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Targeting LSD1 for acute myeloid leukemia (AML) treatment

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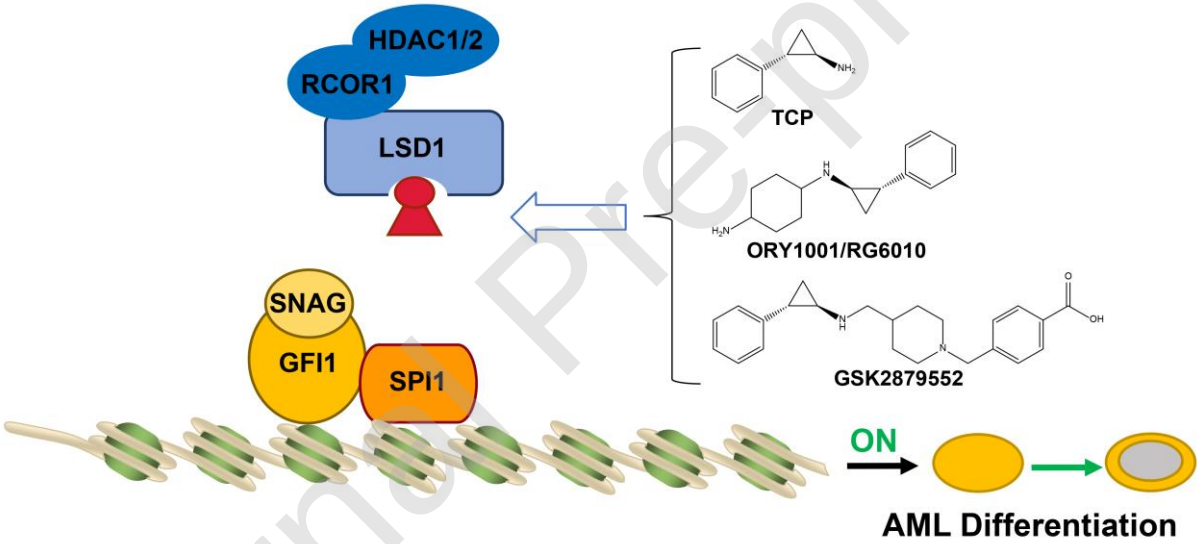
Graphical Abstract



Abstract

Targeted therapy for acute myeloid leukemia (AML) is an effective strategy, but currently there are very limited therapeutic targets for AML treatment. Histone lysine specific demethylase 1 (LSD1) is highly expressed in many cancers, impedes the differentiation of cancer cells, promotes the proliferation, metastasis and invasion of cancer cells, and is associated with poor prognosis. Targeting LSD1 has been recognized as a promising strategy for AML treatment in recent years. Based on these features, in the review, we discussed the main epigenetic drugs targeting LSD1 for AML therapy. Thus, this review focuses on the progress of LSD1 inhibitors in AML treatment, particularly those such as tranylcypromine (TCP), ORY-1001, GSK2879552, and IMG-7289 in clinical trials. These inhibitors provide novel scaffolds for designing new LSD1 inhibitors. Besides, combined therapies of LSD1 inhibitors with other drugs for AML treatment are also highlighted.

Keywords: Histone demethylase, AML treatment, LSD1 inhibitors, Tranylcypromine derivatives, Combination therapy.

1. Introduction

Leukemia is a malignant tumor of the hematopoietic system that seriously harms human health, especially in pediatric malignancies(1, 2). Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults(3, 4). AML is an aggressive malignant disorder of hematopoietic cells, characterized by limited differentiation and uncontrolled proliferation of myeloid progenitor cells(5-8). The classification and prognosis of leukemia are very complex. At present, the treatment of leukaemia mainly includes: chemotherapy, targeted therapy, differentiation therapy, immunotherapy, hematopoietic stem cell transplantation (HSCT) and other methods (Fig. 1)(9-12). Firstly, traditional chemotherapy as follows: the standard therapy is still induction therapy with Anthracycline and Cytarabine, “3+7”, followed by chemotherapy or HSCT(13-15). New cytotoxic chemotherapy drugs include CPX-351

and Vosaroxin. CPX-351 is a liposome contains cytosine arabinoside and daunorubicin at a ratio of 5:1, showing higher efficacy in animal models than using the same traditional drug. Phase II clinical trial for the treatment of AML is ongoing (NCT02286726)(16-18). Vosaroxin is a novel, non-anthracycline quin-olone derivative. A Phase II study of vosaroxin and decitabine is currently being evaluated in elderly patients with newly diagnosed AML or high-risk myelodysplastic syndrome (MDS) (NCT01893320)(19-21). However, many patients with chemotherapy drugs have a poor prognosis and eventually develop recurrent refractory tumors, with a 5-year survival rate of only 20%(22). In addition, for the immunotherapy, T cells expressing chimeric antigen receptors (CAR) have created an impressive efficacy in patients with lymphocytic leukemia(23), and further studies have confirmed that Folate Receptor beta (FR-beta) is a wonderful target used to treat AML with CAR T-cell, but clinical studies into the efficacy of anti-AML treatment are lacking(24). Moreover, given that the HSCT requires high individual specificity and low universality, the clinical application of HSCT in AML therapy is limited(24-26).

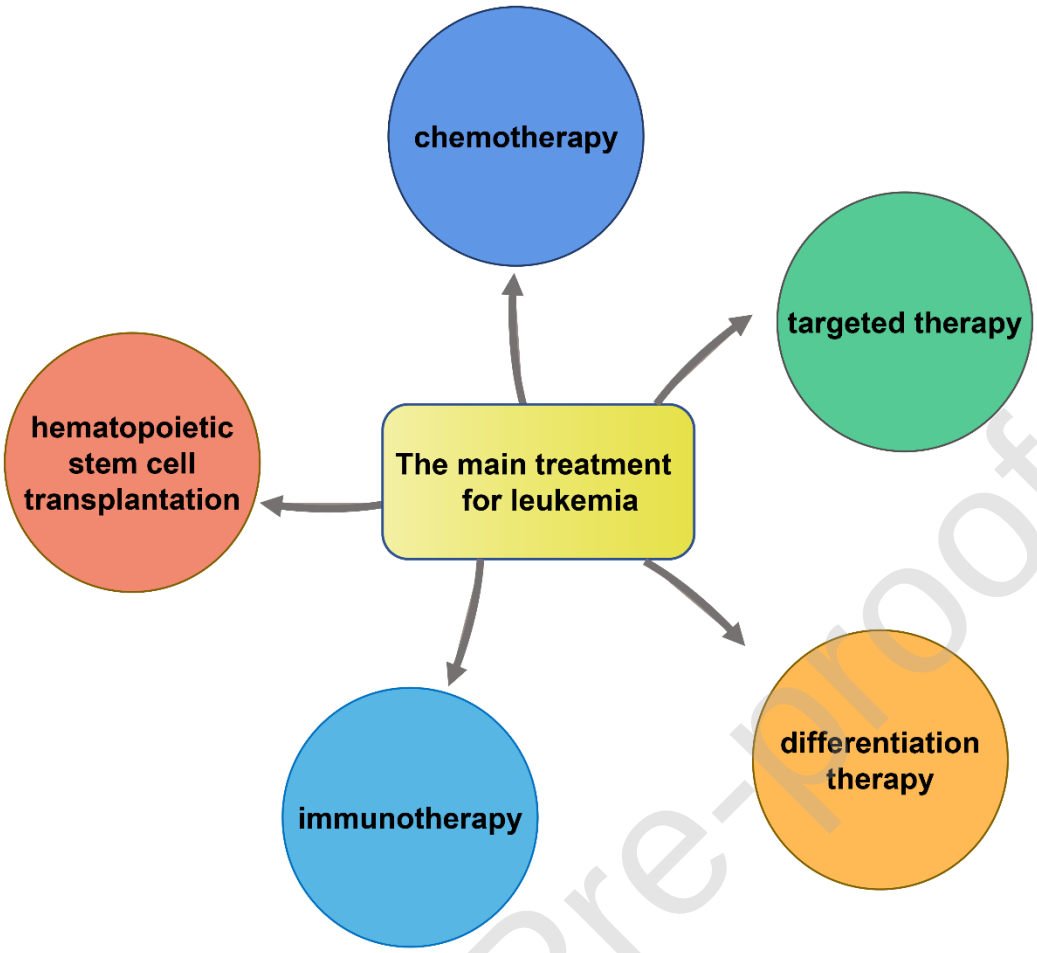


Figure 1. The therapeutic methods of treatment of leukemia. the treatment of leukemia mainly includes: chemotherapy, targeted therapy, differentiation therapy, immunotherapy and hematopoietic stem cell transplantation (HSCT).

Furthermore, AML also can be effectively treated by induced differentiation. In 1988, Wang et al, successfully applied ATRA used to treat acute promyelocytic leukemia (APL), which initiated the clinical application of differentiation inducers in the treatment of leukemia. Subsequently, researchers found that ATRA combined with arsenic trioxide (ATO) was very effective in treating APL(27-29). However, when ATRA was used on AML cells without the APL subtype, the results were not satisfactory. And the irreversible drug resistance induced by ATRA and arsenic trioxide can lead to clinical complete remission failure. Additionally, $1,25(OH)_2D_3$ or vitamin D analogues (VDAs) also can effectively induce differentiation of AML cells both in vivo and in vitro, which is the reason for early clinical trials in patients with

AML and MDS(30-32). While, clinical trials are restricted by the dose-limiting hypercalcemia, and the risk of development of resistance to $1,25(OH)_2D_3$(33, 34). Therefore, according to the above reasons, it is necessary to explore safer and more effective AML therapeutic strategies.

Epigenetic drugs have also played an irreplaceable role in the treatment of AML in recent years. Epigenetic modifications associated with AML include DNA methylation, histone methylation, and histone deacetylation (Fig. 2)(35-39). DNA methyltransferase inhibitors, azacitidine and decitabine, approved by FDA for use in adult MDS, have also been confirmed to extend survival in elderly AML patients(40, 41). The latest clinical study evaluated a new regimen of low-intensity chlorpropidine combined with low-dose cytosine alternating with decitabine, providing a new strategy for elderly patients with AML(42). In addition, Histone methyltransferase inhibitor, 3-deazaneplanocin A (DZNep), has been shown in vitro and in animal studies to be applicable to AML(43, 44). Moreover, Histone deacetylase (HDAC) inhibitor panobinostat combined with vorinostat were used for treatment of AML or high-risk patients with MDS, and currently in phase II/III clinical studies(45, 46). The other two HDAC inhibitors, entinostat and pracinostat, are still in the early stages of development(47-49). Furthermore, LSD1 is also an irreplaceable target in AML. In this review, we aim to summarize the research progress of LSD1 inhibitors in the treatment of AML, focusing on some novel LSD1 inhibitor scaffolds and new strategies for combining LSD1 inhibitors with other drugs for the AML therapy, which may provide fresh approaches for AML.

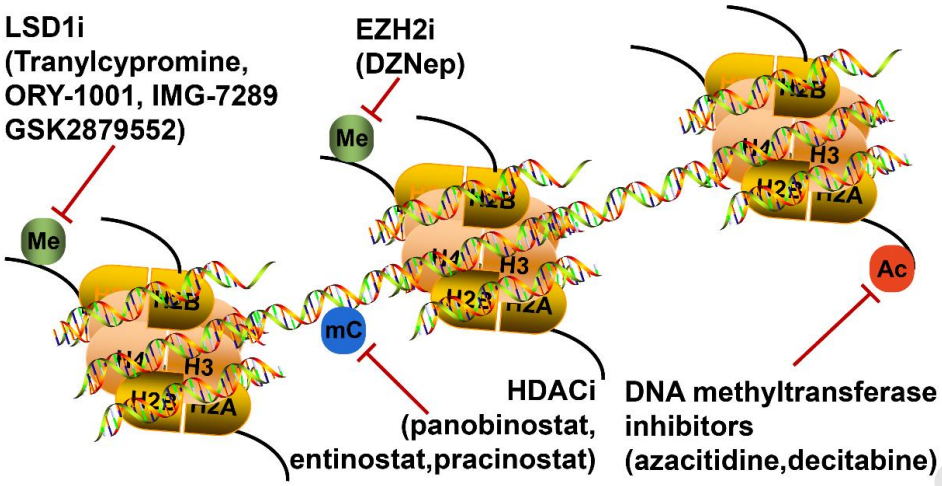


Figure 2. Inhibitors targeting epigenetic modifiers in acute myeloid leukemia. Inhibitors targeting epigenetic modifiers include: DNA methyltransferase inhibitors, azacitidine and decitabine; histone methyltransferase inhibitor, 3-deazaneplanocin A (DZNep); histone deacetylase (HDAC) inhibitors, panobinostat, entinostat and pracinostat; Histone lysine specific demethylase 1 (LSD1) inhibitors, Tranylcypromine, ORY-1001, IMG-7289 and GSK2879552.

2. Current status of LSD1 inhibitor in AML therapy

In 1987, Holiday proposed that epigenetics is the study of heritable gene expression changes without DNA sequence changes. While genetic changes are irreversible, epigenetic modifications are reversible. Therefore, epigenetic modification plays an irreplaceable role used to treat diseases and is a great target for drug therapy(50-52). Histone methylation modification is one of the epigenetic regulatory mechanisms. The histone lysine specific demethylase 1 (abbreviated as LSD1, also known as KDM1A, AOF2, BHC110 or KIAA0601), the first histone demethylase discovered by professor Shi Yang in 2004, is a member of the flavin adenine dinucleotide (FAD)-dependent amine oxidase family of demethylases(53). Inhibition of LSD1 can target both the scaffold and the enzymatic function of this protein. In terms of enzyme activity, LSD1 has a dual function of transcriptional inhibition and activation in response to differences in sites 4 and 9 of histone H3. Generally, LSD1 demethylates H3K4me2/1 and inhibits gene transcription by binding to CoREST or nucleosome

remodeling and deacetylase repressive complex. However, when LSD1 activity specifically targets H3K9, it promotes transcriptional activation by binding to the androgen receptor (AR) or estrogen receptor (ER) (Fig. 3A and B)(35, 54-56). In particular, LSD1-NuRD complex, as an inactivated enhancer of pluripotency program during differentiation, is crucial to embryonic stem cell (ESC) gene expression program. Studies have shown that LSD1 is the key to the inactivation of enhancers during the differentiation of mouse ESCs(57). Additionally, Mohammad et al. reported that the LSD1 inhibitor GSK2879552 increased LSD1 signal enrichment of the SCLC specific typical and super enhancers(58).

LSD1 can also play a gene regulatory role as a protein scaffold. lncRNA Hotair scaffolds HBXIP and the Hotair of LSD1 acted as scaffolding to form c-MYC /HBXIP/Hotair/LSD1 complex, leading to c-MYC target gene transcription in human MCF-7 breast cancer cells (Fig. 3C) [59]. In addition, differentiation of myeloid leukemia cells resulting from LSD1 inhibitor also depended on LSD1 scaffold function. Such as, Maiques Diaz et al. demonstrated that drug-induced differentiation of myeloid leukemia cells was mainly due to the physical separation of LSD1/RCOR1 complex from GFI1, leading to the activation of the dependent myeloid transcription factor genes, rather than histone demethylation (Fig. 4A and B)[60].

Based on the biological characteristics of LSD1, an increasing number of studies indicate that LSD1 plays a vital role in cancer and is a wonderful target used to treat AML(59-62). Numerous small molecule inhibitors of LSD1 are being developed for cancer treatment. Among them, a number of irreversible LSD1 inhibitors have entered clinical trials for the treatment of AML with broad prospects.

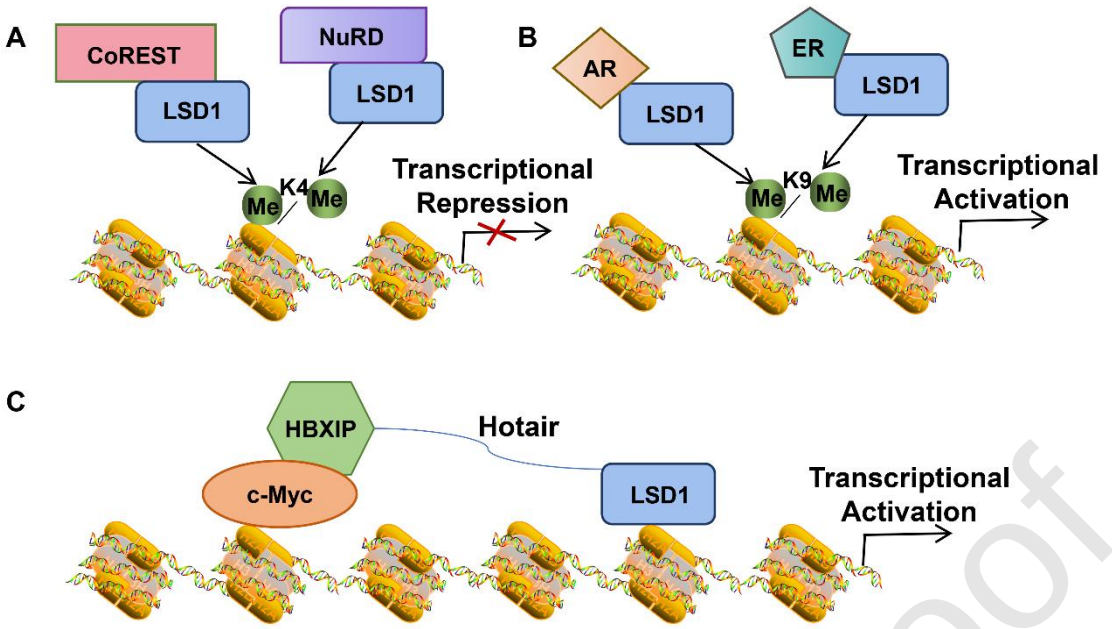


Figure 3. Lysine specific demethylase 1 (LSD1) dual functions as transcriptional repressor and activator. LSD1 that demethylates both 'Lys-4' (H3K4me) and 'Lys-9' (H3K9me) of histone H3, thereby acting as a coactivator or a corepressor, depending on the context. A. Acts as a corepressor by mediating demethylation of H3K4me, a specific tag for epigenetic transcriptional activation. B. Acts as a coactivator by mediating demethylation of H3K9me. C. LSD1 can also play a gene regulatory role as a protein scaffold. lncRNA Hotair scaffolds HBXIP and the Hotair of LSD1 acted as scaffolding to form c-MYC /HBXIP/Hotair/LSD1 complex, leading to c-MYC target gene transcription in human MCF-7 breast cancer cells.

2.1 The role of LSD1 in the progress of AML

LSD1 and corepressor CoREST regulate hematopoietic differentiation by mediating GFI1 and GFI1b. GFI1 and GFI1b regulate the proliferation, differentiation and survival of blood cells and are irreplaceable transcription factors in the hematopoietic process. Mouse model studies have confirmed that GFI1 is involved in the development and function of hematopoietic stem cells (HSCs), B and T cells, dendritic cells, granulocytes and macrophages, while GFI1b is necessary for the development of megakaryocytic and erythroid(63, 64). GFI1 controls the proliferation and differentiation of myeloid progenitor cells and plays a crucial role in the promotion of myeloid progenitor cells. LSD1 restricts the proliferation of hematopoietic progenitor and is a necessary condition for terminal differentiation. For

instance, by constructing an in vivo knockdown model, it was reported that LSD1 knockdown (LSD1-KD) caused granulomonocytic, erythroid and megakaryocytic progenitors to proliferate. However, it significantly inhibited the formation of terminal granulopoiesis, erythropoiesis and platelet. This suggests some serious side effects of LSD1 inhibitors such as thromobotopenia. Notably, studies indicated that peripheral granulocytopenia, mononucleosis, anemia and thrombocytopenia are reversible after LSD1-KD termination(65, 66).

Not only in the hematopoietic process, but also in AML, LSD1 inhibitors work by blocking the interaction between LSD1 and the chromatin transcription factor GFI1b(67). The inhibition of LSD1 prevents GFI1-mediated inhibition of PU.1 target genes to induce AML differentiation. Inhibition of LSD1 plays an anti-leukemia role by reactivating PU.1 and C/EBP alpha-dependent enhancers in AML(68-71). In addition, in the constructed AML xenotransplantation model, pharmacological inhibition of LSD1 led to the complete elimination of tumor growth in the AML xenograft model containing runx1-runx1t1 translocations(71). At present, some irreversible inhibitors developed based on tranylcypromine (TCP) have entered clinical trials of AML therapy, and numerous new TCP derivatives are considered to be effective LSDI inhibitors. While, the development of effective reversible inhibitors faces enormous challenges now. At the same time, LSD1 inhibitor combined with some other drugs to further enhance the efficacy and overcome the resistance of acute myeloid leukemia cells to LSD1 inhibition is also under investigation.

2.2 LSD1 inhibitors in clinical trials of AML therapy

Tranylcypromine, a clinical treatment for depression (named TCP and PCPA), is a monoamine oxidase inhibitor (MAO), also known as an irreversible LSD1 inhibitor(72-74). Three clinical trials of Tranylcypromine used to treat AML and MDS are undergoing (https://www.clinicaltrials.gov/ct2/home). for instance, on October 10th, 2014, a Phase I/II study of the pharmacodynamics and efficacy of ATRA and TCP in patients with relapsed or refractory AML and AML without

intensive treatment was performed (CT identifier: NCT02261779). On October 23th, 2014, safety and tolerance of ATRA and TCP in combination was evaluated. in a phase I study. In addition, on March 24th, 2016, a Phase I/II study which investigated the effects of TCP-sensitized non-M3 AML cells on ATRA was implemented to determinate the maximum tolerated dose (MTD) of TCP in combination with ATRA or with AraC (Cytarabine), and to evaluate the efficacy of TCP at the Recommended Phase II Dose (RP2D) in combination with ATRA or with AraC (CT identifier: NCT02717884).

Tranylcypromine (TCP) is the dominant stent for the design of irreversible LSD1 inhibitors. Currently, LSD1 inhibitors which design based on TCP include ORY-1001 (Oryzon Genomics Barcelona, Spain), GSK2879552 (GlaxoSmithKline) and IMG-7289 (Imago Biosciences), Clinical trials of LSD1 inhibitors used alone or in combination with ATRA for AML and MDS are being evaluated (https://www.clinicaltrials.gov/ct2/home) (Table 1). Such as, Oryzon Genomics reported ORY-1001 (also abbreviated as iadademstat, RG6016 or RO7051790), is an extremely efficient and selective covalent LSD1 inhibitor. Maes and colleagues determined in the mice PDX (patient-derived xenograft) model of T cell acute leukemia, ORY-1001 showed strong synergistic effects with standard therapeutic drugs or other selective epigenetic inhibitors to reduce the growth of AML xenograft models and extend survival(75, 76). Additionally, a phase I study of pharmacokinetics and safety of ORY1001 is currently undergoing used to treat patients with relapsed or refractory AML (EudraCT 2013-002447-29). Moreover, another irreversible LSD1 inhibitor, GSK2879552, developed by GlaxoSmithKline, is also used to treat AML, but a Phase I Dose Escalation Study of GSK2879552 in patients With Acute Myeloid Leukemia has been terminated because the risk benefit of relapsed refractory AML does not support the study (CT identifier: NCT02177812). Furthermore, a phase I study of IMG-7289 (Imago Biosciences), with or without ATRA, used to treat patients with AML or MDS have been completed (CT identifier: NCT02842827). Although these LSD1 inhibitors have shown favourable results in clinical trials, but given the urgent clinical need for new drugs to treat AML, so, it is very necessary to

explore novel LSD1 inhibitors.

Table 1 LSD1 inhibitors in clinical trials

LSD1 inhibitors	Phase	Trial number	Disease(s)	Study	Status
ORY-1001	I/II	EudraCT 2013-002447-29	Relapsed or refractory AML	A phase I study of pharmacokinetics and safety of ORY1001	Unknown
GSK2879552, ATRA	I	NCT02177812	AML	A Phase I Dose Escalation Study of GSK2879552 in Subjects With Acute Myeloid Leukemia (AML)	Terminated
IMG - 7289, all-trans retinoic acid	I	NCT02842827	AML and MDS	IMG-7289, With and Without ATRA, in Patients With Advanced Myeloid Malignancies	Completed
Tranylcypromine (TCP),Tretinoin	I/II	NCT02261779	Relapsed or refractory AML	Phase I/II Trial of ATRA and TCP in Patients With Relapsed or Refractory AML and no Intensive Treatment is Possible (TCP-AML)	Unknown
Tranylcypromine (TCP),Tretinoin	I	NCT02273102	AML,MDS and Leukemia	Phase 1 Study of TCP-ATRA for Adult Patients With AML and MDS (TCP-ATRA)	Active, not recruiting
Tranylcypromine (TCP), all-trans retinoic acid, cytarabine	I/II	NCT02717884	AML and MDS	A phase I/II study of sensitization of Non-M3 AML blasts to ATRA by TCP treatment	Recruiting

2.3 The research progression of Novel LSD1 inhibitors in the treatment of AML

2.3.1 Irreversible LSD1 inhibitors

Novel cyclopropylamine derivatives

In addition to these irreversible inhibitors developed based on tranylcypromine (TCP) which have entered clinical trials, some new TCP derivatives are also under active development (Table 2). TCP derivatives induce differentiation of AML by preventing GFI1-mediated inhibition of PU.1 target genes(68). Trifiro et al. reported new TCP derivatives substituted on the cyclopropyl moiety (**5a**) can significantly improve the survival rate after oral administration in promyeloid leukemia mouse models(77). In addition, Fioravanti et al. prepared three series of TCP analogs, in which **compound 3** could significantly inhibit the proliferation of MV4-11 AML. Simultaneously, compounds 3 induced the expression of target genes GFI1b, ITGAM and KCTD12.(78). Besides, another novel class of LSD1 inhibitors, N-substituted derivative **7v** and **7ad** of TCP, clinical candidates used to treat AML, are selective to monoamine oxidase (MAO-A and MAO-B) and effectively inhibits colony formation of leukemia cells(79). Furthermore, N-alkylated trans-2-phenylcyclopropylamine-based LSD1 Inhibitors, S2116 and S2157, exhibited enhanced LSD1 inhibitory activity and showed better selectivity over MAO(80).

However, most studies on the structure-activity relationship (SAR) of these TCP derivatives are racemes. Ji et al. provided SAR data for a series of TCP-based LSD1 inhibitors, including racemes and enantiomers that increase CD86 expression in human MV4-11 AML cells(81). Additionally, Valente et al. reported that compounds **11b**, **11g**, and **11h** consumingly inhibited the cloning potential of promyelocytes in mice, and both inhibited LSD1 by inducing the expression of GFI1b and ITGAM genes(82).

Non-cyclopropylamine derivatives

The first irreversible LSD1 inhibitor that is not derived from a monoamine oxidase inhibitor **9e** effectively inhibited THP-1 cell proliferation(83).

2.3.2 Reversible LSD1 inhibitors

Although numerous TCP derivatives have been proved to be effective irreversible inhibitors of LSD1, there are still big challenges in developing effective reversible

LSD1 inhibitors (Table 3). Li and colleagues indicated that the triazole-fused pyrimidine derivatives compound 15u had a reversible inhibitory effect on LSD1 and competed with H3K4me2, and the selectivity of **15u** to LSD1 was higher than MAO-A/B, which provides a new scaffold for LSD1 inhibitors. The IC_{50} of 15u in four leukemia cell lines were 1.79, 1.30, 0.45, and 1.22 μM, respectively(84). Besides, Wu et al. showed that **compound 17** has high selectivity to the related MAO-A and B (> 160x). It is a competitive inhibitor of dimethylated H3K4 substrates and has a intense proliferation inhibition effect on a few leukemia cells with an EC50 value of 280nM(85). Mold et al. developed acyclic scaffold-hops from gsk-690, further optimization of scaffold (4-cyanophenyl) glyceramide was used to obtain (4-cyanophenyl) glycine derivative **compound 32**, which is a novel LSD1 inhibitor(86). In addition, they found 4-(pyrrolidin-3-yl) benzonitrile derivatives, compound **21g**, which significantly increased the expression of CD86 in human THP-1 cells(87).

In addition, reversible LSD1 inhibitors have many other structural compounds. The 5-arylidene barbiturate derivative **12a** has a strong differentiation inducing effect on the NB4 cell line of AML and significantly up-regulates the methylation level of H3K4(88). The stilbene derivative compound **8c** can up-regulate the expression of the substitute cell marker CD86 in THP-1, and has a good inhibitory effect on THP-1 and MOLM-13 cells, with IC_{50} values of 5.76 and 8.34 μM, severally(89). The polyamine analogue LSD1 inhibitor **2d** induced cytotoxicity in AML cells and increases the global level of monomethylated and dimethylated of H3K4 proteins(90). 5-hydroxypyrazole derivative compound **11p** up-regulated the expression of CD86 in human THP-1 cells (91). **Complex 2**, the first vanadium-based LSD1 inhibitor, with an IC_{50} value of 19.0 μM, has a good selectivity to MAO(92).

Some natural products also have selective inhibition on LSD1. Natural protoberberine alkaloids epiberberine has obvious inhibitory effect on LSD1. Epiberberine also can significantly induce the expression of CD86, CD11b and CD14 in THP-1 and HL-60 cells and prolong the survival of the mice engrafted with THP-1 cells(93). It is suggested that natural protoberberine alkaloids epiberberine can be

used to further develop LSD1 inhibitors.

Table 2 Novel irreversible LSD1 inhibitors used in the treatment of AML

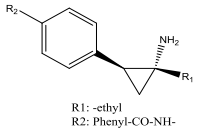
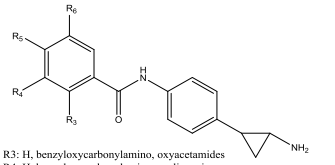
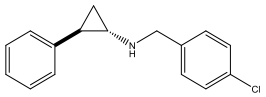
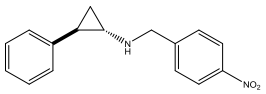
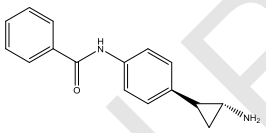
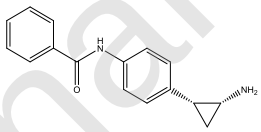
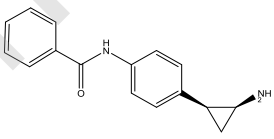
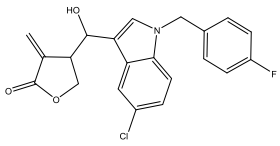
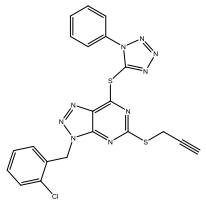
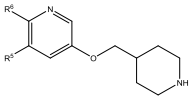
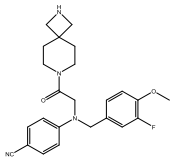
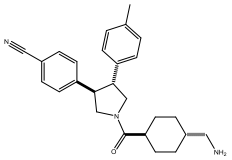
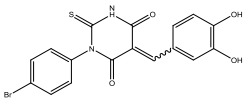
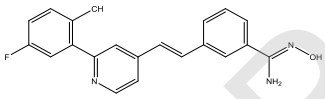
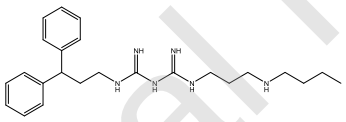
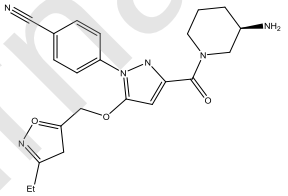
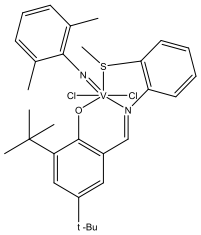
Compound Names	Structure	In vitro or vivo Effects	Ref
5a	 R1: -ethyl R2: Phenyl-CO-NH-	Improved the survival rate after oral administration in promyeloid leukemia mouse models	[77]
Compounds 3	 R3: H, benzyloxycarbonylamino, oxyacetamides R4: H, benzyloxycarbonylamino, cyclic amines R5: H, Br, benzyloxycarbonylamino, cyclic amines, phenoxy,phenylthio R6: H, benzamido	Inhibited proliferation in MV4-11 AML and APL NB4 cells	[78]
7v		Inhibited colony formation of leukemia cells in culture	[79]
7ad		Inhibited colony formation of leukemia cells in culture	[79]
11b		Inhibited the cloning potential of promyelocytes in mice	[82]
11g		Inhibited the cloning potential of promyelocytes in mice	[82]
11h		Inhibited the cloning potential of promyelocytes in mice	[82]
9e		Inhibited the proliferation of THP-1 cells	[83]

Table 3 Novel reversible LSD1 inhibitors used in the treatment of AML

Compound Names	Structure	In vitro or vivo Effects	Ref
15u		Inhibited proliferation in OCL-AML3, K562, THP-1 and U937	[84]
Compound 17		Inhibited proliferation in a few leukemia cells	[85]
Compound 32		Inhibited colony formation of leukemia cells in culture	[86]
21g		Increased the expression of the cell marker CD86 in human THP-1 cells	[87]
12a		Induced differentiation on the NB4 cell line of acute promyelocytic leukemia	[88]
8c		up-regulated the expression of the substitute cell marker CD86 in THP-1	[89]
2d		increased the global level of monomethylated and dimethylated of H3K4 proteins	[90]
compound 11p		up-regulated the expression of CD86 in human THP-1 cells	[91]
Complex 2		Inhibited proliferation in OCL-AML3, K562, THP-1 and U937	[92]

2.4 The current status of LSD1 inhibitors combined with other drugs in the treatment of AML

2.4.1 LSD1 inhibitors in combination with ATRA for AML therapy

ATRA

Generally, romyelocytic leukemia (PML)-retinoic acid receptor alpha (RARalpha) translocation always occurs in APL patients. Traditional drugs such as ATRA and arsenic trioxide (ATO) are adopted for the treatment of APL(94, 95). Kayser, S et al. showed that patients with ATRA or CTX/ATRA with ATO in t-APL presented a higher overall survival rate than those with CTX/ATRA(96). However, ATRA and ATO induced irreversible resistance which could explain the clinical failure of complete remission. In addition, ATRA was clinically used for the treatment of APL. In contrast, ATRA-based treatment was not effective in non-APL AML patients(97-99). Therefore, the combination of ATRA with other drugs used to treat non-APL was a promising therapeutic strategy.

LSD1 inhibitors combined with ATRA

LSD1 inhibitors combined with ATRA are expected to significantly alleviate non-APL AML patients. As a combination treatment, TCP and its derivative IMG-7289 were using with ATRA to evaluate the clinical outcome against leukemia. Significant effects on cytotoxic and differentiation marker were observed when ATRA and GSK2879552 was applied combinedly(100). Schenk, T et al. substantiated that inhibition of LSD1 could reactivate the ATRA differentiation pathway in AML. And animal experiments confirmed that ATRA + TCP drug combination has strong anti-leukemia effect, which is superior to either drug alone(101). In addition, studies have revealed that acetyltransferase GCN5 promotes ATRA resistance in non-APL. This resistance was observed due to aberrant acetylation of histone 3 lysine 9 (H3K9Ac) residues by GCN5 which regulate the expressions of stem cell and

leukemia-associated genes. It is suggested that the high efficacy of GCN5 and LSD1 inhibitors combined with epigenetic therapy may make it possible for ATRA to be used in the differentiation therapy of non-APL AML(102).

2.4.2 LSD1 inhibitors in combination with HDAC inhibitors for AML therapy

HDAC inhibitors

Histone deacetylase (HDAC) mediatingchromosome modification is also involved in regulating gene transcription. In general, the acetylation of histones is conducive to the dissociation of DNA from histone octamer, which led to the conformation of DNA in an "open" state and the activation of gene transcription. HDAC can promote the deacetylation of histones, make histones binding to DNA closely and gene transcription inhibition(103-105). The inhibition of HDAC can induce apoptosis and prevent the expression of tumor-related proteins(106). The pathogenic protein, AML1/ETO, recruits histone deacetylases (HDACs) that cause t(8;21) acute myeloid leukemia (AML). Panobinostat, one HDACi, was found to produce a strong anti-leukemia effect in mice bearing t(8;21) AML(107). Abnormal translocation of the mixed-lineage leukemia (MLL) genes is one of the factors inducing AML and that MLL- rearranged AML is susceptible to resistance to conventional chemotherapy. The synergistic inhibition of HDAC and MLL-rearranged AML cells, providing a fresh therapeutic strategy for MLL -rearranged leukemia patients with poor prognosis(108, 109).

LSD1 inhibitor combined with HDAC inhibitors

Histone deacetylase inhibitors combined with chemotherapy drugs such as doxorubicin or all-trans retinoic acid can improve the treatment of refractory and high-risk AML patients(110-113). Furthermore, Histone deacetylase inhibitors (HDACi) are used in combination with other epigenetic drugs for the treatment of AML(114-116).

LSD1 inhibitors in combination with other epigenetic drugs can significantly

enhance the efficacy (Table 3). The LSD1 antagonist SP2509 attenuated LSD1 binding to corepressor CoREST and increased levels of P21, P27, and CCAAT/enhancer binding protein in AML cells. SP2509 in combination with histone deacetylase inhibitor panobinostat could significantly enhance the survival of the mice engrafted with human AML cells, and displayed synergistic lethal effects on primary AML cells(117).

2.4.3 LSD1 inhibitors in combination with EZH2 inhibitors for AML therapy

EZH2

Polycomb repressor complex 1 and 2 (PRC1 and PRC2) are transcriptional repressors. PRC2 demonstrates histone lysine methyltransferase activity through its catalytic subunit consisting of EED, EZH2 and SUZ12. EZH2 is the core catalytic element(118-121). Studies have shown that EZH2 is often overexpressed in ovarian cancer, suggesting EZH2 may be an promising therapeutic target. Several small molecule inhibitors of EZH2 are in progress and are currently in clinical trials. High expression of EZH2 inhibits gene transcription, and inhibition of EZH2 induces differentiation of AML(122-124).

LSD1 inhibitor combined with EZH2 inhibitors

The inhibition on both EZH2 and LSD1 can exert synergistic effects against AML in vivo and in primary leukemia cells from AML patients. This synergistic mechanism was demonstrated by up-regulating H3K4me1/2, H3K9Ac and down-regulating H3K27me3, thereby reducing the anti-apoptotic protein Bcl-2. Although EZH2 and LSD1 have opposite histone methylation functions, the combination of SP2509 and EPZ6438 resulted in the methylation changes of their respective sites (H3K4me1/2 and H3K27me3), the effects do not cancel each other. And the combination also led to significant accumulation of H3K9Ac, which altered the expressions of Bcl-2, Bax, and Cyto-C. Notably, no cytotoxicity was detected in normal mononuclear cells isolated from healthy donors with either a single drug or a combination drug(125).

2.4.4 LSD1 inhibitors in combination with other drugs for AML therapy

Ishikawa, y et al. published a new irreversible LSD1 inhibitor, T-3775440, which destroyed the interaction between LSD1 and GFI1b, and finally resulted in increased transcription of nearby genes. (Fig. 4). Further study found that in the subcutaneous tumor xenograft model and disseminated model of AML, the combination of LSD1 inhibitor T-3775440 and the NEDD8-activating enzyme inhibitor pevonedistat could prolong the survival of mice, and synergistic anti-AML effect was achieved through transdifferentiation and DNA replication(126). Notably, although LSD1 has been proven to play a crucial role in the pathogenesis of AML, preclinical studies show that AML cells often exhibit intrinsic resistance to LSD1 inhibitiors. Then, Abdel-aziz, a. k et al. found that inhibition of mTOR in vivo and in vitro can relieve resistance to LSD1 inhibitors in AML cell lines and primary cells are derived from the patient. Functional studies have shown that mTOR complex 1 (mTORC1) signaling is strongly triggered by LSD1 inhibition in drug-resistant leukemia. Insulin receptor substrate 1(IRS1)/ extracellular signaling of the key regulatory kinase ERK1/2 controls LSD1-induced mTORC1 activation(127). It suggested that the combined therapy against LSD1 and mTOR might be a reasonable method for the treatment of AML.

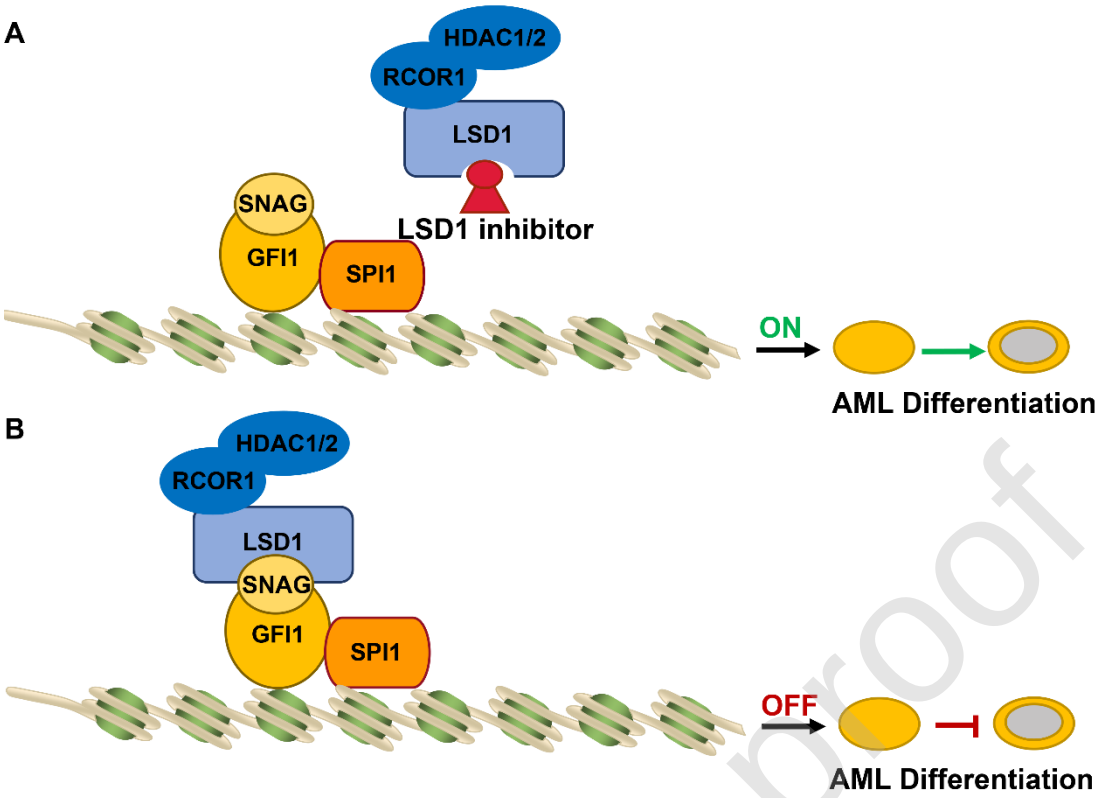


Figure 4. LSD1 inhibition causes separation of LSD1/CoREST from GFI1 at SPI1-bound enhancers, and finally resulted in local increase of histone acetylation and consequent increased transcription of nearby genes.

Table 4 LSD1 inhibitor combined with other drugs in the treatment of AML

LSD1 Inhibitors	Drugs	In vitro or vivo Effects	Ref
SP2509	HDAC inhibitor panobinostat	Enhance the survival of the mice engrafted with human AML cells	[113]
SP2509	EZH2 inhibitor (EPZ6438)	Exert synergistic effects on against AML in vivo and in vitro	[121]
T-3775440	NEDD8-activating enzyme inhibitor (pevonedistat)	Prolong the survival of mice engrafted with human AML cells	[122]

3. Conclusion

AML relies on theclonal malignant proliferation of the hematopoietic myeloid system, mainly manifested as uncontrolled proliferation and the limited differentiation. Classification and prognosis are very complicated, that seriously endanger human

health. At present, the therapy of leukemia includes chemotherapy, targeted therapy, differentiation therapy, monoclonal antibody therapy, stem cell transplantation and so on. However, different limitations have prevented further development for AML treatment. Targeting LSD1 may be a promising strategy for AML treatment. Here, our review focuses on the progress of LSD1 inhibitors, and summarizes the LSD1 inhibitors alone or combined in clinical trials.

At present, some irreversible inhibitors developed based on tranylcypromine（TCP）have entered clinical trials. The discovery of novel scaffolds of LSD1 inhibitors such as phenylcyclopropylamine, polyamine, glycine, indoles, pyrimidines and pyridines provides an ideal strategy for the development of LSD1 inhibitors. LSD1 inhibitors combined with other epigenetic drugs such as EZH2 and HDAC inhibitors can synergistically induce AML differentiation. To address the problem of resistance to LSD1 inhibitors in AML cells, combined LSD1 and mTOR inhibitors can overcome the resistance to LSD1 inhibitors in AML cell lines and primary patient-derived primary cells. These novel LSD1 inhibitors and combination regimens provide new therapeutic strategies for the treatment of AML.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None declared.

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