Mini-review

Histone deacetylase inhibitors as anti-neoplastic agents

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Abstract
Histone deacetylase inhibitors (HDACIs) constitute a novel class of targeted drugs that alter the acetylation status of histones and other important cellular proteins. These agents modulate chromatin structure leading to transcriptional changes, induce pleiotropic effects on functional pathways and activate cell death signaling in cancer cells. Anti-neoplastic activity in vitro was shown in several experimental models of cancer, but the exact mechanism of cytotoxicity and responses are not clearly understood. Phase I/II clinical trials of various HDACIs as single agents conducted to date have shown substantial activity in cutaneous T cell lymphoma (CTCL), preliminary activity in Hodgkin’s disease and modest activity in myeloid neoplasms. Responses have been rare in solid tumors. Several agents are being tested in combination therapy clinical trials, either as chemosensitizers for cytotoxic chemotherapy or radiation therapy, or in association with DNA methylation inhibitors based on in vitro synergy. In this review, we focus on recent basic and clinical data that highlight the anti-neoplastic role of HDACIs.

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1. Introduction

Histone deacetylase inhibitors (HDACIs) belong to an emerging class of anticancer agents aimed at treating neoplasms by targeting gene expression, an approach that has been termed epigenetic therapy [1]. Histones are proteins around which DNA is wound to form nucleosomes, the basic unit of chromatin. Post-translational modifications of histone tails such as acetylation and methylation affect chromatin structure and gene expression, and are one component of epigenetic regulation in mammalian cells [2,3]. Epigenetics, in turn, refer to changes in gene expression that, in adult cells, are stable through mitosis. Epigenetic processes are essential for development, differentiation and stemness. Thus, histones modifications add information content to the primary DNA sequence.

Epigenetic deregulation of gene expression was shown to be implicated in cancer pathogenesis [4]. One of these epigenetic alterations is histone acetylation/deacetylation.

This can occur via aberrant recruitment of histone deacetylases, for example by the fusion gene products of chromosomal translocations, or by recruitment via aberrant DNA methylation at gene promoters. Primary alterations in histone acetylases have also been described in cancer. Histone deacetylation in the promoters of growth regulatory genes has been found in numerous malignancies.

The protein acetylation equilibrium is sustained in cells by interplay of two classes of enzymes: The protein acetylases and deacetylases [5]. These enzymes modulate gene expression by the removal or the addition of acetyl groups to lysine residues of histones. In general, acetylation is associated with active gene expression and deacetylation is associated with gene silencing. Inhibition of histone deacetylases as a therapeutic tool in cancer was arrived at in two parallel tracks [6]. The realization that acetylation was frequently abnormal in cancer raised interest in these agents. Indeed, HDACIs render the chromatin conformation less tightly packed, which leads to the recruitment of the transcriptional machinery and to transcriptional activation. In parallel, an unbiased screen for molecules that can differentiate cancer cells in vitro identified HDACIs as...
a class of agents with substantial activity in this assay. In leukemia in particular, failure of normal differentiation could result from a failure to transcribe genes which encode proteins that either mediate or define the mature phenotype. For optimal transcription of these genes, histones should be in a maximally acetylated state. Therefore, the manipulation of histone acetylation may provide a therapeutic strategy for patients with acute myeloid leukemia (AML), as well as other hematological malignancies.

Recent data uncovered the notion that protein acetylation is a common regulatory mechanisms that is not limited to histones [7]. Thus, the term HDACI is not precise since the substrates of the enzymes inhibited include non-histone proteins such as P53. Indeed, acetylation of P53 is essential for its activation [8]. The class of drugs in question would therefore more accurately be named protein deacetylase inhibitors. In this review, we aim to describe the molecular basis of HDACIs as anti-neoplastic agents and their clinical application in oncology.

2. Molecular basis of HDACI efficacy

Histone deacetylases (HDACs) comprise a family of 18 genes that are subdivided into four classes [3]. Classes I, II, and IV are referred to as “classical” HDACs and are generally simultaneously targeted by most HDACIs. Early work on the mechanism of action of HDACs has focused on their effects on gene transcription. As shown in Fig. 1, HDACs catalyze the removal of acetyl groups from the chromatin core histones. HDACs induce neutralization of the charge on the histones which allows the phosphate backbone of the DNA to open up and therefore facilitate the transcription of many genes, including tumor suppressor genes silenced in cancer. Moreover, acetylation of histones facilitates destabilization of DNA–nucleosome interaction and renders DNA more accessible to transcription factors [2]. The effects of HDACIs on gene expression are highly selective, leading to transcriptional activation of certain genes such as the cyclin-dependent kinase inhibitor p21WAF1/CIP1 but repression of others [3]. As mentioned above, HDAC inhibition not only results in acetylation of histones but also of transcription factors such as P53, GATA-1 and estrogen receptor-alpha. The role of this non-histone protein acetylation in in vitro and clinical responses to HDACIs remains to be clarified.

There is substantial interest in the interactions between histone deacetylation and DNA methylation in the proximity of gene promoters [9,10]. DNA methylation attracts the binding of HDACs to gene promoters thus promoting localized deacetylation [11]. HDACs are also components of the Polycomb group silencing pathway active in stem cells, and this silencing has been shown to promote DNA methylation in cancer [12], suggesting that the level of histone acetylation can directly influence the degree of methylation of a promoter in cancer. On the other hand, HDACIs alone rarely activate the expression of genes silenced by promoter CpG island methylation [13], though they show strong schedule dependent synergy with DNA methylation inhibitors in this regard (with a requirement for demethylation to precede HDACI).

In parallel to effects on gene expression and differentiation, HDACIs have also been shown to be efficient inducers of apoptosis in several cellular systems [14]. The precise mechanisms of this effect are under investigation, with suggestions ranging from effects on cellular networks to oxidative stress induction and to DNA damage induction [15]. For example, using microarray analysis, it was demonstrated that HDACIs induces the expression of the thio-redoxin-binding protein-2 (TRB-2) gene in LNCAP prostate cells [16]. Induction of TRB-2 followed by decreased levels of thio-redoxin (TRX) was proposed to play a critical role in SAHA-induced growth arrest and/or apoptosis in transformed cells. Separately, effects of HDACIs on the molecular chaperone heat shock protein 90 (Hsp90) may also mediate apoptosis. SAHA was shown to induce acetylation and inhibition of Hsp90, and thus depleted the levels of hsp90 [17]. Another HDACI Panobinostat induced hsp90 acetylation and DNA methyltransferase 1 (DNMT1) degradation [18]. These effects on hsp90 may be involved in the observed synergy between HDACIs and many anti-neoplastic agents [14].

3. HDACIs in the clinic

Several HDACIs have shown impressive antitumor activity in vitro with remarkably little toxicity in preclinical studies, suggesting selectivity for neoplastic cells. This has prompted development of additional compounds, many of which have entered phase 1 trials in various malignancies. There are different chemical classes of HDACIs, as summarized in Table 1. Two early lead compounds, suberoylamidile hydroxamic acid (SAHA) and pyroxamide bear structural similarity with trichostatin A, a potent inhibitor of HDAC. The hydroxamic acid-based hybrid polar compounds inhibit HDAC at considerably lower concentrations than those considered being cytotoxic. In recent years, an increasing number of structurally diverse HDACIs have been identified that inhibit proliferation and induce differentiation and/or apoptosis of tumor cells in culture and in animal models. The major HDACI structural classes are hydroxamic acid: SAHA (Merck & co), CRA-024781 (Celera Genomics), LBH589 (Novartis), PXD101 (CuraGen, TopoTarget), NVP-LAQ824 (Novartis), ITF2357 (Italfarma-co), SB939 (SBIO Pte Ltd), R306465 (Johnson & Johnson);
short-chain fatty acids: valproic acid, benzamides: MS-275 (Syndax), MGCD0103 (MethylGene), cyclic peptides: FK228 (Gloucester), thiolate, non-hydroxamic acid, carboxamides, oxadiazoles.

The next set of milestones for this field was to define the optimal profile of HDAC isoform targets by comparing the pan-HDACI hydroxamic acid with other selective HDACIs. A novel HDACI has been developed recently to target the pan-HDACI hydroxamic acid [19]. In fact, HDAC6 is a new class II enzyme which seems to play a role in metastasis, in deacetylation of Hsp90, and in the regulation of apoptosis [20,18]. We describe next the main HDACIs in phase I/II clinical trials.

### 3.1. Vorinostat

Vorinostat (suberoylamide hydroxamic acid, (SAHA), (Zolinza, Merck & Co., Inc.) is a hydroxamic acid that is a pan-HDACI. Vorinostat was approved by the U.S. Food and Drug Administration, for the treatment of Cutaneous T-Cell Lymphoma (CTCL) [21]. This was based on promising data in a phase I study [22], which led to a phase II study in which 33 patients with CTCL were enrolled that produced an overall response rate of 31% at a vorinostat dose of 400 mg [23]. Another major trial supporting vorinostat approval was a single-arm open-label phase IIb multicenter trial that enrolled 74 patients with stage IB and higher CTCL who had failed two systemic therapies (one of which must have contained bexarotene). In this study population, the overall response rate was 30% with median response duration of 168 days [24].

Vorinostat was evaluated in other hematological malignancies, with a response seen in Hodgkin’s disease [22]. A phase I study of vorinostat in patients with leukemias was recently reported [25]. Forty one patients were included, 31 of whom had acute myeloid leukemia (AML). The remaining patients had other leukemias or myelodysplastic syndrome. The subjects received 100–300 mg doses of oral vorinostat two or three times daily for 14 days, followed by 1 week of rest. The maximum tolerated dose (MTD) was 250 mg three times daily. Five patients (12%) had adverse experiences that required dose reduction. Twenty-nine patients dropped out of the study because of disease progression. Seven patients (17%) achieved a complete response (CR), a complete response with incomplete blood count recovery, or hematological improvements; all had AML. All of these patients received vorinostat doses at or below the recommended level.

Vorinostat has been also examined as a single agent in various phase I and phase II studies. In the setting of refractory disease, vorinostat was found to have modest to no activity in myeloma, head and neck cancer, breast cancer, thyroid cancer and other malignancies [26–31].

### 3.2. Depsipeptide

Romidepsin/depsipeptide [32] (FK 228) Gloucester Pharmaceuticals (Cambridge, Massachusetts, USA) is a cyclic peptide that selectively inhibits HDAC isotypes 1, 2, 4 and 6. Phase I studies of depsipeptide yielded several different dose schedules that were evaluated in phase II studies. A common schedule is 17.8 mg/m² on day-1 and -5 every 21 days [33]. In that schedule, dose-limiting toxicities were fatigue, nausea, vomiting, and transient thrombocytopenia and neutropenia. In depsipeptide monotherapy trials, complete responses were reported in CTCL [34] and in AML [35]. A multicenter phase II study of depsipeptide in CTCL is ongoing. Just like vorinostat, minimal efficacy was observed in other malignancies, including lung cancer, renal cancer, colon cancer, CLL and other malignancies [36,33,37–40]. In the lung cancer trial, translational studies did show global gene expression changes after depsipeptide, and it was suggested that the drug could be evaluated further as a biological response modifier [37]. A controversy has arisen over the safety of depsipeptide. Some studies have raised concerns about observed EKG changes and possible cardiac toxicity [41], but a careful review suggested that some of the cardiac events observed were related to established risk factors [42]. Nevertheless, the fact that vorinostat, depsipeptide and another potent HDACI panobinostat all cause EKG changes have raised the issue of a class effect on cardiac toxicity for HDACIs.

### 3.3. Valproic acid

Valproic acid is a short-chain fatty acid that is a weak HDAC inhibitor [43]. Its long term availability as an anti-
seizure drug prompted its evaluation in oncology as an epigenetic acting drug. A single agent study demonstrated minor responses in patients with the myelodysplastic syndrome (MDS) [44]. Most of the clinical data on valproic acid has come from combination studies, discussed below.

3.4. Other HDACIs

Several HDACIs are in ongoing clinical trials, though clinical data so far has not suggested major differences between the different drugs. Belinostat, a potent HDACI in vitro has completed phase I evaluation and entered phase II studies [45,46]. The early data in heavily pre-treated patients has shown stable disease in a fraction of patients, with no major responses. Panobinostat is one of the most potent HDACIs in vitro. Following phase I studies, ongoing studies are evaluating it in CTCL and Hodgkin’s disease with preliminary evidence of activity [47]. The early data in heavily pre-treated patients has shown stable disease in a fraction of patients, with no major responses. Belinostat is one of the most potent HDACIs in vitro. Phase I studies showed the typical side-effects of HDACIs [48,49], with rare responses in heavily pre-treated patients. A phase II study reported promising activity in refractory Hodgkin’s disease [50]. Other studies are summarized in Table 2.

4. Combination studies

4.1. Combinations with DNA methylation inhibitors

As discussed earlier, there is strong, schedule dependent synergy between DNA methylation inhibitors and HDACIs at the level of gene expression regulation. This has prompted several studies of combining these two classes of agents in hematological malignancies, and this concept is now being tested in solid tumors as well. Completed phase I/II studies include decitabine + valproic acid [51], azacitidine + valproic acid + retinoic acid (ATRA) [52] and azacitidine + MS275 [53]. All these studies demonstrated safety of the combinations, and response rates that were encouraging though not definitively superior to single agent DNA methylation inhibitors. A common finding in these studies was relatively rapid time to response, and it was suggested that this may be a surrogate sign for synergy. Those studies also found increased toxicity with the combinations, particularly neurotoxicity (confusion, somnolence) and fatigue, which are common side-effects of HDACIs. These combinations are now being tested in randomized studies in patients with MDS and AML. In parallel, valproic acid combination with azacitidine has also been tested in patients with advanced solid tumors [54]. These studies are too early to comment on efficacy, though encouraging results have been reported.

4.2. Other combinations

Presumably through effects on apoptosis [15], HDACIs have been found to be synergistic with many different therapies including cytotoxics, targeted therapies and radiation therapy. These combinations are slowly making their way to the clinic. Examples of “promising” combinations include valproic acid with epirubicin [55], vorinostat with idarubicin [56], vorinostat with carboplatin and paclitaxel [57] (responses in 11/25 patients with non-small cell lung cancer), etc. Table 2 lists additional recent trials of HDACI combinations in solid tumors. Some of these have already led to randomized studies, which may introduce HDACIs into the mainstream of anti-neoplastic therapy for common diseases.

5. Research issues

Several aspects of epigenetic therapy pose significant clinical and translational challenges. In particular, while HDACIs are considered targeted agents, this approach is conceivably non-specific due to the numerous downstream effects on gene expression. Thus, translational research will be essential to clarify the precise mechanisms of in vivo action and resistance of the drugs.

5.1. In vivo mechanisms of action

A fascinating aspect of the clinical data so far is the selectivity of HDACIs (as single agents) for some lymphoid malignancies such as CTCL and Hodgkin’s disease. The mechanism of this selectivity is mysterious, and, if elucidated, may well prove to be very useful to advance this therapy towards treatment of other malignancies. Data reported so far include preferential induction of apoptosis in CTCL cell lines in vitro [58], expression of HDAC2 in aggressive CTCL [59], gene expression modulation in vivo [47], and a gene expression signature predictive of response in leukemias [25] (in a small number of patients). None of these studies clearly explain the selectivity of HDACIs for CTCL, and a careful evaluation of this issue is one of the most pressing research questions in the field.

5.2. Surrogate assays

Since HDACIs cause accumulation of acetylated histones in tumors and in normal tissues, an assay for the accumulation of acetylated histones might be useful as an intermediary marker of HDAC inhibition and especially to be incorporated into future clinical trials as a surrogate end point for analysis. The assessment of histone H3 and H4 acetylation in peripheral blood mononuclear cells has been the most frequently used molecular model in HDACI pharmacodynamic studies [60]. However, the modulation of histone acetylation has not predicted clinical responses so far and has not been used to guide dose selection. An assay of HDAC enzymatic activity in intact cells using a cell-permeant substrate with a fluorescent read-out was tested in two phase I trials of MGCD0103 [2,49]. It is not clear whether this is superior to measuring histone acetylation directly. There are no reported attempts to measure non-histone protein acetylation in patients treated with HDACIs so far.

5.3. Differences between the HDACI drugs

The proliferation of HDACI leads to the natural question of differences between them. Reported differences include potency, isotype selectivity, administration route and...
Table 2
Recent HDACI studies in solid tumors.

<table>
<thead>
<tr>
<th>HDACI</th>
<th>Dose</th>
<th>Phase</th>
<th>Other Therapy</th>
<th>Disease</th>
<th>N</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAHA</td>
<td>400 mg/day</td>
<td>I</td>
<td>BelCalP</td>
<td>Advanced solid malignancies</td>
<td>9</td>
<td>Four had PR (1 head &amp; neck cancer, 3 NSCLC) &amp; 2 had SD</td>
<td>[68]</td>
</tr>
<tr>
<td>SAHA</td>
<td>200 mg orally twice daily × 14 days, and bevacizumab 15 mg/kg intravenously every 21 days</td>
<td>I/II</td>
<td>Bevacizumab</td>
<td>Renal cell cancer</td>
<td>8</td>
<td>3/7. One pt with mixed response had SD for &gt;18 months. Two pts SD for 5 and 6 months</td>
<td>[69]</td>
</tr>
<tr>
<td>SAHA</td>
<td>400 mg daily for three of four weeks and tamoxifen 20 mg daily, continuously</td>
<td>II</td>
<td>Tamoxifen</td>
<td>Breast cancer</td>
<td>19</td>
<td>Four patients (1 CR, 3 PR: 4/17, 24%)</td>
<td>[70]</td>
</tr>
<tr>
<td>SAHA</td>
<td>200 mg bid × 14 days q 3 weeks</td>
<td>II</td>
<td></td>
<td>Recurrent glioblastoma multiforme HRPC, s/p chemotherapy</td>
<td>68</td>
<td>Five of the first 22 patients (23%) were progression-free at 6 months</td>
<td>[71]</td>
</tr>
<tr>
<td>SAHA</td>
<td>400 mg daily in 21-day cycles</td>
<td>II</td>
<td></td>
<td></td>
<td>23</td>
<td></td>
<td>[72]</td>
</tr>
<tr>
<td>VPA</td>
<td>(mg/kg/day): 15, 30, 45, 60, 75, 90, 100, 120, 140 and 160</td>
<td>I/II</td>
<td>FEC100</td>
<td>Locally advanced or metastatic breast cancer</td>
<td>44-Phase I</td>
<td>In the breast-specific phase II part, PR-4/8 (50%) and SD-2/8 (25%), progression in 1/8 (12.5%)</td>
<td>[73]</td>
</tr>
<tr>
<td>VPA</td>
<td>IV loading (mg/kg) + epirubicin (mg/m²): 15/75, 30/75, 45/75, 60/75, 75/75 and 75/100, oral loading: 75/100, 90/100, 100/100, 120/100, 140/100 and 160/100</td>
<td>I</td>
<td>Epirubicin</td>
<td>Advanced solid tumors</td>
<td>42</td>
<td>PR 7/37 (19%)</td>
<td>[73]</td>
</tr>
<tr>
<td>MGCD0103</td>
<td>50 mg, 75 mg, and 90 mg + Gemcitabine</td>
<td>I</td>
<td>Gemcitabine</td>
<td>Refractory solid tumors</td>
<td>21</td>
<td>SD 16/37 (43%)</td>
<td>[74]</td>
</tr>
<tr>
<td>MGCD0103</td>
<td>50 mg, 75 mg, and 90 mg + Gemcitabine</td>
<td>I/II</td>
<td>Gemcitabine</td>
<td>Refractory solid tumors</td>
<td>25 in phase I and 4 in phase II</td>
<td>14 response-evaluable phase I pts, 2/5 PR in pancreatic Cancer</td>
<td>[75]</td>
</tr>
<tr>
<td>MGCD0103</td>
<td>Five dose levels have been evaluated (mg/m²): 12.5, 20, 27, 36, and 45</td>
<td>I</td>
<td></td>
<td>Advanced solid tumors</td>
<td>28</td>
<td>Two unconfirmed PR 2/14 SD</td>
<td>[76]</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>13 mg/m² intravenously over 4 h on days 1, 8, and 15 of a 28-day cycle</td>
<td>II</td>
<td></td>
<td>Refractory or metastatic renal cell cancer</td>
<td>25</td>
<td>2/25(8%)</td>
<td>[77]</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>1, 2, 3, 5, 7, 9 mg/m²</td>
<td>I</td>
<td></td>
<td>Thyroid and other advanced cancers</td>
<td>19</td>
<td>11-SD</td>
<td>[78]</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td>4 h infusion followed by gemcitabine over 30 min on days 1, 8, and 15 of a 28 day cycle initial romidepsin/gemcitabine dose level was 10/800 mg/m² 13 mg/m² as a 4-h iv infusion on days 1, 8, and 15 of a 28-day cycle</td>
<td>I</td>
<td>Gemcitabine</td>
<td>Pancreatic and other advanced solid tumors</td>
<td>33</td>
<td>One patient with ovarian cancer experienced a minor response (29%) and 12 pts SD for &gt; 4 cycles (5 pancreatic, 4 breast, 1 NHL, 1 ovarian, 1 ampullary cancer)</td>
<td>[79]</td>
</tr>
<tr>
<td>Depsipeptide</td>
<td></td>
<td>II</td>
<td></td>
<td>Previously treated CRC patients with advanced disease</td>
<td>25</td>
<td>No Objective response</td>
<td>[80]</td>
</tr>
</tbody>
</table>

(continued on next page)
spectrum of side-effects. Whether these are clinically relevant to efficacy, remains to be determined. It is striking that every HDACI tested in CTCL so far has shown substantial efficacy, suggesting a shared mechanism of action despite in vitro differences.

5.4. Toxicity

HDACIs have been largely well tolerated with a reasonable toxicity profile. An interesting group of side-effects has emerged as a common feature of HDACIs in the clinic, suggesting a class effect. The mechanisms underlying this class effect are not known. The most common adverse effects to many HDACIs were fatigue and weakness [61]. Gastrointestinal toxicity including diarrhea resulting in electrolyte disturbances is common but mild and tolerable in most patients. Neurocortical manifestations were reported primarily with phenylbutyrate and valproic acid. Cardiac side-effects such as non-specific EKG changes were reported in phase I trials of romidepsin while sudden cardiac death reported in the phase II trials although other risk factors for sudden death were present in those patients [42]. Prolonged QT interval has also been demonstrated in both intravenous and oral vorinostat formulations [62] and in a dose dependent fashion with intravenous panobinostat [63]. Thrombocytopenia has been dose limiting in some studies but is usually mild and transient. Anemia and neutropenia were infrequent, and septic complications were rare.

5.5. Mechanisms of resistance

The initial and acquired resistance to HDACIs [25] may explain some of their limited benefit. A number of studies demonstrated several pathways that are involved in the biology of resistance and sensitivity to HDACIs and vorinostat in particular. In a transgenic mouse model of B-cell lymphoma, the overexpression of the antiapoptotic proteins Bcl-2 or Bcl-XL or deletion of the proapoptotic BH3-only proteins Bim and Bid was shown to convey resistance to vorinostat therapy [64]. Another study using a functional genetic screen found that the ectopic expression of two genes, RAR-alpha and PRAME, a repressor of RA signaling can cause resistance to growth arrest and apoptosis induced by HDACI of different chemical classes [65]. Recently, an HDACI resistant HL60 cell line clone was reported to be lacking HDAC6 expression [66]. There have been very few studies on in vivo mechanisms of HDACI resistance. In one such study, using immunohistochemical analysis of STAT1 and phosphorylated tyrosine STAT3 (pSTAT3) in skin biopsies obtained from CTCL patients, it was demonstrated that nuclear accumulation of STAT1 and high levels of nuclear pSTAT3 in malignant T cells correlates with a lack of clinical response [67]. This suggested that constitutive activation of signal transducers and activators of transcription predicts vorinostat resistance in CTCL. Clearly more such studies are needed to guide the next generation of clinical trials.
6. Conclusions

The use of HDACIs allows the potential switching on or off of genes deregulated in cancer. These drugs also have other effects on neoplastic cells, including through acetylation of non-histone proteins. Clinically, promising results have been observed in lymphoid neoplasms but, as monotherapy, efficacy has been limited in other malignancies. Nonetheless, novel combinations of HDACIs with DNA methylation inhibitors or with cytotoxic therapy may lead to augmented antitumor activity. Many questions have been raised by this relatively non-specific therapy: Precise mechanisms of in vivo activity or resistance, mechanisms of class-effect toxicities, minimally effective dose and predictive markers for response. An understanding of the HDACIs multisystemic effects [15] will provide better insights to advance the field through defining appropriate dosages, minimizing untoward effects and investigating HDACIs for a broad range of indications.

Conflict of Interest

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

References


