Appl Microbiol Biotechnol (2007) 75:499–514
DOI 10.1007/s00253-007-0912-1

MINI-REVIEW

Histone deacetylase inhibitors—turning epigenic mechanisms of gene regulation into tools of therapeutic intervention in malignant and other diseases

Daniel Riester · Christian Hildmann · Andreas Schwienhorst

Received: 6 February 2007 / Revised: 26 February 2007 / Accepted: 26 February 2007 / Published online: 22 March 2007

Abstract Histone deacetylase inhibitors reside among the most promising targeted anticancer agents that are potent inducers of growth arrest, differentiation, and/or apoptotic cell death of transformed cells. In October 2006, the US Food and Drug Administration approved the first drug of this new class, vorinostat (**1**, Zolinza, Merck). Several histone deacetylase (HDAC) inhibitors more are in clinical trials. HDAC inhibitors have shown significant activity against a variety of hematological and solid tumors at doses that are well tolerated by patients, both in monotherapy as well as in combination therapy with other drugs. This paper reviews the most recent developments in HDAC inhibitor design, particularly in the context of anticancer therapy, and other possible pharmaceutical applications.

Keywords Histone deacetylase inhibitors · Epigenetics · Cancer drug design · Hydroxamates · Benzamides · Clinical trials

Introduction

Covalent histone modifications are involved in many nuclear processes such as DNA packaging, DNA replication, DNA repair, transcriptional regulation, as well as chromosome condensation, and segregation during mitosis. In transcription, the acetylation of lysine residues particularly in the N-terminal tails of core histones regulates protein–protein interaction and protein access to DNA. In general, acetylation activity is correlated with transcriptional activation, whereas deacetylation activity is accompanied by transcriptional repression (Grunstein 1997; Wade et al. 1997; Peterson 2002). However, recent findings show that deacetylation inhibition may not only lead to gene activation but also to gene repression, depending on the nature of the gene (Glaser et al. 2003). Two types of enzymes, histone acetyltransferases (HAT) and histone deacetylases (HDAC), have been shown to maintain the delicate dynamic equilibrium in the acetylation level of nucleosomal histones and may very well be active in the regulation of other cellular processes as well (Grozinger and Schreiber 2002; Hildmann et al. 2007). Both the activity of HAT and, in particular, HDAC affect angiogenesis, cell-cycle arrest, apoptosis, the terminal differentiation of different cell types, and the pathogenesis of malignant disease (Chung 2002).

D. Riester · C. Hildmann · A. Schwienhorst (✉)
Department of Molecular Genetics and Preparative Molecular Biology, Institute for Microbiology und Genetics,
Grisebachstr. 8,
37077 Göttingen, Germany
e-mail: aschwie1@gwdg.de

HDAC inhibitors in cancer therapy

Particularly, the functions of histone deacetylase inhibitors as anticancer agents are manifold and, in most cases, seem to primarily affect gene expression regulation by either specifically activating the gene expression through the inhibition of histone deacetylation or by blocking the deacetylation of transcription factors. Major consequences frequently observed upon treatment with HDAC inhibitors include the induction of differentiation, cell cycle arrest, apoptosis, and the inhibition of angiogenesis (Liu et al. 2006). In the following, due to space limitations, only some examples of the different modes of HDAC inhibitor action are discussed in some detail (for a more comprehensive review, see Johnstone 2002; Vigushin and Coombes 2002; Bi and Jiang 2006; Huang 2006; Kouraklis et al. 2006; and Quaissi and Quaissi 2006).

Direct structural alterations in HDACs associated with cancers appear to be rare (Ropero et al. 2006), in contrast to translocations, deletions, and point mutations found in HAT genes (Drummond et al. 2005a,b; Linggi et al. 2005). However, HDACs are involved in the function of translocation fusion proteins associated with various forms of leukemia and lymphoma (Ferrick and Hiebert 1998; Rosato and Grant 2003; Marks et al. 2004; Drummond et al. 2005a,b). Translocations affect DNA-binding proteins such as BCL6, PLZF, RARα, RUNX1, and TAL1. A well-studied example is the translocation t(11;17) where promyelocytic leukemia zinc finger protein (PLZF) is fused to the retinoic acid receptor α (RARα; Fenrick and Hiebert 1998). The PLZF–RARα fusion proteins are no longer responsive to physiological levels of retinoic acid, resulting in the repression of retinoic acid-inducible genes that normally would promote myeloid differentiation. The consequence is a clonal expansion of cells arrested in the promyelocyte stage of development, the hallmark of acute promyelocytic leukemia (APL). The treatment of patients with high levels of all-trans retinoic acid (ATRA) has been unsuccessful. Presumably, the reason is that both the PLZF and the RARα part associate with co-repressor complexes (containing HDACs) but only the RARα part releases the co-repressor complex upon ATRA treatment. Consistent with these findings, HDAC inhibitors are capable of restoring RA responsiveness to PLZF–RARα and can result in complete remission in APL patients (Warrell et al. 1998). The mechanism by which HDAC inhibitors disintegrate co-repressor complexes is possibly based on the induction of a conformational change in histone deacetylases upon inhibitor binding (Riester et al. 2007).

Histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) **1** or trichostatin A are also capable of inducing cell cycle arrest. One of the most commonly induced genes is that of the cyclin-dependent kinase (CDK) inhibitor $p21^{WAF1}$, a central regulator of the sequential activation of cyclin/CDK complexes that modulate progression through the cell cycle (Gartel and Tyner 2002). In this connection, HDAC inhibitors target the promoter directly by inducing the hyperacetylation of associated histones and modulate the transcription factors associated with specific binding sites such as Sp1 (Gartel and Tyner 1999; Huang et al. 2000; Gui et al. 2004). As a consequence of elevated levels of $p21^{WAF1}$, downregulation of cyclinA and cyclinD, hypophosphorylation of Rb, p107, and p130, and thus, cell, growth inhibition as well as G1 and G2/M cell-cycle arrest have been observed in various cancer cells (Archer et al. 1998; Huang and Pardee 2000; Kim et al. 2000; Suzuki et al. 2000).

Experimental evidence also indicates that HDAC inhibitors may induce apoptosis in different cancer cells, activating the death receptor and/or the intrinsic apoptotic pathways (reviewed in Johnstone 2002; Kouraklis et al. 2006). As an example of the latter, the HDAC inhibitors SAHA **1** and trichostatin A (TSA) increase BAX protein levels in human pancreatic adenocarcinoma cells. As a consequence, the excess of free BAX molecules translocate to the mitochondria, followed by the release of an apoptosis-inducing factor (AIF) and Omi/HtrA2 from the mitochondria, the relocalization of AIF into the nuclei with the induction of DNA fragmentation (Garcia-Morales et al. 2005). By contrast, valproic acid **14** was demonstrated to selectively activate the death receptor apoptosis pathway in leukemia cells by upregulating the transcription of TRAI, DRS, FAS, and FASL (Insiga et al. 2005; Nebbioso et al. 2005).

Other major anticancer effects of HDAC inhibitors include the suppression of angiogenesis (Kim et al. 2001; Cao et al. 2006; Qian et al. 2006a,b) and repression of metastasis (Coradini et al. 2004). In this connection, it is noteworthy that there is evidence suggesting that the deacetylation of microtubules by HDAC6 is an important factor for tumor cells to migrate and metastasize (Haggarty et al. 2003). However, somewhat in contrast to these findings, HDAC6 expression is positively correlated with better survival in breast cancer (Zhang et al. 2004). HDAC inhibitors are also capable of stimulating the host immune response (Magner et al. 2000; Mishra et al. 2001). The latter was also recently used as a novel principle to enhance the immune responses to DNA vaccination (Vanniasinkam et al. 2006).

Other functions of HDAC inhibitors

In addition to anticancer effects, HDAC inhibitors have demonstrated pronounced in vitro and in vivo anti-inflammatory effects (Blanchard and Chipoy 2005; Adcock 2006) mainly by modulating NF-κB and STAT transcriptional activity and by suppressing the production of proinflammatory mediators, like cytokines (Huang 2006), and downregulation, particularly of the tumor necrosis factor alpha (TNF-α) receptor (Imre et al. 2006). In line with these findings, thiol-specific antioxidant was reported to attenuate airway inflammation in a mouse asthma model (Choi et al. 2005). However, things may not be that simple. For example, researchers recently found a correlation between the loss of HDAC activity and increased inflammation in the lungs of patients suffering from chronic obstructive pulmonary disorder (COPD; Ito et al. 2005). Previous research had shown that theophylline is able to restore HDAC activity and simultaneously helps to relax the bronchial tubes in COPD patients (Ito et al. 2002). Despite the fact that an in-depth understanding of the role of HDACs in inflammation is still missing, companies such as

Chroma Therapeutics have already begun to develop HDAC inhibitors for autoimmune and inflammatory disorders.

HDAC inhibitors such as TSA and sodium butyrate also appear to be effective chondroprotective agents that modulate metalloproteinase gene expression and, thereby, block cartilage destruction (Young et al. 2005). Recent work has also demonstrated that HDAC inhibitors are active modulators of cellular hypertrophy including chondrocyte hypertrophy (Vega et al. 2004) and cardiac hypertrophy (Hoshijima and Chien 2002; Kook et al. 2002). In models of cardiac hypertrophy, HDAC inhibitors were able to modulate cardiomyocyte growth with no evidence of cell death and, therefore, hold promise as potential future therapeutic agents in hypertrophic heart disease (Metzger 2002; Antos et al. 2003; Hamamori and Schneider 2003; Kee et al. 2006; Kong et al. 2006; see also US patent 6946441).

The evasion strategies of tumors and protozoan parasites share some notable similarities (Quaissi and Quaissi 2005). Particularly, HAT and HDACs are also important regulators in the life cycle of parasites including *Trypanosoma brucei*, *Plasmodium falciparum*, and *Leishmania spp*. It is, therefore, not surprising that HDAC inhibitors interfere with parasite development, making them an interesting therapeutic approach in sleeping sickness, malaria, and leishmaniasis (reviewed in Quaissi and Quaissi 2006).

Histone deacetylase inhibitors may also be beneficial in the treatment of neurological diseases. Already a common treatment strategy for schizophrenia and bipolar disorder is the use of HDAC inhibitor valproic acid **14** as an adjunctive to atypical antipsychotics. Recent work suggests that benzamides such as MS275 **15** may be more advantageous than valproic acid **14** in association with atypical antipsychotics (Simonini et al. 2006). Furthermore, the HDAC inhibitor phenyl butyric acid **13**, particularly in combination with an antioxidant, exerts neuroprotective effects in a transgenic mouse model of amyotrophic lateral sclerosis (Petri et al. 2006). Cytoprotective effects have also been reported in the case of dentatorubral–pallidoluysian atrophy. In this study, HDAC inhibitors significantly reduced polyglutamine-induced cell death (Kariya et al. 2006). Similar results have been obtained in the Drosophila model (Steffan et al. 2001). More recently, a report on the treatment of spinal muscular atrophy, an α-motoneuron disorder with insufficient survival motor neuron protein levels was published (Hahnen et al. 2006). It was demonstrated that SAHA **1** but not MS275 **15** was able to activate the survival motor neuron gene 2 and, thus, has the potential of decelerating progressive a-motoneuron degeneration. And on top of that, recent insights into the cAMP-response element-binding protein (CREB)/CREB-binding protein (CBP) pathway suggest that HDAC inhibitors could also work as potential memory enhancers in neurodegenerative disorders like Alzheimer's disease (Beglopoulos and Shen 2006). For example, long-term potention and memory deficits were improved in $Cbp^{+/-}$ mice after treatment with a HDAC inhibitor (Alarcon et al. 2004).

The design of histone deacetylase inhibitors

The search for new HDAC inhibitors is largely dependent on the existence of bioassays well suited for inhibitor screening (reviewed in Wegener et al. 2003a,b). At present, many researchers favor fluorogenic assays (Wegener et al. 2003a,b) because of their suitability for high-throughput screening. Further developments recently included the design of HDAC subtype-selective fluorogenic substrates (Heltweg

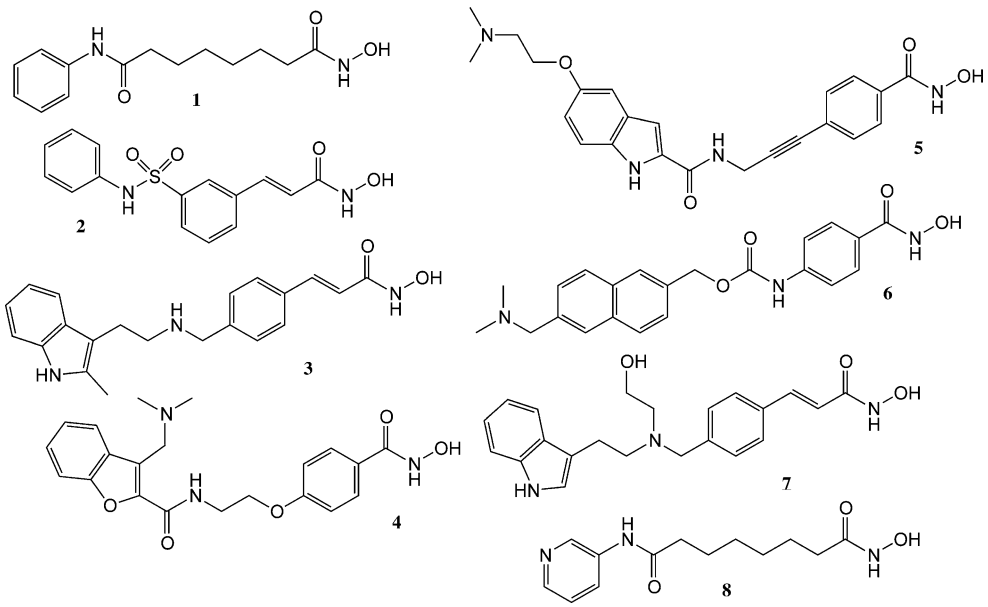

Fig. 1 HDAC inhibitor structures: hydroxamic acids. *1* SAHA, *2* PDX101, *3* LBH589, *4* CRA-024781, *5* CRA-026440, *6* ITF-2357 (as deduced from US6034096; Leoni et al. 2005), *7* NVP-LAQ824, *8* pyroxamide

et al. 2004; Riester et al. 2004; Riester et al. (2007) Profiling of histone deacetylase specificity based on combinatorial fluorogenic substrate libraries, submitted for publication), the development of the first non-isotopic, competition binding assay for HDAC inhibitors (Riester et al. 2007), and a very elegant noninvasive method to monitor HDAC activity in living cells (Sankaranarayanapillai et al. 2006).

The discovery of histone deacetylase inhibitors dates back to times when even histone deacetylases had not yet been discovered. Over the past years, a large number of natural and synthetic compounds belonging to different structural classes have been discovered. A comprehensive survey of the HDAC inhibitor field certainly would go beyond the scope of this article. For review, the reader should refer to a number of recent publications (Monneret 2005; Moradei et al. 2005; Suzuki and Miyata 2005; Weinmann and Ottow 2005; Minucci and Pelicci 2006). In the following, only HDAC inhibitors that reached clinical trials (Figs. 1, 2, and 3) are described in some detail (Table 1).

Hydroxamic acids

In October 2006, a very important landmark was reached with the Food and Drug Administration (FDA) approval of the first HDAC inhibitor, vorinostat **1** (SAHA, Zolinza®; Fig. 1; Merck), for cutaneous T-cell lymphoma (CTCL), a rare form of non-Hodgkin's lymphoma that affects the skin. SAHA was discovered in the pioneering work of Paul Marks (Memorial Sloan–Kettering Cancer Center, New York; Marks and Beslow 2007). SAHA had previously been tested in several clinical studies (Acharya et al. 2005). The major trial supporting approval was conducted with patients who had failed two systemic therapies and oral administration of the drug. In this study, skin disease was monitored using a severity-weighted assessment tool (SWAT) based on the total body surface area involved in patch, plaque, or tumor lesions. A total of 30% of the patients experienced responses (≥50% decrease in SWAT). Major adverse events were reported to be diarrhea, fatigue, nausea, dehydration, and anorexia, as well as hematologic laboratory abnormalities like anemia, thrombocytopenia, low white blood cell, and low neutrophil count. In most patients, these adverse events were of low grades in severity (Merck 2006; O'Connor 2006; Duvic et al. 2007). Previously, a phase I trial had revealed no dose-limiting toxicities (Kelly et al. 2003). As the major mechanism of therapeutic action, SAHA **1** induces apoptosis in CTCL cells (Zhang et al. 2005). Meanwhile, SAHA also proved effective in other cancer cells (Munster et al. 2001;

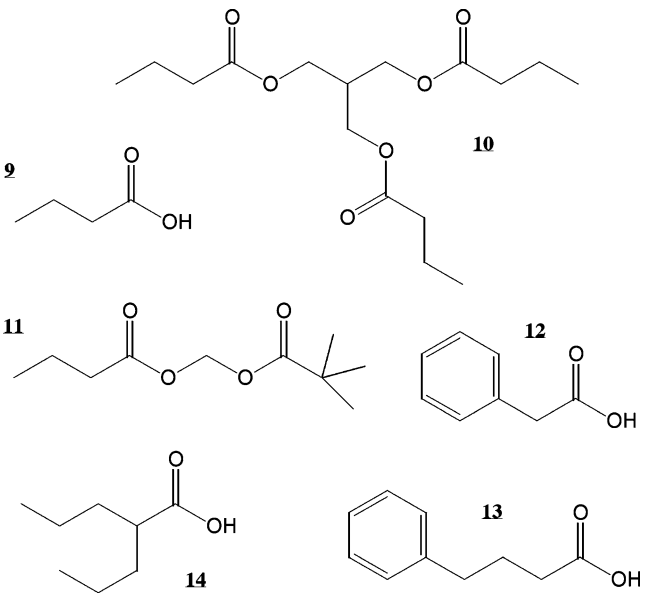

Fig. 2 HDAC inhibitor structures: short-chain fatty acids and their derivatives. *9* Butyric acid, *10* tributyrin, *11* pivanex, *12* phenyl acetic acid, *13* phenyl butyric acid, *14* valproic acid

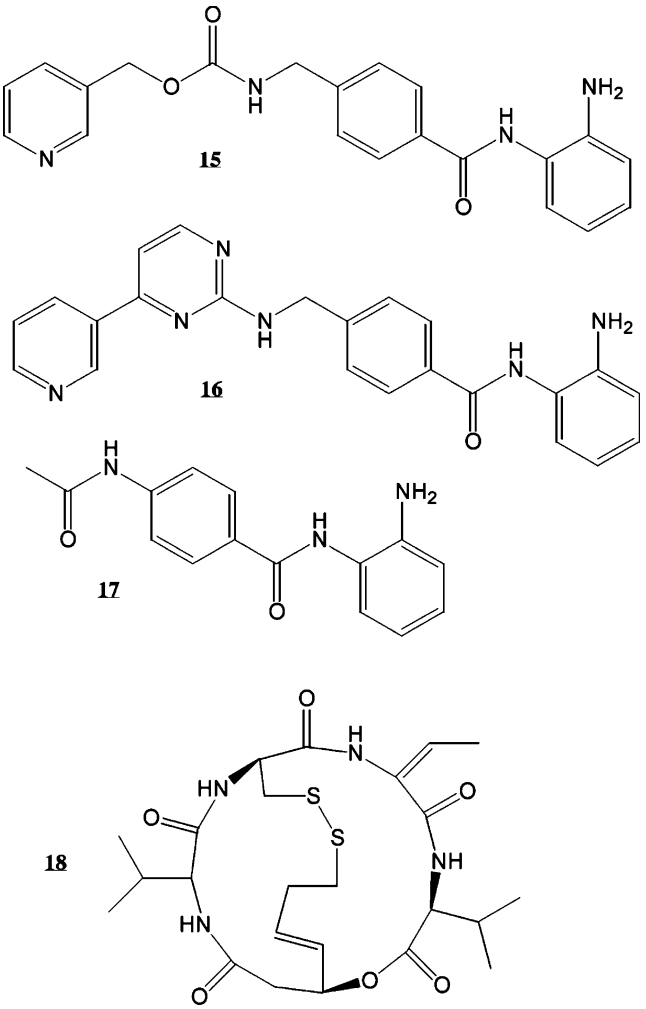

Fig. 3 HDAC inhibitor structures: benzamides and cyclic peptides. *15* MS-275, *16* MGCD0103, *17* CI-994, *18* FK-228 (depsipeptide), *19* trapoxin A

Table 1 Histone deacetylase inhibitors in clinical trials

Inhibitor	Company	Compound class	Stage of development	Active clinical trials
SAHA	Merck (Aton)	HX	FDA approval for CTCL	Yes
PDX 101	TopoTarget/Curagene	HX	II	Yes
LBH589	Novartis	HX	II	Yes
CRA-024781	Pharmacyclics/Celera	HX	I	Yes
ITF-2357	Italfarmaco	HX	II	Yes
NVP-LAQ824	Novartis	HX	I	?
Pyroxamide	Aton	HX	I	?
Butyric acid		FA		
Tributyrin				
Pivanex	Titan Pharma		II	?
VX-563	Vertex		I	No
Phenylacetic acid		FA	II	?
Phenylbutyric acid		FA	I (FDA approved for urea cycle disorder)	?
Valproic acid		FA	(FDA approved as an anti-seizure drug)	
Savicol	TopoTarget		II	Yes
Baceca	TopoTarget		II	Yes
Avugane	TopoTarget		II	Yes
PEAC	TopoTarget		II	Yes
MS-275	Schering	BZ	II	Yes
MGCD0103	Pharmion/MethylGene/Taiho	BZ	II	Yes
CI-994	Pfizer	BZ	II	No
FK-228	Gloucester/Fujisawa	PEP	II	Yes

HX Hydroxamate, *FA* small fatty acid, *BZ* benzamide, *PEP* peptide, *CTCL* cutaneous T-cell lymphoma

Butler et al. 2002; Cohen et al. 2002; Hsi et al. 2004; Reddy et al. 2004; Eyüpoglu et al. 2005; Garcia-Manero et al. 2005; Luong et al. 2006; O'Connor et al. 2006; Sonnemann et al. 2006a,b; Xu et al. 2006). Therefore, it is also being investigated in other indications including myeloma, mesothelioma, and a variety of other cancers that have entered phase I, II, and III clinical trials since 2005.

Besides SAHA **1**, other drug candidates in this class will not be far behind. PDX101 **2** (TopoTarget/CuraGen) is currently in phase II trials for multiple myeloma, T-cell lymphoma, myelodysplastic syndrome, and ovarian cancer after already promising preclinical data (Plumb et al. 2003; Qian et al. 2006a,b). It is also in phase I trials for acute myeloid leukaemia (AML), liver, and colorectal cancer. PXD101 **2** showed very low penetration into the cerebrospinal fluid of rhesus monkeys after intravenous administration (Warren et al. 2006).

LBH589 **3** (Novartis) is a cinnamic hydroxamic acid analog that has been studied as an intravenous drug in a phase I trial in patients with advanced solid tumors. Six out of 13 patients were reported to show stable disease (Acharya et al. 2005). The drug also was well tolerated in phase I studies with consistent antileukemic effects in patients with refractory hematologic malignancies (Giles et al. 2006). In this study, LBH589 **3** was administered intravenously. However, preliminary results using an oral formulation of the drug were also reported to be clinically active. Previously, LBH589 **3** was shown to be an efficient antimyeloma agent inducing apoptosis (Maiso et al. 2006). In addition, the drug also affects tumor angiogenesis (Qian et al. 2006a,b). It is now planned to start a pivotal phase II registration study in patients with CTCL.

CRA-024781 **4** (PCI-24781; Pharmacyclics/Celera) is another hydroxamic acid-based HDAC inhibitor with antitumor activity in vitro and in vivo (Buggy et al. 2006). After efficacy was shown in xenograft cancer models, CRA-024781 **4** is now under evaluation in phase I clinical trials in patients with refractory solid malignancies (Celera 2005). The substance inhibits many class 1 and 2 enzymes in the nanomolar range and induces apoptosis in a whole variety of tumor cell lines. Additionally, Celera Genomics has other programs in the lead optimization stage to develop other variants of HDAC inhibitors, preferentially with more selectivity in targeting cancer cells. CRA-026440 **5** is among these HDAC inhibitors in early development and was in-licensed by Pharmacyclics in 2006, together with CRA-024781 **4**. CRA-026440 **5** proved to be a broad-spectrum HDAC inhibitor with potent antitumor activity and good efficacy in xenograft cancer models. In addition, CRA-026440 **5** was reported to show antiangiogenic activity (Cao et al. 2006).

ITF-2357 (Italfarmaco SpA) was reported to be an orally active, synthetic HDAC inhibitor containing a hydroxamic acid moiety linked to an aromatic ring, as described in patent WO 97/43251, US6034096 (**6**; Leoni et al. 2005), shown to inhibit proliferation and induce cell death in

hepatocellular carcinoma cell lines (Armeanu et al. 2005) without causing cell death in primary human hepatocytes. It also induces apoptosis in leukemia cells but not in mesenchymal stromal cells (Golay et al. 2006). Recently, the drug was also reported to possess anti-inflammatory activities in vivo and in vitro (Leoni et al. 2005). Interestingly, the substance was originally developed as an oral active TNF-α inhibitor for Crohn's disease and other TNF-α related diseases, and was reported in 2005 to be in phase II clinical trials.

NVP-LAQ824 **7** (Novartis), a cinnamic hydroxamic acid derivative, was shown to inhibit HDAC enzymatic activities in vitro and to exhibit anti-proliferative effects in a number of cancer cells including leukemia (Weisberg et al. 2004). In many of these cancer cells, but not in normal cells, apoptosis was induced (Atadja et al. 2004). Furthermore, tumor cells treated with NVP-LAQ824 **7** showed acetylation of HSP90 and degradation of its cargo oncoproteins (Atadja et al. 2004; Kristeleit et al. 2004). The drug also exhibited antitumor effects in colon, lung, and breast tumor xenografts (Remiszewski et al. 2003; Drummond et al. 2005a,b). In 2004, promising results of a phase I trial in patients with advanced solid tumors for intravenously administrated NVP-LAQ824 **7** were published (e.g., Kristeleit et al. 2004; Acharya et al. 2005). In this study, 3 out of 28 patients showed stable disease. In another phase I clinical study, in patients with hematologic malignancies, 6 out of 21 patients showed stable disease (Acharya et al. 2005). Many researchers speculate that further studies have been discontinued because of occasional cardiac side effects observed and reported by Novartis.

Pyroxamide **8** (Aton) is a hydroxamic acid derivative that induces terminal differentiation in murine erythroleukemia (MEL) cells and caused growth inhibition by cell-cycle arrest/apoptosis in MEL, prostate carcinoma, bladder carcinoma, and neuroblastoma cells (Butler et al. 2001). In 2002, a phase I study in patients with advanced malignancies was conducted. However, no active clinical trials have been reported since then.

Among the most promising hydroxamic acid inhibitors in preclinical development is presumably (S)-HDAC-42, which was reported to be orally bioavailable and significantly more potent than SAHA in suppressing the viability of various cancer cell lines and the growth of prostate tumor xenografts (Kulp et al. 2006). Another interesting candidate is M344, a promising candidate for a therapy of spinal muscular atrophy (Riesland et al. 2006). However, no clinical data is available so far.

Short-chain fatty acids and derivatives thereof

Short-chain fatty acids (Fig. 2) have become a favorite research topic in the cancer field because they are believed to emerge from bacterial fermentation of dietary fiber and may protect against colon cancer (Archer et al. 1998). Already two decades before, short-chain fatty acids had been shown to increase histone acetylation, although the molecular mechanism was not clear at this time (Riggs et al. 1977). Particularly, butyric acid **9** and its prodrug, tributyrin **10** (Gaschott et al. 2001), have since been used in a variety of in vivo tumor models and clinical studies. The drug is known to cause histone hyperacetylation and $p21^{WAF1}$ induction (Archer et al. 1998), as well as induction of malignant cell differentiation followed by arrest of cell growth and apoptosis (Schröder and Maurer 2002; Kuefer et al. 2004; Entin-Meer et al. 2005). Reports from phase I studies in patients with solid tumors indicate that tributyrin **10** is well tolerated at levels associated with in vitro activity (Conley et al. 1998; Edelman et al. 2003). However, no active clinical trials have since been reported. For another prodrug of butyric acid (Entin-Meer et al. 2005), pivaloyloxymethyl butyrate **11** (Pivanex, AN-9; Titan Pharmaceuticals), the results of a phase I trial in patients with solid tumors and a phase II clinical study for patients with refractory non-small cell lung cancer have been reported. In the latter, 2 out of a total of 47 patients had partial responses and 18 had stable disease (Kelly et al. 2002; Acharya et al. 2005). In a phase II study (combination with docetaxel) in patients with advanced non-small cell lung cancer, 3 out of 12 patients achieved a partial response (Acharya et al. 2005). Another phase II clinical study for patients with refractory chronic lymphocytic leukemia and refractory malignant melanoma has been announced in 2004 (Farrel 2004). However, no information on active clinical trials have been reported since then. VX-563 (Vertex) is another butyrate prodrug (Archer et al. 2001). It was reported to induce differentiation and cell cycle arrest in colon cancer cells. Preclinical studies have also demonstrated that the drug can stimulate embryonic or fetal globin gene expression, suggesting that it may have potential for the treatment of sickle cell disease. VX-563 was reported to have entered phase I clinical trials. No detailed clinical results were disclosed so far. However, the company finally announced not to proceed with additional trials. Structural variants of butyrate **9** generally appeared to be of little advantage. An exception is maybe HA-But, a hyaluronic acid esterified with butyric acid. HA-But tends to concentrate in the liver and spleen and appears to be a promising new drug for the treatment of intrahepatic tumor lesions (Coradini et al. 2004).

Phenyl acetic acid **12** and phenyl butyric acid **13** are both also differentiation inducers (Bar-Ner et al. 1999; Miller et al. 1999). For phenyl acetic acid **12**, two-phase I trials in patients with solid tumors have been reported. An additional phase II trial in patients with recurrent malignant glioblastoma revealed that 3 out of 40 patients achieved

partial response, whereas 7 had stable disease (Kelly et al. 2002; Acharya et al. 2005). However, no further active clinical trials have been reported. For phenyl butyric acid **13**, phase I trials for solid tumors and myeloid malignancies, a phase I trial (in combination with azacitidine) for solid tumors, and a phase I trial (in combination with retinoic acid) for APL have been reported (Kelly et al. 2002; Acharya et al. 2005). Although, no further information on clinical trials in the cancer field has been disclosed, data on a trial of phenyl butyric acid **13** in spinal muscular atrophy has been published (Mercuri et al. 2007) recently. However, at the conditions used in this study, efficacy was low.

Valproic acid **14** (G2M-777, Depakote, Depakene), an extensively used anti-epileptic, was reported to be a moderately active histone deacetylase inhibitor that causes hyperacetylation of histones, inhibition of proliferation, and induction of apoptosis (Tang et al. 2004; Armeanu et al. 2005) or cellular differentiation (Göttlicher et al. 2001; Gurvich et al. 2004). Its different formulations, savicol (orally available), Baceca, Avugane, and pulse-enhanced acetylation (PEAC; TopoTarget) are in clinical investigations. Savicol is currently in phase II studies for familial adenomatous polyposis. Baceca (in combination with all-trans retinoic acid) is in phase II trials for basal cell carcinoma (topical treatment). Avugane is in phase II trials for acne vulgaris. PEAC has entered phase II evaluation for patients with genetic predisposition to develop colon cancer. Different publications describe the first results of clinical evaluations of valproic acid. For patients with advanced leukemia, the results from a phase I/II trial (in combination with 5-aza-2′-deoxycitidine; Garcia-Manero et al. 2006) indicate that the combination was found safe and active with 19% of the patients showing complete remission. Promising results were also reported from other clinical trials (in combination with all-trans retinoic acid; Bug et al. 2005; Kuendgen et al. 2005; Cimino et al. 2006; Stapnes et al. 2006). For patients with advanced solid tumors, the results of a clinical phase I trial (in combination with epirubicin) have been reported, indicating that plasma levels of the drug needed for biological effects are easily achieved with minimal toxicity (Munster et al. 2006). In line with these findings, a remarkable response of a radiochemotherapy–refractory glioblastoma multiforme to valproic acid was recently published. After ambulant therapy with oral valproic acid **14** (at a final serum concentration of 140 mg/l), the clinical condition of the patient improved with a documented complete remission after 10 months of treatment (Witt et al. 2004).

Benzamides

A number of companies developed *o*-amino benzamides as yet another class of HDAC inhibitors (Fig. 3. MS-275 **15** (MS-27-275; Schering), the best-known member of this class, is an orally active synthetic inhibitor with selectivity for class 1 HDACs (Hildmann et al. 2006). Unlike many other potent HDAC inhibitors, MS-275 **15** is a brain region-selective inhibitor (Eyüpoglu et al. 2006; Simonini et al. 2006) with a reported half-life of up to 80 h in human (results from a phase I study; Ryan et al. 2005). Chemotherapeutic efficacy in vivo against malignant gliomas has been demonstrated (Eyüpoglu et al. 2006). One phase I study for patients with hematologic malignancies and two phase I trials for patients with solid tumors and lymphomas were conducted. In one of the latter, one melanoma patient with partial response was observed (Acharya et al. 2005). A phase II study for patients with metastatic melanoma was recently completed. Preliminary results from this study suggest that MS-275 **15** is well tolerated and shows long-lasting tumor stabilization (Hausschild et al. 2006). However, objective tumor responses were not observed with this single-agent treatment. Currently, MS-275 **15** (in combination with azacitidine) is in a clinical phase I/II trials for myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia with multilineage dysplasia. MS-275 **15** (in combination with azacitidine) is also in clinical phase I/II trials for patients with recurrent advanced nonsmall-cell lung cancer.

Researchers at MethylGene have also extensively explored benzamides as HDAC inhibitors. The most promising candidate, MGCD0103, is further developed together with MethylGene's partners, Pharmion and Taiho Pharmaceuticals. MGCD0103 **16** is a rationally designed, oral, isotype-specific HDAC inhibitor. It showed complete bone marrow responses in three of nine patients in a phase I trial for myelodysplastic syndromes or acute myelogenous leukemia. The drug is currently in phase II clinical trials for patients with refractory or relapsed diffuse large B-cell lymphoma and follicular lymphoma. In addition, a single-agent phase II trial and a combination phase I/II trial (combination with azacitidine) for patients with high-risk myelodysplastic syndromes or relapsed or refractory acute myelogenous leukemia was initiated. Furthermore, a phase I/II combination trial (combination with gemcitabine) for patients with solid tumors and pancreatic cancer, and a phase II single-agent trial in patients with refractory or relapsed Hodgkin's lymphoma was announced recently.

CI-994 **17** (acetyldinaline, PD-123654) is an orally available, acetylated derivative of dinaline. The latter originally was developed as an anticonvulsant agent and later was reported to have antitumor activity (Berger et al. 1985). CI-994 **17** is a relatively weak HDAC inhibitor that has broad preclinical antitumor activity (LoRusso et al. 1996). In a single-agent phase I trial for patients with solid tumors, 1 of 53 patients achieved a partial response. In a

single-agent phase I trial for patients with nonsmall-cell lung cancer, 2 of 32 patients showed a partial response (Kelly et al. 2002; Acharya et al. 2005). Phase II studies were conducted in patients with nonsmall-cell lung cancer, renal cell carcinoma, and pancreatic cancer. Two out of 32 patients with nonsmall-cell lung cancer had a partial response. Stable disease was observed in 28 and 58% of the patients with nonsmall-cell lung cancer and renal cell carcinoma, respectively (Kelly et al. 2002). In contrast, patients with pancreatic cancer achieved no objective responses (Zalupski et al. 2000). In addition to monotherapy, combinations with other drugs proved to be efficacious (Acharya et al. 2005). In a phase I trial (combination with gemcitabine), in 20 patients with advanced cancer, 2 patients achieved minor response, whereas 12 had stable disease (Nemunaitis et al. 2003). In a phase I trial (combination with capecitabine), in 14 patients with refractory solid tumors, 1 patient with colorectral cancer achieved a partial response (Acharya et al. 2005). In a phase I trial (combination with carboplatin and paclitaxel), 24 patients received more than one cycle of treatment. Of these, five achieved partial response and two achieved complete response (esophageal and bladder cancer) (Pauer et al. 2004). In contrast, the combination with gemcitabine offered no advantage over gemcitabine alone (Richards et al. 2006).

A number of other benzamides have been disclosed that are expected to enter clinical trials soon (Weinmann and Ottow 2005).

Cyclic peptides

A structurally diverse class of HDAC inhibitors is constituted by compounds with cyclic peptide structures such as natural products like FK-228 **18** (Fig. 3), the trapoxins A **19** and B, apicidin, and the cyclic hydroxamic acid-containing peptides (CHAPs). FK-228 **18** (depsipeptide, FR901228, NSC 630176, romidepsin; Gloucester), a unique bicyclic peptide isolated from *Chromobacterium violaceum* strain WB968, so far, is the only notable inhibitor of this class that is currently in clinical trials. FK-228, however, already has a checkered career. After being dropped because of cardiac toxicity observed in dogs, it came back into the race when the National Cancer Institute (NCI) devised a new dosing regimen. In a single-agent phase I trial comprising 37 patients with refractory neoplasms, one patient with renal cell carcinoma achieved a partial response and 8 patients had stable disease (Sandor et al. 2002; Acharya et al. 2005). In a small phase I trial in four patients with CTCL/peripheral T-cell lymphomas, three partial and one complete response were noted (Kelly et al. 2002). In contrast, two recent phase I trials in patients with chronic lymphocytic leukemia/acute myeloid leukemia (Byrd et al. 2005) as well as in pediatric patients with refractory solid tumors (Fouladi et al. 2006) revealed no partial or complete responses, whereas the drug was generally well tolerated. Currently, FK-228 is in clinical phase II studies for patients with CTCL and for patients with hormone refractory prostate cancer with interim results reported at the 2006 annual meeting of the American Society of Clinical Oncology. In the study on CTCL, 2 out of 28 patients experienced complete responses, 7 achieved partial responses, and 16 patients had stable disease. In the study on metastatic hormone refractory prostate cancer, 1 patient out of 22 achieved a partial response; in up to 7 patients, stable disease was observed. As far as cardiac toxicity is concerned, the outcome of clinical trials is somewhat contradictory. One recent study revealed no significant myocardial damage or impaired cardiac function associated with the administration of depsipeptide (Piekarz et al. 2006). In contrast, electrocardiogram changes and even sudden deaths are reported from other trials (Garber 2007). Nevertheless, Gloucester intends to file FK-228 for FDA approval in late 2007.

Potential class 3 therapeutics

Finally, it is noteworthy that the year 2006 not only yielded the FDA approval of the first inhibitor of class 1, 2, and 4 histone deacetylases. Also, the first class 3 or sirtuin therapeutic, a resveratrol derivative and SIRT1 activator, was announced to have successfully finished phase I trials (Elliott 2006). Furthermore, several sirtuin inhibitors are currently under development (Weinmann and Ottow 2005; Heltweg et al. 2006).

Monotherapy versus combination therapy

In addition to being used as anticancer agents for monotherapy, several studies have shown that HDAC inhibitors may act synergistically in combination therapy. It is for example obvious to simultaneously attack the cellular cytoskeleton through two different pathways, combining the inhibition of HDAC6-dependent tubulin deacetylation and the taxane-based targeting of mitotic structures. Exactly, this strategy is now followed by Merck by combining SAHA with docetaxel. Other recent examples include combinations of HDAC inhibitors with ATRA (Bug et al. 2005; Kuendgen et al. 2005; Cimino et al. 2006; Stapnes et al. 2006), classical chemotherapeutics (5-fluorouracil, oxaliplatin, irinotecan, idarubicin, epirubicin, doxorubicin, melphalan; Kim et al. 2003; Khan et al. 2006; Munster et al. 2006; Piacentini et al. 2006; Sanchez-Gonzalez et al. 2006; Sato et al. 2006; Zhang et al. 2006), different kinase inhibitors (gefitinib; Piacentini et al. 2006),

dasatinib (Fiskus et al. 2006a,b), AMN107 (Fiskus et al. 2006a,b), staurosporine, UCN-01 (Yeow et al. 2006), flavopiridol (Dashmahapatra et al. 2006), PKC412 (Bali et al. 2004), methyltransferase inhibitors (gemcitabine; Zhang et al. 2006), 5-aza-2′-deoxycitidine (Garcia-Manero et al. 2006; Gore et al. 2006; Hurtubise and Momparler 2006), HAT inhibitors (curcumin; Chen et al. 2006), chaperone inhibitors (17-AAG; George et al. 2005), proteasome inhibitors (bortezomib; Catley et al. 2006; Horton et al. 2006; Nawrocki et al. 2006; Sutheesophon et al. 2006), P-gp/MRP1 inhibitors (verapamil, MK571; Okada et al. 2006a,b), apoptosis inducer [(TNF)-related apoptosis-inducing ligand (TRAIL); Butler et al. 2006; Sonnemann et al. 2006a,b], antibodies (Ten Cate et al. 2007), oncolytic adenoviral agents (Bieler et al. 2006; Okada et al. 2006a,b; Watanabe et al. 2006). Furthermore, HDAC inhibitors proved to selectively radiosensitize various human cancer cells (Miller et al. 1999; Entin-Meer et al. 2005; Chinnaiyan et al. 2006; Karagiannis and El-Osta 2006; Kim et al. 2006). It is noteworthy that the effect can be reversed upon too-short pretreatment with HDAC inhibitors (Miller et al. 1999).

There is also evidence for antagonist effects of combinations of HDAC inhibitors and other antitumor agents. For example, neuroblastoma cells that have been driven into cell-cycle arrest and differentiation by HDAC inhibitor BL1520 no longer appear to be sensitive to gemcitabine (De Ruijter et al. 2006). FK228 (**18**)/ATRA induced the expression of the multidrug resistance 1 gene product P-gp, resulting in the prevention of growth inhibition and apoptosis in leukemia cells (Tabe et al. 2006). P-gp and the multidrug resistance-associated protein also play a role in the resistance of certain osteosarcoma and Ewing's sarcoma cell lines against FK228 **18** and apicidin. Interestingly, resistance could be reversed by the application of P-gp inhibitor verapamil and MRP1 inhibitor MK571 (Okada et al. 2006a,b).

Perspectives and trends in HDAC inhibitor discovery

Currently, the excitement about the initial clinical results of HDAC inhibitors in cancer patients predominates the judgement of many researchers active in the field. Indeed, promising results have been obtained for cancer treatment in a number of clinical trials with different drugs. Nearly each clinical trial revealed a clinical effect in patients, and even long-term and sometimes dramatic responses have been described several times. Many HDAC inhibitors are, generally, rather well tolerated. Only some HDAC inhibitors such as TSA or trapoxin are of limited therapeutic use due to toxic side effects, or other factors such as poor bioavailability in vivo, poor stability, and mutagenicity (as reported for apicidin; Yoo and Lee 2005). Nevertheless, chronic constitutional symptoms (e.g., fatigue, nausea, and electrolyte disturbances) have been observed for different clinical HDAC inhibitors (summarized in Byrd et al. 2005) and, therefore, possibly are general clinical manifestations of HDAC inhibition (or our present state-of-the-art of HDAC inhibitors). There might be other drawbacks of a HDAC inhibitor-based therapy. In a recent paper, Moreth et al. (2006) presented experimental evidence that HDAC inhibitors such as SAHA **1** or MS-275 **15** may also block lipase and liver esterase activity. These results suggest that nonselectivity of our present HDAC inhibitors may be responsible for some of their adverse effects. On the other hand, additional functions besides direct HDAC modulation may play a significant role in the ability of HDAC inhibitors to induce differentiation or apoptosis, e.g., in cancer cells (Newmark and Young 1995; Ma et al. 2006; Mora et al. 2006). Another issue to be considered is the acquired resistance of cancer cells to HDAC inhibitors (Xiao et al. 2005; Okada et al. 2006a,b; Ropero et al. 2006). However, at least in some cases, resistance can be reversed or prevented through combination therapy, e.g., with P-gp inhibitor verapamil or MRP1 inhibitor MK571 (Okada et al. 2006a,b). Notwithstanding, caution should be employed when considering combination therapy. Despite the fact that a large number of drugs synergize with HDAC inhibitors, there are also examples of antagonist effects of combinations of HDAC inhibitors and other antitumor agents (De Ruijter et al. 2006; Tabe et al. 2006), not to speak of possible side effects that only become apparent under conditions of drug combination.

Despite the fact that we are close to understanding the catalytic mechanism of histone deacetylases already enabling structure-based inhibitor design (Lu et al. 2005; Wang et al. 2005; Hildmann et al. 2006; Shinji et al. 2006), our knowledge of HDAC biology is still very limited. With the increasing number of proteins known to be deacetylated by HDACs, it can even be questioned whether histone acetylation is a good measure to predict anticancer activity of a drug. Furthermore, the role of individual HDAC isoforms, for example, is still under investigation, and it is an open question whether subtype-specific inhibitors would be more useful in therapy, e.g., by minimizing adverse effects. First examples of such compounds that are at least class-selective (e.g., Mai et al. 2003, 2006; Wang et al. 2005; Shinji et al. 2006; Suzuki et al. 2006) have been reported recently and more and more researchers are focussing now on this topic. At least, these selective inhibitors are welcome as biochemical tools to dissect the roles of specific HDAC subtypes. Another line of research focuses on new warheads and, particularly substitutes of hydroxamic acids which would better meet criteria of 'druglikeness', i.e. favorable physicochemical and pharma-

cokinetic properties (reviewed in Moradei et al. 2005; Suzuki and Miyata 2005; Weinmann and Ottow 2005). Whereas many new structures cannot compete with the existing Zn-binding motifs in regard of HDAC inhibitory and antitumor activity (Hanessian et al. 2006), particularly electrophilic ketones, which have been shown to be inhibitors of various hydrolytic enzymes, appear to be attractive HDAC inhibitor structures (Frey et al. 2002; Wada et al. 2003). More recent examples of this promising class of HDAC inhibitors include α-mercaptoketones or α-thioacetoxyketone (Gu et al. 2006), bromomethylketones, and hydroxymethylketones (Bhuiyan et al. 2006). In this context, it might be worth to reconsider the class of trifluoroketones that already had demonstrated antiproliferative activity but, unfortunately, also showed significant metabolic liabilities (Frey et al. 2002). With the first non-hydroxamate crystallographic structure, a trifluoroketone inhibitor in complex with FB188 HDAH, now available (Nielsen et al. 2006), the structure-based design of derivatives with optimized properties is now largely facilitated. Most of the aforementioned electrophilic ketones had given up the principle of bidentate zinc binding and rely on additional contacts, e.g., through fluor atoms that participate in the interactions to the enzyme (Nielsen et al. 2006). In contrast, other inhibitors such as mercaptoamides (Anandan et al. 2005) were designed as bidentate zinc chelators similar to hydroxamates. It remains an open question whether these reactive compounds can be turned into therapeutically useful drugs.

The diversity of natural products always has been a rich source for new pharmaceutically active compounds including HDAC inhibitors. Recent studies in this field particularly focus on dietary HDAC inhibitors. Although it is still a matter of debate if blood concentrations achievable through diet are sufficient to affect HDAC activity in vivo, particularly natural isothiocyanates from cruciferous vegetables and their synthetic counterparts appear to be a promising class of HDAC inhibitors. For example, sulforaphane, an isothiocyanate from broccoli was recently reported to inhibit HDACs in vivo and suppress tumorigenesis in Apc^{min} mice (Myzak et al. 2004, 2006). In addition, phenylhexyl isothiocyanate was shown to inhibit HDACs and induce growth arrest in human leukemia and prostate cancer cells, as well as in xenografted prostate tumors (Ma et al. 2006). However, the exact mechanism of antitumor activity still has to be elucidated. Our group has screened a natural product library for inhibitors of FB188 HDAH, a model of class 2 HDACs, and identified a number of novel inhibitor structures including disaccharide and benzochinone derivatives that possibly exhibit unusual modes of binding to the enzyme (D. Wegener and A. Schwienhorst, personal communication). Furthermore, with the new binding assay for direct HDAC inhibitors (Riester et al. 2007), it is now even conceivable to specifically screen for nonactive-site versus active-site binders. Thus, it might be possible to identify HDAC inhibitors that do not depend on canonical active-site binding, e.g., zinc coordination, but instead block for example the internal cavity of the enzymes. However, progress in inhibitor design should not make us forget that it is equally important to identify biomarkers that predict tumor sensitivity to HDAC inhibitors and, thus, susceptible patients.

In conclusion, with our recent progress in understanding the role of histone modification (and nonhistone protein modification) in cancer, we are now on the edge of turning epigenic mechanisms of gene regulation into powerful tools of therapeutic intervention in malignant and other diseases.

Acknowledgment This work was supported in part by the grant from BioFuture 0311852 from the Bundesministerium für Forschung und Technologie, Germany, and Human Frontier Science Program (HFSP) grant RGY56/2004. The authors are grateful to colleagues in the field for sharing valuable information, in particular, T. Beckers, R. Ficner, S. Guccione, M. Jung, A. Kuhn, F.-J. Meyer-Almes, R. Schneider, D. Wegener, H. Weinmann, and O. Witt. A.S. thanks K. Schwienhorst and the staff at the FSZ Hannover for critically reading the manuscript. A.S. also would like to thank all his coworkers for many years of fruitful research and a friendly atmosphere.

References

Acharya MR, Sparreboom A, Venitz J, Figg WD (2005) Rational development of histone deacetylase inhibitors as anticancer agents: a review. Mol Pharmacol 68:917–932

Adcock IM (2006) Histone deacetylase inhibitors as novel anti-inflammatory agents. Curr Opin Investig Drugs 7:966–973

Alarcon JM, Malleret G, Touzani K, Vronskaya S, Ishii S, Kandel ER, Barco A (2004) Chromatin acetylation, memory, and LTP are impaired in CBP+/−mice: a model for the cognitive deficit in Rubinstein–Taybi syndrome and its amelioration. Neuron 42:947–959

Anandan S-K, Ward JS, Brokx RD, Bray MR, Patel DV, Xiao X-X (2005) Mercaptoamide-based non-hydroxamic acid type histone deacetylase inhibitors. Bioorg Med Chem 15:1969–1972

Antos CL, McKinsey TA, Dreitz M, Hollingsworth LM, Zhang C-L, Schreiber K, Rindt H, Gorczynski RJ, Olson EN (2003) Dose-dependent blockade to cardiomyocyte hypertrophy by histone deacetylase inhibitors. J Biol Chem 278:28930–28937

Archer SY, Meng S, Shei A, Hodin RA (1998) p21(WAF1) is required for butyrate-mediated growth inhibition of human colon cancer cells. Proc Natl Acad Sci USA 95:6791–6796

Archer SY, Tang R, Kim H-J, Hodin RA (2001) A novel butyrate prodrug induces differentiation and the program of cell cycle inhibition in colon cancer cells. Surg Forum 52:254–255

Armeanu S, Pathil A, Venturelli S, Mascagni P, Weiss TS, Gottlicher M, Gregor M, Lauer UM, Bitzer M (2005) Apoptosis on hepatoma cells but not on primary hepatocytes by histone deacetylase inhibitors valproate and ITF2357. J Hepatol 42:210–217

Atadja P, Hsu M, Kwon P, Trogani N, Bhalla K, Remiszewski SW (2004) Molecular and cellular basis for the anti-proliferative effects of the HDAC inhibitor LAQ824. Novartis Found Symp 259:249–266

Bali P, George P, Cohen P, Tao J, Guo F, Sigua C, Vishvanath A, Scuto A, Annavarapu S, Fiskus W, Moscinski L, Atadja P, Bhalla K (2004) Superior activity of the combination of histone deacetylase inhibitor LAQ824 and FLT-3 kinase inhibitor PPKC412 against human acute myelogenous leukemia cells with mutant FLT-3. Clin Cancer Res 10:4991–4997

Bar-Ner M, Thibault A, Tsokos M, Magrath IT, Samid D (1999) Phenylbutyrate induces cell differentiation and modulates Epstein–Barr virus expression in Burkitt's lymphoma cells. Clin Cancer Res 5:1509–1516

Beglopoulos V, Shen J (2006) Regulation of CRE-dependent transcription by presenilins: prospects for therapy of Alzheimer's disease. Trends Pharmacol Sci 27:33–40

Berger MR, Bischoff H, Fritschi E, Henne T, Herrmann M, Pool BL, Satzinger G, Schmahl D, Weiershausen U (1985) Synthesis, toxicity and therapeutic efficacy of 4-amino-N-(2′-aminophenyl) benzamide: a new compound preferentially active in slowly growing tumors. Cancer Treat Rep 69:1415–1424

Bhuiyan MPI, Kato T, Okauchi T, Nishino N, Maeda S, Nishino TG, Yoshida M (2006) Chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylase. Bioorg Med Chem 14:3438–3446

Bi G, Jiang G (2006) The molecular mechanism of HDAC inhibitors in anticancer effects. Cell Mol Immunol 3:285–290

Bieler A, Mantwill K, Dravits T, Bernshausen A, Glockzin G, Kohler-Vargas N, Lage H, Gansbacher B, Holm PS (2006) Novel three-pronged strategy to enhance cancer cell killing in glioblastoma cell lines: histone deacetylase inhibitor, chemotherapy, and oncolytic adenovirus d1520. Hum Gene Ther 17:55–70

Blanchard F, Chipoy C (2005) Histone deacetylase inhibitors: new drugs for the treatment of inflammatory diseases? Drug Discov Today 10:197–204

Bug G, Ritter M, Wassmann B, Schoch C, Heinzel T, Schwarz K, Romanski A, Kramer OH, Kampfmann M, Hoelzer D, Neubauer A, Ruthardt M, Ottmann OG (2005) Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. Cancer 104:2717–2725

Buggy JJ, Cao ZA, Bass KE, Verner E, Balasubramanian S, Liu L, Schultz BE, Young PR, Dalrymple SA (2006) CRA-024781: a novel synthetic inhibitor of histone deacetylase enzymes with antitumor activity in vitro and in vivo. Mol Cancer Ther 5:1309–1317

Butler LM, Webb Y, Agus DB, Higgins B, Tolentino TR, Kutko MC, LaQuaglica MP, Drobnjak M, Cordon-Cardo C, Scher HI, Beslow R, Richon VM, Rifkind RA, Marks PA (2001) Inhibition of transformed cell growth and induction of cellular differentiation by pyroxamide, an inhibitor of histone deacetylase. Clin Cancer Res 7:962–970

Butler LM, Zhoudagger X, Xu W-S, Scher H I, Rifkind RA, Marks PA, Richondagger VM (2002) The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredoxin-binding protein-2, and down-regulates thioredoxin. Proc Natl Acad Sci USA 99:11700–11705

Butler LM, Liapis V, Bouralexis S, Welldon K, Hay S, Thai le M, Labrinidis A, Tilley WD, Findlay DM, Evdokiou A (2006) The histone deacetylase inhibitor, suberoylanilide hydroxamic acid, overcomes resistance of human breast cancer cells to Apo2L/TRAIL. Int J Cancer 119:944–954

Byrd JC, Marcucci G, Parthun MR, Xiao JJ, Klisovic RB, Moran M, Lin TS, Liu S, Sklenar AR, Davis ME, Lucas DM, Fischer B, Shank R, Tejaswi SL, Binkley P, Wright J, Chan KK, Grever MR (2005) A phase I and pharmacodynamic study of depsipeptide (FK228) in chronic lymphocytic leukemia and acute myeloid leukemia. Blood 105:959–967

Cao ZA, Bass KE, Balasubramanian S, Liu L, Schultz B, Verner E, Dai Y, Molina RA, Davis JR, Misialek S, Sendzik M, Orr CJ, Leung L, Callan O, Young P, Dalrymple SA, Buggy JJ (2006) CRA-026440: a potent, broad-spectrum, hydroxamic histone deacetylase inhibitor with antiproliferative and antiangiogenic activity in vitro and in vivo. Mol Cancer Ther 5:1693–1701

Catley L, Weisberg E, Kiziltepe T, Tai Y-T, Hideshima TPN, Tassone P, Atadja P, Chauhan D, Munshi NC, Anderson K C (2006) Aggresome induction by proteasome inhibitor bortezomib and a-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood 108:3441–3449

Celera (2005) http://www.redorbit.com/modules/news/tools.php?tool=print&id=172745

Chen J, Bai H, Wang C, Kang J (2006) Trichostatin A improves the anticancer activity of low concentrations of curcumin in human leukemia cells. Pharmazie 61:710–716

Chinnaiyan P, Allen GW, Harari PM (2006) Radiation and new molecular agents, part II: targeting HDAC, HSP90, IGF-IR, PI3K, and Ras. Semin Radiat Oncol 16:59–64

Choi JH, Oh SW, Kang MS, Kwon HJ, Oh GT, Kim D-Y (2005) Trichostatin A attenuates airway inflammation in mouse asthma model. Clin Exp Allergy 35:89–96

Chung D (2002) Histone modification: the "next wave" in cancer therapeutics. Trends Mol Med 8:S10–S11

Cimino G, Lo-Coco F, Fenu S, Travaglini L, Finolezzi E, Mancini M, Nanni M, Careddu A, Fazi F, Padula F, Fiorini R, Spiriti MAA, Petti MC, Venditti A, Amadori S, Mandelli F, Pelicci PG, Nervi C (2006) Sequential valproic acid/all-trans retinoic acid treatment reprograms differentiation in refractory and high-risk acute myeloid leukemia. Cancer Res 66:8903–8911

Cohen LA, Marks PA, Rifkind RA, Amin S, Desai D, Pittman B, Richon VM (2002) Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, suppresses the growth of carcinogen-induced mammary tumors. Anticancer Res 22:1497–1504

Conley BA, Egorin MJ, Tait N, Rosen DM, Sausville EA, Dover G, Fram RJ, Van Echo DA (1998) Phase I study of the orally administered butyrate prodrug tributyrin, in patients with solid tumors. Clin Cancer Res 4:629–634

Coradini D, Zorzet S, Rossin R, Scarlata I, Pellizzaro C, Turrin C, Bello M, Cantoni S, Speranza A, Sava G, Mazzi U, Perbellini A (2004) Inhibition of hepatocellular carcinomas in vitro and hepatic metastases in vivo in mice by the histone deacetylase inhibitor HA-But. Clin Cancer Res 10:4822–4830

Dashmahapatra G, Almenara JA, Grant S (2006) Flavopiridol and histone deacetylase inhibitors promote mitochondrial injury and cell death in human leukemia cell that overexpress Bcl-2. Mol Pharmacol 69:288–298

De Ruijter AJ, Leen R, Hoebink J, Caron HN, van Kuilenburg AB (2006) Antagonist effects of sequential administration of BL1521, a histone deacetylase inhibitor, and gemcitabine to neuroblastoma cells. Cancer Lett 233:240–246

Drummond DC, Marx C, Guo Z, Scott G, Noble C, Wang D, Pallavicini M, Kirpotin DB, Benz CC (2005a) Enhanced pharmacodynamic and antitumor properties of a histone deacetylase inhibitor encapsulated in liposomes or ErbB2-targeted immunoliposomes. Clin Cancer Res 11:3392–3401

Drummond DC, Noble CO, Kirpotin DB, Guo Z, Scott GK, Benz CC (2005b) Clinical development of histone deacetylase inhibitors as anticancer agents. Annu Rev Pharmacol Toxicol 45:495–528

Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, Chiao JH, Reilly JF, Ricker JL, Richon VN, Frankel S (2007) Phase II trial of oral vorinostat (Suberoylanilide Hydroxamic Acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 109:31–39

Edelman MJ, Bauer K, Khanwani S, Tait N, Trepel J, Karp J, Nemieboka N, Chung E-J, Van Echo D (2003) Clinical and pharmacologic study of tributyrin: an oral butyrate prodrug. Cancer Chemother Pharmocol 51:439–444

Elliott P (2006) http://sirtrispharma.hubspot.com/News/PressReleases/tabid/3693/articleType/ArticleView/articleId/1062/Default.aspx

Entin-Meer M, Rephaeli A, Yang X, Nudelman A, VandenBerg SR, Haas-Kogan DA (2005) Butyric acid prodrugs are histone deacetylase inhibitors that show antineoplastic activity and radiosensitizing capacity in the treatment of malignant gliomas. Mol Cancer Ther 4:1952–1961

Eyüpoglu IY, Hahnen E, Buslei R, Siebzehnrübl FA, Savaskan NE, Lüders M, Tränkle C, Wick W, Weller M, Fahlbusch R, Blümcke I (2005) Suberoylanilide hydroxamic acid (SAHA) has potent anti-glioma properties in vitro, ex vivo and in vivo. J Neurochem 93:992–999

Eyüpoglu IY, Hahnen E, Tränkle C, Savaskan NE, Siebzehnrübl FA, Buslei R, Lemke D, Wick W, Fahlbusch R, Blümcke I (2006) Experimental therapy of malignant glioma using the inhibitor of histone deacetylase MS-275. Mol Cancer Ther 5:1248–1255

Farrel R (2004) http://www.titanpharm.com/press/Pivanex-Melanoma.htm

Fenrick R, Hiebert SW (1998) Role of histone deacetylase in acute leukemia. J Cell Biochem 30/31(Suppl):194–202

Ferrick R, Hiebert SW (1998) Role of histone deacetylases in acute leukemia. J Cell Biochem 30/31(Suppl):194–202

Fiskus W, Prampat M, Balasis M, Bali P, Estrella V, Kumaraswamy S, Rao R, Rocha K, Herger B, Lee F, Richon V, Bhalla K (2006a) Cotreatment with vorinostat (suberoylanilide hydroxamic acid) enhances activity of dasatinib (BMS-354825) against imtinib mesylate-sensitive or imtinib mesylate-resistant chronic myelogenous leukemia cells. Clin Cancer Res 12:5869–5878

Fiskus W, Pranpat M, Bali P, Balasis M, Kumaraswamy S, Boyapalle S, Rocha K, Wu J, Giles F, Manley PW, Atadja P, Bhalla K (2006b) Combined effects of novel tyrosine kinase inhibitor AMN107 and histone deacetylase inhibitor LBH589 against Bcr-Abl-expressing human leukemia cells. Blood 108:645–652

Fouladi M, Furman WL, Chin T, Freeman BB III, Dudkin L, Stewart CF, Krailo MD, Speights R, Ingle AM, Houghton PJ, Wright J, Adamson PC, Blaney SM (2006) Phase I study of depsipeptide in pediatric patients with refractory solid tumors: a children's oncology group report. J Clin Oncol 24:3678–3685

Frey RR, Wada CK, Garland RB, Curtin ML, Michaelides MR, Li J, Pease LJ, Glaser KB, Marcotte PA, Bouska JJ, Murphy SS, Davidsen SK (2002) Trifluoromethyl ketones as inhibitors of histone deacetylase. Bioorg Med Chem Lett 12:3443–3447

Garber K (2007) HDAC inhibitors overcome first hurdle. Nat Biotechnol 25:17–19

Garcia-Manero G, Yang H, Sanchez-Gonzalez B et al (2005) Final results of a phase I study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with leukemia and myelodysplastic syndrome. Blood 106:123a, (Abstract 408)

Garcia-Manero G, Kantarjian HM, Sanchez-Gonzalez B, Yang H, Rosner G, Verstovsek S, Rytting M, Wierda WG, Ravandi F, Koller C, Xiao L, Faderl S, Estrov Z, Cortes J, O'Brien S, Estey E, Bueso-Ramos C, Fiorentino J, Jabbour E, Issa J-P (2006) Phase I/II study of the combination of 5-aza-2′-deoxycytidine with valproic acid in patients with leukemia. Blood 108:3271–3279

Garcia-Morales P, Gómez-Martinez A, Carrato A, Martinez-Lacaci I, Barberá VM, Soto JL, Carrasco-Garcia E, Menéndez-Gutierrez MP, Castro-Galache MD, Ferragut JA, Saceda M (2005) Histone deacetylase inhibitors induced caspase-independent apoptosis in human pancreatic adenocarcinoma cell lines. Mol Cancer Ther 4:1222–1230

Gartel AL, Tyner AL (1999) Transcriptional regulation of the p21 (WAF1/CIP1) gene. Exp Cell Res 246:280–289

Gartel AL, Tyner AL (2002) The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. Mol Cancer Ther 1:639–649

Gaschott T, Steinhilber D, Milovic V, Stein J (2001) Tributyrin, a stable and rapidly absorbed prodrug of butyric acid, enhances antiproliferative effects of dihydroxycholecalciferol in human colon cancer cells. J Nutr 131:1839–1843

George P, Bali P, Annavarapu S, Scuto A, Fiskus W, Guo F, Sigua C, Sondarva G, Moscinski L, Atadja P, Bhalla K (2005) Combination of the histone deacetylase inhibitor LBH589 and the hsp90 inhibitor 17-AAG is highly active against human CML-BC cells and AML cells with activating mutation of FLT-3. Blood 105:1768–1776

Giles F, Fischer T, Cortes J, Garcia-Manero G, Beck J, Ravandi F, Masson E, Rae P, Laird G, Sharma S, Kantarjian H, Dugan M, Albitar M, Bhalla K (2006) A phase I study of intravenous LBH589, a novel cinnamic hydroxamic acid analogue histone deacetylase inhibitor, in patients with refractory hematological malignancies. Clin Cancer Res 12:4628–4635

Glaser KB, Staver MJ, Waring JF, Stender J, Ulrich RG, Davidsen SK (2003) Gene expression profiling of multiple histone deacetylase (HDAC) inhibitors: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. Mol Cancer Ther 2:151–163

Golay J, Cuppini L, Leoni F, Micò C, Domenghini M, Lombardi L, Neri A, Barbui AM, Salvi A, Porro G, Pagani P, Fossati G, Mascagni P, Introna M, Rambaldi A (2006) The histone deacetylase inhibitor ITF2357 induces apoptosis of leukemia cells and inhibits IL-6 and VEGF production by bone marrow mesenchymal stromal cells. Haematol Rep 2:16

Gore SD, Baylin S, Sugar E, Carraway H, Miller CB, Carducci M, Grever M, Galm O, Dauses T, Karp JE, Rudek MA, Zhao M, Smith BD, Manning J, Jiemjit A, Dover G, Mays A, Zwiebel J, Murgo A, Weng LJ, Herman JG (2006) Combined DNA methyltransferase and histone deacetylase inhibition in the treatment of myeloid neoplasms. Cancer Res 66:6361–6369

Göttlicher M, Minucci S, Zhu P, Krämer OH, Schimpf A, Giavara S, Sleeman JP, Coco FL, Nervi C, Pelicci PG, Heinzel T (2001) Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J 20:6969–6978

Grozinger CM, Schreiber SL (2002) Deacetylase enzymes: biological functions and the use of small-molecule inhibitors. Chem Biol 9:3–16

Grunstein M (1997) Histone acetylation in chromatin structure and transcription. Nature 389:349–352

Gu W, Nusinzon I, Smith RD, Horvarth CM, Silverman RB (2006) Carbonyl- and sulfur-containing analogs of suberoylanilide hydroxamic acid: potent inhibition of histone deacetylases. Bioorg Med Chem 14:3320–3329

Gui CY, Ngo L, Xu WS, Richon VM, Marks PA (2004) Histone deacetylase (HDAC) inhibitor activation of p21WAF1 involves changes in promoter-associated proteins, including HDAC1. Proc Natl Acad Sci USA 101:1241–1246

Gurvich N, Tsygankova OM, Meinkoth JL, Klein PS (2004) Histone deacetylase is a target of valproic acid-mediated cellular differentiation. Cancer Res 64:1079–1086

Haggarty SJ, Koeller KM, Wong JC, Grozinger CM, Schreiber SL (2003) Domain-selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. Proc Natl Acad Sci USA 100:4389–4394

Hahnen E, Eyupoglu IY, Brichta L, Haastert K, Trankle C, Siebzehnrubl FA, Riessland M, Holker I, Claus P, Romstock J, Buslei R, Wirth B, Blumcke I (2006) In vitro evaluation of second-generation histone deacetylase inhibitors for the treatment of spinal muscular atrophy. J Neurochem 98:193–202

Hamamori Y, Schneider MD (2003) HATs off to Hop: recruitment of a class I histone deacetylase incriminates a novel transcriptional pathway that opposes cardiac hypertrophy. J Clin Invest 112:824–826

Hanessian S, Vinci V, Auzzas L, Marzi M, Giannini G (2006) Exploring alternative Zn-binding groups in the design of HDAC inhibitors: squaric acid, *N*-hydroxyurea, and oxazoline analogues of SAHA. Bioorg Med Chem 16:4784–4787

Hausschild A, Trefzer U, Garbe C, Kaehler K, Ugurel S, Kiecker F, Eigentler T, Krissel H, Schadendorf D (2006) A phase II multicenter study on the histone deacetylase (HDAC) inhibitor MS-275, comparing two dosage schedules in metastatic melanoma. J Clin Oncol 24:18S, (8044)

Heltweg B, Dequiedt F, Marshall BL, Brauch C, Yoshida M, Nishino N, Verdin E, Jung M (2004) Subtype selective substrates for histone deacetylases. J Med Chem 47:5235–5243

Heltweg B, Gatbonton T, Schuler AD, Posakony J, Li H, Goehle S, Kollipara R, DePinho RA, Gu Y, Simon JA, Bedalov A (2006) Antitumor activity of a small-molecule inhibitor of human silent information regulator 2 enzymes. Cancer Res 66:4368–4377

Hildmann C, Wegener D, Riester D, Hempel R, Schober A, Merana J, Giurato L, Guccione S, Nielsen TK, Ficner R, Schwienhorst A (2006) Substrate and inhibitor specificity of class 1 and class 2 histone deacetylases. J Biotechnol 124:258–270

Hildmann C, Riester D, Schwienhorst A (2007) Histone deacetylases–an important class of cellular regulators with a variety of functions. Appl Microbiol Biotechnol (in press)

Horton TM, Gannavarapu A, Blaney SM, D'Argenio DZ, Plon SE, Berg SL (2006) Bortezomib interactions with chemotherapy agents in acute leukemia in vitro. Cancer Chemother Pharmacol 58:13–23

Hoshijima M, Chien KR (2002) Mixed signals in heart failure: cancer rules. J Clin Invest 109:849–855

Hsi LC, Xi X, Lotan R, Shureiqi I, Lippman SM (2004) The histone deacetylase inhibitor suberoylanilide hydroxamic acid induces apoptosis via induction of 15-lipoxygenase-1 in colorectal cancer cells. Cancer Res 64:8778–8781

Huang L (2006) Targeting histone deacetylases for the treatment of cancer and inflammatory diseases. J Cell Physiol 209:611–616

Huang L, Pardee AB (2000) Suberoylanilide hydroxamic acid as a potential therapeutic agent for human breast cancer treatment. Mol Med 6:849–866

Huang L, Sowa Y, Sakai T, Pardee AB (2000) Activation of the p21WAF1/CIP1 promoter independent of p53 by the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) through the Sp1 sites. Oncogene 19:5712–5719

Hurtubise A, Momparler RL (2006) Effect of histone deacetylase inhibitor LAQ824 on antineoplastic action of 5-Aza-2′-deoxycytidine (decitabine) on human breast carcinoma cells. Cancer Chemother Pharmacol 58:618–625

Imre G, Gekeler V, Leja A, Beckers T, Boehm M (2006) Histone deacetylase inhibitors suppress the inducibility of nuclear factor-kappaB by tumor necrosis factor-alpha receptor-1 down regulation. Cancer Res 66:5409–5418

Insiga A, Monestiroli S, Ronzoni S, Gelmetti V, Marchesi F, Viale A, Altucci L, Nervi C, Minucci S, Pelicci PG (2005) Inhibitors of histone deacetylases induce tumor-selective apoptosis through activation of the death receptor pathway. Nat Med 11:71–76

Ito K, Lim S, Caramori G, Cosio B, Chung KF, Adcock IM, Barnes PJ (2002) A molecular mechanism of action of theophylline: induction of histone deacetylase activity to decrease inflammatory gene expression. Proc Natl Acad Sci USA 99:8921–8926

Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, Barczyk A, Hayashi S, Adcock IM, Hogg JC, Barnes PJ (2005) Decreased histone deacetylase activity in chronic obstructive pulmonary disease. New Engl J Med 352:1967–1976

Johnstone RW (2002) Histone–deacetylase inhibitors: novel drugs for the treatment of cancer. Nat Rev 1:287–299

Karagiannis TC, El-Osta A (2006) Modulation of cellular radiation responses by histone deacetylase inhibitors. Oncogene 25:3885–3893

Kariya S, Hirano M, Uesato S, Nagai Y, Nagaoka Y, Furiya Y, Asai H, Fujikake N, Toda T, Ueno S (2006) Cytoprotective effect of histone deacetylase inhibitors against polyglutamine toxicity. Neurosci Lett 392:213–215

Kee HJ, Sohn IS, Nam KI, Park JE, Yin Z, Ahn Y, Jeong MH, Bang YJ, Kim N, Kim JK, Kim KK, Epstein JA, Kook H (2006) Inhibition of histone deacetylation blocks cardiac hypertrophy induced by angiotensin II infusion and aortic banding. Circulation 113:51–59

Kelly WK, O'Connor OA, Marks PA (2002) Histone deacetylase inhibitors: from target to clinical trials. Expert Opin Investig Drugs 11:1695–1713

Kelly WK, Richon VM, O'Connor O, Curley T, MacGregor-Curtelli B, Tong W, Klang M, Schwartz L, Richardson S, Rosa E, Drobnjak M, Cordon-Cordo C, Chiao JH, Rifkind R, Marks PA, Scher H (2003) Phase I clinical trial of histone deacetylase inhibitor: suberoylanilide hydroxamic acid administered intravenously. Clin Cancer Res 9:3578–3588

Khan SB, Maududi T, Barton K, Ayers J, Alkan S (2006) Analysis of histone deacetylase inhibitor, depsipeptide (FR901228), effect on multiple myeloma. Br J Haematol 125:156–161

Kim YB, Ki SW, Yoshida M, Horinouchi S (2000) Mechanisms of cell cycle arrest caused by histone deacetylase inhibitors in human carcinoma cells. J Antibiot 53:1191–1200

Kim MS, Kwon HJ, Lee YM, Baek JH, Jang JE, Lee SW, Moon EJ, Kim HS, Lee SK, Chung HY, Kim CW, Kim KW (2001) Deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. Nat Genet 7:437–443

Kim MS, Blake M, Baek JH, Kohlhagen G, Pommier Y, Carrier F (2003) Inhibition of histone deacetylase increases cytotoxicity to anticancer drugs targeting DNA. Cancer Res 63:7291–7300

Kim IA, Shin JH, Kim IH, Kim JH, Kim JS, Wu HG, Chie EK, Ha SW, Park CI, Kao GD (2006) Histone deacetylase inhibitor-mediated radiosensitization of human cancer cells: class differences and the potential influence of p53. Clin Cancer Res 12:940–949

Kong Y, Tannous P, Lu G, Berenji K, Rothermel BA, Olson EN, Hill JA (2006) Suppression of class I and II histone deacetylases blunts pressure-overload cardiac hypertrophy. Circulation 113:2579–2588

Kook H, Lepore JJ, Gitler AD, Lu MM, Yung WW-M, Mackay J, Zhou R, Ferrari V, Gruber P, Epstein JA (2002) Cardiac hypertrophy and histone deacetylase-dependent transcriptional repression mediated by the atypical homeodomain protein Hop. J Clin Invest 112:863–871

Kouraklis G, Misiakos EP, Theocharis S (2006) Histone deacetylase inhibitors as a potential therapeutic agent for human cancer treatment. Targeted Oncol 1:34–41

Kristeleit RS, Tandy D, Atadja P, Patnaik A, Scott J, De Bono JS, Judson I, Kaye SB, Workman P, Aherne W (2004) Effects of the histone deacetylase inhibitor (HDACI) LAQ824 on histone acetylation, Hsp70 and c-Raf in peripheral blood lymphocytes from patients with advanced solid tumours enrolled in a phase I clinical trial. J Clin Oncol 22:3023

Kuefer R, Hofer MD, Altug V, Zorn C, Genze F, Kunzi-Rapp K, Hautmann RE, Gschwend JE (2004) Sodium butyrate and tributyrin induce in vivo growth inhibition and apoptosis in human prostate cancer. Br J Cancer 90:535–541

Kuendgen A, Schmid M, Schlenk R, Knipp S, Hildebrandt B, Steidl C, Germing U, Haas R, Dohner H, Gattermann N (2005) The histone deacetylase (HDAC) inhibitor valproic acid as monotherapy or in combination with all-trans retinoic acid in patients with acute myeloid leukemia. Cancer 106:112–119

Kulp SK, Chen C-S, Wang D-S, Chen C-Y, Chen C-S (2006) Antitumor effects of a novel phenylbutyrate-based histone

deacetylase inhibitor, (S)-HDAC-42, in prostate cancer. Clin Cancer Res 12:5199–5206
Leoni F, Fossati G, Lewis EC, Lee J-K, Porro G, Pagani P, Modena D, Moras ML, Pozzi P, Reznikov LL, Siegmund B, Fantuzzi G, Dinarello CA, Mascagni P (2005) The histone deacetylase inhibitor ITF2357 reduces production of proinflammatory cytokines in vitro and systemic inflammation in vivo. Mol Med 11:1–15
Linggi BE, Brandt SJ, Sun Z-W, Hiebert SW (2005) Translating the histone code into leukemia. J Cell Biochem 96:938–950
Liu T, Kuljaca S, Tee A, Marshall GM (2006) Histone deacetylase inhibitors: multifunctional anticancer agents. Cancer Treat Rev 32:157–165
LoRusso PM, Demchik L, Foster B, Knight J, Bissery M-C, Polin LM, Leopold WR III, Corbett TH (1996) Preclinical antitumor activity of CI-994. Invest New Drugs 14:349–356
Lu Q, Wang D-S, Chen C-S, Hu Y-D, Chen C-S (2005) Structure-based optimization of phenylbutyrate-derived histone deacetylase inhibitors. J Med Chem 48:5530–5535
Luong QT, O'Kelly J, Braunstein GD, Hershman JM, Koeffler HP (2006) Antitumor activity of suberoylanilide hydroxamic acid against thyroid cancer cell lines in vitro and in vivo. Clin Cancer Res 12:5570–5577
Ma X, Fang Y, Beklemisheva AA, Dai W, Feng J, Ahmed T, Liu D, Chiao JW (2006) Phenylhexyl isothiocyanate inhibits histone deacetylases and remodels chromatins to induce growth arrest in human leukemia cells. Int J Oncol 28:1287–1293
Magner WJ, Kazim AL, Stewart C, Romano MA, Catalano G, Grande C, Keiser N, Santaniello F, Tomasi TB (2000) Activation of MHC class I, II, and CD40 gene expression by histone deacetylase inhibitors. J Immunol 165:7017–7024
Mai A, Massa S, Pezzi R, Rotili D, Loidl P, Brosch G (2003) Discovery of (aryloxopropenyl)pyrrolyl hydroxamides as selective inhibitors of class IIa histone deacetylase homologue HD1-A. J Med Chem 46:4826–4829
Mai A, Massa S, Rotili D, Simeoni S, Ragno R, Botta G, Nebbioso A, Miceli M, Altucci L, Brosch G (2006) Synthesis and biological properties of novel, uracil-containing histone deacetylase inhibitors. J Med Chem 49:6046–6056
Maiso P, Carvajal-Vergara X, Ocio EM, López-Pérez R, Mateo G, Gutiérrez N, Atadja P, Pandiella A, San Miguel JF (2006) The histone deacetylase inhibitor LBH589 is a potent antimyeloma agent that overcomes drug resistance. Cancer Res 66:5781–5789
Marks PA, Beslow R (2007) Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug. Nat Biotechnol 25:84–90
Marks PA, Richon VM, Miller T, Kelly WK (2004) Histone deacetylase inhibitors. Adv Cancer Res 91:137–168
Merck (2006) http://www.fda.gov/cder/Offices/OODP/whatsnew/vorinostat.htm
Mercuri E, Bertini E, Messina S, Solari A, D'Amico A, Angelozzi C, Battini R, Berardinelli A, Boffi P, Bruno C, Cini C, Colitto F, Kinali M, Minetti C, Mougini T, Morandi L, Neri G, Orcesi S, Pane M, Pelliccioni M, Pini A, Tiziano FD, Villanova M, Vita G, Brahe C (2007) Randomized, double-blind, placebo-controlled trial of phenylbutyrate in spinal muscular atrophy. Neurology 68:51–55
Metzger J (2002) HDAC lightens a heavy heart. Nat Med 8:1078–1079
Miller AC, Whittaker T, Thibault A, Samid D (1999) Modulation of radiation response of human tumour cells by the differentiation inducers, phenylacetate and phenylbutyrate. Int J Radiat Biol 72:211–218
Minucci S, Pelicci PG (2006) Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev 6:38–51
Mishra N, Brown DR, Olorenshaw IM, Kammer GM (2001) Trichostatin A reverses skewed expression of CD154 interleukin-10, and interferon-g gene and protein expression in lupus T cells. Proc Natl Acad Sci USA 98:2628–2633
Monneret C (2005) Histone deacetylase inhibitors. Eur J Med Chem 40:1–13
Mora FD, Jones DK, Desai PV, Patny A, Avery MA, Feller DR, Smillie T, Zhou Y-D, Nagle DG (2006) Bioassay for the identification of natural product-based activators of peroxisome proliferator-activated receptor-g (PPAR g): the marine sponge metabolite psammaplin A activates PPAR g and induces apoptosis in human breast tumor cells. J Nat Prod 69:547–552
Moradei O, Maroun CR, Paquin I, Vaisburg A (2005) Histone deacetylase inhibitors: latest developments, trends and prospects. Curr Med Chem 5:529–560
Moreth K, Riester D, Hildmann C, Hempel R, Wegener D, Schober A, Schwienhorst A (2006) Active site tyrosine is essential for amidohydrolase but not for esterase activity of a class 2 histone deacetylase-like bacterial enzyme. Biochem J 401:659–665
Munster PN, Troso-Sandoval T, Rosen N, Rifkind R, Marks PA, Richon VM (2001) The histone deacetylase inhibitor suberoylanilide hydroxamic acid induces differentiation of human breast cancer cells. Cancer Res 61:8492–8497
Munster PN, Marchion DC, Bicaku E, Schmitt ML, Padilla B, Stauffer P, Garrett C, Chiappori A, Sullivan DM, Daud AI (2006) Phase I trial of sequence-specific combination of the HDAC inhibitor, valproic acid (VPA), and the topoisomerase II inhibitor, epirubicin, in advanced solid tumors: clinical results and correlative studies. J Clin Oncol 24(18S):3068
Myzak MC, Karplus PA, Chung F-L, Dashwood RH (2004) A novel mechanism of chemoprotection by sulforaphane: inhibition of histone deacetylase. Cancer Res 64:5767–5774
Myzak MC, Dashwood WM, Orner GA, Ho E, Dashwood RH (2006) Sulforaphane inhibits histone deacetylase in vivo and suppresses tumorigenesis in Apc-minus mice. FASEB J 20:506–508
Nawrocki ST, Carew JS, Pino MS, Highshaw RA, Andtbacka RH, Dunner K, Pal A, Bornmann WG, Chiao PJ, Huang P, Xiong H, Abbruzzese JL, McConkey DJ (2006) Aggresome disruption: a novel strategy to enhance bortezomib-induced apoptosis in pancreatic cancer cells. Cancer Res 66:3773–3781
Nebbioso A, Clarke N, Voltz E, Germain E, Ambrosino C, Bontempo P, Alvarez R, Schiavone EM, Ferrara F, Bresciani F, Weisz A, de Lera AR, Gronemeyer H, Altucci L (2005) Tumor-selective action of HDAC inhibitors involves trail induction in acute myeloid leukemia cells. Nat Med 11:77–84
Nemunaitis JJ, Orr D, Eager R, Cunningham CC, Williams A, Mennel R, Grove W, Olson S (2003) Phase I study of oral CI-994 in combination with gemcitabine in treatment of patients with advanced cancer. Cancer J 9:58–66
Newmark HL, Young CW (1995) Butyrate and phenylacetate as differentiating agents: practical problems and opportunities. J Cell Biochem 22(Suppl):247–253
Nielsen TK, Hildmann C, Riester D, Wegener D, Schwienhorst A, Ficner R (2006) Complex structure of a bacterial class 2 histone deacetylase homologue with a trifluoromethylketone inhibitor. Acta Crystallogr F (in press)
O'Connor OA (2006) Clinical experience with the novel histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in patients with relapsed lymphoma. Br J Cancer 95:S7–S12
O'Connor OA, Heaney ML, Schwartz L, Richardson S, Willim R, MacGregor-Cortelli B, Curly T, Moskowitz C, Portlock C, Horwitz S, Zelenetz AD, Frankel S, Richon V, Marks P, Kelly WK (2006) Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. J Clin Oncol 24:166–173
Okada T, Tanaka K, Nakatani F, Sakimura R, Matsunobu T, Li X, Hanada M, Nakamura T, Oda Y, Tsuneyoshi M, Iwamoto Y

(2006a) Involvement of P-glycoprotein and MRP1 in resistance to cyclic tetrapeptide subfamily of histone deacetylase inhibitors in the drug-resistant osteosarcoma and Ewing's sarcome cells. Int J Cancer 118:90–97

Okada T, Uchibori R, Itawa-Okada M, Takahashi M, Nomoto T, Nonaka-Sarukawa M, Ito T, Liu Y, Mizukami H, Kume A, Kobayashi E, Ozawa K (2006b) A histone deacetylase inhibitor enhances recombinant adeno-associated virus-mediated gene expression in tumor cells. J Am Soc Gene Ther 13:738–746

Pauer LR, Olivares J, Cunningham C, Williams A, Grove A, Kraker A, Olson S, Nemunaitis J (2004) Phase I study of oral CI-994 in combination with carboplatin and paclitaxel in the treatment of patients with advanced solid tumors. Cancer Invest 22:886–896

Peterson CL (2002) HDAC's at work: everyone doing their part. Mol Cell 9:921–929

Petri S, Kiaei M, Kipiani K, Chen J, Calingasan NY, Crow JP, Beal MF (2006) Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis. Neurobiol Dis 22:40–49

Piacentini P, Donadelli M, Costanzo C, Moore PS, Palmieri M, Scarpa A (2006) Trichostatin A enhances the response of chemotherapeutic agents in inhibiting pancreatic cancer cell proliferation. Virchows Arch 448:797–804

Piekarz RL, Frye AR, Wright JJ, Steinberg SM, Liewehr DJ, Rosing DR, Sachdev V, Fojo T, Bates SE (2006) Cardiac studies in patients treated with depsipeptide FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res 12:3762–3773

Plumb JA, Finn PW, Williams RJ, Bandara MJ, Romero MR, Watkins CJ, La Thangue NB, Brown R (2003) Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. Mol Cancer Ther 3:721–728

Qian DZ, Kato Y, Shabbeer S, Wei Y, Verheul HMW, Salumbides B, Sanni T, Atadja P, Pili R (2006a) Targeting tumor angiogenesis with histone deacetylase inhibitors: the hydroxamic acid derivative LBH589. Clin Cancer Res 12:634–642

Qian X, LaRochelle WJ, Ara G, Wu F, Petersen KD, Thougaard A, Sehested M, Lichenstein HS, Jeffers M (2006b) Activity of PXD101, a histone deacetylase inhibitor, in preclinical ovarian cancer studies. Mol Cancer Ther 5:2086–2095

Quaissi A, Quaissi M (2005) Molecular basis of Trypanosoma cruzi and Leishmania interaction with their host(s): exploitation of immune and defense mechanisms by the parasite leading to persistence and chronicity, features reminiscent of immune system evasion strategies in cancer diseases. Arch Immunol Ther Exp 53:102–114

Quaissi M, Quaissi A (2006) Histone deacetylase enzymes as potential drug targets in cancer and parasitic diseases. J Biomed Biotechnol 2006:1–10

Reddy P, Maeda Y, Hotary K, Liu C, Reznikov LL, Dinarello CA, Ferrara JLM (2004) Histone deacetylase inhibitor suberoylanilide hydroxamic acid reduces acute graft-versus-host disease and preserves graft-versus-leukemia effect. Proc Natl Acad Sci USA 101:3921–3926

Remiszewski SW, Sambuccetti LC, Bair KW, Bontempo J, Cesarz D, Chandramouli N, Chen R, Cheung M, Cornell-Kennon S, Dean K, Diamantis G, France D, Green MA, Howell KL, Kashi R, Kwon P, Lassota P, Martin MS, Mou Y, Perez LB, Sharma S, Smith T, Sorensen E, Taplin F, Trogani N, Versace R, Walker H, Weltchek-Engler S, Wood A, Wu A, Atadja P (2003) *N*-hydroxy-3-phenyl-2-propenamides as novel inhibitors of human histone deacetylase with in vivo antitumor activity: discovery of (2E)-*N*-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide (NVP-LAQ824). J Med Chem 46:4609–4624

Richards DA, Boehm KA, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, Grove W, Macdonald K, Gulyas S, Clark M, Dasse KD (2006) Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study. Ann Oncol 17:1096–1102

Riesland M, Brichta L, Hahnen E, Wirth B (2006) The benzamide M344, a novel histone deacetylase inhibitor, significantly increases SMN2 RNA/protein levels in spinal muscular atrophy cells. Hum Genet 120:101–110

Riester D, Wegener D, Hildmann C, Schwienhorst A (2004) Members of the histone deacetylase superfamily differ in substrate specificity towards small synthetic substrates. Biochem Biophys Res Com 324:1116–1123

Riester D, Hildmann C, Schwienhorst A, Meyer-Almes F-J (2007) Histone deacetylase inhibitor assay based on fluorescence resonance energy transfer. Anal Biochem 401:659–665

Riggs MG, Whittaker RG, Neumann JR, Ingram VM (1977) *n*-Butyrate causes histone modification in HeLa and Friend erythroleukaemia cells. Nature 268:462–464

Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, Boix-Chornet M, Caballero R, Alaminos M, Setien F, Paz MF, Herranz M, Palacios J, Arango D, Orntoft TF, Aaltonen LA, Schwartz SJ, Esteller M (2006) A truncating mutation of HDAC2 in human cancers confers resistance to histone deacetylase inhibition. Nat Genet 38:566–569

Rosato RR, Grant S (2003) Histone deacetylase inhibitors in cancer therapy. Cancer Biol Ther 2:30–37

Ryan QC, Headlee D, Acharya M, Sparreboom A, Trepel JB, Ye J, Figg WD, Hwang K, Chung EJ, Murgo A, Melillo G, Elsayed Y, Monga M, Kalnitskiy M, Zwiebel J, Sausville EA (2005) Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma. J Clin Oncol 23:3912–3922

Sanchez-Gonzalez B, Yang H, Bueso-Ramos C, Hoshino K, Quintas-Cardama A, Richon VM, Garcia-Manero G (2006) Antileukemia activity of the combination of an anthracycline with a histone deacetylase inhibitor. Blood 108:1174–1182

Sandor V, Bakke S, Robey RW, Kang MH, Blagosklonny MV, Bender J, Brooks R, Piekarz RL, Tucker E, Figg WD, Chan KK, Goldspiel B, Fojo AT, Balcerzak SP, Bates SE (2002) Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res 8:718–728

Sankaranarayanapillai M, Tong WP, Maxwell DS, Pal A, Pang J, Bornmann WG, Gelovani JG, Ronen SM (2006) Detection of histone deacetylase inhibition by noninvasive magnetic resonance spectroscopy. Mol Cancer Ther 5:1325–1334

Sato T, Suzuki M, Sato Y, Echigo S, Rikiishi H (2006) Sequence-dependent interaction between cisplatin and histone deacetylase inhibitors in human oral squamous cell carcinoma cells. Int J Oncol 28:1233–1241

Schröder CP, Maurer HR (2002) Tributyrin-induced differentiation promotes apoptosis of LS174T colon cancer cells in vitro. Int J Oncol 20:195–200

Shinji C, Maeda S, Imai K, Yoshida M, Hashimoto Y, Miyachi H (2006) Design, synthesis, and evaluation of cyclic amide/imide-bearing hydroxamic acid derivatives as class-selective histone deacetylase (HDAC) inhibitors. Bioorg Med Chem 14:7625–7651

Simonini MV, Camargo LM, Dong E, Maloku E, Veldic M, Costa E, Guidotti A (2006) The benzamide MS-275 is a potent, long-lasting brain region-selective inhibitor of histone deacetylases. Proc Natl Acad Sci USA 103:1587–1592

Sonnemann J, Gange J, Pilz S, Stotzer C, Ohlinger R, Belau A, Lorenz G, Beck JF (2006a) Comparative evaluation of the treatment efficacy of suberoylanilide hydroxamic acid (SAHA)

and paclitaxel in ovarian cancer cell lines and primary ovarian cancer cells from patients. BMC Cancer 6:183

Sonnemann J, Kumar KS, Heesch S, Müller C, Hartwig C, Maass M, Bader P, Beck JF (2006b) Histone deacetylase inhibitors induce cell death and enhance the susceptibility to ionizing radiation, etoposide, and TRAIL in medulloblastoma cells. Int J Oncol 28:755–766

Stapnes C, Ryningen A, Gjertsen BT, Bruserud O (2006) Treatment with valproic acid, all-trans retinoic acid (ATRA) and theophyllamine for 9 days caused a persistent increase in peripheral blood platelet counts for a patient with acute myelogenous leukemia. Acta Oncol 45:346–349

Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, Apostol BL, Kazantsev A, Schmidt E, Zhu Y-Z, Greenwald M, Kirokawa R, Housman DE, Jackson GR, Marsh JL, Thompson LM (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 413:739–743

Sutheesophon K, Kobayashi Y, Takatoku MA, Ozawa K, Kano Y, Ishii H, Furukawa Y (2006) Histone deacetylase inhibitor depsipeptide (FK228) induces apoptosis in leukemia cells by facilitating mitochondrial translocation of Bax, which is enhanced by the proteasome inhibitor bortezomib. Acta Haematol 115:78–90

Suzuki T, Miyata N (2005) Non-hydroxamate histone deacetylase inhibitors. Curr Med Chem 12:2867–2880

Suzuki T, Yokozaki H, Kuniyasu H, Hayashi K, Naka K, Ono S, Ishikawa T, Tahara E, Yasul W (2000) Effect of trichostatin A on cell growth and expression of cell cycle- and apoptosis-related molecules in human gastric and oral carcinoma cell lines. Int J Cancer 88:992–997

Suzuki T, Kouketsu A, Itoh Y, Hisakawa S, MAeda S, Yoshida M, Nakagawa H, Miyata N (2006) Highly potent and selective histone deacetylase 6 inhibitors designed based on a small-molecular substrate. J Med Chem 49:4809–4812

Tabe Y, Konopleva M, Contractor R, Munsell M, Schober WD, Jin L, Tsutsumi-Ishi Y, Nagaoka I, Andreef M (2006) Up-regulation of MDR1 and induction of doxorubicin resistance by histone deacetylase inhibitor depsipeptide (FK228) and ATRA in acute promyelocytic leukemia cells. Blood 107:1546–1554

Tang R, Faussat A-M, Majdak P, Perrot J-Y, Chaoui D, Legrand O, Marie J-P (2004) Valproic acid inhibits proliferation and induces apoptosis in acute myeloid leukemia cells expressing P-gp and MRP1. Leukemia 18:1246–1251

Ten Cate B, Samplonius DF, Bijma T, de Leij LFMH, Helfrich W, Bremer E (2007) The histone deacetylase inhibitor valproic acid potently augments gemtuzumab ozogamicin-induced apoptosis in acute myeloid leukemia cells. Leukemia 21:248–252

Vanniasinkam T, Ertl H, Tang Q (2006) Trichostatin-A enhances adaptive immune responses to DNA vaccination. J Clin Virol 36:292–297

Vega RB, Masuda K, Oh J, Barbosa AC, Yang X, Meadows E, McAnally J, Pomajzl C, Shelton JM, Richardson JA, Karsenty G, Olson EN (2004) Histone deacetylase 4 controls chondrocyte hypertrophy during skeletogenesis. Cell 119:555–566

Vigushin DM, Coombes RC (2002) Histone deacetylase inhibitors in cancer treatment. Anticancer Drugs 2:1–13

Wada CK, Frey RR, Curtin ML, Garland RB, Holms JH, Pease LJ, Guo J, Glaser KB, Marcotte PA, Richardson PL, Murphy SS, Bouska JJ, Tapang P, Magoc TJ, Albert DH, Davidsen SK, Michaelides MR (2003) Alpha-keto amides as inhibitors of histone deacetylase. Bioorg Med Chem Lett 13:3331–3335

Wade PA, Pruss D, Wolffe AP (1997) Histone acetylation: chromatin in action. Trends Biochem Sci 22:128–132

Wang D-F, Helquist P, Wiech NL, Wiest O (2005) Toward selective histone deacetylase inhibitor design: homology modeling docking studies, and molecular dynamics simulations of human class I histone deacetylases. J Med Chem 48:6936–6947

Warrell RP, He LZ, Richon V, Calleja E, Pandolfi PP (1998) Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. J Natl Cancer Inst 90:1621–1625

Warren K, McCully CL, Dvinge H, Tjornelund J, Sehested M, Lichenstein HS, Balis FM (2006) http://www.curagen.com/uploaded_files/AACR20_3.PDF

Watanabe T, Hioki M, Fujiwara T, Nishizaki M, Kagawa S, Taki M, Kishimoto H, Endo Y, Urata Y, Tanaka N, Fujiwara T (2006) Histone deacetylase inhibitor FR901228 enhances the antitumor effect of telomerase-specific replication-selective adenoviral agent OBP-301 in human lung cancer cells. Exp Cell Res 312:256–265

Wegener D, Hildmann C, Schwienhorst A (2003a) Recent progress in the development of assays suited for histone deacetylase inhibitor screening. Mol Genet Metab 80:138–147

Wegener D, Wirsching F, Riester D, Schwienhorst A (2003b) A fluorogenic histone deacetylase assay well suited for high-throughput activity screening. Chem Biol 10:61–68

Weinmann H, Ottow E (2005) Histone deacetylase inhibitors: a survey of recent patents. Expert Opin Ther Pat 15:1677–1690

Weisberg E, Catley L, Kujawa J, Atadja P, Remiszewski S, Fuerst P, Cavazza C, Anderson K, Griffin JD (2004) Histone deacetylase inhibitor NVP-LAQ824 has significant activity against myeloid leukemia cells in vitro and in vivo. Leukemia 18:1951–1963

Witt O, Schweigerer L, Driever PH, Wolff J, Pekrun A (2004) Valproic acid treatment of glioblastoma multiforme in a child. Pediatr Blood Cancer 43:181

Xiao JJ, huang Y, Dai Z, Sadée W, Chen J, Liu S, Marcucci G, Byrd J, Covey JM, Wright J, Grever M, Chan KK (2005) Chemoresistance to depsipeptide FK228 is mediated by reversible MDR1 induction in human cancer cell lines. J Pharmacol Exp Ther 314:467–475

Xu WS, Ngo L, Perez G, Dokmanovic M, Marks PA (2006) Intrinsic apoptotic and thioredoxin pathways in human prostate cancer cell response to histone deacetylase inhibitor. Proc Natl Acad Sci USA 103:15540–15545

Yeow WS, Ziauddin MF, Maxhimer JB, Shamimi-Noori S, Baras A, Chua A, Schrump DS, Nguyen DM (2006) Potentiation of the anticancer effect of valproic acid, an antiepileptic agent with histone deacetylase inhibitory activity, by the kinase inhibitor Staurosporine or its clinically relevant analogue UCN-01. Br J Cancer 94:1436–1445

Yoo EJ, Lee BM (2005) Comparative mutagenicity of apicidin and apicidin derivatives (SD-0203 and SD-2007), histone deacetylase inhibitors. J Toxicol Environ Health A 68:2097–2109

Young DA, Lakey RL, Pennington CJ, Jones D, Kevorkian L, Edwards DR, Cawston TE, Clark IM (2005) Histone deacetylase inhibitors modulate metalloproteinase gene expression in chondrocytes and block cartilage resorption. Arthritis Res Ther 7: R503–R512

Zalupski M, O'Shaughnessy JA, Vukelja SJ, Shields A, Diener K, Grove W (2000) Phase II trial of CI-994 in patients (pts) with advanced pancreatic cancer (APC). Proc Annu Meet Am Soc Clin Oncol 19:285a, (Abstract 1115)

Zhang Z, Yamashita H, Toyama T, Sugiura H, Omoto Y, Ando Y, Mita K, Hamaguchi M, Hayashi S-I, Iwase H (2004) HDAC6 expression is correlated with better survival in breast cancer. Clin Cancer Res 10:6962–6968

Zhang C, Richon V, Ni X, Talpur R, Duvic M (2005) Selective induction of apoptosis by histone deacetylase inhibitor SAHA in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. J Invest Dermatol 125:1045–1052

Zhang X, Yashiro M, Ren J, Hirakawa K (2006) Histone deacetylase inhibitor, trichostatin A, increases the chemosensitivity of anticancer drugs in gastric cancer cell lines. Oncol Rep 16:563–568