithelial-mesenchymal transition (EMT), stemness maintenance, invasion, metastasis and therapy adaptation (5,17-21). However, in certain contexts, PRMT7 may exert tumor-suppressive effects. Understanding the mechanistic basis of this functional duality is therefore essential for clarifying its biological significance and therapeutic relevance.

This functional diversity may reflect differences in substrate and pathway availability, interactions with other PRMT family members and epigenetic regulators (10,22,23), and the cellular and tumor-microenvironmental (TME) states present in individual cancers (24,25). Accordingly, a cross-cancer mechanistic framework is needed to explain how these contextual factors shape the biological output of PRMT7 and influence its suitability as a therapeutic target.

Therapeutic targeting of PRMTs has become an active area of anticancer drug development (5,17). Several inhibitors against type I PRMTs and PRMT5 have entered clinical trials, underscoring the feasibility of pharmacologically targeting arginine methylation (5). By contrast, PRMT7-specific inhibitor discovery is still in the early stages of development. Given the unique structure and context-dependent oncogenic functions of PRMT7, a systematic evaluation of its biological roles and targetability is timely (26). In the present review,

current knowledge of PRMT7 structure and function were summarized, its mechanistic roles across different cancer types were discussed, and recent progress in PRMT inhibitor development was examined, with particular emphasis on strategies and challenges for targeting PRMT7 in cancer.

2. Structural and biochemical basis of PRMT7 function

Structural organization and catalytic architecture of PRMT7. PRMT7 is structurally distinct from other members of the PRMT family and represents the only type III PRMT identified in mammals (Fig. 1A) (23,27-29). Despite differences in domain organization and methylation products, mammalian PRMTs share a conserved catalytic core composed of a Rossmann-like fold responsible for S-adenosylmethionine binding, a β -barrel domain involved in substrate recognition, and characteristic catalytic elements such as the double-E and THW loops (30,31). In most type I and type II PRMTs, a single catalytic module is present in each polypeptide, and two or more protein molecules associate through dimerization interfaces to form homodimers or higher-order oligomeric assemblies (30,31). By contrast, PRMT7 contains two tandem PRMT modules within a single polypeptide, forming an intramolecular pseudo-dimer that resembles the dimeric architecture of other PRMTs (Fig. 1B) (23,27,29). This tandem organization is considered to have arisen through duplication of an ancestral PRMT-like domain, with the two resulting modules folding together to form a dimer-like arrangement within a single polypeptide chain (22,23). Like other PRMT family members, each PRMT7 module comprises a conserved Rossmann fold domain and a β -barrel/ β -bucket-like domain, whereas PRMT7 additionally contains a zinc-finger motif positioned between the N-terminal and C-terminal modules (23). Structural studies have shown that only the N-terminal module is catalytically competent, while the C-terminal module is inactive because of substitutions in residues required for methyl donor binding and catalysis (23,29). Thus, unlike the relatively symmetric organization of conventional PRMT homodimers, the two modules of PRMT7 are structurally and functionally asymmetric: The N-terminal module provides the principal catalytic site, whereas the C-terminal module contributes mainly to the overall pseudo-dimeric architecture (9,32). Importantly, the zinc-finger motif is not merely a structural insertion but also contributes to substrate recognition, particularly for basic sequence contexts enriched in R-X-R motifs, thereby helping define the substrate selectivity of PRMT7 (23,29,33,34).

Monomethylation specificity and PRMT7-mediated methylation relay. A central biochemical feature of PRMT7 is its strict ability to generate MMA only (23,35). All three PRMT classes catalyze an initial methyl transfer to generate MMA, but they differ in whether and how they subsequently methylate this intermediate: Type I PRMTs generate asymmetric dimethylarginine, type II PRMTs generate symmetric dimethylarginine, whereas type III PRMT7 terminates the reaction after the first methyl-transfer step (5,36). This product specificity is determined by the spatial constraints of its catalytic pocket, especially the configuration of the conserved double-E loop and surrounding active-site residues,

Table I. Classification, catalytic properties, structural features, and substrate preferences of the PRMT family.

Type	Members	Catalytic Products	Structural Characteristics	Substrate Specificity and Representative Substrates
Type I	PRMT1, PRMT3, PRMT4, PRMT6	MMA → ADMA (asymmetric dimethylarginine)	Homodimers (head-to-tail arrangement via dimerization arm; essential for activity and processivity). PRMT3 contains an N-terminal zinc-finger domain; PRMT4 possesses unique N- and C-terminal extensions. Active-site geometry (double-E loop and THW loop) permits reorientation of monomethyl-arginine for a second methylation on the same terminal nitrogen atom.	Strong preference for glycine-arginine-rich (GAR/RGG) motifs (PRMT1, PRMT3, PRMT6); PRMT4 prefers proline-glycine-methionine (PGM)-rich sequences. Key substrates: Histone H4R3me2a (PRMT1/PRMT3), H3R17me2a/H3R26me2a (PRMT4), H3R2me2a (PRMT6); numerous RNA-binding proteins and DNA repair factors (for example, MRE11, 53BP1).
Type II	PRMT5, PRMT9	MMA → SDMA (symmetric dimethylarginine)	PRMT5 forms a hetero-octameric complex with MEP50 (PRMT5 ₄ -MEP50 ₄); contains an N-terminal TIM-barrel domain for complex assembly and substrate recruitment. PRMT9 features duplicated methyltransferase modules (N-terminal catalytic, C-terminal structural). Active-site geometry favors methylation on the opposite guanidino nitrogen.	PRMT5 prefers GAR/RGG motifs; PRMT9 exhibits narrow specificity and minimal activity on canonical GAR sequences. Key substrates: Histone H3R8me2s/H4R3me2s and spliceosomal Sm proteins (PRMT5); SF3B2/SAP145 at Arg508 (PRMT9, highly specific and non-redundant).
Type III	PRMT7	MMA only	Monomeric protein with tandem duplication of PRMT-like modules forming an intramolecular pseudodimer (N-terminal catalytic domain + C-terminal structural module). Constricted active-site cavity (double-E loop and THW loop) prevents a second methylation.	Strong preference for RXR motifs flanked by basic residues (Lys/Arg-rich regions). Key substrates: Histone H2B (RKRSR sequence at positions 29-33), HSP70 family (for example, R469), translation initiation factors (eIF2α), and DNA damage response proteins.

PRMT, protein arginine methyltransferase; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; MMA, mono-methyl-arginine; GAR, glycine-arginine-rich; PGM, proline-glycine-methionine; RXR, arginine-X-arginine.

which tightly position the guanidino group of arginine and restrict accommodation of a second methyl transfer (8,9). Thus, PRMT7 retains the conserved catalytic framework of the PRMT family while modifying this shared architecture in a manner that favors monomethylation. Importantly, PRMT7-mediated monomethylation can also function as a regulatory intermediate within the arginine methylation network rather than merely representing a terminal modification. A representative example is the PRMT7-PRMT5

methylation relay, in which PRMT7-generated H4R17me1 enhances PRMT5-mediated H4R3 symmetric dimethylation (H4R3me2s) through an allosteric mechanism, illustrating how PRMT7-derived MMA can modulate the activity of other PRMT family members (10). As a result, PRMT7 catalyzes only the first methylation step and cannot efficiently generate asymmetric or symmetric dimethylarginine (8,23,35). This biochemical property distinguishes PRMT7 from type I and type II PRMTs and suggests that PRMT7 may function as a

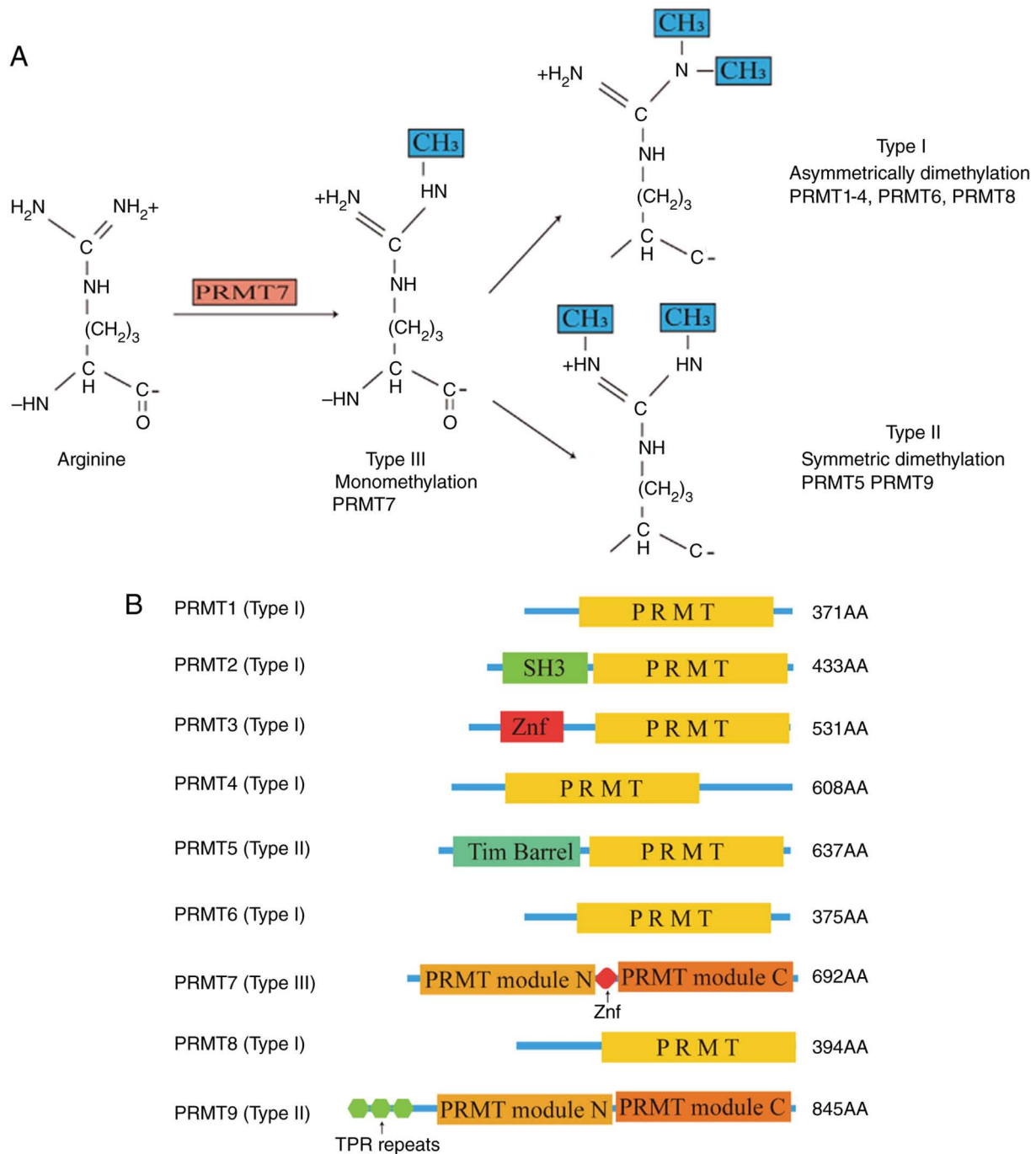


Figure 1. Catalytic classification and domain architecture of the PRMT family. (A) Overview of PRMT classification according to methylarginine products. Type I PRMTs catalyze the formation of MMA and asymmetric dimethylarginine, type II PRMTs produce MMA and symmetric dimethylarginine, and type III PRMT7 catalyzes MMA formation only. (B) Schematic representation of the structural domains of mammalian PRMT family members. In addition to the conserved PRMT catalytic module, some PRMTs contain accessory domains such as SH3, ZnF, TIM-barrel and N-terminal regulatory regions. PRMT7 is structurally distinct in containing tandem N-terminal and C-terminal PRMT modules within a single protein, which underlies its unique catalytic and substrate-recognition properties. PRMT, protein arginine methyltransferase; MMA, monomethyl-arginine.

more selective regulator of arginine methylation-dependent signaling (7,23). Rather than acting as a binary molecular switch, PRMT7-mediated MMA may serve as a fine-tuning modification that subtly modulates chromatin state, protein interaction networks, and stress-responsive signaling pathways (7,23).

The structural and catalytic features of PRMT7 are closely linked to its cancer-relevant functions. Because PRMT7 preferentially recognizes arginine-rich motifs, including

R-X-R-containing sequences, its substrates include both histone and non-histone proteins, such as histone H4R3, H2AR3 and several stress- or RNA-associated proteins including HSP70 family members (14,15,23,33,35,37). Through selective monomethylation of proteins involved in epigenetic regulation, stress adaptation, RNA metabolism and cell plasticity, PRMT7 is positioned to influence tumor cell survival, invasion, metastatic dissemination and therapeutic response (5,14,23). These unique mechanistic properties provide the basis for the

context-dependent functions of PRMT7 in cancer, which are discussed in the following sections.

Reversibility of arginine methylation and current controversies. The reversibility of arginine methylation remains an unresolved question. Although PRMTs responsible for installing arginine methylation marks have been extensively characterized, the existence of dedicated arginine demethylases remains controversial. Given that PRMT7 predominantly generates MMA, understanding whether and how MMA marks are removed is important for defining the dynamics of PRMT7-mediated regulation.

Peptidyl-arginine deiminase 4 (PAD4/PADI4) has been proposed as a mechanism that can reduce methylated arginine levels through deamination (38,39). PAD4 converts methylated arginine residues into citrulline, accompanied by the release of methylamine (38). Although this reaction results in the loss of methylated arginine, it does not represent classical demethylation because the original arginine residue is irreversibly converted into citrulline and cannot be remethylated. Therefore, PAD4-mediated regulation is considered an irreversible residue-conversion mechanism rather than a reversible demethylation cycle.

JMJD6 was initially reported as a histone arginine demethylase capable of removing methyl groups from histone arginine residues (40). However, subsequent studies demonstrated that JMJD6 primarily functions as a lysyl hydroxylase involved in RNA splicing regulation rather than as a bona fide arginine demethylase (41). Further biochemical analyses found that the reported demethylase activity of JMJD6 has been difficult to reproduce, leaving its role as an arginine demethylase controversial (42).

Currently, no universally accepted arginine demethylase analogous to lysine demethylases has been identified. Therefore, the turnover of arginine methylation is considered to depend mainly on mechanisms such as protein degradation, replacement of modified proteins and irreversible residue conversion. The lack of a clearly established arginine demethylation system may contribute to the persistence of arginine methylation-dependent regulatory states after modulation of PRMT activity and represents an important consideration for the development of PRMT-targeted therapies.

Regulation of PRMT7 expression and activity. Understanding how PRMT7 expression and enzymatic activity are regulated is essential for elucidating how this methyltransferase responds to different cellular contexts. Emerging evidence indicates that PRMT7 regulation occurs at multiple levels, including transcriptional control, post-transcriptional regulation, and intrinsic structural mechanisms that modulate its catalytic activity.

At the transcriptional level, PRMT7 expression can be regulated by cellular signaling pathways and genomic regulatory elements. In inflammatory contexts, NF- κ B/RelA signaling has been shown to transcriptionally induce PRMT7 expression in monocytes, linking inflammatory signaling with PRMT7-dependent epigenetic regulation (43). In addition, PRMT7 transcriptional upregulation has been observed during satellite cell activation, suggesting that PRMT7 expression is dynamically regulated during cellular-state transitions (44). In

HCC, enhancer-mediated regulation of the PRMT7 locus has also been reported, in which a risk-associated enhancer variant promotes HNF4A binding and increases PRMT7 transcription (44). Post-transcriptionally, microRNA (miR)-24-2 has been shown to target PRMT7 and suppress its expression in liver cancer stem cells (45).

PRMT7 activity is also regulated by intrinsic structural features. Although the C-terminal PRMT-like module lacks catalytic activity, it contributes to intramolecular regulation by interacting with the N-terminal catalytic module and imposing an autoinhibitory constraint (23,32). In addition, PRMT7 automethylation at R531 has been reported to regulate its chromatin recruitment and functional activity in BC models, providing another layer of post-translational regulation (46).

Together, these findings indicate that PRMT7 is regulated through multiple mechanisms, including transcriptional control, post-transcriptional regulation, and structural modulation of enzymatic activity. Such multilayered regulation may contribute to the context-dependent functions of PRMT7 in different physiological and pathological settings.

3. PRMT7 and cancer

Accumulating evidence indicates that PRMT7 is an important and context-dependent regulator in cancer. In different malignancies, PRMT7 has been implicated in transcriptional regulation, EMT, metabolic adaptation, stemness maintenance and tumor immunity. Although PRMT7 exhibits predominantly pro-tumorigenic functions in most cancer types, its biological effects may vary depending on tumor context and downstream substrates (Fig. 2, Table II). In the following sections, we summarize the roles and molecular mechanisms of PRMT7 across major hematologic and solid tumors.

PRMT7 in leukemia. Emerging evidence indicates that PRMT7 plays a context-dependent but predominantly pro-leukemogenic role in hematologic malignancies (47). In T-cell acute lymphoblastic leukemia (T-ALL), PRMT7 is highly expressed relative to normal T cells, particularly in more differentiated leukemic subtypes, suggesting that its aberrant activation is associated with leukemic transformation (48). Mechanistically, PRMT7-dependent arginine monomethylation has been linked to dysregulation of RUNX1 target genes, indicating that PRMT7 may fine-tune transcriptional programs critical for T-ALL pathogenesis (48). In chronic myeloid leukemia (CML), PRMT7 has attracted particular attention because it appears to be required for the maintenance of leukemia stem cells (LSCs) (24). Genetic or pharmacological inhibition of PRMT7 selectively impairs LSC survival while sparing normal hematopoietic stem cells (HSCs), highlighting PRMT7 as a potential therapeutic vulnerability in stemness-driven leukemia (24).

In addition to transcriptional control, PRMT7 may support leukemic cell fitness through stress-adaptive and metabolic mechanisms. PRMT7-dependent rewiring of glycine metabolism has been directly implicated in the maintenance of CML LSCs, whereas studies in other cellular contexts have shown that PRMT7-mediated methylation of HSP70 family proteins promotes proteostasis and stress tolerance, suggesting a broader adaptive function that may also be relevant to

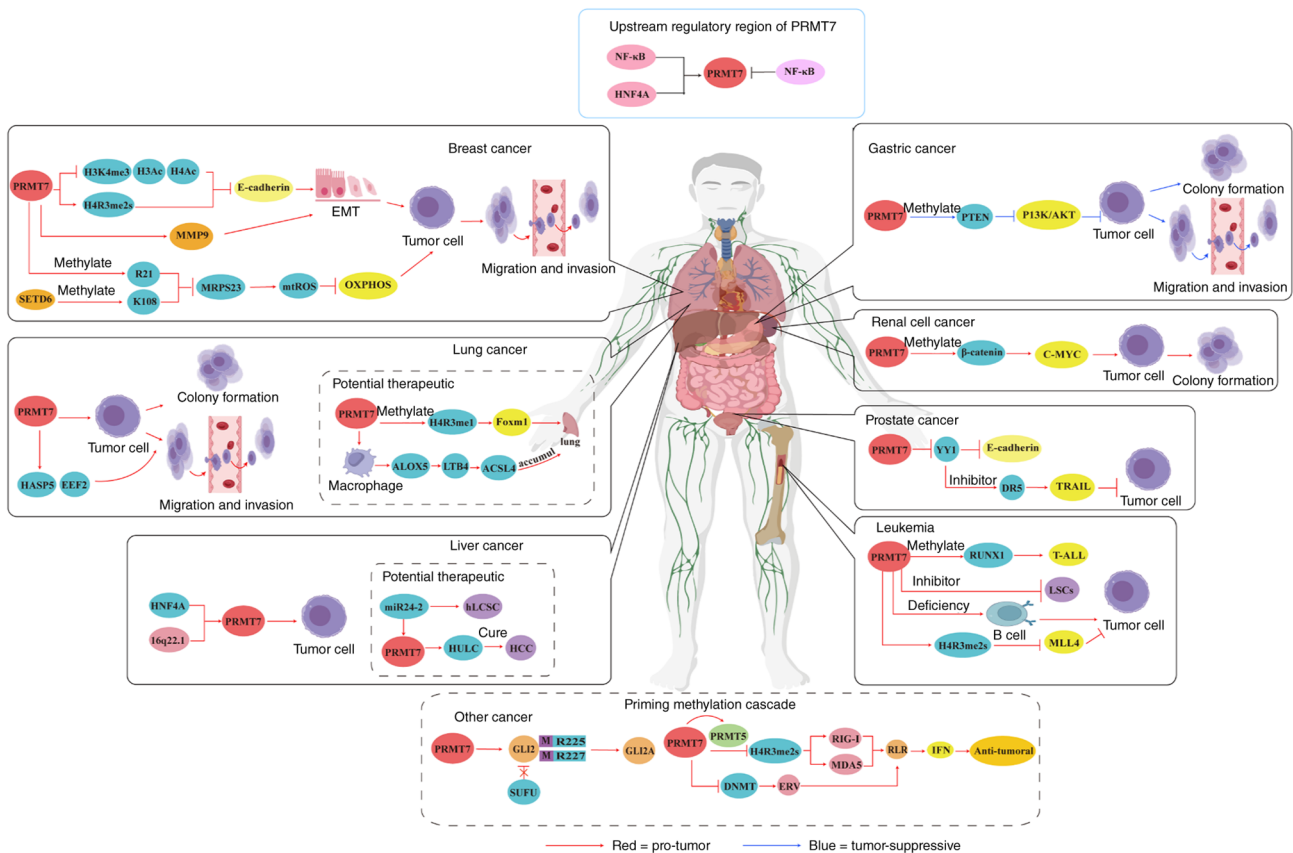


Figure 2. Overview of the cancer-type-specific roles of PRMT7. Schematic illustration of the major molecular pathways and biological processes regulated by PRMT7 across different cancer types. PRMT7 is involved in the control of transcriptional programs, epithelial-mesenchymal transition, stemness, metabolic adaptation, oncogenic signaling and tumor immunity in a context-dependent manner. Although PRMT7 displays predominantly pro-tumorigenic functions in most malignancies, its biological effects may vary across tumor types and molecular settings. PRMT, protein arginine methyltransferase.

leukemia (24). These observations position PRMT7 not only as an epigenetic regulator but also as a metabolic and stress-response modulator in leukemia. In addition, studies in B-cell systems indicate that PRMT7 negatively regulates BCL6 expression and influences germinal center responses, further supporting its role in lymphoid lineage homeostasis and malignant transformation (49).

Collectively, these observations suggest that the leukemogenic role of PRMT7 extends beyond transcriptional control and is closely tied to stem cell maintenance, proteostasis and metabolic adaptation, particularly in LSCs.

PRMT7 in BC. Among solid tumors, the role of PRMT7 has been most extensively characterized in BC, where it is generally considered a metastasis-promoting factor. PRMT7 is upregulated in primary breast tumors, lymph node metastases and highly invasive BC cell lines, and its depletion suppresses invasion *in vitro* and metastasis *in vivo*, whereas ectopic expression enhances the aggressive phenotype (50). A central mechanism underlying this effect is the induction of EMT. In BC cells, PRMT7 represses E-cadherin transcription by occupying the proximal E-cadherin promoter and facilitating the recruitment of YY1 and HDAC3, thereby establishing a repressive chromatin state characterized by increased H4R3me2s and reduced H3K4me3, H3 acetylation and H4 acetylation (46). Notably, given that PRMT7 is a type III PRMT restricted to MMA formation, the H4R3me2s enrichment observed at the

E-cadherin promoter is more appropriately interpreted as part of a PRMT7-dependent repressive chromatin environment rather than a direct catalytic output of PRMT7. Consistent with this model, loss of PRMT7 or disruption of its auto-methylation at R531 weakens its YY1-dependent recruitment to the E-cadherin promoter, reduces H4R3me2s at this locus, restores E-cadherin expression, and attenuates migratory and invasive behavior (46).

In addition to EMT-associated chromatin regulation, PRMT7 also promotes BC aggressiveness through other pathways. PRMT7 upregulates MMP9 expression, and exogenous MMP9 can partially rescue the invasive defect caused by PRMT7 depletion, indicating that MMP9 is an important downstream effector of PRMT7-driven invasion (18). PRMT7 has also been reported to influence mitochondrial homeostasis through methylation-dependent regulation of MRPS23, thereby affecting oxidative phosphorylation and mitochondrial reactive oxygen species (mtROS)-associated metastatic traits (16).

Collectively, these findings place PRMT7 as an important regulator of BC invasiveness, acting through coordinated effects on EMT, non-histone substrate methylation and mitochondrial reprogramming.

PRMT7 in LC. PRMT7 has also been implicated in LC progression, particularly in non-small cell LC (NSCLC). Early functional studies showed that PRMT7 overexpression

Table II. Cancer-type-specific functions, molecular mechanisms, and therapeutic implications of PRMT7.

First author/s, year	Cancer type	Role in cancer	Major phenotype	Key molecular mechanism	(Refs.)
Liu <i>et al</i> , 2022; Oksa <i>et al</i> , 2022; Ying <i>et al</i> , 2015	Leukemia	Predominantly oncogenic	Leukemia stem cell maintenance, transcriptional dysregulation	RUNX1 target gene deregulation in T-cell acute lymphoblastic leukemia; glycine metabolism rewiring in chronic myeloid leukemia stem cells; BCL6-associated lymphoid regulation	(24,48,49)
Liu <i>et al</i> , 2021; Baldwin <i>et al</i> , 2015; Geng <i>et al</i> , 2017; Yao <i>et al</i> , 2014	Breast cancer	Oncogenic	epithelial-mesenchymal transition, invasion, metastasis	E-cadherin repression via YY1/HDAC3-associated chromatin remodeling; MMP9 induction; MRPS23-dependent mitochondrial reprogramming	(16,18,46,50)
Cheng <i>et al</i> , 2018; Zhang <i>et al</i> , 2025; Liao <i>et al</i> , 2018; He <i>et al</i> , 2021	Lung cancer	Oncogenic	Invasion, clonogenicity, metastatic behavior	Interaction with HSPA5 and EEF2; Stabilization of SOX9 via antagonizing ubiquitination; FOXM1-centered regulation	(51-54)
Liu <i>et al</i> , 2020	Renal cell carcinoma	Oncogenic	Tumor growth, proliferation	Stabilization of β -catenin and activation of the β -catenin/C-MYC axis	(55)
Shen <i>et al</i> , 2022; Wang <i>et al</i> , 2020	Hepatocellular carcinoma	Oncogenic	Tumor-promoting signaling, stemness-associated progression	16q22.1 enhancer variant/HNF4A-dependent PRMT7 upregulation; miR24-2-linked non-coding RNA regulatory network	(44,45)
Wan <i>et al</i> , 2025; Rodrigo-Faus <i>et al</i> , 2024; Lin <i>et al</i> , 2024	Prostate cancer	Oncogenic	Proliferation, migration, invasion, enzalutamide resistance	Methylation of FoxK1 promoting metastasis; NUDT21 monomethylation regulating alternative polyadenylation; Cell-cycle signaling	(57-59)
Wang <i>et al</i> , 2023	Gastric cancer	Tumor-suppressive	Reduced proliferation and migration	PTEN-associated inhibition of PI3K/AKT signaling	(60)
Srour <i>et al</i> , 2022; Vuong <i>et al</i> , 2019	Other cancers/immune context	Context-dependent	Hedgehog activation; enhanced tumor immunogenicity upon PRMT7 loss	GLI2 methylation weakens SUFU binding; PRMT7 ablation enhances immune checkpoint blockade response in melanoma	(25,62)

PRMT, protein arginine methyltransferase.

enhances invasion, clonogenic growth and metastatic potential in NSCLC cells, and identified HSPA5 and EEF2 as PRMT7-interacting proteins. Silencing either HSPA5 or EEF2 attenuated PRMT7-driven invasion, suggesting that PRMT7 may promote malignant behavior through protein homeostasis and translation-related networks (51).

More direct mechanistic evidence has recently established a post-translational role for PRMT7 in NSCLC through regulation of SOX9 stability. PRMT7 was shown to mono-methylate SOX9 at arginine 160 (R160), thereby antagonizing FBXW7- and KEAP1-mediated ubiquitination and proteasomal degradation, ultimately stabilizing SOX9 protein and promoting NSCLC progression (52). Functionally, this PRMT7-SOX9 axis enhanced tumor cell proliferation and tumorigenic capacity, and elevated PRMT7/SOX9 expression was associated with poorer clinical outcome, supporting a well-defined oncogenic role for PRMT7 in NSCLC (15).

In addition to this directly validated post-translational mechanism, transcriptional regulation may represent another potential dimension of PRMT7 function in the lung. FOXM1 is a well-established master regulator of cell-cycle progression, proliferation and stemness-associated transcriptional programs (53). Although direct evidence in NSCLC remains limited, studies in lung mesenchymal cells have shown that PRMT7 can promote H4R3 monomethylation at the *Foxm1* locus and enhance *Foxm1* transcription, supporting the existence of a PRMT7-*Foxm1* regulatory axis in lung tissue (54).

Taken together, available evidence indicates that PRMT7 contributes to lung tumor progression through multiple layers of regulation. Among them, SOX9 stabilization by R160 mono-methylation currently represents the most direct and best-defined mechanism in NSCLC, whereas the proposed *Foxm1*-centered transcriptional program remains supportive but indirect evidence that may broaden the functional landscape of PRMT7 in lung tissues.

PRMT7 in renal cancer. In clear cell RCC (ccRCC), PRMT7 is generally viewed as an oncogenic factor. PRMT7 expression is elevated in ccRCC cells and promotes tumor growth by enhancing proliferative signaling (55). Mechanistically, PRMT7 has been shown to stabilize β -catenin through arginine methylation-dependent inhibition of its ubiquitin-mediated degradation, resulting in increased C-MYC expression and activation of a β -catenin/C-MYC growth-promoting axis (55). Because both β -catenin and C-MYC are major drivers of renal tumor progression, this pathway provides a plausible mechanistic basis for the tumor-promoting function of PRMT7 in RCC.

Current evidence therefore supports a model in which PRMT7 promotes ccRCC progression, at least in part, by sustaining β -catenin stability and reinforcing downstream C-MYC-dependent proliferative signaling.

PRMT7 in liver cancer. PRMT7 is implicated in HCC through both genetic susceptibility and downstream oncogenic signaling. A susceptibility locus within the PRMT7 region at 16q22.1 has been linked to HCC risk, and allele-specific regulation by HNF4A at an enhancer element has been shown to increase PRMT7 expression (44). Upregulated PRMT7 is associated with HCC-promoting phenotypes

in vitro and *in vivo*, suggesting that PRMT7 may function as a downstream effector connecting inherited susceptibility to tumor-promoting molecular programs (44).

At the post-transcriptional level, PRMT7 is also integrated into non-coding RNA regulatory networks. miR-24-2 directly targets the 3' untranslated region (UTR) of PRMT7 and suppresses its translation, thereby altering histone H4R3 methylation and contributing to the malignant progression of liver cancer stem cell (45). In this context, PRMT7 is positioned within a broader regulatory network involving HULC-, Nanog-, and stemness-associated signaling rather than acting as an isolated effector (45).

Collectively, the available evidence indicates that PRMT7 participates in HCC progression through integrated genetic, epigenetic and non-coding RNA-dependent mechanisms.

PRMT7 in PC. Clinical evidence has provided translational support for the involvement of PRMT7 in PC progression. Grypari *et al* (56) integrated public datasets with patient cohort-based analyses and demonstrated that PRMT7 expression was elevated in PC tissues compared with normal prostate tissues. Furthermore, PRMT7 expression increased with aggressive disease characteristics and was enhanced following androgen deprivation therapy, suggesting a potential association between PRMT7 expression and advanced PC progression. PRMT7 expression was also correlated with EMT-related and cell-cycle-associated molecular features, further supporting its clinical relevance as a potential biomarker and therapeutic target in PC (56).

Beyond these clinical observations, accumulating evidence supports a pro-tumorigenic role for PRMT7 in PC. PRMT7 expression has been reported to be elevated in PC tissues and cell lines, and PRMT7 depletion suppresses proliferation, migration and invasion while promoting apoptosis, indicating that PRMT7 contributes to disease progression (57).

Mechanistic understanding of PRMT7 function in PC has also advanced substantially in recent studies. One study demonstrated that PRMT7 promotes the invasive phenotype of metastatic castration-resistant PC by methylating the transcription factor FoxK1, thereby altering the expression of adhesion-related molecules and enhancing metastatic capacity (58). This finding identifies FoxK1 as a direct functional substrate of PRMT7 in advanced PC and provides a concrete explanation for how PRMT7 facilitates tumor dissemination.

In addition to its role in invasion and metastasis, PRMT7 has also been linked to therapeutic resistance in PC. A recent study showed that PRMT7-mediated monomethylation of NUDT21 regulates alternative polyadenylation and promotes 3'UTR shortening, whereas loss of this methylation event contributes to resistance to enzalutamide (59). These results establish a PRMT7-NUDT21 axis as a key post-transcriptional mechanism involved in antiandrogen response and resistance, further expanding the functional spectrum of PRMT7 in PC biology.

Earlier studies also suggested that PRMT7 may participate in a YY1/TP53/CCND2/CDK6/RB1-associated signaling axis linked to cell-cycle control and malignant behavior (57). Thus, contrary to earlier assumptions that the downstream mechanisms of PRMT7 in PC remain largely undefined,

recent studies have identified at least two direct mechanistic axes, namely PRMT7-FoxK1 in metastatic progression and PRMT7-NUDT21 in enzalutamide resistance (58,59).

PRMT7 in GC. Unlike its predominantly oncogenic role in numerous tumor types, PRMT7 appears to exert tumor-suppressive functions in GC. PRMT7 expression is reduced in GC tissues, and low expression is associated with adverse clinicopathological features, including larger tumor size, poor differentiation, lymph node metastasis and advanced TNM stage. Functional studies indicate that PRMT7 suppresses proliferation and migration of GC cells (60). Mechanistically, PRMT7 has been reported to interact with PTEN and promote its arginine methylation, thereby suppressing the downstream PI3K/AKT pathway (60). This distinguishes GC from most other aforementioned cancers, where PRMT7 tends to support malignant progression, and further highlights the context-dependent nature of PRMT7 biology.

Taken together, the available evidence suggests that PRMT7 may restrain GC progression, at least in part, through PTEN-associated inhibition of PI3K/AKT signaling.

PRMT7 in tumor immunity. Recent studies have expanded the functional landscape of PRMT7 beyond tumor-cell-intrinsic regulation by demonstrating its role in shaping the tumor immune microenvironment. In addition to regulating oncogenic signaling pathways within cancer cells, PRMT7 can influence tumor immune visibility through epigenetic control of endogenous retroviral elements, innate immune sensing pathways, and immune-related transcriptional programs (25,61).

In melanoma, PRMT7 functions as an epigenetic regulator of tumor immune evasion. Genetic depletion of PRMT7 enhances tumor sensitivity to immune checkpoint blockade (ICB) by relieving repression of endogenous retroviral elements, activating RIG-I/MDA5-mediated innate immune sensing and type I interferon responses, and increasing immune-related programs such as antigen presentation and chemokine expression. These findings indicate that PRMT7 limits tumor immune visibility by maintaining an immunosuppressive epigenetic state (25).

Emerging evidence suggests that this immunomodulatory function may extend beyond melanoma. In BC, PRMT7 expression is associated with reduced CD8⁺ T-cell infiltration and unfavorable clinical outcomes. In immunocompetent mouse models, Prmt7 deficiency suppresses tumor growth, enhances CD8⁺ T-cell infiltration, and increases susceptibility to cytotoxic T lymphocyte-mediated elimination, whereas these effects are attenuated under immunodeficient conditions (61). These findings suggest that PRMT7 may contribute to immune escape by limiting adaptive antitumor immunity.

Collectively, current evidence indicates that PRMT7 contributes to tumor immune evasion through both innate and adaptive immune mechanisms. These findings suggest that PRMT7 may represent a potential therapeutic vulnerability for tumors with immune-evasive phenotypes. However, further studies are required to determine whether these immunomodulatory functions extend to additional cancer types.

Cross-cancer analysis: Common mechanisms and context-dependent duality. Taken together, studies across different cancer types indicate that PRMT7 most often predominantly exerts tumor-promoting effects, particularly in BC, LC, renal cancer, leukemia and HCC (16,24,44-46,48,50,51,55). By contrast, a tumor-suppressive role has been reported in GC, although this finding currently relies on a single study and requires independent validation (60). Across the tumor types in which PRMT7 exhibits oncogenic activity, several recurrent functional themes emerge, including the promotion of EMT and metastasis (16,46,50,51,58), reinforcement of stem-like properties (24), regulation of metabolic and proteostatic adaptation (14-16,24), and activation or stabilization of oncogenic signaling components, including the β -catenin/C-MYC axis (55) and SOX9 (52,62). In addition, studies in non-malignant lung mesenchymal cells suggest that PRMT7 may regulate *Foxm1* transcription, indicating a potential broader role of PRMT7 in lung-associated transcriptional programs (53,54). These contrasting findings suggest that the biological output of PRMT7 is not determined by its catalytic activity alone, but is shaped by the specific substrates, regulatory partners, and cellular states present in each cancer context (Fig. 3).

One major dimension underlying the context-dependent function of PRMT7 is the substrate and pathway context. Although PRMT7 consistently catalyzes arginine monomethylation, the biological consequence of this modification depends on the identity and function of the substrate involved. In RCC, PRMT7 enhances β -catenin stability and activates the downstream β -catenin/C-MYC axis (55). In T-ALL, PRMT7 is highly expressed, particularly in mature T-ALL subtypes, and its genetic depletion reduces leukemic-cell colony formation and deregulates RUNX1 target-gene expression, suggesting that PRMT7 contributes to T-ALL pathogenesis through RUNX1-associated transcriptional programs. In NSCLC, PRMT7 monomethylates SOX9 at R160, thereby antagonizing ubiquitin-mediated degradation and stabilizing SOX9 to promote tumor progression (52). In PC, PRMT7-mediated regulation of FOXK1 and NUDT21 contributes to metastatic dissemination and alternative polyadenylation-associated enzalutamide resistance, respectively (58,59). In BC, PRMT7-mediated methylation of MRPS23 alters mitochondrial oxidative phosphorylation and mtROS production, thereby promoting invasion and metastasis (16). In broader cellular contexts, PRMT7-mediated methylation of eIF2 α has been linked to eIF2 α -dependent stress-granule formation and cellular stress responses (15), whereas PRMT7-dependent methylation of HSP70-family proteins has been associated with proteostasis and cellular adaptation to heat and proteasomal stress (14). However, the cancer-type-specific relevance of these mechanisms remains incompletely defined. By contrast, in GC, PRMT7 interacts with and promotes the arginine methylation of PTEN, leading to suppression of PI3K/AKT signaling and inhibition of tumor-cell proliferation and migration (60). Together, these findings suggest that the functional output of PRMT7 is strongly influenced by the availability and biological role of its substrates in a given tumor context. However, the proposed tumor-suppressive role of PRMT7 in GC is currently supported by a single study and requires independent validation.

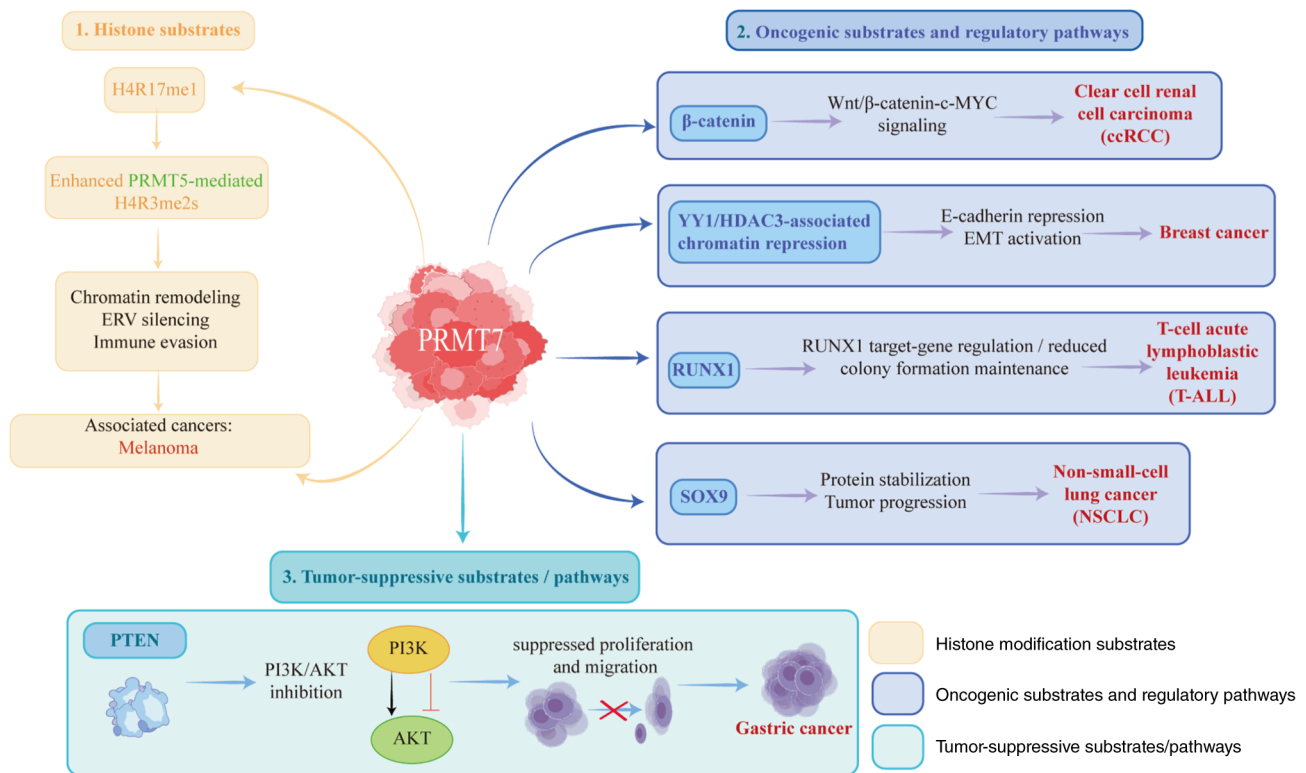
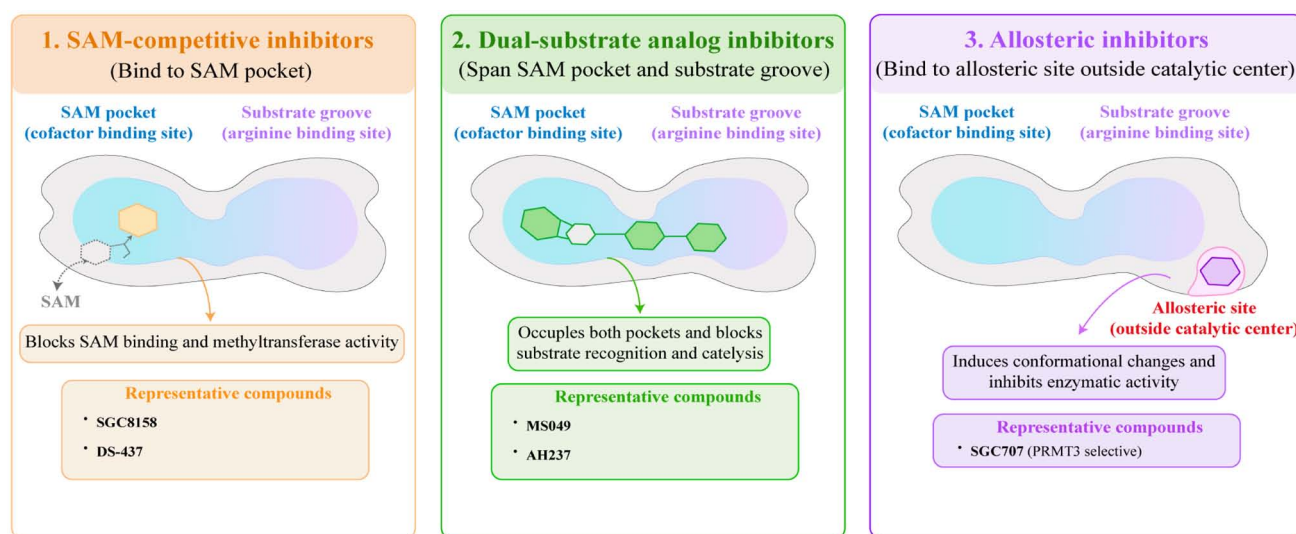


Figure 3. Representative PRMT7 substrates, regulatory pathways, and cancer-associated phenotypes. PRMT7 regulates tumor development through both histone and non-histone targets in a context-dependent manner. In the histone axis, PRMT7 catalyzes H4R17 monomethylation (H4R17me1), which serves as a priming modification to enhance PRMT5-mediated H4R3 symmetric dimethylation (H4R3me2s), thereby contributing to chromatin remodeling, transcriptional repression, ERV silencing, and immune regulation. Representative non-histone substrates and regulatory pathways include β -catenin, SOX9, PTEN, YY1-associated chromatin repression and RUNX1 target-gene regulation, which collectively influence Wnt/ β -catenin signaling, EMT, PI3K/AKT signaling and T-cell acute lymphoblastic leukemia-associated transcriptional programs. These pathways contribute to diverse cancer-associated phenotypes across multiple tumor types. The molecules and pathways shown represent selected examples summarized from the current literature rather than a comprehensive list of all reported PRMT7-regulated mechanisms. PRMT, protein arginine methyltransferase; ERV, endogenous retroviral; EMT, epithelial-mesenchymal transition.

Another major dimension underlying the context-dependent function of PRMT7 is the PRMT-family and epigenetic interaction context. PRMT7 does not necessarily act as an isolated monomethyl-transferase, because its catalytic products can influence broader arginine-methylation and chromatin-regulatory networks. A representative example is PRMT7-catalyzed H4R17 monomethylation, which acts as an allosteric signal to enhance PRMT5-mediated symmetric dimethylation of H4R3 (H4R3me2s), thereby establishing a sequential histone methylation relay (10). Because H4R3me2s is frequently associated with transcriptional repression, this relay may reinforce repressive chromatin states in specific cellular contexts (63,64). PRMT7 may also cooperate with transcription factors and chromatin-associated coregulators, as illustrated by the YY1/HDAC3-associated repression of E-cadherin in BC (46). At the non-histone level, methylome profiling has revealed partially overlapping substrate networks among PRMT4, PRMT5 and PRMT7, particularly involving RNA-binding and splicing-related proteins (13). For example, hnRNP A1 has been identified as a shared substrate of these PRMTs, and its methylation-dependent regulation influences pre-mRNA binding and alternative splicing (13). These findings suggest that PRMT-family crosstalk may also extend to the convergent regulation of non-histone substrates. Taken together, these histone- and

non-histone-level interactions suggest that the biological effects of PRMT7 may vary across tumor types depending on the activity of other PRMT family members and the availability of relevant chromatin regulators and transcriptional cofactors. However, the extent and functional consequences of these PRMT-family and epigenetic interactions have not been systematically validated across individual cancers and therefore cannot yet be regarded as a universal explanation for the oncogenic activity of PRMT7.

A further possible dimension underlying the context-dependent function of PRMT7 is the cellular and TME context. PRMT7 may be particularly important in stem-like tumor-cell populations that depend on metabolic plasticity. In CML, PRMT7 supports LSC self-renewal through the regulation of glycine metabolism, whereas its loss selectively impairs LSCs while largely sparing normal hematopoietic stem and progenitor cells (24). The TME context may also shape PRMT7 function. In melanoma, PRMT7 suppresses endogenous retroviral elements and cytosolic RNA-sensing pathways involving RIG-I and MDA5, thereby limiting antitumor immune activation. PRMT7 ablation enhances immune-cell infiltration and sensitizes tumors to immune-checkpoint blockade, identifying PRMT7 as a context-dependent epigenetic regulator of tumor immune evasion (25). The tumor-suppressive effect reported in GC raises the possibility that PRMT7 may exert distinct



Inhibitor class	Representative compounds	Representative target	Binding mode	Key features
SAM-competitive inhibitors	SGC8158, DS-437	PRMT7	Bind to SAM (cofactor) pocket	Compete with SAM; JS1310 $IC_{50} \approx 5 \mu M$; highly selective for PRMT7
Dual-substrate analog inhibitors	MS049, AH237	Multiple PRMTs	Span both SAM pocket and substrate groove	Mimic both SAM and substrate; broad-spectrum inhibition
Allosteric inhibitors	SGC707	PRMT3	Bind to allosteric site outside catalytic center	Subtype-selective; do not compete with SAM

Figure 4. Representative small-molecule inhibitor strategies targeting PRMTs. Three major approaches have been developed for pharmacological inhibition of PRMTs: (1) SAM-competitive inhibitors, which bind to the SAM cofactor-binding pocket and prevent methyl donor binding; (2) dual-substrate analog inhibitors, which simultaneously occupy the SAM-binding pocket and the substrate-binding groove to block both cofactor and substrate recognition; and (3) allosteric inhibitors, which bind to regulatory sites outside the catalytic center and inhibit enzymatic activity through conformational modulation. Representative compounds are shown for each strategy. As the binding mechanism of JS1310 has not been fully established, it is discussed separately in the text and is not assigned to a specific inhibitor class in this schematic. PRMT, protein arginine methyltransferase; SAM, S-adenosyl-L-methionine.

functions in more differentiated cellular contexts (60). However, current evidence remains insufficient to establish a general relationship between cellular differentiation, immune context and PRMT7 dependency across cancers.

4. PRMT inhibitors

Overview of the PRMT inhibitor landscape. The development of PRMT inhibitors has progressed most rapidly for type I enzymes and PRMT5, providing the conceptual framework for targeting arginine methylation in cancer (5,65–67). Among type I PRMTs, multiple inhibitors and chemical probes have been developed against PRMT1, PRMT3, PRMT4 and PRMT6, whereas PRMT5 has produced the most advanced translational candidates, including compounds that have entered clinical evaluation (5,68–89). These efforts collectively show that PRMTs are chemically tractable drug targets and that both potent enzymatic inhibition and clear cellular target engagement can be achieved (90).

From a medicinal chemistry perspective, three major small-molecule inhibition strategies targeting PRMTs have emerged (Fig. 4). The first is SAM-competitive inhibition, which remains the most common approach because the cofactor pocket is well defined and structurally conserved across PRMTs (5). The second is substrate-competitive or bi-substrate-inspired inhibition, in which compounds exploit features of both the cofactor and peptide-binding regions to improve potency and isoform preference (91). The third is

allosteric inhibition, exemplified by the PRMT3 probe SGC707, which binds a site outside the catalytic center and achieves high selectivity by exploiting isoform-specific conformational features (92). This last strategy is especially informative for PRMT7 because active-site conservation across PRMT family members makes strict selectivity difficult to achieve through SAM-pocket binding alone.

These precedents suggest two major lessons for PRMT7 inhibitor design. First, potency alone is insufficient; selectivity and cellular permeability are equally critical, particularly for SAM-mimetic compounds. Second, where active-site homology limits selectivity, non-canonical binding modes, including extension into adjacent substrate pockets or targeting less conserved conformational features, may provide a more productive route. For this reason, the detailed IC_{50} values, compound series and structural classes of type I and type II inhibitors are better summarized in Table III, while the main text should focus on design logic rather than compound enumeration.

Emerging PRMT7 inhibitors and why PRMT7 is harder to drug. Compared with type I PRMTs and PRMT5, the PRMT7 inhibitor landscape is still sparse. The first widely used scaffold in this area was DS-437, an early dual PRMT5/PRMT7 inhibitor derived from SAM-inspired design (93). DS-437 behaves as a cofactor-competitive inhibitor and inhibits both PRMT5 and PRMT7 with micromolar potency, illustrating that the conserved cofactor pocket can be exploited pharmacologically,

Table III. Comparative landscape of PRMT family inhibitors highlighting the scarcity of PRMT7-targeting agents.

First author/s, year	PRMT Isoform	Inhibitor/ Compound	IC ₅₀ (Biochemical)	Notes/Selectivity	(Refs.)
Zhao <i>et al.</i> , 2023	PRMT1	ZJG51, ZJG58	~11.8 μ M (ZJG51)	Selective vs. PRMT5; strong antiproliferative activity in 4 cancer cell lines; ZJG51 relatively selective to HeLa	(69)
Wang <i>et al.</i> , 2022	PRMT1	WCJ-394	1.21 μ M	Most potent in series; inhibits TGF- β 1-induced epithelial-mesenchymal transition and migration in A549 cells	(73)
Kim <i>et al.</i> , 2020	PRMT1	TC-E 5003	1.5 μ M	Selective; reduces LPS-induced NO production and inflammatory gene expression	(74)
Cura <i>et al.</i> , 2016	PRMT2	Cp1	16.3 $\pm$ 3.8 μ M	First synthetic PRMT2 inhibitor; slightly more potent than SAH	(75)
Kaniskan <i>et al.</i> , 2015; de Jong <i>et al.</i> , 2022	PRMT3	SGC707	31 $\pm$ 2 nM (KD =53 $\pm$ 2 nM)	First potent, selective, cell-active allosteric PRMT3 chemical probe	(76,92)
Liu <i>et al.</i> , 2013	PRMT3	14u	0.48 μ M	Allosteric, non-competitive with substrate and cofactor	(77)
Kaniskan <i>et al.</i> , 2018	PRMT3	29, 30, 36	Low nM range (potent)	Highly potent steroid-based allosteric inhibitors; cell-active; 49-51 as negative controls	(78)
Nakayama <i>et al.</i> , 2018	PRMT4	TP-064	<10 nM (enzyme); 43 $\pm$ 10 nM (MED12); 340 $\pm$ 30 nM (BAF155)	Potent, selective, cell-active chemical probe; inhibits myeloma proliferation	(79)
Shen <i>et al.</i> , 2016	PRMT4/ PRMT6	MS049	34 nM (PRMT4); 43 nM (PRMT6)	Potent, selective, cell-active dual inhibitor	(91)
Guo <i>et al.</i> , 2019	PRMT4	49 (tetrahydr oisoquinoline)	Potent (<i>in vivo</i>)	Significant antitumor efficacy in AML xenograft model (oral)	(80)
Al-Hamashi <i>et al.</i> , 2020	PRMT4/ PRMT5	AH237	2.8 nM (PRMT4); 0.42 nM (PRMT5)	Bisubstrate analogue; high selectivity vs. >40 methyltransferases	(81)
Brehmer <i>et al.</i> , 2021	PRMT5	JNJ-64619178 (Onametostat)	0.14 nM	Clinical-stage; long-duration inhibition	(68)
Liu <i>et al.</i> , 2021; Wang <i>et al.</i> , 2018	PRMT5	EPZ015666	22 nM	Widely used tool compound; antitumor effects in glioblastoma and bladder cancer	(82,83)
Bonday <i>et al.</i> , 2018	PRMT5	LLY-283	22 $\pm$ 3 nM (<i>in vitro</i>); 25 $\pm$ 1 nM (cellular)	Selective; antitumor activity in xenografts	(84)
Zhu <i>et al.</i> , 2018	PRMT5	4b14	2.71 $\pm$ 0.21 μ M	Induces cell-cycle arrest and apoptosis in leukemia/lymphoma cells	(85)
Chen <i>et al.</i> , 2024	PRMT5	A2, A8	Stronger than JNJ-64619178 (AlphaLISA)	Novel nucleoside scaffold	(86)
Shen <i>et al.</i> , 2021	PRMT6	(R)-2 (SGC6870)	77 $\pm$ 6 nM	Highly selective allosteric inhibitor; (S)-2 inactive as negative control	(87)
Shen <i>et al.</i> , 2020	PRMT6	MS117	18 nM (time- dependent)	First potent, cell-active irreversible covalent inhibitor	(88)
Zhang <i>et al.</i> , 2023	PRMT6	a25	Potent (nM range)	>25-fold selective vs. PRMT1/8; >50-fold vs. PRMT3/4/5/7; induces apoptosis	(89)
Smil <i>et al.</i> , 2015	PRMT5/ PRMT7	DS-437	6 μ M (both)	Dual inhibitor; inactive against 29 other MTases	(93)

Table III. Continued.

First author/s, year	PRMT Isoform	Inhibitor/ Compound	IC ₅₀ (Biochemical)	Notes/Selectivity	(Refs.)
Liu <i>et al</i> , 2022; Nicot <i>et al</i> , 2022	PRMT7	JS1310	5 μ M	Highly selective vs. Type I PRMTs and PRMT5; eliminates leukemia stem cells without affecting normal hematopoietic stem cells	(24,96)
Szewczyk <i>et al</i> , 2020	PRMT7	SGC8158 (active form of SGC3027)	~294 nM (HSPA8); <2.5 nM optimized	SAM-competitive; broad anti-proliferative activity including MDR cells	(14,95)
Smil <i>et al</i> , 2015	PRMT7	EPZ004777	7.5 $\pm$ 0.5 μ M	Also inhibits PRMT5 (500 nM) and DOT1L	(93)
Liu <i>et al</i> , 2018	PRMT7	V009-0749	Potent (cellular)	Virtual screening hit; reduces H4R3me2s and induces G1 arrest/apoptosis	(99)
Li <i>et al</i> , 2025	PRMT7	A33	0.50 μ M	No inhibition of other tested PRMTs at IC ₅₀ >100 μ M	(98)
Feoli <i>et al</i> , 2023	PRMT7/ PRMT9	EML734 (compound 1a)	0.32 μ M (PRMT7) 0.89 μ M (PRMT9)	First reported dual PRMT7/PRMT9 inhibitor; Displays weaker activity against other tested PRMT family members	(97)
Feoli <i>et al</i> , 2023	PRMT7/ PRMT9	EML1102 (compound 1i)	0.54 μ M (PRMT7) 2.47 μ M (PRMT9)	Shorter homolog of EML734; For other PRMTs, inhibition was weak or absent	(97)

PRMT, protein arginine methyltransferase.

but also underscoring the selectivity problem: Compounds that bind this region often struggle to discriminate PRMT7 from other PRMT family members (93). Nonetheless, DS-437 remains conceptually important because it raised the possibility that dual PRMT5/7 blockade may be therapeutically useful in settings where both enzymes contribute to malignant phenotypes (93,94).

A major advance came with the development of SGC8158, together with its cell-permeable prodrug SGC3027 (14). SGC8158 is a potent SAM-competitive PRMT7 inhibitor, whereas SGC3027 was designed to overcome the poor cellular permeability typical of SAM-like molecules by releasing SGC8158 intracellularly (14). This probe pair provided the first robust pharmacological system for studying PRMT7 catalysis in cells and demonstrated that PRMT7 inhibition reduces methylation of HSP70 family substrates and compromises tolerance to proteotoxic stress (14). The SGC3027/SGC8158 platform therefore established not only chemical tractability, but also a clear link between PRMT7 catalytic activity, substrate methylation, and stress adaptation in living cells (14,95).

More recently, the development of JS1310, a selective small-molecule PRMT7 inhibitor, provided pharmacological evidence supporting PRMT7 as a potential therapeutic target in LSCs (24). In that context, PRMT7 inhibition selectively impairs LSC survival while sparing normal HSCs, consistent with a PRMT7-dependent program involving metabolic adaptation rather than universal cytotoxicity (24,96). This is important conceptually because it suggests that PRMT7 inhibitors may be most effective when deployed against state-specific dependencies, such as stemness, stress resistance,

or metabolic rewiring, rather than as broad-spectrum antiproliferative agents alone.

Recent medicinal chemistry efforts have also begun to move beyond the earliest PRMT7 probes. A first potent PRMT7/9 inhibitor with a defined binding mode was reported in 2023, indicating that carefully designed compounds can span both the cofactor and substrate regions to exploit features not captured by simple SAM mimetics (97). In 2025, a newer selective PRMT7 inhibitor, A33, was reported with antitumor activity in PC models, suggesting that PRMT7 inhibitor development is now entering a more optimization-driven stage rather than remaining limited to proof-of-concept probes (98,99).

Several factors likely explain why PRMT7 inhibitors remain markedly less numerous than PRMT5 inhibitors. First, the SAM-binding pocket of PRMT7 is homologous to that of other PRMTs, which makes active-site selectivity intrinsically difficult (14,93). Second, PRMT7 has an unusual tandem double-module architecture and a comparatively distinctive substrate-recognition surface, meaning that classical inhibitor templates developed for dimeric type I/II enzymes do not always translate efficiently (23,29). Third, until the appearance of SGC8158/SGC3027, the field lacked a strong cell-active probe, which slowed target validation and medicinal chemistry iteration (14). Finally, PRMT7 biology has historically been less extensively mapped than PRMT5 biology, reducing the availability of robust pharmacodynamic biomarkers and disease settings for rapid compound testing (23,68).

Taken together, experience from type I and type II PRMT inhibitors suggests that future PRMT7 drug discovery will likely benefit from three complementary strategies: Improving SAM-pocket binders for permeability and selectivity,

exploiting substrate-adjacent or dual-pocket binding modes, and considering rational dual-target approaches such as PRMT5/7 co-inhibition when tumor biology supports it. In this sense, the challenge of PRMT7 is not simply that it is a type III enzyme, but that its catalytic conservation and structural uniqueness coexist in a way that makes conventional inhibitor design only partially transferable from other PRMT family members.

Clinical translation opportunities and challenges. Although PRMT7-targeted therapies remain in the early stages of development, accumulating mechanistic evidence suggests several potential opportunities for clinical translation. Given the context-dependent functions of PRMT7 across tumor types, a major challenge and opportunity will be the identification of tumor subsets that exhibit particular dependency on PRMT7 activity.

Tumors characterized by PRMT7-dependent biological programs may represent potential candidates for PRMT7-targeted intervention. For example, leukemia models have demonstrated a functional requirement for PRMT7 in LSC maintenance through the regulation of glycine metabolism, suggesting that tumors relying on PRMT7-associated stem-cell programs may represent a potential therapeutic setting (24). In addition, PRMT7 inhibition may be particularly relevant in tumors with immune-evasive phenotypes, as PRMT7 loss enhances antitumor immune responses and improves sensitivity to ICB in melanoma and BC models (25,61). Furthermore, PRMT7 has been implicated in PC progression and metastasis, while NUDT21-dependent alternative polyadenylation has been associated with enzalutamide resistance, suggesting that PRMT7-related pathways may warrant further investigation in therapy-resistant PC (57-59). However, these potential indications remain largely based on preclinical evidence and require validation in clinically relevant models.

The development of predictive biomarkers will be essential for effective patient selection (5). Potential biomarkers for patient stratification remain an important unmet need. PRMT7 expression, PRMT7-dependent cellular states such as stem-cell-associated programs, and immune-related features including T-cell infiltration patterns represent candidate biomarkers that warrant investigation (18,24,25,52). However, none of these biomarkers have been clinically validated to predict response to PRMT7-targeted therapies.

Combination strategies represent another potential avenue for PRMT7-targeted therapy. The functional interaction between PRMT7 and other PRMT family members, particularly the PRMT7-PRMT5 histone methylation relay, provides a mechanistic rationale for investigating combinations targeting multiple arginine methylation pathways (10). However, whether combined inhibition of PRMT7 and other PRMTs produces therapeutic synergy remains to be determined. A stronger translational rationale currently exists for combining PRMT7 inhibition with ICB, as PRMT7 loss enhances tumor immunogenicity and improves responses to checkpoint inhibitors in preclinical models (25).

Despite these opportunities, several challenges must be addressed before clinical translation of PRMT7-targeted therapies. First, the biological effects of PRMT7 are highly context dependent, with both tumor-promoting and

tumor-suppressive roles reported across different cancer types, highlighting the need for precise patient stratification. Second, the lack of validated pharmacodynamic biomarkers currently limits the assessment of target engagement and therapeutic response. Third, the physiological functions of PRMT7 in normal tissues require further investigation to define an appropriate therapeutic window. Therefore, future development of PRMT7-targeted therapies will require selective inhibitors, biomarker-guided patient selection, and rational combination strategies.

5. Conclusions and future perspectives

PRMT7 has emerged as a distinctive and context-dependent regulator in cancer. As the only type III PRMT in mammals, it catalyzes arginine monomethylation and exerts biological effects that differ in important ways from those of type I and type II PRMTs (29,35,54). Accumulating evidence indicates that PRMT7 regulates multiple cancer-associated processes, including EMT, stemness maintenance, stress adaptation, metabolic regulation and tumor immunity. Its functional output is determined by the interplay between substrate availability, interactions with other PRMT family members and epigenetic regulators, and the cellular and TME context. These context-dependent regulatory features may explain why PRMT7 predominantly exhibits tumor-promoting functions across many cancer types, while a potential tumor-suppressive role has also been reported in GC. Collectively, current evidence establishes PRMT7 as an important regulator of cancer biology with distinctive mechanistic characteristics and potential therapeutic relevance.

An important future direction is the development of combination strategies based on the immunoregulatory functions of PRMT7 (100). It has been recently suggested that PRMT7 inhibition can enhance tumor immunogenicity by promoting interferon signaling, antigen presentation, chemokine expression and immune-cell infiltration (25). These observations provide a rationale for combining PRMT7 inhibitors with ICB, particularly PD-1/PD-L1-directed therapies, to overcome immune evasion and improve antitumor responses in selected cancers (101).

At the same time, progress in this field will require a deeper structural understanding of PRMT7. Most current mechanistic models rely on catalytic-domain analysis and peptide-based substrates, whereas substrate recognition in cells is likely to be strongly influenced by full-length protein conformation and dynamic molecular context. Additional structures of PRMT7 in complex with full-length substrates or substrate-containing assemblies will therefore be essential for clarifying its catalytic specificity, substrate selectivity, and opportunities for rational inhibitor design.

These unresolved mechanistic questions are closely related to the current barriers to clinical translation. In contrast to PRMT5 and some type I PRMT inhibitors, no PRMT7 inhibitor has yet entered clinical trials (102). The main bottlenecks likely include limited isoform selectivity, suboptimal bioavailability, insufficient pharmacodynamic biomarkers, and uncertainty regarding toxicity and therapeutic window in different tumor settings. Addressing these challenges through integrated advances in cancer biology, structural

biology and medicinal chemistry will be critical for moving PRMT7-targeted strategies toward clinical application.

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Authors' contributions

YHe conceived the study, determined the overall framework of the review, coordinated the collaboration among all authors, integrated the manuscript content, and drafted the final version of the manuscript. JL conducted the literature search and analysis on the PRMT family, and was primarily responsible for summarizing the structural characteristics, biological functions, and tumor-related roles of PRMT7 in selected cancers. YHu performed the literature search and critical review on PRMT7 in multiple tumor types and the development of PRMT inhibitors and contributed to the sections on therapeutic targeting and future perspectives. WD prepared the tables, figures, and visual summaries, participated in data organization, and assisted in manuscript design and presentation. XC revised the manuscript for language, formatting, and logical flow, and contributed to the literature collection and writing of the section related to PRMT7 and melanoma immunotherapy. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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