

# Insights into novel emerging epigenetic drugs in myeloid malignancies

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**Abstract:** Epigenetics has been defined as ‘a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence’ and several epigenetic regulators are recurrently mutated in hematological malignancies. Epigenetic modifications include changes such as DNA methylation, histone modifications and RNA associated gene silencing. Transcriptional regulation, chromosome stability, DNA replication and DNA repair are all controlled by these modifications. Mutations in genes encoding epigenetic modifiers are a frequent occurrence in hematologic malignancies and important in both the initiation and progression of cancer. Epigenetic modifications are also frequently reversible, allowing excellent opportunities for therapeutic intervention. The goal of epigenetic therapies is to reverse epigenetic dysregulation, restore the epigenetic balance, and revert malignant cells to a more normal condition. The role of epigenetic therapies thus far is most established in hematologic malignancies, with several agents already approved by the US Food and Drug Administration. In this review, we discuss pharmacological agents targeting epigenetic regulators.

**Keywords:** acute myeloid leukemia, BET inhibitors, demethylases, DOT1L inhibitors, epigenetic modifications, histone modification, hypomethylating agents, IDH inhibitors, LSD1 inhibitors, myelodysplastic syndrome, novel agents

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## Introduction

Epigenetics refers to regulatory mechanisms that lead to heritable changes in gene expression that are not due to a change in the DNA coding sequence. Differentiation in normal hematopoiesis is dependent on tightly regulated, ongoing epigenome remodeling.<sup>1,2</sup> Dysregulation of epigenetic regulators such as direct-DNA modifications, histone tail modifications and noncoding RNAs can lead to widespread alterations in the normal patterns of gene expression.<sup>3</sup> These alterations of genes regulating the cellular epigenome are known offenders in tumorigenesis and occur frequently in a spectrum of hematologic malignancy diseases. For example, in the landmark The Cancer Genome Atlas (TCGA) study analyzing the genome of 200 adult cases of *de novo* acute myeloid leukemia (AML) identified mutations in 44% of DNA methylation-related genes and 30% of

chromatin-modifying genes.<sup>4</sup> Owing to the prevalence of epigenetic dysregulation and inherent plasticity of the epigenome, several classes of cancer therapeutics targeting epigenetic aberrations have emerged.

In mammalian cells, genomic DNA is packaged into condensed complexes of DNA and histone proteins known as nucleosomes that are units of chromatin that protect DNA structure and sequence, as well as regulating gene expression and DNA replication.<sup>5</sup> Nucleosomes are repeating units of chromatin that are composed of 147 base pairs of DNA wrapped around eight histone proteins that are very stable protein–DNA complexes, but remain dynamic and are tightly regulated.<sup>5</sup> Chromatin can be reversibly altered in many ways (addition or removal of epigenetic marks on DNA or chromatin and RNA silencing)

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that lead to changes in gene activity and cellular phenotypes, and it reorganizes to regulate transcriptional activity at a particular locus based on intrinsic and extrinsic stimuli.<sup>6</sup> Alterations in the epigenetic program of the cell are common in many human cancers and therefore are an attractive therapeutic target.<sup>7</sup>

In this review, we discuss both established and emerging epigenetic therapies in hematologic malignancies.

### **DNA methylation: targeting DNA methyltransferases, TET, and IDH mutations**

Alteration in DNA methylation status is a characteristic epigenetic change in many cancers including hematological malignancies. DNA methylation is the addition of a methyl group to DNA, usually at the 5' position of the cytosine ring within CpG (cytosine preceding guanine) dinucleotides that often modifies genes and noncoding genomic regions, affecting gene expression. Tightly regulated DNA methylation plays a key role in embryonic development, cellular differentiation, and genome stability, and disruption of methylation affects the expression of protein coding genes and noncoding RNAs resulting in tumorigenesis.<sup>8–10</sup> Mutations in the DNA methylation regulators DNMT3A, TET1/2, and IDH1/2 are recurrent in hematologic malignancies.

#### *DNA methyltransferases*

DNA methylation is catalyzed by a group of enzymes known as DNA methyltransferases (DNMTs).<sup>8,11</sup> The main DNMTs include DNMT1, which is responsible for the maintenance of existing methylation patterns by replicating CpG methylation patterns from the mother to daughter strand during DNA replication and antagonizing DNA demethylation, and DNMT3A and DNMT3B that are essential for *de novo* methyltransferase activity, targeting previously unmethylated CpG dinucleotides.<sup>12</sup>

Although mutations in all the above methyltransferases have been noted in cancer, recurrent mutations in DNMT3A are most prevalent by far, and have been noted in approximately 22% of patients with AML, 13% of patients with myelodysplastic syndrome (MDS), 9% of patients with myeloproliferative neoplasms (MPN), and 11% of patients

with T cell lymphomas.<sup>13–19</sup> In AML, the DNMT3A mutations usually involve the p.882 codon, and are an early event in clonal hematopoiesis.<sup>20,21</sup> Mutations in the p.882 codon of DNMT3A produces a hypomorphic protein that inhibits the remaining wild-type (WT) DNMT3A, thereby markedly reducing cellular DNMT activity, leading to global hypomethylation.<sup>20,22</sup> Numerous studies agree that DNMT3A-mutant AML patients have a significantly lower overall survival (OS) compared with those with WT DNMT3A regardless of age, even though there is no statistically significant difference between complete remission (CR) and relapse-free survival (RFS) between the patients with or without the DNMT3A mutations.<sup>15,23–26</sup> Poor clinical outcomes of patients with DNMT3A-mutations are primarily due to relative anthracycline resistance; patients who received standard-dose daunorubicin-based induction therapy have poor outcomes, however the adverse prognostic impact of DNMT3A mutations is mitigated by daunorubicin dose intensification.<sup>26–30</sup> Patients with DNMT3A mutations have increased likelihood of CR in patients with MDS or previously untreated AML who receive hypomethylating agents (HMAs).<sup>31,32</sup>

Mutations in DNMT3A enzymes cannot be directly targeted at present, primarily due to the detrimental role of DNMT3A loss in hematopoiesis. However, the antineoplastic activity of HMAs azacitidine (AZA) and decitabine (DEC) in all patients with AML and MDS (regardless of mutational status) is clear.<sup>33</sup> The exact mechanism of action of these HMAs is unclear, but the antileukemic effects are thought to be secondary to degradation of DNMTs that lead to global DNA hypomethylation, gene reactivation, DNA damage, and eventual cell death.<sup>34</sup> AZA and DEC are US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved for the treatment of MDS, chronic myelomonocytic leukemia (CMML), and AML, with slight variations in specific approvals in Europe and the United States.<sup>35</sup> For example, DEC has FDA, but not EMA, approval in the setting of MDS. In the setting of AML, DEC has EMA, but not FDA, approval.

*Novel formulations of HMAs.* Although the role of HMAs is well established in myeloid malignancies, advances in the field have come from new

formulations that are designed to improve patient comfort and improve benefits by prolonging drug exposure that are now in clinical trials. These include oral AZA (CC-486), oral DEC with cedazuridine, a novel cytidine deaminase inhibitor (ASTX727) and subcutaneous guadecitabine (GDAC, SGI-110), a next-generation hypomethylating drug that has a longer half-life than its active metabolite DEC.

All these agents (GDAC (SGI-110), oral AZA (CC-486), and ASTX727) are in phase III assessment as single-agent therapy (ClinicalTrials.gov identifiers: NCT03306264, NCT02920008, and NCT01757535) in MDS, CMML and MDS in the treatment naïve setting, and are also being assessed after relapse with traditional HMA therapy. In the case of GDAC, the results of the randomized phase III study of GDAC [ASTRAL-1 (ClinicalTrials.gov identifier: NCT02348489)] in treatment-naïve unfit patients did not meet its coprimary endpoints of superior CR rate and OS when compared with HMA or cytarabine.<sup>36</sup> However, a recently published phase II study that included intermediate- and high-risk MDS and CMML both in the treatment-naïve of HMA relapsed or refractory setting demonstrated a 40–55% overall response rate (ORR) in all subgroups.<sup>37</sup> Of the 53 HMA refractory patients included on this study, there were 2 complete responses to GDAC.<sup>37</sup> Although toxicity was considered acceptable, 12% of patients withdrew from the study based on serious adverse events; the overall adverse event profile was similar to traditional HMA therapy.<sup>37–39</sup> ASTX727 is a fixed-dose combination of DEC and cedazuridine, a novel cytidine deaminase inhibitor. Phase I studies with previously treated or newly diagnosed MDS and CMML were published recently; ASTX727 was confirmed to have a safety profile similar to that of DEC.<sup>40</sup> Phase II dose confirmation was presented at the 2017 ASH and EHA meetings, and a multicenter, phase III randomized, study of ASTX727 *versus* IV DEC for patients with MDS and CMML is currently active (ClinicalTrials.gov identifier: NCT03306264). Finally, the oral formulation of AZA, CC-486, has been evaluated in phase I and has been generally well tolerated even with extended dosing in patients with treatment-naïve and refractory AML and MDS.<sup>41–43</sup> It has also been evaluated in the post-transplant maintenance in AML and MDS.<sup>44</sup> This agent is currently in later phase

evaluation in studies such as QUAZAR AML-001 (ClinicalTrials.gov identifier: NCT01757535).

#### *IDH mutations*

Isocitrate dehydrogenase-1 and -2 (IDH1/2) mutations occur in ~20% of AML, and up to 12% of patients with MDS. IDH enzymes catalyze the conversion of isocitrate to  $\alpha$ -ketoglutarate (aKG) in the citric acid cycle.<sup>45</sup> There are three conserved mutational hotspots in the IDH enzymes that alter their function and lead to the production of (R)-2-hydroxyglutarate (2HG), an oncometabolite with numerous downstream effects, including impairment of normal TET catalytic activity, and histone lysine demethylases, both of which are crucial to epigenetic regulation.<sup>46–48</sup>

*Mutant IDH inhibitors.* Recently 2-IDH inhibitors, enasidenib for mutant IDH2 and ivosidenib for mutant IDH1 were approved by the FDA for relapsed/refractory AML. The mIDH1 inhibitor ivosidenib gained FDA approval for the treatment of patients with relapsed/refractory IDH1 mutant AML based on the phase I, multicenter, open-label, dose-escalation, and dose-expansion study.<sup>49</sup> In this study, that was most recently updated at ASCO annual meeting in 2018, 179 patients with IDH1-positive relapsed/refractory AML were treated 500 mg oral ivosidenib that resulted in CR in 24.7% ( $n = 43$ ; 95% CI 18.5–31.8) and CR with partial hematologic improvement (CRi) rate in 8% ( $n = 14$ ; 95% CI 4.5–13.1). The median duration of CR + CRi was 8.2 months (range, 5.6–12). The ORR was 41.9% (95% CI 34.6–49.5%) and median time to best response was 2.0 months (range, 0.9–5.6). Of the patients treated with ivosidenib, 21 patients were eventually received hematopoietic stem cell transplantation (HSCT).<sup>49</sup> The most serious adverse effects included QT prolongation, and the potentially fatal differentiation syndrome that led to a boxed warning for the drug.<sup>49,50</sup> This expansion cohort is ongoing (ClinicalTrials.gov identifier: NCT02074839) and based on the early success with this agent, ivosidenib is being examined in the upfront setting in AML who are candidates for nonintensive treatment [AGILE trial (ClinicalTrials.gov identifier: NCT03173248)], in high-risk MDS (ClinicalTrials.gov identifier: NCT03503409), and in numerous combination studies primarily in myeloid malignancies.

The IDH2 inhibitor enasidenib was the first in class IDH2 mutation-specific inhibitor. Similar to ivosidenib, in a phase I/II study of enasidenib in patients with relapsed/refractory AML with IDH2 mutations, 40.3% of patients responded to therapy, 19.3% achieved CR and the median OS was 9.3 months for all study participants, but 19.7 months for patients who achieved CR.<sup>51</sup> Ivosidenib, the recently approved IDH1 mutation-specific inhibitor, demonstrated similar results with a 41.6% ORR, 30.4% CR/CRi rate including a 21.6% CR rate.<sup>49</sup> *IDHENTIFY* (ClinicalTrials.gov identifier: NCT02577406), a phase III randomized, open-label study comparing single-agent enasidenib *with* conventional care regimens (CCR) in older patients relapsed or refractory IDH2 mutant AML is currently enrolling.<sup>52</sup> This agent is also being examined in the upfront AML setting (ClinicalTrials.gov identifier: NCT02632708), MDS as a single agent (ClinicalTrials.gov identifiers: NCT03744390 and NCT03383575), in combination with other drugs such as AZA or venetoclax (ClinicalTrials.gov identifier: NCT02677922), and in the post-transplant setting as a maintenance agent (ClinicalTrials.gov identifier: NCT03728335). Although the above agents were the first in class to receive FDA approval, there are numerous others mutant IDH inhibitors such as FT-2102 (mIDH1), BAY 1436032 (pan mIDH1), and the combined IDH1 and IDH2 inhibitor AG-881 currently in clinical trials. Interestingly, recent publications have determined that patients who relapse almost uniformly develop either resistance mutations that impede IDH inhibitor binding or isoform switch from one IDH enzyme to the other.<sup>53,54</sup>

### Histone modifications

In addition to changes in DNA methylation, modifications of the core of eight histone proteins play an important role in genetic expression and, thus, genomic regulation. There are several histone modifying processes including methylation, acetylation, ubiquitination, phosphorylation, sumoylation, and glycosylation that are involved in cancer pathogenesis.<sup>54</sup> Histones themselves have an accessible lysine rich amino-terminal that can be both acetylated and methylated.

#### *Histone methylation and demethylation*

Histone methylation status is a dynamic process that is essential to the transcriptional program of

a cell. Similar to DNA methylation, histone methylation is a process by which methyl groups are transferred to histones leading to structural modification of chromatin, transcriptional modification, and eventually alteration in gene expression. Histone methyltransferases are a class of catalytic enzymes responsible for the transfer of methyl groups from S-adenosyl methionine onto the lysine (lysine methyltransferase or KMTs) or arginine residues [protein arginine methyltransferases (PRMTs)] leading to transcriptional activation or repression depending on the degree and sites of methylation.<sup>55</sup> Aberrations in histone methyltransferases have been noted in several hematological malignancies including myeloid malignancies as well as B and T cell lymphomas.<sup>56–59</sup> Conversely, histone demethylases remove methyl groups from histones and belong to two families of proteins: the lysine-specific demethylase (LSD) family and the JumonjiC (JMJC) family of histone demethylases.<sup>60</sup>

*Histone methyltransferase (KMT) inhibitors: EZH2 inhibitors.* Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the Polycomb repressive complex 2 (PRC2) that is responsible for transcriptional repression of target genes by trimethylation of lysine 27 on histone H3 (H3K27me3).<sup>61</sup> In hematopoiesis EZH2 is a regulator of adult hematopoietic stem cell (HSC) differentiation, proliferation and apoptosis.<sup>62,63</sup> It regulates these pathways by repression of negative cell cycle regulators (such as CDKN2A), repression of differentiation transcription factors (such as BLIMP and IRF4), and repression of pro-apoptotic genes (such as NOX and p21).<sup>62,64,65</sup>

The fact that changes in expression, gain of function, and loss of function mutations in EZH2 contribute may contribute to the development of hematologic malignancies suggests that EZH2 can act not only as an oncogene, but also as a tumor suppressor, depending on the cell context. Gain of function mutations, or overexpression of EZH2, is frequently seen in patients with Burkitt lymphoma, high-grade follicular lymphomas, diffuse large B cell lymphomas (DLBCL), and multiple myeloma with 4;14 translocations.<sup>57,66,67</sup> Loss of function mutations have been reported more frequently in myeloid malignancies such as MDS, atypical chronic myelogenous leukemia (CML) and myelofibrosis, and are generally associated with a poorer prognosis with shorter OS and event-free survival.<sup>68,69</sup> Loss of function and

deletions EZH2 mutations were also noted in up to a quarter of patients with T cell acute lymphoblastic leukemia (T-ALL).<sup>70</sup>

Several *EZH2 inhibitors* have been developed and a few are in early phase clinical trials, primarily for high grade lymphomas. Phase I studies were recently completed on tazemetostat (EPZ-6438), a potent and highly selective EZH2 inhibitor that had previously shown antiproliferative/antitumor activity in *in vitro* and in B cell non-Hodgkin lymphoma xenograph models bearing EZH2 activating mutations.<sup>71,72</sup> The open-label, multicenter, dose-escalation, phase I study that included both solid tumors and relapsed/refractory B cell non-Hodgkin lymphoma that was recently published established the recommended phase II dose of 800 mg twice daily and demonstrated durable objective responses, including complete responses, were observed in 8/21 patients with B cell non-Hodgkin lymphoma.<sup>73</sup> Phase II data in epithelioid sarcoma was presented at ASCO 2017, but is immature in the lymphoid malignancies. Studies with this drug were recently paused by the FDA based on a patient with a solid tumor malignancy enrolled in a phase I trial who developed a secondary T cell lymphoma but resumed as of September 2018. Other EZH inhibitors in clinical trial are listed in Table 1. Of note, recent work has demonstrated that dual inactivation of both EZH1 and EZH2, leading to complete inactivation disruption of PRC2 was effective at eliminating aggressive quiescent leukemic stem cells in MLL-AF9 leukemia.<sup>74</sup> This has led to the development of novel EZH1/2 inhibitors that has shown promise in preclinical studies.<sup>75</sup>

*Histone methyltransferase (KMT) inhibitors: DOT1L inhibitors.* Disruptor of telomeric silencing 1-like (DOT1L) is the only known a methyltransferase that triggers histone H3 lysine 79 (H3K79) methylation. H3K79 methylation is the only known histone lysine methylation without at least one known corresponding histone demethylase to date and increasing H3K79 methylation has been noted as a part of aging. DOT1L also has known roles in DNA-repair mechanisms, cell-cycle regulation, and maintenance of genome stability.<sup>76</sup> H3K79 methylation is implicated in several processes, including transcription elongation by RNA polymerase II, the DNA damage response, and cell cycle checkpoint activation.<sup>77-79</sup>

Approximately 10% of all leukemias harbor *MLL1* translocations, and these translocations are particularly enriched in pediatric leukemia and therapy-related leukemia secondary to etoposide. MLL rearranged leukemias have with distinct clinical features and portend a poor prognosis. The majority of MLL translocations result in oncogenic fusion proteins in which the native methyltransferase domain is replaced by sequences that interact with DOT1L directly or indirectly.<sup>80,81</sup> MLL-rearranged leukemia is dependent on aberrant H3K79 methylation by DOT1L, which make DOT1L inhibitors an attractive target.<sup>82</sup> Pinometostat (EPZ-5676) was the first-in-class, small-molecule inhibitor of the histone methyltransferase DOT1L, is currently in clinical testing. Results from a phase I study with 51 patients with relapsed/refractory MLL leukemia of pinometostat were modest, with only 2/51 patients achieving CR with 9/51 experiencing grade 3 or higher drug-related events.<sup>83</sup> Based on these data, it seems unlikely that DOT1L inhibition will be sufficient for management of MLL leukemia as a single agent, but may be incorporated into rational combination therapy.

*Histone demethylase inhibitors targeting LSD1.* Histone modifications are reversible and epigenetic marks, such as methylation or acetylation, can be removed. Enzymes capable of reversing methylation come in two classes: LSD1/LSD2 or KDM1A/KDM1B; and the larger family of JMJC domain-containing histone demethylases.<sup>81,84</sup>

LSD1 is a key regulator of self-renewal and differentiation in human embryonic stem cells, is pivotal to maintenance of hematopoietic stem cells and differentiation of granulopoiesis.<sup>85,86</sup> It causes transcriptional repression by demethylating mono- or di-methylated H3K4, but can also stimulate transcription upon interactions with the androgen receptor.<sup>87</sup> LSD1 can also demethylate many nonhistone substrates such as p53, DNMT1, and STAT3.<sup>88,89</sup> LSD1 is overexpressed in a several malignancies including solid tumors (gastric, esophageal, breast, lung, colon, etc.), as well as hematopoietic and lymphoid neoplasms including AML, ALL, MPNs, CMML, and MDS.<sup>90</sup> LSD1 inactivation inhibited cancer cell differentiation, proliferation, invasion and migration, and tumor growth in animal models and demonstrated the therapeutic potential of LSD1 inhibitors.<sup>91-93</sup>

**Table 1.** Selected trials of novel emerging epitherapies.

<b>Select trials targeting DNA modification</b>			
<b>Drug</b>	<b>Target</b>	<b>ClinicalTrials.gov identifier</b>	<b>Malignancy</b>
Guadecitabine (SGI-110)	DNMT	NCT02907359 NCT02920008 NCT03075826 NCT02131597 NCT03075826	MDS, AML, CMML, MPN
Oral Azacitidine (CC-486)	DNMT	NCT03723135 NCT03703375 NCT03450343	MDS, AML, T cell lymphoma, DLBCL
<b>Select trials targeting Histone modification</b>			
<b>Drug</b>	<b>Target</b>	<b>NCT</b>	<b>Malignancy</b>
Tazemetostat (EPZ-6438)	EZH2	NCT03456726 NCT03603951 NCT01897571 NCT03213665 NCT02875548	DLBCL, HL, NHL, histiocytic disorders
CPI-1205	EZH2	NCT02395601	B cell lymphoma
PF-06821497	EZH2	NCT03460977	Follicular lymphoma
MAK683	EZH2	NCT02900651	DLBCL
Pinometostat (EPZ-5676)	DOT1L	NCT03724084	AML-MLL
GSK2879552	LSD1	NCT02929498	MDS
Tranylcypromine	LSD1	NCT02273102	AML MDS
IMG-7289	LSD1	NCT03136185 NCT02842827	Myelofibrosis AML MDS
INCB059872	LSD1	NCT02712905	Hematologic malignancies
4SC-202	HDAC	NCT01344707	Hematologic malignancies
Abexinostat (PCI24781)	HDAC	NCT01149668 NCT03600441 NCT00724984 NCT00473577	B cell lymphomas, any hematologic malignancy
Givinostat	HDAC	NCT01901432 NCT01761968	MPN
Mocetinostat	HDAC	NCT00431873	CLL
Resminostat	HDAC	NCT02953301	T cell lymphoma,
Rocilinostat	HDAC	NCT02091063 NCT01583283	Lymphoma, multiple myeloma
ABBV-075	BET	NCT02391480	AML, NHL, multiple myeloma

*(Continued)*

**Table 1.** (Continued)

Select trials targeting Histone modification			
Drug	Target	NCT	Malignancy
CPI-0610	BET	NCT02158858	Myelofibrosis
FT-1101	BET	NCT02543879	Hematologic malignancies
GSK525762/I-BET762	BET	NCT01943851	Hematologic malignancies
INCB054329	BET	NCT02431260	Hematologic malignancies
PLX51107	BET	NCT02683395	AML, MDS, NHL
RO6870810/TEN-010	BET	NCT03068351 NCT03255096	Multiple myeloma, DLBCL

AML, acute myeloid leukemia; BET, bromodomain and extra-terminal domain; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; DLBCL, diffuse large B cell lymphoma; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; HL, Hodgkin's lymphoma; LSD, lysine-specific demethylase; MDS, myelodysplastic syndrome; MLL, mixed-lineage leukemia; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin's lymphoma.

Numerous LSD inhibitors [trans-2-phenylcyclopropylamine derivatives, monoamine oxidase (MAO) inactivators, peptide-based, polyamine-based, and others] have been developed and fall into two categories: reversible or irreversible inhibition.<sup>91,94</sup> Some of these inhibitors are currently in early phase clinical trials and there is no mature trial data. Myelosuppression from LSD1 inhibitors at therapeutic doses may prohibit their use in myeloid malignancies, owing to the role in normal hematopoiesis and terminal myeloid differentiation, but this remains to be seen. JMJC domain-containing histone demethylases, a much larger class of histone demethylation agents, are still being explored in the lab and although inhibitors are being developed, they have not entered the clinical realm.

#### *Histone acetylation and deacetylation*

Similar to methylation, histone acetylation status is an important mechanism that regulate of chromatin structure, transcription, and DNA repair. Histone lysine acetyltransferases (HATs) are responsible for acetylation of histones that relax chromatin structures, exposed promoter regions, and increased transcription. Mutations in HATS that affect their catalytic activity are frequent in lymphoid malignancies, occurring in up to 40% of DLBL, 60% of follicular lymphoma (FL), and less frequently in B cell ALL, T cell ALL, and cutaneous T cell lymphoma (CTCL).<sup>95-99</sup> HAT mutations are also notable

in some myeloid malignancies, specifically with CBP mutations or translocations, however effectively targeting HAT activity remains in the laboratory for now.<sup>4,100,101</sup>

Histone deacetylases (HDACs) oppose this action by catalyzing deacetylation that leads to chromatin condensation and resultant gene silencing.<sup>102-104</sup> HDACs are a very diverse group of enzymes, that are subdivided into four classes (I, II, III, and IV) based on homology to yeast proteins, subcellular location, and enzymatic activities. They lead to tumorigenesis by repression of tumor suppressor gene expression or modification of oncogenic cell-signaling pathways.<sup>105-107</sup> In line with variety of HDAC proteins, HDAC inhibitors are a structurally varied class of medications that vary in their potency and specificity to different classes of HDACs including hydroxamates, cyclic peptides, aliphatic acids, benzamides, and electrophilic ketones. HDAC inhibitors induce cancer cell cycle arrest, differentiation, and cell death. They also reduce angiogenesis and modulate immune response.<sup>108</sup> Although HATs have not yet proven themselves as druggable targets, the role of HDAC inhibition has been established in several hematologic malignancies. FDA-approved HDAC inhibitors (HDACi) include vorinostat for the management of CTCL, romidepsin for CTCL and peripheral T cell lymphoma (PTCL), belinostat for PTCL, and panobinostat is FDA approved for the management of multiple myeloma.<sup>109-112</sup>

There are a plethora of other HDACis currently in early phase clinical trials, including the established agents mentioned above, as well as a whole host of newer agents (Abexinostat (PCI24781), AR42, Givinostat, Mocetinostat, Quisinostat (JNJ-26481585), Resminostat (4SC201), Rocilinostat (ACY1215), Tacedinaline (CI994), as well as others) in phase I and II clinical trials. Some ongoing trials of these novel agents are listed in Table 1. It is useful to note that although there are ongoing monotherapy trials in select hematologic malignancies, most trials at present are focused on combination therapy both for drug synergy and to overcome resistance to HDACi monotherapy.<sup>113</sup>

#### *Epigenetic 'readers': bromodomain proteins*

The previously described targets included epigenetic 'writers' or 'erasers' in that they were involved in the addition or removal of chemical groups onto either histone tails or the DNA. The bromodomain and extra-terminal domain (BET) family of adaptor proteins are epigenetic 'readers', or chromatin regulators that possess specialized domains that survey the epigenetic landscape and dock at specific regions within the genome.<sup>114</sup> These proteins then serve as scaffolds for transcription factors and chromatin-modifying enzymes to assemble functional complexes onto specific loci and facilitate DNA-templated processes.

The BET family of epigenetic readers have two tandem bromodomains, an extra-terminal domain and a C-terminal domain.<sup>115</sup> Bromodomains (BRDs) have acetyl-lysine binding pockets and bind to acetylated lysines on histone tails and recruit other chromatin factors and transcriptional machinery to regulate gene transcription.<sup>116</sup> The BET family has four members, three of which (BRD2, BRD3, and BRD4) are expressed ubiquitously, and germ cell specific BRDT.<sup>114</sup> In addition to transcriptional regulation where it is important for both initiating and continuing transcription, BET proteins also have an essential role in cell-cycle regulation.<sup>117</sup>

BET protein disruption is associated with cancer and the study of BET proteins, and BET inhibitors, has been an area of robust research over the past decade. Early studies employing BET inhibitors revealed the importance of BET in regulation of MYC an oncogenic driver.<sup>118</sup> BET inhibition in the early studies led to downregulation of c-Myc, cell-cycle arrest and cellular senescence in

myeloma models, and prolonged survival in Burkitt's lymphoma and AML murine xenograft models.<sup>118,119</sup> In lymphoma, BET proteins were found to preferentially bind in the proximity of critical lymphoma-related oncogenes.<sup>120</sup> Early lymphoma cell line studies showed that although BET inhibitors were cytostatic in most cases, but induced apoptosis in a subgroup of cell lines.<sup>121</sup> Preclinical efficacy of BET inhibitors has been demonstrated in AML while several other papers have documented similar efficacy in several hematologic malignancies.<sup>122-126</sup>

Early phase clinical trials of BET inhibitor monotherapy in hematologic malignancies have shown that BET inhibitors are tolerated at therapeutic doses and there is some signal of limited efficacy.<sup>127-129</sup> In the acute leukemia cohort of 41 patients five patients demonstrated some degree of response to the BET inhibitor OTX015.<sup>128</sup> Limited antitumor activity was also noted in patients with relapsed or refractory lymphomas in a phase I study of the BET inhibitor CPI-0610.<sup>130</sup> Like with HDACis, thoughtful combinations utilizing BET inhibitors are more likely to derive clinical benefit than BET inhibitor monotherapy. Combinations with agents such as cell-cycle inhibitors, DNA damage repair inhibitors, apoptosis inhibitors, checkpoint inhibitors, or other epitherapies such as HDACi have demonstrated preclinical efficacy.<sup>117</sup> Combinations may induce cytotoxicity and help to overcome resistance to a single targeted agent. Numerous trials currently ongoing, some of which are listed in Table 1.

#### **Micro-RNA**

MicroRNAs (miRNAs) are evolutionarily conserved 21–23-nucleotide single-stranded noncoding RNAs that typically destabilize messenger RNA and are crucial to regulating gene expression.<sup>131</sup> Alterations in miRNA mediate processes in tumorigenesis such as inflammation, cell-cycle regulation, stress response, differentiation, apoptosis, and invasion, and are implicated in the generation or maintenance of cancer.<sup>132</sup> Significant differences have been noted in the miRNA expression between normal and cancer tissues, where miRNAs acting as tumor suppressors or oncogenes.<sup>133</sup> These changes in miRNA expressions may be due to mutations, translocations of other epigenetic changes, and are being assessed as prognostic markers in most hematologic malignancies.<sup>134</sup>

There are two classes of miRNA-targeted therapeutics have also entered early phase clinical trials (e.g. ClinicalTrials.gov identifiers: NCT03713320 and NCT02580552 for mycosis fungoides, chronic lymphocytic leukemia, DLBCL, or ATLL). MicroRNA mimics aim to restore lost miRNA expression (tumor suppressor miRNA) and miRNA inhibitors that bind to their target and inhibit the target oncogenic miRNA function.<sup>135</sup> There have been early successes in pre-clinical models with several miRNA therapies, however these agents are yet to make a splash in cancer therapy and are in the early staged of clinical evaluation. We are likely to see these epitherapies in the future, potentially in combination with chemotherapy, as several miRNAs have been shown to be sensitive cancer cells to chemotherapy.<sup>136,137</sup> Improved understanding of the miRNA targetome will also help refine the development of these agents.

### Conclusion

Although there has been a relative boom in the emergence of novel epigenetic therapies, optimal implementation of these agents will require significant efforts. Targeting the cancer epigenome remains challenging because of several overlapping dependent and independent phenomena such as DNA modifications, covalent post-translational modifications of histones, histone variants, noncovalent remodeling of chromatin, and microRNA expression. Improved understanding of the epigenetic mechanisms in normal cells, and defective epigenetic mechanisms in neoplastic cells, will help in designing optimal combinations while minimizing drug-related toxicities in the future. Capitalizing on interdependent mechanisms in cancer, such as cancer epigenetics and cancer immunology or metabolism are also likely to lead to more significant gains.

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