

Review

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Review

Designing Effective Protein Lysine and Arginine Methyltransferase Inhibitors for Chemotherapeutic Targeting

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Abstract

Standard cancer chemotherapy is increasingly being supplemented with novel therapeutics to overcome known chemoresistance pathways. Resistance to treatment is common across various tumor types, driven by multiple mechanisms. One emerging contributor is protein methylation, a post-translational modification mediated by protein methyltransferases (PMTs), which regulate protein function by adding methyl groups, mainly on lysine and arginine residues. Dysregulation of protein lysine methyltransferases (PKMTs) and protein arginine methyltransferases (PRMTs) has been linked to cancer progression and drug resistance, making them attractive therapeutic targets. Consequently, several small-molecule PMT inhibitors have been developed, with some progressing to clinical trials. However, many candidates showing promise in preclinical studies fail to demonstrate efficacy or safety in later stages, limiting clinical success. This gap highlights the need to rethink current approaches to PMT inhibitor design. A deeper understanding of PMT mechanisms, catalytic domains, and their roles in chemoresistance is essential for creating more selective, potent, and clinically viable inhibitors. This review will summarize major chemoresistance pathways and PMTs implicated in cancer, then explore current and prospective PMT inhibitor classes. Building on mechanistic insights, we propose strategies to develop next-generation inhibitors with improved therapeutic potential against chemoresistant cancers.

Keywords: protein methylation; protein methyltransferases (PMTs); PMT inhibitors; methylproteomics; chemoresistance

1. Introduction

1.1. Challenge to Treatment

Chemoresistance is recognised as the greatest challenge in the successful treatment of cancer by chemotherapy, with development and proliferation of highly aggressive phenotypes, resulting in an associated poor prognosis.

Given the well-documented impact of methylation on protein expression levels through its action on histones, it is no surprise that protein methyltransferase (PMT) inhibitors have been considered as potential therapeutics to prevent or counter specific chemoresistance mechanisms at least in a sub-set of patients, in the hopes of increasing the possibility of obtaining long-term benefits with the currently administered chemotherapeutic regimens. However, despite this knowledge related to histones, there is at present a lack of understanding as to the biological relevance of non-histone proteins targeted by PMTs as part of chemoresistance mechanisms.

The greatest stumbling block presently is that the functional role played by PMTs in either the development or the maintenance of chemoresistance is close to unknown. Inhibiting the function of

a type of methylation without knowing the expected outcome is an issue that magnifies itself when translated to the clinical setting, with patient responses to therapy varying greatly, presenting side effects which might, but are not necessarily, linked to the use of PMT inhibitors in the combinatorial treatment.

For this reason, understanding at least the core mechanism of methylation addition for the different PMT families and their role in the major chemoresistance pathways is essentially needed for designing inhibitors that act with high specificity and sensitivity.

1.2. Chemoresistance Mechanisms

The evasion of cancer therapeutics is generally achieved by one or more of the following strategies employed by malignant cells irrespective of cancer origin. These mechanisms have been reviewed in detail elsewhere (Mansoori et al., 2017; Kannampuzha and Gopalakrishnan, 2023; Khan et al., 2024) but an overview will be provided in order to build the discussion in relation to PMTs.

From a genetic perspective, mutations that result in structural changes to the enzymes that the drugs interact with, such as alterations to catalytic sites that affect either drug binding or enzyme activation. For example mutated topoisomerase II confers resistance to etoposide and doxorubicin (Elton et al., 2020), mutations in the EGFR kinase domain grant resistance against Gefitinib (Kobayashi et al., 2005), mutations of the extracellular receptor smoothened (Zhang et al., 2018) limit cyclopamine effectiveness, mutations in nucleoside transporters (Galmarini et al., 2001; Damaraju et al., 2003) block nucleoside drugs such as cytosine arabinoside (ara-C, cytarabine) or 2-chlorodeoxyadenosine (2-CdA) whilst mutations in folate transporters (Gao et al., 2021) inhibit toxic folate analogues, such as methotrexate.

Another dominant mechanism is increased efflux of chemotherapeutic drugs, often mediated by either overexpression or increased activity of transporter proteins including ATP-binding cassette (ABC) transporters. For example, increased expression of ABCB1 (P-glycoprotein, multidrug resistance 1) provides resistance to various anti-cancer drugs, including paclitaxel, olaparib (Vaidyanathan et al., 2016), and doxorubicin (Hui et al., 2008; Mirzaei et al., 2022). The increased expression of ABCG2 provides resistance to doxorubicin (Roh et al., 2018), oxaliplatin (Hsu et al., 2018), and 5-fluorouracil (Kim et al., 2020). Similarly, ABCC2 (multidrug resistance protein 2; MRP2) confers resistance to cisplatin (Chen et al., 2021) and oxaliplatin (Biswas et al., 2019).

Equally widespread among tumours is enhanced activity of detoxifying enzymes like cytochrome P450, which increases drug inactivation. For example, increased expression of Glutathione transferases (GST) and production of glutathione (GSH) are effectively employed by tumours to detoxify many alkylating agents and platinum-based drugs (Pljesa-Ercegovac et al., 2018).

Epigenetic and epiproteomic alterations are also frequently observed. Epigenetic changes are most commonly DNA methylation changes, including aberrant methylation of the *ABCB1*, *ABCC1* and *ABCG2* promoters to increase their expression (Spitzwieser et al., 2016; Li et al., 2016; Sumarpo et al., 2020) but can also involve post-transcriptional modifications through microRNAs (miRNAs) (Mondal and Meeran, 2021). Epiproteomic changes encompass various histone modifications that alter gene expression patterns (Arrigoni et al., 2016), including histone H3 hyperacetylation (Shui et al., 2024) or an enzyme such as Histone deacetylase 2 (HDAC2) upregulating the expression of ABCB1 (Ye et al., 2016).

Other mechanisms include enhanced DNA repair capabilities (Sakthivel and Hariharan, 2017; Abad et al., 2020; Li et al., 2021), activation of other signalling pathways to bypass drug effects (Pan et al., 2016; Alimbetov et al., 2018), and alterations in apoptotic pathways to evade cell death (Alimbetov et al., 2018; Chen et al., 2018).

2. Protein Methylation

2.1. Types and Function

The cell has the ability to broadly modulate protein properties through the addition of post-translational modifications (PTMs), particularly methylation. These epiproteomic changes allow for fast responses at low cellular cost.

Protein methylation involves the transfer of a CH₃ group from the methyl donor S-adenosylmethionine (SAM or AdoMet) to an amino acid residue on a protein. The residues altered are mainly lysine (K) and arginine (R) residues and the methyl group is added onto nitrogen making it N-methylation. A number of other amino acids can undergo N-methylation, namely asparagine (N), histidine (H), proline (P) and alanine (A). Two other types of methylation, S- and O- methylation, exist. The amino acids methionine (M) and cysteine (C) can undergo S-methylation, while aspartate (D) and glutamate (E) can undergo O-methylation (Deng et al., 2016; Cloutier et al., 2013; Clarke, 2013).

One or more CH₃ groups can be added to both K and R residues with the epsilon (ε) amine of the former being able to undergo mono- (Kme1), di- (Kme2) or tri- (Kme3) methyl addition by protein lysine methyltransferases (PKMTs), while the guanidinium moiety of the latter can undergo mono- (MMA/Rme1), di-symmetrical (SDMA/sRme2) or di-asymmetrical (ADMA/aRme2) methyl addition by protein arginine methyltransferases (PRMTs) (Greer and Yang, 2012).

Multiple CH₃ groups can be added to the protein before the protein dissociates from the PMT, which is referred to as a processive addition mechanism. On the other hand, if only a single CH₃ group is added before the protein is dissociated from the PMT and subsequent methylations are added by the same or different PMTs, this is referred to as a distributive addition mechanism (Copeland et al., 2009; Al-Hamashi et al., 2020; Fulton et al., 2018). PKMTs and PRMTs implement both these mechanisms.

At a protein level, whilst methylation does not affect the overall charge of the residue, there is an associated increase in both hydrophobicity and bulkiness around the modified residue, which in turn can alter protein properties such as protein-protein interactions and recognitions, having a downstream impact on gene regulation (Kaniskan et al., 2015).

In the context of cancer, the most well-studied substrates for methylation are histones, with exceptional focus on histones 3 and 4. However, studies have in recent years expanded this investigation to non-histone proteins, including proteins such as tumour protein 53 (p53), heat shock proteins 70 or 90 (HSP70 or HSP90), Nuclear factor kappa B (NF-κB) and Retinoblastoma 1 (RB1) (Hamamoto et al., 2015; Wei et al., 2014). Nevertheless, not much is known about the methylation status and functional role of these key cancer proteins following chemoresistance.

2.2. The Methyl Cycle: S-Adenosylmethionine Production

The primary methyl group donor for methylating various substrates, including DNA, RNA, proteins, lipids, and other molecules, is S-adenosylmethionine (SAM). SAM is synthesised from the conjugation of adenosine from adenosine triphosphate (ATP) with methionine. The reaction is catalysed by SAM synthetase (a.k.a. methionine adenosyltransferase; MAT), which dephosphorylates a molecule of ATP in the presence of potassium and magnesium ions (Mato et al., 2002), together with cleavage of the C5'-O5' bond of ATP and changing the conformation of the ribose ring from C4'-exo to C3'-endo such that the S of Met makes a nucleophilic attack on the C5' to form SAM (Komoto et al., 2004).

Methylation reactions are catalysed by methyltransferases and release S-adenosylhomocysteine (SAH or AdoHC). SAH is a competitive inhibitor of MTases and is hydrolysed by adenosylhomocysteinase (AHCY) to homocysteine (Hcy). This reaction is reversible, meaning that increased Hcy levels can lead to the accumulation of SAH, which can bring about a lower methylation capacity. This can be represented as the SAM/SAH ratio (Hao et al., 2016). Homocysteine is re-methylated to regenerate methionine using 5-methyltetrahydrofolate (5-MTHF) or betaine via betaine

homocysteine methyltransferase (BHMT) (Pascale et al., 2022). 5-MTHF, produced from dietary folate (dihydrofolate) through the folate cycle, donates a methyl group, catalysed by methionine synthase (MTR) using vitamin B12 (cobalamin, Cbl) as its cofactor (Nazki et al., 2014). These steps all form part of what is called the methyl cycle (Figure 1) (Froese et al., 2019). The essential nutrients for this cycle are thus methionine, folic acid (for CH₃-THF), and choline (to generate betaine).

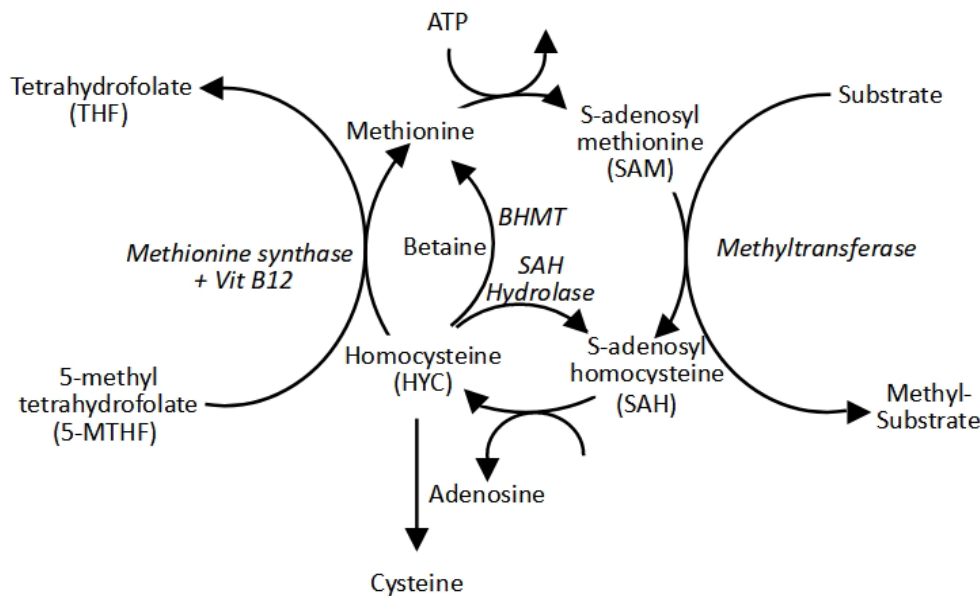


Figure 1. The methyl cycle.

The dysregulation of SAM leads to alterations in over a hundred methyltransferase reactions, which modulate metabolic pathways (Loenen, 2006). SAM has been shown to have anti-cancer properties, limiting proliferative, inducing apoptosis, and preventing metastasis, although the mechanisms were not identified (Mosca et al., 2020; Wang et al., 2017). It has also been shown to sensitise CRC cells to 5-FU treatment via p-glycoprotein inhibition and a reduction in NF- κ B acetylation/NF- κ B protein ratio, suppressing NF- κ B Activation (Mosca et al., 2021). SAM has been tested as both a diagnostic and prognostic biomarker in different cancers in the form of the SAM/SAH ratio and has been studied as a potential chemotherapeutic, both on its own and as a chemosensitising agent in combination with other drugs, in a wide variety of cancer types (Fernández-Ramos et al., 2025).

2.3. Protein Methyltransferases

Methyltransferases across all families, irrespective of their substrates, typically have catalytic domains consisting of a well-conserved SAM-binding pocket, together with highly variable substrate acceptor regions (Richon et al., 2011; Copeland et al., 2009). These two compartments are linked via a hydrophobic channel, allowing the transfer of a CH₃ group from SAM to the target residue through an S_N2 transition (Kaniskan et al., 2018).

In the most basic arrangement, the Rossmann-like fold consists of regions of alternating β -strands and α -helices. This produces a flat β -sheet at the centre, with a set of helices on either side of the sheet. In such an arrangement, the N-terminal β -strand is located in the middle of the sheet, with the strand topology following the order 3-2-1-4-5-7-6, and having the 7th strand anti-parallel to the other strands. Furthermore, functionally important, conserved residues in such enzymes are often found either at the C-termini of the β -strands or else in the adjoining loops (Kozbial and Mushegian, 2005).

Whilst there is a wide variety of PMTs, most can be clustered based on the overall structure and sequence similarities of their enzymatic domain, forming three superfamilies, namely the Seven- β -strand (7 β S) domain family, the SpoU-TrmD (SPOUT) domain family and the Su(var)3-9, enhancer

of zeste (E(z)), and trithorax (trx) (SET) domain family (Clarke, 2013; Husmann and Gozani, 2019; Zhang et al., 2015).

The 7 β S family features a core structure containing two domains, a seven-stranded Rossmann-fold domain forming the binding site for the methyl donor SAM and a β -barrel for dimerisation (Schapira and de Freitas, 2014). The SET domain family has small β -sheets forming a knot-like structure, surrounded by a pre- and post-SET domain together with an iSET domain forming a helical structure adjacent to the substrate binding cleft (Kozbial and Mushegian, 2005). The SPOUT methyltransferase family contain a distinctive α/β knot-like structure (Petrosian et al., 2010; Tkaczuk et al., 2007; Clarke, 2013; Young et al., 2012).

For the scope of this review the focus will be on the 7 β S and SET domain families since the two major groups of PMTs i.e. protein lysine methyltransferases (PKMTs) and protein arginine methyltransferases (PRMTs) fall within these families.

2.3.1. Protein Lysine Methyltransferases (PKMTs)

Over 50 PKMTs have been identified in humans (Yang and Bedford, 2013; Hamamoto et al., 2015; Carlson and Gozani, 2016; Husmann and Gozani, 2019). The PKMTs can be grossly subdivided into two groups: those enzymes containing a SET-domain and those that do not (i.e. class 1 canonical Rossmann-fold-like methyltransferases) (Clarke, 2013; Kaniskan et al., 2018). PKMTs are more finely subdivided into eight groups (KMT1-KMT8) based on the sequence similarity flanking the SET domain, activity, and substrates (Allis et al., 2007; Kaniskan et al., 2018; Zhang et al., 2015; Zhang, Wen and Shi, 2012). However, given that numerous KMTs have no known substrates and consequently uncertain activity, categorising such enzymes is speculative and imprecise (Carlson et al., 2016).

Those PKMTs having a SET domain present the typical small β -sheets that produce a knot-like structure, with a pre-SET, post-SET and iSET domains. The helical structure formed by the iSET domain contributes to the formation of a narrow channel connecting the SAM binding surface and the substrate pocket through which the amine of the lysine residue to be methylated on the substrate is oriented and can access the SAM (Kozbial and Mushegian, 2005). All these domains are essential for enzymatic activity. Additionally, the SET proteins also contain four conserved sequence motifs, SET motif I (GXG), SET motif II (YXG), SET motif III (RFINHXCPN), and SET motif IV (ELXFDY), where each motif is involved in the methylation reaction (Cheng et al., 2005; Kaniskan et al., 2018).

The non-SET domain KMT category is currently composed of disruptor of telomeric silencing-1-like (DOT1L) (which makes up KMT4) and a few members of the Methyltransferase-like (METTL) family (Kaniskan et al., 2018; Richon et al., 2011; Cloutier et al., 2013). DOT1L has a 7 β S as part of its N-terminal catalytic domain, which contains seven conserved sequence motifs (I, II, III, IV, VI, VIII and X) as a methyl donor binding site and an active site pocket covered with conserved hydrophobic residues (Falnes et al., 2016; Cheng et al., 2005; McGrath and Trojer, 2015; Wood, Tellier and Murphy, 2018). The lysine methylating METTL enzymes in this group include METTL10, METTL12, METTL13, METTL20, METTL21A, METTL21B, METTL21C, METTL21D, METTL21E and METTL22 (Cloutier et al., 2013; Falnes et al., 2016; Wong et al., 2021; Falnes et al., 2023).

2.3.2. Protein Arginine Methyltransferases (PRMTs)

A total of nine PRMTs have been identified in humans. As part of the 7 β S family, the PRMT family members share a common overall structure consisting of a methyltransferase domain, a 7- β -barrel Rossmann fold domain (that interacts with SAM) and a dimerisation arm (Xu and Richard, 2021). In detail, PRMTs harbour a catalytic domain composed of six conserved sequence motifs, where motif I is at the core of the SAM-binding pocket with three highly conserved glycine residues (VLD/VGxGxG), post-motif I hydrogen bonds to SAM either through the use of an glutamic or aspartic acid residue (V/I-X-G/A-X-D/E), motif II forms a β -sheet that stabilises motif I (E/K/VDII), the 'double-E' motif positions the arginine substrate residue via two glutamic acid residues (SExMGxxLxxExM), motif III forms a parallel β -sheet with motif II (LK/xxGxxxP) and finally the

THW loop that is essential for both substrate binding and N-terminal stabilisation. (Wei et al., 2014, Tewary et al., 2019).

These 9 enzymes are divided into three sub-types, with all three sub-types giving rise to MMA, but then Type I and Type II PRMTs subsequently proceed further to produce ADMA and SDMA respectively (Obianyo et al., 2011). The Type I group consists of PRMT 1, 2, 3, 4, 6, and 8, the Type II group is made up of PRMT 5 and 9, while Type III only includes PRMT7 (Al-Hamashi et al., 2020; Fulton et al., 2018).

Moreover, PRMTs have preferences for certain motifs flanking the arginine to be methylated. PRMT1, PRMT3, PRMT6, PRMT8 prefer glycine-arginine-rich (GAR/RGG/RG) motifs (Tewary et al., 2019; Al-Hamashi et al., 2020), PRMT4 (also named CARM1) prefers proline-glycine-methionine-rich (PGM) motifs (Tewary et al., 2019), PRMT5 recognises RGG, RXR, and RG motifs (Tewary et al., 2019), PRMT7 can recognise RXR XR or RXR motifs (Tewary et al., 2019; Kaniskan et al., 2018; Al-Hamashi et al., 2020) and PRMT9 uniquely recognises the CFKRKYL motif in SAP145 (Yang et al., 2015).

2.3.3. Cancer Dysregulation

The increased expression of PKMTs, particularly Euchromatic histone-lysine N-methyltransferase 2 (EHMT2), Enhancer of zeste 2 (EZH2), SET domain containing 7 (SETD7), SETD8, SET And MYND Domain Containing 2 (SYMD2) and SYMD3 as well as PRMTs including PRMT1, PRMT3, PRMT5 and PRMT6 in a variety of tumours of different types and origins has been shown to promote chemoresistance through cell cycle progression (Zhang et al., 2019), cancer stem cell (CSC) renewal (Lin et al., 2018) and the alteration of key signalling pathways such as the Wnt or Notch pathways (Shailesh et al., 2021; Chai et al., 2023). The clinical evidence thus supports the targeting of PMTs as a promising cancer treatment (Vougiouklakis et al., 2020; Ning et al., 2023).

2.4. Classes of Methyltransferase Inhibitors

PMTs have a generic structure composed of two key pockets, the SAM binding pocket and the methyl-substrate binding pocket. PMT inhibitors can thus be sub-divided based on the region of the enzyme they target and their mode of action (either covalent and non-covalent binders). More specifically, inhibitors can be designed to compete with the methyl donor, the methylation substrate or an essential cofactor, or alternatively bind at allosteric sites found either within the active or at alternative inactive states (Schapira and de Freitas, 2014).

2.4.1. SAM Competitive Inhibitors

SAM competitors or mimetics compete with the methyl donor for the SAM binding pocket of the PMT thus preventing the enzyme from functioning and adding the methylation to the target protein (Campagna-Slater et al., 2011). A few examples of the more successful SAM inhibitors due to their selective nature include the EHMT2 inhibitor BRD9539 and its methyl ester BRD4770 (Yuan et al., 2012), the SMYD2 inhibitor PFI-5 (Taylor et al., 2019), the EZH2 inhibitors EPZ6438 (tazemetostat) and SKLB1049 (Wei et al., 2024), the DOT1L inhibitors EPZ004777 and its derivative EPZ5676 (Pinometostat) (Waters, 2017), and the PRMT5 inhibitor LLY-283 and its derivative PF-0685580 (Lin and Luengo, 2019).

Despite a large number of SAM competitors having been developed, unfortunately, many such inhibitors present limited specificity given that all methyltransferases use SAM as their methyl donor. Designing SAM competitive inhibitors is a challenge due to the high hydrophilicity of SAM requiring inhibitors to have a high enough polarity to be able to interact with the SAM binding pocket, whilst at the same time presenting sufficient hydrophobicity to be able to traverse cellular membranes in order to reach their target. However, the greatest limitation to such inhibitors is the high intracellular levels of SAM with which they must compete (Ferreira de Freitas et al., 2019).

2.4.2. Substrate Competitive Inhibitors

This class of inhibitors compete with the protein substrate to be methylated for the substrate binding pocket of the PMT. The development of substrate competitive inhibitors is a preferred strategy due to ample structural diversity within the substrate binding pocket of PMTs, allowing for increased specificity (given the selective nature of substrate recruitment) as well as having a lower polarity requirement compared to SAM competitive inhibitors (Ferreira de Freitas et al., 2019).

A few examples of the more potent and promising substrate inhibitors are presented in Table 1.

Table 1. Noteworthy examples of substrate competitive inhibitors for some of the more popular methyltransferases.

Substrate	Inhibitor	Reference
EHMT2	UNC0642	Liu et al., 2013
	UNC0925	Konze et al., 2014
	A-366	Sweis et al., 2014
	MS152	Wang et al., 2024
EZH2	UNC1999	Konze et al., 2013
	CPI-1205	Vaswani et al., 2016
	PF-06821497	Kung et al., 2018
	EBI-2511	Lu et al., 2018
SETD7	(R)-PFI-2	Barsyte-Lovejoy et al., 2014
	Cyproheptadine	Takemoto et al., 2016
SMYD2	BAY-598	Eggery et al., 2016
	EPZ030456	Mitchell et al., 2016
	A-893	Sweis et al., 2015
	LLY-507	Nguyen et al., 2015
	EPZ033294	Thomenius et al., 2018
SMYD3	BCI-121	Peserico et al., 2015
	EPZ028862	Thomenius et al., 2018
	BAY-6035	Gradl et al., 2018
SETD8	UNC0379	Ma et al., 2014
	SPS8I1	Blum et al., 2014
	MS2177	Butler et al., 2016
PRMT5	GSK3326595/EPZ015938 (Pemrametostat)	Gerhart et al., 2018
	GSK3235025/EPZ015666	Chan-Penebre et al., 2015
	GSK3203591/EPZ015866	Duncan et al., 2016

2.4.3. Bisubstrate Inhibitors

Inhibitors within this class occupy both the SAM and substrate PMT pockets. There are very few confirmed inhibitors within this class, with a few documented examples being the SET7/9 inhibitor set of AzaAdoMet substituted with various alkylamino groups (Mori et al., 2010), the PRMT1 inhibitor decamidine (Zhang et al., 2017), a PRMT4 inhibitor designed as a 5-methylcytosine-

adenosine derivative (Halby et al., 2018), the PRMT5 inhibitor CMP5 (Alinari et al., 2017), and the PRMT6 inhibitor 6'-methyleneamine sinefungin (GMS) (Wu et al., 2016).

2.4.4. Allosteric Inhibitors

This class of inhibitors impede enzyme activity by binding to sites on the PMT other than its two active site pockets. The best known of such inhibitors is the PRMT3 inhibitor SGC707. Since PRMT3 forms homodimers to perform its function, SGC707 binds to the pocket at the base of the dimerisation arm of the first monomer and the α -Y segment of the activation helix of the second monomer, inhibiting the formation of the PRMT3 homodimer as a result of its introduction (Kaniskan et al., 2015). One of the few other allosteric inhibitors available is the SMYD3 inhibitor dipiperodon, which binds to an allosteric site the same allosteric binding site, located within the C-terminus domain, adjacent to the active site containing domain (Talibov et al., 2021).

2.4.5. Complex Disrupting Inhibitors

Many PMTs form multi sub-unit complexes where the integrity of the complex is critical in order for the PMTs to perform their function. This provides alternative targets for inhibition other than the catalytic domain.

EZH1/2 must form part of the PRC2 complex together with at least three other PRC2 sub-units in order to be enzymatically active. One of these sub-units is Embryonic Ectoderm Development (EED). Numerous inhibitors have thus been developed that bind to EED and disrupt the formation of the PRC2 complex (Liu et al., 2022). A few noteworthy inhibitors include SAH-EZH2 (Kim et al., 2013), EED226 (Qi et al., 2017), A-395 (He et al., 2017), BR-001 (Dong et al., 2019) and EEDi-5285 (Rej et al., 2020).

Mixed-Lineage Leukemia protein 1 (MLL1 a.k.a. Histone-lysine N-methyltransferase 2A - KMT2A) or MLL fusion proteins form a complex with the transcriptional regulators Menin or WD repeat-containing protein 5 (WDR5). Although these proteins are not required for MLL1 catalytic activity, they are still critical components of context-specific MLL complexes and as such can be targeted to indirectly block the activity of MLL. Menin interacts with the N-terminal region of MLL proteins (Yokoyama et al., 2005), whilst WDR5 interacts with the WIN motif of MLL proteins (Alicea-Velázquez et al., 2016). Of note are the Menin inhibitors KO-539 (ziftomenib) (Copeland, 2018) and M-808 (Xu et al., 2020), as well as the WDR5 inhibitors OICR-9429 (Grebien et al., 2015) and DDO-2093 (Chen et al., 2021).

PRMT5 forms a complex with methylosome protein 50 (MEP50 a.k.a. WDR77 or p44), which acts as a co-factor, in order to achieve its methyltransferase activity (Ho et al., 2013; Antonysamy, 2017) and this dependence upon a co-factor is unique among the PRMTs. Further proteins are recruited as adaptors to specify substrate selection including Chloride conductance regulatory protein (pICln), RIO kinase 1 (RioK1) and Cooperator of PRMT5 (COPR5) (Mulvaney et al., 2021). So far only one inhibitor has been developed to block the interaction between PRMT5 and MEP50 - by interacting with the hydrophobic pocket within the TIM barrel of PRMT5 (Asberry et al., 2022) whilst another has been developed to block the interaction between PRMT5 and RioK1 or pICln (Krzyzanowski et al., 2022).

2.4.6. Covalent Inhibitors

The vast majority of PMT inhibitors developed so far, irrespective of which region of the enzyme they bind to, tend to be reversible (non-covalent) inhibitors. Covalent inhibitors are designed to consist of a peptide sequence or chemical structure that can covalently bind to a nucleophilic amino acid that is not well conserved within or in the immediate vicinity of the PMT active site via a reactive group, called a warhead, which is generally an alkylating, acylating, phosphonylating, or sulfonylating functional group (Powers et al., 2002). Targeting such a residue improves selective inhibition of the intended PMT over other family members (Li et al., 2019). Most covalent inhibitors

are currently designed to target a non-catalytic cysteine residue through an acrylamide or other α,β -unsaturated carbonyl compound (Powers et al., 2002; Gehring and Laufer, 2018; Gambini et al., 2019).

Targeting PMTs with covalent inhibitors offers several advantages compared to using non-covalent equivalents. Covalent inhibitors often exhibit superior potency and biochemical efficiency due to their irreversible, non-equilibrium-based mechanism of action (Ábrányi-Balogh et al., 2018; Li et al., 2019). Unlike reversible inhibitors, covalent binders do not compete with either the ligands or SAM cofactor, enabling sustained target engagement and reduced dosing amount and frequency, thus reducing off-target effects. Their long residence time on the target translates into extended duration of action, which is especially beneficial when the protein of interest has a slow turnover rate (Ábrányi-Balogh et al., 2018). A diversity of warheads are available for PMT covalent inhibitors targeting cysteine, which can be tailored to exploit the spatial and chemical reactivity of the active site, allowing for the design of smaller, more selective molecules without compromising potency, thereby improving drug-likeness. This is particularly important given that many drug candidates fail due to absorption, distribution, metabolism, and excretion (ADME)-related issues (Gehring and Laufer, 2018; Li et al., 2019). Moreover, covalent inhibitors can enhance target occupancy even at low plasma concentrations, offering improved therapeutic efficacy and an advantage in overcoming drug resistance (Ábrányi-Balogh et al., 2018).

A few noteworthy examples include the EZH2 inhibitor SKLB-03176 (Zhang et al., 2022), the EHMT2 inhibitor MS8511 (Park et al., 2022), the SETD8 inhibitor MS453 (Butler et al., 2016), the PRMT5 inhibitor hemiaminal 9 (Lin et al., 2019) and the PRMT6 inhibitor MS117 (Shen et al., 2020).

2.4.7. PROTAC Inhibitors

More recently, targeted protein degradation has been applied to PMT inhibition through PROteolysis Targeting Chimeras (PROTACs). These are bifunctional molecules consisting of a bait moiety that binds to the target protein and a moiety that binds an E3 ubiquitin ligase such as Von Hippel-Lindau (VHL) or Cereblon (CRBN) (Sakamoto et al., 2001; Diehl and Ciulli, 2022). SAM-competitive, substrate-competitive, and allosteric binders can all be utilised as the bait moiety in PROTAC design. Once the PROTAC brings the target protein, it can recruit an E3 ubiquitin ligase, which is then able to polyubiquitinate the target. The polyubiquitin group signals the proteolytic degradation of the target protein by the ubiquitin-proteasome system (UPS).

The inhibition of methylation by PROTACs has so far only been implemented against a small number of PKMTs and PRMTs namely the PKMTs EHMT2, EZH2 and NSD2 and the PRMTs PRMT3, PRMT4 and PRMT5. As for the PKMT PROTACs, MS8709 (Velez et al., 2024), AMB-03-378 (Mukherjee, 2025), G9D-4 (Shi et al., 2024) target EHMT2, MS8847 (Velez et al., 2024), MS8815 (Dale et al., 2022), MS177 (Wang et al., 2022), U3i (Wang et al., 2022), YM181 and YM281 (Tu et al., 2021), MS1943 (Ma et al., 2020), PROTAC E7 (Liu et al., 2012) target EZH2 and MS9715 (Xu et al., 2022), MS159 (Meng et al., 2022), LLC0424 (Liu et al., 2024), together with a handful of unnamed PROTACs (Sun et al., 2022; LegaardAndersson et al., 2023) target NSD2 for degradation. For the PRMTs, there are only degrader "11" (Zou et al., 2024) for PRMT3, C199 (Ju et al., 2025) for PRMT4 and MS4322 (Shen et al., 2020), MS115 (Zhong et al., 2025) and YZ-836P (Guo et al., 2024) for PRMT5.

Apart from targeting the PMTs directly, interacting sub-units of the PMTs within protein complexes have also been targetted for degradation resulting in the destabilisation of the entire complex. The two proteins targetted in this manner so far are EED as part of the PRC2 complex and WDR5 as part of the MLL (KMT2A) complex. The PROTACs designed to target EED are UNC6852 (Potjewyd et al., 2020), PROTAC 1 and PROTAC 2 (Hsu et al., 2020) and UNC7700 (Bashore et al., 2023), while the ones targeting WDR5 are 8g and 17b (Doñlle et al., 2021), MS33 and MS67 (Yu et al., 2021), MS40 and MS169 (Li et al., 2022) and MS132 (Yu et al., 2023).

Compared to conventional inhibitors, these PROTACs have been reported to at times be more potent than their parent inhibitor. However, despite the promise displayed so far, there are still challenges in transitioning these molecules from *in vitro* to clinical testing, one of which is the

development of resistance by tumour cells to the commonly used E3 ubiquitin ligase ligands VHL and CRBN through mutations or down-regulation of the ubiquitin ligase mechanism (Békés et al., 2022). That being said, PROTACs against PMTs are not straightforward to design (Martin et al., 2024), and the general understanding is still in its early stages, with effective development still requiring further optimisation (Wang et al., 2022). Moreover, since the choice of E3 ligase ligand in PROTACs affects selectivity and degradation efficiency, alternative, highly selective ligase ligands need to be sought to further optimise PROTAC design (He et al., 2024).

2.4.8. Inhibitor Limitations

As can be seen from the above exposition, currently selective inhibitors are only available against a very small number of the known PMTs. This is due to the fact that the enzymatic domain is highly conserved. Segregating methyltransferases based on the structural diversity of their SAM-binding site produces two groups, with the first containing SET domain PMTs, whilst a second contains PRMTs, small molecule-, DNA- and RNA-methyltransferases, which all share a cofactor-binding Rossmann fold. This clustering underscores the high likelihood of off-target effects when attempting to design an inhibitor that targets the SAM-binding site of a selected PRMT (Schapira and de Freitas, 2014).

Although the relatively high sequence conservation at the SAM-binding site makes inhibitor design challenging, given that the ATP-binding pocket of kinases and the cofactor binding pocket of PMTs have been shown to present a similar level of structural diversity (Campagna-Slater et al., 2011), and selective kinase inhibitors have been successfully developed, isoform-selective inhibitors could be designed for selected PMTs by exploiting the few variable positions available (Schapira and de Freitas, 2014). More selective inhibitors that target specific PMTs as potential therapeutics, especially for application in cancer combinatorial therapy, can be designed by leveraging advances in structure-based design and high-throughput screening (Copeland, 2018).

Furthermore, most of the inhibitors developed thus far are reversible and despite the apparent benefits of covalent inhibitors, it is still difficult to identify adequate warheads to covalently bind to weaker nucleophilic amino acids such as lysine and methionine and since PMT targets do not always contain adequate cysteine, lysine or methionine residues within their active sites, targeting other nucleophilic residues such as tyrosine, serine, threonine, and histidine, is harder since these are less explored (Li et al., 2019), and not so easy to target with the currently available warhead chemistry (Gehring and Laufer, 2018). For this reason, it is important to optimise the effectiveness of currently available warheads (particularly acrylamide derivatives) as well as explore the development of novel electrophilic warheads in order to facilitate covalent PMT inhibitor discovery and produce potent and selective molecules that can meet the required clinical standards (Li et al., 2019). The investigation of targeting less commonly studied nucleophilic residues (i.e. lysine, tyrosine, serine, threonine, and histidine) may yield alternative options for the development of a new spectrum of covalent inhibitors (Powers et al., 2002; Gambini et al., 2019).

Another issue is the ubiquitous existence and continuous development of pan PMT inhibitors, which offer little clinical benefit, not only because they target PMTs that might be essential for basic cellular function, making it difficult to predict the overall impact on tissues and organs but more so because such inhibitors generally present very different potencies for the respective PMTs they target and finding a balance in the dosing that provides adequate inhibition of the various targets is extremely difficult, which leads to the issue of toxicity.

3. Failure to Clinic

Most of the inhibitors developed so far are only useful for *in-vitro* experiments since their specificity and sensitivity are not always up to the desired clinical standard. Moreover, even those inhibitors that do make it to clinical trials run the risk of becoming ineffective due to the development of resistance. The basis for designing more effective inhibitors is a clear understanding of why the pre-clinical or clinical trials failed from a biochemical and physiological perspective.

Various reviews have listed the compounds that have entered clinical trials, their use, and failure point (Talukdar et al., 2022; Dempke et al., 2023; Rossi et al., 2024; Tong et al., 2024; Micallef et al., 2024; Zhu et al., 2024). Unfortunately, so far, PMT inhibitors have failed to demonstrate sufficient therapeutic efficacy at non-toxic doses in clinical trials. Having a wide range of protein targets involved in numerous biochemical pathways leads to off-target effects, which bring about significant side effects, outweighing any tangible benefits. In essence, the beneficial therapeutic range, with acceptable side effect and toxicity levels in patients, is very narrow and as a result, it is a significant challenge to achieve the desired therapeutic effect (Micallef et al., 2024).

Computational chemistry, through the implementation of molecular docking, combined with structural biology using PMT crystal structures, provides an invaluable tool set to guide drug design. The data collected from failed trials will provide a stronger basis for *in silico* prediction using high-throughput screening assays, including virtual screenings (Talukdar et al., 2022; Wang et al., 2022) to confidently shortlist the more promising candidates to be tested further in the wet lab.

4. Considerations for Designing Novel PMT Inhibitors

PMT inhibitors need to have sufficient potency, selectivity, and cell permeability to be successfully implemented in the clinic. Developing selective PMT inhibitors and improving the efficacy of inhibitors, particularly for clinical applications will need to go beyond the production of refined iterations of successful inhibitory molecules in the hope of obtaining something better, ideally by focusing on investigating alternative inhibitory mechanisms. However, this is particularly challenging and the options are somewhat limited considering that all PMTs use SAM as the methyl donor and function through an almost identical mechanism to incorporate the methyl group, given that SAM-binding and residue-binding pockets present a significant similarity across PMTs. In turn, targeting the non-catalytic domains of PMTs is still relatively unexplored, making the assessment of their chemical tractability a compelling area for further research.

Specifically to improve peptide-based inhibitors, one possibility is to replace the peptide backbone with peptide mimics, called peptoids or peptidomimetics. Peptide inhibitors suffer from poor stability and short half-lives due to proteolytic degradation. These peptoids consist of chains of N-substituted glycine residues, such that the side chain is on the nitrogen of the peptide backbone, instead of the α -carbon as in peptides. As a result of this difference, peptoids are less susceptible to degradation by hydrolysis, resulting in improved stability and longer half-lives as well as often having improved cellular permeability and bioavailability compared to their peptide analogues (Powers et al., 2002; Brekker et al., 2022). The success of this approach has been shown in the development of a peptoid inhibitor against SETD3 (Hintzen et al., 2021) and another against PRMT1 (Brekker et al., 2022). Peptoids targeting SETD3 were designed based on a 16-mer β -Actin peptide (residues 66-81) with the histidine at position 73 (H73) being replaced by a panel of methionine analogues, which acted as substrate competitive inhibitors offered varying degrees of inhibition, with selenomethionine being the strongest inhibitor. These molecules showed that a 3-carbon core side chain seemed to be the optimal length and that apart from methionine and selenomethionine, inhibition of SETD3 could also be achieved by β -Actin peptides containing homomethionine, S-methylcysteine, leucine, norleucine, norvaline, and aminobutyric acid (Hintzen et al., 2021). A peptoid that targets PRMT1 was constructed covering the first 16 residues of histone H4 and the guanidine on arginine at position 3 (R3) was replaced with a chloracetamidine group as a warhead, which is well-known to modify cysteine and used to target PRMT1 via cysteine at position 101 (C101) found within the active site, that is not conserved in most other PRMT family members such that it could bring about selective and irreversible modification of PRMT1 (Brekker et al., 2022).

Despite all the available literature, many specifics related to the mode of action of the current inhibitors are still unknown, limiting the design of improved inhibitors. In order to make PMT inhibitor targeting safe for clinical application, the broad use of SAM by a wide variety of enzymes and the similarity between the active sites of enzymes within the same family pose significant challenges to overcome in PMT inhibitor specificity. Considering that each PMT has hundreds of

substrate proteins fulfilling very diverse cellular roles, it is expected that perturbing the PMT concentration will have implications on numerous biochemical pathways, some of which may be essential and non-redundant for non-cancerous cells.

Given the growing repertoire of PMT inhibitors, there is a pressing need for comprehensive biochemical and biophysical characterisation, at least for the more successful and promising of the existing PMT inhibitors (Kaniskan et al., 2018). Demonstrating direct interaction between the inhibitor and PMT is imperative and can be achieved through methods such as isothermal titration calorimetry (ITC) or surface plasmon resonance (SPR). Generating structures of the enzyme-inhibitor complexes by using NMR or X-ray crystallography is essential to elucidate the mode of binding and how specificity is being achieved. Functionally important is the demonstration of selectivity of the designed inhibitors for targeting their intended PMT by interrogation against a panel covering a broad range of methyltransferases through robust cellular assays (Kaniskan et al., 2014; Kaniskan et al., 2015).

Inhibitor validation should begin with an *in vitro* assessment of the level of inhibition of methylation activity. This can be achieved either by quantifying methylated protein products or the by-product SAH, for which both direct or indirect approaches exist (Luo, 2012; Zeng and Wu, 2015). Radiometric assays and top-down mass spectrometry, often in combination with electrophoretic methods such as 2D-PAGE, enable direct quantification of methylated proteins. Alternatively, digested peptides may be analysed using bottom-up or middle-down mass spectrometry, often following antibody enrichment (Luo, 2012).

SAH quantification can be performed directly using anti-SAH antibodies or mass spectrometry. Indirect SAH-quantification methods include radioisotope-labelled assays (using SAM with a tritiated methyl group), a variety of enzyme-coupled spectrophotometric (colorimetric/fluorescence/luminescence) assays (such as reactive thio-mediated chromogenic assays, adenine/xanthine-mediated colorimetric assays, ATP-mediated luminogenic assays, fluorescence polarisation assays and fluorescence lifetime assays), antibody-based assays (namely enzyme-linked immunosorbent assays (ELISA) or dissociation-enhanced lanthanide fluoroimmunoassays (DELFA)), proximity assays (in the form of proximity homogeneous assays or time-resolved fluorescence resonance energy transfer (TR-FRET) assays), microfluidic capillary electrophoresis, and reporter assays (either using chemical labelling of methyltransferase substrates or cell-based reporter assays) (Luo, 2012; Zeng and Wu, 2015).

Ultimately, the most promising inhibitors will need to be evaluated in disease-relevant or animal models to demonstrate their bioavailability, cell permeability and target engagement within cells as well as their impact on upstream and downstream signalling pathways, thereby bridging the gap from *in vitro* potency to therapeutic relevance (Luo, 2012; Kaniskan et al., 2015).

Both the mechanistic information on substrate docking and the interaction crystal structure provide key information that not only helps to better understand the mode of action and biological effects that these inhibitors have on their target PMTs but also to identify the strengths and limitations of the different design strategies. Such information should thus become a benchmark for any future inhibitors developed.

A particularly important segment of missing information is related to the impact that the dysregulated PMTs have on the mechanisms of specific chemotherapeutic drug classes. Since each cancer type is treated with a limited number of chemotherapeutics and generally has a handful of commonly dysregulated PMTs, knowing such information would be key towards providing more targeted treatment regimens and avoiding administration of ineffective medication (Micallef et al., 2024).

Another aspect to consider is what the inhibitor is designed to target. In most cases, the inhibitor docking is designed against the canonical sequence and 3D shape; however this does not represent the active form of the PMT. Proteins can be active within cells as functionally different molecules stemming from a combination of genetic polymorphisms, RNA splice variants, and multiple PTMs, and this chemical diversity at a protein level produced from a single gene is collectively described as

proteoforms (Aebersold et al., 2018; Smith et al., 2021; Marx et al., 2024). This is particularly relevant to PMT inhibition because proteoform expression generally varies both spatially (across cells and tissues) as well as temporally (with age or over time, as well as after specific events such as disease), affecting both their abundances and interactions, following potentially altered sub-cellular localisation (Smith et al., 2021; Naryzhny, 2024). That being said, it depends very much on the PMT being targetted for inhibition, since some proteins (e.g. actin or histones) present hundreds of proteoforms, while others (and this is probably the category in which most PMTs fall) only present one or two active proteoforms (Naryzhny, 2024). For these reasons, it is important to investigate and identify which proteoform of a specific PMT needs to be targetted in a particular disease context i.e. if it differs from the main proteoform found in healthy cells or other tissues and organs. This would provide a more targetted approach and increase the chances of success in the clinical setting.

As further efforts are made to transition such PMT inhibitors towards clinical application, it is important to also remember that cancer cells will eventually find ways of developing resistance to at least some of these inhibitors, and any prior biochemical and biophysical knowledge will come in handy to overcome such resistance. The best document case so far is for EZH2, where in lymphomas, resistance against inhibitors such as GSK126, EPZ6438 and UNC1999 was acquired through single point mutations at positions I109K, Y111L/N/D, Y661D, C663Y and Y726F, which prevented inhibitor binding (Baker et al., 2015; Gibaja et al., 2016; Bissier and Wajapeyee, 2018) but could also be due to NSD1 loss (which mediated H3K36 dimethylation) (Drosos et al., 2022).

Despite the acquisition of resistance against a specific inhibitor, treatment with an inhibitor that targets the same PMT through a different binding mechanism might be able to bypass the acquired resistance in at least some of the tumours (Bissier and Wajapeyee, 2018). Alternatively, a co-factor within the active complex might need to be targeted (Qi et al., 2017; He et al., 2017) or a different inhibition strategy needs to be adopted (Hsu et al., 2020). Combinatorial therapy blocking epigenetic crosstalk with acetylation (e.g. H3K27ac) and phosphorylation (e.g. Ribosomal S6 kinase 4 (RSK4) or Cyclin-dependent kinase inhibitor (CDKN) 1A/2A/2B) (Pang et al., 2023; Kazansky et al., 2024) and their mediated downstream oncogenic activation (e.g. phosphorylation of Extracellular signal-regulated kinase (ERK) or Aurora kinase B (AURKB)) (Huang et al., 2018; Kazansky et al., 2024) should also be considered for personalised medicine applications.

5. Conclusions and Future Perspectives

In order to gain a more comprehensive understanding of what the roles of at least the major PMTs implicated in cancer chemoresistance are, a collection of patient tumour data from cancer cohorts that are characterised at a protein level, not just genetically, will be essential. So far the literature mostly presents data related to the effects of inhibitors on PMTs dysregulated at the onset of tumour formation. Protein data collected before and after patient treatment with such PMT inhibitors would also provide information on off-target effects as well as key downstream outcomes linked to the combined action of the PMT inhibitor and the chemotherapeutic drug, allowing for improved design or dose administration adjustments. There is, as of yet, very limited literature related to PMT inhibitor efficacy, particularly in relation to countering chemoresistance.

In order to collect reliable data in this regard, there is a need to develop novel experimental techniques for determining PMT inhibitor efficacy, PMT expression quantification, and activity testing. This goes hand in hand with improved or new strategies for higher efficiency protein or peptide enrichment, as well as technological advances in mass spectrometry techniques, which would allow for higher confidence PTM identification and quantification (Deng et al., 2016; Levy, 2019; Micallef and Baron, 2023; Wang et al., 2017). Over and above all this, it is expected that with the current trend of implementing AI-driven design, there will be a push towards improving the currently promising molecules using AI to integrate data from various experimental inputs.

A particularly interesting and impactful future consideration involves the investigation of combinatorial therapies of PMT inhibitors with other small molecule therapeutics (already approved for clinical use), given that tumours often employ multiple chemoresistance mechanisms in parallel.

These could include immunomodulatory molecules such as immune checkpoint inhibitors as well as signalling pathway modulators, particularly PI3K, MAPK, or Wnt pathway inhibitors (including via kinase inhibitors).

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