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Emerging epigenetic-modulating therapies in lymphoma

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Abstract

Despite considerable advances in the treatment of lymphoma, the prognosis of patients with relapsed and/or refractory disease continues to be poor; thus, a continued need exists for the development of novel approaches and therapies. Epigenetic dysregulation might drive and/or promote tumorigenesis in various types of malignancies and is prevalent in both B cell and T cell lymphomas. Over the past decade, a large number of epigenetic-modifying agents have been developed and introduced into the clinical management of patients with haematological malignancies. In this Review, we provide a concise overview of the most promising epigenetic therapies for the treatment of lymphomas, including inhibitors of histone deacetylases (HDACs), DNA methyltransferases (DNMTs), enhancer of zeste homologue 2 (EZH2), bromodomain and extra-terminal domain proteins (BETs), protein arginine *N*-methyltransferases (PRMTs) and isocitrate dehydrogenases (IDHs), and highlight the most promising future directions of research in this area.

Epigenomics describes the regulation of transcription and translation of genetic information independent of mutations. The prototypical examples of such mechanisms include DNA and histone modification through the transfer of acetyl or methyl groups, which can lead to the silencing of tumour-suppressor genes and/or the overexpression of proto-oncogenes. Epigenetic dysregulation has been shown to have a major role in the pathogenesis of most haematological malignancies, although the use of drugs designed to target epigenetic mechanisms in clinical practice has, thus far, mainly been limited to patients with acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), multiple myeloma or T cell lymphoma (TCL). FDA-approved epigenetic-modulating agents include the histone deacetylase (HDAC) inhibitors vorinostat (2006), romidepsin (2009), panobinostat (2015) and belinostat (2015), the DNA methyltransferase (DNMT) inhibitors azacitidine (2004) and

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decitabine (2006) and the isocitrate dehydrogenase (IDH) inhibitors enasidenib (2017) and ivosidenib (2018) (FIG. 1). Research conducted over the past decade has demonstrated a high frequency of somatic mutations in genes that encode epigenetic enzymes in B cell lymphomas[1–5]. Additionally, patterns of aberrant DNA methylation have been observed in diffuse large B cell lymphoma (DLBCL) and are associated with different clinical outcomes in specific epigenetic subgroups[6]. Consequently, epigenetic dysregulation has been exploited for the development of novel agents.

In this Review, we describe the most promising epigenetic-modifying agents currently under investigation for various types of lymphoma. We include drugs that are already approved by the FDA, those that are currently in clinical trials and agents that are currently in the preclinical setting but are likely to soon be translated into first-in-human and/or proof-of-concept trials (Box 1). The various classes of agent include inhibitors of HDACs, DNMTs, enhancer of zeste homologue 2 (EZH2), bromodomain and extra-terminal domain proteins (BETs), protein arginine *N*-methyltransferases (PRMTs) and IDHs.

HDAC inhibitors

Histone and non-histone protein acetylation is regulated through the opposing functions of histone acetyl-transferases (HATs) and HDACs. Human HDACs are classified into four major classes on the basis of sequence homology to yeast proteins and shared cellular localization and function: class I (HDAC1, HDAC2, HDAC3 and HDAC8); class II (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10), class III (NAD-dependent protein deacetylase sirtuin 1 (SIRT1)-SIRT7); and class IV (HDAC11)[7]. Acetylation typically increases gene expression by inducing an open chromatin state that improves the ability of various transcription factors to bind to DNA, as well as by enhancing the activity of transcriptional activators (such as p53) or impairing the function of transcriptional repressors (such as BCL-6)[8,9] (FIG. 2a).

Multiple findings suggest that histone acetylation has a key role in lymphoid malignancies and particularly in germinal centre-derived tumours. Loss-of-function mutations in genes encoding proteins with established roles in histone acetylation, such as *CREBBP* and, less frequently, *EP300,* are commonly observed in DLBCL (~25% of patients) and in follicular lymphoma (FL; 60% of patients) but can also be found in small subsets of patients with other types of lymphoma[2,5] (BOX 2). Somatic mutations in *CREBBP* result in impaired p53 activation while also promoting the oncogenic effects of BCL-6 (REF[5]); additionally, loss-of-function mutations of CREBBP also result in repression of genes that are important for exit from the germinal centres, including most genes regulated by BCL-6 (REFS[10,11]). Among these target genes, silencing of those involved in MHC class II-mediated antigen presentation might have important roles such as disruption of immune surveillance[11,12]. Other acetyltransferases implicated in lymphoma include TIP60 (also known as KAT5), which accelerates the development of MYC-driven tumours when deleted in mice and is expressed at lower levels in a small fraction of FLs and DLBCLs[13]; other genes involved in epigenetic regulation are infrequently mutated. Data from translational studies have confirmed the activity of HDAC inhibitors either alone or in combination with hypomethylating agents, targeted therapies or chemotherapy in a range of haematological

malignancies including acute lymphoblastic leukaemia (ALL), cutaneous T cell lymphoma (CTCL), DLBCL, Hodgkin lymphoma (HL) and Burkitt lymphoma (BL)[14–20]. Furthermore, inhibition of HDAC6 has been shown to upregulate CD20 and enhances the efficacy of anti-CD20 monoclonal antibodies, such as rituximab[21]. Collectively, these data suggest that deregulation of either HDACs or HATs is an important mechanism of lymphomagenesis and thus an attractive target for pharmacological inhibition.

Five HDAC inhibitors are currently approved by the FDA[22–26] (FIG. 1). As the initial HDAC inhibitor approved for TCL, vorinostat has been tested in patients with relapsed non-Hodgkin lymphoma (NHL), including FL, marginal zone lymphoma (MZL) and mantle cell lymphoma (MCL). In general, this agent has shown modest levels of single-agent activity, with the exception of FL, in which an overall response rate (ORR) of47–49% and a complete response (CR) rate of 23% was observed[27,28]. In addition to its established role in myeloma, panobinostat has shown promise in HL (27% ORR), DLBCL (17.1% ORR) and CTCL (17.3% ORR)[29–31]. Other HDAC inhibitors currently in development have shown signs of activity in lymphomas, including abexinostat and quisinostat (broad-spectrum HDAC inhibitors), mocetinostat and entinostat (both of which inhibit HDAC1, HDAC2, HDAC3 and HDAC11) and chidamide (which inhibits HDAC1, HDAC2, HDAC3 and HDAC10). Response rates range between 12% and 56% depending on both the drug and the lymphoma subtype, with the most robust responses seen with abexinostat in FL (56% ORR) and chidamide in peripheral T cell lymphoma (PTCL) (28% ORR and 14% CR rate) (TABLE 1; Supplementary Table 1). Treatment with HDAC inhibitors is frequently associated with thrombocytopenia (in 80–90% of patients), fatigue (in 30–50%) and gastrointestinal toxicities (in 40–60%), with exact frequencies depending on the specific agent[32–36]. Whether or not the presence of mutations in genes encoding HAT enzymes serves as a reliable biomarker of response to HDAC inhibitors currently remains to be seen. In a phase II trial exploring the safety and efficacy of panobinostat in patients with relapsed DLBCL, mutations in myocyte-specific enhancer factor 2B (*MEF2B*) were detected in 15.4% of patients and were associated with an improved response to therapy. However, these findings are based on data from only 6 patients harbouring the *MEF2B* mutation out of a small study population of 39 patients. Furthermore, data on copy number variations were not included in the analysis. Lastly, no association was determined between mutations in *CREBBP* or *EP300* and response to therapy[37].

Novel HDAC inhibitor-based combination regimens are being evaluated in patients with a variety of lymphoid malignancies (TABLE 2). HDAC inhibitors seem to have synergistic effects when used in combination with anti-CD20 monoclonal antibodies, proteasome inhibitors or immunomodulatory agents[37–40]. In a report published in November 2017, romidepsin combined with the antimetabolite pralatrexate demonstrated impressive levels of activity in patients with PTCL, with a 71% ORR, as well as a 33% ORR when TCLs were excluded from the analysis[41]. Also of note, the novel first-in-class dual HDAC and PI3K inhibitor CUDC-907 has shown exceptional levels of activity (55% ORR) and tolerability (grade ≥3 adverse events in 43%) in patients with either transformed or de novo DLBCL, as well as in those with other lymphoma subtypes (57% ORR) in a phase I first-in-human trial[42]. As a result of these promising initial observations, this agent is currently being

investigated further in a phase II cohort of adult patients with DLBCL and a phase I trial involving paediatric patients with lymphomas (NCT02674750 and NCT02909777).

Clinical trials designed to investigate the added benefit of HDAC inhibitors in combination with standard chemotherapy regimens, as part of either frontline or salvage therapy, in larger cohorts of patients have had mixed results. For example, vorinostat was found to cause high rates of febrile neutropenia and sepsis when combined with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in 72 patients with newly diagnosed advanced-stage DLBCL and fell short of the predefined efficacy end points (2-year progression-free survival (PFS) and overall survival (OS) of 73% and 86%, respectively)[43]. Studies involving smaller cohorts of patients receiving vorinostat or panobinostat combined with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) have demonstrated a 70% ORR (30% had CRs) across all types of lymphoma and an 82% CR rate in patients with HL[44,45]. However, the combination therapy in the latter study was associated with considerable levels of haematological toxicities, including grade 4 neutropenia (in 55% of patients) and thrombocytopenia (in 100%)[45]. Vorinostat has also been tested in combination with gemcitabine, busulfan and melphalan as part of the conditioning regimen before autologous stem cell transplantation (ASCT). This combination was found to be safe and highly active, with 25-month event-free survival (EFS) and OS values of 61.5% and 73%, respectively, in patients with DLBCL[46]. This regimen, combined with lenalidomide, is currently being investigated in a phase I trial involving patients with non-germinal centre B cell (GCB)-like DLBCL (NCT02589145). Romidepsin has also been combined with chemotherapy in patients with T cell lymphomas. Combinations include with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in a phase I trial involving 37 patients with previously untreated PTCL and with ifosfamide, carboplatin and etoposide (ICE) in a phase I trial involving 17 patients with relapsed PTCL. Both trials seem to suggest safety, tolerability and clinical benefit from this combination; thus, randomized studies with larger cohorts of patients are warranted[47,48]. Other clinical trials combining HDAC inhibitors with chemotherapy are currently ongoing (Supplementary Table 1).

DNMT inhibitors

DNMTs catalyse the transfer of methyl groups onto cytosine nucleotides within CpG sequences in DNA strands, resulting in changes in conformation that prevent the binding of transcription factors and thus silence the expression of methylated genes. DNMTs include DNMT1, which maintains pre-existing methylation patterns, and DNMT3A and DNMT3B, which establish new sites of methylation[49] (FIG. 2b). In general, the DNA of nonmalignant cells is heavily methylated, with the exception of CpG islands, which are typically located near gene promoters. The traditional model linking DNA methylation with oncogenesis describes the hypermethylation of promoters controlling tumour-suppressor genes and genome-wide hypomethylation leading to genomic instability[6]. Indeed, the presence of specific DNA methylation patterns is associated with tumorigenesis as well as prognosis across a variety of malignancies. Specific genes that have been found to be hypermethylated and subsequently lead to lymphomagenesis include *TP63* in chronic lymphocytic leukaemia (CLL), *DAPK1* in FL, *miR-34A* in DLBCL, *CDKN2B* in MCL, *P16* (also known as *CDKN2A*) in TCL and genes regulated by components of the polycomb repressive complex

2 (PRC2) in BL[50–55]. In DLBCL, the disruption of DNA methylation patterns is associated with unfavourable clinical outcomes and is potentially more prognostically relevant than the International Prognostic Index score[6,56,57]. Differences in DNA methylation signatures also characterize molecular subtypes of DLBCL (for example, GCB and non-GCB)[58,59]. Heterogeneous DNA methylation has been shown to correlate with reduced time to first treatment and unfavourable markers such as unmutated immunoglobulin heavy chain variable region (IGHV) and *TP53* deletions in patients with CLL[60].

Unlike in myeloid malignancies, alterations in DNA methylation in patients with B cell lymphomas are not known to be caused by specific mutations in DNMTs or other genes that encode enzymes that regulate methylation or demethylation (such as *IDH* or *TET*). Although the precise mechanisms remain unclear, altered DNA methylation has been suggested to, in part, be achieved through the actions of the mutagenic enzyme activation-induced cytidine deaminase, which catalyses the deamination of methylated cytosine nucleotides[61]. This enzyme is expressed specifically in GCBs and induces somatic hypermutation and class switching of the immunoglobulin loci[61]. In addition, DNMT3B can be overexpressed in DLBCL and in BL (in as many as 86% of BLs) and might be regulated by microRNAs; expression of this enzyme might even correlate with adverse outcomes[62,63].

The DNMT inhibitors (or hypomethylators) azacitidine and decitabine represent the first class of epigenetic-modulating drugs to be approved by the FDA. These drugs are pyrimidine nucleoside analogues of cytosine that are able to become incorporated into DNA and form covalent bonds between the 5-azacytosine ring and the DNMT enzyme, thus causing irreversible DNMT inactivation[64]. Logically, DNMT inhibitors would seem likely to function by reversing the silencing of tumour-suppressor genes, although the precise mechanism of action of DNMT inhibitors is poorly understood. However, data published in the past few years indicate that the antitumour effects of these agents might be mediated by stimulation of the immune tumour microenvironment. For example, in non-lymphoma models, DNMT inhibitors have been shown to cause reactivation of endogenous retroviruses, leading to upregulation of the viral defence pathway and a type I interferon response[65]. Data from other studies have also demonstrated increased expression of tumour-associated antigens, such as MAGE and other cancer-testis antigens, and activation of the IFNα-IFNβ signalling pathway, leading to improved immune recognition[66,67].

Both azacitidine and decitabine were initially approved for MDS (FIG. 1), although both agents are also commonly used as off-label treatments for AML mainly in elderly patients (often arbitrarily defined as those ≥60 years of age) or in those who are not fit to receive intensive remission induction therapy, as maintenance following induction and for relapsed and/or refractory disease per National Comprehensive Cancer Network (NCCN) guidelines[68]. In fact, both agents have been shown to improve survival compared with conventional induction therapy in elderly patients, likely owing to the high risk of treatment-related toxicities and the typically unfavourable prognosis of this patient population[69–72].

The potential for expanding the role of azacitidine and/or decitabine beyond myeloid malignancies has led to the initiation of trials designed to investigate the effects of these agents across various lymphoid malignancies and in novel combinations[64,73–80] (TABLE 3).

The outcomes of studies testing these agents as monotherapies in patients with CLL, NHL or HL have been disappointing, with limited levels of clinical benefit observed[73–75]. Furthermore, no strong evidence is available from clinical trials to suggest that DNA methylation status is a reliable biomarker that is predictive of response to DNMT inhibitors. However, DNMT inhibitors have been shown to render chemotherapy-resistant DLBCLs sensitive to the chemotherapies that form the CHOP regimen both in laboratory experiments and in serial biopsy samples from patients with DLBCL enrolled in a phase I clinical trial[64]. Furthermore, the sequential administration of decitabine followed by doxorubicin to mouse xenograft models of lymphoma has been shown to result in a substantial reduction in tumour burden[64]. Building upon preclinical data, similar to HDAC inhibitors, the efficacy of DNMT inhibitors in combination with standard first-line R-CHOP has been explored, and these trials have demonstrated impressive response rates with few added toxicities compared with standard R-CHOP alone[64,76]. Azacitidine has also been combined with chemotherapy as a second-line therapy and in patients who are eligible for high-dose therapy (TABLE 3), and this approach merits further study[77,78]. In conclusion, the future role of DNMT inhibitors in patients with lymphoma is uncertain, although these agents could potentially still have value if used in combination with other regimens or therapies. In particular, a strong scientific rationale exists for the combination of DNMT inhibitors with HDAC inhibitors because both hypermethylated DNA and under-acetylated histones are associated with closed chromatin states that repress gene expression through independent mechanisms. Both therapies can cause substantial toxicities at high doses but also retain their chromatin-modifying properties at lower doses; therefore, further investigations of the performance of this combination at various dosages and treatment durations should be conducted.

EZH2 inhibitors

EZH2 is a component of PRC2, along with EED and SUZ12. EZH2 is the enzymatic subunit that catalyses the methylation of Lys27 of histone H3 (H3K27) with as many as three methyl groups. EZH2 has an essential role in the GCBs that give rise to FL and DLBCL, as documented in mouse models in which deletion of this gene completely abrogated the formation of germinal centres. This effect is mediated by the EZH2-mediated silencing of genes encoding cell cycle checkpoint proteins and those involved in plasma cell differentiation[81–83] (FIG. 2 a).

Mutations in *EZH2* are highly prevalent in patients with B cell lymphomas and occur specifically in GCB-DLBCLs and FLs, with an incidence of approximately 15–20% in both tumour types[3,84]. The vast majority of these genetic lesions involve point mutations resulting in substitution of tyrosine 641 (Y641; either Y641F, Y641N, Y641S or Y641H) within the histone methyl-transferase domain of *EZH2.* These alterations lead to a gain-of-function effect whereby the mutant form of this protein enables more efficient trimethylation of H3K27 (REF[85]). The consequence of these mutations is the aberrant and permanent silencing of the same cell cycle checkpoint and plasma cell differentiation genes that EZH2 represses in nonmalignant cells of the germinal centre[82–86]. In vivo, expression of the gain-of-function mutant allele in GCBs synergizes with BCL-2 deregulation and accelerates the development of lymphomas[82], thus providing a rationale for the development of drugs designed to inhibit EZH2. In preclinical studies, EZH2 inhibitors have been shown to induce

proliferation arrest, differentiation and eventual apoptosis of DLBCL cells over the course of several days. These effects are more rapid in DLBCL cells that harbour *EZH2* mutations but also occur in *EZH2*-wild-type DLBCL cells[82]. These findings have also been demonstrated in mice, in which the EZH2 inhibitor tazemetostat enabled dose-dependent inhibition of tumour growth in both *EZH2*-mutant (Y646F) and *EZH2*-wild-type B cell NHL xenografts associated with a loss of H3K27 trimethylation[87,88]. This general dependency that goes beyond cells harbouring *EZH2* mutations reflects the essential role that EZH2 has in the survival of the GCBs from which these lymphomas arise. In FL, SESTRIN1 (encoded by the tumour-suppressor gene *SESN1,* located within chromosome 6q) seems to be an important target of EZH2 because cells characterized by 6q deletions are rendered less susceptible to EZH2 inhibitors[89]. In contrast to B cell lymphomas, EZH2 acts as a tumour suppressor in T cell malignancies, which manifest loss-of-function mutations of *EZH2* and genes encoding other components of PRC2 (REF[90]). In particular, genes encoding components of PRC2 have an especially high rate of deletions or sequence mutations in early T cell precursor ALL[91]. Homozygous inactivation of EHZ2 in mouse models of leukaemia was found to accelerate the progression of early T cell precursor ALL, in part through activation of the STAT3 pathway[92].

EZH2 inhibitors first entered clinical trials in 2013 (FIG. 1). Results from these initial trials have since been reported for tazemetostat, valemetostat and GSK2816126 and generally show encouraging preliminary results[93–95] (TABLE 4). The largest study with data available thus far is a phase II trial involving 165 patients with relapsed and/or refractory DLBCL or FL. Patients were stratified by *EZH2* mutation status, and results reveal ORRs of 40% and 63% in patients with $EZH2^{+}$ DLBCL and FL, respectively. By contrast, ORRs were 18% and 28% in those with $EZH2^{-}$ DLBCL and FL, respectively. Grade ≥3 adverse events were reported in 18% of patients, and the most common toxicities across all grades were nausea, thrombocytopenia, cough, diarrhoea, fatigue and weakness[96]. In an updated report presented at the Congress of the European Haematology Association (EHA) of 82 evaluable patients with FL (as of 1 May 2018), an ORR of 71% with CRs in 11% of patients was reported in patients with $EZH2^{+}$ disease. Again, a modest ORR (33%) was observed in patients with $EZH2^{-}$ disease[97]. On the basis of the above evidence, a role clearly exists for *EZH2* mutation status in predicting a response to therapy in both DLBCL and FL (BOX 2). However, because some patients with EZH2-wild-type disease also respond, albeit to a lesser extent than those with mutant EZH2, more selective biomarkers of responsiveness continue to be needed. To this end, an analysis of mutations in genes encoding INI1 (also known as SMARCB1) and SMARCA4 (components of the SWI/SNF complex) was conducted in a cohort of patients with solid tumours receiving tazemetostat. Interestingly, patients whose tumours had a loss of INI1 and SMARCA4 were found to have a better response than those with wild-type disease, most likely owing to higher levels of oncogenic addiction to EZH2 in these tumours[93]. Moving forward, further investigations of the predictive value of this biomarker might be warranted in patients with lymphoma.

Dual inhibition of EZH1 and EZH2 might lead to greater suppression of H3K27 trimethylation and provide higher levels of anti-lymphoma activity than inhibition of EZH2 alone[98]. This discovery has led to the development of valemetostat, which has indeed shown good levels of activity across a range of B cell and T cell NHL subtypes (53% ORR and

86% clinical benefit rate (CBR)) in a phase I trial involving 15 patients. Of particular note, an 80% ORR was reported in patients with T cell lymphomas[95]. Given the encouraging clinical activity and tolerability of this class of drugs, tazemetostat is being investigated in various patient populations and drug combinations such as with chemotherapy (NCT02889523) or immunotherapy (NCT02220842). Furthermore, two phase I pharmacokinetic studies designed to evaluate drug metabolism (drug interactions and gastric pH effects) and the effects of different formulations (such as intravenous or oral administration) (NCT03010982 and NCT03028103) are currently recruiting patients. Of note, as of April 2018, the FDA has placed a partial hold on enrolment in clinical trials investigating the effects of tazemetostat owing to a case of secondary T cell lymphoma that developed in a paediatric patient with sarcoma who had been on tazemetostat for 15 months and had a partial response.

BET inhibitors

Bromodomains are protein motifs that recognize and bind to acetylated lysine moieties located on histone tails. BETs consist of two amino-terminal tandem bromodomains and an extra-terminal (non-bromodomain) region. The BET family includes BRD2, BRD3 and BRD4 and bromodomain testis-specific protein[99]. Upon binding to acetylated lysine groups, BETs induce gene expression either directly by recruiting transcription factors to DNA and initiating transcription or indirectly by interacting with gene super-enhancers (non-coding regions of DNA that bind to transcription factors and activate nearby target genes controlling cellular identity) (FIG. 2a). Thus, BETs contribute to the development and progression of malignancies by both activating and potentiating the expression of key oncogenes[100].

Although *BET* mutations or translocations are rare, BETs can be overexpressed[101]. Consequently, BET inhibition has been shown to be effective in preclinical studies across multiple types of cancers, including breast, neuroendocrine, ovarian and haematological malignancies as well as in rhabdomyosarcoma and glioma[102–106]. In B cell lymphoid malignancies, BETs might activate the *MYC* oncogene and the *BCL2* anti-apoptotic signalling pathways. This suggestion arises from the observation that the binding of BRD4 to super-enhancers such as those that regulate *MYC* is inhibited in myeloma cells exposed to the BET inhibitor JQ1, resulting in a selective decrease in the expression of this oncogene[107]. MYC signalling and other oncogenes associated with super-enhancers seem to be preferentially sensitive to BET inhibition; thus, *MYC* expression could potentially serve as a biomarker in future clinical trials. In patients with double-hit DLBCL, resistance to venetoclax can be overcome by administration of the BET inhibitor CPI-203, likely owing to downregulation of BCL-2-like protein (BFL1)[108]. In patients with CLL, high concentrations of BRD4 have been found to be localized to the sites of super-enhancers known to regulate the transcription of several genes in the B cell receptor signalling pathway, as well as that of genes with oncogenic effects in CLL including *TCL1, miR-21, miR-155, IL4R* and *IL21R.* BET inhibition was then shown to decrease the expression of many of these genes as well as to reduce the tumour burden in mouse models of CLL[101]. BET proteolysis-targeting chimaeras (PROTACs), which induce the degradation of BETs through the targeted sequestration of ubiquitin ligases, have been shown to work analogously to BET inhibitors in preclinical models of MCL and might even be more effective. BET PROTACs induce

apoptosis in ibrutinib-resistant MCL cells and demonstrated improved survival when compared with BET inhibition with OTX015 in mouse models[109]. BET inhibitors are also active in CTCL, Epstein-Barr virus (EBV)-associated lymphoproliferative disease and primary effusion lymphoma and have been shown to decrease the rate of tumour growth and disease progression in mouse xenograft models[110–112]. JQ1 has also been shown to prolong the survival duration of mouse xenograft models of MYC-driven lymphoma, including those that were resistant to etoposide and those carrying *TP53* deletions[113].

Birabresib (also known as OTX-015 or MK-8628) was the first BET inhibitor to enter clinical trials, which happened in 2013 (FIG. 1). The first results, from a phase I trial of 45 patients with relapsed and/or refractory lymphoma or myeloma were reported in 2016 and, most notably, revealed a 47% CBR among 17 evaluable patients with DLBCL; however, only 4 patients with indolent lymphomas had any clinical benefit, and none of the 12 patients with myeloma responded to treatment. The most common adverse events were cytopenias, specifically thrombocytopenia, in virtually all patients including grade ≥3 thrombocytopenia in 58%, anaemia in 91%, neutropenia in 51%, diarrhoea in 47%, fatigue in 27% and nausea in 24%. From this study, a recommended phase II dose and schedule of 80 mg daily for 14 days on, 7 days off was successfully established[114]. CPI-0610 has also been tested in a phase I trial involving 44 patients with relapsed and/or refractory lymphoma (mainly DLBCL, FL or HL), and 12 patients in this study had clinical benefit, including CRs in 2 patients with DLBCL[115]. The third phase I study with published data available was designed to investigate the effects of INCB057643 in patients with solid or haematological malignancies, including four patients with FL and one patient with DLBCL. In this trial, one patient (with FL) had a CR, and two patients had stable disease[116]. A phase I trial investigating the effects of BAY1238097 in eight patients with various advanced-stage malignancies revealed only negative outcomes: all patients either had disease progression or serious adverse events. No maximum tolerated or recommended phase II dose was established for this drug, and the trial was terminated prematurely owing to both safety concerns and a lack of efficacy[117]. Several phase I trials designed to test BET inhibitors, including molibresib, CC-90010 and INCB054329, are currently ongoing for patients with various advanced-stage malignancies (NCT01943851, NCT03220347 and NCT02431260). At the time of an interim analysis of the phase I/II trial investigating the safety and efficacy of INCB054329, four patients with lymphoma had been treated, although the outcomes of these patients are yet to be reported[118]. In December 2018, data from 27 patients with various subtypes of NHL treated with molibresib were presented at the American Society of Hematology (ASH) annual meeting. The ORR among the entire cohort was 18.5%, with one patient with DLBCL having a sustained complete remission after receiving treatment for 54 weeks. Also of note, three out of six patients with T cell lymphomas had a PR[119] (TABLE 5).

PRMT inhibitors

PRMTs catalyse the monomethylation or dimethylation of arginine residues on histone and non-histone proteins. A total of nine human PRMTs are known to exist, although PRMT5 seems to be the most relevant to oncogenesis. PRMT5 is a type II PRMT that specifically

catalyses the symmetrical dimethylation of arginine residues located on the H3 or H4 proteins, resulting in gene silencing[99] (FIG. 2a).

No PRMT inhibitors have thus far received FDA approval, and the first clinical trial designed to investigate a PRMT5 inhibitor (GSK3326595) commenced in 2016 for patients with solid tumours or NHL (NCT02783300). Despite this lack of clinical evidence, a growing body of data from preclinical studies has demonstrated a potentially important role of this class of drug, specifically for the treatment of lymphoid malignancies. Activating mutations in *PRMT5* have not been reported in patients with lymphoma, although PRMT5 is overexpressed in different subtypes and might potentially serve as a biomarker. For example, PRMT5 is highly expressed in EBV^+ human lymphoma cells, in comparison with nonmalignant resting or wild-type B cells[120]. Furthermore, PRMT5 inhibition leads to the selective killing of EBV-transformed lymphoma cells and restoration of tumour-suppressor gene *PTPRO* function, which is typically repressed in EBV^+ lymphoma cells[120]. In a correlative analysis of human DLBCL samples, high levels of PRMT5 expression were found to be associated with inferior outcomes[121]. In the same study, PRMT5-knockout mouse models of MYC^+ lymphoma demonstrated improved disease-free survival durations. Furthermore, PRMT5-depleted human BL cells were shown to have decreased tumorigenic potential in mouse xenograft models. Given the observed interactions between PRMT5 and MYC, the authors concluded that targeting the PRMT5 signalling pathway might be most effective in patients with MYC-driven tumours[121]. PRMT5 might also enhance the activity of BCL-6 in DLBCL cells; for example, PRMT5 inhibitors have been shown to synergize with BCL-6 inhibitors in the killing of BCL-6-expressing DLBCL cells in vitro. Notably, PRMT5 is also required for formation of GCBs, which are the cell of origin in most DLBCLs[122]. PRMT5 overexpression has also been identified in MCL, and PRMT5 inhibition was shown to have cytotoxic effects on MCL cell lines that were associated with downregulation of the genes encoding cyclin D1 (*CCND1*) and the differentiation protein MCL1 (REFS[123–124]). Oral administration of the PRMT5 inhibitor EPZ015666 has been shown to induce dose-dependent reductions in tumour volume in mouse xenograft models of MCL[125]. PRMT5 might also have a role in the development of T cell lymphomas. Similar to EBV-transformed lymphoma, PRMT5 expression is upregulated in human T lymphotropic virus (HTLV)-transformed adult T cell leukaemia/lymphoma (ATLL), and PRMT5 inhibition was shown to have selective cytotoxic effects on $HTLV^+$ lymphoma cells[126]. Overexpression of PRMT5 in ATLL seems to interact with oncogenic CCND1, MYC and NOTCH1 in driving lymphomagenesis and might also directly silence p53 (REF.[127]).

IDH inhibitors

IDH catalyses the oxidative decarboxylation of isocitrate to α-ketoglutarate as part of the tricarboxylic acid (or Krebs) cycle. Mutations in either *IDH1* or *IDH2* lead to the accumulation of 2-hydroxyglutarate (2-HG). This metabolite has been shown to inhibit several demethylation pathways, such as those driven by TET or Jumonji proteins, thus indirectly acting as an epigenetic regulator. As a result of 2-HG accumulation, aberrant DNA or histone methylation can occur[128] (FIG. 2b). As a consequence of this aberrant regulation, *IDH* mutations can essentially be viewed as gain-of-function mutations and are potentially targetable.

Among lymphoid malignancies, dysregulation of the IDH epigenetic pathway has been best characterized in T cell lymphomas. Whole-exome sequencing of peripheral T cell lymphoma samples has demonstrated that approximately 30% of patients with angioimmunoblastic T cell lymphoma (AITL) have *IDH2* mutations, although such mutations occur less frequently in other subtypes of PTCL[129–131]. Similar to AML, R172 is the most prevalent *IDH* mutation, is associated with having the highest levels of 2-HG compared with the other two hotspot mutations, IDH1^{R132} and IDH2^{R140} (REF[132]), and should be considered an important biomarker for the selection of patients to receive IDH inhibitors, potentially regardless of tumour histology. Interestingly, according to results published in the past few years, all cells harbouring *IDH2* mutations are PD-1^{+} and are associated with downregulation of T helper 1 cell-like differentiation genes (such as *STAT1* and IFNG)[129–131]. Furthermore, an analysis of gene expression signatures demonstrated increased methylation of the promoters that regulate T cell receptor signalling and T cell differentiation in IDH2^{R172K} cell lines, illustrating a potential mechanism of lymphoma-genesis[131]. The IDH epigenetic signalling pathway might also have a role in CLL. In CLL samples obtained from 214 patients, leukaemic cells were found to have reduced levels of *IDH2* expression, with overexpression of *IDH1* compared with nonmalignant B cells that was associated with improved treatment-free survival[133]. No data are currently available from preclinical studies testing IDH inhibitors specifically in models of IDH-mutant lymphomas, such as AITL or CLL.

Both the IDH2 inhibitor enasidenib and, subsequently, the IDH1 inhibitor ivosidenib have been approved in the past 2 years for patients with relapsed and/or refractory AML who carry mutations in *IDH2* or *IDH1,* respectively[134,135] (FIG. 1). IDH inhibitors have the unique adverse effect of differentiation syndrome, which can manifest as dyspnoea, fever, pulmonary infiltrates, acute kidney injury, bone and joint pain, lymphadenopathy or rash. In the landmark trial of enasidenib, differentiation syndrome occurred in 11.7% of patients (7% were grade 3–4 in severity) and was managed effectively using systemic corticosteroids. The frequency of this adverse event was similar in patients receiving ivosidenib, of whom 10.6% of patients developed differentiation syndrome, including grade ≥3 differentiation syndrome in 5% of patients. Other common adverse events included hyperbilirubinaemia, anaemia and thrombocytopenia[134–136]. Of note, patients with acquired therapeutic resistance to enasidenib were found to have new point mutations at either Q316 or I319, both of which are associated with increased circulating 2-HG levels[137].

Currently, no results are available from trials of IDH inhibitors in lymphoma. However, clinical trials investigating inhibitors of IDH2 (enasidenib), IDH1 (ivosidenib) and both IDH1 and IDH2 (vorasidenib) in patients with advanced-stage haematological malignancies are currently underway (NCT01915498, NCT02074839 and NCT02492737). Of particular note, enasidenib is currently being investigated in a phase I/II trial specifically for patients with AITL (NCT02273739) (Supplementary Table 2).

Future directions

Efforts to target epigenetic alterations in lymphomas have been successful in a number of disease subtypes, although ample opportunity to maximize the benefits of epigenetic-based

therapies continues to exist. Overcoming inherent or acquired resistance to standard therapies is essential and is particularly important given that patients are living longer and are often being exposed to a growing number of lines of therapy. As discussed above, the efficacy of epigenetic-based monotherapies in lymphoid malignancies is limited. Combination therapy, however, appears to improve the efficacy of these agents substantially, as demonstrated in phase I and phase II trials investigating HDAC or DNMT inhibitors in conjunction with chemotherapy, small-molecule inhibitors or both (TABLES 1–3). This paradigm of using epigenetic-based combination therapies to overcome resistance to single agents by inhibiting cell signalling bypass pathways has been extensively tested in preclinical studies. For example, BET inhibitors have been combined with a multitude of small-molecule inhibitors including those targeting mTOR, BTK, PI3K, ATR, EZH2 and HDACs, in addition to lenalidomide[138–142]. Similarly, decitabine has been combined with inhibitors of BCL-2, JAK-STAT, AKT and BET[143]. Many of these combinations have demonstrated synergistic activity in lymphoma cell lines or mouse xenograft models; therefore, the next rational step would be translation into clinical trials in order to evaluate the safety and efficacy of these combinations.

The combination of epigenetic-modulating agents with immunotherapy provides perhaps the most exciting avenue for future research. Histone modification typically results in closed chromatin states at the MHC class II promoters, and in MCL and DLBCL cells this can be reversed by HDAC inhibition, thus enhancing antigen-specific immune recognition and activation[144,145]. In addition, DNMT inhibitors seem to increase sensitivity to immune-checkpoint inhibition[146,147]. These preclinical observations are beginning to be translated from the laboratory to the clinic as several early phase trials designed to investigate the combination of epigenetic-modulating agents with immune-checkpoint inhibition in patients with lymphoma, including entinostat plus pembrolizumab (NCT03179930), vorinostat plus pembrolizumab (NCT03150329), azacitidine plus avelumab and/or utomilumab (NCT02951156) and tazemetostat plus atezolizumab (NCT02220842). Preliminary results of these studies have not yet been reported; however, on the basis of a strong biological rationale and compelling preclinical data, combining epigenetic-modulating agents with immunotherapies should be further explored.

Investigations of the potential therapeutic value of epigenetic-modifying agents that target other proteins should continue to be pursued. For example, the histone acetyltransferase CREBBP and the lysine-specific histone methyltransferase KMT2D are the two most frequently altered genes in FL and DLBCL[2,4,148,149]. However, both are generally deleted or inactivated, thus acting either directly or indirectly as tumour-suppressor genes, interfering with terminal B cell differentiation and ultimately inducing lymphomagenesis[11,148,149]. Inherent challenges exist in developing agents designed to specifically target loss-of-function mutations, although modulating the downstream targets of such proteins or targeting compensatory signalling pathways that are activated in response to loss of function of the gene of interest might be possible. *CREBBP*-mutant lymphomas have been shown to be biologically addicted to HDAC3, suggesting that HDAC3-specific, or pan-HDAC inhibitors might be useful agents in these patients[11]. Additionally, because *CREBBP* loss is associated with downregulation of MHC class II and immune evasion, and given that this effect is counteracted by HDAC3 inhibitors, combination treatment with immune-

stimulating therapies, such as immune-checkpoint inhibitors, could be considered[11]. Novel histone demethylase inhibitors might counteract the loss of methylation typically observed in KMT2D-inactivated tumours, and the effectiveness of this approach could also be enhanced by combination with immunotherapy[148,149].

Lastly, noninvasive liquid biopsies, such as cell-free DNA (cfDNA) and circulating tumour cells (CTCs), are increasingly being studied and used for the purpose of detection of minimal residual disease, as well as for the genetic profiling of a known malignancy. These modalities can be valuable in patients with most types of solid tumour as well as in those with lymphomas given the limited sensitivity of imaging and the invasiveness and inconvenience of obtaining tissue biopsy samples. Mutations in genes with established roles in epigenetic regulation such as *TET2, DNMT3A* and *IDH2* have been found to be 83% concordant between cfDNA and tissue biopsy samples in patients with AITL[150]. Furthermore, an assay for the analysis of DNA methylation patterns in CTCs has been developed for both prostate and breast cancer cells and has been shown to be both feasible and clinically useful[151]. In summary, these novel techniques show considerable potential and should be further explored in patients with lymphoma to aid in the diagnosis, monitoring, surveillance and prognostication of this disease.

Conclusions

Over the past 10 years, more than 60 manuscripts and abstracts have been published reporting results from clinical trials investigating the safety and/or efficacy of epigenetic-modifying agents in patients with lymphoma, and almost half of these were published in the past 2 years. In addition, more than 50 ongoing clinical trials are currently registered at ClinicalTrials.gov. Given the large number of drugs currently undergoing clinical investigation, in addition to those already approved by the FDA, rational prioritization of the development and selection of these therapies will be extremely important in helping move the field forward. The large body of evidence presented in this Review demonstrates an important clinical role for the epigenetic-modifying drugs across the spectrum of lymphoid malignancies. As HDAC and DNMT inhibitors are the oldest of these drugs and have already been implemented into routine use for patients with certain types of lymphomas and leukaemias, they are, unsurprisingly, also the most extensively studied at this time. As a result, the process of investigating these agents in new contexts and in novel combinations is generally faster and more efficient than the same process for newer classes of drugs. However, the future is remarkably promising for newer epigenetic agents (such as EZH2, BET, PRMT5 and IDH inhibitors), and most of these drugs have only transitioned from the preclinical to the clinical arena within the past 5 years. With the first preliminary results from trials involving these agents beginning to be reported, we are entering a very exciting era for the field of epigenetics in lymphoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

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Box 1 |

Proposed epigenetic-based treatments by lymphoma subtypes

- Follicular lymphoma
  - HDAC inhibitors
  - EZH2 inhibitors
- Diffuse large B cell lymphoma
  - EZH2 inhibitors
  - HDAC inhibitor plus a BCL-2 inhibitor
- Hodgkin lymphoma
  - HDAC inhibitor plus an immune-checkpoint inhibitor
- Cutaneous T cell lymphoma
  - HDAC inhibitors
- Peripheral T cell lymphoma
  - Azacitidine plus CHOP (specifically AITL)

AITL, angioimmunoblastic T cell lymphoma; CHOP cyclophosphamide, doxorubicin, vincristine and prednisone; EZH2, enhancer of zeste homologue 2; HDAC, histone deacetylase.

Box 2 |

Biomarker-driven selection of epigenetic therapies for lymphoma

- HDAC inhibitors
  - Loss of *CREBBP* or *EP300* (HATs) and *TET2* mutations
- DNMT inhibitors
  - Genome-wide or promoter (such as *DAPK1)* méthylation status and *TET2* mutations
- EZH2 inhibitors
  - *EZH2* mutations and loss of *INI1* or *SMARCA4*
- BET inhibitors
  - *MYC* overexpression or translocation
- PRMT5 inhibitors
  - *PRMT5* overexpression and wild-type *TP53*
- IDH inhibitors
  - *IDH1* or *IDH2* mutations

BET, bromodomain and extra-terminal domain protein; DNMT, DNA methyltransferase; EZH2, enhancer of zeste homologue 2; HAT, histone acetyltransferase; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; PRMT5, protein arginine *N*-methyltransferase 5.

Key points

- Epigenetic-modifying drugs are routinely used in acute myeloid leukaemia, myelodysplastic syndrome and T cell lymphomas, but their role in other malignancies, including B cell lymphomas, has not yet been established.
- B cell lymphomas typically have a high frequency of somatic mutations in genes encoding enzymes with a role in epigenetic modifications.
- In addition to expanding the role of histone deacetylase and DNA methyltransferase inhibitors for new indications, novel classes of agents are also being investigated for lymphoma, including enhancer of zeste homologue 2 (EZH2), bromodomain and extra-terminal domain protein (BET), isocitrate dehydrogenase (IDH) and protein arginine *N*-methyltransferase 5 (PRMT5) inhibitors.
- The selection and rational prioritization of epigenetic agents are important for both designing future studies and choosing the most appropriate agents for patients in clinical practice.
- Potential future research directions include investigating novel combinations, exploring the therapeutic role of targeting new epigenetic pathways and discovering new biomarkers to guide patient selection.

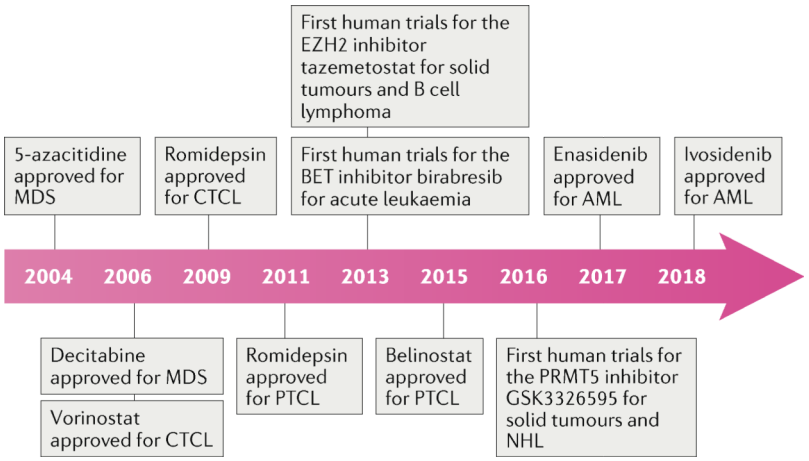

Fig. 1 |. Timeline of FDA approvals of epigenetic-modulating therapies for patients with lymphomas.

AML, acute myeloid leukaemia; BET, bromodomain and extra-terminal domain protein; CTCL, cutaneous T cell lymphoma; EZH2, enhancer of zeste homologue 2; MDS, myelodysplastic syndrome; PRMT5, protein arginine *N*-methyltransferase 5; PTCL, peripheral T cell lymphoma; NHL, non-Hodgkin lymphoma.

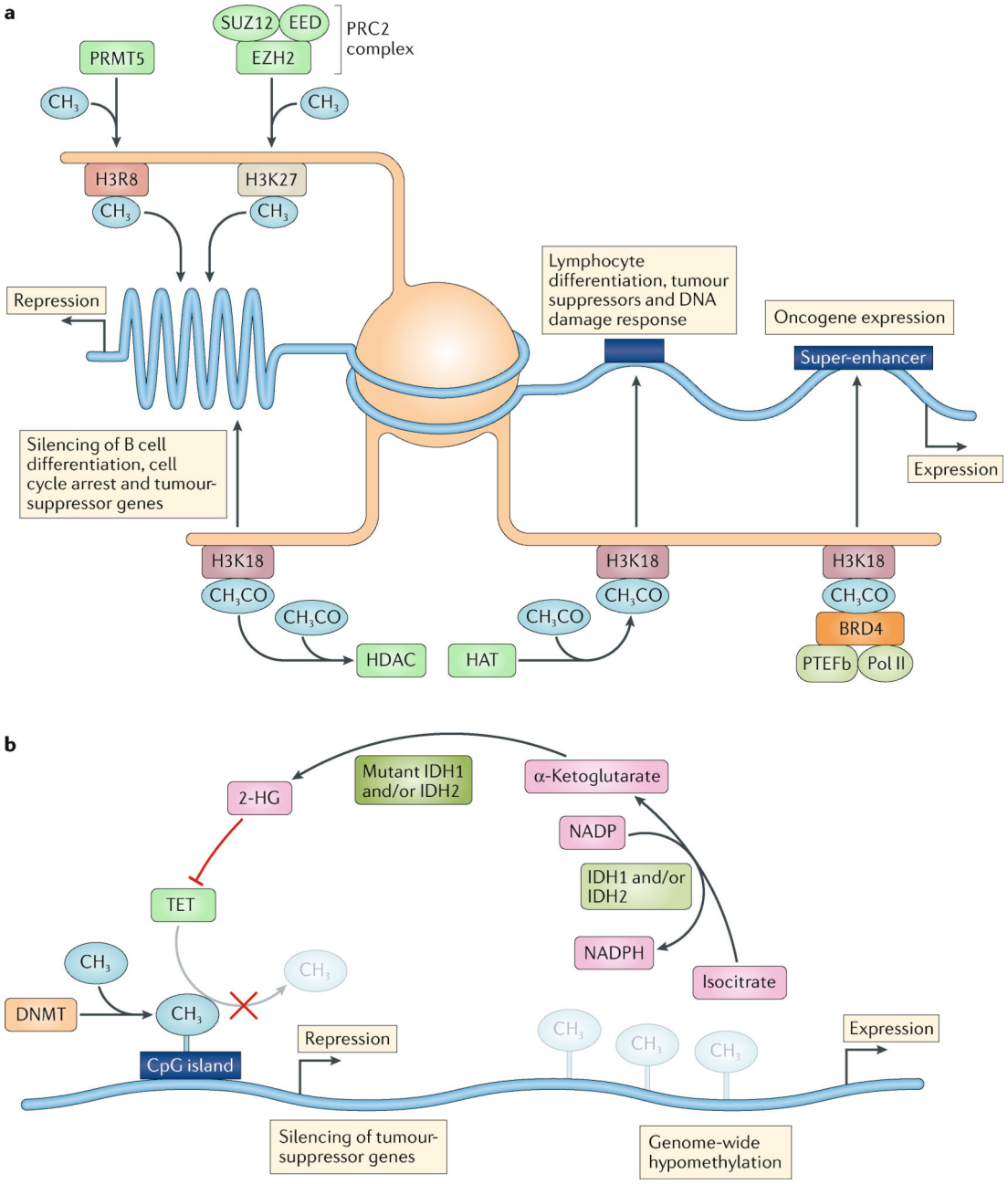

Fig. 2 |. Mechanisms of action of common epigenetic enzymes.

a | Histone acetylation is regulated by the interplay of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyse the transfer of acetyl groups (CH_3CO) from acetyl-CoA onto lysine groups on histone tails (such as histone H3 lysine 18 (H3K18)). HDACs catalyse the removal of acetyl groups. The net effect of acetylation is typically an open chromatin state leading to increased expression of genes controlling lymphocyte differentiation, tumour suppression and DNA damage repair. Reduced levels of acetylation might be caused by upregulation of HDACs or loss of function of HATs. Bromodomain proteins (such as BRD4) bind to acetylated lysine groups and, through the recruitment of positive transcription elongation factor b (PTEFb) and RNA polymerase II (Pol II), are able

to bind to super-enhancers, resulting in expression of oncogenes. Enhancer of zeste homologue 2 (EZH2) associates with the subunits EED and SUZ12 to form polycomb repressive complex 2 (PRC2). This complex then catalyses the transfer of methyl groups (CH_3) to lysine groups on histone tails (such as H3K27), which silences genes that usually regulate B cell differentiation. Protein arginine N-methyltransferases (PRMTs) catalyse the methylation of arginine groups on histone tails (such as H3R8), leading to the development of a closed chromatin state and thus silencing genes with a key role in cell cycle regulation. **b** | DNA methyltransferases (DNMTs) catalyse the transfer of methyl groups to cytosine nucleotides. Methylation of CpG islands within gene promoters leads to the silencing of tumour-suppressor genes and might be caused either by upregulation of DNMTs or loss of function of one or more members of the methylcytosine dioxygenase (TET) family of proteins. Isocitrate dehydrogenase (IDH) enzymes catalyse the synthesis of α-ketoglutarate using the cofactor NADP. Mutations in *IDH1* or *IDH2* produce the oncometabolite 2-hydroxyglutarate (2-HG), which inhibits TET proteins. Genome-wide hypomethylation occurs by spontaneous or enzyme-driven deamination of cytosine residues, causing DNA to become unstable.

Table 1 |

Summary of trials involving single-agent HDAC inhibitors

Agent	*n*	Lymphoma subtype	Outcomes	Common grade ≥3 adverse events (% of patients)	Year	Refs
Panobinostat	35	DLBCL	ORR 17.1% and CRR 11.4%	Thrombocytopenia (83); neutropenia (34); diarrhoea (11)	2018	30
Panobinostat	139	CTCL	ORR 17.3%	Thrombocytopenia (23); neutropenia (13); diarrhoea (6)	2013	31
Panobinostat	129	HL	ORR 27%, CRR 4% and median PFS 6.1 months	Thrombocytopenia (79); neutropenia (21); anaemia (21)	2012	29
Vorinostat	56	FL, NHL and MCL	FL: ORR 49% and median PFS 20 months; NHL: ORR 43%; MCL: ORR 0%	In 80% in total, including thrombocytopenia (48); neutropenia (41); leukopenia (12.5)	2014	27
Vorinostat	35	FL and MZL	FL: ORR 47% and CRR 23%; MZL: ORR 22%	Thrombocytopenia (29); neutropenia (17); lymphopenia (14)	2011	28
Abexinostat	100	NHL and CLL	ORR 28%; FL: ORR 56%	In 82% in total, including thrombocytopenia (80); neutropenia (27); anaemia (12)	2017	32
Mocetinostat	72	DLBCL and FL	DLBCL: ORR 18.9% and CBR 54.1%; FL: ORR 11.5% and CBR 73.1%	In 57% in total, including fatigue (23); neutropenia (15); thrombocytopenia (12)	2017	34
BeLinostat	22	Aggressive BCL	ORR 10.5%	Lymphopenia (10); all other adverse effects occurred in 5% or fewer patients	2016	152
Entinostat	49	HL	ORR 12%, CBR 24%, median PFS 5.5 months and OS 25.1 months	Thrombocytopenia (63); anaemia (47); neutropenia (41)	2016	33
Quisinostat	26	MF	ORR 24% and median PFS 5.1 months	Hypertension (4); fatigue (4); pruritus (4)	2016	35
Chidamide	79	PTCL	ORR 28%, CRR 14%, median PFS 2.1 months and median OS 21.4 months	Thrombocytopenia (22); leukopenia (13); neutropenia (11)	2015	36

All trials included in this table were phase II designs. BCL, B cell lymphoma; CBR, clinical benefit rate; CLL, chronic lymphocytic leukaemia; CRR, complete response rate; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylase; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MF, mycosis fungoides and/or Sezary syndrome; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T cell lymphoma.

Table 2 |

Summary of trials involving HDAC inhibitors in combination with other agents

Drug	Trial phase (*n*)	Lymphoma subtype	Outcomes	Common grade ≥3 adverse events (% of patients)	Year	Refs
Vorinostat + R-ICE	I (29)	AH lymphomas	ORR 70% and CRR 30%	In 86% in total, including hypophosphataemia (41); hypokalaemia (34); febrile neutropenia (28)	2013	44
Vorinostat + bexarotene	I (23)	CTCL	ORR 17.3% and CBR 30.4%	Hypertriglyceridemia (13); neutropenia (13); nausea (4)	2012	153
Vorinostat + Gem/Bu/Mel + HDT-ASCT	I/II (78)	DLBCL, HL and TCL	25-month EFS 61.5% and 25-month OS 73%	Mucositis (38); hyperbilirubinemia (15); rash (8)	2015	46
Vorinostat + R-CHOP	I/II (72)	DLBCL	2-year PFS 73% and 2-year OS 86%	Neutropenia (63); febrile neutropenia (38); anaemia (36)	2018	43
Vorinostat + rituximab	II (28)	FL, MZL and MCL	ORR 46% and median PFS 29.2 months	Fatigue (32); lymphopenia (25); thrombocytopenia (17)	2015	38
Romidepsin + pralatrexate	I (29)	NHL	ORR 58%; PTCL: ORR 71%	Thrombocytopenia (28); anaemia (24); febrile neutropenia (14)	2018	41
Romidepsin + CHOP	I (35)	PTCL	CRR51%	Neutropenia (89); thrombocytopenia (78); anaemia (43)	2015	47
Romidepsin + ICE	I (17)	PTCL	ORR 78% and CRR 64%	Thrombocytopenia (95); neutropenia (84); anaemia (73)	2015	48
Romidepsin + [enalidomide	I/II (21)	TCL	PTCL: ORR 50%; CTCL: ORR 56%	NR	2014	40
Panobinostat + everolimus	I (30)	FL, TCL, MCL and HL	ORR 33%; HL: ORR 43% and CRR 15%	Thrombocytopenia (63); neutropenia (47); anaemia (30)	2013	154
Panobinostat + R-ICE	I/II (23)	HL	CRR 82%	Anaemia (100); thrombocytopenia (100); neutropenia (64)	2018	45
Panobinostat + rituximab	II (40)	DLBCL	ORR 28% and median DOR 14.5 months	Thrombocytopenia (68); neutropenia (32); vomiting (11)	2016	37
Panobinostat + bortezomib	II (23)	PTCL	ORR 43% and CRR 22%	Thrombocytopenia (74); neutropenia (43); diarrhoea (22)	2015	39
CUDC-907	I (44)	DLBCL, tFL and HL	SD in 57%; DLBCL: ORR 55%	In 43% in total, including thrombocytopenia (20); neutropenia (9)	2016	42

CBR, clinical benefit rate; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CRR, complete response rate; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; Gem/Bu/Mel, gemcitabine, busulfan and melphalan; HDAC, histone deacetylase; HDT-ASCT, high-dose therapy-autologous stem cell transplantation; HL, Hodgkin lymphoma; ICE, ifosfamide, carboplatin and etoposide; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T cell lymphoma; R-ICE, rituximab, ifosfamide, carboplatin and etoposide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; SD, stable disease; TCL, T cell lymphoma; tFL, transformed follicular lymphoma.

Table 3 |

Summary of trials involving DNMT inhibitors

Agents	Trial phase (*n*)	Lymphoma subtype	Outcomes	Common grade ≥3 adverse events (% of patients)	Year	Refs or ClinicalTrials.gov identifier
Azacitidine + R-CHOP	I (33)	DLBCL, FL (grade 3b) and tFL	ORR 97% and CRR 85%	In 64% in total, including neutropenia (58); febrile neutropenia (21)	2017	[76]
Azacitidine + romidepsin	II (30)	HL, NHL and TCL	NHL: ORR 28% and CRR 16%; PTCL: ORR 83% and CRR 50%	NR	2017	[79]
Azacitidine+vorinostat + HDT-ASCT	I (60)	DLBCL, HL and TCL	DLBCL: EFS 65% and OS 77%; HL: EFS 76% and OS 95%; TCL: EFS 88% and OS 88% (all at a median follow-up duration of 15 months)	Neutropenic fever (100); mucositis (32); elevated transaminase levels (25)	2016	[78]
Azacitidine + R-CHOP	I (12)	DLBCL	CRR 92%	Neutropenia (100); neutropenic fever (33)	2013	[64]
Azacitidine	II (9)	CLL	ORR 0%	NR	2013	[73]
Azacitidine + R-CV	I (10)	DLBCL, FL,HL, SLL and CTCL	ORR 20%, CRR 10% and CBR40%	Neutropenia (50); thrombocytopenia (40); anaemia (20)	2011	[77]
Decitabine	I (20)	CLL and NHL	ORR 0%	Thrombocytopenia (55); neutropenia (45); febrile neutropenia (35)	2010	[74]
Decitabine + R-CHOP	I/II	DLBCL	Study ongoing	-	2016	NCT02951728
Azacitidine + avelumab + utomilumab	Ib	DLBCL	Study ongoing	-	2016	NCT02951156

CBR, clinical benefit rate; CLL, chronic lymphocytic leukaemia; CRR, complete response rate; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; DNMT, DNA methyltransferase; EFS, event-free survival; FL, follicular lymphoma; HDT-ASCT, high-dose therapy-autologous stem cell transplantation; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PTCL, peripheral T cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CV, rituximab, cyclophosphamide and vincristine; SLL, small lymphocytic leukaemia; TCL, T cell lymphoma; tFL, transformed follicular lymphoma.

Table 4 |

Summary of trials involving EZH2 inhibitors

Drug	Trial phase (*n*)	Lymphoma subtype	Outcomes	Common grade ≥3 adverse events (% of patients)	Year	Refs or ClinicalTrials.gov identifier
Tazemetostat	I (21)	B cell NHL	ORR 38% and CR 14%	In 9% in total, including thrombocytopenia (3); neutropenia (3)	2018	93
Tazemetostat	II (165)	DLBCL and FL	ORR 40% in EZH2-mutant DLBCL and 18% in EZH2-wild-type DLBCL; ORR 63% in EZH2-mutant FL and 28% in *EZH2*–wild-type FL	In 18% in total	2017	96
Valemetostat	I (15)	NHL	ORR 53% and CBR 86%; TCL: 80% ORR	NR	2017	95
GSK2816126	I (14)	NHL	DLBCL: 1 PR; FL: 1 SD	NR	2016	94
Tazemetostat + R-CHOP	Ib/II	DLBCL	Study ongoing	-	2016	NCT02889523
Tazemetostat	II	B cell NHL	Study ongoing	-	2016	NCT02875548
MAK683	I/II	DLBCL	Study ongoing	-	2016	NCT02900651
CPI-1205	I	Lymphomas	Study ongoing	-	2015	NCT02395601
Tazemetostat + atezolizumab	I	DLBCL	Study ongoing	-	2014	NCT02220842

CBR, clinical benefit rate; CR, complete response; DLBCL, diffuse large B cell lymphoma; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; SD, stable disease; TCL, T cell lymphoma.

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Table 5 |

Summary of trials involving BET inhibitors

Drug	Trial phase (n)	Lymphoma subtype	Outcomes	Common grade ≥3 adverse events (% of patients)	Year	Refs or ClinicalTrials.gov identifier
INCB057643	I/II (5)	Advanced-stage malignancies (4 FL and 1 DLBCL)	FL: 1 CR and 2 SD	In 16% in total	2017	116
Birabresib	I (33)	DLBCL or indolent Lymphomas	DLBCL: CBR 47%	Thrombocytopenia (58); anaemia (27); neutropenia (22)	2016	114
INCB054329	I (4)	Advanced-stage malignancies	Not reported for lymphoma	Thrombocytopenia (9); neutropenia (4)	2017	118
MoLibresib	I (27)	NHL	ORR 18.5%; TCL: ORR 50%	Thrombocytopenia (70); hyperbilirubinemia (7); anaemia (7)	2018	119
CPI-0610	I (44)	DLBCL, FL and HL	2 CR and 12 with clinical benefit	NR	2015	115
CC-90010	I	NHL	Study ongoing	—	2017	NCT03220347

BET, bromodomain and extra-terminal domain protein; CBR, clinical benefit rate; CR, complete response; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; SD, stable disease; TCL, T cell lymphoma.