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Review

Development and classes of epigenetic drugs for cancer

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ABSTRACT

Emerging evidence supports an important, etiologic role for epigenetic modifications in cancer. Various post translational modifications of histone proteins together with DNA methylation constitute an 'epigenetic code' regulating the transcriptional status of the cell and aberrant writing and/or interpretation of the code can contribute to a dysregulated, hyperproliferative state. In some cases, epigenetic deregulation has also been reported to result in tumor initiation. The discovery of somatic mutations in some chromatin binding proteins associated with subtypes of lymphomas and the ability to regulate expression of proto oncogenes such as Myc has spurred the development of specific small molecule modulators of histone binding proteins. Several of these compounds have entered clinical development for the treatment of heme malignancies. This review summarizes progress in the discovery and advancement of epigenetic therapeutics for cancer and provides a perspective for future development.

Contents

1. Introduction . . . 58
2. Epigenetic modifications and the 'histone code' . . . 59
3. First generation epigenetic inhibitors . . . 59
   3.1. DNA methyltransferase inhibitors . . . 59
   3.2. Histone deacetylase inhibitors . . . 60
   3.3. Potential of combination therapy . . . 61
4. Second generation epigenetic inhibitors . . . 62
   4.1. Histone methyltransferase inhibitors . . . 62
   4.2. G9a inhibitors . . . 62
   4.3. EZH2 inhibitors . . . 62
   4.4. DOT1L inhibitors . . . 62
   4.5. Histone demethylases . . . 63
   4.6. LSD1 inhibitors . . . 63
   4.7. Jumonji C inhibitors . . . 64
5. Epigenetic reader protein inhibitors . . . 64
   5.1. Acetyl lysine readers . . . 64
   5.2. Methyl lysine readers . . . 65
6. Perspective . . . 65
   References . . . 66

1. Introduction

Significant advances have recently been made in the understanding and recognition of the important contribution of epigenetic factors to the malignant phenotype. More routine molecular profiling of various tumors driven by advances in technologies such as next generation sequencing has allowed for the identification of somatic alterations highlighting epigenetic deregulation as a feature of many cancers (see review by Omar Abdel-Wahab [133]). Reflecting this progress has been an increased interest in developing therapeutics targeting specific

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chromatin associated proteins in much the same way as the successful development of currently used targeted protein kinase inhibitors. Clearly, the analogy can be readily extended to include the possibility of developing 'personalized epigenetic medicines' tailored to a patient's tumor profile and accompanied by both a drug and a molecular diagnostic for patient selection. In this context, it is particularly exciting to note the recent advancement of multiple such potential therapies to clinical evaluation [1,2]. The increased availability not only of clinical agents but also selective, cell permeable 'tool' compounds pioneered by the Structural Genomics Consortium [3] continues to extend and guide research efforts in many laboratories, promising to reveal additional insights to spur the discovery of novel drugs. While not the subject of this Review, it is also worth mentioning the potential for applying epigenetic therapies in non-oncology indications such as neurology [4], metabolism [5], and infectious diseases [6] although critically, an understanding of epigenetic pathways in these processes is only now beginning to emerge.

2. Epigenetic modifications and the 'histone code'

The uncoiled length of nuclear DNA vastly exceeds the size of the cell and therefore exists in a highly compacted form tightly wrapped around the histone proteins H2A, H2B, H3 and H4 in the form of nucleosomes [7]. High resolution X-ray crystal structures of nucleosomes have revealed the presence of short chains ('tails') of ~30 amino acids protruding from the histones [8,9] and subject to various post translational modifications (PTMs) including acetylation, methylation, phosphorylation, ADP-ribosylation, etc. [10]. These PTMs serve to induce local changes in chromatin structure allowing for selective access of transcriptional machinery to the DNA. Importantly, the PTMs are highly dynamic and respond to a variety of signals suggesting a mechanism for the cell to sense and respond to its environment. In addition to histone PTMs, methylation of DNA at cytosine C5 constitutes a second major epigenetic modification and is normally associated with gene silencing (see the review by Hiromu Suzuki [134]). Together, DNA methylation and histone PTMs are both tightly regulated to control the overall transcriptional state of the cell.

Within the histone tails, lysine and arginine residues are the major sites for modification and typically, reversible acetylation and methylation of the basic side chains of these amino acids are common. Indeed, the most recent drug discovery efforts have largely focused on modulating the introduction, removal or interpretation of these modifications. Nonetheless, as mentioned above, phosphorylation, ubiquitination, SUMOylation and crotonylation of serine and threonine residues amongst other modifications have also been observed and affect transcription and/or the cell cycle (e.g. phosphorylation of histone H3 at serine 10 by the Aurora kinases is critical during mitosis, [11]).

Enzymatic acetylation and methylation of histone lysine and arginine amino groups is catalyzed by histone acetyl transferases (HATs) and protein methyl transferases (PMTs) respectively with the latter further subdivided to lysine (KMTs) and arginine (RMTs) targeting proteins [12]. Reversal of the modification is carried out by corresponding deacetylases (HDACs) and lysine/arginine demethylases (K/RDMs). Similarly, *de novo* DNA methylation is accomplished by the methyltransferases DNMT3A and DNMT3B with a second related protein, DNMT1 being responsible for methylation of hemimethylated DNA [13]. Collectively, the dynamic introduction, removal and combinatorial interpretation of the various histone PTMs and DNA methylation has been referred to as the writing, erasing and reading respectively of an 'epigenetic code' [14] by analogy to the more familiar genetic code. Small molecule inhibitors of some of the enzymes and PTM 'reader' proteins have been developed (Table 1) and advanced to clinical studies for a variety of tumor types [15–17]. A number of these will be described below.

3. First generation epigenetic inhibitors

3.1. DNA methyltransferase inhibitors

As mentioned above, the DNA methyltransferases DNMT1, DNMT3A and DNMT3B catalyze the transfer of a methyl group from the methyl donor S-adenosylmethionine (SAM) to the C-5 of cytosine in DNA. In normal cells, the DNMTs play a variety of roles including maintenance of chromosomal stability, silencing of genes, and regulation of embryonic development. In cancer cells, hypermethylation at CpG islands can lead to inactivation of several important tumor suppressor genes including p16 [18] and in order to reverse this epigenetic silencing, small molecule inhibition of DNMT has been pursued as a therapy for several forms of cancer [19,20].

Of the three catalytically active DNA methyltransferases identified, DNMT1 is the most abundant and maintains methylation during DNA replication while DNMT3A and DMT3B both are responsible for establishing methylation patterns during embryonic development. Studies with conditional ablation have shown loss of DNMT3A in human stem cells leads to the inhibition of differentiation and the hypomethylation of multiple genes [21]. Recently, experiments in mice using conditional knockouts have suggested DNMT3A and DNMT3B may also function as tumor

Table 1
Classes and stages of epigenetic inhibitors.

Class	Preclinical	Clinical	Approved
DNMT	SGI-1027, RG-108, procainamide, epigallocatchin, nanomycin A	Zebularine, SGI-110	Azacitidine, decitabine
HDAC	TFMO derivatives	Entinostat, panobinostat, givonostat, belinostat, mocetinostat, tacedinaline, resminostat, AR-42, Kevetrin	Vorinostat, romidepsin
Histone methyltransferases			
G9a	BIX01294,UNC0321, UNC0638,UNC0642,spiroindolamine		
EZH2	Novartis EI1, UNC-1999, GSK343, EPZ-5687	EPZ-6438, GSK126	
DOT1L	SGC-0946, EPZ-4777	EPZ-5676	
PRMTs	BMS PRMT4		
Histone demethylases			
LSD1	OG-1002, GSK354	Tranylcypromine, ORY-1001, GSK9552	
JmjC	GSK-J1, IOX-1		
Bromodomains	JQ1, IBET151, PF-1, RVX-280	IBET762, CPI-0610, OTX015, TEN-010	
MBTL	UNC-669, UNC-1215, UNC-2533		

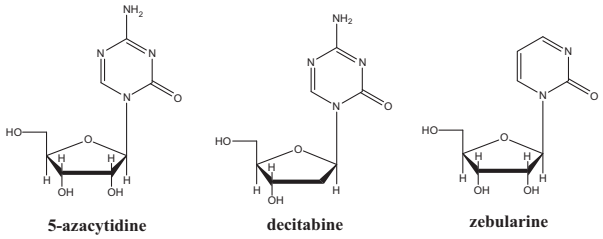

Fig. 1. Chemical structures of DNMT inhibitors.

suppressor genes in their own right and help to prevent lymphoid malignancies [22].

DNMT inhibitors can be broadly divided into nucleoside-derived and non-nucleoside inhibitors. The former class includes the two parenterally administered, FDA approved drugs, azacitidine (Vidaza®) and decitabine (Dacogen®). Azacitidine was first synthesized in 1964 and as a broadly active cytotoxic compound, was initially evaluated in patients with acute myelogenous leukemia (AML). Although promising, the clinical toxicities observed were greatly limiting and the drug failed to progress due to the lack of a sufficiently wide therapeutic window. Following the identification of the hypomethylating mechanism of action of the drug, seminal clinical studies by Kantarjian and Issa using low dose azacitidine demonstrated clinical benefit [23] and led to FDA approval for the treatment of myelodysplastic syndromes (MDS). Decitabine was subsequently approved in 2006 [24]. Both azacitidine and decitabine act as irreversible covalent inhibitors of all catalytically active DNMT isoforms following incorporation into DNA (Fig. 1). Although structurally similar, azacitidine may be somewhat less selective and have more pleiotropic effects based on its ability to affect various RNA processing systems including general ribosomal transcription [25]. More recently, azacitidine has also been shown to inhibit ribonucleotide reductase [26]. In general, the currently used nucleoside-derived DNMT inhibitors suffer from a lack of oral bioavailability, poor plasma stability (short half-life), and pan-DNMT inhibition. Combined, this set of properties may limit clinical utility to rapidly proliferating heme malignancies with high unmet need where a relatively narrow therapeutic window may be acceptable. To provide more convenient dosing options and also to explore the utility of DNMT inhibitors beyond hematological settings, several approaches are being evaluated. A prodrug strategy using SGI-110 (Fig. 2) is the most advanced with clinical trials in MDS already underway [27]. Interestingly, SGI-110 has also been shown to have potential immunomodulatory activity with ability to up-regulate HLA class I antigens associated with tumor associated peptides interaction with cancer/testis cells [28]. If the effect proves to be more widely applicable, the combination of DNMT inhibitors such as SGI-110 with other immunotherapies may provide a novel way to target cancer cells. A variety of newer nucleoside derivatives are currently undergoing clinical trials with for example, zebularine being reported to have better stability and less toxicity compared to the older agents although definitive clinical benefits have not yet been established [29].

Due to the issues associated with the nucleoside derivatives, several groups have pursued identification of non-nucleoside

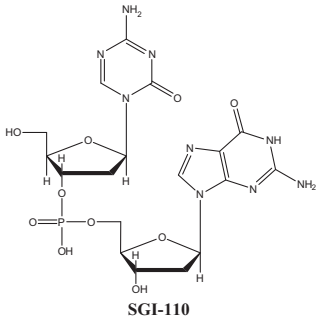

Fig. 2. A DNMT inhibitor prodrug.

DNMT inhibitors (Fig. 3) [30–32]. The compounds show good anti-proliferative effects in a number of cancer cell lines including leukemia, breast, prostate and recent work has identified a number of even more potent analogs [33]. Despite the promise, none of the non-nucleoside DNMT inhibitors has progressed to the clinic and it remains to be demonstrated whether the compounds disclosed thus far are true DNMT inhibitors or if the cellular activity is due to various non-specific off-target effects.

3.2. Histone deacetylase inhibitors

Histone deacetylases (HDACs) catalyze the hydrolysis of N-acetyl lysine residues in histones and act in opposition to the action of histone acetyl transferases (Fig. 4). Importantly, in addition to modifying histones, many HDACs are also known to have deacetylating activity on non-histone proteins [34–36] leading to profound cellular effects. However, a detailed review of these is beyond the scope of this article.

The known HDACs are divided into four main classes with the majority being classified as zinc dependent enzymes. These include the Class I (HDAC 1, 2, 3, 8), Class IIa (HDAC 4, 5, 7, 9), Class IIb (HDAC 6, 10) and Class IV (HDAC 11) enzymes. The non-zinc dependent members are the Class III enzymes and consist of the NAD^+-dependent sirtuins. Data from knockdown experiments has implicated HDACs as crucial mediators of tumor survival and progression [37,38] and there has been a large effort in developing HDAC inhibitors for the treatment of cancer.

To date, two HDAC inhibitors have been approved viz. suberanilohydroxamic (SAHA; vorinostat; Zolinza®) and romidepsin (FK228, Istodax®), with a large number of other compounds still under clinical evaluation. Vorinostat contains a hydroxamic acid group which chelates the catalytic zinc atom of the enzyme ([39]; Fig. 5). Although initially approved for the treatment of cutaneous T-cell lymphoma, multiple subsequent studies have failed to show broader clinical utility for the compound. A phase II study was conducted in both colon and breast cancer patients, but in each case dose limiting toxicities including anorexia, nausea, thrombocytopenia, asthenia, vomiting, and weight loss limited reliable efficacy analysis [40]. As this appears to hold true for other similar HDAC inhibitors evaluated in the clinic [41] and based on the hypothesis that toxicity is related to off-target activities, there

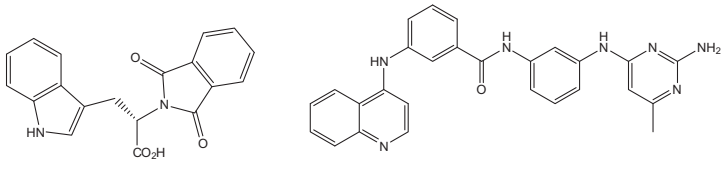

Fig. 3. Reported non-nucleoside DNMT inhibitors.

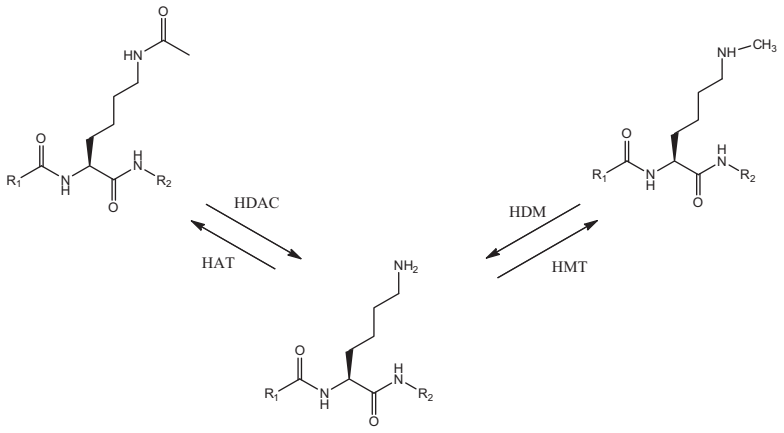

Fig. 4. Modification of the ε-amino group of a lysine residue (R1 and R2 represent the other residues of the histone peptide tail).

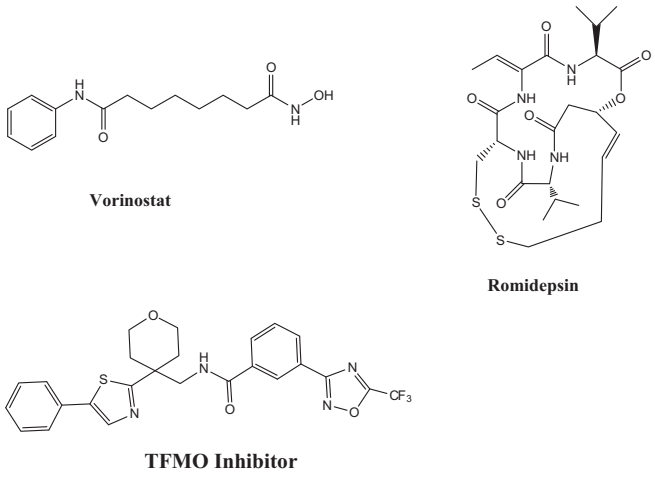

Fig. 5. Histone deacetylase inhibitors with different Zn^{2+} interacting groups.

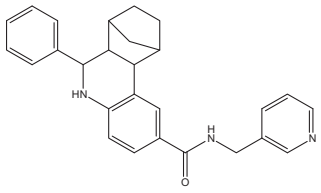

Fig. 6. Sirtuin 2 inhibitor with activity in NSCLC cell lines.

has been considerable effort to develop more selective compounds within a single class or even to target a single HDAC isoform. Published crystal structures of HDACs suggest the catalytic sites are similar with other metalloenzymes such as the matrix metalloprotease (MMP) family and several reported modifications have employed tactics used in the design of compounds for these metalloenzymes [35,42]. Thus by analogy to work in the MMP field, the hydroxamic acid group has been replaced by several Zn^{2+}-engaging heterocycles [43]. For example, the trifluoromethyloxadiazole (TFMO) group has been incorporated to provide several HDAC Class IIa selective inhibitors [44]. Other approaches utilizing a weaker chelating agent in concert with novel affinity enhancing linkers and cap-modifications have been published but thus far the selectivity of such compounds has been limited [45].

The Class III HDACs (sirtuins) have attracted much attention due to their potential central role in cellular nutrient sensing and metabolic regulation [46,47]. However, these proteins have been less well investigated in cancer despite reasonable, albeit emerging genetic evidence showing their role in tumor initiation and progression. Notably, SIRT1 expression has been shown to be a predictive biomarker with regards to tumor stage, differentiation status and response to chemotherapy in NSCLC and genetic inactivation of SIRT1 is sufficient to repress the growth of pancreatic cancer cells [48,49]. Similarly, a SIRT2 inhibitor (Fig. 6) has been claimed to be effective in inducing cell death in NSCLC cell lines [50].

3.3. Potential of combination therapy

The recognition and acceptance of the need for combination therapy for effective and particularly, durable tumor responses has spurred investigation of regimens including epigenetically targeted agents and some promising preclinical and clinical studies have been reported. At the Mayo clinic, combination of decitabine and suramin synergistically decreased the invasive potential of several breast cancer cell lines (e.g. MDA-MB-231) without demonstrating toxicity to cells [51]. The mechanism of action was shown to be due to reexpression of the tumor suppressor gene, protein kinase D1. Similarly, decitabine in combination with SAM blocked the invasiveness and metastatic properties of breast and prostate cancer cells [52]. Combinations with other epigenetic drug classes have also been explored and for example, DNMT inhibitors have shown efficacy with clorgyline and a LSD1 inhibitor in several oncology cell lines including bladder, colorectal, and leukemia [53].

Studies at Johns Hopkins University with a combination of azacitidine and entinostat in patients with refractory advanced NSCLC [54] showed treatment with a low dose of azacitidine with entinostat provided good tumor responses in patients. The study was able to identify a subset of four genes strongly associated with disease recurrence and the combination regimen was associated with improved progression free survival. Recruitment for patients is currently ongoing for several studies to examine the effect of newer HDAC inhibitors such as mocetinostat and AR-42 with azacitidine in AML and NSCLC [55].

In a Phase II trial of patients with stage IIIb or IV NSCLC, combining carboplatin and paclitaxel with vorinostat substantially enhanced the effects of the cytotoxic drugs [56] and demonstrated an overall improvement in progression-free survival and overall survival. Although these studies have thus far only involved limited patient groups, tumor lines and/or compounds, the observations suggest an unanticipated ability of the epigenetically targeted agents to affect positively the therapeutic outcome seen with established interventions. If these initial results are confirmed in future studies, a major additional clinical utility of epigenetic

drugs may well be as enhancers of the action of other targeted drugs with a variety of mechanisms.

4. Second generation epigenetic inhibitors

4.1. Histone methyltransferase inhibitors

Histone methylation is a key PTM known to have important roles in cell cycle regulation, development, DNA damage etc. and there have been several excellent recent reviews describing the role of abnormal histone methylation and the link to cancer [57]. Histone methyltransferases (HMTs) catalyze the methylation of histone lysine and arginine residues using SAM as the methyl group donor. As with the HDACs, many HMTs are known to have activity on non-histone substrates (including cytosolic proteins) and although this emerging aspect is under active investigation in cancer, this article is largely limited to effects derived from direct histone methylation. The most widely studied HMTs are G9a, EZH2, and DOT1L and for the latter two proteins, potent and selective small molecule inhibitors have been identified and advanced to clinical trials (see below).

4.2. G9a inhibitors

G9a is primarily responsible for the dimethylation of lysine 9 on histone H3 (H3K9me2) [58]. The overexpression of G9a has been linked to hepatocellular cancer, B-cell acute lymphoblastic leukemia, and progression of metastatic lung cancer. The first reported G9a inhibitor BIX-01294 exhibited micromolar potency [59] in an enzymatic assay and showed good selectivity against other histone methyltransferases. A related compound UNC0638 has also been reported as a G9a inhibitor which showed excellent potency (IC_{50} = 12 nM) in a fluorescence based SAHH coupled assay and also showed efficacy in reducing H3K9me2 levels in a MDA-MB-231 cell line. This compound was also used to obtain an X-ray structure showing key binding interactions with G9a [60,61]. A second series of compounds exemplified by the spiroindolamine A-366 (Fig. 7) was recently identified from a HTS screen [62]. This compound showed good potency (IC_{50} = 3.3 nM) in an AlphaLisa assay measuring the levels of H3K9 dimethylation. In addition, it demonstrated activity in inhibiting H3K9me2 levels in PC3 cells. More recently, Jin has reported a cell permeable, biotinylated derivative of UNC0638 and has used the compound to chemoprecipitate G9a from whole cells [61].

4.3. EZH2 inhibitors

EZH2 (enhancer of zeste homolog 2) catalyzes methylation of histone H3 lysine 27 (H3K27) and exerts its function as part of the Polycomb repressive complex 2 (PRC2 complex, [63]). EZH2 is the catalytic member of a physiologically functional five unit complex but *in vitro*, an active PRC2 complex can be constituted with a more limited repertoire of EZH2, SUZ12 and EED proteins [64]. Dysregulation of EZH2 has been associated with progression of prostate, breast, kidney, and lung cancer in addition to hematological malignancies such as AML, myelofibrosis, and MDS [65]. In addition, EZH2 has been suggested to play a role in medulloblastoma, a pediatric CNS tumor and as a result EZH2 inhibition has been suggested as a new approach for the treatment of this devastating disorder [66,67].

A number of small molecule inhibitors of EZH2 have been developed and most of the compounds show high structural similarity with a pyridine amide core (Fig. 8). The parental compound in the series was identified via HTS campaigns with careful medicinal chemistry optimization campaigns leading to the design of more potent and selective inhibitors. Amongst the most potent compounds are GSK-126 [68] and EPZ-5687, both with impressive affinity and enzyme selectivity (biochemical K_i = 13 nM, 0.4 nM respectively; >10,000-fold selectivity vs. a panel of other HMTs). Recently Constellation Pharmaceuticals has developed a non-pyridone, tetramethylpiperidinyl benzamide containing series that have good potency (IC_{50} = 32 nM) against the enzyme [64]. This is an advance in the field as it represents a new and distinct template for the inhibition of EZH2. These compounds may serve as potential leads in order to increase the overall diversity of inhibitors of EZH2.

Currently EZH2 inhibitors from GSK and the biotechnology company Epizyme are in human clinical trials. EPZ-6438 is under investigation for diffuse large cell B-lymphoma (DLCBL) and follicular lymphoma. There is excellent evidence in the literature for the use of EZH2 inhibitors in these conditions and it has been reported that approximately 50% of patients with either of these conditions show an oncogenic point mutation in EZH2 [65]. GSK has entered the clinic with an EZH2 inhibitor (GSK126) and the company will begin recruiting for a Phase II study in relapsed/refractory DLCBL and transformed follicular lymphoma [1]. More recently, Epizyme has reported that EZH2 inhibition may also have potential in treating aggressive pediatric cancers such as malignant rhabdoid tumors (MRT) and atypical teratoid rhabdoid tumors (ATRT). Specifically they demonstrated that in SMARCB1-deleted MRT cell lines EPZ-6438 demonstrated antiproliferative effects and also showed efficacy in preventing tumor growth in MRT xenografts in mice [69].

4.4. DOT1L inhibitors

DOT1L catalyzes the transfer one, two, or three methyl groups to histone H3, lysine 79 (H3K79) utilizing SAM as a cofactor (63). DOT1L belongs to the class I methyltransferase family and its substrate is located in the ordered core of histone H3. As with other HMTs, DOT1L has been shown to play an important role in embryonic development with knockout studies in mice showing major irregularities in the cardiovascular system [70,71]. To date most of the studies have pointed to overexpression of this enzyme

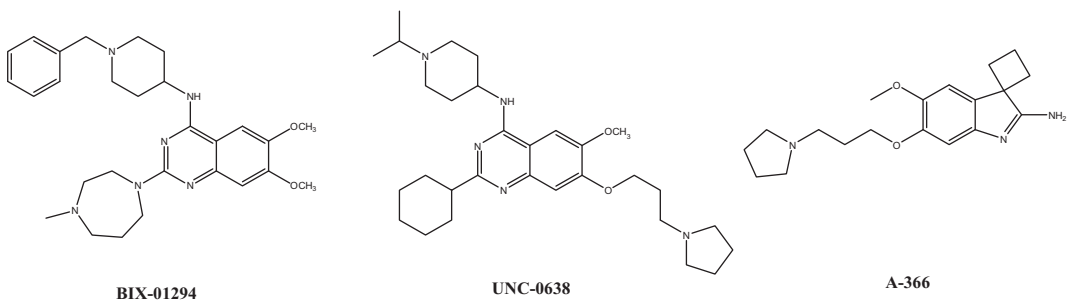

Fig. 7. Known inhibitors of the methyltransferase G9a.

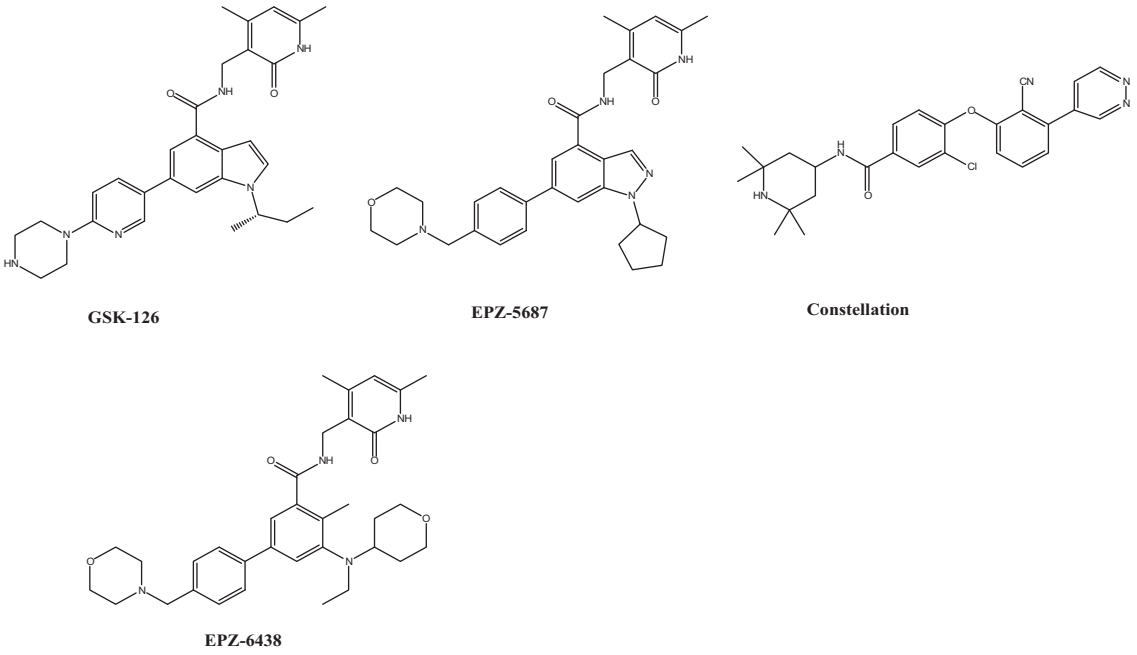

Fig. 8. Small molecule inhibitors of EZH2.

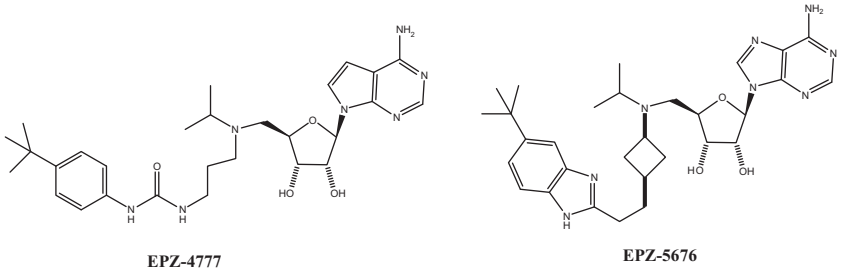

Fig. 9. DOT1L inhibitors structurally related to the cofactor SAM.

having a role in the development of leukemia [72–74]. MLL-fusion proteins gain the ability to recruit DOT1L to MLL target genes where the resulting hypermethylation at H3K79 leads to aberrant expression of genes such as HOXA9 and MEIS1 that drive leukemogenesis. In MLL-rearranged leukemia, several MLL fusion partners were found to be able to physically bind to DOT1L [75]. Gene-expression profiling of knock-in mice also show significant overlap with human MLL.

Due to the clear association of DOT1L and hematological disorders with H3K79 hypermethylation, selective inhibitors have been developed and are presently under clinical evaluation. Epizyme has disclosed a series of compounds exemplified by EPZ4777 (Fig. 9), a potent and selective inhibitor of the enzyme which has been extensively characterized [76]. Although the *in vitro* data is encouraging, the poor preclinical pharmacokinetic properties of EPZ4777 has led to the generation of newer derivatives such as EPZ5676. Indeed, newer publications from Epizyme indicate that the DOT1L inhibitor EPZ5676 is progressing in clinical trials and the company has recently reported a positive proof of concept in a Phase I study [77,78].

4.5. Histone demethylases

The first histone demethylase was discovered in 2004 and since then histone demethylation has been suggested to play a role in several forms of cancer including multiple myeloma, breast, colon, and prostate cancer [79]. The lysine-specific demethylase LSD1 catalyzes the demethylation of mono- and dimethylated histone H3 at lysine 4 and lysine 9 (H3K4 and H3K9 respectively). The effect of this can either be gene activation or repression depending on the exact substrate. The over expression of LSD1 has been reported in a variety of tumors [80,81]. More recently the Jumonji C class of demethylases has been described and been implicated in breast cancer and multiple myeloma [82,83].

4.6. LSD1 inhibitors

The sequence homology between the active sites of MAO-A and B and LSD1 prompted evaluation of known monoamine oxidase inhibitors for histone demethylase inhibitory activity. Most of the compounds examined were weak LSD1 inhibitors but the tranylcypromine based analogs have served as promising starting points for further optimization [84] with the derivative OG-L002 reported to be a potent and selective inhibitor. This mechanism based, irreversible inhibitor has nanomolar biochemical potency against the enzyme and remarkably, exhibits more than 1000-fold selectivity against MAO-A and B. Furthermore, there have been a number of approaches to develop non-covalent inhibitors on the hypothesis these will be less toxic and/or show differential pharmacology by virtue of having a distinct inhibitory mechanism [85,86]. The

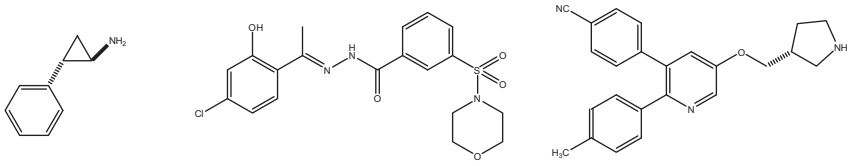

Fig. 10. Inhibitors of the lysine specific demethylase 1 (LSD1).

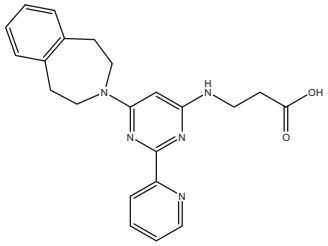

Fig. 11. GSKJ1 – A selective inhibitor of the Jumonji subfamily member JMJD3.

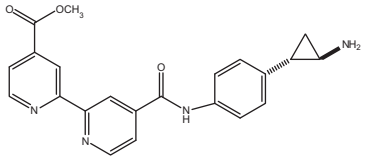

Fig. 12. Dual inhibitor of the lysine demethylases LSD1 and JMC KDM4A/C.

Huntsman Cancer Institute reported a potent hydrazone derivative with good activity against the enzyme but unfortunately, this compound lacked cellular potency. In contrast, the GlaxoSmithKline group has disclosed the structure of a reversible inhibitor, GSK690 [87,88] (Fig. 10) with both high biochemical potency and good cellular activity. Nonetheless, in terms of clinical development, a presumed irreversible compound, GSK9552 has been reported to be under investigation in patients with small cell lung carcinoma [89]. In addition, ORYZON has recently reported that the LSD1 inhibitor ORY-1001 has received approval from the Medicines and Healthcare Regulatory Agency (MHRA) to enter clinical trials in patients with relapsed or refractory acute leukemia [90].

4.7. Jumonji C inhibitors

The Jumonji C (JmjC) family of enzymes represents the largest group of lysine demethylases with 30 known proteins containing this domain [91,92]. These enzymes use α-ketoglutarate and iron to oxidatively demethylate lysine. There is considerable evidence linking overexpression of JmjC containing proteins to various cancers including breast, bladder, and multiple myeloma [93].

Reported inhibitors of the JmjCs have taken advantage of the affinity of a carboxylic acid moiety for the catalytic iron in the enzyme active site. While such derivatives have shown modest inhibitory potency [94,95], more effective inhibitors have been obtained from structure based design approaches with the Jumonji subfamily member JmjD3 (Fig. 11). In this case, one of the compounds obtained clearly demonstrated the importance of JmjD3 catalytic activity in proinflammatory gene activation.

In addition to selective LSD1 and JmjC inhibitors, hybrid analogs combining both activities (PAN inhibitors) have been discovered (Fig. 12). The underlying rationale for targeting dual LSD1 and JmjC KDM4A/C inhibition is based on the premise of synergistic effects on prostate and colon cancer cell lines [96]. Consistent with this hypothesis, the compounds showed good inhibitory activity in LNCaP and HCT116 cells whereas selective LSD1 or JmjC inhibitors had no effect. Interestingly, the compounds synthesized were rationally designed using crystallographic analysis of both the LSD and JmjC structures and contain the cyclopropyl unit found in classical LSD1 irreversible inhibitors and an aryl carboxylate group common in JmjC inhibitors.

5. Epigenetic reader protein inhibitors

5.1. Acetyl lysine readers

Beyond modulators of the writer and eraser enzymes, small molecule inhibitors of histone reader domains have attracted much attention following independent breakthroughs reported by the Bradner and Tarakhovsky groups [97,98], the latter in close partnership with GlaxoSmithKline. As a class, the reader domains are conveniently divided into proteins recognizing either an acetylated or a methylated lysine moiety [99]. In the context of potential cancer therapeutics, the bromodomain family (BRDs; named on the basis of their discovery in *brm* genes [100]) has been the most intensively studied and are recognized to be key components in a variety of physiologically relevant processes with abnormal expression being associated with tumor genesis [101]. Largely as a result of significant efforts by the Structural Genomics Consortium (SGC) and others, over 40 crystal structures have been published covering the majority of the subclasses within this family. In the 'bromodomain and extra terminal' (BET) subgroup of BRDs, such structural studies [102] have exposed a deep, well-defined acetyl lysine binding pocket highly amenable to interacting with drug-like molecules. Compounds such as (+)-JQ1 and IBET762 (Fig. 13) together with various structurally related derivatives show high affinity binding to all BET-subfamily members and promote dramatic antiproliferative and/or pro-apoptotic effects in a variety of tumor cell lines *in vitro* and induce tumor growth delays in *in vivo* mouse xenograft models [103,104]. Most significantly however, in heme malignancies (e.g. MLL-fusion leukemia, multiple myeloma) BET inhibition has been linked to transcriptional silencing of the key proto oncogene cMyc [105–107]. Given the critical role of this protein in other cancers, efforts have now expanded to the evaluation of BET inhibitors in tumors driven by or dependent on the various Myc isoforms. Further, the ability of BET inhibition with JQ1 and IBET762 to dramatically reduce the growth of NUT-midline carcinoma (NMC), a rare but aggressive and lethal pediatric tumor, has led to the initiation of clinical studies in this indication [108]. Beyond these observations, RVX-208, a compound currently undergoing clinical trials for atherosclerosis, has been shown to function also as a modestly potent BET inhibitor and able to upregulate levels of ApoA [109] suggestive of a wider therapeutic potential of BET inhibitors outside of oncology. Amongst the newest of compounds disclosed with nanomolar potency and selectivity for the BET domains is PF-1 discovered by the SGC and Pfizer [110]. In cellular models, the compound inhibited proliferation of several leukemia cell lines and transcriptionally attenuated Aurora B expression.

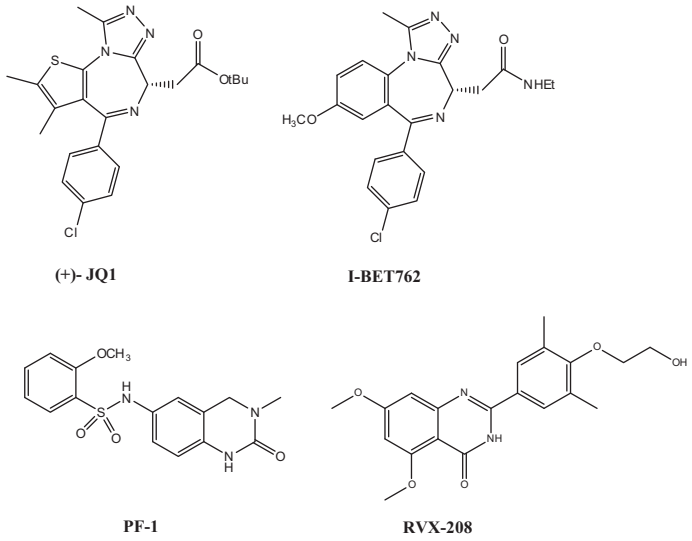

Fig. 13. Antagonists of the BET acetyl lysine reader domains.

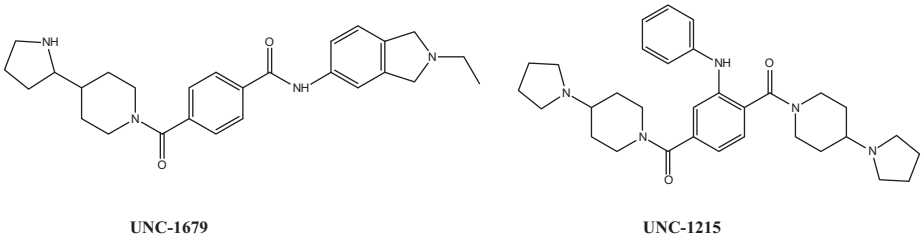

Fig. 14. Probe molecules targeting the malignant brain tumor family protein L3MBTL3.

The detailed structural information available on various bromodomains has also enabled the *de novo* design of inhibitors with a broader but still restricted spectrum of activities. For example, a series of dual HDAC/BET inhibitors have been reported exemplified by DUAL946 [111]. Though no real increase in potency in inhibiting growth in NMC and AML cells was observed when compared to the parent molecules, the simultaneous modulation of two epigenetic proteins may serve to induce more profound effect(s) in other malignancies or conditions. Interestingly, the Knapp group has published work showing that several clinically used kinase inhibitors also possess significant BET inhibitory activity. The polo-like kinase inhibitor BI-6727 (volasertib) also has good BET inhibitory activity (IC_{50} = 79 nM) and suggests the design of dual PLK-BET inhibitors, or dual JAK-BET inhibitors is feasible and may open up new avenues for 'combination' therapy approaches in oncology.

5.2. Methyl lysine readers

The methyl-lysine reader modules are principally made up of the "Royal" (i.e. Tudor, Chromo, etc.) and PHD family of proteins [112]. The Tudor domains (named for the Tudor gene in drosophila) have ~60 amino acids arranged in 4–5 antiparallel β-sheets to form a barrel like structure [113,114]. Of the thirty mammalian Tudor containing proteins identified to date, several have been associated with cancer. For example, Tumor domain-containing protein 1 (TDRD1) is overexpressed in ERG-rearranged prostate cancer [115]. The UNC group has reported a probe molecule (Fig. 14) for the study of L3MBTL3, a member of the malignant brain tumor (MBT) family of proteins. Structurally, the compound behaves as an aryl aniline lysine mimic, binds in the aromatic cage common to the methyl lysine readers, and has good *in vitro* potency and cellular activity [116,117]. The authors were also able to obtain a co-crystal structure of UNC1215 and L3MBTL1 and exploited the structural information obtained to design more selective compounds. Thus, UNC1679 demonstrates much higher affinity (IC_{50} = 160 nM) and selectivity for L3MBTL3 when compared with the related L3MBTL1 protein (IC_{50} > 10 μM).

6. Perspective

Working in concert with the genome, chromatin associated proteins are increasingly being recognized as important mediators of the cancer phenotype. The discovery of somatic mutations in some of these proteins in cancer reinforces the idea of an epigenetic driver in these malignancies. Furthermore, mutations in some non-chromatin proteins may also be linked to well recognized epigenetic proteins (e.g. IDH1 mutations and the TET DNA demethylases [118–120]) and offers the possibility of developing orthogonal and in principle, synergistic interventional strategies. Spurring the efforts to discover and develop therapeutics acting on chromatin binding proteins has been the ability to design and/or identify from various compound collections, drug-like molecules with a sufficient preclinical therapeutic index to allow clinical evaluation in appropriately stratified patient populations.

Notwithstanding the promise of recent advances, it is important to acknowledge the first generation inhibitors of the DNMTs and HDACs have seen only limited utility in some heme malignancies (MDS and CTCL respectively) due to toxicity and off target effects. Efforts to derive more selective and/or less pleotropic inhibitor scaffolds are continuing and may provide efficacy in a broader set of tumors. Second generation compounds hold more promise

for several reasons. These new clinical agents have intrinsically greater selectivity for their molecular target and will be developed in indications where the target is known to be a driver or key mediator of the malignancy (e.g. DOT1L in MLL-rearranged leukemia with H3K79me3, EZH2 in DLBCL with high H3K27me3, etc.). As a result, there is greater likelihood of observing a robust clinical signal at doses well separated from toxic levels. Undoubtedly, the development of appropriate pharmacodynamic biomarkers and diagnostic protocols will be critical for the success of this approach.

As with other cancer therapies, the deployment of epigenetic therapies will likely require the development of rational combination therapies with cytotoxics, targeted kinase inhibitors, immunotherapies, or different classes of epigenetic drugs. A promising albeit provocative approach dubbed 'epigenetic priming' [121–123] may prove to be particularly useful in combination therapy with cytotoxic agents. The concept has been used to reverse the resistance to cisplatin in patient derived ovarian cancer cells and, if observed in other tumor types, could be used to resensitize chemo resistant cells. In addition, at Massachusetts General Hospital, a team has examined the relationship between γ-secretase inhibitors (GSIs) and BRD4 inhibitors in T-cell acute lymphoblastic leukemia (T-ALL) [124]. Although GSIs inhibit the expression of NOTCH1, an important oncogene in T-ALL, these compounds have not proved to be effective in practice due in part, to the emergence of chemoresistance. However, genetic knockdown screens identified BRD4 as essential for the viability of the drug resistant cells and combination of a NOTCH inhibitor with a BRD4 inhibitor significantly prolonged the survival of T-ALL xenografted mice relative to either agent alone. The ability to inhibit the bromodomain proteins with small molecules has been a highly significant advance in the field and clinical data on the multiple BET inhibitors currently under investigation is eagerly awaited. The observation of Myc silencing via BET inhibition is remarkable and for the first time offers the exciting opportunity to abrogate the activity of this potent proto oncogene in multiple cancers. Since the BET proteins subfamily is clearly 'druggable', it is likely at least some of the other acetyl lysine readers will succumb to selective inhibition and indeed, early results support this notion [125]. Further progress will depend on developing new chemical and screening technologies to study and block such protein–protein interactions.

The availability of specific, bioavailable inhibitors will allow for the examination of the role of epigenetic targets in autoimmune and central nervous system disorders. In rheumatoid arthritis for example, epigenetic changes occur in synoviocytes and these changes may lead to initiation and progression of the disease [126]. Neuroepigenetic research focused on the role of neuronal plasticity in the development of neurodegenerative disorders is another area of growing interest. In Huntington's disease, HDACs have been suggested to play a role in the progression of the disease and inhibitors have been shown to improve neurodegeneration in cellular and *in vivo* models [127,128]. In addition, several reports have indicated a relationship between DNMT1 and α-synuclein in Parkinson's disease [129,130]. As modulators of chromatin associated proteins are advanced into the clinic for chronic disorders, questions related to safety issues such as heritable phenotypic effects will need to be addressed. Towards this end, the Goodell group has shown that DNMT3A loss causes hematopoietic stem cells to lose their ability to differentiate over the course of serial transplantation and suggests that some preclinical toxicological evaluations may also have to also examine effects on progeny animals. However, the initial concerns of trans generational effects of inhibiting epigenetic enzymes have not been a factor with the first generation drugs despite evidence of hypomethylation activity in patients [131,132].

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