Epigenetic targets and drug discovery

Part 2: Histone demethylation and DNA methylation

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ABSTRACT

Chromatin structure is dynamically modulated by various chromatin modifications, such as histone/DNA methylation and demethylation. We have reviewed histone methyltransferases and methyllysine binders in terms of their small molecule screening and drug discovery in the first part of this review series. In this part, we will summarize recent progress in chemical probe and drug discovery of histone demethylases and DNA methyltransferases. Histone demethylation and DNA methylation has attracted a lot of attention regarding their biology and disease implications. Correspondingly, many small molecule compounds have been designed to modulate the activity of histone demethylases and DNA methyltransferases, and some of them have been developed into therapeutic drugs or put into clinical trials.

Keywords: **histone demethylation, DNA methylation, inhibitor, chemical probe, drug discovery**

Contents

Abbreviations: LSD, Lysine-specific histone demethylase; HDAC, Histone deacetylase; REST, REST corepressor; DNMT, DNA methyltransferase; MAO, monoamine oxidase; AML, acute myeloid leukemia; KDM, Lysine-specific demethylase; MLL, mixed lineage leukemia; FAD, flavin adenine dinucleotide; PCPA, trans-2-phenylcyclopropylamine; PDCA, 2, 4-pyridindicarboxylic acid; PHD, plant homeobox domain; SCLC, small cell lung cancer; JHDMs, JmjC-domain-containing histone demethylases; NOG, N-oxalylglycine; IOX1, 5-Carboxy-8-hydroxyquinoline; MDS, myelodysplastic syndrome; 2-OG, a-ketoglutarate; G9a, euchromatic histone-lysine N-methyltransferase 2; CoREST complex, restin corepressor complex; SAH, S-Adenosyl-L-homocysteine; SWI complex, ATP dependent chromatin remodeling complexes; Pan-Histone Demethylase Inhibitor, the inhibitor can simultaneously inhibit both LSDs and JHDMs; LSC colony, leukaemic stem cell colony; Pan JmjC domain-containing demethylase inhibitor, the inhibitor can simultaneously inhibit all the members of JHDMs; E2F1, E2F transcription factor 1; E2F2, E2F transcription factor 2; RCC, renal cell carcinoma.

1. Introduction

Dynamic chromatin structure controls many biological processes, such as gene transcription, DNA replication, cell differentiation and proliferation, embryonic development and tumorigenesis, and chromatin structure is tightly modulated by various spatiotemporal chromatin modifications, including DNA/histone modifications and chromatin remodeling. Any alterations in these epigenetic control mechanisms will lead to changes in gene expression patterns and may contribute to human diseases including cancers. Without any doubt, proteins involved in

chromatin modifications and epigenetic regulation are attractive therapeutic targets for drug discovery, and tremendous progress has been made in this field so far.

In the first part of this review series, we have discussed the histone methyltransferases and histone methyllysine reader proteins (Liu et al., 2014). In this installation, we will focus on the recent progress in histone demethylases and DNA methyltransferases in terms of their biological/biochemical functions, along with their associated disease implications and progress in drug discovery.

2. LSD1/2: mono- and di-methyl lysine histone demethylases

To date, five lysine residues on the tails of either histones H3 or H4 (H3K4, H3K9, H3K27, H3K36 and H4K20) and one lysine residue located in the core domain of histone H3 (H3K79) have been shown to be the methylation sites (Zhang & Reinberg, 2001; Margueron et al., 2005). Lysine residues can be mono-, di-, or trimethylated, and two families of enzymes are responsible for maintaining the balance of lysine methylation: histone methyltransferases and histone demethylases, which add or remove methyl marks from the target lysine residues, respectively. Two groups of demethylases have been identified thus far, including the LSD family and the JmjC domain-containing protein family (Strahl & Allis, 2000; Shi et al., 2004; Tsukada et al., 2005; Klose et al., 2006; Kouzarides, 2007; Karytinos et al., 2009).

The LSD family belongs to the flavoenzyme-dependent demethylases. There are two members in this family: LSD1 (also called KDM1A) and LSD2 (also known as KDM1B) (Shi et al., 2004; Karytinos et al., 2009). Crystallographic studies show that LSD1 and LSD2 share a conserved C-terminal amine oxidase domain (AOD) and a SWIRM domain. LSD1 functions to demethylate H3K4me1/2, H3K9me1/2, and non-histone proteins including p53, E2F1 and DNMT1 (Metzger et al., 2005; Garcia-Bassets et al., 2007; Huang et al., 2007; Wang et al., 2008; Xie et al., 2011). LSD1 is present in different protein complexes, such as the HDAC/CoREST/REST complex (Lee et al., 2005; Shi et al., 2005) and the Mi-2/nucleosome remodeling and deacetylase (NuRD) complex (Wang et al., 2009), and displays diverse functions. Even in the HDAC/CoREST/REST complex, LSD1 could either positively or negatively regulate androgen receptor (AR)-associated genes, dependent on its demethylation substrates (Cai et al., 2014). As a component of the NuRD complex, LSD1 can directly interact with one of the three metastasis tumor antigens (MTA) 1/2/3, which in turn target promoter regions of genes and control gene expression (Wang et al., 2009). One important target gene of the LSD1/NuRD complex is TGFβ1 (transforming growth factor β1). It is well established that overexpression of TGFβ1 is linked to breast cancer metastasis. Interestingly, the expression level of TGFβ1 is negatively correlated with that of LSD1. Consistently, LSD1 inhibits invasion of breast cancer cells *in vitro* and downregulation of LSD1 causes breast carcinomas (Wang et al., 2009).

LSD1 is also associated with the MLL (mixed lineage leukemia) supercomplex (Nakamura et al., 2002) or the ELL (elongation factor RNA polymerase II) complex (Biswas et al., 2011). LSD1 was discovered to be an important regulator of leukemia stem cells (LSCs), as it can sustain the growth of MLL-AF9 acute myeloid leukemia (AML) cells via prevention of differentiation and apoptosis, suggesting that LSD1 is involved in carcinogenesis (Harris et al., 2012). Moreover, LSD1 is proposed to be a biomarker for aggressive malignancies and tumor relapse (Kahl et al., 2006; Schulte et al., 2009; Lim et al., 2010). LSD1 is overexpressed in

undifferentiated neuroblastomas compared with the normal one. Knockdown of LSD1 using small interfering RNA (siRNA) or small inhibitors of LSD1 prevented tumor growth in xenograft mouse model *in vivo* (Schulte et al., 2009). Similar results have also been reported in estrogen and progesterone receptor negative breast cancers, especially in the aggressive breast cancers (Lim et al., 2010). It was found that LSD1 up-regulates *CCNA2* (*cyclin A2*) and *ERBB2* (*human epidermal growth factor receptor 2*) in aggressive breast cancers, which promotes the cell proliferation and may play an important role in tumor development and progression (Lim et al., 2010). As well, overexpression of LSD1 has been discovered in other cancers, such as bladder, lung and colon cancers (Hayami et al., 2011; Zhao et al., 2013; Fiskus et al., 2014). Furthermore, prostate tumors with both high mRNA level and protein expression of LSD1 were reported to relapse significantly earlier and more frequently compared to those with low LSD1 expression after radical prostatectomy (Kahl et al., 2006). Thus, LSD1 is proposed to be a predictive biomarker for tumor recurrence and to monitor treatment during therapy.

LSD2 was also identified as an oncogene. It was reported that *LSD2* is located at chromosome 6p22, a genomic region containing high incidence of chromosomal translocations, deletions or amplifications, which is involved in the pathogenesis of many different cancers (Orlic et al., 2006; Heidenblad et al., 2008). However, LSD2 is thought to be involved in biological functions distinct from that of LSD1, because it demethylates H3K4me1/2 of nucleosomes located mainly in the gene body rather than in the promoters, and LSD2 has not been found in any LSD1-containing protein complexes (Fang et al., 2010). To date, LSD2 has been found to play multiple biological roles ranging from gene transcription, DNA damage repair and DNA replication (Fang et al., 2010). LSD2 is associated with elongation factor cyclin T1 (p-TEFb complex) and phosphorylated RNA polymerase II, as well as euchromatic histone methyltransferases such as EHMT1/2 and NSD3, which are located within coding regions of actively transcribed genes to facilitate the gene expression (Fang et al., 2010). In addition, deletion of LSD2 reduced DNA methylation by blocking the methyltransferase activity of DNMTs, leading to the abnormal DNA methylation and contributing to aberrant gene silencing (Katz et al., 2014). Furthermore, LSD2 is highly expressed in breast cancers, especially in invasive tumors; however, the ONCOMINE cancer database also shows the decreased levels of LSD2 in leukemia and seminoma, suggesting that the biological function of LSD2 and its exact role in cancer are likely cell-type or tissue dependent (Katz et al., 2014; ONCOMINE cancer database, Compendia Bioscience; Ann Arbor, MI).

The initial inhibitors for the LSD family were developed based on the inhibitors for monoamine oxidases A and B (MAO A/B) that share homologous catalytic domain with LSDs (Huang et al., 2007; Metzger et al., 2005; Lee et al., 2006). Among these MAO inhibitors (MAOIs), trans-2-phenylcyclopropylamine (PCPA, tranylcypromine) is the most potent LSD1 inhibitor, as it forms a covalent adduct with the flavin adenine dinucleotide (FAD) cofactor of LSD1, resulting in the irreversible inhibition of LSD1 (Lee et al., 2006; Schmidt & McCafferty, 2007; Yang et al., 2007) (Table 1 and Fig. 1A). Based on this chemotype scaffold, a series of tranylcypromine derivatives were designed and tested (Ueda et al., 2009; Binda et al., 2010; Mimasu et al., 2010; Liang et al., 2013) (Table 1 and Fig. 1B-C). Currently, two patents have been filed based on the tranylcypromine derivatives (Patent Numbers WO2011035941A1 and WO2011131576A1). These compounds showed inhibition of cell growth, enhanced differentiation, and even exhibited anti-tumor activity on leukemic cells (Muñoz et al., 2010; Minucci et al., 2011). In addition, polyaminoguanidine derivatives, the analogues of

tranylcypromine, are another interesting set of inhibitors for LSDs (Patent number WO2010084160A1) (Table 1). Remarkably, some of these LSD inhibitors demonstrated selectivity to suppress clonogenic potential and induce differentiation in both murine and human MLL-AF9 AML cells by inhibition of LSD1 *in vitro* and *in vivo* (Guibourt et al., 2010; Harris et al., 2012). Furthermore, one of the Pan-Histone Demethylase Inhibitors, which are able to simultaneously target LSDs and JmjC domain-containing demethylases, was designed by combining the PCPA and JmjC domain-containing protein inhibitors, 2, 2′ -bipyridine or 5-carboxy-8HQ scaffolds. This compound could induce apoptosis in human LNCaP prostate and HCT116 colon cancer cells with low or no toxicity to non-cancer cells; however, these inhibitors have poor selectivity to LSDs (Rotili et al., 2013) (Table 1).

Recently, two tranylcypromine derivatives, ORY-1001 and GSK2879552, are in clinical trials for patients with AML and/or small cell lung cancers (SCLC) (Rhyasen, 2015; Finley & Copeland, 2014; Mohammad et al., 2014) (Table 1). ORY-1001 is in phase I clinical trials by Oryzon, a private European-based biotech company (Trial Number 2013-002447-29). It was reported that ORY-1001 shows more potency than PCPA (over 1,000-fold) with a high selectivity to LSD1 over other monoamine oxidases (Maes et al., 2013). In addition, ORY-1001 was shown to reduce leukaemic stem cell (LSC) colony formation and induce differentiation in AML cell lines (Helin & Dhanak, 2013; Rhyasen, 2015). Concurrently, GlaxoSmithKline developed a potent, selective and mechanism-based irreversible LSD1 inhibitor, GSK2879552. Similar to ORY-1001, GSK2879552 is able to promote the differentiation of AML cells and inhibit the growth of SCLC and AML cells, and an extended survival is also observed in a mouse model after administration of this drug *in vivo* (Trial Numbers NCT02177812 and NCT02034123) (Mohammad et al., 2014). Thus, tranylcypromine derivatives demonstrate the potential to become novel epigenetic anticancer drugs.

In addition to tranylcypromine derivatives, other MAOIs were also modified to develop new LSD inhibitors, such as 1,2,3-triazole–dithiocarbamates, coumarin–1,2,3-triazole–dithiocarbamate hybrids and phenelzine analogues (Zheng et al., 2013; Prusevich et al., 2014; Ye et al., 2014) (Table 1). Of these compounds, the bizine (phenelzine analogue) and compound 8k (a coumarin–1,2,3-triazole–dithiocarbamate hybrid) were identified as the most potent and selective inhibitors of LSD1 with an IC_{50} of 0.059 μM and 0.39 μM, respectively, which show low or no selectivity to other MAOs and even LSD2 (Prusevich et al., 2014; Ye et al., 2014) (Table 1). Furthermore, two histone peptide mimics, aziridinyl-K4H3 (1-21) and propargyl-K4H3 (1-21) were synthesized based on the MAOIs and the LSD1 substrate histone H3 (Culhane et al., 2006; Szewczuk et al., 2007). Despite progress being made with these MAOIs and substrate-based LSD inhibitors, there are some limitations for these compounds, such as large molecular weight, low specificity and potency. Therefore, a series of lysine-mimicking probes containing a propargylamine warhead (compound 5f) were synthesized, which could inhibit LSD1 and result in histone hypermethylation in breast cancer cells (Schmitt et al., 2013) (Table 1 and Fig. 1D).

In order to identify small drug-like molecules as therapeutic agents of LSD1, Hitchin, et al. screened a fragment library of 2,466 compounds, which led to the discovery of a series of fragment-based LSD1 inhibitors (Table 1). However, these compounds were toxic to cells at high concentration, which limits their application in cellular studies., On the other hand, they confirmed GSK354 as a reversible inhibitor of LSD1 and reported that this compound displayed

high potency and selectivity to LSD1 without cytotoxicity at low concentration (Hitchin et al., 2013) (Table 1). By means of structure-based virtual screening (VS) of ~2 million compounds, a potent and selective LSD1 inhibitor, compound 12 (a N′-(1-phenylethylidene) benzohydrazide analogue), was discovered, which specifically inhibits H3K9me2 demethylation of LSD1 (Sorna et al., 2013) (Table 1). It is noteworthy that compound 12 also exhibits strong selectivity to LSD1 over other MAOs, and inhibits the growth of several cancer cell lines including endometrial, breast, colorectal, pancreatic, AML and prostate cancers (Sorna et al., 2013; Fiskus et al., 2014). Kinetic results revealed that compound 12 is noncompetitive with the N-terminus of H3 peptide (Sorna et al., 2013). Currently, patents have been filed for the substituted (E)-N′-(1-phenylethylidene) benzohydrazide analogues by the University of Utah (Patent Number WO2013025805) (Vakayalapati et al., 2012).

3. KDM4: a subfamily of JmjC domain-containing protein demethylases

About 30 JmjC domain-containing proteins have been identified as lysine demethylases in the human genome (Cloos et al., 2008). Based on histone lysine sites and demethylation states, the JmjC domain-containing protein family is divided into six subfamilies: KDM2, KDM3, KDM4, KDM5, KDM6 and PHF (Pedersen & Helin, 2010). The JmjC domain-containing proteins belong to the Fe(II) and 2-oxoglutarate (2-OG)-dependent dioxygenases, which demethylate a variety of targets, including histones (H3K4, H3K9, H3K27, H3K36 as well as H1K26) and non-histone proteins (Gray et al., 2005; Tsukada et al., 2005; Klose et al., 2006; Shi 2007; Shin & Janknecht, 2007; Ponnaluri et al., 2009). Unlike the LSD family, the JmjC-domain-containing histone demethylases (JHDMs) are able to erase all three kinds of histone lysine-methylation states since the JHDMs do not require protonated nitrogen for demethylation (Klose et al., 2006; Rotili & Mai, 2011).

The *KDM4* gene family, first identified *in silico*, consists of six members, including *KDM4A*, *KDM4B*, *KDM4C*, *KDM4D*, *KDM4E* and *KDM4F* (Katoh & Katoh, 2004). According to their domain structures, the KDM4 family can be further classified into two groups: KDM4A, KDM4B and KDM4C as one group, and KDM4D, KDM4E and KDM4F as the other group. The first group of proteins contains two PHD domains and two Tudor domains in addition to a JmjN and a JmjC domain, whereas the second group of proteins only contains a JmjN and a JmjC domain (Katoh & Katoh, 2004). KDM4A/B/C remove methyl groups from both methylated H3K9 and H3K36 with KDM4A showing some preference for the methylated H3K9 over H3K36 (Klose et al., 2006; Whetstine et al., 2006; Hillringhaus et al., 2011). In addition to histone proteins, KDM4A/B/C exhibit demethylase activity on non-histone proteins, such as WIZ, CDYL1 and G9a (Ponnaluri et al., 2009). In contrast, KDM4D is only able to demethylate H3K9 (Klose et al., 2006; Shin & Janknecht, 2007; Krishnan & Trievel, 2013). *KDM4E* and *KDM4F* are adjacent to *KDM4D* in the chromosome, but are pseudogenes due to their lack of the promoters (Whetstine et al., 2006). KDM4E has shown demethylase activity when ectopically expressed (Hillringhaus et al., 2011).

KDM4 proteins are associated with different protein complexes. KDM4A and KDM4B interact with the SWI/SNF-B complex, whereas KDM4C is associated in the SWI/SNF-A complex, both leading to transcriptional activation through histone demethylation (Kawazu et al., 2011). KDM4 proteins also associate with HDAC complexes to suppress gene transcription. For example, KDM4A interacts with class I HDACs and retinoblastoma protein (pRb), leading to

HDAC-mediated gene inactivation (Gray et al., 2005). Therefore, the KDM4 demethylases are able to function as both transcriptional activators and repressors depending on which complexes they are associated with, and are involved in diverse cellular processes, such as regulation of cell cycle, DNA damage repair and even carcinogenesis (Cloos et al., 2006; Shin & Janknecht, 2007; Li et al., 2011; Berry et al., 2012; Kim et al., 2012; Mallette et al., 2012). An abundance of evidence has demonstrated that overexpression of KDM4 demethylases is involved in numerous cancers. For instance, KDM4A/B/C overexpression has been discovered in breast, prostate, lung, gastric, bladder, lymphoma, medulloblastomas and colorectal cancers, whereas deletion or knockdown of KDM4A/B/C reduced cancer cell proliferation and growth (Cloos et al., 2006; Cloos et al., 2008; Northcott et al., 2009; Rui et al., 2010; Kawazu et al., 2011; Toyokawa et al., 2011; Berdel et al., 2012; Berry & Janknecht, 2013). Therefore, it is highly prudent to target KDM4 as a novel option for cancer therapy.

, Several potential inhibitor chemotype skeletons of the KDM4 family have been identified, such as N-oxalyl amino acids, hydroxamic acids, daminozide, pyridine carboxylates, bipyridyl inhibitors, and 8-hydroxyquinolines (Rose et al., 2008; King et al., 2010; Chang et al., 2011; Chu et al., 2014). Specifically, Rose, et al. identified 2, 4-pyridindicarboxylic acid (PDCA), a pyridine carboxylate, as a potent inhibitor for KDM4 with an IC_{50} of 0.7 μM for KDM4A and 1.4 μM for KDM4E, respectively (Rose et al., 2008) (Table 2). Recently, on the basis of PDCA, a series of pyridine carboxylate derivatives have been synthesized and analyzed for KDM families, which generated some more highly potent inhibitors of KDM over the original compound (Labelle et al., 2014; Patent Number WO2014053491A1_Epitherapeeutics) (Table 2). In addition, a series of 4-Carboxy-2, 2'-Bipyridyl compounds (bipyridyl inhibitors) were screened against KDM4 subfamily, leading to potent compound 15c with an IC_{50} of 0.11 μM for KMD4E (Chang et al., 2011) (Table 2). The complex structure of KDM4A with bipyridyl inhibitor revealed that this compound inhibits KDM4A not only by competing with 2-OG, but also by occupying part of the binding site of the polypeptide backbone. In addition, compounds containing the 4-carboxylate group are 300-fold more potent than compounds without it, implying that the 4-caboxylate group can be further utilized to develop more potent inhibitors for the KDM4 proteins in the future (Chang et al., 2011) (Fig. 2A).

King, et al. screened 236,000 molecules against KDM4E by quantitative high-throughput screening (qHTS), which identified 5-Carboxy-8-hydroxyquinoline (IOX1), an 8-hydroxyquinoline derivative, as an effective inhibitor to KDM4E with nanomolar potency (IC_{50} of 0.2 μM *in vitro*). This compound is less active toward FIH and PHD2, suggesting that 5-Carboxy-8-hydroxyquinoline is a more suitable prodrug for the KDM4 proteins (King et al., 2010) (Table 2). Similar to PDCA, the structure of KDM4A in complex with IOX1 revealed that this compound inhibits KDM4A in a competitive manner with respect to 2-OG, in addition to binding to the other side chains of the active binding sites (Rose et al., 2008; King et al., 2010) (Fig. 2B). Due to the poor cell permeability of IOX1, a series of 8-hydroxyquinoline derivatives has been designed. An n-octyl ester derivative of IOX1 was reported by Schiller et al., which showed not only high cell permeability but also high selectivity and even less toxicity with preserving cell viability (Schiller et al., 2014) (Table 2). Comparing the complex structures of KDM4A with IOX1 and the n-octyl ester derivative of IOX1 by docking, it was discovered that the KDM4A active site can accommodate IOX1 ester derivatives, but the length of the alkyl chain is likely to affect the binding affinity. It is interesting to note that SD70, an anticancer drug for prostate cancer, also contains an 8-hydroxyquinoline moiety. It was found that SD70

preferentially suppresses the androgen-dependent prostate cancer cells growth *in vitro* and *in vivo* by inhibiting the H3K9me2 demethylation of KDM4C (Jin et al., 2014) (Table 2). In addition, the reported Pan-Histone Demethylase Inhibitor (Rotili2014_cmpd1) also shows a potent inhibition to KDM4 family (Rotili et al., 2013) (Table 2). Therefore, it is desirable to further modify the 8-hydroxyquinoline compound to develop it into a prodrug of KDM4 proteins.

Structurally, KDM4A contains a Cys3-His Zn(II) binding site that is close to the N-methyl lysine-residue binding site; thus, chemical probes, such as ebselen, disulfiram and its pyrrolidinyl substituents, have been designed to eject Zn(II) to inhibit the catalytic activity of KDM4A (Nathan, 2009). Moreover, based on the complex crystal structures of JmjC domain-containing proteins, N-methyl lysine peptides and 2-OG or inhibitors (such as N-oxalyl-D-cysteine (DNOC1) compound), several selective and potent inhibitors for KDM4 were synthetized (Luo et al., 2011; Woon et al., 2012). As described in Luo, et al., compound 1, containing a methyllysine mimic, a 2-OG mimic, and a 4-carbon linker combining these two parts, was identified and found to specifically inhibit KDM4 over other JmjC domain-containing proteins *in vitro* (Table 2). However, compound 1 had low cell permeability, so they designed and tested a methyl ester-containing prodrug, Methylstat (Table 2). Methylstat exhibited high stability in cells and was able to induce increase in levels of H3K4me3 and H3K9me3 in a concentration-dependent manner. It is noteworthy that it also inhibits growth of the esophageal carcinoma cell line KYSE150 (Luo et al., 2011). In sum, these discoveries lay the foundation for future studies regarding the development of new potent and selective inhibitors of KDM4.

Recently, Wang, et al. identified a Pan JmjC domain-containing demethylase inhibitor JIB-04, which contains a pyridine hydrazine with two isomers, E- and Z- isomer, and found that only the E-isomer of JIB-04 can exhibit the inhibitory activity (Wang et al., 2013). JIB-04 selectively inhibits the JHDMs rather than other epigenetic enzymes by chelating iron in the catalytic site and disrupting histone substrate binding of JHDMs. Among the KDM4 subfamily, JIB-04 is the most potent to KDM4D with an IC_{50} of 0.29 μM, which is five-fold more potent over the PDCA (with an IC_{50} of 1.4 μM) *in vitro*. In addition, there is decreased level of H3K9me2 product from H3K9me3 demethylation *in vitro*, in cancer cells as well as in tumors mice when treated with JIB-04, suggesting that JIB-04 can inhibit the demethylase activity of KDM4 (Wang et al., 2013). Furthermore, JIB-04 selectively diminished cancer cells growth with a decreased rate of tumor growth and lower tumor weights *in vivo* in tumor xenografts mice injected with human lung cancer cells, but showed no toxicity in the normal mice. Meanwhile, treated with JIB-04, the mice with mammary tumors showed longer survival compared with the untreated one. This may be linked to the transcriptional changes in genes involved with cell proliferation, cell death, the energy-deprivation responses and glycolytic metabolism, which are regulated by JHDMs, such as proliferative genes *CCNB1* (*cyclin B1*) and *PCNA* (*proliferating cell nuclear antigen*), the oncogene *SKP2* (*S-phase kinase-associated protein 2*), and the proapoptotic genes *DDIT4* (*DNA-damage-inducible transcript 4*) and *CCNG2* (*cyclin G2*) (Wang et al., 2013). So far, many inhibitors of KDM4 demethylases have been reported, but JIB-04 is the only reported inhibitor that can modulate the cancer survival environment by directly inhibiting epigenetic enzymatic activity, and the only compound going into preclinical trial to date.

4. The other subfamilies of JmjC domain-containing protein demethylases

4.1 KDM2 subfamily

The KDM2 (also named FBXL) subfamily includes two members: KDM2A and KDM2B. KDM2A is able to demethylate histone H3K36me1/2 and non-histone proteins, like RelA (p65), a subunit of nuclear factor-κB (NF-κB) (Lu et al., 2010). Although all the three methylated states of H3K36 can insert into the catalytic pocket of KDM2A, steric hindrance to the rotation of 2-OG prevents it changing from the ‘‘off-line’’ to ‘‘in-line’’ modes in the presence of H3K36me3 (Cheng et al., 2014). In contrast, KDM2B can demethylate not only H3K36me1/2 but also H3K4me3 (Tsukada et al., 2005; Pfau et al., 2008; Tzatsos et al., 2009; Janzer et al., 2012; Liang et al., 2012). Since KDM2 proteins are partner-dependent demethylases, they are involved in diverse biological processes, such as ribosomal RNA transcription, cell proliferation, apoptosis, differentiation, and even carcinogenesis (Suzuki et al., 2006; Koyama-Nasu et al., 2007; Tanaka et al., 2010; Dong et al., 2013; Wagner et al., 2013; Kawakami et al., 2014; Huang et al., 2015). Reduced expression of KDM2A and KDM2B is linked to prostate cancers and glioblastomas, respectively, and overexpression of KDM2B is implicated in bladder cancer, T-cell and B-cell acute lymphoblastic leukemias (T-ALL and B-ALL), AML, seminomas, breast and pancreatic adenocarcinomas (Frescas et al., 2007; Frescas et al., 2008; Kottakis et al., 2011; Zhang et al., 2011; Curtis et al., 2012; Tzatsos et al., 2013). This is indicative of the cell-type or tissue-specific effects of KDM2A/B expression.

Rose, et al. screened a set of 2-OG oxygenase inhibitors through activity-based AlphaScreens (amplified luminescence proximity homogeneous assays) and identified daminozide as an inhibitor to KDM2A with IC_{50} of 1.5 μM (Rose et al., 2012) (Table 2). Kinetic analyses revealed that daminozide is predominantly a competitive inhibitor through replacing the 2-OG cofactor of KDM2A (Rose et al., 2012). Due to the genotoxicity of daminozide, Suzuki, et al. designed a series of compounds based on hydroxamate, and identified a phenyl ring containing compound (compound 13 as referred to in the reference), which shows a more potent inhibiting activity to KDM2A (Suzuki et al., 2013) (Table 2). In addition, the reported Pan-Histone Demethylase Inhibitor (Rotili2014_cmpd1) also shows a potent inhibition to KDM2A (Rotili et al., 2013) (Table 2). Hence, these discoveries allow for further development of more specific inhibitors to KDM2A as a potential cancer therapeutic.

4.2 KDM5 subfamily

The KDM5 subfamily contains four enzymes: KDM5A, KDM5B, KDM5C and KDM5D, which specifically remove methyl marks from H3K4me2/3 (Rotili & Mai, 2011). Of these enzymes, KDM5A, KDM5B and KDM5C have been shown to interact with the HDAC-containing complexes, such as NCoR and Sin3 complexes, and are involved in a variety of biological processes including cell differentiation, development, senescence, signal transduction, and metabolic processes (Tan et al., 2003; Barrett et al., 2007; Hayakawa et al., 2007; Klose et al., 2007; Tahiliani et al., 2007; van Oevelen et al., 2008; Hayakawa & Nakayama, 2010; Liefke et al., 2010; Huang et al., 2011; Zou et al., 2014). In addition, *KDM5D*, a homolog of mouse *SMCY*, was first isolated in the short arm of Y chromosome (Agulnik et al., 1994; Kent-First et al., 1996). KDM5D directly interacts with Ring6a/MBLR, homologs of Bmi1 and Mel18 proteins that are components of the polycomb complex PRC1 (Lee et al., 2007). Furthermore, KDM5D can modulate the transcriptional repression together with NURF (nucleosome remodeling factor), a chromatin remodeling complex, in the brain (Lee et al., 2007).

The KDM5 enzymes have been implicated in tumorigenesis, and overexpression of KDM5A has been observed in lung and gastric cancers (Zeng et al., 2010; Qi et al., 2014), while KDM5B was overexpressed in bladder cancer, lung cancer, AML, breast cancer, chronic myelogenous leukemia (CML), cervical cancer, metastatic prostate cancer, testicular cancer and renal cell carcinoma (RCC), which were not discovered in the corresponding non-neoplastic tissues (Hayami et al., 2010). Moreover, the knockdown of KDM5B by siRNA diminished the cancer cell growth, which purportedly resulted from the decreased expression of E2F1 and E2F2 that are the downstream modulators regulated by KDM5B in the retinoblastoma protein (pRb) pathway (Barrett et al., 2002; Xiang et al., 2007; Yamane et al., 2007; Hayami et al., 2010; Yamamoto et al., 2014). A large number of point mutations have been identified within the *KDM5C* gene in patients with X-linked mental retardation (XLMR) (Wu et al., 1994; Brown et al., 1995; Jensen et al., 2005; Santos et al., 2006; Tzschach et al., 2006).

GSK-J1 and GSK-J4 were first identified as specific inhibitors for the KDM6 subfamily, as described in section 4.3. However, it was also found that GSK-J1 and GSK-J4 inhibit the H3K4me3/me2 demethylation of KDM5B and KMD5C with five-fold to ten-fold less potency than KDM6B and KDM6A, suggesting that GSK-J1/J4 compounds are not strictly specific to KDM6 subfamily (Heinemann et al., 2014) (Table 2). In addition, as described in section 3 in this review, JIB-04, the Pan JmjC domain-containing demethylase inhibitor, can inhibit the demethylase activity of KDM5A with an IC_{50} of 0.23 μM in noncompetitive manner with 2-OG, which can be further optimized for development of the specific inhibitor of KDM5 subfamily (Wang et al., 2013) (Table 2). Recently, a patent was filed for pyridine carboxylate derivative inhibitors of KDM families, which will shed light on the direction for the development of more potent inhibitors for KDM5 (Patent Number WO2014053491A1_Epitherapeeutics; Labelle et al., 2014) (Table 2).

4.3 KDM6 subfamily

In the human genome, the KDM6 subfamily is comprised of KDM6A, KDM6B and UTY, which share a well-conserved JmjC histone catalytic domain. However, KDM6A and KDM6B show higher catalytic activity to H3K27me2/3 over UTY (Agger et al., 2007; Lan et al., 2007; Lee et al., 2007; Walport et al., 2014). To date, KDM6A and KDM6B were reported to be associated with the H3K4 MLL methyltransferase complex, which can lead to activation of homeobox (*HOX*) cluster genes through the removal of repressive marks (H3K27me2/3) and the simultaneous addition of an active mark (H3K4me3) (Agger et al., 2007; Cho et al., 2007; De Santa et al., 2007; Issaeva et al., 2007; Lee et al., 2007). Extensive KDM6A mutations are present in some cells that are involved in multiple myeloma, esophageal squamous cell carcinoma and RCCs (van Haaften et al., 2009; Dalgliesh et al., 2010). KDM6B can activate the tumor suppressors, p16INK4A and p14ARF, that are coded by the INK4A–ARF locus, indicating that KDM6B mutations or dysregulation might be involved in carcinogenesis (Agger et al., 2009).

Recently, based on the complex structure of KDM6B with H3K27me3, Kruidenier, et al. identified a selective compound, GSK-J1, for KDM6A and KDM6B by screening the GlaxoSmithKline corporate compound library (Kruidenier et al., 2012) (Table 2). GSK-J1 is able to selectively inhibit KDM6B with IC_{50} of 60 nM through competition with the 2-OG binding site and interacting with the catalytic metal (Fig. 2C). Considering the low cellular permeability

of GSK-J1, they generated a prodrug GSK-J4 with an ethyl ester, which exhibits higher intracellular concentrations than GSK-J1 (Kruidenier et al., 2012) (Table 2). Furthermore, GSK-J4 prevents the loss of H3K27me3 marker induced by KDM6B in cells. In addition, GSK-J1 also inhibits KDM6C, KDM5B and KDM5C (Heinemann et al., 2014; Walport et al., 2014). Moreover, JIB-04, described in section 3 in this review, can inhibit the demethylase activity of KDM6B with IC_{50} of 0.85 μM in addition to the KDM4 and KDM5 subfamilies (Wang et al., 2013). Thus, further optimization of these GSK and JIB-04 compounds would warrant development of more specific inhibitors for KDM6.

5. DNMTs: DNA methyltransferases

DNA methylation at the 5-position of cytosine (5mC) is a key epigenetic mark playing crucial roles in vertebrate development, genomic imprinting and X-chromosome inactivation (Sheardown et al., 1997; Lefebvre et al., 1998; Ng & Adrian, 1999). DNA methylation mainly appears within CpG dinucleotides, and approximately 80% of CpG dinucleotides are methylated. In mammals, DNA methylation is established by the *de novo* methyltransferases DNMT3A and DNMT3B, and maintained by the maintenance methyltransferase DNMT1. The genomes of the cancer patients are globally hypomethylated, but many promoter-associated CpG islands of those tumor suppressor genes become hypermethylated. Therefore, alterations in DNA methylation are associated with carcinogenesis (Razin & Cedar,1993; Kanai et al., 1996; Eguchi et al., 1997; Kanai et al., 1997; Kanai et al., 1998; Kanai et al., 2000).

DNMT1, as the first identified DNA methyltransferase, preferentially methylates hemi-methylated DNA over unmodified DNA *in vitro*, which plays a critical role in cellular differentiation as well as in dividing cells (Leonhardt et al., 1992). DNMT1 directly interacts with the E3 ubiquitin-protein ligase UHRF1 to target the replication forks and damage repair sites (Bostick et al., 2007). Unlike DNMT1, the methyltransferases DNMT3A and DNMT3B display no preference to hemi-methylated DNA (Lei et al., 1996; Okano et al., 1999). DNMT3A and DNMT3B can initially methylate unmodified DNA, hence they are also named *de novo* methyltransferases. *DNMT3A*-null mice appear to be grossly normal at birth, but they display organ defects and lethality within weeks after birth, whereas deficient *DNMT3B* is linked to drastic defects in minor satellite repeat methylation, leading to immunodeficiency, centromere instability, and facial anomalies (ICF) syndrome (Okano et al., 1999; Jin et al., 2008). Similar to DNMT1, DNMT3A and DNMT3B also require a partner protein, DNMT3L, which is homologous to DNMT3A/B but lacks enzymatic activity, to target nucleosomes (Aapola et al., 2002; Chédin et al., 2002; Suetake et al., 2004; Chen et al., 2005; Ooi et al., 2007).

DNA methylation is linked to various human cancers through distinct mechanisms, including deregulation of DNA methylation, activating or inactivating mutations and aberrant expression of DNA methyltransferases. Dysregulation of DNA methylation is associated with hematologic malignancies, systemic lupus erythematosus, asthma, lymphomas and myelodysplastic syndrome (MDS) (Rice et al., 2007; Ho, 2010; Patel & Richardson, 2010; Wierda et al., 2010). Hitherto, mutations in DNA methyltransferases have been discovered in various diseases, such as colorectal cancer, hereditary sensory and autonomic neuropathy type 1 (HSAN1), MDS, AML, T-cell lymphoma, ICF syndrome, breast and lung adenomas (Wijmenga et al., 2000; Shen et al., 2002; Kanai et al., 2003; Wang et al., 2006; Ley et al., 2010; Klein et al., 2011; Walter et al., 2011; Yan et al., 2011; Couronné et al., 2012; Ribeiro et al., 2012; Winkelmann et al., 2012). It

was reported that the carcinogenesis-related mutations are present in both the catalytic domain and non-catalytic domains of DNMT3A and DNMT3B (Wang et al., 2006; Ley et al., 2010). Overexpression of DNMT1, DNMT3A and DNMT3B was discovered in diverse tumors, such as bladder cancer, colorectal cancer, kidney cancer, AML and CML (Sun et al., 1997; Robertson et al., 1999; Mizuno et al., 2001; Saito et al., 2001). DMNT1 is also a prognostic biomarker. It was reported that patients with low DNMT1 expression correlated with high chemosensitivity and showed significantly better clinical responses and overall survival than patients with high level of DNMT1 (Saito et al., 2003; Peng et al., 2005; Mutze et al., 2011). Since many tumor suppressor genes are silenced by DNA methylation during carcinogenesis, DNA methyltransferase inhibitors have been actively sought after in the past two decades in an attempt to re-activate these tumor suppressor genes. At the present time, three drugs, including 5-azacytidine (azacitidine, AZA), 5-aza-2′-deoxycytidine (decitabine, DAC) and RX-3117, have been approved by the Food and Drug Administration (FDA), and four other inhibitors are in clinical trials, including 5-Fluoro-2'-deoxycytidine (FdCyd), SGI-110, Hydralazine and genistein. Due to the low efficacy, the clinical trials for 1-β-D-arabinofuranosyl-5-azacytosine (Fazarabine), dihydro-5-azacytidine (DHAC), and MG98 were stopped (Table 3).

Nucleosidic DNA Methylation Inhibitors

The DNA methylation inhibitors, AZA and DAC, have been approved by the FDA for the treatment of MDS and AML (Jones & Taylor, 1980; Jones et al., 1982; Santi et al., 1984; Cheng et al., 2004; Bryan et al., 2011; Lübbert, 2000; Robak, 2011). As a side-effect, AZA and DAC can incorporate into the genome as part of its mechanism of action, which can cause mutations in the daughter cells if the cell does not die (Jones & Taylor, 1980; Santi et al., 1984; Davidson et al., 1992). In fact, these compounds were toxic to the bone marrow (Davidson et al., 1992; Jüttermann et al., 1994; Stresemann et al., 2006; Constantinides et al., 1977; Jones & Taylor, 1980; Cheng et al., 2003). On the basis of AZA, Fazarabine and DHAC were synthesized and tested in clinical trials (Beisler et al., 1977; Beisler et al., 1979); however, both trials were stopped due to the low efficacy in cancer therapies (Holoye et al., 1987; Casper et al., 1992; Ben-Baruch et al., 1993; Creagan et al., 1993; Williamson et al., 1995; Samuels et al., 1998; Goffin & Eisenhauer, 2002). Some azacytidine analogues, such as 5,6-dihydroazacytidine (5,6-dihydro-AZA), 5-Fluoro-2'-deoxycytidine (FdCyd), and 1-(beta-d-ribofuranosyl)-1,2-dihydropyrimidin-2-one (Zebularine) were also shown to inhibit DNMTs (Zhou et al., 2002; Cheng et al., 2003; Cheng et al., 2004; Thottassery et al., 2014). FdCyd has been utilized to treat solid tumors combined with tetrahydrouridine (THU), an inhibitor of cytidine deaminase, in clinical studies (Fahy et al., 2012). Remarkably, Zebularine's potency is less than AZA and DAC, but it is able to suppress tumorigenesis with reduced toxicity and also displays better oral bioavailability, implying that Zebularine is a good candidate as a prodrug of DNMTs (Cheng et al., 2003; Cheng et al., 2004). Although no pharmaceutical or clinical studies have been reported, Zebularine is widely used as a reference compound and patents have been filed (Patent Numbers WO2003012051 and WO2005082144) (Table 3).

Astex Pharmaceuticals, an Otsuka Pharmaceutical company, synthesized a series of prodrugs based on DAC, and identified SGI-110 as a potent inhibitor to DNMTs. SGI-110 displays desirable pharmacokinetics and metabolic stability, and is currently in Phase II clinical trials for patients with MDS and AML (Yoo et al., 2007; Chuang et al., 2010; Singh et al., 2013; Tanq et al., 2013; Fang et al., 2014; Srivastava et al., 2014; Tellez et al., 2014). RX-3117,

another nucleoside analogue, was designed and developed based on cyclopentenyl-cytosine derivatives by Rexahn, a clinical stage biopharmaceutical company. Like azacitidine, RX-3117 is able to incorporate into RNA and DNA resulting in inhibition of DNMTs (Fahy et al., 2012). RX-3117 has been approved by the FDA for the treatment of pancreatic cancers. In addition, more nucleoside analogues were designed and studied for their ability to inhibit DNMTs, such as 2-(p-nitrophenyl) ethoxycarbonyl-DAC (NPEOC-DAC), CP-4200, 4'-thio-2'-deoxycytidine (T-dCyd), and 5-aza-4'-thio-2'-deoxycytidine (5-aza-T-dCyd) (Patent Numbers WO2009042766, WO2009042767, WO2011109012 and US 20110218170 A1) (Byun et al., 2008; Brueckner et al., 2010; Thottassery et al., 2010; Thottassery et al., 2014) (Table 3). Collectively, these findings suggest we are close to finding low toxicity DNMT-depleting anticancer drugs.

Non-Nucleosidic DNA Methylation Inhibitors

Some non-nucleoside inhibitors also have been shown to inhibit the methyltransferase activity of DNMTs, such as Hydralazine, Procaine, Mithramycin A (MMA), Nanaomycin A, SGI-1027, RG108, SAH analogues, and oligonucleotides MG98 and miR29a (Brueckner et al., 2005; Amato, 2007; Lin et al., 2007; Datta et al., 2009; Garzon et al., 2009; Isakovic et al., 2009; Kuck et al., 2010) (Table 3). Among these inhibitors, a phase II clinical study for Hydralazine has been carried out to test its efficacy in treating refractory solid tumors combined with valproate, a histone deacetylase inhibitor (Trial Number NCT00404508). In addition, MG98, an antisense oligonucleotide, was shown to inhibit DNMT1 by reducing both mRNA and protein levels in a dose dependent manner in cancer cells, which slows the growth of cancer cells by inhibiting cell proliferation (Agrawal & Iyer, 1997; Amato, 2007). However, due to its low effect in treatment of metastatic renal cancer, the clinical trials for MG98 were stopped (Davis et al., 2003; Plummer et al., 2009).

DNMT enzymes transfer the methyl group from the methyl donor SAM (S-adenosylmethionine) to substrates, producing SAH (S-Adenosyl-L-homocysteine) and methylated substrates. Thus, SAH can act as a general inhibitor of DNA methyltransferases. Hitherto, a number of SAH analogue inhibitors of DNMTs have been developed and patented (Patent Number WO2006078752). Interestingly, Sinefungin, an antifungal antibiotic isolated from Streptomyces griseolus and was first identified as a potent inhibitor of viral mRNA methyltransferases in 1978, has now been shown to inhibit DNMT1 (Isakovic et al., 2009) (Table 3 and Fig. 3). In addition, some other non-nucleosidic DNA methylation inhibitors were also patented, such as procainamide derivatives (Patent Number WO2012087889), cyclopenta and cyclohexathiophene derivatives (Patent Number WO2010098866), alcyne derivatives (Patent Number WO2008098077), substituted amino-benzoic acid derivatives (Patent Number WO2012038417), small organic compounds (Patent Numbers WO2007007054 and WO2008033744), flavones and flavanones derivatives (Patent Number WO2011029956 A1), and substituted alkine derivatives (Patent Number WO2008098077). Despite progress in the development of non-nucleosidic DNA methylation inhibitors, one study found that 5-aza-T-dCyd far exceeded this class of drugs (specifically hydralazine and procainamide) in the ability to inhibit DNA demethylation and reactivate genes (Chuang et al., 2005).

Interestingly, some natural compounds have also been reported to repress the methyltransferase activity of DNMTs, such as (-)-epigallocatechin-3-gallate (EGCG), genistein and curcumin, which are the major active ingredients of green tea, soybean and the Indian curry

spice turmeric, respectively (Fang et al., 2005; Medina-Franco et al., 2011) (Table 3). Remarkably, genistein is being studied to treat patients with prostate cancer in phase II clinical trials (Trial Number NCT01126879) (Delpu et al., 2013).

6. Conclusion

Presently, a large amount of data has been amassed for histone demethylases as well as DNA methyltransferases with regards to their biological functions and disease implications, implying that epigenetic markers play an important role in the pathogenesis of cancers and other diseases. Therefore, proteins involved in this field are attractive therapeutic targets for drug design and development. In this review, we systematically reviewed the progresses in the discovery of chemical probes and therapeutic compounds for histone demethylases and DNA methyltransferases. These compounds could subsequently be used to further study the biological functions and pathogenesis of these targets. The growing number of crystal structures of these protein targets and their co-crystals will provide critical sources of information for the design and optimization of future epigenetic-specific drugs.

Conflict of interest statement

The authors declare no conflicts of interest.

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References

Aapola, U., Liiv, I., & Peterson, P. (2002). Imprinting regulator DNMT3L is a transcriptional repressor associated with histone deacetylase activity. *Nucleic Acids Res 30*(16), 3602-3608.

Agger, K., Cloos, P. A., Christensen, J., Pasini, D., Rose, S., Rappsilber, J., et al. (2007). UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. *Nature 449*(7163), 731-734.

Agger, K., Cloos, P. A., Rudkjær, L., Williams, K., Andersen, G., Christensen, J., et al. (2009). The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A–ARF

locus in response to oncogene-and stress-induced senescence. *Genes Dev 23*(10), 1171-1176.

Agrawal, S., & Iyer, R. P. (1997). Perspectives in antisense therapeutics. *Pharmacol Ther 76*(1), 151-160.

Agulnik, A. I., Mitchell, M. J., Lerner, J. L., Woods, D. R., & Bishop, C. E. (1994). A mouse Y chromosome gene encoded by a region essential for spermatogenesis and expression of male-specific minor histocompatibility antigens. *Hum Mol Genet 3*(6), 873-878.

Amato, R. J. (2007). "Inhibition of DNA methylation by antisense oligonucleotide MG98 as cancer therapy." *Clin Genitourin Canc 5* (7), 422-426.

Barrett, A., Madsen, B., Copier, J., Lu, P. J., Cooper, L., Scibetta, A. G., et al. (2002). PLU‐1 nuclear protein, which is upregulated in breast cancer, shows restricted expression in normal human adult tissues: A new cancer/testis antigen? *Int J Cancer 101*(6), 581-588.

Barrett, A., Santangelo, S., Tan, K., Catchpole, S., Roberts, K., Spencer Dene, B., et al. (2007). Breast cancer associated transcriptional repressor PLU‐1/JARID1B interacts directly with histone deacetylases. *Int J Cancer 121*(2), 265-275.

Beisler, J. A., Abbasi, M. M., & Driscoll, J. S. (1979). Synthesis and antitumor activity of 5-azacytosine arabinoside. *J Med Chem 22*(10), 1230-1234.

Beisler, J. A., Abbasi, M. M., Kelley, J. A., & Driscoll, J. S. (1977). Synthesis and antitumor activity of dihydro-5-azacytidine, a hydrolytically stable analog of 5-azacytidine. *J Med Chem 20*(6), 806-812.

Ben-Baruch, N., Denicoff, A. M., Goldspiel, B. R., O'Shaughnessy, J. A., & Cowan, K. H. (1993). Phase II study of fazarabine (NSC 281272) in patients with metastatic colon cancer. *Invest New Drugs 11*(1), 71-74.

Berdel, B., Nieminen, K., Soini, Y., Tengström, M., Malinen, M., Kosma, V., et al. (2012). Histone demethylase GASC1-a potential prognostic and predictive marker in invasive breast cancer. *BMC cancer 12* (1), 516.

Berry, W. L., & Janknecht, R. (2013). KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells. *Cancer Res 73*(10), 2936-2942.

Berry, W. L., Shin, S., Lightfoot, S. A., & Janknecht, R. (2012). Oncogenic features of the JMJD2A histone demethylase in breast cancer. *Int J Oncol 41*(5), 1701-1706.

Binda, C., Valente, S., Romanenghi, M., Pilotto, S., Cirilli, R., Karytinos, A., et al. (2010). Biochemical, structural, and biological evaluation of tranylcypromine derivatives as inhibitors of histone demethylases LSD1 and LSD2. *J Am Chem Soc 132*(19), 6827-6833.

Biswas, D., Milne, T. A., Basrur, V., Kim, J., Elenitoba-Johnson, K. S., Allis, C. D., et al. (2011). Function of leukemogenic mixed lineage leukemia 1 (MLL) fusion proteins through distinct partner protein complexes. *Proc Natl Acad Sci U S A 108*(38), 15751-15756.

Bostick, M., Kim, J. K., Estève, P., Clark, A., Pradhan, S., & Jacobsen, S. E. (2007). UHRF1 plays a role in maintaining DNA methylation in mammalian cells. *Science 317*(5845), 1760-1764.

Brown, C. J., Miller, A. P., Carrel, L., Rupert, J. L., Davies, K. E., & Willard, H. F. (1995). The DXS423E gene in Xp11. 21 escapes X chromosome inactivation. *Hum Mol Genet 4*(2), 251-255.

Brueckner, B., Boy, R. G., Siedlecki, P., Musch, T., Kliem, H. C., Zielenkiewicz, P., et al. (2005). Epigenetic reactivation of tumor suppressor genes by a novel small-molecule inhibitor of human DNA methyltransferases. *Cancer Res 65*(14), 6305-6311.

Brueckner, B., Rius, M., Markelova, M. R., Fichtner, I., Hals, P., Sandvold, M. L., et al. (2010). Delivery of 5-azacytidine to human cancer cells by elaidic acid esterification increases therapeutic drug efficacy. *Mol Cancer Ther 9*(5), 1256-1264.

Bryan, J., Kantarjian, H., Garcia-Manero, G., & Jabbour, E. (2011). Pharmacokinetic evaluation of decitabine for the treatment of leukemia. *Expert Opin Drug Metab Toxicol 7*(5), 661-672.

Byun, H., Choi, S. H., Laird, P. W., Trinh, B., Siddiqui, M. A., Marquez, V. E., et al. (2008). 2′ -Deoxy-N4-[2-(4-nitrophenyl) ethoxycarbonyl]-5-azacytidine: a novel inhibitor of DNA methyltransferase that requires activation by human carboxylesterase 1. *Cancer lett 266*(2), 238-248.

Cai, C., He, H. H., Gao, S., Chen, S., Yu, Z., Gao, Y., et al. (2014). Lysine-Specific Demethylase 1 Has Dual Functions as a Major Regulator of Androgen Receptor Transcriptional Activity. *Cell Rep 9*(5), 1618-1627.

Casper, E. S., Schwartz, G. K., & Kelsen, D. P. (1992). Phase II trial of fazarabine (arabinofuranosyl-5-azacytidine) in patients with advanced pancreatic adenocarcinoma. *Invest New Drugs 10*(3), 205-209.

Chang, K. H., King, O. N., Tumber, A., Woon, E. C., Heightman, T. D., McDonough, M. A., et al. (2011). Inhibition of Histone Demethylases by 4‐Carboxy‐2, 2′ -Bipyridyl Compounds. *ChemMedChem 6*(5), 759-764.

Chédin, F., Lieber, M. R., & Hsieh, C. (2002). The DNA methyltransferase-like protein DNMT3L stimulates de novo methylation by Dnmt3a. *Proc Natl Acad Sci U S A 99*(26), 16916-16921.

Chen, Z. X., Mann, J. R., Hsieh, C. L., Riggs, A. D., & Chédin, F. (2005). Physical and functional interactions between the human DNMT3L protein and members of the de novo methyltransferase family. *J Cell Bio chem 95*(5), 902-917.

Cheng, J. C., Matsen, C. B., Gonzales, F. A., Ye, W., Greer, S., Marquez, V. E., et al. (2003). Inhibition of DNA methylation and reactivation of silenced genes by zebularine. *J Natl Cancer Inst 95*(5), 399-409.

Cheng, J. C., Yoo, C. B., Weisenberger, D. J., Chuang, J., Wozniak, C., Liang, G., et al. (2004). Preferential response of cancer cells to zebularine. *Cancer cell 6*(2), 151-158.

Cheng, Z., Cheung, P., Kuo, A. J., Yukl, E. T., Wilmot, C. M., Gozani, O., et al. (2014). A molecular threading mechanism underlies Jumonji lysine demethylase KDM2A regulation of methylated H3K36. *Genes Dev 28*(16), 1758-1771.

Cho, Y., Hong, T., Hong, S., Guo, H., Yu, H., Kim, D., et al. (2007). PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. *J Biol Chem 282*(28), 20395-20406.

Chu, C., Wang, L., Hsu, K., Chen, C., Cheng, H., Wang, S., et al. (2014). KDM4B as a target for prostate cancer: structural analysis and selective inhibition by a novel inhibitor. *J Med Chem 57*(14), 5975-5985.

Chuang, J. C., Warner, S. L., Vollmer, D., Vankayalapati, H., Redkar, S., Bearss, D. J., et al. (2010). S110, a 5-Aza-2′ -Deoxycytidine–Containing Dinucleotide, Is an Effective

DNA Methylation Inhibitor In vivo and Can Reduce Tumor Growth. *Mol Cancer Ther 9*(5), 1443-1450.

Chuang, J. C., Yoo, C. B., Kwan, J. M., Li, T. W., Liang, G., Yang, A. S., et al. (2005). Comparison of biological effects of non-nucleoside DNA methylation inhibitors versus 5-aza-2′ -deoxycytidine. *Mol Cancer Ther 4*(10), 1515-1520.

Cloos, P. A., Christensen, J., Agger, K., & Helin, K. (2008). Erasing the methyl mark: histone demethylases at the center of cellular differentiation and disease. *Genes Dev 22*(9), 1115-1140.

Cloos, P. A., Christensen, J., Agger, K., Maiolica, A., Rappsilber, J., Antal, T., et al. (2006). The putative oncogene GASC1 demethylates tri-and dimethylated lysine 9 on histone H3. *Nature 442*(7100), 307-311.

Constantinides, P. G., Jones, P. A., & Gevers, W. (1977). Functional striated muscle cells from non-myoblast precursors following 5-azacytidine treatment. *Nature* 267(5609), 364 - 366 .

Couronné, L., Bastard, C., & Bernard, O. A. (2012). TET2 and DNMT3A mutations in human T-cell lymphoma. *New Engl J Med 366*(1), 95-96.

Creagan, E. T., Schaid, D. J., Hartmann, L. C., & Loprinzi, C. L. (1993). A phase II study of 5, 6-dihydro-5-azacytidine hydrochloride in disseminated malignant melanoma. *Am J Clin Oncol 16*(3), 243-244.

Culhane, J. C., Szewczuk, L. M., Liu, X., Da, G., Marmorstein, R., & Cole, P. A. (2006). A mechanism-based inactivator for histone demethylase LSD1. *J Am Chem Soc 128*(14), 4536-4537.

Curtis, C., Shah, S. P., Chin, S., Turashvili, G., Rueda, O. M., Dunning, M. J., et al. (2012). The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature 486*(7403), 346-352.

Dalgliesh, G. L., Furge, K., Greenman, C., Chen, L., Bignell, G., Butler, A., et al. (2010). Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. *Nature 463*(7279), 360-363.

Dang, L., White, D. W., Gross, S., Bennett, B. D., Bittinger, M. A., Driggers, E. M., et al. (2009). Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature 462*(7274), 739-744.

Datta, J., Ghoshal, K., Denny, W. A., Gamage, S. A., Brooke, D. G., Phiasivongsa, P., et al. (2009). A new class of quinoline-based DNA hypomethylating agents reactivates tumor suppressor genes by blocking DNA methyltransferase 1 activity and inducing its degradation. *Cancer Res 69*(10), 4277-4285.

Davidson, S., Crowther, P., Radley, J., & Woodcock, D. (1992). Cytotoxicity of 5-aza-2′ -deoxycytidine in a mammalian cell system. *Eur J Cancer 28*(2), 362-368.

Davis, A. J., Gelmon, K. A., Siu, L. L., Moore, M. J., Britten, C. D., Mistry, N., et al. (2003). Phase I and pharmacologic study of the human DNA methyltransferase antisense oligodeoxynucleotide MG98 given as a 21-day continuous infusion every 4 weeks. *Invest New Drugs 21*(1), 85-97.

De Santa, F., Totaro, M. G., Prosperini, E., Notarbartolo, S., Testa, G., & Natoli, G. (2007). The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. *Cell 130*(6), 1083-1094.

Delpu, Y., Cordelier, P., Cho, W. C., & Torrisani, J. (2013). DNA methylation and cancer diagnosis. *Int J Mol Sci 14*(7), 15029-15058.

Dong, C., Zhang, H., Xu, C., Arrowsmith, C. H., & Min, J. (2014). Structure and function of dioxygenases in histone demethylation and DNA/RNA demethylation. *IUCrJ 1*(6), 540-549.

Dong, R., Yao, R., Du, J., Wang, S., & Fan, Z. (2013). Depletion of histone demethylase KDM2A enhanced the adipogenic and chondrogenic differentiation potentials of stem cells from apical papilla. *Exp Cell Res 319*(18), 2874-2882.

Eguchi, K., Kanai, Y., Kobayashi, K., & Hirohashi, S. (1997). DNA hypermethylation at the D17S5 locus in non-small cell lung cancers: its association with smoking history. *Cancer Res 57*(21), 4913-4915.

Etoh, T., Kanai, Y., Ushijima, S., Nakagawa, T., Nakanishi, Y., Sasako, M., et al. (2004). Increased DNA methyltransferase 1 (DNMT1) protein expression correlates significantly with poorer tumor differentiation and frequent DNA hypermethylation of multiple CpG islands in gastric cancers. *Am J Pathol 164*(2), 689-699.

Fahy, J., Jeltsch, A., & Arimondo, P. B. (2012). DNA methyltransferase inhibitors in cancer: a chemical and therapeutic patent overview and selected clinical studies. *Expert Opin Ther Pat 22*(12), 1427-1442.

Fang, F., Munck, J., Tang, J., Taverna, P., Wang, Y., Miller, D. F., et al. (2014). The Novel, Small-Molecule DNA Methylation Inhibitor SGI-110 as an Ovarian Cancer Chemosensitizer. *Clin Cancer Res 20*(24), 6504-6516.

Fang, M. Z., Chen, D., Sun, Y., Jin, Z., Christman, J. K., & Yang, C. S. (2005). Reversal of hypermethylation and reactivation of p16INK4a, RARβ, and MGMT genes by genistein and other isoflavones from soy. *Clin Cancer Res 11*(19), 7033-7041.

Fang, R., Barbera, A. J., Xu, Y., Rutenberg, M., Leonor, T., Bi, Q., et al. (2010). Human LSD2/KDM1b/AOF1 regulates gene transcription by modulating intragenic H3K4me2 methylation. *Mol Cell 39*(2), 222-233.

Finley, A., & Copeland, R. A. (2014). Small Molecule Control of Chromatin Remodeling. *Chem Biol 21*(9), 1196-1210.

Fiskus, W., Sharma, S., Shah, B., Portier, B. P., Devaraj, S., Liu, K., et al. (2014). Highly effective combination of LSD1 (KDM1A) antagonist and pan-histone deacetylase inhibitor against human AML cells. *Leukemia 28*(11), 2155-2164.

Frescas, D., Guardavaccaro, D., Bassermann, F., Koyama-Nasu, R., & Pagano, M. (2007). JHDM1B/FBXL10 is a nucleolar protein that represses transcription of ribosomal RNA genes. *Nature 450*(7167), 309-313.

Frescas, D., Guardavaccaro, D., Kuchay, S. M., Kato, H., Poleshko, A., Basrur, V., et al. (2008). KDM2A represses transcription of centromeric satellite repeats and maintains the heterochromatic state. *Cell Cycle 7*(22), 3539-3547.

Ganapathy-Kanniappan, S., & Geschwind, J. F. (2013). Tumor glycolysis as a target for cancer therapy: progress and prospects. *Mol Cancer 12*(152), 4512-4598.

Garcia-Bassets, I., Kwon, Y., Telese, F., Prefontaine, G. G., Hutt, K. R., Cheng, C. S., et al. (2007). Histone methylation-dependent mechanisms impose ligand dependency for gene activation by nuclear receptors. *Cell 128*(3), 505-518.

Garzon, R., Heaphy, C. E., Havelange, V., Fabbri, M., Volinia, S., Tsao, T., et al. (2009). MicroRNA 29b functions in acute myeloid leukemia. *Blood 114*(26), 5331-5341.

Goffin, J., & Eisenhauer, E. (2002). DNA methyltransferase inhibitors—state of the art. *Ann Oncol 13*(11), 1699-1716.

Gray, S. G., Iglesias, A. H., Lizcano, F., Villanueva, R., Camelo, S., Jingu, H., et al. (2005). Functional characterization of JMJD2A, a histone deacetylase-and retinoblastoma-binding protein. *J Biol Chem 280*(31), 28507-28518.

Guibourt, N., Munoz, A. O., & Laria, J. C. (2010). Phenylcyclopropylamine derivatives and their medical use: Google Patents.

Harris, W. J., Huang, X., Lynch, J. T., Spencer, G. J., Hitchin, J. R., Li, Y., et al. (2012). The histone demethylase KDM1A sustains the oncogenic potential of MLL-AF9 leukemia stem cells. *Cancer cell 21*(4), 473-487.

Hayakawa, T., & Nakayama, J. (2010). Physiological roles of class I HDAC complex and histone demethylase. *J Biomed Biotechnol*. http://dx.doi.org/10.1155/2011/129383.

Hayakawa, T., Ohtani, Y., Hayakawa, N., Shinmyozu, K., Saito, M., Ishikawa, F., & et al. (2007). RBP2 is an MRG15 complex component and down‐regulates intragenic histone H3 lysine 4 methylation. *Genes Cells 12*(6), 811-826.

Hayami, S., Kelly, J. D., Cho, H. S., Yoshimatsu, M., Unoki, M., Tsunoda, T., et al. (2011). Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers. *Int J Cancer 128*(3), 574-586.

Hayami, S., Yoshimatsu, M., Veerakumarasivam, A., Unoki, M., Iwai, Y., Tsunoda, T., et al. (2010). Overexpression of the JmjC histone demethylase KDM5B in human carcinogenesis: involvement in the proliferation of cancer cells through the E2F/RB pathway. *Mol Cancer 9*(59). doi: 10.1186/1476-4598-9-59.

Heidenblad, M., Lindgren, D., Jonson, T., Liedberg, F., Veerla, S., Chebil, G., et al. (2008). Tiling resolution array CGH and high density expression profiling of urothelial carcinomas delineate genomic amplicons and candidate target genes specific for advanced tumors. *BMC Med Genomics.* doi: 10.1186/1755-8794-1-3.

Heinemann, B., Nielsen, J. M., Hudlebusch, H. R., Lees, M. J., Larsen, D. V., Boesen, T., et al. (2014). Inhibition of demethylases by GSK-J1/J4. *Nature 514*(7520), E1-E2.

Helin, K., & Dhanak, D. (2013). Chromatin proteins and modifications as drug targets. *Nature 502*(7472), 480-488.

Hillringhaus, L., Yue, W. W., Rose, N. R., Ng, S. S., Gileadi, C., Loenarz, C., et al. (2011). Structural and evolutionary basis for the dual substrate selectivity of human KDM4 histone demethylase family. *J Biol Chem 286*(48), 41616-41625.

Hitchin, J. R., Blagg, J., Burke, R., Burns, S., Cockerill, M. J., Fairweather, E. E., et al. (2013). Development and evaluation of selective, reversible LSD1 inhibitors derived from fragments. *Med Chem Comm 4*(11), 1513-1522.

Ho, S. (2010). Environmental epigenetics of asthma: an update. *J Allergy Clin Immunol 126*(3), 453-465.

Holoye, P. Y., Dhingra, H. M., Umsawasdi, T., Murphy, W. K., Carr, D. T., & Lee, J. S. (1987). Phase II study of 5, 6-dihydro-5-azacytidine in extensive, untreated non-small cell lung cancer. *Cancer Treat Rep 71*(9), 859-860.

Huang, P., Chen, C., Chou, C., Sargeant, A. M., Kulp, S. K., Teng, C., et al. (2011). Histone deacetylase inhibitors stimulate histone H3 lysine 4 methylation in part via

transcriptional repression of histone H3 lysine 4 demethylases. *Mol Pharmacol 79*(1), 197-206.

Huang, Y., Greene, E., Stewart, T. M., Goodwin, A. C., Baylin, S. B., Woster, P. M., et al. (2007). Inhibition of lysine-specific demethylase 1 by polyamine analogues results in reexpression of aberrantly silenced genes. *Proc Natl Acad Sci U S A 104*(19), 8023-8028.

Huang, Y., Liu, Y., Yu, L., Chen, J., Hou, J., Cui, L., et al. (2015). Histone demethylase KDM2A promotes tumor cell growth and migration in gastric cancer. *Tumor Biol 36*(1), *271-278*.

Isakovic, L., Saavedra, O. M., Llewellyn, D. B., Claridge, S., Zhan, L., Bernstein, N., et al. (2009). Constrained (l-)-S-adenosyl-l-homocysteine (SAH) analogues as DNA methyltransferase inhibitors. *Bioorg Med Chem Lett 19*(10), 2742-2746.

Issaeva, I., Zonis, Y., Rozovskaia, T., Orlovsky, K., Croce, C. M., Nakamura, T., et al. (2007). Knockdown of ALR (MLL2) reveals ALR target genes and leads to alterations in cell adhesion and growth. *Mol Cell Biol 27*(5), 1889-1903.

Janzer, A., Stamm, K., Becker, A., Zimmer, A., Buettner, R., & Kirfel, J. (2012). The H3K4me3 histone demethylase Fbxl10 is a regulator of chemokine expression, cellular morphology, and the metabolome of fibroblasts. *J Biol Chem 287*(37), 30984-30992.

Jensen, L. R., Amende, M., Gurok, U., Moser, B., Gimmel, V., Tzschach, A., et al. (2005). Mutations in the JARID1C Gene, Which Is Involved in Transcriptional Regulation and Chromatin Remodeling, Cause X-Linked Mental Retardation. *Am J Hum Genet 76*(2), *227-236.*

Jin, B., Tao, Q., Peng, J., Soo, H. M., Wu, W., Ying, J., et al. (2008). DNA methyltransferase 3B (DNMT3B) mutations in ICF syndrome lead to altered epigenetic modifications and aberrant expression of genes regulating development, neurogenesis and immune function. *Hum Mol Genet 17*(5), 690-709.

Jin, C., Yang, L., Xie, M., Lin, C., Merkurjev, D., Yang, J. C., et al. (2014). Chem-seq permits identification of genomic targets of drugs against androgen receptor regulation selected by functional phenotypic screens. *Proc Natl Acad Sci U S A 111*(25), 9235-9240.

Jones, P. A., & Taylor, S. M. (1980). Cellular differentiation, cytidine analogs and DNA methylation. *Cell 20*(1), 85-93.

Jones, P. A., Taylor, S. M., Mohandas, T., & Shapiro, L. J. (1982). Cell cycle-specific reactivation of an inactive X-chromosome locus by 5-azadeoxycytidine. *Proc Natl Acad Sci U S A 79*(4), 1215-1219.

Jüttermann, R., Li, E., & Jaenisch, R. (1994). Toxicity of 5-aza-2'-deoxycytidine to mammalian cells is mediated primarily by covalent trapping of DNA methyltransferase rather than DNA demethylation. *Proc Natl Acad Sci U S A 91*(25), 11797-11801.

Kahl, P., Gullotti, L., Heukamp, L. C., Wolf, S., Friedrichs, N., Vorreuther, R., et al. (2006). Androgen receptor coactivators lysine-specific histone demethylase 1 and four and a half LIM domain protein 2 predict risk of prostate cancer recurrence. *Cancer Res 66*(23), 11341-11347.

Kanai, Y., Ushijima, S., Hui, A. M., Ochiai, A., Tsuda, H., Sakamoto, M., et al. (1997). The E‐cadherin gene is silenced by CpG methylation in human hepatocellular carcinomas. *Int J Cancer 71*(3), 355-359.

Kanai, Y., Ushijima, S., Kondo, Y., Nakanishi, Y., & Hirohashi, S. (2001). DNA methyltransferase expression and DNA methylation of CPG islands and peri‐centromeric satellite regions in human colorectal and stomach cancers. *Int J Cancer 91*(2), 205-212.

Kanai, Y., Ushijima, S., Nakanishi, Y., Sakamoto, M., & Hirohashi, S. (2003). Mutation of the DNA methyltransferase (DNMT) 1 gene in human colorectal cancers. *Cancer lett 192*(1), 75-82.

Kanai, Y., Ushijima, S., Ochiai, A., Eguchi, K., Hui, A., & Hirohashi, S. (1998). DNA hypermethylation at the D17S5 locus is associated with gastric carcinogenesis. *Cancer lett 122*(1), 135-141.

Kanai, Y., Ushijima, S., Tsuda, H., Sakamoto, M., & Hirohashi, S. (2000). Aberrant DNA methylation precedes loss of heterozygosity on chromosome 16 in chronic hepatitis and liver cirrhosis. *Cancer lett 148*(1), 73-80.

Kanai, Y., Ushijima, S., Tsuda, H., Sakamoto, M., Sugimura, T., & Hirohashi, S. (1996). Aberrant DNA methylation on chromosome 16 is an early event in hepatocarcinogenesis. *Cancer Sci 87*(12), 1210-1217.

Karytinos, A., Forneris, F., Profumo, A., Ciossani, G., Battaglioli, E., Binda, C., et al. (2009). A novel mammalian flavin-dependent histone demethylase. *J Biol Chem 284*(26), 17775-17782.

Katoh, M., & Katoh, M. (2004). Identification and characterization of JMJD2 family genes in silico. *Int J Oncol 24*(6), 1623-1628.

Katz, T. A., Vasilatos, S. N., Harrington, E., Oesterreich, S., Davidson, N. E., & Huang, Y. (2014). Inhibition of histone demethylase, LSD2 (KDM1B), attenuates DNA methylation and increases sensitivity to DNMT inhibitor-induced apoptosis in breast cancer cells. *Breast Cancer Res Treat 146*(1), 99-108.

Kawakami, E., Tokunaga, A., Ozawa, M., Sakamoto, R., & Yoshida, N. (2014). The histone demethylase fbxl11/kdm2a plays an essential role in embryonic development by repressing cell-cycle regulators. *Mech Dev 135*, 31-42.

Kawazu, M., Saso, K., Tong, K. I., McQuire, T., Goto, K., Son, D., et al. (2011). Histone demethylase JMJD2B functions as a co-factor of estrogen receptor in breast cancer proliferation and mammary gland development. *PLoS One 6*(3), e17830.

Kent-First, M. G., Maffitt, M., Muallem, A., Brisco, P., Shultz, J., Ekenberg, S., et al. (1996). Gene sequence and evolutionary conservation of human SMCY. *Nat Genet 14*(2), 128-129.

Kim, T., Oh, S., Shin, S., & Janknecht, R. (2012). Regulation of tumor suppressor p53 and HCT116 cell physiology by histone demethylase JMJD2D/KDM4D. *PloS one 7*(4), e34618.

King, O. N., Li, X. S., Sakurai, M., Kawamura, A., Rose, N. R., Ng, S. S., et al. (2010). Quantitative high-throughput screening identifies 8-hydroxyquinolines as cell-active histone demethylase inhibitors. *PloS one 5*(11), e15535.

Klein, C. J., Botuyan, M., Wu, Y., Ward, C. J., Nicholson, G. A., Hammans, S., et al. (2011). Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. *Nat Genet 43*(6), 595-600.

Klose, R. J., Kallin, E. M., & Zhang, Y. (2006). JmjC-domain-containing proteins and histone demethylation. *Nat Rev Genet 7*(9), 715-727.

Klose, R. J., Yamane, K., Bae, Y., Zhang, D., Erdjument-Bromage, H., Tempst, P., et al. (2006). The transcriptional repressor JHDM3A demethylates trimethyl histone H3 lysine 9 and lysine 36. *Nature 442*(7100), 312-316.

Klose, R. J., Yan, Q., Tothova, Z., Yamane, K., Erdjument-Bromage, H., Tempst, P., et al. (2007). The retinoblastoma binding protein RBP2 is an H3K4 demethylase. *Cell 128*(5), 889-900.

Kottakis, F., Polytarchou, C., Foltopoulou, P., Sanidas, I., Kampranis, S. C., & Tsichlis, P. N. (2011). FGF-2 regulates cell proliferation, migration, and angiogenesis through an NDY1/KDM2B-miR-101-EZH2 pathway. *Mol Cell 43*(2), 285-298.

Kouzarides, T. (2007). Chromatin modifications and their function. *Cell 128*(4), 693-705.

Koyama-Nasu, R., David, G., & Tanese, N. (2007). The F-box protein Fbl10 is a novel transcriptional repressor of c-Jun. *Nat Cell Biol 9*(9), 1074-1080.

Krishnan, S., & Trievel, R. C. (2013). Structural and functional analysis of JMJD2D reveals molecular basis for site-specific demethylation among JMJD2 demethylases. *Structure 21*(1), 98-108.

Kruidenier, L., Chung, C., Cheng, Z., Liddle, J., Che, K., Joberty, G., et al. (2012). A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. *Nature 488*(7411), 404-408.

Kuck, D., Caulfield, T., Lyko, F., & Medina-Franco, J. L. (2010). Nanaomycin A selectively inhibits DNMT3B and reactivates silenced tumor suppressor genes in human cancer cells. *Mol Cancer Ther 9*(11), 3015-3023.

Labelle, M., Boesen, T., Mehrotra, M., Khan, Q., & Ullah, F. (2014). INHIBITORS OF HISTONE DEMETHYLASES: US Patent 20, 140, 371, 195.

Lan, F., Bayliss, P. E., Rinn, J. L., Whetstine, J. R., Wang, J. K., Chen, S., et al. (2007). A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature 449*(7163), 689-694.

Lee, M. G., Norman, J., Shilatifard, A., & Shiekhattar, R. (2007). Physical and functional association of a trimethyl H3K4 demethylase and Ring6a/MBLR, a polycomb-like protein. *Cell 128*(5), 877-887.

Lee, M. G., Villa, R., Trojer, P., Norman, J., Yan, K., Reinberg, D., et al. (2007). Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science 318*(5849), 447-450.

Lee, M. G., Wynder, C., Cooch, N., & Shiekhattar, R. (2005). An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature 437*(7057), 432-435.

Lee, M. G., Wynder, C., Schmidt, D. M., McCafferty, D. G., & Shiekhattar, R. (2006). Histone H3 lysine 4 demethylation is a target of nonselective antidepressive medications. *Chem Biol 13*(6), 563-567.

Lefebvre, L., Viville, S., Barton, S. C., Ishino, F., Keverne, E. B., & Surani, M. A. (1998). Abnormal maternal behaviour and growth retardation associated with loss of the imprinted gene Mest. *Nat Genet 20*(2), 163-169.

Lei, H., Oh, S. P., Okano, M., Juttermann, R., Goss, K. A., Jaenisch, R., et al. (1996). De novo DNA cytosine methyltransferase activities in mouse embryonic stem cells. *Development 122*(10), 3195-3205.

Leonhardt, H., Page, A. W., Weier, H., & Bestor, T. H. (1992). A targeting sequence directs DNA methyltransferase to sites of DNA replication in mammalian nuclei. *Cell 71*(5), 865-873.

Ley, T. J., Ding, L., Walter, M. J., McLellan, M. D., Lamprecht, T., Larson, D. E., et al. (2010). DNMT3A mutations in acute myeloid leukemia. *New Engl J Med 363*(25), 2424-2433.

Li, B., Zhang, M., Luo, C., Yang, P., Li, H., Xu, H., et al. (2011). Effects of RNA interference-mediated gene silencing of JMJD2A on human breast cancer cell line MDA-MB-231 in vitro. *J Exp Clin Cancer Res*. doi: 10.1186/1756-9966-30-90.

Liang, G., He, J., & Zhang, Y. (2012). Kdm2b promotes induced pluripotent stem cell generation by facilitating gene activation early in reprogramming. *Nat Cell Biol 14*(5), 457-466.

Liang, Y., Quenelle, D., Vogel, J. L., Mascaro, C., Ortega, A., & Kristie, T. M. (2013). A novel selective LSD1/KDM1A inhibitor epigenetically blocks herpes simplex virus lytic replication and reactivation from latency. *MBio 4*(1), e512-e558.

Liefke, R., Oswald, F., Alvarado, C., Ferres-Marco, D., Mittler, G., Rodriguez, P., et al. (2010). Histone demethylase KDM5A is an integral part of the core Notch–RBP-J repressor complex. *Genes Dev 24*(6), 590-601.

Lim, S., Janzer, A., Becker, A., Zimmer, A., Schüle, R., Buettner, R., et al. (2010). Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology. *Carcinogenesis 31*(3), 512-520.

Lin, R., Hsu, C., & Wang, Y. (2007). Mithramycin A inhibits DNA methyltransferase and metastasis potential of lung cancer cells. *Anti-cancer drugs 18*(10), 1157-1164.

Liu, G., Bollig-Fischer, A., Kreike, B., van de Vijver, M. J., Abrams, J., Ethier, S. P., et al. (2009). Genomic amplification and oncogenic properties of the GASC1 histone demethylase gene in breast cancer. *Oncogene 28*(50), 4491-4500.

Liu, Y., Liu, K., Qin, S., Xu, C., & Min, J. (2014). Epigenetic targets and drug discovery: Part 1: Histone methylation. *Pharmacol Ther 143*(3), 275-294.

Lu, T., Jackson, M. W., Wang, B., Yang, M., Chance, M. R., Miyagi, M., et al. (2010). Regulation of NF-κB by NSD1/FBXL11-dependent reversible lysine methylation of p65. *Proc Natl Acad Sci U S A 107*(1), 46-51.

Lübbert, M. (2000). DNA methylation inhibitors in the treatment of leukemias, myelodysplastic syndromes and hemoglobinopathies: clinical results and possible mechanisms of action. *Curr Top Microbiol Immunol 249*, 135-164.

Luo, X., Liu, Y., Kubicek, S., Myllyharju, J., Tumber, A., Ng, S., et al. (2011). A selective inhibitor and probe of the cellular functions of Jumonji C domain-containing histone demethylases. *J Am Chem Soc 133*(24), 9451-9456.

Maes, T., Tirapu, I., Mascaro, C., Ortega, A., Estiarte, A., Valls, N., et al. (2013). Preclinical characterization of a potent and selective inhibitor of the histone demethylase KDM1A for MLL leukemia. *J ClinOncol Abstr 31*, e13543.

Mallette, F. A., Mattiroli, F., Cui, G., Young, L. C., Hendzel, M. J., Mer, G., et al. (2012). RNF8 ‐ and RNF168 ‐ dependent degradation of KDM4A/JMJD2A triggers 53BP1 recruitment to DNA damage sites. *EMBO J 31*(8), 1865-1878.

Margueron, R., Trojer, P., & Reinberg, D. (2005). The key to development: interpreting the histone code?. *Curr Opin Genet Dev 15*(2), 163-176.

Medina-Franco, J. L., López-Vallejo, F., Kuck, D., & Lyko, F. (2011). Natural products as DNA methyltransferase inhibitors: a computer-aided discovery approach. *Mol Divers 15*(2), 293-304.

Metzger, E., Wissmann, M., Yin, N., Müller, J. M., Schneider, R., Peters, A. H., et al. (2005). LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature 437*(7057), 436-439.

Mimasu, S., Umezawa, N., Sato, S., Higuchi, T., Umehara, T., & Yokoyama, S. (2010). Structurally Designed trans-2-Phenylcyclopropylamine Derivatives Potently Inhibit Histone Demethylase LSD1/KDM1. *Biochemistry 49*(30), 6494-6503.

Minucci, S., Mai, A., & Mattevi, A. (2011). Tranylcypromine derivatives as inhibitors of histone demethylases lsd1 and/or lsd2: Google Patents.

Mizuno, S., Chijiwa, T., Okamura, T., Akashi, K., Fukumaki, Y., Niho, Y., et al. (2001). Expression of DNA methyltransferases DNMT1, 3A, and 3B in normal hematopoiesis and in acute and chronic myelogenous leukemia. *Blood 97*(5), 1172-1179.

Mohammad, H., Smitheman, K., van Aller, G., Cusan, M., Kamat, S., Liu, Y., et al. (2014). 212 Novel anti-tumor activity of targeted LSD1 inhibition by GSK2879552. *Eur J Cancer 50*, 72.

Muñoz, A. O., Laria, J. C., & Fyfe, M. C. T. (2010). Lysine specific demethylase-1 inhibitors and their use: Google Patents.

Mutze, K., Langer, R., Schumacher, F., Becker, K., Ott, K., Novotny, A., et al. (2011). DNA methyltransferase 1 as a predictive biomarker and potential therapeutic target for chemotherapy in gastric cancer. *Eur J Cancer 47*(12), 1817-1825.

Nakamura, T., Mori, T., Tada, S., Krajewski, W., Rozovskaia, T., Wassell, R., et al. (2002). ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. *Mol Cell 10*(5), 1119-1128.

Nathan, R. (2009). Inhibition of the histone lysine demethylase JMJD2A by ejection of structural Zn (II). *Chem Commun 42*, 6376-6378.

Ng, H., & Adrian, B. (1999). DNA methylation and chromatin modification. *Curr Opin Genet Dev 9*(2), 158-163.

Northcott, P. A., Nakahara, Y., Wu, X., Feuk, L., Ellison, D. W., Croul, S., Mack, S., et al. (2009). Multiple recurrent genetic events converge on control of histone lysine methylation in medulloblastoma. *Nat Genet 41*(4), 465-472.

Okano, M., Bell, D. W., Haber, D. A., & Li, E. (1999). DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell 99*(3), 247-257.

Ooi, S. K., Qiu, C., Bernstein, E., Li, K., Jia, D., Yang, Z., et al. (2007). DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature 448*(7154), 714-717.

Orlic, M., Spencer, C. E., Wang, L., & Gallie, B. L. (2006). Expression analysis of 6p22 genomic gain in retinoblastoma. *Genes Chromosomes Cancer 45*(1), 72-82.

Patel, D. R., & Richardson, B. C. (2010). Epigenetic mechanisms in lupus. *Curr Opin Rheumatol 22*, 478-482.

Pedersen, M. T., & Helin, K. (2010). Histone demethylases in development and disease. *Trends Cell Biol 20*(11), 662-671.

Peng, D. F., Kanai, Y., Sawada, M., Ushijima, S., Hiraoka, N., Kosuge, T., et al. (2005). Increased DNA methyltransferase 1 (DNMT1) protein expression in precancerous conditions and ductal carcinomas of the pancreas. *Cancer Sci 96*(7), 403-408.

Pfau, R., Tzatsos, A., Kampranis, S. C., Serebrennikova, O. B., Bear, S. E., & Tsichlis, P. N. (2008). Members of a family of JmjC domain-containing oncoproteins immortalize embryonic fibroblasts via a JmjC domain-dependent process. *Proc Natl Acad Sci U S A 105*(6), 1907-1912.

Plummer, R., Vidal, L., Griffin, M., Lesley, M., de Bono, J., Coulthard, S., et al. (2009). Phase I study of MG98, an oligonucleotide antisense inhibitor of human DNA methyltransferase 1, given as a 7-day infusion in patients with advanced solid tumors. *Clin Cancer Res 15*(9), 3177-3183.

Ponnaluri, V. K., Vavilala, D. T., Putty, S., Gutheil, W. G., & Mukherji, M. (2009). Identification of non-histone substrates for JMJD2A–C histone demethylases. B*iochem Biophys Res Commun 390*(2), 280-284.

Prusevich, P., Kalin, J. H., Ming, S. A., Basso, M., Givens, J., Li, X., et al. (2014). A Selective Phenelzine Analogue Inhibitor of Histone Demethylase LSD1. *ACS Chem Biol 9*(6), 1284-1293.

Qi, L., Zhu, F., Li, S., Si, L., Hu, L., & Tian, H. (2014). Retinoblastoma Binding Protein 2 (RBP2) Promotes HIF-1α–VEGF-Induced Angiogenesis of Non-Small Cell Lung Cancer via the Akt Pathway. *PloS one 9*(8), e106032.

Razin, A., & Cedar, H. (1993). DNA methylation and embryogenesis. *DNA Methylation, EXS 64,* 343-357.

Rhee, I., Bachman, K. E., Park, B. H., Jair, K., Yen, R. C., Schuebel, K. E., et al. (2002). DNMT1 and DNMT3b cooperate to silence genes in human cancer cells. *Nature 416*(6880), 552-556.

Rhyasen, G. "Chromatin as a cancer target." (2015). *Oncology Discovery*.

Ribeiro, A. F. T., Pratcorona, M., Erpelinck-Verschueren, C., Rockova, V., Sanders, M., Abbas, S., et al. (2012). Mutant DNMT3A: a marker of poor prognosis in acute myeloid leukemia. *Blood 119*(24), 5824-5831.

Rice, K. L., Hormaeche, I., & Licht, J. D. (2007). Epigenetic regulation of normal and malignant hematopoiesis. *Oncogene 26*(47), 6697-6714.

Robak, T. (2011). New nucleoside analogs for patients with hematological malignancies. *Expert Opin Investig Drugs 20*(3), 343-359.

Robertson, K. D., Uzvolgyi, E., Liang, G., Talmadge, C., Sumegi, J., Gonzales, F. A., et al. (1999). The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumors. *Nucleic Acids Res 27*(11), 2291-2298.

Rose, N. R., Ng, S. S., Mecinovic, J., Liénard, B. M., Bello, S. H., Sun, Z., et al. (2008). Inhibitor Scaffolds for 2-Oxoglutarate-Dependent Histone Lysine Demethylases. *J Med Chem 51*(22), 7053-7056.

Rose, N. R., Woon, E. C., Tumber, A., Walport, L. J., Chowdhury, R., Li, X. S., et al. (2012). Plant growth regulator daminozide is a selective inhibitor of human KDM2/7 histone demethylases. *J Med Chem 55*(14), 6639-6643.

Rotili, D., & Mai, A. (2011). Targeting histone demethylases a new avenue for the fight against cancer. *Genes Cancer 2*(6), 663-679.

Rotili, D., Tomassi, S., Conte, M., Benedetti, R., Tortorici, M., Ciossani, G., et al. (2013). Pan-Histone Demethylase Inhibitors Simultaneously Targeting Jumonji C and Lysine-Specific Demethylases Display High Anticancer Activities. *J Med Chem 57*(1), 42-55.

Rui, L., Emre, N. C., Kruhlak, M. J., Chung, H., Steidl, C., Slack, G., et al. (2010). Cooperative epigenetic modulation by cancer amplicon genes. *Cancer cell 18*(6), 590-605.

Saito, Y., Kanai, Y., Nakagawa, T., Sakamoto, M., Saito, H., Ishii, H., et al. (2003). Increased protein expression of DNA methyltransferase (DNMT) 1 is significantly correlated with the malignant potential and poor prognosis of human hepatocellular carcinomas. *Int J Cancer 105*(4), 527-532.

Saito, Y., Kanai, Y., Sakamoto, M., Saito, H., Ishii, H., & Hirohashi, S. (2001). Expression of mRNA for DNA methyltransferases and methyl‐CpG–binding proteins and DNA methylation status on CpG islands and pericentromeric satellite regions during human hepatocarcinogenesis. *Hepatology 33*(3), 561-568.

Samuels, B. L., Herndon, J., Harmon, D. C., Carey, R., Aisner, J., Corson, J. M., et al. (1998). Dihydro‐5‐azacytidine and cisplatin in the treatment of malignant mesothelioma. *Cancer 82*(8), 1578-1584.

Santi, D. V., Norment, A., & Garrett, C. E. (1984). Covalent bond formation between a DNA-cytosine methyltransferase and DNA containing 5-azacytosine. *Proc Natl Acad Sci U S A 81*(22), 6993-6997.

Santos, C., Rodriguez-Revenga, L., Madrigal, I., Badenas, C., Pineda, M., & Milà, M. (2006). A novel mutation in JARID1C gene associated with mental retardation. *Eur J Hum Genet 14*(5), 583-586.

Schiller, R., Scozzafava, G., Tumber, A., Wickens, J. R., Bush, J. T., Rai, G., et al. (2014). A Cell‐Permeable Ester Derivative of the JmjC Histone Demethylase Inhibitor IOX1. *ChemMedChem 9*(3), 566-571.

Schmidt, D. M., & McCafferty, D. G. (2007). trans-2-Phenylcyclopropylamine is a mechanism-based inactivator of the histone demethylase LSD1. *Biochemistry 46*(14), 4408-4416.

Schmitt, M. L., Hauser, A., Carlino, L., Pippel, M., Schulz-Fincke, J., Metzger, E., et al. (2013). Nonpeptidic Propargylamines as Inhibitors of Lysine Specific Demethylase 1 (LSD1) with Cellular Activity. *J Med Chem 56*(18), 7334-7342.

Schulte, J. H., Lim, S., Schramm, A., Friedrichs, N., Koster, J., Versteeg, R., et al. (2009). Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy. *Cancer Res 69*(5), 2065-2071.

Sheardown, S. A., Duthie, S. M., Johnston, C. M., Newall, A. E., Formstone, E. J., Arkell, R. M., et al. (1997). Stabilization of Xist RNA Mediates Initiation of X Chromosome Inactivation. *Cell 91*(1), 99-107.

Shen, H., Wang, L., Spitz, M. R., Hong, W. K., Mao, L., & Wei, Q. (2002). A novel polymorphism in human cytosine DNA-methyltransferase-3B promoter is associated with an increased risk of lung cancer. *Cancer Res 62*(17), 4992-4995.

Shi, Y. (2007). Histone lysine demethylases: emerging roles in development, physiology and disease. *Nat Rev Genet 8*(11), 829-833.

Shi, Y., Lan, F., Matson, C., Mulligan, P., Whetstine, J. R., Cole, P. A., et al. (2004). Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell 119*(7), 941-953.

Shi, Y., Matson, C., Lan, F., Iwase, S., Baba, T., & Shi, Y. (2005). Regulation of LSD1 histone demethylase activity by its associated factors. *Mol Cell 19*(6), 857-864.

Shin, S., & Janknecht, R. (2007). Diversity within the JMJD2 histone demethylase family. *Biochem Biophys Res Commun 353*(4), 973-977.

Singh, V., Sharma, P., & Capalash, N. (2013). DNA methyltransferase-1 inhibitors as epigenetic therapy for cancer. *Curr Cancer Drug Targets 13*(4), 379-399.

Sorna, V., Theisen, E. R., Stephens, B., Warner, S. L., Bearss, D. J., Vankayalapati, H., et al. (2013). High-throughput virtual screening identifies novel N′-(1-phenylethylidene)-benzohydrazides as potent, specific, and reversible LSD1 inhibitors. *J Med Chem 56*(23), 9496-9508.

Srivastava, P., Paluch, B. E., Matsuzaki, J., James, S. R., Collamat-Lai, G., Karbach, J., et al. (2014). Immunomodulatory action of SGI-110, a hypomethylating agent, in acute myeloid leukemia cells and xenografts. *Leukemia Res 38*(11), 1332-1341.

Strahl, B. D., & Allis, C. D. (2000). The language of covalent histone modifications. *Nature 403*(6765), 41-45.

Stresemann, C., Brueckner, B., Musch, T., Stopper, H., & Lyko, F. (2006). Functional diversity of DNA methyltransferase inhibitors in human cancer cell lines. *Cancer Res 66*(5), 2794-2800.

Suetake, I., Shinozaki, F., Miyagawa, J., Takeshima, H., & Tajima, S. (2004). DNMT3L stimulates the DNA methylation activity of Dnmt3a and Dnmt3b through a direct interaction. *J Biol Chem 279*(26), 27816-27823.

Sun, L., Hui, A. M., Kanai, Y., Sakamoto, M., & Hirohashi, S. (1997). Increased DNA methyltransferase expression is associated with an early stage of human hepatocarcinogenesis. *Cancer Sci 88*(12), 1165-1170.

Suzuki, T., Ozasa, H., Itoh, Y., Zhan, P., Sawada, H., Mino, K., et al. (2013). Identification of the KDM2/7 Histone Lysine Demethylase Subfamily Inhibitor and its Antiproliferative Activity. *J Med Chem 56*(18), 7222-7231.

Suzuki, T., Minehata, K. I., Akagi, K., Jenkins, N. A., & Copeland, N. G. (2006). Tumor suppressor gene identification using retroviral insertional mutagenesis in Blm‐deficient mice. *EMBO J 25*(14), 3422-3431.

Szewczuk, L. M., Culhane, J. C., Yang, M., Majumdar, A., Yu, H., & Cole, P. A. (2007). Mechanistic analysis of a suicide inactivator of histone demethylase LSD1. *Biochemistry 46*(23), 6892-6902.

Tahiliani, M., Mei, P., Fang, R., Leonor, T., Rutenberg, M., Shimizu, F., et al. (2007). The histone H3K4 demethylase SMCX links REST target genes to X-linked mental retardation. *Nature 447*(7144), 601-605.

Tan, K., Shaw, A. L., Madsen, B., Jensen, K., Taylor-Papadimitriou, J., & Freemont, P. S. (2003). Human PLU-1 Has transcriptional repression properties and interacts with the developmental transcription factors BF-1 and PAX9. *J Biol Chem 278*(23), 20507-20513.

Tanaka, Y., Okamoto, K., Teye, K., Umata, T., Yamagiwa, N., Suto, Y., et al. (2010). JmjC enzyme KDM2A is a regulator of rRNA transcription in response to starvation. *EMBO J 29*(9), 1510-1522.

Tanq, J., Fang, F., Wang, Y., Taverna, P., Miller, D. F., Choy, G., et al. (2014). The novel, small molecule DNA methylation inhibitor SGI-110 as an ovarian cancer chemosensitizer. J *Clin Cancer Res 20*, 6504-6516.

Tellez, C. S., Grimes, M. J., Picchi, M. A., Liu, Y., March, T. H., Reed, M. D., et al. (2014). SGI‐110 and entinostat therapy reduces lung tumor burden and reprograms the epigenome. *Int J Cancer 135*(9), 2223-2231.

Thottassery, J. V., Sambandam, V., Allan, P. W., Maddry, J. A., Maxuitenko, Y. Y., Tiwari, K., et al. (2014). Novel DNA methyltransferase-1 (DNMT1) depleting anticancer nucleosides, 4′ -thio-2′ -deoxycytidine and 5-aza-4′ -thio-2′ -deoxycytidine. *Cancer Chemother Pharmacol 74*(2), 291-302.

Thottassery, J., Tiwari, K. N., Parker, W. B., & Secrist III, J. A. (2010). Use of 2'-deoxy-4'-thiocytidine and its analogues as dna hypomethylating anticancer agents: Google Patents.

Toyokawa, G., Cho, H., Iwai, Y., Yoshimatsu, M., Takawa, M., Hayami, S., et al. (2011). The histone demethylase JMJD2B plays an essential role in human carcinogenesis through positive regulation of cyclin-dependent kinase 6. *Cancer Prev Res 4*(12), 2051-2061.

Tsukada, Y., Fang, J., Erdjument-Bromage, H., Warren, M. E., Borchers, C. H., Tempst, P., et al. (2005). Histone demethylation by a family of JmjC domain-containing proteins. *Nature 439*(7078), 811-816.

Tzatsos, A., Paskaleva, P., Ferrari, F., Deshpande, V., Stoykova, S., Contino, G., et al. (2013). KDM2B promotes pancreatic cancer via Polycomb-dependent and-independent transcriptional programs. *J Clin Invest 123*(2), 727-739.

Tzatsos, A., Pfau, R., Kampranis, S. C., & Tsichlis, P. N. (2009). Ndy1/KDM2B immortalizes mouse embryonic fibroblasts by repressing the Ink4a/Arf locus. *Proc Natl Acad Sci U S A 106*(8), 2641-2646.

Tzschach, A., Lenzner, S., Moser, B., Reinhardt, R., Chelly, J., Fryns, J. P., et al. (2006). Novel JARID1C/SMCX mutations in patients with X‐linked mental retardation. *Hum Mutat 27*(4), 389.

Ueda, R., Suzuki, T., Mino, K., Tsumoto, H., Nakagawa, H., Hasegawa, et al. (2009). Identification of cell-active lysine specific demethylase 1-selective inhibitors. *J Am Chem Soc 131*(48), 17536-17537.

Vakayalapati, H., Soma, V., Warner, S. L., Stephens, B., Bearss, D. J., & Sharma, S. (2012). Substituted (e)-n'-(1-phenylethylidene) benzohydrazide analogs as histone demethylase inhibitors: Google Patents.

van Haaften, G., Dalgliesh, G. L., Davies, H., Chen, L., Bignell, G., Greenman, C., et al. (2009). Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. *Nat Genet 41*(5), 521-523.

van Oevelen, C., Wang, J., Asp, P., Yan, Q., Kaelin Jr, W. G., Kluger, Y., et al. (2008). A role for mammalian Sin3 in permanent gene silencing. *Mol Cell 32*(3), 359-370.

Vander Heiden, M. G. (2011). Targeting cancer metabolism: a therapeutic window opens. *Nat Rev Drug Discov 10*(9), 671-684.

Wagner, K. W., Alam, H., Dhar, S. S., Giri, U., Li, N., Wei, Y., Giri, D., et al. (2013). KDM2A promotes lung tumorigenesis by epigenetically enhancing ERK1/2 signaling. *J Clin Invest 123*(12), 5231-5246.

Walport, L. J., Hopkinson, R. J., Vollmar, M., Madden, S. K., Gileadi, C., Oppermann, U., et al. (2014). Human UTY (KDM6C) is a Male-Specific Nϵ-Methyl Lysyl-Demethylase. *J Biol Chem 289*, 18302-18313.

Walter, M. J., Ding, L., Shen, D., Shao, J., Grillot, M., McLellan, M., et al. (2011). Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. *Leukemia 25*(7), 1153-1158.

Wang, J., Hevi, S., Kurash, J. K., Lei, H., Gay, F., Bajko, J., et al. (2008). The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. *Nat Genet 41*(1), 125-129.

Wang, L., Chang, J., Varghese, D., Dellinger, M., Kumar, S., Best, A. M., et al. (2013). A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. *Nat Commun 4*, 2035 | DOI: 10.1038/ncomms3035.

Wang, L., Wang, J., Sun, S., Rodriguez, M., Yue, P., Jang, S. J., et al. (2006). A novel DNMT3B subfamily, DeltaDNMT3B, is the predominant form of DNMT3B in non-small cell lung cancer. *Int J Oncol 29*(1), 201-207.

Wang, Y., Zhang, H., Chen, Y., Sun, Y., Yang, F., Yu, W., et al. (2009). LSD1 is a subunit of the NuRD complex and targets the metastasis programs in breast cancer. *Cell 138*(4), 660-672.

Whetstine, J. R., Nottke, A., Lan, F., Huarte, M., Smolikov, S., Chen, Z., et al. (2006). Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. *Cell 125*(3), 467-481.

Wierda, R. J., Geutskens, S. B., Jukema, J. W., Quax, P. H., & van den Elsen, P. J. (2010). Epigenetics in atherosclerosis and inflammation. *J Cell Mol Med 14*(6a), 1225-1240.

Wijmenga, C., Hansen, R. S., Gimelli, G., Bjoerck, E. J., Davies, E. G., Valentine, D., et al. (2000). Genetic variation in ICF syndrome: evidence for genetic heterogeneity. *Hum Mutat 16*(6), 509-517.

Williamson, S. K., Crowley, J. J., Livingston, R. B., Panella, T. J., & Goodwin, J. W. (1995). Phase II trial and cost analysis of fazarabine in advanced non-small cell carcinoma of the lung: a Southwest Oncology Group study. *Invest New Drugs 13*(1), 67-71.

Winkelmann, J., Lin, L., Schormair, B., Kornum, B. R., Faraco, J., Plazzi, G., et al. (2012). Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy. *Hum Mol Genet 21*(10), 2205-2210.

Woon, E. C., Tumber, A., Kawamura, A., Hillringhaus, L., Ge, W., Rose, N. R., et al. (2012). Linking of 2‐Oxoglutarate and Substrate Binding Sites Enables Potent and Highly Selective Inhibition of JmjC Histone Demethylases. *Angew Chem Int Ed Engl 51*(7), 1631-1634.

Wu, J., Salido, E. C., Yen, P. H., Mohandas, T. K., Heng, H. H., Tsui, L., et al. (1994). The murine Xe169 gene escapes X-inactivation like its human homologue. *Nat Genet 7*(4), 491-496.

Xiang, Y., Zhu, Z., Han, G., Ye, X., Xu, B., Peng, Z., et al. (2007). JARID1B is a histone H3 lysine 4 demethylase up-regulated in prostate cancer. *Proc Natl Acad Sci U S A 104*(49), 19226-19231.

Xie, Q., Bai, Y., Wu, J., Sun, Y., Wang, Y., Zhang, Y., et al. (2011). Methylation-mediated regulation of E2F1 in DNA damage-induced cell death. *J Recept Signal Transduct Res 31*(2), 139-146.

Yamamoto, S., Wu, Z., Russnes, H. G., Takagi, S., Peluffo, G., Vaske, C., et al. (2014). JARID1B Is a Luminal Lineage-Driving Oncogene in Breast Cancer. *Cancer cell 25*(6), 762-777.

Yamane, K., Tateishi, K., Klose, R. J., Fang, J., Fabrizio, L. A., Erdjument-Bromage, H., et al. (2007). PLU-1 is an H3K4 demethylase involved in transcriptional repression and breast cancer cell proliferation. *Mol Cell 25*(6), 801-812.

Yan, X., Xu, J., Gu, Z., Pan, C., Lu, G., Shen, Y., et al. (2011). Exome sequencing identifies somatic mutations of DNA methyltransferase gene DNMT3A in acute monocytic leukemia. *Nat Genet 43*(4), 309-315.

Yang, M., Culhane, J. C., Szewczuk, L. M., Jalili, P., Ball, H. L., Machius, M., et al. (2007). Structural basis for the inhibition of the LSD1 histone demethylase by the antidepressant trans-2-phenylcyclopropylamine. *Biochemistry 46*(27), 8058-8065.

Ye, X., Zheng, Y., Duan, Y., Wang, M., Yu, B., Ren, J., et al. (2014). Synthesis and biological evaluation of coumarin–1, 2, 3-triazole–dithiocarbamate hybrids as potent LSD1 inhibitors. *MedChemComm 5*(5), 650-654.

Yoo, C. B., Jeong, S., Egger, G., Liang, G., Phiasivongsa, P., Tang, C., et al. (2007). Delivery of 5-aza-2′ -deoxycytidine to cells using oligodeoxynucleotides. *Cancer Res 67*(13), 6400-6408.

Zeng, J., Ge, Z., Wang, L., Li, Q., Wang, N., Björkholm, M., et al. (2010). The histone demethylase RBP2 Is overexpressed in gastric cancer and its inhibition triggers senescence of cancer cells. *Gastroenterology 138*(3), 981-992.

Zhang, J., Baran, J., Cros, A., Guberman, J. M., Haider, S., Hsu, J., et al. (2011). International Cancer Genome Consortium Data Portal—a one-stop shop for cancer genomics data. *Database*. doi: 10.1093/database/bar026.

Zhang, Y., & Reinberg, D. (2001). Transcription regulation by histone methylation: interplay between different covalent modifications of the core histone tails. *Genes Dev 15*(18), 2343-2360.

Zhao, Y., Butler, E. B., & Tan, M. (2013). Targeting cellular metabolism to improve cancer therapeutics. *Cell Death Dis 4*, e532.

Zhao, Z., Dong, P., Gu, J., Chen, L., Zhuang, M., Lu, W., et al. (2013). Overexpression of LSD1 in hepatocellular carcinoma: a latent target for the diagnosis and therapy of hepatoma. *Tumor Biol 34*(1), 173-180.

Zheng, Y., Duan, Y., Ma, J., Xu, R., Zi, X., Lv, W., et al. (2013). Triazole–Dithiocarbamate Based Selective Lysine Specific Demethylase 1 (LSD1) Inactivators Inhibit Gastric Cancer Cell Growth, Invasion, and Migration. *J Med Chem 56*(21), 8543-8560.

Zhou, L., Cheng, X., Connolly, B. A., Dickman, M. J., Hurd, P. J., & Hornby, D. P. (2002). Zebularine: a novel DNA methylation inhibitor that forms a covalent complex with DNA methyltransferases. *J Mol Biol 321*(4), 591-599.

Zou, M. R., Cao, J., Liu, Z., Huh, S. J., Polyak, K., & Yan, Q. (2014). Histone Demethylase Jumonji AT-Rich Interactive Domain 1B (JARID1B) Controls Mammary Gland Development by Regulating Key Developmental and Lineage Specification Genes. *J Biol Chem 289*, 17620-17633.

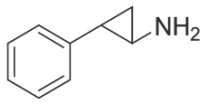
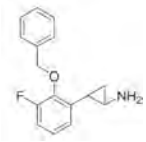
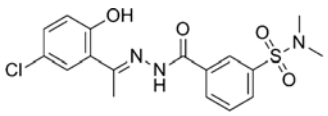
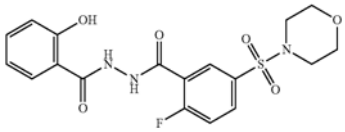
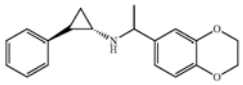
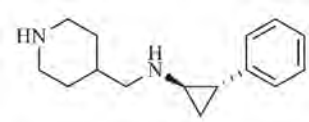
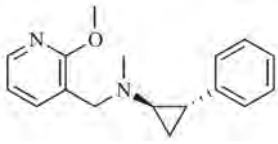
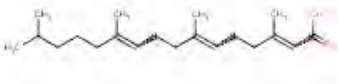
Figure legends

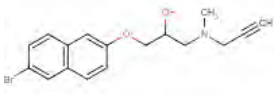
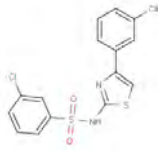
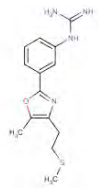
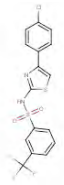
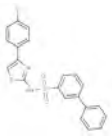
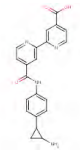
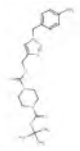
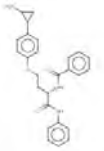
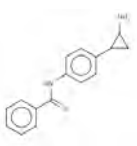
Fig. 1. Complex structures of LSD1 bound to inhibitors. (A) FAJ in complex with LSD1, (B) M84 in complex with LSD1, (C) S1201 in complex with LSD1, (D) LYP in complex with LSD1. Protein residues in contact with inhibitors are depicted by stick models colored in pink. Inhibitors are shown as stick models colored in green. Hydrogen bonds are marked with black dashed line. FAJ: FAD adduct of tranylcypromine; M84 and S1201: tranylcypromine derivatives; LYP: the catalytic substrate K4 analog (N~6~-methyl-N~6~-propyl-L-lysine).

Fig. 2. Complex structures of KDM proteins bound to inhibitors. (A) KC6 in complex with KDM4A, (B) IOX1 in complex with KDM4A, (C) GSK-J1 in complex with KDM6B. KC6: bipyridyl inhibitor (4'-[(2-aminoethyl) carbamoyl]-2,2'-bipyridine- 4-carboxylic acid); IOX1: 5-Carboxy-8-hydroxyquinoline. Inhibitors are shown in stick models colored in green. Hydrogen bonds between protein residues and inhibitors are marked with black dashed line, while hydrogen bonds involved in Ni^{2+} (which is substituted Fe^{2+}) are marked with red dashed line.

Fig. 3. Close-up view of the SFG compound in complex with DNMT1. Protein residues in contact with SFG are depicted by stick models colored in cyan, whereas SFG (derivative of SAH) is shown in stick colored in pink. Hydrogen bonds between protein residues and SFG are marked with black dashed line.

Table 1 Inhibitors of LSD1

Compound Name	**Chemical structure**	**IC50 (μM)**	**PDB code of complex structure**	**PMID**
Tranylcypromine (PCPA)		2	2UXX 2EJR	16793513 (Lee et al., 2006) 22406747 (Schenk et al., 2012)
S1201 tranylcypromine derivatives		8.1	3ABU	20568732 (Mimasu et al., 2010)
N′ (1-Phenylethylidene)-benzohydrazides derivatives		0.014		24237195 (Sorna et al., 2013)
N′ (1-Phenylethylidene)-benzohydrazides derivatives		0.013		24237195 (Sorna et al., 2013)
polyaminoguanidines derivatives		0.005		WO2010084160 A1 (Guibourt et al., 2012)
GSK2879552				25237863 (Finley et al., 2012)
ORY-1001				25237863 (Finley et al., 2012)
Sakane, 14,15-dihydro GGA		22		24406160 (Sakane et al., 2014)

Compound 5f		22		24007511 (Schmitt et al., 2013)
Hitchin2013_cmpd 19c		10.2		*Med Chem. Commun*., 2013, 4, 1513-1522
Dulla_cmpd_9a		9.5		23575971 (Dulla et al., 2013)
Hitchin2013_cmpd 16q		9.5		*Med Chem. Commun*., 2013, 4, 1513-1522.
Hitchin2013_cmpd 16k		7.5		*Med Chem. Commun*., 2013, 4, 1513-1522.
Rotili2014_cmpd1		2.2		24325601 (Rotili et al., 2014)
Zheng_cmpd26		2.1		24131029 (Zheng et al., 2013)
ueda09_cmpd2		1.9		19950987 (Ueda et al., 2009)
binda10_cmpd1		Ki=1.3		20415477 (Binda et al., 2010)
binda10_cmpd1		1.1		20415477 (Binda et al., 2010)

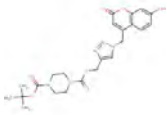
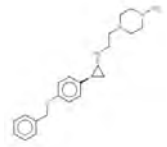
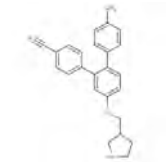
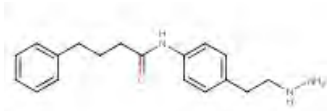
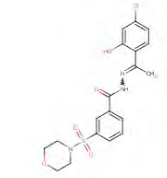
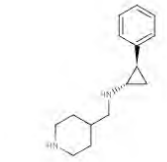
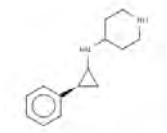
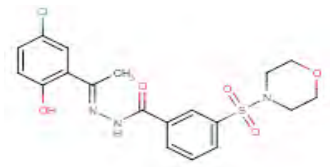
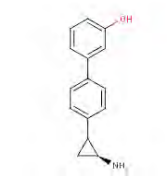
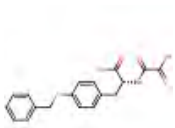
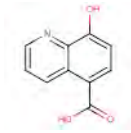
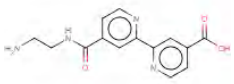
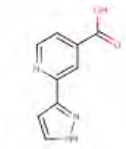
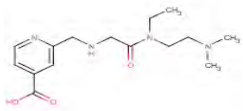
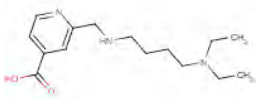
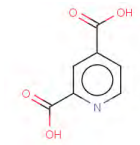
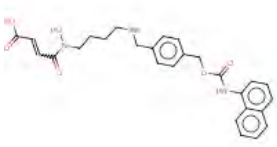
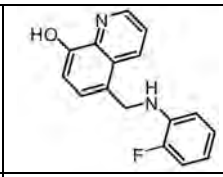
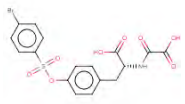
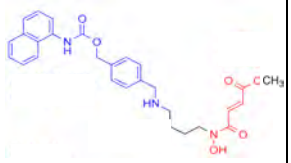
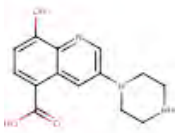
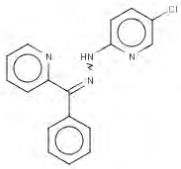
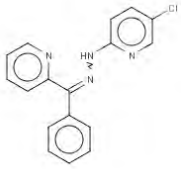
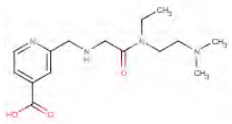
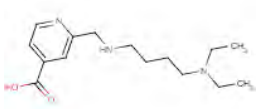
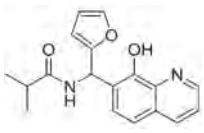
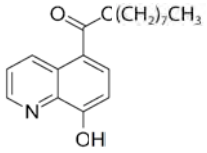
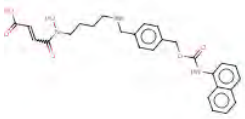
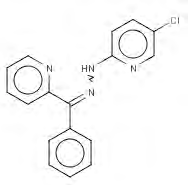
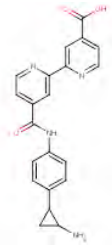
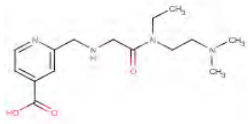
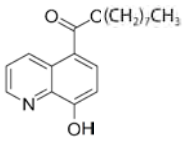
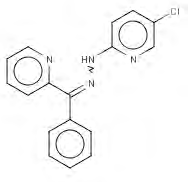
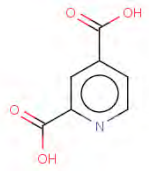
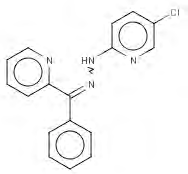
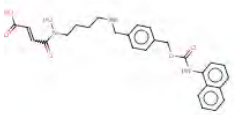
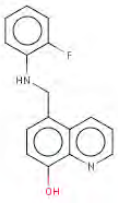
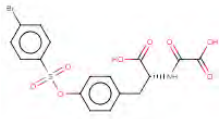
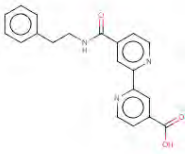
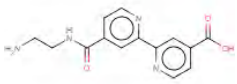
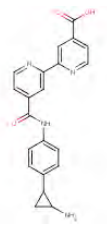
mimasu10_S2101		1		20568732 (Mimasu et al., 2010)
Compound 8k		0.39		*Med Chem. Commun*., 2014, 5,650:654
Ortega11_cmpd10		0.1		WO2011035941 A1
GSK345		0.09		*Med Chem. Commun*., 2013, 4, 1513-1522
Bizine - Prusevich2014_cmpd12d		0.059		24707965 (Prusevich et al., 2014)
Hitchin2013_cmpd24		0.04		*Med Chem. Commun*., 2013, 4, 1513-1522
Example_5		0.022		WO2013057320
GSK-LSD1		0.016		http://www.thesgc.org/chemical-probes/LSD1
Compound 12		0.013		24237195 (Sorna et al., 2013)
Ortega_OG-L002		0.02		23386436 (Liang et al., 2013)

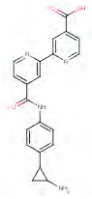
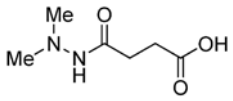
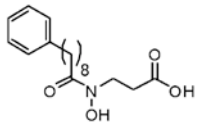
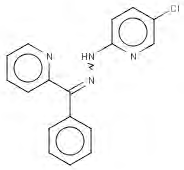
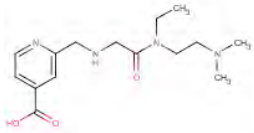
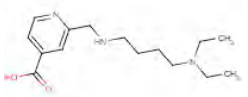
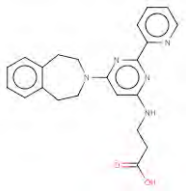
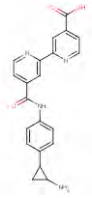
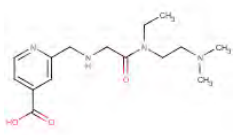
Table 2 Inhibitors of JmjC domain-containing protein family

Protein name	Compound Name	Chemical structure	IC50 (μM)	PDB code of complex structure	PMID
KDM4A	Y28 O-benzyl-N-(carboxycarbonyl)-D-tyrosine			2WWJ	20088513 (Rose et al., 2010)
	IOX1 8-hydroxyquinoline-5-carboxylic acid			3NJY	21124847 (King et al., 2010)
	chang11_cmpd13a			3PDQ	21412984 (Chang et al., 2011)
	0WS 2-(1H-pyrazol-3-yl)pyridine-4-carboxylic acid			4GD4	(King et al., 2012)
	labelle06_epitherapeutics_Example49		0.1		WO2014053491 A1_Epitherapeutics
	labelle06_epitherapeutics_Example48		0.1		WO2014053491 A1_Epitherapeutics
	PDCA		0.7	2VD7	18942826 (Rose et al, 2008)
	compound 1		4.3		21585201 (luo et al., 2011)

KDM4A	sid_852641		8.2		21124847 (King et al., 2010)
	rose10_cmpd7		12		20088513 (Rose et al., 2010)
	methylstat				21585201 (luo et al., 2011)
	HQ2 8-hydroxy-3-(piperazin-1-yl)quinoline-5-carboxylic acid			3RVH	(King et al.)
	JIB-04		0.44		23792809 (Wang et al., 2013)
KDM4B	JIB-04		0.43		23792809 (Wang et al., 2013)
	labelle06_epitherapeutics_Example49		0.1		WO2014053491 A1_Epitherapeutics
	labelle06_epitherapeutics_Example48		0.1		WO2014053491 A1_Epitherapeutics
KDM4C	SD70				24928520 (Jin et al., 2014)

KDM4C	n-octyl ester derivative of IOX1		3.9		24504543 (Schiller et al., 2014)
	compound 1		3.4		21585201 (luo et al., 2011)
	JIB-04		1.1		23792809 (Wang et al., 2013)
	Rotili2014_cmpd 1		0.07		24325601 (Rotili et al., 2014)
	labelle06_epitherapeutics_Example49		0.1		WO2014053491A1_Epitherapeeutics
	labelle06_epitherapeutics_Example48		0.1		WO2014053491A1_Epitherapeeutics
	n-octyl ester of IOX1		3.9		24504543 (Schiller et al., 2014)
KDM4D	JIB-04		0.29		23792809 (Wang et al., 2013)

KDM4E	PDCA		1.4	2W2I	18942826 (Rose et al., 2008) http://www.pdb.org/pdb/explore/explore.do?structureId=2W2I
	JIB-04		0.34		23792809 (Wang et al., 2013)
	compound 1		5.9		21585201 (luo et al., 2011)
	sid_852641		6		21124847 (King et al., 2010)
	rose10_cmpd7		5.4		20088513 (Rose et al., 2010)
	Compound 15c		0.11		21412984 (Chang et al., 2011)
	chang11_cmpd13a		0.18		21412984 (Chang et al., 2011)
	Rotili2014_cmpd1		0.42		24325601 (Rotili et al., 2014)

KDM2A	Rotili2014_cmpd 1		0.22		24325601 (Rotili et al., 2014)
	daminozide		1.5		22724510 (Rose et al., 2012)
	compound 13		2.9		23964788 (Suzuki et al., 2013)
KDM5A	JIB-04		0.23		23792809 (Wang et al., 2013)
KDM5B	labelle06_epitherapeutics_Example49		0.1		WO2014053491 A1_Epitherapeutics
	labelle06_epitherapeutics_Example48		0.1		WO2014053491 A1_Epitherapeutics
	GSK-J1		0.17		25279926 (Heinemann et al., 2014) http://www.thesgc.org/chemical-probes/GSKJ1
KDM5C	Rotili2014_cmpd 1		0.07		24325601 (Rotili et al., 2014)
	labelle06_epitherapeutics_Example49		0.1		WO2014053491 A1_Epitherapeutics

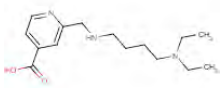
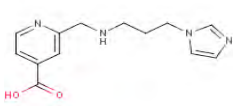
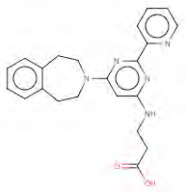
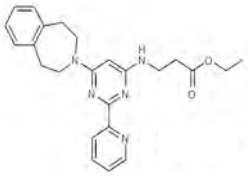
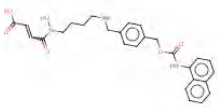
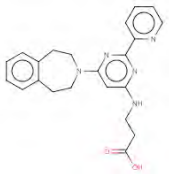
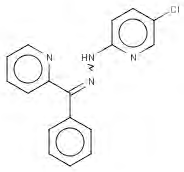
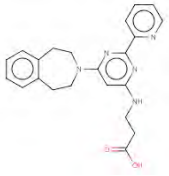
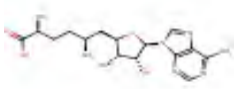
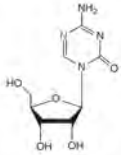
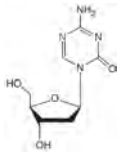
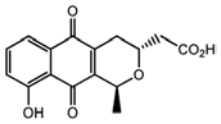
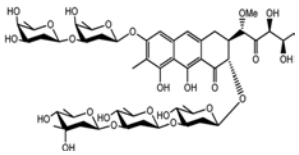
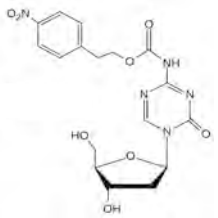
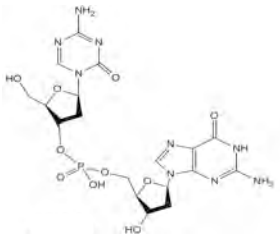
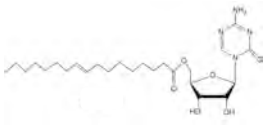
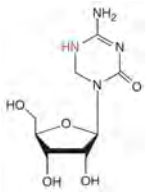
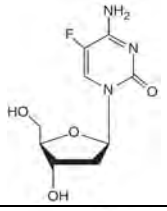
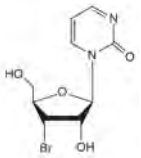
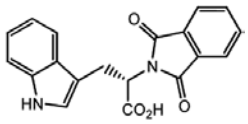
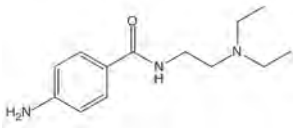
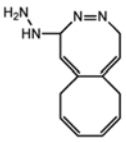
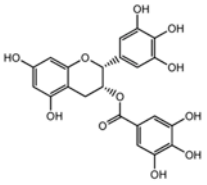
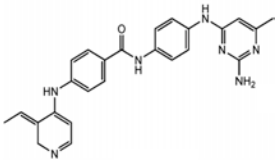
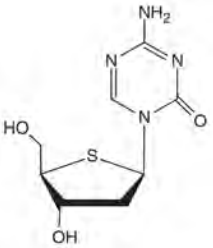
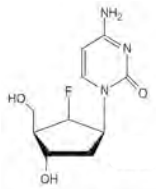
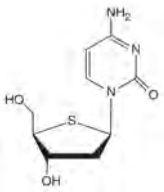
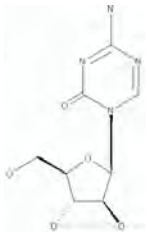
KDM5C	labelle06_epitherapeutics_Example48		0.1		WO2014053491A1_Epitherapeeutics
	labelle06_epitherapeutics_Example1		0.1		WO2014053491A1_Epitherapeeutics
	GSK-J1		0.55		25279926 (Heinemann et al., 2014) http://www.thesgc.org/chemical-probes/GSKJ1
KDM6A/6B	CSK-J4				22842901 (Kruidenier et al., 2012) http://www.thesgc.org/chemical-probes/GSKJ1
KDM6B	compound 1		43		21585201 (luo et al., 2011)
	CSK-JI		0.06	4ASK	22842901 (Kruidenier et al., 2012) http://www.thesgc.org/chemical-probes/GSKJ1
	JIB-04		0.85		23792809 (Wang et al., 2013)
KDM6C	CSK-JI			3ZPO	24798337 (Walport et al., 2014) (Vollmar et al., 2014)

Table 3 Inhibitors of DNMTs

Compound Name	**Chemical structure**	**PDB code of complex structure**	**PMID**
Sinefungin		3SWR	19364644 (Isakovic et al., 2009)
Azacitidine			6156004 (Jones et al., 1980)
Decitabine			6156004 (Jones et al., 1980)
Nanaomycin A			20833755 (Kuck et al., 2010)
Mythramycin A			17893516 (Lin et al., 2007)
NPEOC-DAC			18499340 (Byun et al., 2008)
SGI-110			20442312 (Chuang et al., 2010)
CP-4200			20442313 (Brueckner et al., 2010)

5, 6-Dihydro-5-azacitidine (DHAC)			10368689 (Izbicka et al., 1999)
5-Fluoro-2'-deoxycytidine			6156004 (Jones et al., 1980)
zebularine			12618505 (Cheng et al., 2003)
RG-108			16024632 (Bodo et al., 2005)
procainamide			2066944 (Scheinbart et al.1991)
hydralazine			12632429 (Deng et al., 2003)
(-)-epigallocatechin-3-gallate			14633667 (Fang et al., 2003)
SGI-1027			19417133 (Datta et al., 2009)
5-aza-T-dCyd			US20110218170 A1 23033952 (Fahy et al., 2009)

RX-3117			20006515 (Kuck et al., 2010)
T-dCyd			US20110218170 A1 23033952 (Fahy et al., 2009)
Fazarabine			69026 (Beisler et al., 1977)

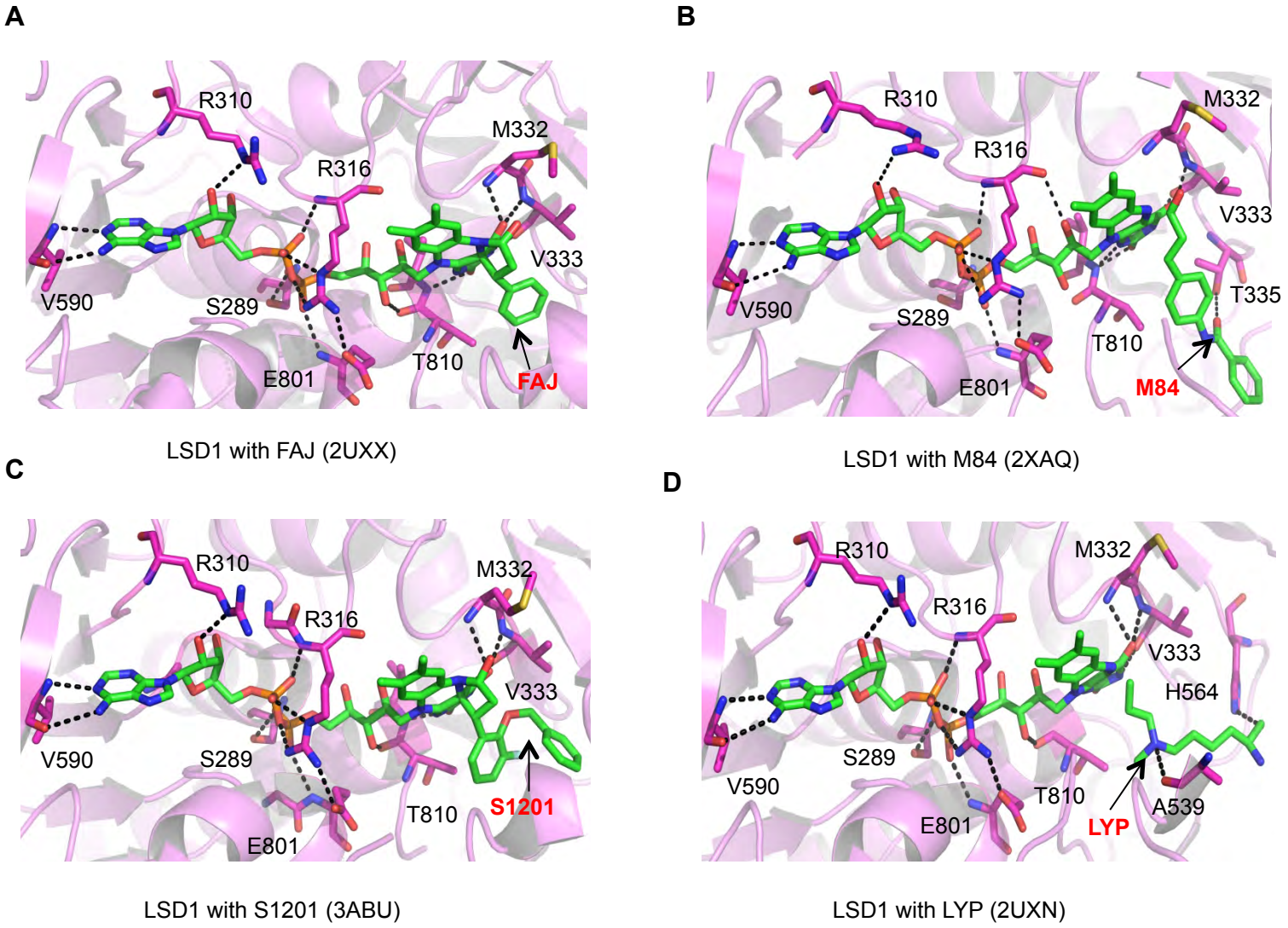
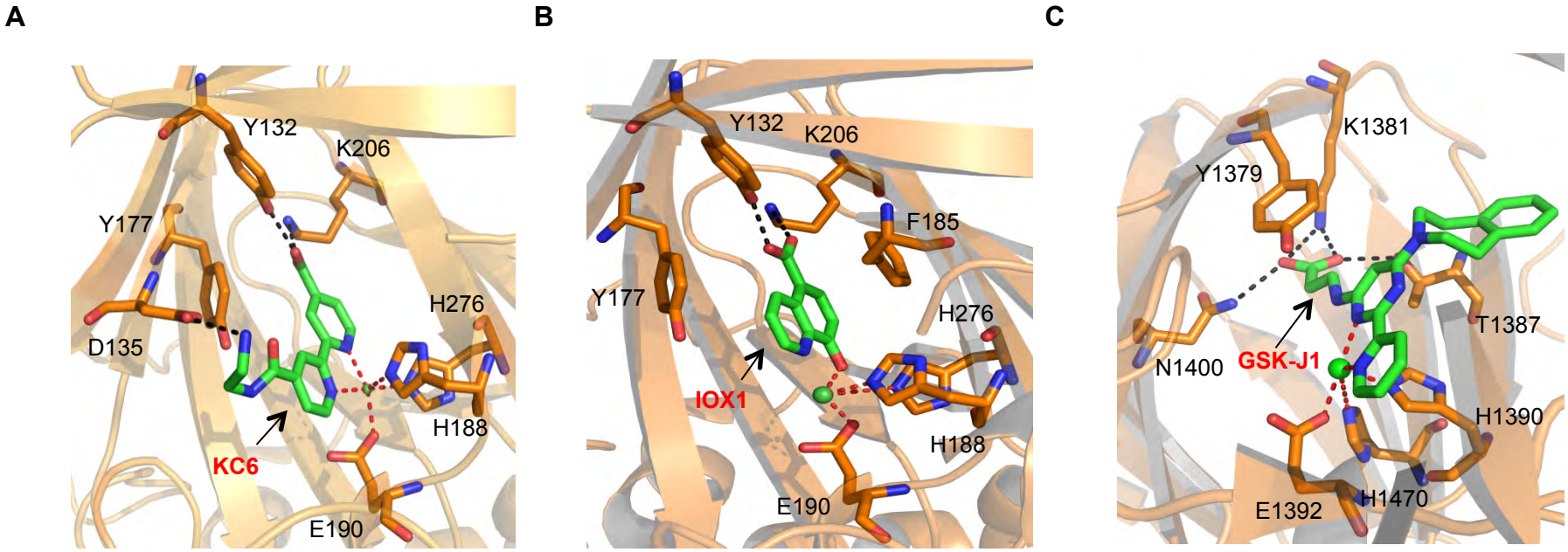

A
R310
M332
R316
V333
V590
S289
T810
E801
FAJ
LSD1 with FAJ (2UXX)
B
R310
M332
R316
V333
T335
V590
S289
T810
E801
M84
LSD1 with M84 (2XAQ)
C
R310
M332
R316
V333
V590
S289
T810
S1201
E801
LSD1 with S1201 (3ABU)
D
R310
M332
R316
V333
H564
S289
V590
T810
A539
E801
LYP
LSD1 with LYP (2UXN)

Fig.1

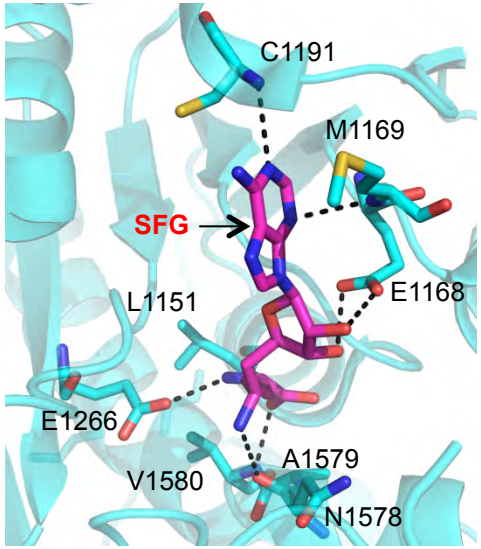


KDM4A with KC6 (3PDQ)

KDM4A with IOX1 (3NJY)

KDM6B with GSK-J1 (4ASK)

Fig. 2



DNMT1 with SFG (3SWR)

Fig. 3