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Review

Epigenetic targets in B- and T-cell lymphomas: latest developments

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Marcelo Lima Ribeiro, Salvador Sánchez Vinces, Laura Mondragon and Gael Roué

***Abstract*:** Non-Hodgkin's lymphomas (NHLs) comprise a diverse group of diseases, either of mature B-cell or of T-cell derivation, characterized by heterogeneous molecular features and clinical manifestations. While most of the patients are responsive to standard chemotherapy, immunotherapy, radiation and/or stem cell transplantation, relapsed and/or refractory cases still have a dismal outcome. Deep sequencing analysis have pointed out that epigenetic dysregulations, including mutations in epigenetic enzymes, such as chromatin modifiers and DNA methyltransferases (DNMTs), are prevalent in both B- cell and T-cell lymphomas. Accordingly, over the past decade, a large number of epigenetic-modifying agents have been developed and introduced into the clinical management of these entities, and a few specific inhibitors have already been approved for clinical use. Here we summarize the main epigenetic alterations described in B- and T-NHL, that further supported the clinical development of a selected set of epidrugs in determined diseases, including inhibitors of DNMTs, histone deacetylases (HDACs), and extra-terminal domain proteins (bromodomain and extra-terminal motif; BETs). Finally, we highlight the most promising future directions of research in this area, explaining how bioinformatics approaches can help to identify new epigenetic targets in B- and T-cell lymphoid neoplasms.

Keywords: BET inhibitors, bioinformatics, clinical testing, DNMT, drug combination, epigenetics, EZH2, HAT, HDAC, non-Hodgkin's lymphoma

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Correspondence to:
Gael Roué
Lymphoma Translational Group, Josep Carreras Leukaemia Research Institute, IJC. Ctra de Can Ruti, Camí de les Escoles s/n, 08916 Badalona, Barcelona, Spain.
groue@carrerasresearch.org

Laura Mondragon
T Cell Lymphoma Group, Josep Carreras Leukaemia Research Institute, IJC. Ctra de Can Ruti, Camí de les Escoles s/n, 08916 Badalona, Barcelona, Spain.
lmondragon@carrerasresearch.org

Marcelo Lima Ribeiro
Lymphoma Translational Group, Josep Carreras Leukaemia Research Institute, Badalona, Spain
Laboratory of Immunopharmacology and Molecular Biology, Sao Francisco University Medical School, Braganca Paulista, Brazil

Salvador Sánchez Vinces
Laboratory of Immunopharmacology and Molecular Biology, Sao Francisco University Medical School, Braganca Paulista, Brazil

Introduction

Non-Hodgkin's lymphoma (NHL) is a common type of hematological malignant tumor, composed of multiple subtypes that originate from B lymphocytes, T lymphocytes, and natural killer (NK) cells. These entities are sub-divided into distinct categories based on the differentiation stage of the malignant cells and on the presence of specific genetic alterations, being diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), T-cell lymphoma (TCL), and NK-T-cell lymphoma (NKTCL) the most common subtypes.

Characteristics of B-NHL

At the origin of roughly 90% of the cases of lymphoma, B-NHLs comprise a heterogeneous group of lymphoid neoplasms originated from either mature or immature B cells, the diagnosis of which is based on morphological, immunophenotypic, and genetic features, and most of them being dictated by the cell of origin[1] (see Figure 1). B-NHL subtypes range in their severity from well-controlled, indolent diseases, to extremely aggressive forms with urgent unmet medical needs that still require the development of novel therapeutic options.

The most common B-NHL subtype is DLBCL, which accounts for 25–35% of all cases. This aggressive disease is characterized by a heterogeneous molecular pathogenesis that can lead to different clinical characteristics.[2] Despite high-throughput sequencing having recently

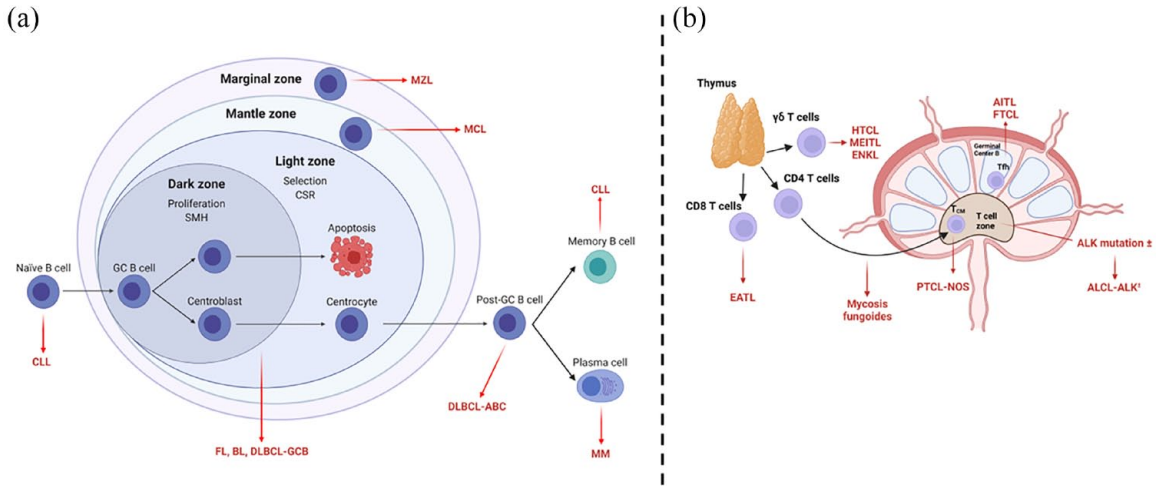

Figure 1. B- and T-cell lymphomagenesis.
(a) Emergence of the main subtypes of B-cell non-Hodgkin's lymphoma (B-NHL). Naive B cells first participate in the formation of germinal centers (GCs) upon interacting with antigens. In the dark zone, centroblasts prolife and undergo somatic hypermutation (SMH), while in the light zone, centrocytes are sorted on B-cell receptor (BCR)-based affinity and undergo class switch recombination (CSR). GC cells are the normal counterparts of follicular lymphoma (FL), Burkitt's lymphoma (BL), and diffuse large B-cell lymphoma (DLBCL) of GC subtype (GCB). DLBCL of the activated B-cell subtype (ABC) originates from post-GC cells, and multiple myeloma (MM) arises from differentiated plasma cells. Chronic lymphocytic leukemia (CLL) can originate from either naïve or differentiated memory B cells. Mantle cell (MCL) and marginal zone lymphoma (MZL) arise from B cells located in the mantle and marginal zone of lymphoid follicles, respectively. (b) Intrinsic or extrinsic factors may favor TCLs pathogenesis through immune evasion, alterations in T cell receptor (TCR) signaling pathways, activation of transcription factors and proto-oncogenes, that favor the emergence of different entities during T cell differentiation from the thymus to lymph nodes.
AITL, angioimmunoblastic T-cell Lymphoma; ALCL-ALK+, anaplastic large cell lymphoma, ALK-positive; EATL, enteropathy-associated T-cell lymphoma; ENKL, extranodal natural killer/T-cell lymphoma; FTCL, follicular T-cell lymphoma; HTCL, hepatosplenic γδ T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T cell lymphoma; PTCL, peripheral T-cell lymphoma.

identified up to seven genetic subtypes,[3–5] gene expression profiling (GEP)-mediated identification of germinal center B-cell (GCB), activated B-cell (ABC), and unclassifiable subgroup[6] remains widely used in the clinical management of these patients. Patients with ABC-DLBCL or genetic alterations in *MYC* and *BCL2* and/or *BCL6*, called double hit (DHLs) or triple hit lymphomas (THLs), have generally a poor survival prognosis.

The second most common B-NHL is FL, another germinal center (GC)-derived malignancy that accounts for 20% of all cases. FL is characterized by the t(14;18)(q32;q21) translocation that leads to the overexpression of the *BCL2* anti-apoptotic gene.[7] FL represents a paradigm of dependence on the microenvironment. Seminal microarray studies in lymph node (LN) biopsies from the Leukemia and Lymphoma Profiling Project (LLMPP) series established for the first time that FL prognosis was not given by the tumor cell *per se* but by the composition of non-malignant cells.[8] Although the clinical course is mostly indolent, about 20% of patients may relapse or progress to a transformed (more aggressive) form of FL (t-FL).

Burkitt lymphoma (BL) is a third GC-derived lymphoma, which represents 1–5% of all NHL, and which is characterized by the deregulation of *MYC* due to translocations such as t(8;14)(q23;q32). Three subtypes have been described, namely endemic, sporadic, and immunodeficiency-associated form, which is mostly found in patients infected with the human immunodeficiency virus (HIV).[9]

Originated from mature B-cells of the mantle zone of the LN, mantle cell lymphoma (MCL) accounts for 3–10% of B-NHL, being the t(11;14)(q13;q32) translocation and the expression of the

cell cycle regulator cyclin D1 (*CCND1*), physiologically undetectable in normal B cells, the main characteristics of the disease. Supporting the notion that t(11;14) translocation is an epigenetic event, the Eμ and 3′ Cα cis IgH enhancer elements and the regions upstream of the *CCND1* gene are hypomethylated on the translocated allele, and histones surrounding the translocation have shown hyperacetylation.[10] MCL is also characterized by a high genomic instability with a high number of secondary genetic alterations involving cell cycle regulation, DNA damage response, cell death, nuclear factor kappa B (NF-κB), or epigenetic modifiers, with a median number of six secondary events. *ATM, CCND1, TP53*, and *RB1* are among the most recurrently mutated genes.[11] MCL has poor prognosis due to diagnosis often at a disseminated stage and an aggressive clinical evolution.

Physiopathology of T-cell lymphoma

Contrasting with B-cell lymphoma, T-cell lymphomas (TCLs) are characterized by numerous T-cell subsets, functional plasticity of which depends on the microenvironment. As a result, appearance of features that do not fit with the cell originating the tumor is common,[12–14] thereby preventing tumor classification and a proper diagnosis of the disease and affecting the clinical management of the patients. Introduction of global GEP technologies are slowly improving our knowledge in the pathological origin of TCLs, but there is still room for improvement.

Mechanisms implicated in TCL development can be intrinsic and imply recurrent mutations leading to: (1) immune evasion, being the most clear example of the nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) oncogene, expressed in ALK+ anaplastic large cell lymphoma (ALCL), which regulates the expression of the immunosuppressive protein programmed death-ligand 1 (PD-L1);[15] (2) alterations within T cell receptor (TCR) signaling pathway, such as mutations affecting the RhoA GTPase[16] or gain-of-function mutations in regulators of T-cell activation and function such as phospholipase C gamma 1 (*PLCG1*), phosphatidylinositol-3 kinase (PI3K) family, catenin beta-1 (*CTNNB1*), *CD28*, caspase recruitment domain family member 11 (*CARD11*), vav guanine nucleotide exchange factor 1 (*VAV1*), interferon regulatory factor 4 (*IRF4*), mainly observed in peripheral T-cell lymphomas (PTCLs), including adult T-cell leukemia/lymphoma (ATLL) and angioimmunoblastic T-cell lymphoma (AITL);[14,17] (3) the implication of whole families of genes or signaling pathways, such as the PI3K-AKT-mTOR axis found to be constitutive activated during TCL pathogenesis,[18,19] or the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, in which mutations in kinases and transcription activators such as *STAT3* or *STAT5B, JAK1, JAK3*, or *JAK5*, may not directly induce the lymphoma, but rather confer clinical aggressiveness due to increased cytokine-dependent signaling and consequent promotion of cell growth, immune response, tumor metabolism, and cell death blockade;[17,18,20,21] (4) alteration in transcription factors such as activator protein-1 (AP-1), musculoaponeurotic fibrosarcoma (MAF) and basic leucine zipper ATF-like (BAF) transcription factor families, which are commonly involved in cutaneous T-cell lymphoma (CTCL) and CD30 + PTCL development, by activating the expression of the T-cell growth and survival genes, *MYC* and *CD30*, or driving the production of pro-tumoral cytokines;[22,23] (5) PI3K-AKT-mTOR-mediated deregulation or glutamine, nucleotides, and lipid metabolism, and consequent enhancement of lymphoma cell growth;[24,25] (6) altered mitochondrial functions, including a STAT3-mediated deregulation of mitochondrial respiration,[26,27] and as recently described, a glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) overexpression-driven development of AITL-like disease;[28] and (7) epigenetic deregulation, leading to the silencing of tumor-suppressor genes or the overexpression of several proto-oncogenes (see Figure 1).

Beside these intrinsic mechanisms, a number of extrinsic factors also favor TCLs pathogenesis, such as pro-inflammatory cytokines and chemokines, which build a microenvironment that promote and sustain the survival of the tumor cells, or oncogenic Epstein–Barr virus (EBV)- and T-cell lymphotropic virus type 1 (HTLV-1)-derived viral factors that promote oncogenesis from indolent cutaneous lymphoproliferative diseases to extremely aggressive TCLs such as ATLL.[29,30]

Epigenetic deregulations in B- and T-cell lymphoma

A high level of alteration in chromatin state and a frequent deregulation of several epigenetic modulators, are common hallmarks that have been highlighted in most B-NHL subtypes in early 2000s.

Modification of DNA methylation patterns (either hypo- or hyper- DNA methylation status) have been associated for years to somatic mutations in epigenetic regulators of DNA methylation and to a generally repressed conformation of the chromatin in B-NHL.[31,32] Loss-of-function (LOF) mutations (truncation or frameshift mutations) affecting the SET domain of the histone-lysine N-methyltransferase 2D (*MLL2*/*KMT2D*) gene is the most frequently epigenetic alteration in DLBCL and FL, occurring, respectively, in about 30% and 90% of the cases, respectively. Inactivation of *KMT2D* leads to the expansion of GC-derived B cells, impedes class switch recombination and cooperates with the deregulation of *BCL2* to increase the incidence of tumors, in association with reduced H3K4 methylated levels.[33–38]

While LOF and/or deleterious mutations in the CREB binding protein (*CREBBP*) and E1A binding protein 300 (*EP300*) coding for two histone acetyltransferases (HATs) were detected in about 40% of DLBCL and FL cases,[35,39] these two entities also share the presence of point mutations in the myocyte enhancer binding factor 2B (*MEF2B*) gene codifying for a HAT recruiter (13% of GCB-DLBCL cases and 15% of FL patients).[39] From one side, mutant CREBBP and EP300 proteins are deficient in acetylating BCL6 and p53 leading, respectively, to constitutive oncogenic properties and to decreased tumor suppressor activity, thus favoring an increased tolerance for DNA damage mediated by impaired apoptosis triggering and cell cycle arrest.[40] In parallel, *MEF2B* mutations decrease the transcriptional activity of this factor, thereby lowering B-cell lymphoma 6 (BCL6) expression levels and leading to decreased activity of the *TGFB1* tumor suppressor gene, encoding for transforming growth factor β, together with an increased expression of MYC. The global biological impact of these modifications consists in a reduced inhibition of chemotaxis and in the promotion of B-cell lymphomagenesis.[41]

In a lower extent, activating mutations of the enhancer of zeste homolog 2 (*EZH2*) histone methyltransferase (*HMT*) gene are specifically found in GC-derived NHL, such as GCB-DLBCL (22% of the patients) and FL (7% of the patients)[42,43] (see Figure 2). Expression of the EZH2^{Y641F} mutant was associated with the reprogramming of the immunological niche, a process by which the supporting activity of T cells toward GC-B cell development becomes ensured by follicular dendritic cells (FDCs).[44] Finally, despite genes coding for histone deacetylases (HDACs) remained unmutated in B-NHL patients, an overexpression of *HDAC1*, *HDAC2*, and *HDAC6* with a consequent global decrease in the activity of the transcription machinery, has been reported in DLBCL cases.[45] In particular, *HDAC6* exerts a crucial role in the response to proteotoxic stress, as it orchestrates the acetylation-dependent stability of heat shock protein of 90 kD (HSP0) and the recruitment of misfolded protein cargo to dynein motors for their transport to intracellular aggresomes.[46]

TCLs present a similar mutation spectrum of epigenetic genes than B-cell lymphoma, which includes missense mutations, concomitantly to a general chemo-resistant phenotype.[14,47] Genetic alterations in DNA methylation genes affect Tet methylcytosine dioxygenase 2 (*TET2*), DNA methyl transferase 3 A (*DNMT3A*) and isocitrate dehydrogenase 2 (*IDH2*). These alterations are mainly found in T follicular helper (Tfh) cell-derived PTCLs and constitute the hallmark of AITL, a disease where the three genes are affected simultaneously.[48] TET2 and DNMT3A deregulations are also found in CTCL.[47] Similar mutations of *TET2* are found in the hematopoietic stem and progenitor cells (HSPCs) of some AITL patients. Notwithstanding, none of these mutations will lead to lymphoma appearance, but will rather favor a premalignant status characterized by a disrupted homeostasis within the hematopoietic stem/progenitor compartment, being the malignant transformation achieved upon the acquisition of further defects in key genes such as *RHOA, PLCG1*, or *NOTCH2*.[49]

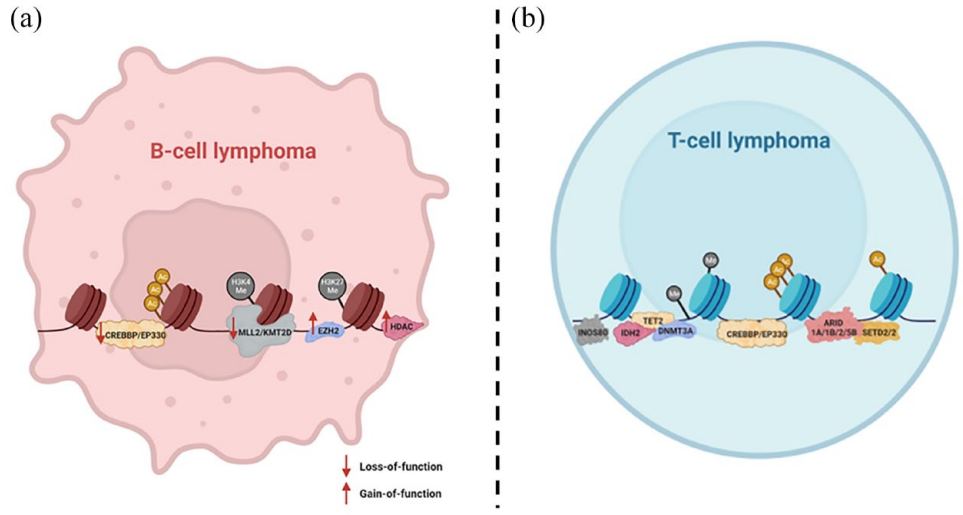

Figure 2. Alterations of chromatin states in B- and T-cell lymphoma.
(a) Loss-of-function mutations affecting epigenetic regulators such as the SET domain of the histone-lysine N-methyltransferase 2D (*MLL2/KMT2D*), CREB binding protein (*CREBBP*), and E1A binding protein 300 (*EP300*) genes, as well as activating mutations of the enhancer of zeste homolog 2 (*EZH2*) histone methyltransferase (*HMT*) gene and the overexpression of *HDAC1/2/6* have been reported in B-cell lymphoma cases. (b) Genetic alterations in DNA methylation genes affect Tet methylcytosine dioxygenase 2 (TET2), DNA methyl transferase 3 A (DNMT3A) and isocitrate dehydrogenase 2 (IDH2), as well as in chromatin remodelers such as *SETD2, SETD1B, INO80, ARID1B, ARID2, ARID5B, SMARCC1* and histone acetylation genes such as *EP300/CREBBP* are found in T-cell lymphoma.

Modifications in chromatin remodelers such as SET domain containing 2 (*SETD2*), *INO80*, involved in DNA repair and cell cycle regulation, and AT-Rich Interaction Domain 1B (*ARID1B*), have been found in up to 62% of hepatosplenic γδ T-cell lymphoma (HTCL) patients.[50] *SETD2*, which acts as a tumor suppressor gene, was the most silenced gene in HTCL and is mutated in monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). Loss of *SETD2* has been further associated with increased cell growth, altered expression of cell cycle genes, and compromised DNA damage response and repair.[51] *ARID2, ARID1B, SETD1B* mutations are also found in PTCL-NOS.[52] *ARID1A, ARID5B*, and *SMARCC1* mutations are present in CTCL.[53] Finally, *ARID1A* mutations have been detected in NKTCL.[54] While *ARID1A* expression is sufficient to suppress cellular proliferation and tumor growth in mouse models of cancers, in-frame mutations of this gene lead to the nuclear retention of this tumor suppressor, due to its increased degradation and incapacity to stimulate the expression of the cell cycle inhibitor gene, *CDKN1A*.[55]

Defects in histone methylation have been associated to mutations in *KMT2C, KM2D*, and *KDM6A* genes in PTCL-NOS.[52] NKTC lymphoma harbors mutations in *KMT2D, EZH2*, and also in ASXL transcriptional regulator 3 (*ASXL3*) genes, a phenomenon linked to altered histone deubiquitination.[54] Histone acetylation genes such as *EP300* and *CREBBP* are mutated in PTCL-NOS[52] (see Figure 2). Deregulated expression and/or activity of these epigenetic writers, lead to genome-wide DNA and histone modification pattern alterations, modifying the chromatin structure, and thereby leading to cancer development.[56]

Importantly, HDACs have become a promising therapeutic targets (see below) in the context of some TCLs such as CTCL, through their role in the silencing of different BCL-2 proapoptotic family members and in the regulation of autophagy.[57]

Role of epigenetic drugs in B- and T-cell lymphoma

DNA methylation inhibitors

DNA methyltransferases (DNMTs) family includes three major members that have functional methylation activities, namely DNMT1, which mediates maintenance methylation during cell division, and DNMT3A and DNMT3B, that regulate *de novo* DNA methylation.[58,59] Accumulating evidences have shown that DNMTs regulation of methylation have an important role in normal hematopoiesis.[60,61] On the contrary, aberrant methylation is a key molecular event on the development of hematological malignancies. Indeed, hypermethylation of CDKN2A/p16 is associated with aggressive forms of B-NHL, and can drive progression of T-cell malignancies.[62,63] Considering that an altered methylation pattern is frequently observed in most types of cancers, including B- and T-cell lymphoma, the development of epigenetic drugs to restore methylation levels seems to be an interesting strategy for the treatment of these diseases.[64]

In the 1970s, the nucleoside analogs 5-azacytidine and 5-aza-20-deoxycytidine (or decitabine) appeared in the clinic as a chemotherapeutic option against acute leukemia. Mechanistically, these cytidine analogs are incorporated into DNA, promoting an irreversible blockage of DNMT1, which consequently leads to global demethylation.[65–67] Although azacytidine and decitabine were considered as promising chemotherapeutic agents, the early clinical trials showed a disappointing response and a pronounced toxicity in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) patients.[68–70] Subsequently, *in vitro* data indicated that low doses of azacytidine can induce a decrease in DNA methylation level, supporting its use as an epigenetic drug.[71] Given the remarkable improvement of the overall survival (OS), and more generally the excellent clinical response of MDS patients to this agent, azacytidine became in 2004 the first drug approved by Food and Drug Administration (FDA) for this indication.[72,73] In B-NHL patients, only two phase I studies using decitabine as a single agent have been completed so far.[74,75] However, until now, the use of DNMT inhibitors (DNMTis) as monotherapy yielded disappointing results in lymphoid malignancies.[76] Currently, azacytidine and decitabine are being evaluated mostly in combination with other drugs in approximately 95 active clinical trials involving B- and T-cell lymphoma patients. In this review, we will present clinical data from completed or terminated clinical trials (see Table 1).

Azacytidine was evaluated, in a phase II clinical study (NCT01998035), in combination with the HDAC inhibitor (HDACi) romidepsin. This combination was safe and demonstrated to be an effective regimen for treatment-naïve patients and R/R PTCL cases. The reported overall response (ORR) and complete response (CR) rates were 61% and 48%, respectively, therefore

Table 1. Clinical evaluation of epidrug and epidrug-based combination therapies in B- and T-cell lymphoma.

Targets	Drug/Regimen	Trial ID	Phase/ Status	No. of patients	Diseases	Response	Toxicity	Study
DNMT	Decitabine + Tetrahydrouridine	NCT02846935	I Completed	7	R/R- HL, DLBCL, PTCL, AITL	OR 57%	Grade 3–4 AEs: TP 100%	Hill *et al.*[77]
DNMT	Azacitidine + Vorinostat + Gemcitabine + Busulfan + Melphalan	NCT01983969	I/II Completed	61	DLBCL, HL, T-cell NHL, FL, MCL	EFS 75%	Not serious AEs: 100%	Clinical trial[78]
DNMT	Azacitidine + Lenalidomide	NCT01121757	II Terminated	9	R/R – FL, MZL	CR 17%	Grade 3–4 AEs: Toxicities 100%, TP 33%	Clinical trial[79]
DNMT	Azacitidine + Vorinostat	NCT01120834	I/II Completed	18	R/R DLBCL	ORR 6.7%	Grade 3–4 AEs: Toxicities 100%, Anemia 7%, TP 33%	Clinical trial[80]
DNMT	Azacitidine + RCHOP	NCT01004991	I/II Completed	12	DLBCL	CR 91.7%	Grade 3–4 AEs: NP 100%	Clinical trial[81]
DNMT	Azacitidine + RCHOP	NCT02343536	I Completed	52	DLBCL, FL, tFL	ORR 94.9%, CR 88.1% 1- and 2-year PSF 84.1% and 78.6%	Grade 3–4 AEs: NP 62.7%, febrile NP 25.4%	Martin *et al.*[82]
DNMT	Azacitidine + Romidepsin	NCT01998035	I/II Terminated	23	R/R–NHL, HL	ORR 61% CR 48%	Grade 3–4 AEs: TP 48%, NP 40%, LP 32%, anemia 16%	Falchi *et al.*[83] O'Connor et al.[84]
DNMT	Azacitidine + Avelumab + Utomilumab +	NCT02951156	III Terminated	9	R/R DLBCL	ORR 0	No dose-limiting toxicities were reported	Hawkes *et al.*[85]
DNMT	Vincristine + Prednisone + Etoposide + Thioguanine, Cytarabine + Asparaginase + Methotrexate	NCT00002590	II Completed	86	Children with lymphoma	5-year OS 80% 5-year EFS 68%	Grade 4 AEs: NP 82%, TP 66%, anemia 38%, hepatotoxicity 4%	Lowe *et al.*[86]
HDAC	Belinostat	NCT00274651	II Terminated	53	R/R cutaneous and peripheral TCL	ORR 25% (PTCL) and 14% (CTCL)	Grade 3–4 AEs: 77%	Johnston *et al.*[87]
HDAC	Belinostat + CHOP	NCT01839097	II Completed	23	PTCL first line	ORR 86% CR 71%	No additional toxicity was observed with the combination SAEs 43%	Johnston *et al.*[88]
HDAC	Belinostat	NCT00865969	II Completed	129	R/R PTL	ORR 25.8%	Grade 3–4 AEs 47.29%	Campbell and Thomas[89]
HDAC	Panobinostat + Bortezomib	NCT00901147	II Completed	25	R/R–PTL lymphoma or NK/TCL	ORR 43% CR 22%	Grade 3–4 AEs: TP 68%, NP 20%, diarrhea 20%	Tan *et al.*[90]
HDAC	Panobinostat	NCT01523834	II Completed	35	DLBCL	ORR 17.1% CR 11.4%	Grade 3–4 AEs: TP >5%	Duvic *et al.*[91]
HDAC	Panobinostat	NCT00425555	II Completed	139	Refractory CTL	PR 21.6% CR 0.7%	Grade 3–4 AEs: 28.8	Duvic *et al.*[91]
HDAC	Panobinostat	NCT01034163	III Completed	41	HL	Not Completed 100%	Grade 3–4 AEs: TP 27%, NP 27%, diarrhea 89%	Clinical trial[92]

(Continued)

Table 1. (Continued)

Targets	Drug/Regimen	Trial ID	Phase/ Status	No. of patients	Diseases	Response	Toxicity	Study
HDAC	Panobinostat + Everolimus	NCT00967044	I/II Completed	31	R/R lymphoma	ORR 10% (TCL, MCL, HL) ORR 43% (HL) CR 15% (HL)	Grade 3–4 AEs: TP 64%, NP 47%, anemia 20%	Oki *et al.*[93]
HDAC	Valproic acid + RCHOP	NCT01622439	I/II Completed	495	DLBCL	1-year PFS 97.0%, 2-year PFS 84.7% 1-year OS 100% 2-year OS 96.8%	No toxicity reported	Drott *et al.*[94]
HDAC	Abexinostat	NCT00724984	I/II Completed	87	R/R lymphoma, NHL, and CLL	ORR 28% CR 5%	Grade 3 AEs: TP 80%, NP 27%, anemia 12%	Evens *et al.*[95] and Ribrag et al.[96]
HDAC	Mocetinostat	NCT00358982	II Terminated	51	R/R HL	PR 30% CR 10%	Grade 3–4 AEs: TP 21.5%, NP 13.7%	Younes *et al.*[97]
HDAC	Fimepinostat + Rituximab, Venetoclax	NCT01742988	I Completed	44	R/R DLBCL, MYC-altered DLBCL	DLBCL ORR 37% CR 11.2% PR 14.6 MYC-altered DLBCL ORR 64% CR 36% PR27%	Grade 3–4 AEs: TP 20%, NP 7%	Younes *et al.*[98]
HDAC	Vorinostat + Rituximab + Combination chemotherapy	NCT00601718	I/II Completed	29	R/R lymphoma or untreated TNHL, MCL	ORR 70% CR 30%	Grade 3 AEs: gastrointestinal toxicity 33%	Budde *et al.*[99]
HDAC	Vorinostat + Niacinamide + Etoposide	NCT00691210	I Completed	40	HL, NHL	ORR 24%, CR 10% PR 14% 7.5%. Twelve patients achieved SD (57%).	Grade 3–4 AEs: 27.5%	Amengual *et al.*[100]
HDAC	Vorinostat + Chemotherapy + Rituximab	NCT01193842	I/II Completed	86	HIV-related DLBCL or other aggressive BCL	CR 74% *versus* 68% for EPOCH *versus* EPOCH-vorinostat	Grade 4 AEs: NP (47% and 20%), LP (20% and 7%), and TP (29% and 2%) for vorinostat-EPOCH and EPOCH alone, respectively	Ramos *et al.*[101]
HDAC	Vorinostat + Fludarabine phosphate + Cyclophosphamide + Rituximab	NCT00918723	I/II Completed	40	CLL 32, SLL 8	ORR 91% CR 74%, PR 11%	Grade 4 AEs: hematologic 36%, electrolyte abnormalities 9%, gastrointestinal 8%, and cardiovascular 6%	Shadman *et al.*[102]
HDAC	Vorinostat + Cladribine + Rituximab	NCT00764517	I/II Completed	57	MCL, R/R-CLL, or BNHL	ORR 39% in R/R patients, ORR 97%, CR 80% in MCL	Grade 2–3 AEs: NP 67%, TP 42%, anemia 14%	Spurgeon *et al.*[103]
HDAC	Vorinostat + Bortezomib	NCT00992446	II Completed	27	NHL	ORR 74% CR 42%	Grade 4 AEs: NP 30%	Holmberg *et al.*[104]

(Continued)

Table 1. (Continued)

Targets	Drug/Regimen	Trial ID	Phase/ Status	No. of patients	Diseases	Response	Toxicity	Study
HDAC	Vorinostat	NCT00253630	II Completed	35	R/R-FL, MZL, MCL	FL-ORR 47%, CR 23.5%, PR 23.5%, MZL-ORR 22%, CR 11%, PR 11%	Acceptable safety profile	Kirschbaum *et al.*[105]
HDAC	Vorinostat	NCT00875056	II Completed	50	R/R-FL, BNHL, MCL	FL-ORR 49%, CR 10%, PR 31%.	Grade 3–4 AEs: TP 93%, NP 68%	Ogura *et al.*[106]
HDAC	Vorinostat + Rituximab + Cyclophosphamide + Etoposide + Prednisone	NCT00667615	I/II Completed	30	R/R DLBCL	ORR 57%, CR 35%, PR 22%	Grade 3–4 AEs: LP 90%, leucopenia 66%, NP 52%, TP 41%, and anemia 31%	Straus *et al.*[107]
HDAC	Vorinostat + Rituximab	NCT00720876	II Completed	28	iNHL	ORR 41%, CR 27%, PFS 29.2 months	Grade 3–4 AEs: Fatigue 32%, LP 25%	Chen *et al.*[108]
HDAC	Chidamide + CHOP	NCT02809573	I/II Completed	383	PTCL	ORR 39% as chidamide monotherapy, ORR 51% combined therapy	Grade 3–4 AEs: TP 18.1%, NP 12.6%, anemia 7.1%, and fatigue 5.5%	Shi *et al.*[109]
HDAC	Romidepsin	NCT00007345	II Completed	71	TCL, PTCL	ORR 34%, CR 20%	Grade 3–4 AEs TP 47%, leucopenia 47%, granulocytopenia 45%, anemia 40%, LP 17%	Piekarz *et al.*[110]
HDAC	Romidepsin + Alisertib	NCT01897012	I Completed	25	R/R aggressive BCL and TCL	ORR 28% CR 12%	Grade 3–4 AEs: TP 40%, NP 24%, anemia 28%	Strati *et al.*[111]
HDAC	Romidepsin + 5-azacitidine	NCT01998035	I/II Terminated	25	PTCL, FL	PTCL ORR 61%, CR 48%, FL ORR 80%, CR 67%	Grade 3–4 AEs: TP 48%, NP 40%, LP 32%, and anemia 16%	Falchi *et al.*[83]
HDAC	Romidepsin	NCT00106431	II Completed	96	R/R CTCL	ORR 34%, CR 8%, DOR of 15.0 months	AEs: 96.2%	Duvic *et al.*[112]
HDAC	Romidepsin	NCT01456039	I/II Completed	40	R/R PTCL	ORR 43%, CR 25%, DFS 5.6 months	Grade 3–4 AEs: TP 98%, LP 88%, leukopenia 84%, NP 80%, and anemia 34%	Maruyama *et al.*[113]
HDAC	Romidepsin	NCT00426764	II Completed	131	Progressive or relapsed PTCL	ORR 25%, CR 15%, DOR 28 months	Grade 3–4 AEs: TP 40%	Foss *et al.*[114]
HDAC	Romidepsin + Gemcitabine	NCT01822886	II Completed	20	R/R PTCL	ORR 30%, CR 15%, 2-year OS 50%, PSF 11.2%	Grade 3 AEs: TP 60%, NP 50%, anemia 20%	Pellegrini *et al.*[115]
HDAC	Entinostat	NCT00866333	II Terminated	59	R/R HL	PR 12%	Grade 3 AEs: TP 63%, anemia 47%, NP 41%, leukopenia 10%,	Tan *et al.*[116]
HDAC	Ricolinostat	NCT02091063	I Completed	21	TCL, HL, PTLD, FL, DLBCL, CTCL	56 days of disease stabilization for 50% of patients	Grade 3–4 AEs: anemia 9.5% and hypercalcemia 9.5%	Amengual *et al.*[117]

(Continued)

Table 1. (Continued)

Targets	Drug/Regimen	Trial ID	Phase/ Status	No. of patients	Diseases	Response	Toxicity	Study
EZH2	Tazemetostat	NCT03009344	I Completed	10	R/R NHL	ORR 57%, CR 14.3%	Grade 3–4 AEs: TP and dysgeusia 42.9%	Munakata *et al.*[118]
EZH2	Tazemetostat	NCT03456726	II Completed	165	R/R BNHL $EZH2^{mut}$	ORR 40% (DLBCL $EZH2^{mut}$) 18% in patients DLBCL $EZH2^{wt}$; ORR 63% (FL $EZH2^{mut}$) 28% (FL $EZH2^{wt}$)	Grade 3–4 AEs: 18%	Izutsu *et al.*[119]
EZH2	Tazemetostat + Atezolizumab	NCT02220842	I Completed	43	R/R-FL and DLCBL	ORR 16%, CR 5%, PR 12%	Grade 3–4 AEs: anemia 12%, NP 9%, TP 9%	Palomba *et al.*[120]
EZH2	Tazemetostat	NCT03010982	I Completed	3	BCL	Not reported	Grade 3–4 AEs: 66%	Argon *et al.*[121]
EZH2	Tazemetostat + Fluconazole + Omeprazole + Repaglinide	NCT03028103	I Completed	16	BCL	ORR 15.4%, CR 7.7%, PR 7.7%	Grade 3–4 AEs: 25% tazemetostat-related	Clinical trial[122]
EZH2	Tazemetostat	NCT01897571	I/II Completed	99	DLBCL $EZH2^{wt}$ and mut	ORR 69% ($EZH2^{mut}$) and 35% ($EZH2^{wt}$), CR 13% ($EZH2^{mut}$) and 4% ($EZH2^{wt}$)	Grade 3–4 AEs: TP 3%, NP 3%, anemia 2%	Morschhauser *et al.*[123]
EZH2	GSK2816126	NCT02082977	I Terminated	20	R/R DBCL, tFL and NHL	Insufficient evidence of clinical activity	Grade 3–4 AEs: 32%	Yap *et al.*[124]
BET	Birabresib	NCT01713582	I Completed	17	DLCBL	DOR 17%	Grade 3–4 AEs: TP 58%	Amorim *et al.*[125]
BET	RO6870810 + Venetoclax + Rituximab	NCT03255096	I Completed	39	DLBCL	ORR 38.5%, CR 20.5, PR 17.9%	Grade 3–4 AEs: NP 28%, anemia and TP 23% each	Dickinson *et al.*[126]
BET	INCB057643	NCT02711137	I/II Terminated	16	Lymphoma	PR 25%, CR 12.5%	Grade 3–4 AEs: TP 32%	Falchook *et al.*[127]
BET	INCB054329	NCT02431260	I/II Terminated	4	Lymphoma	Not reported	Grade 3–4 AEs: TP 33%	Falchook *et al.*[127]
BET	CPI-0610	NCT01949883	I Completed	64	Progressive lymphoma	ORR 7.8%, CR 3%	Grade 3–4 AEs: TP 45%	Blum *et al.*[128]
BET	FT-1101	NCT02543879	I Completed	10	NHL	SD 33%	Grade 3–4 AEs: pleural effusion 20%	Patel *et al.*[129]

AEs, adverse effects; AITL, angioimmunoblastic T-cell lymphoma; BCL, B-cell lymphoma; BET, bromodomain and extra-terminal motif; CLL, chronic lymphocytic leukemia; CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; HDAC, histone deacetylase; MCL, mantle cell lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NA, not available; NHL, non-Hodgkin's lymphoma; NP, neutropenia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; R/R, relapsed and refractory; SD, stable disease; TP, thrombopenia.

supporting the use of oral azacytidine and romidepsin in both first-line and R/R settings, including as a bridging therapy.[83,84] The mechanism of action underlying this combinatorial activity might be related to the enhanced expression of several cancer-testis antigens involved in the promotion of tumor immunogenicity.[130] The combination of azacytidine with avelumab (anti-PD-L1 antibody) and utomilumab (4-1BB/CD137 agonist) was evaluated in R/R DLBCL patients. However, due to insufficient clinical activity, the study was prematurely discontinued.[85]

High levels of cytidine deaminase (CDA) were reported to decrease the half-life of decitabine and azacytidine.[131,132] Based on this observation, the effect of tetrahydrouridine (THU), a CDA inhibitor, was evaluated in relapsed B- and T-cell malignancies (NCT02846935, see Table 1). The overall results indicated a significant reduction in tumor burden, together with subjective improvements in symptoms in 57% of the patients; however, these effects were lost upon treatment interruptions consequent to neutropenia.[77] Decitabine was also evaluated in treatment-naïve DLBCL patients prior to receiving R-CHOP. The results from this clinical trial (NCT02951728) indicated that 86% of the patients responded to the treatment, with 74% CR and 11% PR.[133]

Besides the above-described FDA-approved DNA methylation inhibitors, over the last decades several new DNMTis have been developed, showing promising results in pre-clinical models of hematological disorders. Among them it is worth to highlight the thioguanine [2-amino-1,7-dihydro-6H-purine-6-thione (6-tG)] that was FDA-approved for the treatment of AML patients.[134] Thioguanine is currently included in the NHL-BFM90 protocol.[135] The main findings reported by the large European network applying this protocol for the management of childhood and adolescent NHL, indicated that the 5-year event-free survival (EFS) was in the range 82–90% (NCT00275106 and NCT00004228, respectively, see Table 1), while 5-year OS was in the range 87–96%.[136]

HDAC inhibitors

As commented above, HDACs play a crucial role in the control of cell proliferation and growth, and angiogenesis. Accordingly, their overregulation promotes the occurrence of cancer, making the use of HDACis an efficient anticancer approach as these agents can trigger apoptosis, cell cycle arrest or even regulate the immune system.[57,137,138] Among the growing list of clinical trials exploring the possible therapeutic application of HDACi (see Table 1), the most successful ones are depicted below.

Vorinostat is a hydroxamic acid presenting inhibitory activity against classes I and II HDACs.[139] It has been used successfully in monotherapy in different subtypes of B-NHL, including FL and MCL,[106,140] and has been approved in 2006 by FDA to treat R/R CTCL.[141] This agent has also been tested with success in combination with multiple drugs such as the anti-CD20 monoclonal antibody rituximab, cladribine, fludarabine phosphate, cyclophosphamide, niacinamide, prednisone, or etoposide, for the treatment of indolent or aggressive B-NHL, including relapsed cases, in R/R CLL cases and in previously untreated T-NHL.[99,107,108,142–145]

Mocetinostat, a selective HDAC class I and IV inhibitor developed by Methylgene has also been approved for R/R CTCL,[146] while its therapeutic effect in the context of R/R Hodgkin's lymphoma (HL) managed to control the disease evolution in half of the treated patients.[97]

Belinostat is a sulfonamide-hydroxamic acid acting as a pan-HDACi[147] developed by TopoTarget. While its use has been approved for the treatment of R/R PTCL, it also demonstrated remarkable activity when assessed in CTCL patients.[87,89,148] Conversely, this agent exhibited poor activity as monotherapy in B-cell lymphoma patients. Interestingly, when combined to CHOP chemotherapeutic regimen as a first-line treatment for PTCL patient, it achieved a significant CR rate.[149]

Chidamide is a selective HDAC class I inhibitor[150] currently approved by the China Food and Drug Administration (CFDA) as a treatment for R/R PTCL, alone or in combination with CHOP regimen. A new clinical trial involving refractory extranodal NKTCL patients, and the results of which will be released in 2023, has already shown promising results.[151] Its applicability to the management of AITL is also under evaluation. Several clinical trials aiming at evaluating chidamide as a therapeutic strategy for B-NHL treatment alone or in combination with R-GDP, DICE, R-CHOP have been registered and are in recruiting processes.

Ricolinostat, a selective HDAC6 inhibitor,[152] exerted a synergic antitumor effect in combination with the BTK inhibitor ibrutinib, the alkylating agent bendamustine, the ALK inhibitor crizotinib and the proteasome inhibitor carfilzomib, in preclinical models of DLBCL and MCL, but possible translation into human subjects is still under evaluation.[57] In a clinical study including patients with R/R B/T-lymphomas, this agent harbored lower toxicity compared with other pan-HDACis and achieved the stabilization of half of the patients, although in the absence of CR or partial response (PR).[145]

Fimepinostat, which dually targets HDAC and PI3K, has been tested in combination with rituximab in relapsed DLBCL and MYC-altered DLBCL patients.[98,153] Response to treatment was achieved most notably in MYC-altered DLBCL (64% *versus* 37% in non-MYC-altered).

Romidepsin is a depsipeptide from bacterial origin able to inhibit Class I HDACs.[154] While its use has been approved for R/R CTCL and PTCL,[114,155–158] it also showed additive effect when combined with other agents employed for the treatment of PTCL, FL, or R/R T-cell lymphomas, such as the nucleoside analog gemcitabine, 5-azacitidine or the aurora kinase inhibitor alisertib.[159–161]

Panobinostat, a hidroxamic acid with therapeutic activity as pan-HDAC inhibitory, has been evaluated up to phase III clinical trials in R/R HL patients. Unfortunately, it failed to achieve the therapeutic effect expected from previous phases.[162] Similarly, phase II clinical trials involving R/R DLBCL patients demonstrated a modest activity of the drug.[163] In T-cell lymphoma and HL, some degree of clinical response was observed when associating this agent with the mTOR inhibitor everolimus.[93] Further drug assessment in HL, but not in CTCL patients, employing panobinostat in combination with ICE, also showed initial positive response.[164,165] Panobinostat was also administered to R/R HL patients in combination with the immunomodulatory drug lenalidomide, showing good tolerances but low therapeutic activity.[166] Finally, this HDACi has been tested in combination with bortezomib for the treatment of R/R TCL, providing a good response rate, but also producing serious adverse effects (AEs) in almost half of the cases.[167]

Entinostat is a HDAC I and III inhibitor, therapeutic effect of which has been tested in R/R HL. Different dosages were tested, achieving an ORR of 12%, and a mean tumor size reduction of 58%.[116]

Abexinostat, a pan-HDAC inhibitor, has been tested in a subset of R/R NHL and CLL patients. A phase II trial demonstrated that it can be successfully considered for the treatment of FL, TCL, and DLBCL,[95] with ORRs in the 56–31% range (see Table 1).

Valproic acid, an organic weak acid previously used as anticonvulsant, also exhibits HDAC inhibition properties. Several clinical trials aimed at evaluating its effect in lymphoma patients have been carried out, showing that it significantly improved the efficacy of the R-CHOP chemoimmunotherapy as a first-line treatment for DLBCL, as shown by a reduced rate of relapsed disease and a 96.8% OS at 2 years.[94]

HMT inhibitors

Currently, the development of HMT inhibitors is mainly focused on *EZH2* targeting. This gene encodes an HMT that forms the catalytic subunit of the polycomb repressive complex 2, which mediates gene silencing via the addition of methyl groups to H3K27. *EZH2* overexpression has been correlated with poor prognosis in several tumor types including hematological malignancies.[168–171] Moreover, it has been shown that the gain-of-function mutation at Y641 residue of EZH2, leads to its enzymatic activity converting mono- or di-methylated H3K27 to the tri-methylated state, promoting the repression of cell differentiation and the downregulation of tumor suppressor genes.[172] Interestingly, these gain-of-function EZH2 mutations has been frequently associated with the presence of *BCL2* rearrangement in both FL (28%) and GCB-DLBCL groups (33%), and it has been shown to be a crucial regulator of MYC-associated lymphomagenesis in B cells.[173–175] Thus, EZH2 activity is currently a potential therapeutic strategy to treat B-NHL.

In this context, several selective EZH2 inhibitors have been developed in the last decade, for the treatment of hematological patients. Among these molecules, GSK126 demonstrated an improved inhibitory capacity toward mutant EZH2 in preclinical studies.[176,177] However, its clinical

evaluation in R/R patients, including cases with DLBCL, transformed tFL, MM, and other NHL, (NCT02082977) was stopped prematurely due to insufficient therapeutic activity.[124] Another small molecule called CPI-1205, which showed promising activity in xenograft mouse models and in human B-NHL cell lines,[178] is currently being evaluated in a phase I trial involving DLBCL patients (NCT02395601). At this time, no data have been released regarding the efficacy and the safety of this agent in these heavily pretreated patients. Antitumoral effects of EZH2 inhibitors have been also reported in TCL cell lines.[179] The use of EZH1/2 inhibitor, valemetostat, has been evaluated in clinical trial including B- and T-NHL subtypes (NCT02732275). The observed ORR was 53% in a phase I trial involving 15 patients, being the cases with TCL by far the best responders (80% ORR).[180]

Tazemetostat, a potent and selective EZH2 inhibitor, first demonstrated encouraging preclinical activity, in both *in vitro* and *in vivo* models (including xenografts) of EZH2-mutant NHL.[181] An initial phase I study showed that tazemetostat, as single agent, was safe and exerted notable antitumor activity (OR = 38%) in patients with refractory B-NHL.[182] Based on pharmacodynamic and toxicity profiling, a phase II study including $EZH2^{mut}$ and $EZH2^{wt}$ R/R FL patients was carried out. Surprisingly, an ORR of 69% was observed among $EZH2^{mut}$ patients, and 35% in $EZH2^{wt}$ cohort.[123] Based on these data, FDA granted accelerated approval of this agent for R/R-FL patients with $EZH2^{mut}$. Similarly, two independent cohorts of R/R DLBCL and FL patients corroborated that tazemetostat was effective in R/R $EZH2^{mut}$ FL patients.[118,119] Tazemetostat was also evaluated in combination with the anti-PD-L1 antibody atezolizumab in R/R DLBCL patients (NCT02220842). However, this combination did not provide additional efficacy.[120] Thus, further clinical trials are needed to establish new drug combinations based on HMT inhibitors to improve the OS of the patients.

Although the clinical development of HMT inhibitors is centered on the targeting of EZH2 in B-NHL patients, other indirect strategies have shown encouraging results in preclinical models of the disease. Among these approaches, the carbocyclic adenosine analog 3-deazaneplanocin A (DZNep), is an inhibitor of S-adenosylhomocysteine hydrolase (AdoHcyase), that triggers intracellular accumulation of 5-adenosylhomocystein, followed by the blockade of several methyltransferases, including EZH2. Despite a strong apoptogenic effect in different preclinical cancer models, DZNep antitumor effect was not restricted to EZH2-mutated cases and may involve EZH2-independent targets, therefore, hinting as potential undesired effects in patients.[183] Blockade of the transfer of a methyl group from S-adenosyl methionine (SAM) to a lysine or arginine residue can also be achieved upon exposure to 2-chloro-2′-deoxyadenosine (2-CdA, cladribine), a drug that inactivates S-adenosyl-L-homocysteine hydrolase (SAH), thereby impairing the capacity of genomic DNA (gDNA) to accept methyl groups. Although cladribine was shown to efficiently reduce the level of methylated cytosines in myeloid cells,[184] its clinical activity as single agent in lymphoid malignancies, including CLL, MCL, hairy cell leukemia, and marginal zone lymphoma (MZL), was initially associated to its capacity, as a purine analog, to selectively target and suppress lymphocyte growth.[185] However, in MCL, induction therapy associating a purine analog to rituximab and cyclophosphamide demonstrated a lower response rate than standard R-CHOP regimen,[186] contrasting with the impressive 97% ORR observed in patients receiving a cladribine-containing immuno-epigenetic combo.[142] Therefore, it is highly plausible that, at least in MCL patients, the remarkable clinical activity of cladribine is derived from its epigenetic modulatory properties.

Bromodomain inhibitors

Bromodomain-containing family of proteins comprise 46 members, including nuclear proteins with HAT or HMT activity, chromatin remodelers, helicases, transcription co-activators, and mediators or scaffold proteins. Undoubtedly most of the scientific attention was focused on BRD2, BRD3, and BRD4.[187] Interestingly, these proteins have a bromodomain and extra-terminal motif (BET) domain, which is responsible for protein–protein interactions,[187,188] that acts as DNA enhancers for oncogene regulation.[189] BET bromodomains are important regulators of several players with a central role in several cancers, including hematological malignancies, such as MYC, cell cycle

regulators, and NF-κB-related genes.[190] Thus, in early 2000s, the development of BET inhibitors (BETi) rapidly gained a growing attention as a promising anticancer strategy.

The first BETi to enter into clinical development was birabresib. The data from the initial dose-escalation, open-label, phase I trial (NCT01713582) indicated that, when used as monotherapy, birabresib achieved a 47% CR rate in 17 R/R DLBCL patients, while durable OR was reported for only 18% of them.[125] A dose exploration study of this drug, involving DLBCL and AML patients (NCT02698189), was closed prematurely due to a lack of efficacy.

Others BETis, INCB054329 and INCB057643, were evaluated as monotherapy in a small cohort of patients with hematologic malignancies (NCT02431260 and NCT02711137, respectively). In both cases, the clinical trial was terminated due to a lack of responses and notable toxicity.[127]

CPI-0610 is another BETi, which was evaluated in B-NHL patients, reaching a modest 7% OR rate (NCT01949883). Mechanistically, the analysis of BET target genes demonstrated a dose-dependent decrease (2–8 h post-dose) in *interleukin-8* (*IL8*) and *C-C motif chemokine receptor 1* (*CCR1*) transcript levels.[128]

FT-1101, is a small molecule that presents a potent anti-proliferative activity *in vitro*, which was subsequently confirmed in B-NHL patients in a phase I clinical trial (NCT02543879). Although this agent showed an acceptable safety profile, a modest clinical activity was observed.[129]

Given the strong synergy between BET and BCL-2 inhibitors *in vitro*,[191] a phase Ib trial evaluated the effects of RO6870810 combined to the BCL2 antagonist, venetoclax, with or without rituximab in R/R DLBCL patients. ORR was 38.5%, including 20.5% CR and 17.9% PR. A stable disease (SD) was observed in 15.4% of the patients, whereas 30.8% maintained a progressive disease (PD). Although the triple combination resulted in higher response rates when compared with single agents, authors concluded to a lack of synergistic effect of this combinatorial approach.[126]

Future perspectives: paving the way for precision medicine with epidrugs in B- and T-cell lymphoma and implementing bioinformatics approaches to identify new epigenetic targets in hematological cancers

Personalized epigenome targeting in NHL

The identification of recurrent mutations in NHL provides a rationale to introduce epigenetic drugs for the design of selective and personalized therapies for these patients. Supported by promising results obtained in preclinical and clinical trials, the notion that epigenetic alterations can be used for lymphoma diagnosis and as valuable clinical biomarkers of response to therapy, represents a game changer for the clinical management of these patients.

Several preclinical studies have already shown that a genetic or epigenetic alteration could be specifically targeted by a particular drug. As described in the section 'HMT inhibitors', EZH2 inhibitors have demonstrated enhanced preclinical and clinical activity against EZH2-mutated B-NHL. Preclinical studies evaluating the safety and efficacy of a new class of LSD1 inhibitors showed that this class of agents had a very potent activity against proliferation of MLL-rearranged leukemia cells, with EC50 values in the nanomolar range. These cell-permeable molecules were found to significantly increase the levels of H3K4me2 in MLL-rearranged leukemic cells, to significantly reduce tumor burden, and to expand the life expectancy of leukemic mice, demonstrating the potential of this class of compounds to become clinically useful for MLL-rearranged leukemia.[192]

In a different context, HDAC3 inhibition using the novel molecule BRD3308 led to the upregulation of the cell cycle inhibitor, p21, resulting in cell cycle blockade and in proliferation arrest exclusively in CBP/p300-mutated DLBCL cells, characterized by the presence of BCL6–HDAC3 complexes that repress the transcription of the p21-encoding gene, *CDKN1A*.[193]

Despite these significant advances in the design of personalized treatments that could target a specific epigenetic alteration by means of one or several epidrugs, until recently efforts were still to be made to elaborate the best treatment approach for a determined patient with altered epigenome. The implementation of massive sequencing in early 2000s, followed by the standardization of big data processing, responded partly to these crucial needs.

In silico *epigenetic profiling: basic concepts*

Bioinformatics tools have enabled the interpretation of complex and dynamic phenomena, such as epigenetics, as well as the development of large-scale (big data), highly selective (e.g. single cell chip), and high-throughput modern molecular biology techniques.[194] These latter are aimed at facilitating the prediction of epigenetic events such as DNA methylation, chromatin conformation changes, histone modifications and non-coding RNA activity, and their relationship with other sources of biological information (e.g. phenotype, transcriptomic, and proteomic), with the final objective to improve the diagnosis and prognosis of different diseases,[195] and the design of effective and safe epidrugs,[196] and breeding strategies.[197] Epigenomic data, defined as the set of variations in certain genes, regions, or in the whole genome,[198] can be evaluated by methods that vary according to (1) the analytical platform used for data collection (e.g. array, sequencing, immunoprecipitation)[199–201], (2) the stage of analysis (e.g. preprocessing of raw data, statistical comparison, variable selection, functional analysis, and drug-target structural analysis),[202] or (3) the objective of the study (e.g. multiomics, single cell, drug repurposing).[203–205]

Epigenetics-based drug therapy is primarily aimed at reversing aberrant gene expression that may be found in the development and progression of lymphoma and understanding the potential to affect multiple cellular processes. These bioinformatics targets can be found by directly affecting regulatory regions of genes, such as in the methylome or DNA methylation information sets, or by altering histone proteins and related structures.[206] The methylome can be profiled experimentally by bisulfite sequencing, while the main technique for identifying histone alteration profiles is immunoprecipitation of these proteins.

Computational validation of epigenetic alterations in B- and T-cell lymphoma

The first stages of bioinformatics analysis of epigenetic data are data acquisition, quality control, and preprocessing. At these levels, the characteristics of the bioinformatics methods depend on the particularities of the experimental techniques. Chromatin immunoprecipitation (ChIP), followed by DNA identification by microarray (ChIP-on-chip) or sequencing (ChIP-seq), and mass spectrometry (MS) are the most common experimental approaches to profile histone post-translational modifications. ChIP-on-chip data require the normalization of hybridized fragment intensities, followed by the selection of representative peaks, and the merging of overlapping over-represented regions.[207] Many packages have been developed for this purpose such as Ringo,[208] Tilescope,[209] HMMTiling,[210] among others. ChIP-seq analyses require mapping short histone-associated DNA fragments to reference genomes. This step constitutes a challenge in both ChIP-on-chip and ChIP-seq. This so-called peak calling step needs more attention and quality control to avoid false overrepresentation and to map sequences that are actually in contact with our protein of interest (e.g. histones). Several open source (e.g. Bowtie, BLAT, or EpiChip)[211–213] or proprietary (e.g. Broad Institute sequencing platform)[214] programs or packages have been developed for reference alignment. In addition, packages such as SAMtools can be used for removal of duplicate reads due to amplification artifacts, to finally perform peak calling using some of the available approaches that best fit the experimental design.[215] In this sense, Peakzilla uses predefined cutoff values,[216] while MACS uses Poisson model to analyze the distribution of reads,[217] and JAMM retrieves information from biological replicates to determine the amplitude of enriched sites.[218] There are several studies using the ChIP technique to confirm whether alterations in chromatin structure and expression of certain genes are restored after epidrug treatment.[219–221]

MS has been used to determine the altered structure of proteins of interest, although there are limitations in recognizing the large number of ions inherent to histones or other cellular proteins. Different algorithms have been developed depending on the integrity of the quantified protein (total, peptides or amino acids), THRASH

being one of the most versioned although it still depends on the structural reference database.[222] These MS methods have recently been used to accurately target EZH2 and HDAC in lymphoma.[223]

The methylome encompasses information on DNA methylation at the genomic level, a well-studied phenomenon for which there are analytical methods based on bisulfite modification followed by sequencing[200] or microarray[224] analysis, and enrichment methods such as methylated DNA immunoprecipitation (MeDIP) or methyl-binding domain proteins (MethylCap) followed by DNA sequencing.[225,226] Bisulfite sequencing is based on the quantification of cytosines sequenced as thymines, after interaction with bisulfites that do not affect methylated bases. The bioinformatics algorithms used in the data generated by this technique have, as their main objective, the correct alignment to a reference genome and the calculation of the rate of cytosines and thymines that represent the methylation level of the genome studied. In addition to the previously mentioned methods for ChIP-seq, there are specific approaches that consider cytosine mismatches implemented, such as RRBSMAP[227] or Segemehl,[228] among others, that consider a three-base alignment (T, G, and A) such as MethylCoder or BRAT-nova.[229,230] With the sequences already aligned, it is possible to quantify the frequency of cytosines and thymines in certain regions of the genomes using probabilistic algorithms such as Bis-SNP and MethylExtract.[231,232]

Different databases have compiled and organized the data of epigenetic modifications and the information related to each deposited project. These platforms provide information for planning future projects and facilitate meta-analyses that may lead to new conclusions not seen in individual studies.[233] Databases such as NCBI epigenomics and ENCODE collect data from several large-scale projects.[234,235] MethDB and Methbank, among others, provide data exclusively on DNA methylation, while ChromatinDB and HHMD contain information on histone post-translational modifications for different species.[236–239]

The epigenetic alterations evaluated in previous steps can be used to define a differential profile that can be related to other types of omics data, especially gene expression data that are directly affected by such phenomena. As an example, the relationship between differential gene expression and binding analysis was used to point out the reversion of *CREBBP* mutations by HDAC3 selective inhibitors.[193] Programs such as diffReps[240] allow the detection of differential sites in ChIP-seq data where differences in the transcriptomic profile generated in those same regions are expected to be seen. Although it is often difficult to determine this association due to the variability of peak callers, some studies have shown its importance in, for example, defining genes and pathways associated with doxorubicin resistance.[241] Some studies have successfully used data on DNA sequence variations (e.g. in the differentiation of MCL subtypes),[242] protein or metabolite abundance, and clinical information.[243] This approach was also used to determine the association between metabolic and sensitivity to HDACis,[244] and to establish the relevance of phosphoproteomics data, gene expression and protein–protein interaction for the deciphering of a novel mechanism of regulation of KMT2D.[245] These types of associations could allow the reconstruction of multilevel regulatory networks.[246] The methods used to analyze this integration can vary greatly depending on the type of data used, between probabilistic models,[247] machine learning[248] (i.e. a model of protein-compound interaction with epigenetic targets using different machine learning methods),[249] coexpression networks[250] (i.e. differential coexpression and regulation networks to propose therapeutic factor for adult T-cell LL),[251] based on dimensionality reduction and clusterization,[252] integrated as networks based on quantitative relationships or described in previous literature, among others. Finally, we can use the structural information of the proteins responsible for modulating epigenetic marks in nucleosomes and their activity in the covalent bonds that generate these modifications. These data may help in the discovery of new epidrugs and epiprobes.[253] The main computer-aided drug design (CADD) methods in this area include druggability prediction,[254] virtual screening,[255] pharmacophore modeling,[256] and molecular dynamics simulations.[257]

Conclusion and future perspectives

In the last decade, the advances in high-throughput sequencing technologies have provided multitude of information on the role of both genomic and epigenomic deregulations in malignant transformation and in the physiopathology of B and T

lymphoid neoplasms. Besides helping the characterization of some lymphoma subtypes considered so far unclassifiable, the identification of recurrent mutations affecting epigenetic enzymes with crucial functions in the determination of B and T cell fate, fostered the development and evaluation of several epigenetic drugs, which rapidly showed high degree of efficacy, first in preclinical settings, and further in clinical trials essentially in relapsed NHL patients. Single agents and combination therapies involving HDAC inhibition or DNMT blockade have shown remarkable activity in specific subsets of B-cell and T-cell lymphoma, which remained unresponsive to or relapsed after chemo-immunotherapeutic regimens. However, beside general inhibitors of acetylation and demethylase, specific epigenetic drugs, including class-specific HDACi, EZH2 inhibitors or BET antagonists are showing significant clinical activity and have already been broadly implemented in the clinical management of determined subtypes of NHL patients. In combination therapy, some of these agents have demonstrated their ability to facilitate the response of B-NHL patients to anti-CD20 treatment. Among them, vorinostat was able to improve the outcomes of R/R FL, MCL, and MZL patients when associated to rituximab;[258] however, this effect seemed barely additive and the combined use of additional chemotherapeutic combo such as ICE or CHOP may be a prerequisite to achieve synergistic antitumor activity (NCT00601718, NCT00972478). Other HDACis such as panobinostat, fimepinostat, belinostat, or valproic acid either failed to exhibit such combinatorial activity with rituximab-based regimens or were associated with important AEs that limited their clinical development.[94,153,259] Within the family of methylation modulators, cladribine also exhibits combinatorial activity with rituximab, as MCL patients receiving this combination presented a superior CR rate than the group of patients treated with cladribine alone (52% *versus* 42%, respectively).[260] In previously untreated patients, the observed responses were even higher when vorinostat was added to this doublet (97% ORR and 80% CR).[142] Importantly, these last studies showed a plateau in PFS and OS as well as a prolonged PFS, implying potential curative potential for cladribine–rituximab based regimens. In the case of EZH2 inhibitors, the first results of the phase Ib Epi-R-CHOP study combining tazemetostat to rituximab-CHOP suggested that this combo, although generally well tolerated, does not appear to substantially improve rituximab-CHOP toxicity and efficacy profiles.[261] Thus, in determined but limited conditions, epidrug therapy may significantly improve the outcome of NHL patients receiving anti-CD20-based regimens.

Despite these outstanding advances, further field of development include the identification of *ad hoc* biomarkers that may facilitate patient selection for their inclusion in clinical trials, and the design of rationally based combination regimens, may help reaching the final aim of establishing selective and personalized therapies for this subgroup of patients. One of the latest and most promising approach, which will help selecting the most relevant targeted therapies in the near future, is the multiomic characterization of each patient sample. However, the considerable volume of information provided by the latest technologies, including single-cell proteogenomics, requires a rigorous and reproducible analytical workflow that is nowadays within our reach, thanks to the recent improvements in bioinformatic data analysis. These approaches will allow us to be closer to the complete mapping of B- and T-cell lymphoma and, therefore, will empower the design of optimal therapeutic scheme, including new epigenetic drug combinations.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Marcelo Lima Ribeiro: Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Salvador Sánchez Vinces: Methodology; Resources; Software; Writing – original draft; Writing – review & editing.

Laura Mondragon: Conceptualization; Investigation; Supervision; Writing – original draft; Writing – review & editing.

Gael Roué: Conceptualization; Funding acquisition; Investigation; Supervision; Writing – original draft; Writing – review & editing.

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ORCID iDs
Salvador Sánchez Vinces https://orcid.org/0000-0001-7041-6544

Gael Roué https://orcid.org/0000-0003-0245-2257

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