



Review

RETRACTED: Impact of Histone Modifications and Their Therapeutic Targeting in Hematological Malignancies

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Abstract: Hematologic malignancies are a large and heterogeneous group of neoplasms characterized by complex pathogenetic mechanisms. The abnormal regulation of epigenetic mechanisms and specifically, histone modifications, has been demonstrated to play a central role in hematological cancer pathogenesis and progression. A variety of epigenetic enzymes that affect the state of histones have been detected as deregulated, being either over- or underexpressed, which induces changes in chromatin compaction and, subsequently, affects gene expression. Recent advances in the field of epigenetics have revealed novel therapeutic targets, with many epigenetic drugs being investigated in clinical trials. The present review focuses on the biological impact of histone modifications in the pathogenesis of hematologic malignancies, describing a wide range of therapeutic agents that have been discovered to target these alterations and are currently under investigation in clinical trials.

Keywords: histones; epigenetics; hematological malignancies; methylation; acetylation; phosphorylation; leukemia; lymphoma



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1. Introduction

Hematologic malignancies are a large and heterogeneous group of neoplasms, characterized by hallmark genetic alterations, incidence, and prognosis. Some of these cancers have protracted courses with better behavior, whereas others have a more acute onset and/or a less favorable prognosis, rendering their classification and diagnosis rather challenging for patients. Based on the 2016 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [1], the hematologic malignancies are divided into the mature lymphoid, histiocytic, and dendritic neoplasms, as well as the myeloid neoplasms and acute leukemias. The family of mature lymphoid, histiocytic, and dendritic neoplasms is further differentiated into mature B-cell neoplasms, mature T and natural killer (NK) neoplasms, Hodgkin lymphomas, post-transplant lymphoproliferative disorders (PTLDs), and histiocytic and dendritic cell neoplasms. In turn, the myeloid neoplasms and acute leukemias are distinguished into myeloproliferative neoplasms (MPNs); mastocytosis; myeloid/lymphoid neoplasms with eosinophilia and a rearrangement of platelet-derived growth factor receptor alpha (PDGFRA) and beta (PDGFRB), or fibroblast growth factor 1 (FGFR1), or with pericentriolar material 1 protein (PCM1)-Janus kinase 2 (JAK2); myelodysplastic/myeloproliferative neoplasms (MDSs/MPNs); myelodysplastic syndromes (MDSs); myeloid neoplasms with germ line predisposition; acute myeloid leukemia (AML); and related neoplasms such as blastic plasmacytoid dendritic cell neoplasm, acute leukemias of ambiguous lineage, B-lymphoblastic leukemia/lymphoma, and T-lymphoblastic leukemia/lymphoma. Among these neoplasms, diffuse large B-cell lymphoma (DLBCL) has the greatest incidence, followed by chronic lymphocytic leukemia (CLL) [2].

The interplay of genetic and epigenetic factors constitutes a major field of study in hematologic cancers, which involves chemical modifications that do not directly affect the

DNA sequence but can regulate gene expression [3]. In this way, epigenetic modifications act as a reversible cellular mechanism to fine-tune gene expression in response to environmental stimuli. These alterations include histone and nonhistone methylation, acetylation, ubiquitinylation, demethylation, and deacetylation, as well as DNA methylation, acetylation, demethylation, and deacetylation [4]. Histones, being the structural proteins of chromatin, form octamers composed of four main histone pairs (H2A, H2B, H3, and H4) which allow for DNA wrapping and nucleosome formation. Epigenetic modifications commonly occur at the N-terminal tails and globular domains of histones and can either activate or inhibit gene expression, depending on their type [5].

In this context, histone methylation plays a major role in epigenetic gene regulation, being carried out by specific enzymes known as histone methyltransferases (HMTs), which can methylate either lysine, arginine, or histidine residues [6]. The SET domain-containing and disruptor of telomeric silencing 1-like (DOT1L) families of proteins mediate histone lysine methylation, whereas arginine methyltransferases (PRMTs) establish methylation of arginine residues [6]. By contrast to HMTs, histone demethylases work to remove the methylation marks from histones. In a similar way, histone acetylation is established by the respective acetylases and removed by deacetylases. Generally, histone methylation leads to the increased compaction of chromatin ("closed" state), which inhibits the binding of enzymes involved in the transcriptional machinery, leading to downregulation of gene expression [3]. On the other hand, histone acetylation generally leads to the decompaction of chromatin, exposing more sites for the binding of transcriptional enzymes [7]. This decompaction allows the expression of genes contained within this specific area and is referred to as "relaxed" chromatin. In concert, azacytidine and decitabine, two DNA methyltransferase inhibitors (DNMTi) targeting these epigenetic modifications, have already been approved by the FDA for the treatment of hematologic malignancies [8]. The recent advances in epigenetics have further revealed new therapeutic targets, with many drugs being investigated in clinical trials. A prominent example is panobinostat, the first histone deacetylase inhibitor (HDACi) approved for the treatment of patients with relapsed or relapsed and refractory multiple myeloma (MM) [9].

In the following sections, we describe the pivotal role of histone modifications in the development and progression of main hematologic malignancies and provide an update on the wide range of therapeutic targets that have been discovered in recent research studies and are currently under evaluation in clinical trials.

2. Histone Modifications in Hematological Malignancies

A variety of epigenetic enzymes that affect the state of histones have been detected to be deregulated, being over- or underexpressed, in various hematological malignancies. Changes in chromatin compaction alter the expression of target genes, subsequently affecting malignant progression.

2.1. Histone Methylation

Histone methylation has been shown to play a key role in hematologic cell development and differentiation, as well as tumorigenesis [10]. A prominent example is the histone 3 lysine 4 (H3K4) methyltransferases, which play an integral role in physiologic hematopoiesis and participate in *Hox* gene regulation during the developmental stage [11]. Increased activity of various histone methyltransferases has been noted in several hematological neoplasms, such as B- and T-cell lymphomas and myeloid malignancies [12–15], being causally associated with tumorigenesis. Although histone methyltransferases are classically associated with chromatin suppression, the result of their activity in tumors is not always predictable and can be associated with a series of transcriptional modifications based on the recruitment of specific transcription factors, as well as on the interaction with other proteins, such as initiation and elongation factors [16]. Mutations in genes encoding histone methyltransferases, such as the mixed-lineage leukemia (*MLL*) and enhancer of

zeste homolog 2 (*EZH2*) genes, have been frequently documented to affect the normal function of gene regulation elements [17].

The methyltransferase *EZH2*, a catalytic subunit of the polycomb repressive complex 2 (PRC2) which is responsible for establishing the histone 3 lysine 27 trimethylation (H3K27me3) mark and inducing the concomitant transcriptional repression of target genes, has been also shown to play a vital role in normal hematopoiesis. *EZH2* regulates the differentiation, proliferation, and apoptosis of the adult hematopoietic stem cells [18] by repressing negative cell-cycle regulators, including cyclin-dependent kinase inhibitor 2A (CDKN2A); differentiation transcription factors, including BLIMP and interferon regulatory factor 4 (IRF4); as well as pro-apoptotic genes, including NADPH oxidase (*NOX*) and *p21* [18–20]. Changes in *EZH2* expression and the loss- or gain-of-function mutations may contribute to the development of hematologic malignancies. Depending on the context, however, *EZH2* may act either as an oncogene or as a tumor suppressor. *EZH2* overexpression or gain-of-function mutations are frequently seen in high-grade follicular lymphoma, DLBCL, Burkitt lymphoma, natural killer/T-cell (NKT) lymphoma [21], and 4;14 translocation MM patients [13,22,23]. Of note, this is one of the most common translocations in MM and induces the formation of the immunoglobulin heavy locus (IgH)-Wolf-Hirschhorn syndrome candidate 1 protein (WHSC1) fusion gene. Overexpression of WHSC1 in MM has been associated with enhanced histone 3 lysine 36 dimethylation (H3K36me2).

On the contrary, loss-of-function *EZH2* mutations have been observed more frequently in MDSs, atypical chronic myelogenous leukemia (CML), myelofibrosis, and T-cell acute lymphoblastic leukemia (T-ALL) [12], where they have been associated with a worse prognosis [24]. At the same time, several oncoproteins appear to inhibit *EZH2* activity in MDS cells, such as splicing factor serine- and arginine-rich splicing factor 2 (*SRSF2*) mutations that induce abnormal *EZH2* splicing and promote MDS development [25]. Therefore, it is evident that *EZH2* can either act as an oncogene in B-cell and NKT lymphomas, presenting increased activity or function as a tumor suppressor in MDSs and T-ALL. Mutations in other PRC2 members, such as the embryonic ectoderm development (EED) and polycomb repressive complex 2 subunit (SUZ12), have also been described in some MDS and T-ALL cases, whereas additional sex combs-like 1, transcriptional regulator (*ASXL1*) mutations promote myeloid transformation through the loss of PRC2-mediated gene repression [26].

Regarding the H3K4 methyltransferase *MLL*, which is a critical regulator of *HOX* genes, frequent translocations of *MLL1* with other oncogenic partners have been detected in AML and ALL [27], as well as in leukemias post-etoposide treatment [28]. Of note, approximately 10% of all leukemias harbor *MLL1* translocations. These leukemia types follow an aggressive course with poor conventional chemotherapy responses and frequent early relapses. The resulting chimeric proteins lack the normal catalytic SET domain of *MLL1*, which is replaced by sequences derived from AF4, AF9, AF10, and ENL that allow for the interaction with other oncogenic factors and cause uncontrolled transcription, leading to leukemogenesis. These sequences further allow direct or indirect interactions with the DOT1L methyltransferase [28], the only human histone 3 lysine 79 (H3K79) methyltransferase involved in normal hematopoiesis [29]. More than 70 translocation partners have been reported, many of which belong to protein complexes that alter the structure and function of chromatin [30]. Some of the most common fusion proteins (FPs), accounting for approximately 80% of *MLL* rearrangements, are members of the SEC or DOT1L complex (AF4/FMR2 Family Member 1 (AFF1/AF4), MLLT3 super elongation complex subunit (MLLT3/AF9), MLLT1 super elongation complex subunit (MLLT1/ENL), MLLT10 histone lysine methyltransferase DOT1L cofactor (MLLT10/AF10), and elongation factor for RNA polymerase II (ELL)), playing a key role in transcriptional regulation [31]. In this context, the integrase-binding domain of the chromatin-binding protein lens epithelium-derived growth factor p75 splice variant (LEDGF) is needed for *MLL1*-dependent transcription and leukemic transformation, as it can directly interact with *MLL1* and menin, an essential oncogenic cofactor required for the leukemogenic activity of *MLL*-FP [32]. Meanwhile, LEDGF binds to dimethylated H3K36 through its PWWP domain [33]. LEDGF is essential

in MLL-rearranged leukemia, but not hematopoiesis, which highlights the therapeutic potential of LEDGF targeting on the hematopoietic system without side effects [34].

H3K79 levels and DOT1L methyltransferase have been also shown to be aberrantly elevated in leukemia [35]. In more detail, the DOT1L H3K79 methyltransferase is involved in several cellular processes including transcriptional control, cell-cycle progression, telomeric silencing, and DNA repair and replication [36], along with its involvement in normal hematopoiesis [29]. Misdirected H3K79 methylation by DOT1L has also been shown to sustain the expression of key pro-leukemic genes such as the homeobox A (*HOXA*) genes and MEIS homeobox 1 (*MEIS1*) [37,38]. On the other hand, DOT1L dysregulation or H3K79 methylation appears to decrease malignant gene expression.

Similarly, the coactivator-associated arginine methyltransferase 1/protein arginine *N*-methyltransferase-4 (*CARM1/PRMT4*), which induces histone 3 arginine 17 asymmetrical dimethylation (H3R17me2a) and histone 3 arginine 26 asymmetrical dimethylation (H3R26me2a), leading to transcriptional activation, has been enhanced in multiple myeloma. *PRMT4* knockdown in leukemia cell lines inhibits cell-cycle progression and promotes apoptosis while downregulating *E2F* and *MYC* target genes [39]. The arginine methyltransferase *PRMT5*, which regulates important genes involved in proliferation, DNA damage response, and apoptosis such as *p5*, *p21*, growth arrest and DNA damage inducible alpha (*GADD45*), and P53-upregulated modulator of apoptosis (*PUMA*) [40], has also been highly overexpressed in B-cell- non-Hodgkin lymphoma (B-NHL) subtypes, such as DLBCL and MCL [41]. Opposite effects have been reported in respect to the most common *JAK* mutation, *JAK2 V617F*, which may interact with *PRMT5* in hematopoietic cells. This is a gain-of-function mutation that allows *JAK2* to phosphorylate *PRMT5* [42], reducing the histone methyltransferase activity, and resulting in a global decrease in histone 2 (H2)/histone 4 (H4) arginine 3 (R3) methylation marks with modified gene expression. *PRMT5* inhibition activity ultimately promotes progenitor cell proliferation.

Lastly, several other transcriptional regulatory proteins have also been dysregulated in hematological neoplasms. Particularly, MDS1 and EVI1 complex locus (*MECOM*), PBX homeobox 1 (*PBX1*), phosphatase and tensin homolog (*Pten*), and PR domain-containing 16 (*PRDM16*) methyltransferase gene rearrangements have been reported in some AML and MDS cases [43,44]. *MECOM* expression was shown to be ectopically activated through the repositioning of the distal enhancer *GATA2* [45], whereas the reciprocal translocation t(1:3)(q36;q21) induces *PRDM16* upregulation. *MECOM* or *PRDM16* rearrangements in AML share mutual biological features, such as the presence of micromegakaryocytes, low myeloperoxidase-expressing blasts, multilineage dysplasia, and poor prognosis [46]. In addition, the simultaneous disruption of both suppressor of variegation 3-9 homolog (*Suv39h*) genes, which code for the Suv39 histone lysine methyltransferase that regulates the cell cycle through the silencing of *E2F*-responsive genes [47], dramatically decreases the viability in mice and favors chromosomal instabilities, resulting in an increased risk of B-cell lymphoma development [48]. H3K9 methylation, therefore, appears to protect cells from genetic instabilities and its dysfunction may cause tumorigenesis. Finally, recurrent nonsense or frameshift SET domain-containing 2 (*SETD2*) mutations have been described in AML and B-ALL [49]. These are, most commonly, loss-of-function mutations which alter the expression of various cell-cycle-related genes [50]. In *SETD2*-mutated leukemic blasts, a global loss of H3K36me3 has been observed.

Finally, distinct recognition motifs, broadly divided into the two main groups of the royal family (Tudor domains, chromo domains, and malignant brain tumor (MBT) domains) and plant homeodomain (PHD) fingers, can recognize lysine methylation from other modifications while their aberrant function has been causally linked to hematologic malignancies. For example, the retained function of the H3K4me3 reader PHD finger controls leukemogenesis in a subset of nucleoporin 98kDa (NUP98)-translocated AMLs. The aberrant function of these fusion proteins subsequently causes the upregulation of many critical oncogenes, such as *HOXA9* and *MEIS1* (Figure 1) [51].

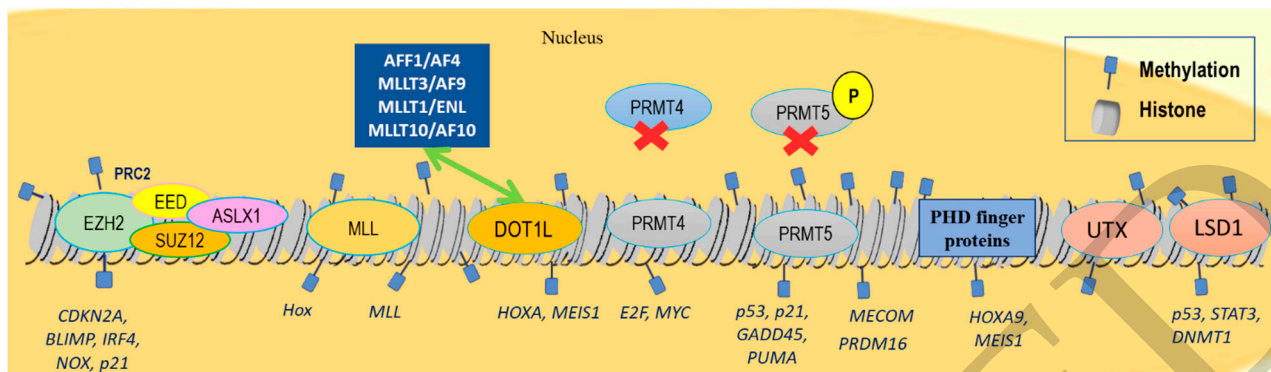


Figure 1. Chromatin landscape indicating histone methylation changes related to hematological malignancies. EZH2 methyltransferase regulates the differentiation, proliferation, and apoptosis of the adult hematopoietic stem cells by repressing *CDKN2A*, *BLIMP*, and *IRF4*, as well as pro-apoptotic genes, *NOX* and *p21*. EZH2 overexpression or gain-of-function mutations have been detected in high-grade follicular lymphoma, DLBCL, and NKT lymphomas. Loss-of-function *EZH2* mutations have been observed in MDSs, atypical CML, myelofibrosis, and T-ALL. Mutations in other PRC2 members, such as *EED*, and *SUZ12*, have been observed in some MDS and T-ALL cases, whereas *ASXL1* mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Frequent *MLL1* translocations have been detected in AML and ALL. Most common fusion partners accounting for approximately 80% of *MLL* rearrangements are *AFF1/AF4*, *MLLT3/AF9*, *MLLT1/ENL*, and *MLLT10/AF10*, which interact with *DOT1L* that further sustains the expression of key pro-leukemic genes *HOXA* and *MEIS1*. *PRMT4* knockdown inhibits cell-cycle progression and promotes apoptosis by downregulating *E2F* and *MYC* target genes in leukemic cell lines. *PRMT5* is overexpressed in DLBCL and MCL via regulation of *p53*, *p21*, *GADD45*, and *PUMA* genes. *MECOM* and *PRDM16* are rearranged in AML. PHD finger proteins recognize lysine methylation, upregulating *HOXA9* and *MEIS1* gene activity in AML. Lysine demethylase *UTX* is also frequently mutated in MM and ALL, and *LSD1* is overexpressed in ALL, AML, CML, MPNs, and MDSs, repressing *p53*, *STAT3*, and *DNMT1* activity.

2.2. Histone Demethylation

Deregulation of lysine demethylases has been linked to hematologic malignant processes, such as mutations in lysine demethylase 6A (*UTX/KDM6A*), which has been associated with malignant transformation [52]. In more detail, loss-of-function point mutations or deletions within the Jumonji C (JmjC) domain of *UTX* inactivate the H3K27 demethylase activity in MM and ALL [52,53]. Interestingly, an allelic expression analysis demonstrated that *KDM6A* escapes the X-inactivation in normal T-cells and T-ALL lymphoblasts in females, which explains why the loss of one *UTX* copy leads to tumor development in males, but not in females [54]. Deletions and mutations of the *KDM2B* gene have also been discovered in about 5% of DLBCL [55].

In addition, lysine demethylase 1A (*KDM1A/LSD1*), which interacts with multiple protein complexes and may simultaneously act as a transcriptional activator and repressor in normal cells, is highly expressed in hematopoietic neoplasms, including ALL, AML, CML, MPNs, and MDSs [56,57]. It is mainly responsible for transcriptional repression through the demethylation of mono- or dimethylated H3K4, but is further capable of demethylating nonhistone targets, such as *p53*, signal transducer and activator of transcription 3 (*STAT3*), and DNA methyltransferase 1 (*DNMT1*) [58,59]. It may also favor transcription by interacting with the androgen receptor [60]. Overall, *KDM1A* is an important regulator of differentiation and self-renewal in human embryonic stem cells (ESCs), and a crucial regulator of granulopoiesis differentiation, as well as hematopoietic stem cell maintenance [61]. In *MLL*-FP models, *KDM1A* is required for leukemic stem cell function, whereas in other AML-subtype cell line models, its inhibition prevents tumor growth by inhibiting cancer cell proliferation, differentiation, invasion, and migration [62,63]. It

has also been reported that the oncogenic driver, *MYC* in B-NHL, interacts with KDM1A demethylase and lysine demethylase 4B (KDM4B) [64]. KDM1A inhibition in AML leads to the transcriptional activation of integrin subunit alpha M (*ITGAM*) and cluster of differentiation 86 (*CD86*) myeloid lineage genes, reducing AML cell proliferation. Of note, *KDM1A* silencing appears to be accompanied by increased H3K4me2 and H3K4me3 levels at the *ITGAM* and *CD86* promoter regions, whereas global H3K4me2 levels remain constant [65].

2.3. Histone Acetylation

Recurring mutations in lysine acetyltransferases (KATs) CBP and p300 have been detected in a series of hematological malignancies, particularly in lymphoid neoplasms [66]. They are often present in 40% of DLBCL, 60% of follicular lymphoma (FL), and less frequently, in B-cell ALL, T-cell ALL, and cutaneous T-cell lymphoma [66–70]. Mutations in genes encoding the p300 and CBP KATs lead to the abnormal acetylation of histone and nonhistone targets, such as B-cell lymphoma 6 protein (BCL-6) and p53 [66]. These inactivating mutations of *p300* prevent terminal differentiation and enhance responsiveness to mitogenic stimuli [71]. Recently, increased KAT7, KAT2A, KAT6B, and cysteine-rich protein 2-binding protein (CSRP2BP) expression levels were found in B-ALL. KAT2A was shown to acetylate the E2A-PBX homeobox 1 (PBX1) oncoprotein in B-ALL cells that results from the fusion of transcription factor 3 (*TCF3*)-*PBX1* genes, increasing its stability [72]. Moreover, p300/CBP-mediated H3K27 acetylation has been observed in super-enhancer regions. Super-enhancers consist of clusters of active enhancers, which are associated with transcription factors and cofactors and are able to promote the high-level transcription of genes that determine the cell's identity [73,74]. Super-enhancers have been associated with active oncogenes, indicating that they could play a crucial role in tumor development [75]. In this context, bromodomain-containing 4 (BRD4) is commonly found to be associated with enhancer regions with increased p300/CBP-mediated histone 3 lysine 27 acetylation (H3K27ac) and decreased H3K4me3 [76]. These regions control genes which are associated with cell renewal and pluripotency, such as *Nanog* and *OCT4* [77,78].

In addition, chromosomal translocations that involve KATs, such as lysine acetyltransferase 6A (MOZ)- nuclear receptor coactivator 2 (TIF2) [79] and MLL-CBP [80] are commonly seen in myeloid malignancies. The MOZ-TIF2 fusion protein appears to be sufficient for leukemic transformation because of its ability to bind to nucleosomes and recruit CBP, promoting the acquisition of stem cell properties, as well as the activation of a self-renewal cell program [81,82]. Similarly, the KAT and bromodomain of CBP were particularly shown to be necessary for leukemic transformation in MLL-CBP leukemia murine models after an initial myeloproliferative phase [83]. A study showed that 84% of ALL patients presented an overexpression of CBP at diagnosis but not in remission [84], whereas the inducible CAMP early repressor (ICER) that inhibits CBP activity was downregulated at diagnosis [84].

The acetyltransferase activity of KATs may also target nonhistone substrates and regulate the interactions as well as the activity of various proteins. One example is the acetylation of the leukemic FP RUNX family transcription factor 1 (AML1)-RUNX1 partner transcriptional corepressor 1 (ETO) by KAT3B (p300), which plays a significant role in its cellular self-renewal effects and leukemogenicity [85].

Finally, oncogenic drivers of B-NHL, such as *BCL-6* and *MYC*, are able to recruit chromatin-modifying enzymes that cause alterations in the normal epigenetic landscape. More specifically, *MYC* may interact with the acetylation writers p300, lysine acetyltransferase 2A (GCN5), and lysine acetyltransferase 5 (Tip60), as well as histone deacetylase 1 and 3 (HDAC1 and HDAC3) [64]. On the other hand, *BCL-6* is capable of recruiting CBP, and class I and II HDACs [66,86–88].

Acetylated lysine residues can be recognized by bromodomain-containing proteins [89] and, particularly, by the subfamily II that includes mutated bromodomain testis-associated (mBRDT), BRD2, BRD3, and BRD4, which is highly significant. Its members regulate transcription factors and gene expression [90]. Specifically, BRD4 stimulates positive

transcription elongation factor b (P-TEFb), subsequently enhancing RNA polymerase II phosphorylation and resulting in ongoing transcription [91]. In MM, BRD4 interacts with super-enhancers that are related to pivotal MM genes, including cyclin D2 (*CCDN2*), PR/SET domain 1 (*PRDM1*), X-Box binding protein 1 (*XBPI*), or myeloid cell leukemia sequence 1 (BCL2-Related) (*MCL1*) [74], and recruits lysine methyltransferases and arginine demethylases (Figure 2) [92].

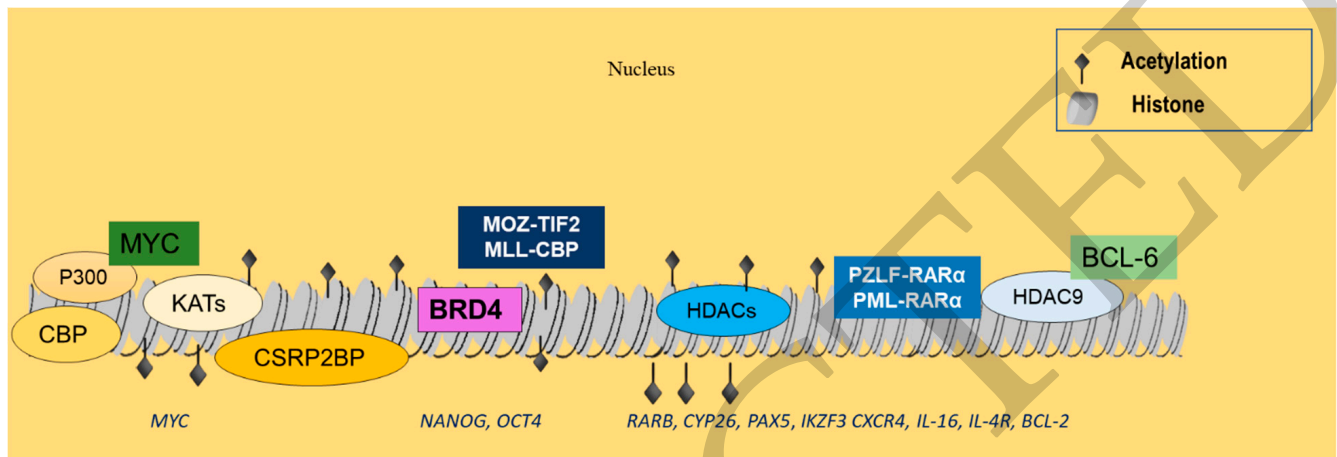


Figure 2. Histone acetylation events related to hematological malignancies. CBP and p300 are often dysregulated in lymphoid neoplasms, leading to abnormal acetylation of histones, as well as nonhistone targets, such as *BCL-6* and *p53*. KAT7, KAT2A, KAT6B, and CSRP2BP are overexpressed in B-ALL and may interact with *MYC*, implicating them in tumor development. BRD4 further associates with p300/CBP-mediated acetylation-enhanced regions, controlling genes associated with cell renewal and pluripotency, such as *Nanog* and *OCT4*. MOZ-TIF2 and MLL-CBP are commonly rearranged in myeloid malignancies, resulting in the respective FPs that have been implicated in leukemic transformation. Increased HDAC expression is also common in ALL, regulating *RARB*, *CYP26*, *Pax5*, *IKZF3*, *CXCR4*, *IL-16*, *IL-4R*, and *Bcl-2* gene expression. HDACs, and in particular HDAC9, also interact with the PML-RAR α and PLZF-RAR α FPs, as well as with *BCL-6* to promote the development of hematologic malignancies.

2.4. Histone Deacetylation

On the other hand, the increased expression of histone deacetylases (HDACs) appears to commonly occur in a variety of cancers and correlates with a significant reduction in both disease-free and overall survival, predicting a poor prognosis [93–95]. HDACs oppose histone acetylation by catalyzing deacetylation, which leads to chromatin condensation and gene silencing [96]. HDACs present a very diverse group of enzymes that are subdivided into four classes (I, II, III, and IV) based on their homology to yeast proteins, subcellular location, and enzymatic activities. They lead to tumorigenesis by repressing tumor suppressor gene expression or by modifying oncogenic cell signaling pathways [97,98].

In more detail, HDAC1 and 4 were shown to be overexpressed in T-cell ALL, whereas HDAC6 and 9 were found to be upregulated in B-cell ALL [99] and HDAC2 in ALL [100]. HDAC3, 7, and 9 upregulation has been linked to a poor prognosis in childhood ALL [99,101]. H4 acetylation has been suggested as a prognostic marker in newly diagnosed ALL or in recently relapsed patients with higher levels of H4 acetylation, as its associated with an increased overall survival [102,103]. HDAC3 has been shown to be recruited to the retinoic acid receptor beta (RARb) promoter as well as to the cytochrome P26 (CYP26) promoter by PML-RAR α in APL [104]. In a similar way, HDAC4 has been shown to interact with the promyelocytic leukemia zinc finger (PLZF)-RAR α , causing the downregulation of differentiation-associated genes in leukemic cells [105]. HDAC7 has a tumor suppressor role in hematopoietic malignancies, such as pro-B ALL and Burkitt lymphoma. In these malignancies, the ectopic expression of HDAC7 inhibits *c-MYC* transcription, promotes

apoptosis, and suppresses in vivo oncogenic potential [106]. HDAC1 has been shown to modulate the expression of several genes including *Pax5*, IKAROS family zinc finger 3 (*IKZF3*), members of the B-Cell receptor (BCR) pathway, immune regulators such as C-X-C motif chemokine receptor 4 (*CXCR4*), interleukin-16 (*IL-16*), interleukin-4 receptor (*IL-4R*), and *Bcl-2* in CLL [107]. A dysregulation of HDAC mRNA levels has also been detected with HDAC1-8 mRNA being overexpressed in ALL, whereas increased HDAC 3, 7, and 9 levels have been correlated with a poor prognosis [99].

Interestingly, HDAC-BCL6 complexes are abundant in lymphoma development. In normal physiology, CBP is able to acetylate BCL-6 and p53, which leads to the inhibition of the first and activation of the latter [66]. However, in FL and DLBCL, *CBP* mutations lead to a deficient CBP, which is unable to acetylate these substrates and the BCL6-nuclear receptor corepressor 2 (SMRT)-HDAC3 causes unopposed deacetylation. This deacetylation alters the transcriptive state of the B-cell signal transduction enhancers and immune response gene expression, leading to lymphomagenesis [66,108]. Furthermore, the dysregulated expression of the HDAC9-BCL6 complex promotes the development of hematologic malignancies. More specifically, HDAC9 overexpression regulates pathways involved in growth and survival, and also negatively influences the function of p53 while promoting the function of BCL-6 [108].

As mentioned above, HDACs are also recruited by a series of oncogenic proteins to aberrantly initiate or sustain malignant gene transcription programs. Examples include the leukemic FPs PZLF-RAR α and PML-RAR α , which are able to recruit HDACs containing repressive complexes, leading to abnormal gene silencing [109–112]. Therefore, HDAC inhibition appears to re-establish normal cancer cell levels of histone acetylation and allows for the reactivation of tumor suppressor genes. Increased histone acetylation in B-NHL cells also appears to cause apoptosis and cell-cycle arrest, induce DNA damage, and reduce proliferation [113]. HDAC inhibition can further alter the acetylation of nonhistone targets, such as *MYC*, *p53*, or nuclear factor kappa B (*NF- κ B*) [114], thus indirectly altering the gene expression by interfering with the transcriptional machinery.

2.5. Histone Phosphorylation

One of the most commonly observed changes in malignant transformation is the aberrant kinase activity [115], which often involves histone phosphorylation and regulation of nuclear functions [116] (Figure 3). JAK2, a nonreceptor tyrosine kinase essential for cytokine signaling in physiologic hematopoiesis, is commonly activated in MPNs. JAK2 nuclear activity closely correlates with the levels of phosphorylated H3Y41 (H3Y41ph). This is justified by the fact that JAK2 can specifically phosphorylate H3Y41 in the nucleus, causing the detachment of heterochromatin protein 1-alpha (HP1 α) from chromatin, a transcriptional repressor, and the activation of LIM domain only 2 (LMO2) and other hematopoietic oncogenes [117]. More than 2000 potential JAK2 target genes have been identified that may be modulated by the phosphorylation of H3Y41 and by HP1 α displacement [117], including genes encoding the histone demethylase Jumonji domain-containing protein 2C (*JMJD2C*), *JAK2* itself, or *c-Myc* [118]. Several genes with the H3Y41ph mark are also attached to STAT family members, suggesting that the functional interaction between JAK kinases and STAT proteins extends beyond the cytoplasm to the chromatin interface.

Additionally, the phosphorylation of histone 3 serine 10 (H3S10) is responsible for the immediate condensation of chromatin in the late G2 phase of the cell cycle and, thus, can function as a marker that is present only in dividing cells [119]. Indeed, the levels of phosphorylated H3 have been used to determine mitotic activity and to experimentally, as well as clinically, measure cellular proliferation in different cancer types, including lymphomas [120–122].

PIM1, another H3S10 kinase, plays a pivotal role in tumorigenesis and cancer progression. Only when simultaneously overexpressed with MYC is MYC-induced lymphomagenesis dramatically accelerated, resulting in aggressive lymphomas which start in utero or peripartum [123–125]. After being stimulated by a growth factor, PIM1 forms a complex with the MYC dimer and its interacting protein, MYC-associated factor X (MAX). This complex further interacts with the MYC target genes, such as immediate early genes (*IEGs*), FOS-like 1, AP-1 transcription factor subunit (*FOSL1*), and the inhibitor of DNA-binding 2 (*ID2*) [126]. PIM1 then phosphorylates H3S10, enabling those genes to be transcriptionally activated. PIM1 inhibition, on the other hand, reduces the MYC-mediated cellular transformation [127].

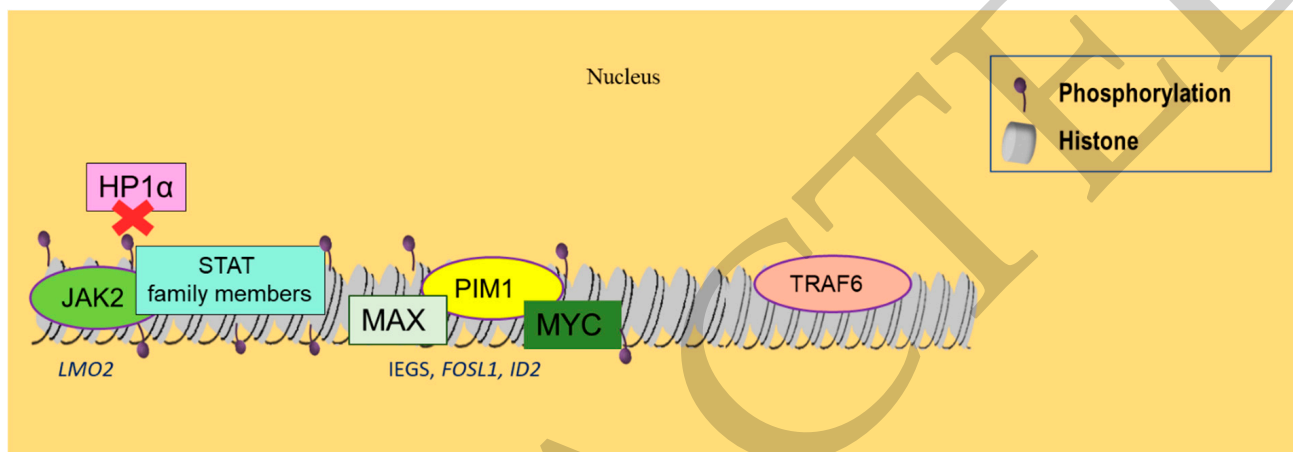


Figure 3. Histone phosphorylation and SUMOylation alterations related to hematological malignancies. JAK2 kinase is commonly activated in MPNs, resulting in histone phosphorylation, which induces the disassembly of HP1 α from chromatin and the activation of *LMO2* oncogene. Phosphorylated genes also attract STAT family members, enabling a functional interaction between JAK kinases and STAT proteins. PIM1 kinase, when simultaneously overexpressed with MYC, promotes lymphomagenesis. It can form complexes with MYC and MAX, activating *IEGs*, *FOSL1*, and *ID2*. Finally, SUMOylation reduces gene expression of the E3 ubiquitin ligase TRAF6 in DLBCL and further represses gene transcription.

2.6. Other Histone Modifications

Other histone modifications include SUMOylation, which describes the covalent conjugation of a small ubiquitin-like modifier (SUMO) to lysine residues. SUMOylation appears to regulate a series of important cellular processes and is usually associated with reduced gene expression [128]. More specifically, TNF receptor-associated factor 6 (TRAF6), an E3 ubiquitin ligase that correlates with worse prognosis in DLBCL patients [129], can be SUMOylated and repress gene transcription through HDAC recruitment in B cells (Figure 3) [130].

Ubiquitination of histones is another important chromatin modification process, which upon dysregulation, promotes oncogenesis and cellular proliferation through alterations in the tumor suppressor and oncogene transcription [131]. Studies have revealed frequent alterations in genes encoding histone E3 ubiquitin ligases and deubiquitinases.

A summary of the main histone-modifying enzymes and respective marks in hematological malignancies is given in Table 1.

Table 1. Histone-modifying enzymes involved in hematological cancers.

Enzyme	Histone Mark	Malignancy Type	Target Genes	Reference
Histone methylation				
EZH2	H3K27	High-grade FL, DLBCL, Burkitt lymphoma, NKTL, 4;14 translocation	CDKN2A, BLIMP, IRF4, NOX, p21	[18–20]
MLL1	H3K4	AML, ALL	HOX	[27]
DOT1L	H3K79	Leukemias	HOXA, MEIS1	[37,38]
CARM1 (PRMT4)	H3R17 and H3R26	MM	E2F and MYC target genes	[39]
PRMT5	H2/H4R3	DLBCL, MCL	p53, p21, GADD45, PUMA	[40]
MECOM (EVI1)	H3K9	AML, MDSs	GATA2, PBX1, Pten	[43,44]
Suv39h	H3K9	B-cell lymphoma	E2F-responsive genes	[47]
SETD2	H3K36	Leukemias	Cell-cycle genes	[49]
Histone demethylation				
UTX (KDM6A)	H3K27	T-ALL	Different cell-type-specific genes	[53,54]
LSD1 (KDM1A)	H3K4	ALL, AML, CMML, MPNs, MDSs	CD11b/ITGAM, CD86	[65]
Histone acetylation				
CBP and p300	H3K27	DLBL, FL, B-ALL, T-ALL, cutaneous T-cell lymphoma	Nanog, OCT4	[77,78]
Histone deacetylation				
HDACs		T- ALL, B-ALL, CLL, FL, DLBCL	RARb, CYP26, Pax5, IKZF3, CXCR4, IL16, IL4R, Bcl2	[104,107]
Histone phosphorylation				
JAK2	H3Y41	Lymphomas and other malignancies	LMO2 and >2000 JAK2 target genes, such as JMJD2C, JAK2, c-Myc	[117,118]
PIM1	H3S10	Various malignancies	IEGs, FOSL1, ID2	[126,127]

3. Therapeutic Targeting of Histone Modifications

3.1. Histone Methyltransferase Inhibitors

With respect to histone methyltransferases, several inhibitors have been developed that are currently being evaluated in preclinical and clinical studies (Table 2).

Table 2. Ongoing and completed clinical trials on histone methyltransferase inhibitors in hematologic malignancies.

No	NCT Number	Title	Conditions	Intervention	Mechanism of Action
EZH2 Inhibitors					
1	NCT04762160	SYMPHONY-2, A Trial to Examine Combination of Tazemetostat with Rituximab in R/R FL	R/R FL	Tazemetostat, rituximab	Tazemetostat: EZH2 inhibitor. Rituximab: anti-CD20 monoclonal antibody.
2	NCT05205252	Multi Cohort Study of Tazemetostat in Combination with Various Treatments For R/R Hematologic Malignancies	R/R lymphomas and MM	Tazemetostat in combination with: tafasitamab, lenalidomide, acalabrutinib, daratumumab, hyaluronidase-fihj, pomalidomide 4 MG, dexamethasone 20mg, dexamethasone 40mg	Tazemetostat: EZH2 inhibitor. Tafasitamab: anti-CD19 mAb. Lenalidomide: immune modulator. Acalabrutinib: inhibitor of tyrosine phosphorylation of ERK, IKB, and AKT downstream targets. Daratumumab: anti-CD38 mAb. Hyaluronidase-fihj: degrades hyaluronan and increases permeability of subcutaneous tissue. Pomalidomide: immune modulator and antineoplastic agent. Dexamethasone: glucocorticoid that modulates the immune reaction.

Table 2. Cont.

No	NCT Number	Title	Conditions	Intervention	Mechanism of Action
3	NCT02395601	Study Evaluating CPI-1205 in Patients With B-Cell Lymphomas	B-cell lymphomas	CPI-1205	CPI-1205: small-molecule EZH2 inhibitor.
4	NCT03603951	Phase I Study of SHR2554 in Subjects with R/R mature lymphoid neoplasms	R/R mature lymphoid neoplasms	SHR2554	SHR2554: selective small-molecule inhibitor.
5	NCT04407741	Phase I/II Study of Combination with SHR1701 in Patients with Advanced Solid Tumors and B-cell Lymphomas	Advanced pretreated solid tumors and B-cell lymphomas	SHR2554, SHR1701	SHR2554: selective small-molecule inhibitor. SHR1701: anti-PD-L1/TGF- β antibody
6	NCT04224493	Study in Subjects with Relapsed/Refractory Follicular Lymphoma	R/R FL	Tazemetostat, lenalidomide, rituximab	Tazemetostat: EZH2 inhibitor. Lenalidomide: immune modulator. Rituximab: anti-CD20 mAb.
7	NCT02082977	Study investigating the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK2816126 in Subjects with R/R DLBCL, transformed FL, NHL, MM, solid tumors	R/R DLBCL, transformed FL, NHL, MM, solid tumors	GSK2816126	GSK2816126 inhibits EZH2 and mEZH2. It also inhibits EZH1 with less potency.
8	NCT04104776	Study of CPI-0209 in Patients with Advanced Solid Tumors and Lymphomas	Advanced solid tumor, DLBCL, T-cell lymphoma, mesothelioma, castration-resistant malignant prostatic neoplasms	CPI-0209	CPI-0209: a second-generation EZH2 inhibitor.
9	NCT03460977	PF-06821497 Treatment of Relapsed/Refractory SCLC, Castration Resistant Prostate Cancer, and Follicular Lymphoma	Small-cell lung cancer, FL, castration-resistant prostate cancer	PF-06821497	PF-06821497: a lactam-derived, orally bioavailable EZH2 inhibitor.
10	NCT03603951	Phase I Study of SHR2554 in Subjects with R/R Mature Lymphoid Neoplasms	R/R mature lymphoid neoplasms	SHR2554	SHR2554: a selective small-molecule inhibitor of EZH2.
PRMT5 Inhibitors					
11	NCT02783300	Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK3326595 in Participants with Solid Tumors and Non-Hodgkin's Lymphoma (Meteor 1)	Solid tumors, NHL	GSK3326595	GSK3326595: selective PRMT5 inhibitor.
12	NCT03573310	Study of JNJ-64619178, an Inhibitor of PRMT5 in Participants with Advanced Solid Tumors, NHL, and Lower Risk MDS	Advanced solid tumors, NHL, lower-risk MDSs	JNJ-64619178	JNJ-64619178: an orally active and pseudo-irreversible PRMT5 inhibitor.

Table 2. Cont.

No	NCT Number	Title	Conditions	Intervention	Mechanism of Action
13	NCT03886831	Study of PRT543 in Participants with Advanced Solid Tumors and Hematologic Malignancies	R/R advanced solid tumors, R/R DLBCL, R/R myelodysplasia, R/R myelofibrosis, adenoid cystic carcinoma, R/R MCL, R/R AML, refractory CML	PRT543	PRT543: selective oral PRMT5 inhibitor.
14	NCT03666988	First Time in Humans (FTIH) Study of GSK3368715 in Participants with Solid Tumors and Diffuse Large B-cell Lymphoma (DLBCL)	Solid tumors, DLBCL	GSK3368715	GSK3368715: a reversible type I PRMT inhibitor.
DOT1L Inhibitors					
15	NCT03724084	Pinometostat With Standard Chemotherapy in Treating Patients with Newly Diagnosed Acute Myeloid Leukemia and MLL Gene Rearrangement	Acute myeloid leukemia	Pinometostat, cytarabine, daunorubicin	Pinometostat: small-molecule inhibitor of DOT1L. Cytarabine: chemotherapeutic drug and precursor to cytarabine-5-triphosphate. Daunorubicin: anthracycline antibiotic-class chemotherapeutic drug.
16	NCT03701295	Pinometostat and Azacitidine in Treating Patients with Relapsed, Refractory, or Newly Diagnosed Acute Myeloid Leukemia With 11q23 Rearrangement	Acute myeloid leukemia with t(9;11)(p21.3;q23.3); MLLT3-MLL, leukemia cutis, R/R acute myeloid leukemia	Pinometostat, azacitidine	Pinometostat: small-molecule inhibitor of DOT1L. Azacitidine: DNA methylation inhibitor.

3.1.1. EZH2 Inhibitors

A few EZH2 inhibitors are already being evaluated in early phase clinical trials, mainly for high-grade lymphomas. In this context, clinical trials including the EZH2 inhibitors tazemetostat (NCT04762160 and NCT05205252), CPI-1205 (NCT02395601), and SHR2554 (NCT03603951 and NCT04407741) are evaluating the efficacy of this approach (Figure 4). Tazemetostat is a highly selective and potent EZH2 inhibitor, shown to have antitumor effects in vitro and in xenograft models of B-NHL bearing *EZH2*-activating mutations [132,133]. Tazemetostat is currently under investigation in a phase I/II study and a phase II study, which are evaluating its combination with other drugs in the treatment of relapsed/refractory follicular lymphomas. Previously, a phase I trial evaluated tazemetostat's efficacy in solid tumors and relapsed/refractory B-cell non-Hodgkin lymphomas and established the recommended phase II dose of 800 mg twice daily. In this trial, the tazemetostat treatment achieved significant responses, with 8/21 B-cell NHL patients exhibiting a full response [134]. A follow-up phase II, open-label, single-arm trial was further carried out to determine the safety and evaluate the activity of tazemetostat in patients with follicular lymphoma [135]. This trial used a pool of 99 patients that received 800 mg of tazemetostat twice per day and observed an objective response rate (ORR) of 69% in the EZH2MUT and an ORR of 35% in the EZH2WT cohort. The median duration of response (DOR) was 10.9 months in the EZH2MUT cohort and 13.0 in the EZH2WT cohort, with a median progression-free survival (PFS) of 13.8 months and 11.1 months, respectively. Patient tolerance to tazemetostat was adequate, with no treatment-related deaths and serious treatment-related adverse effects (AEs) appearing in 4% of patients.

Therefore, tazemetostat's safety and effectiveness have already been demonstrated and the FDA has added this drug as a therapeutic option for patients with follicular lymphoma bearing an EZH2 mutation who have already received two or more systemic therapies or patients with relapsed/refractory (R/R) follicular lymphoma and no alternative satisfactory treatment options.

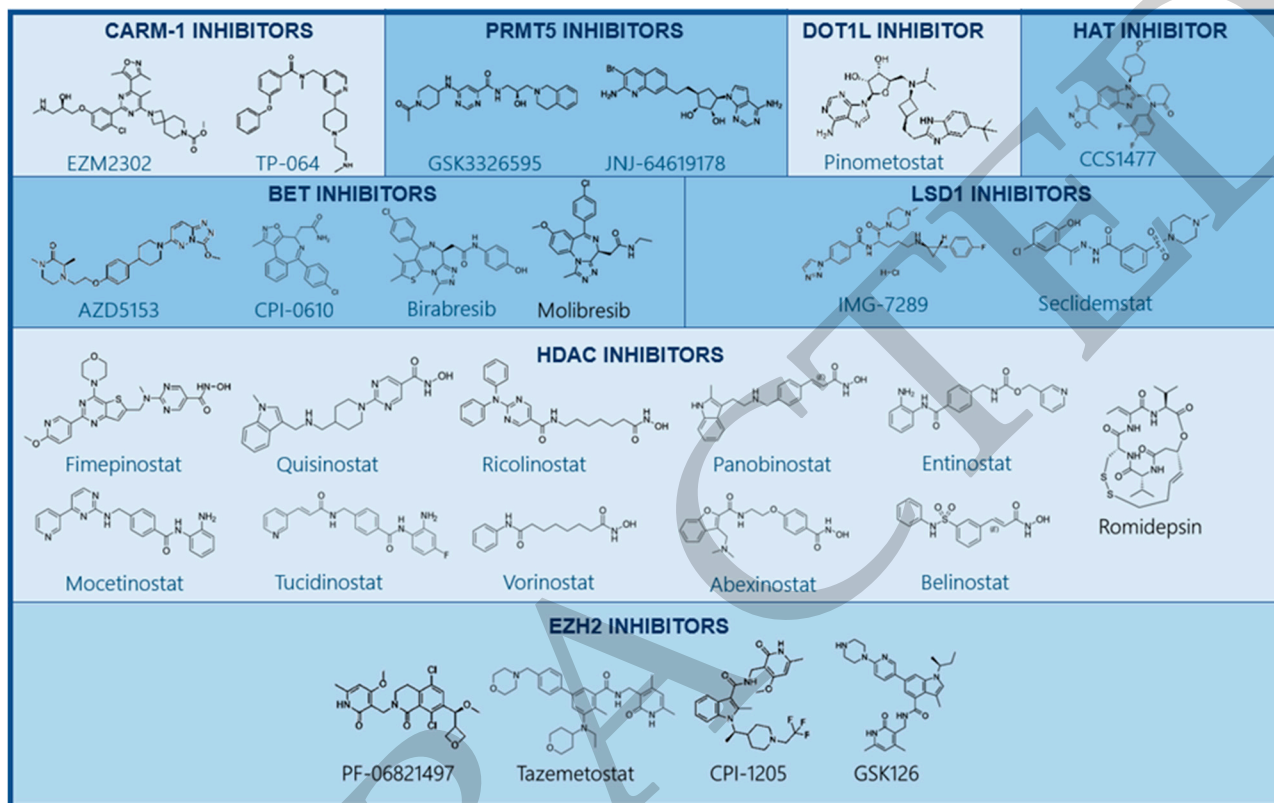


Figure 4. Structure of small-molecule inhibitors targeting epigenetic alterations. Several drugs targeting epigenetic enzymes have been developed and are currently being studied in preclinical and clinical studies. These include small molecules inhibiting CARM-1, PRMT5, DOT1L, EZH2 methyltransferases LSD1, HATs, HDACs, and BET.

Upon evaluation and confirmation of the safety and effectiveness of tazemetostat in hematologic malignancies, clinical trials evaluated the efficacy of its combination with other therapeutic modalities. A phase Ib study assessing the combination of tazemetostat and R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine (Oncovin) and prednisone) in elderly patients with previously untreated high-risk DLBCL showed that the recommended phase 2 dose of tazemetostat was identical to the one used in monotherapy: 800 mg twice daily [136]. They also observed a significant percentage of grade 3 and 4 hematologic adverse effects in 8/17 patients.

In another phase 1b/3 trial currently recruiting, tazemetostat is used in conjunction with lenalidomide and rituximab in patients with R/R follicular lymphoma who completed at least one prior systemic therapeutic regimen (NCT04224493). This trial aims to evaluate the recommended phase 3 dose, the efficacy, and safety of the combination of these drugs when compared to R2 plus placebo.

GSK126 is another methyltransferase inhibitor targeting both the wild-type and mutated EZH2 enzyme, with selectivity over EZH1 [137]. Studies in xenograft models have found that GSK126 exhibits antitumor activity in EZH2MUT DLBCL [138]. An open-label, dose-escalation clinical study (NCT02082977) in patients with advanced cancers, including hematologic malignancies, failed to show similar results. There was insufficient evidence

of GSK126 clinical activity, with more than half the patients (51%) undergoing disease progression and 34% of patients exhibiting stable disease [138].

The selective S-adenosylmethionine (SAM)-competitive inhibitor EI1 can block both EZH2WT- and EZH2MUT-containing PRC2. It was shown to inhibit H3K27 di- and trimethylation in DLBCL in vitro, leading to the suppression of cancer cell proliferation in cell lines bearing EZH2WT or EZH2MUT [139]. Similarly, EPZ011989 inhibits EZH2WT and EZH2MUT and was shown to suppress tumor growth in mouse xenografts of DLBCL.

An indole-based, selective EZH2 inhibitor, CPI-169, showed great antitumor activity in a mouse xenograft model of EZH2MUT DLBCL. However, since oral bioavailability was low, the drug was administered intraperitoneally and showed a synergistic effect when combined with the BRD4 inhibitor CPI-203 [140]. CPI-1205 can inhibit EZH2 and, in higher concentrations, EZH1 as well. It exhibited antitumor activity in vitro and in vivo in DLBCL EZH2MUT after binding to the catalytic site of EZH2 [140]. A subsequent phase I dose-escalation trial on patients with follicular lymphoma and DLBCL revealed grade 2 or lower adverse effects, without having reached the dose-limiting toxicity. One complete remission and five stable diseases were also reported. The effect of CPI-1205 was confirmed by the immunohistochemical detection of H3K27me3 marks. It was, therefore, concluded that CPI-1205 is well-tolerated and has antitumor effects [141]. In a phase I/II study in advanced cancers, CPI-0209, a second generation EZH2 inhibitor, was shown to be generally well tolerated with manageable adverse effects (NCT04104776).

The lactam-derived PF-06821497 [142] and SHR25 are both orally bioavailable EZH2 antagonists, and currently under investigation in phase I dose-escalation trials on patients with R/R follicular lymphoma and DLBCL (NCT03460977) and R/R mature lymphoid neoplasms (NCT03603951).

Interestingly, the inhibition of both EZH1 and EZH2 has proven to be effective in disrupting the inactivation of PRC2 and eliminating quiescent leukemic stem cells in MLL-AF9 leukemia [143]. This has led to the development of novel EZH1/2 inhibitors with great potential in preclinical studies [144]. The first orally bioavailable SAM-competitive inhibitor of both wild-type and mutated EZH2 and EZH1 was UNC1999, with the ability to target EZH2MUT DLBCL cell lines [145]. Lately, two EZH1/2 dual inhibitors, (R)-OR-S1 and (R)-OR-S2, exhibited a greater antitumor activity in in vitro and in vivo EZH2MUT DLBCL models, without any significant toxicity [145].

Furthermore, novel drugs which inhibit resistance to EZH2 inactivation have also attracted scientific interest. Such drugs are used to target the activated insulin growth factor 1 receptor (IGF-1R), phosphoinositide-3-kinase (PI3K), and MAP kinase (MAPK) pathways in DLBCL [146].

It is apparent that EZH2 has been a major topic of interest in regard to B-cell lymphoma treatment. This has led to many novel drugs surfacing and an even greater number of them being developed and evaluated in preclinical studies. The research targeting EZH2 has also shed light on more facets of the complete role of EZH2 in tumorigenesis. To date, tazemetostat is the only EZH2 inhibitor approved by the FDA for use in the treatment of a subgroup of patients with hematologic malignancies. Current efforts are focused on developing more selective, less toxic, and more efficient EZH2 inhibitors, as well as dual EZH1/EZH2 inhibitors.

3.1.2. PRMT5 Inhibitors

Several small molecules inhibiting PRMT5 have been already developed with variable potency and selectivity (Figure 4) [40,147]. EPZ015666 (GSK3235025) is a SAM-cooperative inhibitor of PRMT5 that binds at the peptide binding site of PRMT5 [148]. EPZ015666 is being used in preclinical trials to efficiently inhibit MCL growth in vitro and in mouse models [147,148]. EPZ015666 also appears to significantly inhibit MM cell growth [149], whereas a similar compound, namely, EPZ015866 (GSK3203591), has been explored in in vitro studies [150,151]. EPZ015938 (GSK3326595), a more potent PRMT5 inhibitor, is being investigated in two phase I trials in solid tumors, NHL, and leukemia (NCT02783300).

A combination therapy with other drugs, aiming to lower the dosage of PRMT5 inhibitors, has been proposed to reduce their toxicity and avoid resistance. For example, simultaneous PRMT5 and poly(ADP-ribose) polymerase (PARP) inhibition synergistically leads to the decreased growth of AML cells, whereas normal cord blood cell proliferation is less affected when using the same drug concentrations [152]. Interestingly, in DLBCL-derived cancer cells, PRMT5 targeting further enhances BCL6 inhibitor effectiveness in decreasing cell proliferation [150]. PRMT5 and AKT co-inhibition synergistically inhibits the proliferation of the DLBCL cell line and primary cancer cells, since PI3K-AKT expression depends on PRMT5 [153]. In light of these findings, clinical trials have started evaluating the efficacy of the PRMT5 inhibitors JNJ-64619178 (NCT03573310), PRT811 (NCT04089449), and PRT543 (NCT03886831). A recent clinical trial was unfortunately terminated due to low benefit-to-risk ratios (NCT03666988).

3.1.3. DOT1L Inhibitors

DOT1L methyltransferase inhibition has also been explored in MLL-rearranged leukemias which are highly dependent on abnormal DOT1L H3K79 methylation, indicating DOT1L inhibitors as potential therapeutic agents (Figure 4) [154]. In this context, pinometostat, a small-molecule inhibitor of DOT1L, is being tested in a Ib/II clinical trial along with standard chemotherapy on patients with newly diagnosed acute myeloid leukemia with MLL gene rearrangement (NCT03724084). In a previous phase I study of 51 patients with R/R MLL leukemia, pinometostat showed modest efficacy [155]. Out of 51 patients, 2 showed complete remission and 9 patients experienced grade 3 or higher drug-related adverse effects. This points to DOT1L inhibition not being sufficient as a standalone therapy and opens the possibility of a combinatorial treatment with other standard or novel chemotherapeutic agents for the treatment of MLL leukemia. To this end, a study combining pinometostat with azacitidine in treating patients with R/R or newly diagnosed acute myeloid leukemia with an 11q23 rearrangement has been carried out, but the results are not yet publicly available (NCT03701295).

3.1.4. Preclinical Studies Involving Histone Methylation

Finally, on a preclinical level, studies have explored the potential of SUV39H1 methyltransferase inhibition, which enabled leukemic cell differentiation [156], as well as coactivator-associated arginine methyltransferase 1 (CARM1) and PRMT5 inhibition. CARM1 inhibition through TP-064 reduced DLBCL cell proliferation, with the highest efficacy being observed when cells carried inactivating *CBP* or *p300* gene mutations [157], whereas treatment with EZM2302, a more bioavailable CARM1 inhibitor, reduced the amount of *p300*-mutated DLBCL cells in xenograft models and worked synergistically with *p300*/*CBP* inhibitors [157]. On the other hand, *PRMT5* knockdown increased retinoblastoma protein (pRB) levels, disrupted lymphoma cell proliferation, and promoted cell death [158] while doubling the lifespan of E μ -Myc mice [159]. EPZ015666 (GSK3235025), a PRMT5 inhibitor, further demonstrated significant antiproliferative effects against MCL in vitro and in vivo [148] and also slowed down the proliferation of DLBCL cells [150].

In addition, the cell-type-specific knockout of LSD1 (KDM1A) prolonged the survival of lymphoma-prone mice [160], which supports the use of LSD1 inhibitors in B-NHL. The inhibitor GSK-J4 targets the lysine demethylase KDM6B, which is partially overexpressed in B-NHL [161]. Although GSK-J4 did not show strong effects on B-NHL cell proliferation, the combination with other chemotherapeutic agents was highly synergistic in inducing apoptosis [161].

3.2. Histone Demethylase Inhibitors

3.2.1. LSD1 Inhibitors

Numerous reversible or irreversible LSD inhibitors have been developed, such as monoamine oxidase (MAO) inactivators, trans-2-phenylcyclopropylamine derivatives, and peptide- or polyamine-based inhibitors, among others (Figure 4) [162,163]. Some of these

inhibitors are currently in early phase clinical trials and there are no mature data yet. The LSD1 inhibitor seclidemstat (SP-2577) is under evaluation in a phase I/II trial on patients with myelodysplastic syndrome or chronic myelomonocytic leukemia (NCT04734990). In this trial, seclidemstat is used in conjunction with azacitidine in order to assess the safety, tolerability, and maximum tolerable dose (MTD) of seclidemstat, as well as the overall response rate of patients to this treatment. Seclidemstat is also being evaluated in patients with advanced solid tumors (NCT03895684) and Ewing sarcoma (NCT03600649). In another phase I trial, the LSD1 inhibitor IMG-7289 is being used with and without all-trans-retinoic acid in patients with advanced myeloid malignancies (NCT02842827). Due to the myelosuppression resulting from therapeutic doses of LSD1 inhibitors, their use has been limited in myeloid neoplasms.

3.2.2. JMJC Inhibitors

JMJC domain-containing histone demethylases, a much larger class of histone demethylation agents, are still under investigation, and although inhibitors are being developed, they have not entered the clinical realm.

3.3. Histone Acetyltransferase (HAT) Inhibitors

Several compounds affecting histone acetylation are currently being investigated in preclinical and clinical stages. These mainly involve HAT inhibitors, as well as inhibitors of HDACs and compounds targeting readers of the bromodomain family and extra-terminal domain (BET)-containing proteins.

HAT targeting has been mainly evaluated preclinically, with a few promising results. Only the HAT inhibitor CCS1477-02 has entered clinical development for B-NHL, with an ongoing phase I trial for patients with hematological malignancies (NCT04068597). In preclinical models, CBP/p300 HAT inhibitors, such as C646, have been shown to reduce MYC expression, causing decreased H3K18ac and H3K27ac marks at the transcription start site, and preventing RNA polymerase recruitment [164]. In turn, this induces the apoptosis of lymphoma cells and results in a significant tumor reduction in lymphoma xenografts [164]. MOZ HAT inhibition was shown to induce cellular senescence and arrest lymphoma growth in transplant models [165]. Homozygous loss of the gene encoding general control non-depressible 5 (GCN5)/lysine acetyltransferase 2A (KAT2A) increased the lifespan of E μ -Myc mice by downregulating the expression of cell-cycle-related genes such as *E2f* and *Ccnd1* [166]. This finding led to the pharmacological targeting of GCN5 with the compound MB-3, which induces G2/M cell-cycle arrest [167]. However, the heterozygous knockout of the gene encoding the Tip60 HAT significantly diminished the lifespan of E μ -Myc mice [168]. The potential use of HAT activators is also currently being explored for the treatment of hematological diseases since histones are often under-acetylated.

3.4. Histone Deacetylase Inhibitors (HDACis)

HDACis have shown efficacy in reducing angiogenesis, modulating the immune response, and inducing cancer cell-cycle arrest, cellular differentiation, and death [169]. The importance of HDAC inhibition has been determined in several hematologic cancers. Although initially considered to be exclusive transcription activators through histone hyperacetylation, nonhistone targets of HDACis have also been discovered, including p53, as well as key proteins of the proteasome/aggresome pathways, tubulin, and heat shock protein 90 (HSP90) [170]. In this context, recent evaluations of the antileukemic properties of HDACis in t(8;21) AML revealed the promotion of terminal myeloid differentiation through HDACi-induced AML1/ETO9a FP proteasomal degradation [171].

At the moment, four HDACis have been granted FDA approval for the treatment of hematologic malignancies. Vorinostat has been approved for the treatment of cutaneous T-cell lymphoma (CTCL), romidepsin has been approved for CTCL and peripheral T-cell lymphoma (PTCL), belinostat for PTCL, and panobinostat for the management of multiple myeloma [172–175].

HDACis have been a major topic of research over the last few years, and many of them are currently under clinical investigation. Many of the trials which include HDACis use a combination therapy in order to overcome resistance to HDACi monotherapy [176]. HDACis are divided by their chemical properties into short-chain fatty acids (valproic acid), cyclic tetrapeptides (romidepsin), hydroxamic acids (suberoylanilide Hydroxamic Acid (SAHA), panobinostat, trichostatin A (TSA), and ricolinostat), and benzamides (entinostat and mocetinostat) (Figure 4) [113]. They work by chelating the central zinc ion at the catalytic center of class I, II, and IV HDACs [177].

Sirtuin inhibitors (SIRTi) are also able to inhibit HDACs through the noncompetitive inhibition of NAD⁺ [178] or occupation of the catalytic center [179]. Vorinostat is a specific class I and II HDAC inhibitor [180], whereas naturally occurring microbial metabolites, such as trichostatin A, act as pan-HDACis [181]. In contrast to the first-generation HDACis, the newly developed HDACi compounds are able to selectively inhibit one member or one class of HDAC, thus avoiding the off-target effects and, possibly, the associated adverse effects [182]. However, despite this awe-inspiring progress, only the few HDACis mentioned above have been approved by the FDA.

Concerning the efficacy of these drugs, pan-HDACis such as dacinostat have had potent antiproliferative effects in *in vitro* models of B-NHL and MM [183]. Furthermore, the direct application of vorinostat or panobinostat in *in vivo* models of E μ -Myc mice or lymphoma xenografts increased apoptosis and autophagy and led to a significantly increased median survival [184,185].

In an attempt to identify the most suitable HDAC target in leukemias and lymphomas, Matthews et al. identified that HDAC3 knockdown resulted in decreased lymphoma cell proliferation and a reduced tumor mass in mouse xenografts [186]. Moreover, the combined knockdown of both HDAC1 and HDAC2 potently increased lymphoma cell apoptosis mediated by MYC. Lastly, HDAC1/HDAC2 targeting has not been efficacious in decreasing the viability of B-NHL cells, in contrast to B-ALL cells, which was confirmed by the absence of H2A histone family member X (H2A.X) upregulation [183].

In certain malignancies, HDAC6 has also emerged as a potential target for HDACi treatment [186]. HDAC6 is unique because of its cytoplasmic expression, possessing two catalytic domains and being able to use tubulin and heat shock proteins as substrates [187]. The HDAC6 inhibitor ricolinostat has been found to induce an unfolded protein response and overload the proteasome in DLBCL cells [188]. Moreover, the HDAC6 inhibitor treatment of DLBCL and B-cell lymphoma cells in E μ -Myc mice induced MYC degradation, apoptosis, and inhibition of lymphomagenesis [189].

The HDACi treatment has also shown potential effectiveness in MM [190]. A preclinical model of activation-induced deaminase (AID)-dependent MYC activation in germinal center B-cell, V κ *MYC mice developed typical signs of MM, such as increased antibody production, splenomegaly, and osteolytic lesions, and increased numbers of CD138⁺ plasma cells [191]. Panobinostat treatment managed to reduce the CD138⁺ cells of these mice along with the M-spike from the antibody production, thus managing to prolong survival [192]. Panobinostat has been evaluated as a monotherapy in a B- and T-NHL patient cohort, which led to an ORR of 21%, a median OS of 15 months, and a median PFS of 3 months (NCT01261247). Similar results were observed in a cohort of patients with DLBCL refractory to R-CHOP treatment (NCT01523834). Adding rituximab to the therapeutic regimen was shown to cause no improvement in outcomes (NCT01238692 and NCT01282476) [193]. In three other clinical trials, the combination of panobinostat with everolimus, a mammalian target of rapamycin (mTOR) inhibitor, was evaluated. These clinical trials studied cohorts of B- and T-NHL and HL patients, and found a maximum ORR of 33%, an overall survival (OS) of 35 months, and a PFS of 4.2 months (NCT00918333, NCT00967044, and NCT00978432). The most notable adverse effect observed was thrombocytopenia in both monotherapy and combination trials, with a frequency of over 90% in some trials.

The HDACi ricolinostat, when combined with bortezomib, increased the endoplasmic reticulum (ER) stress in MM cells, causing apoptosis *in vitro* while also increasing the

survival of MM xenografts [194]. In another study, ricolinostat treatment was shown to upregulate the expression of CD38 on the surface of MM cells, thus improving the treatment with daratumumab, an anti-CD38 monoclonal antibody [195]. Ricolinostat has been found to upregulate CD20 on the surface of B-NHL cells. Using the same concept as mentioned above, this effect could be exploited to increase the response to anti-CD20 treatment [196].

A novel HDACi, BRD3308, was shown to upregulate p21 and cause CBP/p300-mutated DLBCL cells to self-mitigate proliferation [197]. In these lymphomas, BCL6-HDAC3 complexes inhibit p21 transcription. Furthermore, BRD3308 increased programmed cell death 1 ligand 1 (PDL1) and human leukocyte antigen-DR isotype (HLADR) expression, thus promoting CD4 and CD8 T-cell recruitment in an in vivo mouse model. A similar picture was observed when HDACis against class I or HDAC6 were evaluated [198,199].

Class III HDAC (sirtuin) inhibitors have previously been tested in combination with a pan-HDACi and exhibited a very good synergy. In their study, Amengual et al. used NAM, a general SIRTi, in conjunction with the four FDA-approved pan-HDACis. Their results showed that the combination of the SIRTi and HDACi induced *Bcl-6* and *p53* acetylation, a finding more pronounced in germinal center (GC)-DLBCL cell lines [200].

Similar synergistic results were observed in λ -MYC transgenic mice when treated with the combination of NAM and romidepsin [200]. This model is designed for studying the development of mature B-cell lymphomas [201]. When comparing different B-NHLs, the SIRT isoforms exhibit a differential functional role in the development and progression of the malignancy. In DLBCL, SIRT1 expression was correlated to a worse survival prognosis [202], whereas in MCL, sirtuin 3 (SIRT3) functions as a tumor suppressor protein [203]. Furthermore, in DLBCL, SIRT1 was shown to activate AMPK in primary effusion lymphoma. Suppression of SIRT1 activity led to an improvement in xenograft survival [204]. In contrast to MCL, SIRT3 acts as an oncogene in DLBCL by regulating the metabolic pathways of cancer cells and increasing the activity of isocitrate dehydrogenase 2 (IDH2) [205]. SIRT6 could also exhibit oncogenic activity. The knockdown of SIRT6 in lymphoma models caused a reduction in tumor volume and increased the expression of p27, a negative cell-cycle regulator [206], indicating that the context is very important for the effect of SIRTs.

Vorinostat has been extensively studied HDACi for lymphoma treatment. Different B-NHL cohorts have shown results ranging from 29% to 40% ORR to vorinostat monotherapy [207,208]. FL patients have demonstrated the highest ORR (49%), with MCL following (27%) and DLBCL being in third (5.5%) (NCT00875056 and NCT00097929) [209]. Unfortunately, a common adverse effect of vorinostat treatment was thrombocytopenia, affecting up to 90% of patients in certain trials. In another study, the addition of rituximab in patients with relapsed FL, MCL, and MZL led to an ORR of 46%, whereas a similar cohort using the combination of ifosfamide, carboplatin, and etoposide (R-ICE) along with rituximab and vorinostat achieved an ORR of 65% (NCT00601718). The combination of vorinostat with cladribine and rituximab in patients with MCL, relapsed CLL, or relapsed B-NHL resulted in a 39% ORR and an impressive 97% ORR when used in previously untreated MCL patients [210]. In a trial of patients with DLBCL, the combination of vorinostat with R-CHOP showed great potential, achieving an overall survival of 86% and progression-free survival of 73% at 2 years (NCT00972478). Adverse effects were frequently observed with all-grade AEs occurring in 70% of participants and serious AEs in 30% in the four clinical trials mentioned. Regarding adverse effects, febrile neutropenia was observed in 35% of DLBCL patients who were treated with vorinostat and R-CHOP.

Drug combinations including vorinostat have also been used in order to precondition patients for autologous stem cell transplantation (ASCT). In this context, event-free survival 100 days post-transplant was 100% in FL and MCL, and 66% in DLBCL (NCT01983969). Adverse effects were frequent; however, no serious adverse effects were reported. In patients with MCL, the combination of vorinostat with bortezomib, a proteasome inhibitor, resulted in an ORR of 27%. In DLBCL patients, the ORR of this therapy was 8% (NCT00703664). When used as a maintenance therapy after ASCT, B- and T-NHL patients showed 84% OS and 74% event-free survival (EFS) 6.5 years post-ASCT (NCT00992446). Combining vorinos-

tat with etoposide and niacinamide in a cohort of 4 patients led to 1 complete remission (CR) (NCT00691210) [200], whereas combining vorinostat with alisertib, an Aurora A inhibitor, led to 2 CRs in a cohort of 12 patients with R/R DLBCL patients (NCT01567709) [211]. Lastly, currently active clinical trials are evaluating combinations which include vorinostat in combination with the programmed cell death 1 (PD-1) immune checkpoint inhibitor pembrolizumab (NCT03150329), the PARP inhibitor olaparib (NCT03259503), and the mTOR inhibitor tacrolimus (NCT04220008 and NCT03842696).

Romidepsin, another HDACi, has been under scrutiny in clinical trials concerning hematologic malignancies. It has been evaluated as a monotherapy in a cohort of nine patients with relapsed DLBCL or MCL, which resulted in a single partial response (NCT00383565). Combinatorial therapies in T-NHL patient cohorts have shown more promising results, even when compared to B-NHL cohorts. Most notably, the combination of romidepsin with pralatrexate in a cohort of four patients with FL resulted in an ORR of 75% (NCT01947140) [212]. Lower ORRs have been reported by trials using a combination of romidepsin and azacitidine (NCT01998035), cisplatin (NCT01846390), dexamethasone, or gemcitabine [213,214]. Lastly, a clinical trial assessing the combination of romidepsin with lenalidomide is currently active (NCT01755975).

Abexinostat monotherapy has shown potential effects in clinical trials of patients with FL. More specifically, two clinical trials (NCT00724984, EudraCT-2009-013691-47) have resulted in an ORR of 56% and a PFS of 10/2 months. Similar results were, unfortunately, not observed in DLBCL and MCL patients [215]. Other trials are currently studying the abexinostat monotherapy in various NHL subtypes (NCT03600441, NCT03936153, and NCT03934567) or in combination with ibrutinib (NCT03939182).

Valproic acid has demonstrated strong activity against DLBCL when combined with R-CHOP. It was shown to result in an OS of 97% and a PFS of 85% at 2 years, with an ORR of 90%. This was accompanied, however, by increased toxicity, with 81% of patients experiencing grade 3 or 4 neutropenia, and auditory toxicity being frequent as well (NCT01622439) [216].

Mocetinostat monotherapy has also shown some activity in FL and DLBCL patients, with a trial achieving an ORR below 20% and a PFS below 3 months (NCT00359086) [217].

Fimepinostat has been used as a monotherapy in DLBCL patients, exhibiting an ORR of 47% and a PFS of 3 months (NCT01742988). Combining fimepinostat with rituximab did not have any therapeutic advantage [218].

Belinostat monotherapy and combinational therapies have not shown any benefit in treating lymphoma patients. The combinations evaluated include ibritumomab tiuxetan, an yttrium-90-labeled anti-CD20 monoclonal antibody (NCT00303953, NCT01273155, and NCT01686165).

Other drugs that have been tested or are being tested on B-NHL patients as monotherapies or in combinational therapies include quisinostat (NCT00677105), tucidinostat (NCT04025593, NCT04661943, NCT04231448, NCT04022005, NCT03974243, and NCT04337606), entinostat (NCT02780804 and NCT03179930), and ricolinostat (NCT02091063).

3.5. BET Inhibitors (BETis)

Acetylated lysine residues are recognized by bromodomains, which are protein-binding motifs that contain critical residues in their hydrophobic binding pocket. Variability in these residues enables diverse bromodomain recognition specificity, providing the opportunity for developing several small-molecule inhibitors, each targeting a different bromodomain family.

Examples include small-molecule inhibitors that target the bromodomain and extra terminal (BET) protein (BRD2, BRD3, BRD4, and BRDt) interactions (Figure 4) [219]. BET proteins are chromatin readers that follow bromodomain-induced localization to acetylated histones, where they recruit transcription factors or other chromatin-modifying enzymes. Pharmacological BET inhibition has shown significant efficacy against MLL FP leukemias *in vitro* and *in vivo* by inducing cell-cycle arrest and apoptosis [219], but also against

NPM1c-mutant leukemias [220]. BET inhibition has been further attempted in ALL, multiple myeloma [221], and non-Hodgkin lymphoma [222]. Of note, BET inhibitors were shown to decrease PD-L1 expression in lymphoma cells in vivo [223].

BRD4 can be targeted by the enantiomer-specific compound (+)-JQ1 and the synthetic histone mimetic I-BET762 (molibresib) compound [224,225]. (+)-JQ1 inhibits BRD4 recruitment for transcriptional activation by MYC and simultaneously downregulates the MYC expression itself and MYC protein levels [221,226]. It also displaces BRD4 in super-enhancers that influence major oncogenic drivers [74]. As a result, (+)-JQ1 appeared to induce cell-cycle arrest, senescence, and apoptosis in MM, BL, and DLBCL [221,227,228].

BETis are being investigated in clinical trials by increasing their stability and bioavailability, as well as by reducing their DLT. I-BET151, a novel dimethylisoxazole BETi, has been shown to induce G1 phase cell-cycle arrest and apoptosis in leukemic cells by downregulating BCL-2 [229]. I-BET151 is an I-BET762 analog with an increased in vivo half-life [219].

The BET inhibitor birabresib has been used as a monotherapy in a clinical trial in a cohort of 22 DLBCL patients, which resulted in an ORR of 10% and a high incidence of AEs. The AEs reported included anemia and thrombocytopenia, which affected more than 90% of patients (NCT01713582) [230]. Another trial evaluating birabresib discontinued its enrollment due to lack of efficacy (NCT02698189).

OTX015 (birabresib) has demonstrated potent antiproliferative effects in panels of DLBCL, MCL, marginal zone lymphoma (MZL), and MM cell lines by suppressing E2F3 target genes and decreasing inflammatory markers and, finally, the tumor volume in xenografts [231].

The benzoisoxazoloazepine CPI-0610 achieved xenograft leukemia tumor growth suppression by decreasing MYC gene transcripts. This effect was enhanced by the doxorubicin treatment [232]. Unfortunately, toxicity side effects included hypocellularity of the bone marrow, which led to anemia and thrombocytopenia as well as lymphoid depletion [232]. Both CPI-0610 and FT-1101 have been assessed in B-NHL patients, with results showing minimal efficacy. In one of the trials, CPI-0610 led to a partial response in 4 DLBCL patients and 1 FL patient of the 64 cases with B-NHL (NCT01949883), and FT-1101 did not achieve a response in any of the 10 B-NHL patients included in the cohort (NCT02543879).

The combination of BETis with venetoclax, a BCL-2 antagonist and BH3 mimetic, was shown to be beneficial in MYC-overexpressing lymphoma cells in preclinical models [233]. In this context, venetoclax was able to inhibit the antiapoptotic effects of BCL-2, which is commonly found to be overexpressed in B-NHL. This led to the induction of apoptosis through the upregulation of the pro-apoptotic BCL2-like 11 (BIM) [233]. Ultimately, this led to reduced tumor burdens and a greatly increased survival in lymphoma xenografts. In another study, the combination of panobinostat and (+)-JQ1 worked to promote apoptosis in MCL cells resistant to ibrutinib, a Bruton tyrosine Kinase (BTK) inhibitor [234]. Lastly, simultaneous inhibition of BET proteins and the chemokine receptor CXCR4 augmented MYC reduction in DLBCL cells, thus leading to a reduced tumor burden in transplanted xenografts [235].

Non-BET bromodomain inhibitors are also an important therapeutic modality in treating hematologic malignancy. These inhibitors work by targeting chromatin-modifying enzymes or remodeling complexes.

CBP or p300 inhibition can be achieved using bromodomain inhibitors such as CCS1477 or I-CBP112, which do not directly target the acetyl transferase catalytic site [236,237].

PFI-3, a bromodomain inhibitor, targets the ATP subunit of the SWItch/sucrose non-fermentable (SWI/SNF) chromatin complex, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 2 (SMARCA2). Furthermore, it is associated with HMT nuclear receptor-binding SET domain protein 2 (NSD2) in a subset of MM [238]. In this subset, PFI-3-induced apoptosis was attributed to the inhibition of myeloma-relevant gene expression without effects on BRD4 [238]. The SWI/SNF also has a BRD9 component which can be exploited for therapeutic targeting with non-BETi I-BRD9 [239]. To date, several binders to human bromodomains have been developed by

the Structural Genomics Consortium [240]. Furthermore, dual inhibitors of both BET and other targets such as BRD7/9, CBP/p300, and HDAC have been generated [241–243]. The antitumor effects of BET-CBP/p300 inhibitors have already been shown in MM, and other inhibitors remain to be tested [241].

INCB054329 and INCB057643 have been evaluated as monotherapies in cohorts of cancer patients which included 4 and 16 cases of lymphoma, respectively. Unfortunately, both these trials were terminated due to the lack of response and increased toxicity [244].

A phase II trial has evaluated molibresib as a monotherapy (NCT01943851), and in another trial, AZD153 is being assessed in the phase I stage (NCT03205176). Lastly, a phase I trial that is currently recruiting will attempt to evaluate the combination of ZEN003694, a BET inhibitor (BETi), with the HDAC entinostat in patients with hematologic malignancies, as well as those with solid tumors overexpressing BET (NCT05053971).

It becomes apparent that a major setback of BETi treatment is the AEs which sometimes can cause problems when being used as a single therapy. This raises the question of whether combinations of classic or other novel chemotherapeutic drugs with BETis could improve both patient outcomes and decrease the AEs [245]. A combination of therapies will also contribute to the treatment of B-cell lymphomas that contain (+)-JQ1-insensitive genes from transcriptional rearrangements, which is most typical for post-GC lymphomas [246].

3.6. Histone Phosphorylation Inhibitors

Targeting histone phosphorylation has also been suggested as a potential treatment against hematological malignancies. Interestingly, preclinical and clinical data support the inhibition of the Aurora B kinase, which colocalizes with phosphorylated H3 and is overexpressed in NHL patients [247], as a novel therapy in DLBCL patients [248]. In a similar context, small-molecule inhibitors of haspin, a different enzyme which phosphorylates H3, have been designed as antimetabolic cancer therapies [249], and the oral administration of SEL120, a haspin inhibitor, led to promising results for the treatment of B-cell lymphomas [250]. Studies have also supported the development of JAK1 inhibitors against activated B-cell (ABC)-DLBCL, but recent data demonstrated an increased B-cell lymphoma risk because of impairment of immune surveillance in JAK inhibitor-treated patients [251,252]. Therefore, although an increase in phosphorylated H3 has been linked to poor prognosis in hematological malignancies, the clinical relevance of histone phosphorylation demands further clarification.

4. Conclusions—Future Perspectives

It becomes evident that chromatin alterations are involved in the pathogenesis of hematological malignancies, with histone-modifying enzymes commonly being dysregulated as over- or underexpressed. Epigenetic drugs that target these enzymes have already been developed and approved for clinical use, whereas others are currently being investigated in different phases of clinical trials (Figure 5). Key protein–protein interactions, as well as essential enzyme cofactors and domains, have also been identified as potential therapeutic targets, presenting a great promise for the successful treatment of hematological malignancies. A large panel of high-throughput molecular tools, enriched with bioinformatic data, have been employed for the identification of key epigenetic alterations in each disease. Along this line, the elucidation of key epigenetic mechanisms and associated alterations of each patient has enabled the selection of drugs to be used to fully exploit each patient's epigenome. In the future, patients should be able to undergo mapping of their methylome either at the level of candidate genes or the whole genome, facilitating future prognoses, diagnoses, responses to therapy, and treatment selection. Novel therapeutic options based on small-molecule inhibitors are expected to be progressively revealed, aiming to facilitate personalized treatment. To this end, it is crucial to discover biomarkers and develop therapeutic protocols, with the precise duration of treatment that will help monitor patients' response to therapy. Another major undiscovered potential arising from these findings is

the use of epigenetic treatment approaches to prevent, rather than just cure, different types of cancers.

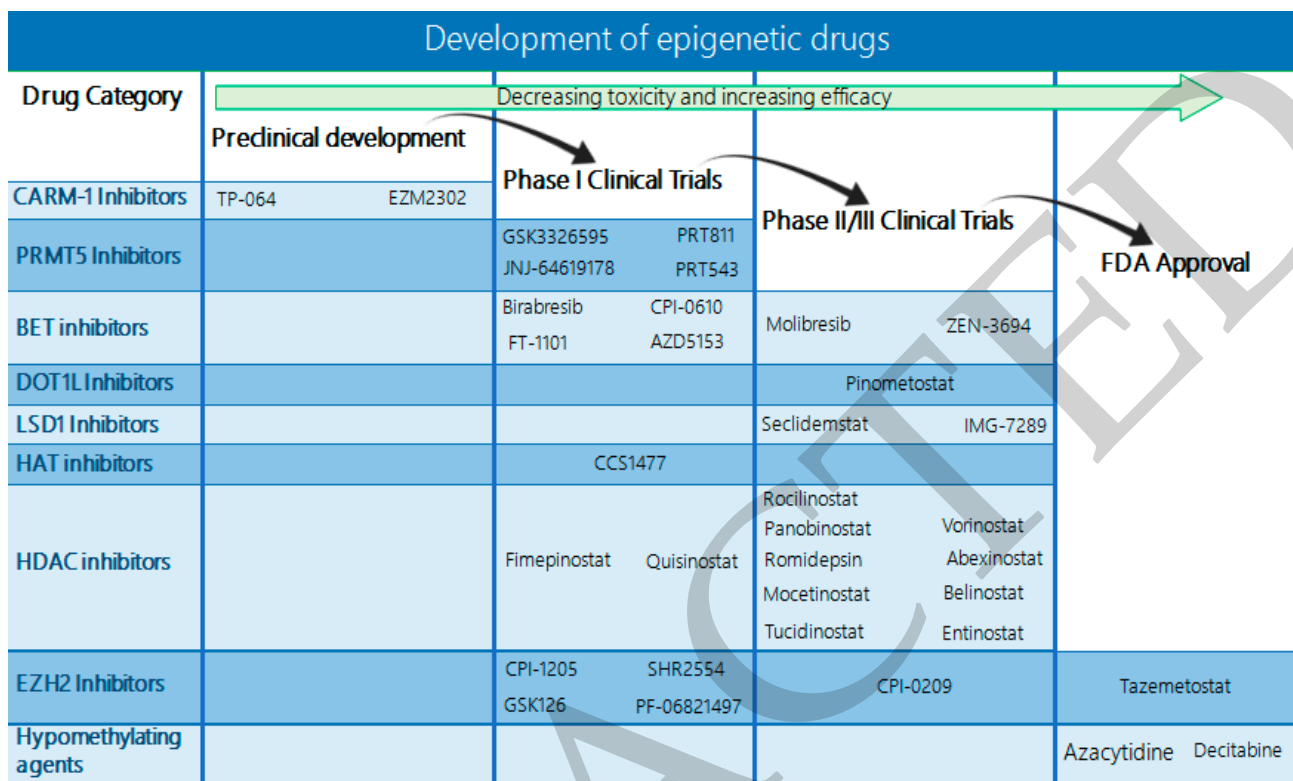


Figure 5. Diagram indicating the status of drugs targeting epigenetic alterations. Currently, only the EZH2 inhibitor tazemetostat and the DNMT inhibitors azacytidine and decitabine have received FDA approval. However, an increasing number of BET, DOT1L, LSD1, HAT, and HDAC inhibitors are already in phase II/III clinical trials with promising results, and several more are under evaluation in phase I trials.

Despite the rapid progress made in the discovery of histone-modifying enzymes and their implications in cancer, there is still much to be investigated in regard to their biological roles and their interplay with other proteins depending on the cellular and disease context. It is notable that the field of histone modifications has a complex character due to the vast number of implicated proteins and cofactors affecting chromatin configurations, which explains the resistance that arises with epigenetic drug monotherapy. Most current trials are, therefore, focused on combining already existing drugs with histone-targeting compounds in order to achieve synergy and overcome resistance. In this context, one epigenetic modification may influence the function of another DNA or histone modification on the same site or at a separate location in chromatin. This can occur by exerting the opposite effect, antagonizing the same binding site, targeting the same substrate or modification pathway, or interfering with the dependence on another chromatin-modifying enzyme, modification, and/or cofactor. Another related important issue is the limited specificity of some epigenetic drugs, whose targets may often be unrelated to histones and can cause unpredictable effects. Examples include some of the HDAC inhibitors that are simultaneously capable of inhibiting PI3K (CUDC-907), EGFR (CUDC-101), etc.

Additional *in vitro* and *in vivo* studies are therefore required in order to develop more selective and effective, but less toxic, epigenetic drugs (Figure 5). The implementation of newly developed molecular tools and genetic screening for a more specific identification of epigenetic alterations occurring in each hematological neoplasm, as well as the discovery of the full range of drug targets, will help limit the off-target side effects of monotherapy. Epigenetic cancer therapies that target the tumor microenvironment, such as immune

effector cells, should also be taken into consideration. Other interesting approaches include the introduction of dual inhibitors in clinical trials, which simultaneously target more than one unrelated class of chromatin-modifying enzymes, as well as the use of epigenetic signatures for the development of biomarkers that will predict the response to therapy.

In summary, further research using novel technological advances will help explore the different histone modifications that occur in hematological neoplasms, as well as their exact mechanism of action and effects in tumor cells, in order to specifically target those that will offer the maximum therapeutic potential. In conclusion, a deeper insight into molecular functions is required before novel epigenetic drugs that target histone modifications are included in the established treatment options for hematological malignancies.

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