

Minireview

Epigenetic Regulation of Multidrug Resistance Protein 1 and Breast Cancer Resistance Protein Transporters by Histone Deacetylase Inhibition

Dahea You,² Jason R. Richardson,¹ and Lauren M. Aleksunes¹

Joint Graduate Program in Toxicology, Rutgers, The State University of New Jersey, Piscataway, New Jersey (D.Y.); Department of Environmental Health Sciences, Robert Stempel School of Public Health and Social Work, Florida International University, Miami, Florida (J.R.R.); Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey (J.R.R., L.M.A.); and Department of Pharmacology and Toxicology, Rutgers, The State University of New Jersey, Ernest Mario School of Pharmacy, Piscataway, New Jersey (L.M.A.)

Received November 7, 2019; accepted February 13, 2020

ABSTRACT

Multidrug resistance protein 1 (MDR1, *ABCB1*, P-glycoprotein) and breast cancer resistance protein (BCRP, *ABCG2*) are key efflux transporters that mediate the extrusion of drugs and toxicants in cancer cells and healthy tissues, including the liver, kidneys, and the brain. Altering the expression and activity of MDR1 and BCRP influences the disposition, pharmacodynamics, and toxicity of chemicals, including a number of commonly prescribed medications. Histone acetylation is an epigenetic modification that can regulate gene expression by changing the accessibility of the genome to transcriptional regulators and transcriptional machinery. Recently, studies have suggested that pharmacological inhibition of histone deacetylases (HDACs) modulates the expression and function of MDR1 and BCRP transporters as a result of enhanced histone acetylation. This review addresses the ability of HDAC inhibitors to modulate the expression and the function of MDR1

and BCRP transporters and explores the molecular mechanisms by which HDAC inhibition regulates these transporters. While the majority of studies have focused on histone regulation of MDR1 and BCRP in drug-resistant and drug-sensitive cancer cells, emerging data point to similar responses in nonmalignant cells and tissues. Elucidating epigenetic mechanisms regulating MDR1 and BCRP is important to expand our understanding of the basic biology of these two key transporters and subsequent consequences on chemoresistance as well as tissue exposure and responses to drugs and toxicants.

SIGNIFICANCE STATEMENT

Histone deacetylase inhibitors alter the expression of key efflux transporters multidrug resistance protein 1 and breast cancer resistance protein in healthy and malignant cells.

Introduction

Transporters facilitate the transcellular movement of various substrates and are classified based on the molecular mechanisms, energetics,

This work was supported by the National Institutes of Health National Institute of Environmental Health Sciences (NIEHS) [Grants R01ES021800 and P30ES005022] and a Graduate Fellowship from Bristol-Myers Squibb to D.Y. Neither NIEHS nor Bristol-Myers Squibb had any role in the conduct of the study, interpretation of data, or decision to publish. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Bristol-Myers Squibb.

¹J.R.R. and L.M.A. denotes equal senior contributors.

²Current affiliation: National Institute of Environmental Health Sciences, Division of the National Toxicology Program, Research Triangle Park, NC.

<https://doi.org/10.1124/dmd.119.089953>.

and directionality of transfer across the plasma membrane. ATP-binding cassette (ABC) transporters are a superfamily of primary active transporters that use energy generated by the hydrolysis of ATP. Upon substrate binding to the transporter, ATP binds to the nucleotide binding domain (NBD) of the transporters to change the protein's conformation to facilitate the transfer of substrates to the extracellular space (Sharom, 2008). In mammals, ABC transporters mediate the efflux of various endo- and xenobiotics. Key ABC transporters, including the multidrug resistance protein 1 (MDR1, *ABCB1*, P-glycoprotein), breast cancer resistance protein (BCRP, *ABCG2*), and multidrug resistance-associated proteins (MRPs, *ABCCs*), play critical roles in regulating the passage of chemicals in kidney proximal tubules, enterocytes, hepatocytes, and brain endothelial capillary cells (Klaassen and Aleksunes, 2010). Modulating the expression and activity of these transporters can

ABBREVIATIONS: A β , amyloid- β ; ABC, ATP-binding cassette; AHR, aryl hydrocarbon receptor; AML, acute myeloid leukemia; BBB, blood-brain barrier; BCRP, breast cancer resistance protein; DRE, dioxin response element; DSP, downstream promoter; HAT, histone acetyltransferase; hCMEC/D3, human brain microvascular endothelial; HDAC, histone deacetylase; HEK, human embryonic kidney 293; MDR1, multidrug resistance protein 1; NBD, nucleotide binding domain; NF- κ B, nuclear transcription factor κ B; PCAF, P300/CBP-associated factor; PXR, pregnane X receptor; SAHA, suberoylanilide hydroxamic acid; SCFA, short chain fatty acid; SIRT, sirtuin; TMD, transmembrane domain; TSA, trichostatin A; TSS, transcription start site; VPA, valproic acid.

influence the tissue kinetics, pharmacology, and toxicity of substrates. Transcriptional regulation of efflux transporters has been widely known and comprehensively covered in several reviews (Kullak-Ublick and Becker, 2003; Miller, 2010; Pavsek and Smutny, 2014; Amacher, 2016). Recently, there has been growing evidence for epigenetic mechanisms, particularly histone acetylation, that can regulate the MDR1 and BCRP transporters. This review highlights key findings regarding the epigenetic regulation of MDR1 and BCRP expression and function by modulating histone acetylation.

Multidrug Resistance Protein 1

Biochemical and Physiologic Characteristics of MDR1. MDR1 is a 170 kDa N-glycosylated protein composed of 1280 amino acids. It is composed of two homologous parts, each of which is composed of a six-segment transmembrane domain (TMD) and a cytoplasmic NBD where ATP binding and hydrolysis occur (van der Blik et al., 1988; Devault and Gros, 1990; Aller et al., 2009). A flexible linker connects the C-terminal of the TMD of one half with the N-terminal of the NBD of the other half. MDR1 is encoded by one gene in humans (*MDR1/ABCB1*), whereas there are two genes, *Mdr1a/Abcb1a* and *Mdr1b/Abcb1b*, that encode mouse Mdr1 (Gros et al., 1986a,b; Ueda et al., 1986; Hsu et al., 1989). There is a high level of sequence similarity (approximately 75%) between the human MDR1 and mouse Mdr1 proteins (Chen et al., 1986; Gerlach et al., 1986; Gros et al., 1986a; Ueda et al., 1987b).

MDR1 is expressed at high levels in epithelial cells of the colon, small intestine, kidney proximal tubules and bile ductules, and endothelial cells of the blood-testis barrier, blood-brain barrier (BBB), blood-mammary tissue barrier, and blood-inner ear barrier (Fojo et al., 1987; Thiebaut et al., 1987). Its expression has also been detected on the luminal surface of the pregnant endometrium as well as placental trophoblasts (Lankas et al., 1998; St-Pierre et al., 2000). The distribution of mouse Mdr1a and Mdr1b combined together approximate the expression profile of human MDR1 (Cornwell, 1991; Klaassen and Aleksunes, 2010). A wide range of compounds is handled by the MDR1 transporter. Generally, MDR1 substrates are large (250–1850 Da) and hydrophobic or weakly amphipathic compounds (Schinkel, 1999). Structurally, many substrates contain planar aromatic rings, but there are also nonaromatic compounds transported by MDR1. Inhibitors of MDR1 can be similarly structured as substrates leading to competitive inhibition of the transporter, while others exert noncompetitive inhibition properties (Schinkel, 1999; Seelig and Landwojowicz, 2000; Wang et al., 2003; Sharom, 2006, 2008). The mouse Mdr1 isoform has a largely similar substrate specificity as the human MDR1 transporter (Ambudkar et al., 1999; Schinkel, 1999). Examples of MDR1 substrates and inhibitors are listed in Table 1.

Clinical Importance of MDR1. MDR1 is not essential for basic physiologic function, as Mdr1 knockout mice are fertile and phenotypically healthy (Schinkel et al., 1997). However, MDR1 imparts important function in determining exposure and, consequently, cellular responses to MDR1-transported drugs or toxicants. For example, in Madin-Darby Canine Kidney II tubule cells transfected with the *ABCB1* gene, the basolateral-to-apical transport (efflux) of the tyrosine kinase inhibitor gefitinib was significantly increased compared with matched control cells (Agarwal et al., 2010). In the presence of the MDR1 inhibitor, LY335979, the efflux of gefitinib in MDR1-transfected cells, was reduced to the same level as observed in control cells. Also, the oral bioavailability of the chemotherapeutic drug paclitaxel was significantly higher in Mdr1a knockout mice, potentially because of reduced epithelial efflux of paclitaxel into the intestinal lumen (Sparreboom et al., 1997). The roles of MDR1 influencing the transport and the toxicity of kidney toxicants have been well-demonstrated, as reviewed by George et al. (2017). The modulation of chemical transport by MDR1

TABLE 1

Example substrates and inhibitors for the MDR1 and BCRP transporters

| MDR1 Substrates | BCRP Substrates |
|--|--|
| Doxorubicin, vinblastine, tyrosine kinase inhibitors, HIV protease inhibitors (ritonavir, indinavir), phenytoin, prazosin, digoxin, diltiazem, tetracycline, morphine, polycyclic compounds (steroid aldosterone), fluorescent dyes (Rhodamine 123), amyloid- β , phospholipids, and lipid-derived signaling molecules | Doxorubicin, methotrexate, tyrosine kinase inhibitors, mitoxantrone, antiviral drugs (abacavir, zidovudine), fluoroquinolone antibiotics, prazosin, glyburide, etoposide, topotecan, zearalenone, aflatoxin B, fluorescent dyes (Hoechst 33342, Rhodamine 123), Genistein, protoporphyrin IX, amyloid- β , cholate |
| MDR1 Inhibitors | BCRP Inhibitors |
| Verapamil, cyclic peptides (cyclosporin A, PSC833), tamoxifen, sildanefil, curcuminoids, flavonoids, LY335979 (zosuquidar), GF120918 (elacridar) | Ko143, omeprazole, fumitremorgin C, GF120918 (elacridar), tyrosine kinase inhibitors, tacrolimus, tamoxifen, cyclosporin A |

is also important for the brain, which is a tightly controlled environment with generally low penetration of chemicals. For instance, Mdr1a/1b knockout mice exhibit higher total brain, as well as brain-to-plasma, concentrations of the MDR1 substrate and analgesic morphine (Xie et al., 1999). In humans, a loss-of-function *ABCB1* rs9282564 genetic polymorphism is associated with more significant adverse drug events from morphine, including respiratory depression (Sadhasivam et al., 2015). MDR1 has also been implicated as an efflux transporter for amyloid- β (A β), a key constituent of pathologic plaques in patients with Alzheimer Disease. Wang et al. (2016) showed that Mdr1a knockout mice accumulate greater A β concentrations in their brains compared with wild-type mice. Collectively, it is critical to understand the regulation of MDR1 function because it is a determining factor influencing tissue levels of drugs and toxicants.

Transcriptional Regulation of MDR1. MDR1 expression and function can be regulated at the transcriptional and post-transcriptional levels. The transcription of MDR1, which is encoded by *ABCB1*, is mediated by the coordinated action of different transcription factors at the *ABCB1* promoter. The *ABCB1* gene is located on chromosome 7q21.1 and has two distinct promoters, an upstream promoter, which is located at the beginning of the exon –1, and a downstream promoter (DSP), which resides within exon 1 (Roninson et al., 1986; Ueda et al., 1987a,b; Cornwell, 1990, 1991). The DSP generates the major transcript and is preferentially transcribed (Fig. 1). There are several response elements at the DSP for transcription factors to bind and stimulate gene activation. The DSP is characterized by the lack of a TATA-box, which is typical for human drug transporter genes (Ueda et al., 1987b; Cornwell, 1991; Scotto, 2003). Instead, the initiator sequence [–6 to +11 bp relative to transcription start site (TSS)] surrounding the TSS plays a role in directing gene activation (van Groenigen et al., 1993). The initiator interacts with RNA polymerase II and facilitates the recruitment of a transcription factor IID complex to efficiently begin gene transcription (Pugh and Tjian, 1991; van Groenigen et al., 1993). Analysis of promoter activity using the deletion mutations suggests that the sequence from –134 to +286 bp relative to the TSS is important for an efficient and high rate of transcription for the *ABCB1* gene (Cornwell, 1990; Goldsmith et al., 1993; Madden et al., 1993).

Indeed, there are several response elements located within the *ABCB1* region –134 to +286 bp to mediate the binding of key transcription factors. There exists a CCAAT box-like sequence (–118 to –113 bp) as well as an inverted CCAAT box or Y box (–82 to –73 bp), which is crucial for the basal expression of the *ABCB1* gene (Ueda et al., 1987b;

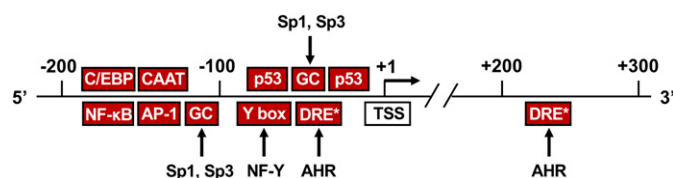


Fig. 1. Regulatory elements at the human *ABCB1* gene promoter. The location of key transcription factor binding sites in the human *ABCB1* promoter are shown as the number of base pairs relative to the transcriptional start site (TSS).

Ogura et al., 1991; Goldsmith et al., 1993; Sundseth et al., 1997; Jin and Scotto, 1998; Gromnicova et al., 2012). Y box is a binding site for nuclear transcription factor Y (NF-Y). NF-Y was shown to interact with P300/CBP-associated factor (PCAF), a transcriptional coactivator with intrinsic histone acetyltransferase (HAT) activity, to induce the histone acetylation at the promoter and facilitate gene transcription (Jin and Scotto, 1998). There are also GC boxes (−110 to −103 bp, −61 to −51 bp) that interact with Sp1 and Sp3 transcription factors (Ueda et al., 1987b; Cornwell and Smith, 1993; Sundseth et al., 1997; Gromnicova et al., 2012). An AP1 response site (−121 to −115 bp) was also identified and found to be involved in the transcriptional activation of *ABCB1* (Daschner et al., 1999). The presence of response elements for xenobiotic-activated transcription factors has also been described. There are two putative dioxin response elements (DREs) starting at −55 bp and at +238 bp (with a single base mismatch), which are binding sites for aryl hydrocarbon receptor (AHR)/AHR nuclear translocator heterodimers (Ueda et al., 1987b; Denison et al., 1988; Madden et al., 1993; Chan et al., 2013b). AHR is a ligand-activated transcription factor that has been consistently shown to mediate *ABCB1* transcription in several tissues. Ligands of AHR include carcinogens such as 2,3,7,8-tetrachlorodibenzodioxin and benzo(a)pyrene as well as flavonoid compounds including β-naphthoflavone (Murray et al., 2014). A pregnane X receptor (PXR) response element was also found to be located distally in the −8 kb upstream enhancer (Geick et al., 2001). Within the *ABCB1* promoter, there are also binding motifs for stress-induced regulators of MDR1 expression, including NF-κB (−167 to 158 bp) and p53 (−72 to −40 bp) (Chin et al., 1992; Thottassery et al., 1997; Deng et al., 2001; Johnson et al., 2001; Sampath et al., 2001). Cooperative interactions between the initiator and different response elements upstream of the TSS are necessary for precise and accurate transcriptional initiation (Scotto, 2003).

Unlike the human *ABCB1* gene, mouse *Abcb1* genes, located on chromosome 5, do contain a TATA-box upstream of the TSS, but overall, there is a high sequence similarity between human *ABCB1* and mouse *Abcb1* (Raymond and Gros, 1989; Hsu et al., 1990; Cornwell, 1991). Two mouse *Mdr1* genes, *Abcb1a* and *Abcb1b*, are also highly similar in sequence to each other, sharing common *cis*-acting regulatory elements. Both *Abcb1a* and *Abcb1b* have CCAAT boxes as well binding sites for AP1 and Sp1 upstream of the TSS, although the exact locations and abundance differ between two genes (Hsu et al., 1989, 1990; Raymond and Gros, 1989, 1990; Cohen et al., 1991). However, Hsu et al. (1990) illustrated an important difference between the two isoforms. They found that the transcription of *Abcb1a*, like that of human *ABCB1*, can be mediated by the two distinct promoters, upstream and downstream (Hsu et al., 1990). The downstream promoter produces the major transcripts that are detected at high levels in normal tissues expressing *Abcb1a*. Consequently, variants of transcripts were generated by the *Abcb1a* gene in certain cells, while a single transcript was associated with *Abcb1b* (Cohen et al., 1991).

Xenobiotic-activated receptors, such as Pxr and Ahr, are also noted as potential regulators of mouse *Mdr1*. The protein expression of mouse

Mdr1 was significantly upregulated in brain microvessels of adult mice treated with dexamethasone, which is a Pxr and glucocorticoid receptor ligand (Chan et al., 2013a). Also, a recent study showed that pregnenolone 16α-carbonitrile, a ligand of murine Pxr, was able to differentially regulate both mRNA and protein expression of *Mdr1* in intestine, liver, and cortex tissues of mice (Yamasaki et al., 2018). An Ahr activator, 3-methylcholanthrene, was also shown to induce the mRNA level of *Abcb1b* in Hepa-1c1c7 mouse hepatoma cells. Furthermore, potential DREs interacting with Ahr were identified at the distal location of *Abcb1b* promoter (Mathieu et al., 2001). Lastly, studies also showed the capability of p53 to differentially regulate rodent *Abcb1a* and *Abcb1b* expression (Thottassery et al., 1997; Lecureur et al., 2001).

In summary, *MDR1* gene regulation involves the interaction of multiple transcription factors at the *ABCB1* promoter that affect gene transcription. Although the structural features of promoters for human *ABCB1* and mouse *Abcb1* genes have some differences, the pathways involved in the transcriptional regulation of *ABCB1* and *Abcb1* genes appear to be similar.

Breast Cancer Resistance Protein

Biochemical and Physiologic Characteristics of BCRP. BCRP is a 72 kDa half-transporter that is 655 amino acids in length. It has one N-terminal NBD and one C-terminal six-segment TMD (Allikmets et al., 1998; Taylor et al., 2017; Jackson et al., 2018). The half-transporter forms a homodimer through disulfide bond formation, an event required for efflux function (Henriksen et al., 2005; Wakabayashi et al., 2006; Khunweeraphong et al., 2017). BCRP is encoded by the *ABCG2* gene in humans and the *Abcg2* gene in rodents (Bailey-Dell et al., 2001; Tanaka et al., 2005; Natarajan et al., 2011).

BCRP is widely expressed across different tissues and generally serves a protective function similar to the MDR1 transporter. The highest expression of BCRP is detected at the apical surface of the syncytiotrophoblasts in the placenta, where the transporter plays a major role in protecting the fetus from exposure to toxic substrates transferred from the maternal blood (Maliepaard et al., 2001; Mao, 2008; Pollex et al., 2008). BCRP is also localized at the apical surfaces of hepatocytes, kidney proximal tubule cells, and enterocytes (Maliepaard et al., 2001; Jonker et al., 2002). Additionally, it is expressed at the blood-testis barrier and the BBB (Cooray et al., 2002; Bart et al., 2004; Enokizono et al., 2008). Mouse Bcrp is expressed in similar types of tissues as humans, though to varying levels. For example, mouse Bcrp is more highly expressed in the kidneys than in the placenta (Tanaka et al., 2005).

The substrate specificity of BCRP transporter has a comparable overlap with that of the MDR1 transporter. Like MDR1, BCRP preferentially targets hydrophobic and lipophilic compounds with planar aromatic systems. Numerous chemotherapeutic agents as well as antiviral drugs are exported by BCRP (Rabindran et al., 1998; Jonker et al., 2005; Pan et al., 2007; Giri et al., 2008; Chen et al., 2009; Agarwal et al., 2010). In addition, several endogenous substrates of BCRP have been identified. For example, BCRP was implicated in the maintenance of heme homeostasis under hypoxia by transporting out porphyrins (Jonker et al., 2002; Susanto et al., 2008). BCRP inhibitors exhibit similar structural characteristics and can competitively interfere with the substrate binding. Alternatively, some BCRP inhibitors can inhibit general ATPase activity (Mao and Unadkat, 2015). The mouse Bcrp transporter was shown to have overlapping substrate and inhibitor preference with the human BCRP isoform (Bakhsheshian et al., 2013). A list of example BCRP substrates and inhibitors is included in Table 1.

Clinical Importance of BCRP. Along with MDR1, the BCRP transporter is a key determinant of the efficacy and/or toxicity of the compounds. In human embryonic kidney 293 (HEK) cells expressing BCRP with a reduced-function polymorphism (C421A), there was significantly higher intracellular accumulation of BCRP substrates, Hoechst 33342, and an antidiabetic agent glyburide compared with the HEK cells expressing wild-type BCRP (Bircsak et al., 2016). In Bcrp knockout pregnant mice, there were higher fetal concentrations as well as elevated fetal-to-maternal concentrations of glyburide compared with wild-type mice (Zhou et al., 2008). The importance of BCRP in regulating brain concentrations of chemicals has also been demonstrated in knockout mice. The brain concentration of dasatinib, a tyrosine kinase inhibitor, was significantly augmented in Mdr1a/1b/Bcrp triple knockout mice compared with Mdr1a/1b knockout mice, signifying the critical role of Bcrp transporter in limiting the penetration of dasatinib into the brain (Chen et al., 2009). Likewise, Bcrp knockout mice retain more A β , a pathologic peptide in Alzheimer Disease, in the brain compared with the wild-type mice, suggesting that BCRP also contributes to the clearance of A β (Do et al., 2012; Zhang et al., 2013). Collectively, this evidence points to BCRP as an important regulator of xenobiotic disposition and, consequently, tissue protection.

Transcriptional Regulation of BCRP. As observed with the *ABCB1* gene, several response elements are present in the *ABCG2* gene that enable recruitment of transcription factors and initiation of gene transcription. The *ABCG2* gene, located on chromosome 4q22, also has two promoters, upstream and downstream, that lead to different splicing in the 5' untranslated region (Bailey-Dell et al., 2001; Campbell et al., 2011). Transcripts with different forms of the 5' untranslated region contribute to the tissue-specific expression of BCRP. The downstream promoter, located at 18 kb upstream of ATG-containing exon, produces the major transcripts (Fig. 2). Therefore, the following discussion will focus on the downstream promoter. The *ABCG2* promoter, like the *ABCB1* promoter, lacks a TATA-box but contains multiple binding sites for Sp1 and AP2 transcription factors in proximity to the TSS (at -49 and -50 bp upstream of the TSS). A potential initiator sequence is also found within the *ABCG2* promoter (CCACTGC). An API binding site, CCAAT box, and additional Sp1 sites were also identified within -400 bp of the 5' flanking region. Analysis of the *ABCG2* promoter activity using deletion constructs revealed that the sequence up to -312 bp upstream from the TSS confers basal promoter activity. Furthermore, this study suggested the presence of positive regulatory element(s) between -1285 and -628 bp and negative regulatory element(s) between -628 and -312 bp upstream of the TSS (Bailey-Dell et al., 2001).

Several ligand-activated receptors have been implicated in the regulation of *ABCG2* transcription. Ee et al. (2004) identified a functional estrogen response element between -187 and -173 bp of the 5'-flanking region of *ABCG2*, which was shown to interact with the estrogen receptor to mediate *ABCG2* gene activation. Also, the sequences from -1285 to -628 bp and from -243 to -115 bp in the 5'-flanking region were critical for progesterone-activated BCRP transcription, suggesting the presence of two putative progesterone

response elements at these locations (Wang et al., 2008). A functional DRE recognized by AHR was also found near the *ABCG2* promoter (-194 to -190 bp) (Tan et al., 2010). Interestingly, the same study revealed that mouse *Abcg2* gene expression in mouse liver, mammary tissue, and intestinal carcinoma cell lines was not regulated by AHR activation. Indeed, the authors found that there were no conserved putative DREs between human *ABCG2* and mouse *Abcg2* genes. Additional response elements of xenobiotic-activated transcription factors, including the constitutive androstane receptor and peroxisome proliferator-activated receptor α and γ , were also found at distal locations in the *ABCG2* gene (Szatmari et al., 2006; Benoki et al., 2012; Hoque et al., 2012, 2015; Lin et al., 2017). Lastly, stress signals such as hypoxia and inflammation are also known to regulate BCRP expression (Krishnamurthy et al., 2004; Wang et al., 2010; Francois et al., 2017). In summary, the *ABCG2* gene, like *ABCB1*, contains binding sites for numerous transcription factors that can interact to regulate the rate and extent of transactivation.

Epigenetic Regulation by Histone Acetylation

Regulation of Histone Acetylation

Epigenetics is the regulation of gene expression that induces heritable changes without altering DNA sequence. This process of transcriptional modification has been implicated in the pathogenesis of various diseases, including cancer and neurologic disorders. There are three main mechanisms of epigenetic regulation: DNA methylation, small noncoding RNAs, and histone modifications. Modifications to histone proteins, including acetylation, methylation, phosphorylation, and ubiquitination, can either activate or suppress gene transcription by altering histone-DNA interactions and accessibility of the gene to transcription factors and transcriptional machinery (Allfrey et al., 1964; Pogo et al., 1966; Sung and Dixon, 1970; Lee et al., 1993; Li et al., 1993; Sun and Allis, 2002). The majority of histone modifications occur at the amino terminal tails of histones, which play a key role in stabilizing histone-DNA interactions (Allfrey et al., 1964; Sung and Dixon, 1970).

Histone acetylation is considered the most common and well-studied histone modification for the regulation of gene expression (Allfrey et al., 1964; Puerta et al., 1995; Kuo et al., 1998; Wang et al., 1998). This process occurs at lysine residues of histone amino terminal tails (Iwai et al., 1970; Zhang et al., 1998). Studies have established that histone acetylation enhances gene transcription by neutralizing the positive charge at the histone tails and decreasing histone affinity to the negatively charged backbone of the DNA. Consequently, the DNA sequence becomes more accessible for interaction with transcription factors (Sung and Dixon, 1970; Cary et al., 1982; Hong et al., 1993). However, evidence also suggests that histone acetylation generates specific docking surfaces for transcriptional activators without significantly altering the electrostatic charges of histones (Lee et al., 1993).

Histone acetylation is a dynamic process that is regulated by specific enzymes. HATs facilitate the addition of acetyl groups to lysine residues on histone tails to reduce their overall positive charge (Kuo et al., 1996; Wang et al., 1998). This results in the loss of tight electrostatic interactions between histones and DNA, transforming DNA into an open and relaxed state (Sung and Dixon, 1970; Cary et al., 1982; Hong et al., 1993). This conformation makes DNA more available to transcription factors and subsequently increases gene expression (Lee et al., 1993; Kuo et al., 1998; Wang et al., 1998). Human HATs are classified into three major subfamilies based on sequence similarity: Gcn5/PCAF, MYST, and p300/CBP (Kuo et al., 1996; Ogryzko et al., 1996; Yang et al., 1996; Wang et al., 1997; Clarke et al., 1999; Iizuka and Stillman, 1999). These subfamilies are distinct from each other in structural properties, substrate binding, and catalytic strategies.

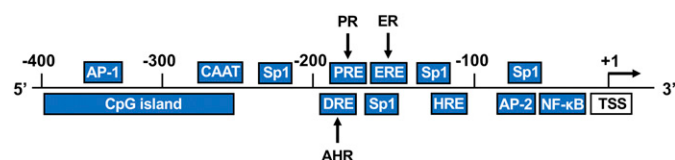


Fig. 2. Regulatory elements at the human *ABCG2* gene promoter. The location of key transcription factor binding sites in the human *ABCG2* promoter are shown as the number of base pairs relative to the transcriptional start site (TSS).

Histone deacetylases (HDACs) hydrolyze and remove acetyl groups on modified histone tails to reestablish tight interaction between histones and DNA (Inoue and Fujimoto, 1969; Hirschhorn et al., 1992; López-Rodas et al., 1993; Kuo et al., 1996, 1998; Taunton et al., 1996). DNA becomes tightly wrapped around histones, and chromatin resumes a dense structure to suppress gene expression. Even though these enzymes are called “histone” deacetylases, they also possess nonhistone targets such as p53, α -tubulin, and heat shock proteins that are involved in a variety of cellular processes (Juan et al., 2000; Vaziri et al., 2001; Hubbert et al., 2002; Bali et al., 2005). In fact, a phylogenetic study suggests that evolution of HDAC enzymes was earlier than that of histone proteins, therefore implying the possibility that the primary targets of HDAC enzymes are nonhistone proteins (Gregoret et al., 2004). Eighteen groups of HDACs are divided into different families and classes based on sequence and functional similarity (Rundlett et al., 1996; Taunton et al., 1996; Grozinger et al., 1999; Gregoret et al., 2004). Representative members of each class of HDAC are summarized in Table 2. A “classical” HDAC family, which requires zinc for its activity, includes classes I, II, and IV (Finnin et al., 1999; de Ruijter et al., 2003). Class III HDACs belong to a zinc-independent and nicotinamide adenine dinucleotide (NAD)-dependent sirtuin (SIRT) enzyme family (Imai et al., 2000; North and Verdin, 2004).

Class I includes HDACs 1 and 2, which are predominantly located in the nucleus, and HDACs 3 and 8, which have been shown to shuttle between the nucleus and cytoplasm (Bjerling et al., 2002; Johnson et al., 2002; Yang et al., 2002). Class I HDACs have intrinsic enzymatic activity to deacetylate all four types of core histones but to varying extents (Hassig et al., 1998; Hu et al., 2000; Johnson et al., 2002). Studies showed that these enzymes are present in different protein complexes, where they exert maximal enzymatic function and possess low activity when isolated alone without associated proteins (Heinzel et al., 1997; Laherty et al., 1997; Zhang et al., 1999; Wen et al., 2000). Class II can be further divided into class IIa, which includes HDACs 4, 5, 7, and 9, and class IIb, which includes HDACs 6 and 10. Class IIa HDACs are capable of shuttling between the nucleus and cytoplasm (Grozinger and Schreiber, 2000; Kao et al., 2000; McKinsey et al., 2000a,b; Fischle et al., 2001; Wang and Yang, 2001; Petrie et al., 2003; Harrison et al., 2010; Sugo et al., 2010). In contrast, HDAC6 functions primarily in the cytoplasm to regulate tubulin acetylation (Verdel et al., 2000; Hubbert et al., 2002). HDAC10, a relatively unknown HDAC that is found in both the nucleus and cytoplasm, was shown to play roles in transcriptional repression and regulation of cell cycle (Guardiola and Yao, 2002; Kao et al., 2002; Li et al., 2015). Early results suggest that class IIa HDACs do not exhibit intrinsic deacetylase capability on histones but instead carry out transcriptional repression via interaction with HDAC3 proteins (Wen et al., 2000; Fischle et al., 2001, 2002). However, findings have indicated that these HDAC enzymes do have

measurable deacetylase activities that are restricted to certain sets of yet undefined substrates (Lahm et al., 2007; Jones et al., 2008). Class IV contains a sole member, HDAC11, that is structurally different from both class I and II HDACs (Gao et al., 2002). The function of HDAC11 is the least studied in the “classical” HDAC family. Class III HDACs includes seven structurally distinct NAD-dependent SIRT enzymes, which have distinct subcellular localizations as listed in Table 2 (North et al., 2003; Michishita et al., 2005; Haigis et al., 2006; Mostoslavsky et al., 2006; Ahuja et al., 2007; Inoue et al., 2007; Scher et al., 2007; Tanno et al., 2007; Nakamura et al., 2008; Grob et al., 2009; Nakagawa et al., 2009; Nasrin et al., 2010; Iwahara et al., 2012; Kiran et al., 2013). SIRT enzymes can perform two enzymatic activities, deacetylase and mono ADP-ribosyltransferase, whose activities are closely linked to each other (Frye, 1999; Tanny et al., 1999; Imai et al., 2000; Landry et al., 2000a,b). These enzymes play roles in various important biologic processes, including the regulation of cell cycle, apoptosis, insulin secretion, and aging (Vaziri et al., 2001; Dryden et al., 2003; Howitz et al., 2003; Cohen et al., 2004; Motta et al., 2004; Moynihan et al., 2005).

Class I HDACs are ubiquitously expressed, except for HDAC8, which is more selectively found in smooth muscle cells (Caron et al., 2001; Waltregny et al., 2004). HDACs 1 through 3 are thought to be widely distributed throughout different regions of the brain (Uhlén et al., 2005, 2015; Broide et al., 2007; Berglund et al., 2008; Lucio-Eterovic et al., 2008; Pontén et al., 2008; Anderson et al., 2015; Thul et al., 2017; Uhlen et al., 2017). Class II HDACs are also distributed widely but to varying extents in different tissues. For example, class IIa HDACs are more predominantly found in muscle and heart, whereas class IIb shows greater expression in liver and kidney (Fischle et al., 1999; Grozinger et al., 1999; Wang et al., 1999; Caron et al., 2001; Dressel et al., 2001; Kao et al., 2002). HDACs 4 and 5 are most highly expressed in the brain, and HDAC6 is abundantly found in cerebellar Purkinje cells (Uhlén et al., 2005, 2015; Broide et al., 2007; Southwood et al., 2007; Berglund et al., 2008; Pontén et al., 2008; Uhlen et al., 2010, 2017; Thul et al., 2017). HDAC11 was detected across a number of tissues, including brain, kidney, testes, and skeletal muscle (Gao et al., 2002; Broide et al., 2007). Each class III SIRT enzyme displays a distinct tissue expression profile (Afshar and Murnane, 1999; Frye, 1999; Onyango et al., 2002). Certain HDACs, including HDACs 4, 8, and 9, appear to be enriched more in tumor tissues than in normal somatic tissues; however, HDACs overall are similarly expressed between normal and tumor tissues, although the level can be largely variable between different tumor types (Caron et al., 2001; de Ruijter et al., 2003).

Modulators of HDAC Activity: HDAC Inhibitors

Because of the critical roles of HATs and HDACs in regulating transcription, the balance between these two classes of enzymes is tightly controlled. Imbalance in the activities of HATs and HDACs can

TABLE 2
Classes of HDACs and their subcellular localizations

| Family | Class | Members | Primary Location |
|---------------------------------|-------|------------|--------------------------|
| Classic, zinc-dependent (HDACs) | I | 1, 2 | Nucleus |
| | | 3, 8 | Nucleus and cytoplasm |
| | IIa | 4, 5, 7, 9 | Nucleus and cytoplasm |
| | | 6 | Cytoplasm |
| Sirtuins, NAD-dependent (SIRTs) | IV | 10 | Nucleus and cytoplasm |
| | | 11 | Nucleus and cytoplasm |
| | III | 1, 2 | Nucleus and cytoplasm |
| | | 3 | Nucleus and mitochondria |
| | | 4, 5 | Mitochondria |
| | | 6 | Nucleus |
| | | 7 | Nucleolus |

lead to aberrant gene expression and dysregulation of key cellular processes including cell proliferation as reviewed in numerous papers (Sommer et al., 1997; Giles et al., 1998; Kruhlak et al., 2001; Timmermann et al., 2001; Lehrmann et al., 2002; Groth et al., 2007; Haberland et al., 2009). This can consequently contribute to the pathogenesis of diseases such as cancer (Petrij et al., 1995; Cress and Seto, 2000; Choi et al., 2001; Murata et al., 2001; Seligson et al., 2005; Haberland et al., 2009). Therefore, these histone-modifying enzymes have been identified as attractive therapeutic targets. Inhibitors of HATs and HDACs have been developed and actively investigated for their ability to reverse disease-associated epigenetic modifications. In particular, HDAC inhibitors have been extensively studied as potential therapy for cancer and neurologic and psychiatric diseases (Hockly et al., 2003; Simonini et al., 2006; Tsankova et al., 2006; Vecsey et al., 2007; Coiffier et al., 2012; Harrison et al., 2015; Schmitt et al., 2016; Zhou et al., 2018). Indeed, some HDAC inhibitors are already approved by the Food and Drug Administration (FDA) for treatment of lymphoma and epilepsy and described below [USFDA, 1978, p.; Koch-Weser and Browne, 1980, p.; Thompson, 2006, p.; Yang, 2011, p.; Depakote divalproex sodium, 1983; Istodax romidepsin, 2009; Package insert].

HDAC inhibitors are a group of structurally diverse compounds that block the activities of HDAC enzymes with varying selectivity and potency. Largely, these compounds can be divided into two groups: classic HDAC inhibitors that target classic zinc-dependent HDAC enzymes and SIRT inhibitors that act on class III SIRT NAD-dependent enzymes. SIRT inhibitors have been less extensively investigated than classic HDAC inhibitors, and the interactions between SIRT inhibitors and efflux transporters have not been identified yet. Thus, the remainder of this review will focus on classic HDAC inhibitors, generally referred to as “HDAC inhibitors.” HDAC inhibitors inactivate HDAC enzymes by competitively inhibiting the binding of zinc within active sites (Finnin et al., 1999). Inhibition of HDACs enhances acetylation of histones and binding of transcription factors to upregulate the expression of multiple genes (Riggs et al., 1977; Vidali et al., 1978; Yoshida et al., 1990; Van Lint et al., 1996; Butler et al., 2000; Glaser et al., 2003). In particular, HDAC inhibitors have been shown to upregulate various tumor suppressor and proapoptotic genes to prevent cancer cell proliferation (Davis et al., 2000; Kim et al., 2001; Peart et al., 2003; Nakata et al., 2004). Consequently, pharmacological inhibitors of HDACs were initially investigated for their potential as anticancer drugs. This research led to the approval of HDAC inhibitors for the treatment of lymphomas, namely, romidepsin (Istodax), suberoylanilide hydroxamic acid or vorinostat (SAHA, Zolinza), belinostat (Belinostat), and panobinostat (Farydak) for multiple myeloma [Belinostat, 2014; Farydak panobinostat, 2015; Istodax romidepsin, 2009; Package insert].

The disruptive effects of HDAC inhibitors can be reversed, and normal cells are more capable than cancer cells to repair or compensate for the molecular changes induced by HDAC inhibitors (McKnight et al., 1980; Richon et al., 1998; Deroanne et al., 2002; Xu et al., 2007). Therefore, HDAC inhibitors have relatively less pharmacological

impact on normal tissues (Burgess et al., 2004; Insinga et al., 2005; Ungerstedt et al., 2005; Xu et al., 2007). Indeed, mice with a genetic deletion of a single isoform HDAC may not exhibit significant phenotypic or pathologic changes, possibly because of compensation by other HDAC enzymes (Montgomery et al., 2007; Zhang et al., 2008). Yet, there are still concerns for undesirable effects of HDAC inhibitors because these compounds are nonspecific, affecting multiple HDACs at the same time (Khan et al., 2008; Bradner et al., 2010). For example, SAHA is a pan-HDAC inhibitor that targets both class I and II HDAC enzymes. It is challenging to develop a highly selective HDAC inhibitor because different isoforms of HDAC enzymes, especially those in the same class, share highly homologous active sites and catalytic mechanisms (Richon et al., 1998; Miller et al., 2003). More extensive investigation regarding the crystalline structures as well as enzymatic mechanisms of HDACs identified few differences between various isoforms and subsequently led to the development of more specific inhibitors that selectively act on only two or three isoforms (Vannini et al., 2004; Wang et al., 2005; Guo et al., 2007; Ficner, 2009; Bürli et al., 2013). For example, romidepsin is a class I HDAC inhibitor that is particularly selective for HDACs 1 and 2 (Furumai et al., 2002). Such difference in target specificity may contribute to the potency, relative toxicity, and/or off-target effects of HDAC inhibitors as well as particular molecular changes elicited by these agents.

Classification of HDAC Inhibitors. HDAC inhibitors can be classified based on the properties of their core chemical structures (Miller et al., 2003). The structural characteristics that divide HDAC inhibitors into different classes are outlined in Table 3. Structural properties of HDAC inhibitors are important determinants of their selectivity as well as potency. The basic pharmacophore of classic HDAC inhibitors generally consists of three main elements: 1) the zinc-binding domain that contains a functional group binding to the active site of HDACs, 2) surface recognition domain that allows for effective interaction of inhibitors with the catalytic pocket of enzymes, and 3) a chain linker domain (Miller et al., 2003). Variation in this core structure affects the inhibitory mechanisms and efficacy of HDAC inhibitors.

Hydroxamates comprise the largest class of HDAC inhibitors and include three FDA-approved HDAC inhibitors, SAHA, belinostat, and panobinostat (Richon et al., 1998; Plumb et al., 2003; Qian et al., 2006; Thompson, 2006; Poole, 2014; Laubach et al., 2015; Lee et al., 2015). The primary functional group of these inhibitors is a hydroxamic acid, which directly interacts with the zinc ion to inhibit the catalytic action of HDAC enzymes. The chain linker domain in hydroxamates can be linear or cyclic (Yoshida et al., 1990; Richon et al., 1998; Miller et al., 2003). They are among the most potent inhibitors. The potency of hydroxamates, as assessed by the IC_{50} on purified HDACs, is in the nanomolar to micromolar range, and each individual compound in this class possesses different ranges of potency and selectivity (Yoshida et al., 1990; Richon et al., 1998; Furumai et al., 2002; Plumb et al., 2003). Generally, hydroxamates are pan-HDAC inhibitors that target both class I and II HDAC enzymes. Trichostatin A (TSA) and SAHA exhibit

TABLE 3
Classes of HDAC inhibitors and their targets

| Class | Examples | HDAC Targets | Potency Range ^a |
|-------------------------|--|-----------------|----------------------------|
| Hydroxamates | SAHA, Trichostatin A (TSA), Belinostat, Panobinostat | Class I and IIb | nM–μM |
| Short chain fatty acids | Valproic Acid (VPA), Sodium Butyrate, Phenylbutyrate | Class I and IIa | mM |
| Cyclic peptides | Romidepsin, Apicidin | Class I | nM |
| Benzamides | MS-275, Mocetinostat, CI-994 | Class I | μM |

^aThis potency range represents general IC_{50} values (50% inhibitory concentrations) for purified HDACs as determined by HDAC activity assays.

greater potency to class I and IIb HDACs than considered to be either a substrate or an inhibitor to class IIa HDACs (Khan et al., 2008; Bradner et al., 2010; Kilgore et al., 2010). Belinostat and panobinostat are considered to be substrates (but not inhibitors) of MDR1, whereas SAHA is generally not considered to be either a substrate or an inhibitor of MDR1 [Beleodaq belinostat, 2014; Farydak panobinostat, 2015; Package insert].

Cyclic peptides are also highly potent HDAC inhibitors that contain functional groups directly interacting with the zinc ion in the catalytic site. These inhibitors are characterized by a surface recognition domain that contains a macrocycle with hydrophobic amino acids (Kijima et al., 1993; Darkin-Rattray et al., 1996; Nakajima et al., 1998; Furumai et al., 2002; Miller et al., 2003). Cyclic peptides are generally known as class I HDAC inhibitors, but there is a large structural dissimilarity within this class of inhibitors, contributing to variable selectivity among them. For example, romidepsin is more selective toward HDACs 1 and 2, whereas apicidin is more potent against HDACs 2 and 3 (Furumai et al., 2002; Matsuyama et al., 2002; Khan et al., 2008; Bradner et al., 2010). Romidepsin is also recognized as a substrate of MDR1 [Istodax (romidepsin), 2009].

In contrast to the previous two classes of HDAC inhibitors, short chain fatty acids (SCFAs) are relatively weak inhibitors with IC_{50} concentrations using purified HDAC enzymes largely in the millimolar range of concentrations (Boffa et al., 1978; Candido et al., 1978; Göttlicher et al., 2001; Phiel et al., 2001; Khan et al., 2008). This relatively weak potency is attributed to suboptimal structural characteristics of SCFAs. First, the inhibitory action of these compounds does not involve an effective interaction with the zinc ion, which is a central component of HDAC activity (Lu et al., 2004). In addition, SCFAs do not possess surface recognition domains that enable tight binding of HDAC inhibitors to target enzymes (Miller et al., 2003). Together, these properties result in the weak potency of SCFAs. However, unlike hydroxamates and cyclic peptides, which can have limited access to brain, SCFAs exhibit good penetration into the brain, making them attractive therapeutic options for brain diseases (Cornford et al., 1985; Phiel et al., 2001; Shin et al., 2011; Hanson et al., 2013). Indeed, valproic acid (VPA) is an FDA-approved SCFA HDAC inhibitor indicated for epilepsy and psychiatric mania (Lewis, 1978; Brown, 1979; Guay, 1995). VPA is not reported to be a substrate or an inhibitor of MDR1 [Depakote (divalproex sodium), 1983].

Benzamides including MS-275 (entinostat) are also brain-penetrant HDAC inhibitors that are more specific and potent than SCFAs (Suzuki et al., 1999; Park et al., 2004; Eyüpoglu et al., 2006; Simonini et al., 2006; Boissinot et al., 2012). A key structural feature of these compounds is a 2' amino/hydroxyl group in benzanilide (Suzuki et al., 1999; Miller et al., 2003). Benzamides selectively target class I HDACs and cross the BBB effectively (Hu et al., 2003; Eyüpoglu et al., 2006; Simonini et al., 2006; Chou et al., 2008; Khan et al., 2008; Boissinot et al., 2012). Also, clinical trials showed that MS-275 had a much longer half-life (over 30 hours) than other classes of HDAC inhibitors (Ryan et al., 2005; Acharya et al., 2006; Kummur et al., 2007). However, benzamide HDAC inhibitors are generally less potent than hydroxamates or cyclic peptides (Park et al., 2004; Beckers et al., 2007; Boissinot et al., 2012).

Clinical Utility of HDAC Inhibitors. Because of their ability to modify the expression of genes and proteins, HDAC inhibitors have been used as drugs to correct aberrant molecular pathways in various diseases, such as cancer and neurologic disorders. Three HDAC inhibitors, SAHA, romidepsin, and belinostat, have been approved by the FDA in 2006, 2009, and 2014, respectively, for treatment of T-cell lymphomas [Beleodaq belinostat, 2014; Istodax romidepsin, 2009; Package insert]. Panobinostat was approved in 2015 for treatment of

multiple myeloma [Farydak (panobinostat), 2015]. HDAC inhibitors induce antitumor effects by: 1) inducing the expression of tumor suppressors including p53 and p21, promoting cell cycle arrest, and inhibiting cell proliferation (Davis et al., 2000; Richon et al., 2000; Kim et al., 2001); 2) activating extrinsic and intrinsic apoptosis by upregulating death receptors and proapoptotic proteins (Kawagoe et al., 2002; Nakata et al., 2004; Insinga et al., 2005); and 3) inhibiting angiogenesis through induction of antiangiogenic genes and repression of proangiogenic genes (Kim et al., 2001; Deroanne et al., 2002; Kwon et al., 2002). Clinical studies are being actively performed to test the effects of HDAC inhibitors in other types of cancer, including glioblastoma (Galanis et al., 2009; Bailey et al., 2016; Kusaczuk et al., 2016; Choi et al., 2017; Barneh et al., 2018; Monga et al., 2018).

Studies also indicate the therapeutic potential of HDAC inhibitors in a wide array of neurologic diseases, including stroke, Parkinson Disease, Alzheimer Disease, and Huntington Disease, as well as psychiatric diseases, including depression and schizophrenia (Hockly et al., 2003; Chen et al., 2006; Faraco et al., 2006; Kontopoulos et al., 2006; Simonini et al., 2006; Tsankova et al., 2006; Kim et al., 2007; Fontán-Lozano et al., 2008; Qing et al., 2008; Suzuki et al., 2009; Xuan et al., 2015). As discussed in the previous section, VPA is FDA-approved to treat epilepsy and psychiatric mania (Lewis, 1978; Brown, 1979; Guay, 1995). There are different pathways by which HDAC inhibitors can ameliorate these brain diseases: 1) eliciting anti-inflammatory responses by decreasing proinflammatory mediators, including interleukin 6, cyclooxygenase-2, and tumor necrosis factor- α (Qi et al., 2004; Sinn et al., 2007); 2) reducing the synthesis or enhancing the degradation of neurotoxic proteins and factors, such as A β and α -synuclein (Kawaguchi et al., 2003; Kontopoulos et al., 2006; Qing et al., 2008; Xuan et al., 2015); and 3) exerting neuroprotection via induction of neurotrophic factors (Chen et al., 2006; Wu et al., 2008). Because of their selective inhibition of class I HDACs and suitable brain penetration, benzamide HDAC inhibitors are being actively investigated as treatments for central nervous system disorders (Eyüpoglu et al., 2006; Simonini et al., 2006; Covington et al., 2009; Zhang and Schluesener, 2013). In addition to these disease states, there are other conditions such as endometriosis, somatic cell nuclear transfer, inflammation, and pulmonary disorders in which HDAC inhibitors could be useful, indicating a broad applicability of these compounds across clinical settings (Plumb et al., 2003; Rybouchkin et al., 2006; Wu et al., 2007).

Histone Acetylation in the Regulation of Efflux Transporters

One challenge for the effective use of HDAC inhibitors to treat cancer has been their ability to alter the expression and/or activity of ABC efflux transporters, which are often the main mediators of multidrug resistance in tumors. In 1989, Mickley et al. showed that sodium butyrate upregulated both the mRNA and protein expression of MDR1 in SW620 and HCT-15 colon carcinoma cells. Increased MDR1 expression in HCT-15 cells was accompanied by enhanced efflux of MDR1-transported chemotherapeutic drugs, highlighting the clinical importance of this observation. Further studies were performed in an array of cancer cell lines to evaluate the effects of various HDAC inhibitors on the expression and activity of MDR1 as well as other ABC transporters, including BCRP. In most cell lines tested, HDAC inhibitors led to an upregulation of transporter expression, though at varying concentrations and time points. Also, the same chemical exerted differential effects depending on the cell type being tested. Subsequent studies explored the mechanisms underlying the induction of efflux transporters by HDAC inhibitors. The results of mechanistic studies

TABLE 4
Effects of HDAC inhibitors on the regulation of MDR1 across various cell types

| Human cells | | | | | |
|-------------|--|-------------|--------------|-------------|---|
| Organ | Cells | HDACi Class | Agent | Observation | References |
| Blood | CEM-Bcl2 CEM-CCRF CEM-A7R (R) KG1a | HA | TSA | ↑[m] ↔[p] | Baker et al., 2005 |
| | | HA | TSA | ↔[m] | El-Osta et al., 2002 |
| | | HA | TSA | ↑[m] | El-Osta et al., 2002 |
| | | HA | TSA | ↑[m] | Eyal et al., 2006; Hauswald et al., 2009; Fuchs et al., 2010 |
| | | SCFA | SAHA | ↑[m] | |
| | | | VPA | ↑[m] ↑[a] | |
| | | | Butyrate | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | HL-60 | HA | TSA | ↑[m] | Hauswald et al., 2009 |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| | CMK | HA | TSA | ↑[m] | Hauswald et al., 2009 |
| | | SCFA | VPA | ↑[m] ↑[a] | |
| | | | Butyrate | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | K562 | HA | TSA | ↑[m] ↔[a] | Xiao et al., 2005; Hauswald et al., 2009; Balaguer et al., 2012 |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| | K562 (R) PEER | CP | Romidepsin | ↑[m] | Balaguer et al., 2012 Valdez et al., 2016 |
| | | HA | TSA | ↓[m] ↑[a] | |
| | | HA | SAHA | ↑[p] | |
| | | | Panobinostat | ↑[m] ↑[p] | |
| | | | Belinostat | ↓[p] | |
| | | | Romidepsin | ↑[m] ↑[p] | |
| | | CP | | ↑[a] | |
| | | | | ↑[p] | |
| | MV4-11 | BZ | LMK-235 | ↔[p] | Valdez et al., 2016 |
| | | HA | Panobinostat | ↔[p] | |
| | | CP | Romidepsin | ↔[p] | |
| | | CP | | ↑[a] | |
| | CMK DAUDI | SCFA | VPA | ↑[m] ↑[a] | Hauswald et al., 2009 Valdez et al., 2016 |
| | | HA | Panobinostat | ↑[p] | |
| | | CP | Romidepsin | ↑[p] | |
| | | CP | Romidepsin | ↑[m] | |
| | NB4 Leukemia primary mononuclear cells | CP | Romidepsin | ↑[m] | Tabe et al., 2006 Odenike et al., 2008, 2015; Hauswald et al., 2009; Gojo et al., 2013 |
| | | HA | SAHA | ↑[m] ↔[p] | |
| | | | | ↔[a] | |
| | | | | ↑[m] | |
| | | SCFA | Belinostat | ↑[m] | |
| | | | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] ↑[a] | |
| | | | Romidepsin | ↑[m] | |
| | Lymphoma primary mononuclear Cells | CP | Romidepsin | ↔/↑[m] ↑[p] | Robey et al., 2006; Bates et al., 2010; Valdez et al., 2016 |
| | | CP | Romidepsin | ↔/↑[m] ↑[p] | |
| Brain | SF295 | HA | SAHA | ↑[m] | To et al., 2008, 2011 |
| | | CP | Panobinostat | ↑[m] | |
| | | | Romidepsin | ↑[m] | |
| | | CP | Apicidin | ↔[m] | |
| | A172 and U87 hCMEC/D3 | HA | TSA | ↑[m] ↑[p] | Kim et al., 2009 You et al., 2019b |
| | | | SAHA | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | | SCFA | VPA | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | | | Butyrate | ↔[m] ↔[p] | |
| | | CP | Apicidin | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | | | Romidepsin | ↔[m] ↔[p] | |
| | | | | ↑[m] ↑[a] | |
| Breast | MCF-7 | HA | TSA | ↑[m] ↑[a] | Xiao et al., 2005; To et al., 2008; Balaguer et al., 2012; Toth et al., 2012 |
| | MCF-7 (R) | CP | Romidepsin | ↑[m] | |
| Cervix | HeLa | HA | TSA | ↔/↓[m] | Balaguer et al., 2012; Toth et al., 2012 Kim et al., 2008, 2009; Huo et al., 2010 |
| | | | SAHA | ↑[m] | |
| | | | VPA | ↑[m] | |
| | | SCFA | Butyrate | ↑[m] | |
| | | CP | Apicidin | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | | BZ | MS-275 | ↑[m] | |
| | | | Apicidin | ↑[m] | |
| | SiHa | CP | Apicidin | ↑[m] | Kim et al., 2009 |

(continued)

TABLE 4—Continued

| Human cells | | | | | |
|-------------|-----------------------|--------------|--------------|-------------|---|
| Organ | Cells | HDACi Class | Agent | Observation | References |
| Colon | KB ^a | HA | TSA | ↔[m] | Kim et al., 2008, 2009 |
| | | | SAHA | ↔[m] | |
| | | SCFA | VPA | ↔[m] | |
| | | | Butyrate | ↔[m] | |
| | | CP | Apicidin | ↔[m] | |
| | KB (R) ^a | BZ | MS-275 | ↔[m] | Kim et al., 2011 |
| | | HA | TSA | ↔[m] | |
| | | | SAHA | ↔[m] | |
| | | CP | Apicidin | ↔[m] | |
| | | BZ | MS-275 | ↔[m] | |
| | SW620 | HA | TSA | ↑[m] ↑[p] | Bates et al., 1992; Frommel et al., 1993; Morrow et al., 1994; Jin and Scotto, 1998; Baker et al., 2005; Eyal et al., 2006; Robey et al., 2006; Gomez-Martinez et al., 2007; To et al., 2008, 2011; Pasvanis et al., 2012 |
| | | | | ↔[a] | |
| | | | SAHA | ↑[m] | |
| | | Panobinostat | | ↑[m] | |
| | | SCFA | VPA | ↑[p] | |
| | | | Butyrate | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | | CP | Romidepsin | ↑[m] ↑[p] | |
| | | | | ↑[a] | |
| | LoVo | HA | TSA | ↔[m] | |
| Colon | Colo320HSR | HA | TSA | ↑[m] | Lee et al., 2008 |
| | HCT-116 | HA | TSA | ↑[m] ↑[p] | Lee et al., 2008; Xu et al., 2012; Wang et al., 2019 |
| | | | SAHA | ↑[m] ↑[p] | |
| | HCT-8 | HA | TSA | ↔[m] | Lee et al., 2008; Xu et al., 2012 |
| | | | SAHA | ↑[m] ↑[p] | |
| | HCT-15 | SCFA | Butyrate | ↑[m] ↑[p] | Frommel et al., 1993 |
| | | | | ↑[a] | |
| | DLD-1 | HA | TSA | ↑[m] | Lee et al., 2008; Kim et al., 2009 |
| | | CP | Apicidin | ↑[m] | |
| | | SCFA | Butyrate | ↑[m] ↑[p] | Frommel et al., 1993 |
| | | | | ↑[a] | |
| | S1 | HA | SAHA | ↑[m] | To et al., 2008, 2011 |
| | | | Panobinostat | ↑[m] | |
| | | CP | Romidepsin | ↑[m] | |
| | SNU-C1 | HA | TSA | ↑[m] | Lee et al., 2008 |
| | SNU-C4 | HA | TSA | ↔[m] | Lee et al., 2008 |
| | Caco-2 | SCFA | Butyrate | ↑[m] ↑[p] | Pasvanis et al., 2012; Yan et al., 2017 |
| | | | | ↑[a] | |
| Colon | HT-29 | HA | TSA | ↑[m] ↔[p] | Gómez-Martínez et al., 2007 |
| | | | | ↔[a] | |
| | HT-29 (R) | HA | TSA | ↑[m] ↔[p] | Gómez-Martínez et al., 2007 |
| | | | | ↔[a] | |
| Kidney | 108, 121 | CP | Romidepsin | ↑[m] ↑[a] | Robey et al., 2006 |
| | 127, 143 | CP | Romidepsin | ↔[m] | Robey et al., 2006 |
| Liver | SK-Hep-1 | HA | SAHA | ↑[m] | Hauswald et al., 2009 |
| | HepG2 | SCFA | VPA | ↑[m] | Cervený et al., 2007 |
| Lung | H69 | HA | TSA | ↑[m] | El-Khoury et al., 2007 |
| | | SCFA | Butyrate | ↑[m] | |
| Lung | H69 (R) | HA | TSA | ↓[m] | El-Khoury et al., 2007 |
| | | SCFA | Butyrate | ↓[m] | |
| Colon | A549 | HA | TSA | ↑[m] ↔/↑[p] | Kaewpiboon et al., 2015; Wang et al., 2019 |
| | | | SAHA | ↑[m] ↑[p] | Wang et al., 2019 |
| | | SCFA | Butyrate | ↑[m] ↑[p] | Zhao et al., 2018 |
| | A549 (R) | HA | TSA | ↓[m] ↓[p] | Kaewpiboon et al., 2015 |
| | H460 | CP | Romidepsin | ↑[m] | To et al., 2008 |
| | H1299 | SCFA | Butyrate | ↑[m] ↑[p] | Zhao et al., 2018 |
| Nerves | SK-mes-1 | SCFA | Butyrate | ↑[m] ↑[p] | Zhao et al., 2018 |
| | SK-N-SH cells | HA | SAHA | ↔[p] | Lautz et al., 2012 |
| Nerves | SK-N-SH cells (R) | HA | SAHA | ↓[m] ↓[p] | Lautz et al., 2012 |
| | SK-N-Be(2)C cells | HA | SAHA | ↔[p] | Lautz et al., 2012 |
| Nerves | SK-N-Be(2)C cells (R) | HA | SAHA | ↓[m] ↓[p] | Lautz et al., 2012 |
| | | | | | |
| Ovary | IGROV1 | HA | TSA | ↑[m] | Xiao et al., 2005; Yatouji et al., 2007 |
| | | CP | Romidepsin | ↑[m] | |
| Pancreas | OC3/P (R) | HA | SAHA | ↓[m] | Liu et al., 2014 |
| | IMIM-PC-1 | HA | TSA | ↑[m] ↔[p] | Balaguer et al., 2012 |
| | | | | ↔[a] | |

(continued)

TABLE 4—Continued

| Human cells | | | | | |
|--------------|------------------------------------|-------------|-------------|---------------------------|-----------------------|
| Organ | Cells | HDACi Class | Agent | Observation | References |
| Placenta | IMIM-PC-2 | HA | SAHA TSA | ↑[m] ↑[m] ↔[p] ↔[a] | Balaguer et al., 2012 |
| | RWP-1 | HA | SAHA TSA | ↑[m] ↑[m] ↔[p] ↔[a] | Balaguer et al., 2012 |
| | HS766T | HA | SAHA TSA | ↑[m] ↑[m] | Balaguer et al., 2012 |
| | PANC-1 | HA | TSA | ↑[m] | Balaguer et al., 2012 |
| | BeWo choriocarcinoma | HA | TSA | ↑[m] ↑[p] | Duan et al., 2017a |
| | JAR choriocarcinoma | HA | SAHA | ↑[m] ↑[p] | Duan et al., 2017a |
| | | HA | TSA | ↑[m] ↑[p] | |
| | Prostate | HA | SAHA | ↑[m] ↑[p] | Henrique et al., 2013 |
| | | HA | TSA | ↑[m] ↑[p] | |
| | | HA | TSA | ↑[m] ↑[p] | |
| | | HA | TSA | ↑[m] ↑[p] | |
| Stomach | 22RV1 | HA | TSA | ↑[m] | Henrique et al., 2013 |
| | SNU-1, 16, 216, 601, 638, 668, 719 | HA | TSA | ↑[m] | Lee et al., 2008 |
| | SNU-5 | HA | TSA | ↔[m] | Lee et al., 2008 |
| Thyroid | SNU-484 | HA | TSA | ↓[m] | Lee et al., 2008 |
| | 8505C | SCFA | Butyrate | ↑[m] | Massart et al., 2005 |
| | FTC 238 | SCFA | Butyrate | ↑[m] | Massart et al., 2005 |
| Animal cells | | | | | |
| Species | Tissue/Cells | HDACi Class | Agent | Observation | References |
| Dog | Leukemia GL-1 cells | HA | TSA | ↑[m] | Tomiyasu et al., 2014 |
| Rat | Lymphoma CLBL-1 cells | HA | TSA | ↑[m] | Tomiyasu et al., 2014 |
| | Hepatoma D12 cells | HA | TSA | Mdr1a ↓[m] Mdr1b ↑[m] | Sike et al., 2014 |
| | Hepatoma D12 cells (R) | HA | TSA | Mdr1a ↓[m] Mdr1b ↑[m] | Sike et al., 2014 |
| | | | | Mdr1a ↑[m] Mdr1b ↑[m] | |
| | Hepatoma H4IIE cells | SCFA | VPA | Mdr1a ↑[m] Mdr1b ↑[m] | Eyal et al., 2006 |
| | | | | Mdr1b ↑[m] | |

a, activity; BZ, benzamides; CP, cyclic peptides; HA, hydroxamic acid; HDACi, HDAC inhibitor; m, mRNA; p, protein; (R), drug-resistance form of cell line; SAHA, suberoylanilide hydroxamic acid; SCFA, short chain fatty acids; TSA, Trichostatin A; VPA, valproic acid.

^aThe authors misidentified these cell lines in their study as oral cancer cells.

point to roles for histone acetylation in regulating ABC transporters. Currently, there are limited findings on the regulation of transporters by HDAC inhibitors in noncancerous cells.

Effects of HDAC Inhibitors on the MDR1 Transporter

The effects of HDAC inhibitors on the regulation of the MDR1 transporter in over 60 different cancer and noncancer cell lines are summarized in Table 4. Overall, the study results indicate that HDAC inhibitors largely upregulate the expression and/or activity of the MDR1 but often in a chemical-specific and a cell type-specific manner. HDAC inhibitors exert their ability to upregulate MDR1 at concentration ranges that correlate with HDAC IC₅₀ ranges (Table 3), as determined using purified HDAC activity assays (Boffa et al., 1978; Göttlicher et al., 2001; Furumai et al., 2002; Miller et al., 2003).

Hydroxamic Acids. Trichostatin A (TSA), a hydroxamate HDAC inhibitor, increased mRNA expression of MDR1 at concentrations ranging from 0.132 to 5 μ M in a wide array of human cell lines, including cancerous cells of colon, stomach, pancreas, prostate, lung, breast, cervix, ovary, bone marrow, and lymphoid organs. In RWP-1 and PANC-1 pancreatic cancer cells, 1 μ M TSA induced MDR1 mRNA as early as 3 hours after treatment, whereas the induction was not observed until later time points in other pancreatic cancer cells such as IMIM-PC-1, IMIM-PC-2, and HS766T (Balaguer et al., 2012). In colon cancer cells, TSA-mediated induction of MDR1 mRNA was observed starting

at 6 hours after the treatment but at lower concentrations (0.1–0.5 μ M) than in pancreatic cancer cells (Jin and Scotto, 1998; Baker et al., 2005; Gómez-Martínez et al., 2007; Lee et al., 2008; Wang et al., 2019).

In other human cancer cells, TSA altered MDR1 mRNA levels generally by 24 hours, although there were some exceptions. For example, TSA caused more than a threefold increase in MDR1 mRNA at 0.33 μ M in HeLa cervical adenocarcinoma cells, whereas it did not alter MDR1 mRNA in HeLa contaminant carcinoma KB cells even at 10-fold higher concentration of 3 μ M (Kim et al., 2008, 2009, 2011; Huo et al., 2010). In BeWo and JAR choriocarcinoma cells, which are in vitro models of human placental trophoblasts, TSA exhibited a dose-dependent and time-dependent regulation of MDR1 expression. TSA upregulated MDR1 by 48 hours at lower concentrations (0.5 and 1 μ M) but by 24 hours when higher concentrations (3 and 5 μ M) were used. The level of MDR1 mRNA and protein returned to the baseline by 72 hours of treatment with TSA in JAR cells, denoting tight temporal regulation of this transporter (Duan et al., 2017a). Time-dependent reversal of MDR1 induction was also seen in human brain microvascular endothelial (hCMEC/D3) cells, an in vitro model of the human BBB, which is a highly regulated structure in the body. In hCMEC/D3 cells, TSA caused approximately twofold increase in MDR1 mRNA at 12 hours, which was largely attenuated by 24 hours (You et al., 2019b).

Induction of MDR1 mRNA by TSA translates into increased protein expression and/or enhanced transporter activity only in certain cell lines. For example, TSA increased MDR1 mRNA without affecting its protein

or function in human colon and pancreatic cancer cell lines, whereas both MDR1 mRNA induction and enhanced transport of the substrate doxorubicin were observed in MCF-7 breast cancer cells treated with TSA (Gómez-Martínez et al., 2007; Balaguer et al., 2012; Toth et al., 2012). The study by Gómez-Martínez et al. (2007) suggested that the differential upregulation of MDR1 protein by TSA could be due to the difference in MDR1 mRNA stability, which consequently affects the translation of MDR1 mRNA into protein (Gómez-Martínez et al., 2007). Therefore, we can infer that varying MDR1 mRNA products in different cell lines may contribute to cell type-specific responses to TSA. Interestingly, conflicting results were observed with hCMEC/D3 brain endothelial cells. Noack et al. (2016) showed that 0.33 μM TSA moderately altered MDR1 function, but not the protein expression, through increasing the cell-to-cell transfer of MDR1 protein. MDR1 intercellular transfer has been implicated in the acquisition of multidrug resistance in tumor cells (Levchenko et al., 2005). By contrast, a recent study demonstrated that the protein expression of MDR1 in hCMEC/D3 cells was significantly increased after 24 hours of treatment with 0.25 μM TSA, which was noted as the highest nontoxic concentration (You et al., 2019b).

Suberyolanilide hydroxamic acid (SAHA, Vorinostat, Zolinza), an FDA-approved hydroxamate HDAC inhibitor for cutaneous and peripheral T-cell lymphoma [Package insert], also exerted an ability to regulate efflux transporter expression in diverse types of human cells, including both cancerous and normal cells. In most cells tested, SAHA induced MDR1 mRNA and protein, but like TSA, SAHA also showed cell type-specific responses. For example, 0.2 μM SAHA was sufficient to upregulate MDR1 in HCT-8 ileocecal colorectal adenocarcinoma cells by 48 hours, whereas HCT-116 colorectal carcinoma cells required a higher concentration to achieve similar results (Xu et al., 2012). Like TSA, SAHA induced MDR1 mRNA in HeLa cells but not in KB cells (Kim et al., 2009, 2011). The average concentration at which SAHA upregulated MDR1 was slightly higher than TSA, as expected based on their relative IC_{50} concentrations obtained from purified HDAC enzyme inhibition studies. The ability to induce transporter expression was seen as early as 8 hours post-treatment in K562 chronic myelogenous leukemia cells, whereas longer exposures to SAHA enhanced MDR1 expression in other cell lines (Xiao et al., 2005; Hauswald et al., 2009). Similar to TSA, SAHA affects MDR1 expression in BeWo and JAR choriocarcinoma cells in a dose- and time-dependent manner (Duan et al., 2017a). Lower concentrations of SAHA (0.5 and 1 μM) could not induce MDR1 in BeWo cells even after 72 hours of exposure, whereas higher concentrations (3 and 5 μM) caused upregulation by 24–48 hours. In JAR cells, SAHA was able to induce MDR1 as early as 24 hours postexposure at 0.5, 1, 3, and 5 μM concentrations. However, as seen with TSA, SAHA-mediated MDR1 induction in JAR cells was absent at 72 hours of treatment. Likewise, MDR1 mRNA in hCMEC/D3 cells was shown to be significantly increased as early as 6 hours following exposure to 10 μM SAHA and then returned to the baseline level by 24 hours. In the same cells, the level of MDR1 protein, which has a longer half-life than MDR1 mRNA, remained elevated until 36 hours after SAHA treatment. Such protein upregulation translated into enhanced functional activity of MDR1, as indicated by reduced intracellular accumulation of Rhodamine 123, a fluorescent MDR1 substrate (You et al., 2019b).

The ability of SAHA to regulate MDR1 expression was also observed in a clinical study. Administration of escalating doses of SAHA for 4–7 days in patients ($n = 8$ paired samples) with relapsed or refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia, secondary AML, or chronic myelogenous leukemia resulted in notable MDR1 mRNA induction in the bone marrow or peripheral blood mononuclear cells of three patients (P values ranging from <0.001 to 0.057).

Interestingly, one patient, who had a significantly higher baseline MDR1 mRNA expression, experienced a significant reduction in MDR1 mRNA by SAHA treatment. Differential responses to SAHA may be due to an altered molecular environment in this patient with more resistant disease, as discussed in a later section of this review. Alternatively, this result suggests that HDAC inhibition does not always favor MDR1 upregulation and that baseline expression of MDR1 may determine the manner by which the HDAC inhibitor affects transcription of the *ABCB1* gene. Unlike changes in mRNA, no significant changes in protein level or activity of MDR1 were observed in the same patient group (Gojo et al., 2013). Future clinical studies with a larger number of subjects are desired to more clearly elucidate the MDR1 regulatory effects of SAHA in humans.

Likewise, belinostat (Beleodaq), also FDA-approved for lymphoma [Beleodaq (belinostat), 2014], caused an increase in MDR1 mRNA in bone marrow aspirate samples of AML patients receiving azacytidine (Odenike et al., 2015). In contrast, belinostat decreased the protein expression of MDR1 in PEER human T-cell acute lymphoblastic leukemia cells after 48 hours of treatment at 6 μM concentration (Valdez et al., 2016). Few studies have evaluated the in vitro effects of belinostat on transporter regulation, and further studies are necessary to better elucidate the ability of belinostat to modulate MDR1 expression. Panobinostat (Farydak), the most recently approved HDAC inhibitor indicated for multiple myeloma [Farydak (panobinostat), 2015], has also been assessed for its ability to modulate MDR1 in several human cancer cells, including SF295 glioblastoma cells (To et al., 2011; Valdez et al., 2016). Panobinostat is more potent in its ability to upregulate MDR1 compared with other hydroxamate-type inhibitors, with induction observed at nanomolar concentrations of panobinostat (15–150 nM) over a period of 9–48 hours after treatment (To et al., 2011; Valdez et al., 2016). In PEER leukemia cells, upregulation of MDR1 expression was reflected in enhanced activity as indicated by increased efflux of 3, 3'-diethyloxycarbocyanine iodide and daunorubicin, two known substrates of MDR1 (Valdez et al., 2016).

Overall, the studies reviewed in this section support that hydroxamate HDAC inhibitors could alter both the expression and the function of MDR1 in various cells, though at varying concentrations and time points. Each cell type may possess different genetic and transcriptomic characteristics or relative expression and activity of various HDAC isoforms, which can also affect the activity of the HDAC inhibitors. Evidence for potential in vivo modulation of MDR1 by hydroxamate HDAC inhibitors has also been presented. Together, these data indicate that the administration of hydroxamate HDAC inhibitors, several of which are clinically used, can lead to altered function of MDR1 transporter, which regulates the trafficking of numerous drugs.

Short Chain Fatty Acids. Short chain fatty acids (SCFAs) such as VPA and butyrates, which are less potent HDAC inhibitors, generally require millimolar concentrations to induce MDR1. In human leukemia cells, SCFAs enhanced both the expression and functional activity of MDR1 as early as 24 hours at concentrations ranging from 0.5 to 6 mM (Eyal et al., 2006; Hauswald et al., 2009; Fuchs et al., 2010). Also, in different lung cancer cell lines, 3 mM sodium butyrate significantly increased both mRNA and protein levels of MDR1 (Zhao et al., 2018). Similar to TSA and SAHA, VPA (0.3–5 mM) was able to modulate MDR1 expression and/or function in hCMEC/D3 brain endothelial cells (Noack et al., 2016; You et al., 2019b). However, 0.25 mM sodium butyrate, which was the highest nontoxic concentration in hCMEC/D3 cells, did not significantly alter the mRNA or protein expression of MDR1 in those cells. Yet, higher concentrations of sodium butyrate (0.5–3 mM) in other cancer cell lines, including thyroid and colon cancer cells, significantly increased the expression and/or activity of MDR1, suggesting that the modulatory effect on MDR1 by sodium butyrate in

hCMEC/D3 cells is likely concentration-dependent (Bates et al., 1992; Frommel et al., 1993; Morrow et al., 1994; Massart et al., 2005; Pasvanis et al., 2012; Yan et al., 2017; Zhao et al., 2018). But, overall, the effects of SCFAs were roughly similar across different cell lines tested. Furthermore, SCFAs were shown to induce Mdr1 mRNA in livers of male Sprague-Dawley rats following intraperitoneal doses of VPA and butyrate for 7 days (Eyal et al., 2006). Likewise, 7-day intraperitoneal treatment with VPA, a brain-penetrable HDAC inhibitor, significantly upregulated the Mdr1 protein in the striatum of C57BL/6 mice along with levels of acetylated histone H3K9/14 (You et al., 2019a). Such *in vivo* data extend the *in vitro* findings and suggest that SCFA HDAC inhibitors can alter MDR1 expression in normal healthy tissues as well as cancer cell lines.

Cyclic Peptides. Cyclic peptides, including apicidin and romidepsin, are highly potent regulators of MDR1 across diverse *in vitro* and *in vivo* systems. The highly selective nature of cyclic peptide HDAC inhibitors to preferentially target only a couple isoforms of HDACs may contribute to the potency of these inhibitors. Apicidin increased the mRNA and/or protein expression of MDR1 in DLD-1 human colon cancer cells, hCMEC/D3 human microvascular endothelial cells, and HeLa and SiHa cervical cancer cells at concentrations ranging from 0.1 to 3 μM (Kim et al., 2008, 2009; You et al., 2019b). In hCMEC/D3 cells, apicidin even led to an enhanced functionality of the MDR1 transporter, as measured by the extent of accumulation of Rhodamine 123, a MDR1 substrate (You et al., 2019b). However, apicidin did not alter MDR1 levels in KB cells or A172 and U87 glioblastoma cells, displaying selectivity in transporter regulation (Kim et al., 2008, 2009, 2011). By comparison, romidepsin upregulated both MDR1 expression and activity at concentrations as low as 1.85 nM in SW620 human colon cancer cells (Robey et al., 2006; To et al., 2008, 2011). In S1 colon cancer cells, the inhibitor also caused induction of MDR1 mRNA but at a higher concentration (9.25 nM) (To et al., 2008). Similarly, romidepsin increased the expression and activity of MDR1 in kidney cancer cell lines but only in a subset (Robey et al., 2006). Furthermore, unlike apicidin, romidepsin did not affect the MDR1 in hCMEC/D3 cells but induced the mRNA expression of MDR1 in SF295 human glioblastoma cells (To et al., 2008, 2011; You et al., 2019b). These results suggest that romidepsin also regulates the MDR1 transporter in a manner quite specific to each cell type.

The upregulatory effects of cyclic peptides on MDR1 regulation were also observed *in vivo*. Our recent study showed that apicidin is capable of altering the transport properties of the normal mouse brain (alongside increased levels of acetylated histone H3K9/14 protein) but in a region-specific manner (You et al., 2019a). A 7-day intraperitoneal injection of apicidin in C57BL/6 mice moderately, yet significantly, increased Mdr1 protein expression in the striatum but not in the cortex, the midbrain, or the hippocampus. Differences in baseline Mdr1 expression across the brain regions may have contributed to selective effects of apicidin. Alternatively, local uptake of apicidin may also differ and contribute to the region-specific pharmacodynamic effects. The extraction of apicidin from the blood may differ between brain regions and in turn affect its pharmacological activity, as noted by differences in the extent of histone acetylation, an indicator of HDAC inhibition. Finally, it is important to note that there are multiple cell types in the brain (endothelial cells, astrocytes, neurons, or microglia) and that apicidin-mediated Mdr1 upregulation could be specific to a certain cell type that may be differentially populated across brain regions.

The ability of romidepsin to regulate MDR1 expression has been assessed in clinical specimens. For example, romidepsin increased MDR1 mRNA in normal peripheral blood mononuclear cells of patients with lymphoma or leukemia up to 4 hours after treatment. In contrast, induction of MDR1 mRNA by romidepsin lasted for 24–48 hours

postdose in tumor samples from patients with lymphomas (Robey et al., 2006; Odenike et al., 2008; Bates et al., 2010). The area under the curve level of romidepsin (2.8 $\mu\text{M}\cdot\text{h}$) in patients after a 4-hour infusion at a 14-mg/m² dose was higher than the maximum plasma concentration (0.7 μM), suggesting that the tissue exposure of romidepsin may be higher than the concentration measured in the circulation [Istodax (romidepsin), 2009]. A potentially higher level of romidepsin in tissues may contribute to a longer upregulatory effect of romidepsin on MDR1 mRNA.

Collectively, the data presented in this section suggest that the ability of cyclic peptide HDAC inhibitors to regulate MDR1 is selective according to certain cell types but that this class of drugs is much more potent than other classes of HDAC inhibitors.

Divergent Responses in Drug-Resistant Cancer Cells. Interestingly, HDAC inhibitors exert divergent effects on MDR1 expression in drug-resistant cancer cell lines. For example, TSA, which upregulated MDR1 mRNA and functional activity in wild-type MCF-7 breast cancer cells, did not affect MDR1 mRNA in drug-resistant MCF-7 cells at comparable concentrations and treatment duration (Toth et al., 2012). In H69 lung cancer cells, the effects of TSA were even in an opposite direction in drug-resistant cells, causing significant reduction of MDR1 mRNA (El-Khoury et al., 2007). Like TSA, sodium butyrate increased MDR1 mRNA in wild-type H69 cells but decreased its expression in resistant cells (El-Khoury et al., 2007). Also, SAHA downregulated both the mRNA and protein expression of MDR1 in drug-resistant SK-N-SH and SK-N-BE(2)C neuroblastoma cells, but it caused no change in matching wild-type cells (Lautz et al., 2012). Overall, HDAC inhibitors appear to downregulate MDR1 in resistant cancer cells. Such differential effects may be related to: 1) a higher baseline MDR1 expression and function in the resistant cells compared with the corresponding wild-type, 2) active efflux potentially of some HDAC inhibitors in drug-resistant cells, and 3) an altered gene expression profile of the resistant cells that affects the pharmacological activity of HDAC inhibitors. Also, it is possible that effects of HDAC inhibitors on cell proliferation, which can indirectly affect the MDR1 levels, may vary between sensitive and resistant cancer cells.

Summary and Conclusion. Different classes of HDAC inhibitors are capable of upregulating the expression and/or activity of the MDR1 transporter, although there is selectivity and specificity in the responses. Important factors that likely impart specificity in HDAC inhibitor-mediated regulation of MDR1 include cell types and tissue origins, cellular and molecular environments, chemical's potency for inhibiting HDAC enzymes, the relative toxicity of the chemicals in different cell types, and the duration of chemical treatment. In general, hydroxamic acids, which are relatively potent pan-HDAC inhibitors targeting a wide range of HDAC isoforms, can alter the MDR1 expression and function in a wide variety of cells, though in different manners. Similarly, SCFAs were shown to influence MDR1 in various cell types, but the effects of these HDAC inhibitors may be limited because of their weak potency. In contrast, cyclic peptides demonstrated more potent and selective activity, possibly because of the selective HDAC enzyme targets of these compounds. All classes of HDAC inhibitors showed some potential for modulating MDR1 *in vivo*, although whether these responses are clinically relevant based on known pharmacokinetic exposures is unknown. Some of the divergent effects of HDAC inhibitors between studies may be simply due to different experimental conditions across laboratories. The relative efficiency and potency of HDAC inhibitors in different systems can be more clearly elucidated by conducting a comprehensive study assessing MDR1 modulation in different representative cell types (for example, cancerous vs. noncancerous cells, sensitive vs. resistant cancer cells, and immortalized vs. primary

cells) treated with HDAC inhibitors over the range of concentrations and treatment durations.

Effects of HDAC Inhibitors on the BCRP Transporter

Similar to the MDR1 transporter, BCRP can also be upregulated by HDAC inhibitors, although some diverging findings have been observed (Table 5). Different classes of HDAC inhibitors are able to induce BCRP mRNA in various human hematologic tumor cells, including KG1a, HL-60, CMK, and K562 leukemia cell lines, at similar concentrations and time points that induced MDR1 (Hauswald et al., 2009; Fuchs et al., 2010). In some cell lines, increases in mRNA expression translated into protein upregulation and enhanced efflux function. Like MDR1, the expression of BCRP in drug-resistant KB cells was resistant to modulation by HDAC inhibitors; neither SAHA nor apicidin were able

to alter BCRP transporter expression after 24 hours of treatment at increasing concentrations (Kim et al., 2011). In S1 colon carcinoma cells, BCRP mRNA levels, like MDR1, were induced by HDAC inhibitors (To et al., 2008, 2011). Furthermore, HDAC inhibitors upregulated BCRP protein expression and transport activity in S1 cells (To et al., 2011). Likewise, BCRP mRNA and protein levels as well as the functional activity were induced by VPA, a SCFA HDAC inhibitor, in a time- and concentration-dependent manner (Rubinchik-Stern et al., 2015). As discussed in the previous section, *ABCB1* and *ABCG2* promoter regions share some common features. Therefore, it is likely that shared molecular mechanisms are used by HDAC inhibitors in those cells in which MDR1 and BCRP transporters are similarly regulated.

BCRP upregulation by HDAC inhibitors has been shown to be mediated in a chemical-specific manner in some cells (Basseville et al., 2012). In Flp-In HEK293 cells transfected with the wild-type *ABCG2*

TABLE 5
Effects of HDAC inhibitors on the regulation of BCRP across various cell types

| Human cells | | | | | |
|---------------|----------------------|-------------|--------------|-----------------|--|
| Organ | Cells | HDACi Class | Agent | Observation | References |
| Blood | KG1a | HA | TSA | ↑[m] | Hauswald et al., 2009; Fuchs et al., 2010 |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] ↑[a] | |
| | | | Butyrate | ↑[m] ↑[p] ↑[a] | |
| | HL-60 | HA | TSA | ↑[m] | Hauswald et al., 2009 |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| | CMK | HA | TSA | ↑[m] | Hauswald et al., 2009 |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] ↑[a] | |
| | | | Butyrate | ↑[m] ↑[p] ↑[a] | |
| | K562 | HA | TSA | ↑[m] | Hauswald et al., 2009 |
| | | | VPA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| Brain | SF295 | HA | SAHA | ↔↑[m] ↔[p] ↔[a] | Hauswald et al., 2009; Kim et al., 2011; Gojo et al., 2013 |
| | | | VPA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| | hCMEC/D3 | HA | Panobinostat | ↓[m] ↓[a] | To et al., 2008, 2011 |
| | | | Romidepsin | ↓[m] | |
| | | CP | TSA | ↑[m] | You et al., 2019b |
| | | | SAHA | ↑[m] | |
| | | SCFA | VPA | ↑[m] | |
| | | | Butyrate | ↑[m] | |
| Breast | MCF-7 | CP | Apicidin | ↑[m] | To et al., 2008 |
| | | | Romidepsin | ↑[m] | |
| | | HA | Romidepsin | ↓[m] | Schech et al., 2015 |
| | | | Entinostat | ↔[m] | |
| Cervix | KB (R) ^a | HA | TSA | ↔[m] | Kim et al., 2011 |
| | | | SAHA | ↔[m] | |
| | | CP | Apicidin | ↔[m] | |
| | | | MS-275 | ↔[m] | |
| | SW620 | HA | SAHA | ↔[a] | To et al., 2008, 2011 |
| | | | SAHA | ↑[m] ↑[a] | |
| | | HA | Panobinostat | ↑[m] | To et al., 2008, 2011 |
| | | | Romidepsin | ↑[m] ↑[p] ↑[a] | |
| | HCT-116 | HA | TSA | ↔[m] ↔[p] | Wang et al., 2019 |
| | | | SAHA | ↔[m] ↔[p] | |
| | | HA | TSA | ↓[m] ↓[p] | Chikamatsu et al., 2013 |
| | | | SAHA | ↓[m] ↓[p] | |
| Head and neck | KUMA-1 | CP | Romidepsin | ↑[m] ↑[a] | To et al., 2011 |
| | | | Romidepsin | ↑[m] | |
| | | HA | TSA | ↓[m] ↔[p] | To et al., 2011 |
| | | | SAHA | ↓[m] ↔[p] | |
| Kidney | 108, 121 | CP | Romidepsin | ↑[m] | Wang et al., 2019 |
| | | | Romidepsin | ↑[m] | |
| | | HA | TSA | ↓[m] ↔[p] | |
| | | | SAHA | ↓[m] ↔[p] | |
| Lung | 127, 143 | HA | TSA | ↔[m] | Kaewpiboon et al., 2015 |
| | | | SAHA | ↑[m] | |
| | | CP | Romidepsin | ↑[m] | To et al., 2008 |
| | | | VPA | ↑[m] ↑[p] ↑[a] | |
| Placenta | A549 | HA | TSA | ↔[m] | Kaewpiboon et al., 2015 |
| | | | SAHA | ↑[m] | |
| | | CP | Romidepsin | ↑[m] | To et al., 2008 |
| | | | VPA | ↑[m] ↑[p] ↑[a] | |
| | H460 | HA | TSA | ↔[m] | Kaewpiboon et al., 2015 |
| | | | SAHA | ↑[m] | |
| | | CP | Romidepsin | ↑[m] | To et al., 2008 |
| | | | VPA | ↑[m] ↑[p] ↑[a] | |
| | BeWo Choriocarcinoma | SCFA | VPA | ↑[m] | Rubinchik-Stern et al., 2015 |
| | | | VPA | ↑[m] | |

a, activity; BZ, benzamides; CP, cyclic peptides; HA, hydroxamic acid; HDACi, HDAC inhibitor; m, mRNA; p, protein; (R), drug-resistant form of cell line; SAHA, suberoylanilide hydroxamic acid; SCFA, short chain fatty acids; TSA, Trichostatin A; VPA, valproic acid.

^aThe authors misidentified these cell lines in their study as oral cancer cells.

gene, SAHA, panobinostat, and romidepsin, which are potent HDAC inhibitors, significantly upregulated both the mRNA and protein expression of BCRP. This change in the expression was reflected in enhanced function as observed by the reduced cytotoxicity of phenophorbide A, a BCRP substrate, in the presence of HDAC inhibitors. By contrast, VPA, a weak HDAC inhibitor, was not able to alter either the expression or the function of BCRP in the same cell line. Differential regulation of BCRP by different HDAC inhibitors may be related to chemical potency or molecular mechanisms. Higher concentrations of VPA may increase BCRP expression but could also be accompanied by greater toxicity to the cells.

In certain cases, BCRP expression appeared to change more sensitively than MDR1 in response to HDAC inhibition. For example, in 127 and 143 human renal cell carcinoma cells, romidepsin notably induced BCRP mRNA, whereas MDR1 expression was not altered (Robey et al., 2006). Similarly, sodium butyrate and romidepsin at their maximal nontoxic concentrations in hCMEC/D3 brain endothelial cells did not alter MDR1 mRNA levels but significantly increased BCRP mRNA expression (You et al., 2019b). It is possible that in these cells in which no changes in MDR1 were observed, tested HDAC inhibitors may modulate BCRP transporters via distinctive molecular pathways.

Interestingly, HDAC inhibitors caused downregulation of BCRP in some cell types. For example, in MCF-7 breast cancer cells, cyclic peptide romidepsin decreased the mRNA levels of BCRP, whereas it increased MDR1 mRNA (To et al., 2008). Likewise, hydroxamate HDAC inhibitors SAHA and panobinostat, which induced MDR1 mRNA in SF295 glioblastoma cells, downregulated BCRP mRNA expression and activity in these cells (To et al., 2011). The effects of romidepsin on BCRP mRNA in SF295 cells also included repression. Similarly, SAHA as well as TSA, another hydroxamate HDAC inhibitor, significantly elevated MDR1 mRNA and protein expression but reduced BCRP mRNA level in A549 lung cancer cells (Wang et al., 2019). These results suggest that in those cells with diverging responses for BCRP and MDR1 transporters after HDAC inhibitor treatment: 1) the overall transport function is more tightly regulated, and thus HDAC inhibitors cause compensatory downregulation of BCRP transporter in response to the MDR1 induction; or 2) HDAC inhibitors may differentially activate molecular pathways to modulate the two transporters.

In conclusion, more diverse patterns of HDAC inhibitor-mediated regulation have been observed for the BCRP transporter. Data from the studies presented support the contention that BCRP and MDR1 transporters are regulated by HDAC inhibitors through distinct mechanisms. However, because of the functional overlap (similar locations and substrate specificity) between these two transporters, regulation of the BCRP and MDR1 transporters may be interdependent.

Potential Mechanisms of HDAC Inhibitor-Mediated Transporter Regulation

Several studies have delved deeper to delineate the mechanisms by which HDAC inhibitors alter efflux transporter expression in various cell types. These studies have consistently revealed a correlation between transporter regulation and alterations in the acetylation status of histones in response to HDAC inhibitors (Jin and Scotto, 1998; El-Osta et al., 2002; Baker et al., 2005; Tabe et al., 2006; El-Khoury et al., 2007; Kim et al., 2008, 2009; Hauswald et al., 2009; Valdez et al., 2016; You et al., 2019a,b). Such association confirmed that HDAC inhibitors did in fact prevent the deacetylation of histone proteins. Increases in global acetylation of both histone H3 and H4 proteins were observed after exposure to HDAC inhibitors, though to varying extents depending on the cell type. A study by Kim et al. (2008) showed that there were

dose-dependent increases in acetylated histone proteins that correlated with induction of MDR1 protein (Kim et al., 2008). Also, VPA- and apicidin-mediated upregulation of Mdr1 and Bcrp protein in different regions of mouse brains was accompanied by increases in acetylated histone H3 proteins (You et al., 2019a). Valdez et al. (2016) showed that the histone acetylation was observed earlier than the induction of MDR1, suggesting that acetylation of histones was a preceding event for MDR1 induction. Histone acetylation was observed particularly at the regions nearby the promoter regions of *ABCB1* and *ABCG2* genes after the treatment with HDAC inhibitors (Jin and Scotto, 1998; Baker et al., 2005; Xiao et al., 2005; Tabe et al., 2006; El-Khoury et al., 2007; Hauswald et al., 2009; Kim et al., 2009). Altogether, these data suggested that transporter upregulation by HDAC inhibitors occurs through increasing the accessibility of transporter gene promoter sequences and consequently promoting gene transcription.

Indeed, the presence of actinomycin D, which is a transcriptional inhibitor, negated the induction of MDR1 by TSA (Baker et al., 2005; El-Khoury et al., 2007). This result confirmed that upregulation of MDR1 by TSA occurred at the transcriptional level. Jin and Scotto (1998) demonstrated that sequences in a DSP region of *ABCB1* gene were critical for TSA-mediated activation of gene transcription. As discussed previously in this review, the sequence from -134 to $+286$ bp is critical for effective transcription of the *ABCB1* gene (Cornwell, 1990; Goldsmith et al., 1993; Madden et al., 1993). In their study, Jin and Scotto (1998) assessed the relative activation of different stably transfected *ABCB1* promoter deletion constructs by TSA in SW620 cells and observed that the sequences from -136 to -75 bp, which contain potential binding sites for critical transcription factors, were important for TSA-mediated activation of MDR1. Particularly, an inverted CCAAT box element (Y box, -82 to -73 bp) was found to be the most important region to mediate TSA activity; mutations specifically in the Y box region significantly reduced *ABCB1* promoter activation by TSA (Jin and Scotto, 1998). Likewise, MDR1 induction by SAHA in immortalized brain endothelial hCMEC/D3 cells involved the most significant increases in histone H3 acetylation at the region from -100 to $+8$ bp, which contains the Y box, GC box, and a putative DRE, a binding site for AHR (You et al., 2019b).

ABCB1 gene activation by other classes of HDAC inhibitors also involved sequences at the DSP region. In their study, Jin and Scotto (1998) showed that sodium butyrate, a SCFA HDAC inhibitor, activated the *ABCB1* promoter in SW620 cells through a Y box. Likewise, the cyclic peptide HDAC inhibitor, apicidin, mediated induction of MDR1 through transactivation of the Y box region. The study by Kim et al., 2009 revealed that apicidin increased histone H3 acetylation in HeLa cells at the *ABCB1* promoter region from -160 to $+85$ bp, which contains numerous transcription factor binding sites, including Y box, GC boxes, and a DRE. Moreover, mutation of the Y box region negated the ability of apicidin to activate *ABCB1* promoter luciferase constructs transfected into HeLa cells (Kim et al., 2009). Altogether, these results suggest that the sequences at the DSP region of the *ABCB1* gene are commonly required by different HDAC inhibitors to induce MDR1.

Yet, the specific transcription factors that are involved in *ABCB1* gene activation appear to differ across various HDAC inhibitors. Jin and Scotto (1998) showed that the binding of NF-Y at Y box was important to mediate the activity of TSA in SW620 cells. The authors further observed that the activity of P300/CBP-associated factor (PCAF), a HAT-containing transcriptional coactivator, also depended on a Y box. In an in vitro transcription-translation and pull-down assay, NF-Y- α and PCAF were shown to interact. From these results, the authors concluded that inhibition of HDACs by TSA increases the activity of PCAF, which is recruited to the Y box through its interaction with NF-Y- α . This would consequently result in an increased histone acetylation

and a perturbed nucleosome structure around the *ABCB1* promoter, leading to *ABCB1* transcriptional activation (Jin and Scotto, 1998). The importance of PCAF activity in TSA-mediated MDR1 activation was also investigated in the study by El-Khoury et al. (2007). They observed MDR1 mRNA induction as well as increased PCAF binding to the Y box of *ABCB1* promoter in wild-type H69 lung carcinoma cells treated with TSA. Interestingly, PCAF occupancy at the *ABCB1* promoter was also increased, though to a lesser extent, in resistant H69 cells in which TSA caused reduction of MDR1 mRNA (El-Khoury et al., 2007). This suggests that factors other than PCAF play a major role in the suppression of MDR1 gene transcription in H69-resistant cells.

By contrast, AHR seemed to play a critical role in MDR1 upregulation by SAHA, another hydroxamate HDAC inhibitor, in hCEC/D3 cells (You et al., 2019b). Our recent study showed that SAHA significantly increased the histone H3 acetylation as well as AHR binding at *ABCB1* DSP region (−100 to +8 bp) where a putative DRE for AHR, a regulator of MDR1, is located, suggesting that histone acetylation mediated by SAHA and subsequent AHR binding at *ABCB1* promoter activates *ABCB1* gene transcription. Moreover, SAHA-mediated increases in MDR1 mRNA and protein levels in hCEC/D3 were further enhanced in the presence of an AHR activator but significantly reduced in the presence of an AHR inhibitor. Yet, SAHA's ability to upregulate MDR1 activity was not completely reversed by AHR inhibition. Because SAHA has a wide range of molecular targets, it is likely that SAHA modulates additional pathways that can also contribute to MDR1 induction.

Apicidin-mediated induction of MDR1 was shown to involve the transcription factor, Sp1. In their study, Kim et al. (2009) observed that coexposure of HeLa cells to mithramycin, a pharmacologic inhibitor of Sp1 binding to the promoters, could negate the MDR1 induction by apicidin, suggesting the absolute requirement of Sp1 for the action of apicidin. Interestingly, this study observed that apicidin did not change the amount of Sp1 binding at *ABCB1* promoter, but it did cause HDAC1 dissociation from and recruit transcription factors PCAF, C/EBP β , and Pol II to the *ABCB1* promoter. Instead, apicidin significantly increased Sp1 phosphorylation, which is critical for the activity of this transcription factor. Further analyses showed that the presence of LY294002, an inhibitor of phosphatidylinositol 3-kinase signaling pathway, strongly inhibited Sp1 phosphorylation, transcription machinery binding to *ABCB1* promoter, and MDR1 upregulation after apicidin exposure (Kim et al., 2009). From these observations, the authors concluded that apicidin causes phosphatidylinositol 3-kinase-mediated phosphorylation of Sp1, which then facilitates HDAC1 dissociation and, subsequently, binding of transcription factors to activate transcription. Collectively, these results imply that HDAC inhibitors can trigger unique molecular events around the *ABCB1* promoter to cause mRNA transcription across different cell lines. This may explain chemical-specific or cell type-specific changes in MDR1 regulation observed with different classes of HDAC inhibitors.

Promoter methylation has emerged as an important factor in the interaction between histone acetylation and transcription of the *ABCB1* gene. Previous studies observed that TSA alone could not induce MDR1 mRNA in CEM-CCRF acute lymphoblastic leukemia cells, which have a hypermethylated *ABCB1* promoter (El-Osta et al., 2002; Baker et al., 2005). However, cotreatment with TSA and 5-azacytidine, a DNA methyltransferase inhibitor, caused a robust increase in MDR1 mRNA in CEM-CCRF cells (El-Osta et al., 2002; Baker et al., 2005). In contrast, MDR1 mRNA expression in CEM-A7R and CEM-Bcl2 cells, which have hypomethylated *ABCB1* promoters, was significantly upregulated by TSA, and this induction was not further elevated by the addition of 5-azacytidine (El-Osta et al., 2002; Baker et al., 2005). From these results, the authors concluded that CpG methylation at the *ABCB1* promoter is

a critical silencer of *ABCB1* transcription and that histone acetylation alone is not sufficient to activate hypermethylated *ABCB1* gene. However, the difference in CpG methylation status does not appear to be the only determinant of the variable effects of TSA on MDR1. In their study, El-Khoury et al. (2007) found that wild-type and drug-resistant H69 lung carcinoma cells, both of which showed hypomethylation at *MDR1* promoter, responded differently to TSA. TSA induced MDR1 mRNA in wild-type cells but decreased its expression in resistant cells (El-Khoury et al., 2007). Collectively, these results imply that there is no single dominant factor but rather multiple interacting factors that regulate the mechanisms by which HDAC inhibitors alter MDR1 expression.

Induction of BCRP expression in the plasma membrane by various HDAC inhibitors, including romidepsin, SAHA, and VPA, was also abrogated in the presence of actinomycin D, implying that HDAC inhibitor-mediated induction of BCRP is also mediated at the transcriptional level (Basseville et al., 2012). Investigation of the molecular mechanisms underlying BCRP induction by HDAC inhibitors revealed increased histone H3 acetylation at the proximal region of the *ABCG2* promoter (−687 to +20 bp) in S1 colon cancer cells treated with romidepsin, with the most consistent change seen at the sequence from −293 to −193 bp (position “P3”) (To et al., 2008). Romidepsin also decreased the binding of HDAC1 and 3 at “P3.” Investigation of the molecular events occurring at “P3” in S1 cells revealed increased binding of AHR, a known BCRP-regulating transcription factor, at that site. Genetic knockdown of AHR reversed the BCRP induction by romidepsin, confirming that the activity of AHR was critical for BCRP regulation by romidepsin, as it was for MDR1 regulation by SAHA (To et al., 2011; You et al., 2019b).

Further analysis showed that romidepsin acetylated Hsp70 to disrupt the chaperone function of Hsp90. Acetylation of Hsp70 indirectly facilitates the dissociation between AHR and Hsp90, thereby increasing AHR activity and consequently activating the *ABCG2* gene by AHR (To et al., 2011). The authors also observed that SAHA caused similar induction of BCRP mRNA and function as well as acetylation of Hsp70 in S1 cells, suggesting that AHR may also play a critical role in SAHA-mediated induction of BCRP in this cell line. Interestingly, SAHA also acetylated Hsp90 unlike romidepsin, which caused acetylation only on Hsp70, implying that SAHA causes more nonspecific acetylation of proteins in these cells. Therefore, these results further support the contention that SAHA targets multiple molecular pathways that can together influence transporter upregulation (To et al., 2011; You et al., 2019b). In SW620 cells, romidepsin caused neither AHR binding at the *ABCG2* promoter nor acetylation of Hsp70 or Hsp90, which likely accounts for the unresponsiveness of SW620 cells to romidepsin-mediated regulation of BCRP (To et al., 2011). These results further illustrate the highly specific effects of HDAC inhibitor on regulating transporter expression across cell types.

Because HDAC inhibitors have several different molecular activities, it is possible that these compounds indirectly regulate MDR1 and BCRP by impacting the expression and/or activity of the transcriptional regulators of these transporters. Increases in global histone acetylation by HDAC inhibitors may likely affect the transcription of genes other than transporters. Indeed, Garrison et al. (2000) demonstrated that TSA and butyrate can increase the promoter activity of *Ahr*, a known transcriptional regulator of MDR1 and BCRP. In addition, some HDAC inhibitors are thought to activate the xenobiotic-activated transcription factors that regulate MDR1 and BCRP. VPA was shown to activate constitutive androstane receptor and consequently induce the transcription of MDR1 in human liver cancer HepG2 cells (Cervený et al., 2007). Such ability to activate constitutive androstane receptor was also demonstrated for other HDAC inhibitors, though to different extents

TABLE 6
Effects of genetic modifications of HDACs in regulating MDR1 and BCRP in cancer cells

| Gene | Knockdown System | Tissues/Cells | Observation | References |
|-------|------------------|---------------------------------------|---------------------|----------------------------------|
| HDAC1 | siRNA | Colorectal adenocarcinoma HCT-8 cells | MDR1 ↑[m] ↑[p] | Xu et al., 2012 |
| | | Colorectal adenocarcinoma HCT-8 cells | MDR1 ↓[m] ↓[p] | Xu et al., 2012 |
| | | Colorectal carcinoma HCT-116 cells | MDR1 ↑[m] ↑[p] | Xu et al., 2012 |
| | | Colorectal carcinoma HCT-116 cells | MDR1 ↓[m] ↓[p] | Xu et al., 2012 |
| | | Cervical adenocarcinoma HeLa cells | MDR1 ↑[m] ↑[p] | Kim et al., 2009 |
| | | Placental choriocarcinoma BeWo cells | MDR1 ↔[m] ↔[p] ↔[a] | Duan et al., 2017b |
| | | Placental choriocarcinoma JAR cells | MDR1 ↔[m] ↔[p] ↔[a] | Duan et al., 2017b |
| | | Colorectal adenocarcinoma HCT-8 cells | MDR1 ↑[m] ↑[p] | Xu et al., 2012 |
| | | Colorectal adenocarcinoma HCT-8 cells | MDR1 ↓[m] ↓[p] | Xu et al., 2012 |
| | | Colorectal adenocarcinoma SW480 cells | MDR1 ↓[m] ↓[p] | Ye et al., 2016 |
| HDAC2 | siRNA | Colorectal carcinoma HCT-116 cells | MDR1 ↓[m] ↓[p] | Xu et al., 2012; Ye et al., 2016 |
| | | Colorectal carcinoma HCT-116 cells | BCRP ↔[m] ↔[p] | |
| | | Colorectal carcinoma HCT-116 cells | MDR1 ↔[m] ↔[p] | Xu et al., 2012 |
| | | Cervical adenocarcinoma HeLa cells | MDR1 ↑[m] ↑[p] | Kim et al., 2009 |
| | | Glioblastoma/Astrocytoma U87 cells | MDR1 ↔[m] ↔[p] | Zhang et al., 2016 |
| | | Glioblastoma A172 cells | BCRP ↔[m] ↔[p] | |
| | | Glioblastoma A172 cells | MDR1 ↔[m] ↔[p] | Zhang et al., 2016 |
| | | Glioblastoma A172 cells | BCRP ↔[m] ↔[p] | |
| | | Placental choriocarcinoma BeWo cells | MDR1 ↑[m] ↑[p] ↑[a] | Duan et al., 2017b |
| | | Placental choriocarcinoma JAR cells | MDR1 ↑[m] ↑[p] ↑[a] | Duan et al., 2017b |
| HDAC3 | siRNA | Melanoma Malme3M cells | MDR1 ↑[p] | Park et al., 2014 |
| | | Hepatocellular carcinoma SNU387 cells | MDR1 ↑[p] | Park et al., 2014 |
| | | Placental choriocarcinoma BeWo cells | MDR1 ↔[m] ↔[p] ↔[a] | Duan et al., 2017b |
| | | Placental choriocarcinoma JAR cells | MDR1 ↔[m] ↔[p] ↔[a] | Duan et al., 2017b |
| HDAC6 | siRNA | Melanoma Malme3M cells | MDR1 ↓[p] | Kim et al., 2015 |
| HDAC8 | siRNA | Hepatocellular carcinoma SNU384 cells | MDR1 ↓[p] | Kim et al., 2015 |
| | | Glioblastoma/Astrocytoma U87 cells | MDR1 ↓[m] | Zhao et al., 2017 |
| | | Neuroblastoma SH-SY5Y cells | MDR1 ↓[m] | Zhao et al., 2017 |
| | | Neuroblastoma SK-N-SH cells | MDR1 ↓[m] | Zhao et al., 2017 |

a, activity; m, mRNA; p, protein.

(Takizawa et al., 2010). As suggested earlier in this section, HDAC inhibitors may exert their regulatory activities on MDR1 and BCRP through multiple mechanisms, which can include both direct interaction with the transporter genes and indirect modulation as discussed here. The ability for this indirect regulation of the transporters may also contribute to the chemical-specific and cell-type changes in the transporters by HDAC inhibitors.

HDAC inhibitors target multiple isoforms of HDACs and can elicit effects beyond transporter regulation. Therefore, studies have performed genetic knockdown of HDACs and identified specific HDAC isoforms responsible for transporters (Table 6). Studies have largely focused on class I HDACs, which are nuclear HDACs that possess an intrinsic capability to deacetylate core histones (Hassig et al., 1998; Hu et al., 2000; Johnson et al., 2002). As observed with HDAC inhibitors, the effects of HDAC knockdown were also highly variable across cell lines. For example, HDAC1 siRNA effectively increased MDR1 mRNA and protein in wild-type HCT-8 and HCT-116 colon carcinoma cells, whereas it did not affect MDR1 expression in BeWo or JAR trophoblast cells (Xu et al., 2012; Duan et al., 2017b). HDAC2 siRNA knockdown resulted in the differential regulation of MDR1 between different colon carcinoma cells. Reduction in HDAC2 protein expression leads to upregulated MDR1 expression in HCT-8 cells, whereas a decrease in MDR1 level was observed in SW480 colon cancer cells transfected with HDAC2 siRNA (Xu et al., 2012; Ye et al., 2016). Unlike HDAC1 knockdown, genetic silencing of HDAC2 significantly increased both the expression and function of MDR1 in BeWo and JAR cells (Duan et al., 2017b). Furthermore, the upregulation of Abcb1a mRNA and Mdr1 protein levels were observed in the placentas of pregnant dams injected with Hdac2 siRNA from embryonic day 7.5 to 15.5 (Duan et al., 2017b). HDAC3 knockdown upregulated the protein expression of MDR1 as well as acetylated histone H3K9/14 and H4K16 in Malme3M melanoma cells and SNU387 hepatocellular carcinoma cells

(Park et al., 2014). However, knocking down HDAC3 caused no change in MDR1 expression or function in BeWo or JAR cells (Duan et al., 2017b). Factors such as the relative expression of HDACs or their associated proteins in different cell types may play roles in differentially regulating transporters following knockdown of specific HDAC isoforms.

Conclusion and Discussion

MDR1 and BCRP control the passage of diverse chemicals in several key organs, such as the liver, kidneys, and brain. They also regulate the responsiveness of cancer cells to chemotherapeutic drugs. A comprehensive understanding of how these transporters can be regulated is important in identifying factors controlling the efficacy and toxicity of chemicals. The evidence reviewed in this paper strongly suggests that the expression of the MDR1 and BCRP transporters can be modulated by histone acetylation following inhibition of HDAC enzymes. Various factors, including differences in biologic properties and molecular environments across different cell types, the characteristics of HDAC inhibitors such as specificity and potency, and disease conditions, seem to interact and determine the ability of HDAC inhibition to regulate these efflux transporters. Also, the molecular events induced by different HDAC inhibitors in various cells can be highly specific, and the regulation of efflux transporters by these compounds can be quite complex. Other important factors such as differences in species and gender, which are not yet fully investigated, are also likely to affect transporter regulation by HDAC inhibitors. Further studies comprehensively assessing the molecular targets of each HDAC inhibitor as well as the transcription factors interacting with *ABCB1* and *ABCG2* genes upon HDAC inhibition will provide a more complete understanding of the differential regulation of MDR1 and BCRP transporters by these epigenetic modulators. A more complete understanding will also

allow us to better predict how HDAC inhibitors will affect efflux transporter expression in different individuals with varying genetic background, age, pre-existing disease conditions, and coadministered drugs. Importantly, more investigations should be performed to assess the effects of HDAC inhibitors on the transporter activity in noncancerous organs, particularly liver, kidney, and intestine, which play key roles in drug disposition. Ultimately, we should recognize and assess the clinical consequences of using HDAC inhibitors where the activity of efflux transporters plays a key role in determining tissue exposure to drugs and toxicants. Such studies will help us identify potential drug interactions caused by HDAC inhibitors, which are often coadministered with other drugs that are substrates of MDR1 and BCRP transporters.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: You, Richardson, Aleksunes.

References

- Acharya MR, Sparreboom A, Sausville EA, Conley BA, Doroshow JH, Venitz J, and Figg WD (2006) Interspecies differences in plasma protein binding of MS-275, a novel histone deacetylase inhibitor. *Cancer Chemother Pharmacol* **57**:275–281.
- Afshar G and Murnane JP (1999) Characterization of a human gene with sequence homology to *Saccharomyces cerevisiae* SIR2. *Gene* **234**:161–168.
- Agarwal S, Sane R, Gallardo JL, Ohlfest JR, and Elmquist WF (2010) Distribution of gefitinib to the brain is limited by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2)-mediated active efflux. *J Pharmacol Exp Ther* **334**:147–155.
- Ahuja N, Schwer B, Carobbio S, Waltregny D, North BJ, Castronovo V, Maechler P, and Verdin E (2007) Regulation of insulin secretion by SIRT4, a mitochondrial ADP-ribosyltransferase. *J Biol Chem* **282**:33583–33592.
- Aller SG, Yu J, Ward A, Weng Y, Chittaboina S, Zhuo R, Harrell PM, Trinh YT, Zhang Q, Urbatsch IL, et al. (2009) Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science* **323**:1718–1722.
- Allfrey VG, Faulkner R, and Mirsky AE (1964) Acetylation and methylation of histones and their possible role in the regulation of Rna synthesis. *Proc Natl Acad Sci USA* **51**:786–794.
- Allikmets R, Schriml LM, Hutchinson A, Romano-Spica V, and Dean M (1998) A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. *Cancer Res* **58**:5337–5339.
- Amacher DE (2016) The regulation of human hepatic drug transporter expression by activation of xenobiotic-sensing nuclear receptors. *Expert Opin Drug Metab Toxicol* **12**:1463–1477.
- Ambudkar SV, Dey S, Hrycyna CA, Ramachandra M, Pastan I, and Gottesman MM (1999) Biochemical, cellular, and pharmacological aspects of the multidrug transporter. *Annu Rev Pharmacol Toxicol* **39**:361–398.
- Anderson KW, Chen J, Wang M, Mast N, Pikuleva IA, and Turko IV (2015) Quantification of histone deacetylase isoforms in human frontal cortex, human retina, and mouse brain. *PLoS One* **10**:e0126592.
- Bailey H, McPherson JP, Bailey EB, Werner TL, Gupta S, Batten J, Reddy G, Bhat G, Sharma S, and Agarwal N (2016) A phase I study to determine the pharmacokinetics and urinary excretion of belinostat and metabolites in patients with advanced solid tumors. *Cancer Chemother Pharmacol* **78**:1059–1071.
- Bailey-Dell KJ, Hassel B, Doyle LA, and Ross DD (2001) Promoter characterization and genomic organization of the human breast cancer resistance protein (ATP-binding cassette transporter G2) gene. *Biochim Biophys Acta* **1520**:234–241.
- Baker EK, Johnstone RW, Zalberg JR, and El-Osta A (2005) Epigenetic changes to the MDR1 locus in response to chemotherapeutic drugs. *Oncogene* **24**:8061–8075.
- Bakhsheshian J, Hall MD, Robey RW, Herrmann MA, Chen JQ, Bates SE, and Gottesman MM (2013) Overlapping substrate and inhibitor specificity of human and murine ABCG2. *Drug Metab Dispos* **41**:1805–1812.
- Balaguer TM, Gómez-Martínez A, García-Morales P, Lacueva J, Calpena R, Reverte LR, Riquelme NL, Martínez-Lacaci I, Ferragut JA, and Saceda M (2012) Dual regulation of P-glycoprotein expression by trichostatin A in cancer cell lines. *BMC Mol Biol* **13**:25.
- Bali P, Prapat M, Bradner J, Balas M, Fiskus W, Guo F, Rocha K, Kumaraswamy S, Boyapalle S, Atadja P, et al. (2005) Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors. *J Biol Chem* **280**:26729–26734.
- Barne H, Salimi M, Goshadrou F, Ashtiani M, Mirzaie M, Zali H, and Jafari M (2018) Valproic acid inhibits the protective effects of stromal cells against chemotherapy in breast cancer: insights from proteomics and systems biology. *J Cell Biochem* **119**:9270–9283.
- Bart J, Hollema H, Groen HJ, de Vries EG, Hendrikse NH, Sleijfer DT, Wegman TD, Vaalburg W, and van der Graaf WT (2004) The distribution of drug-efflux pumps, P-gp, BCRP, MRP1 and MRP2, in the normal blood-testis barrier and in primary testicular tumours. *Eur J Cancer* **40**:2064–2070.
- Basseville A, Tamaki A, Ierano C, Trostel S, Ward Y, Robey RW, Hegde RS, and Bates SE (2012) Histone deacetylase inhibitors influence chemotherapy transport by modulating expression and trafficking of a common polymorphic variant of the ABCG2 efflux transporter. *Cancer Res* **72**:3642–3651.
- Bates SE, Currier SJ, Alvarez M, and Fojo AT (1992) Modulation of P-glycoprotein phosphorylation and drug transport by sodium butyrate. *Biochemistry* **31**:6366–6372.
- Bates SE, Zhan Z, Steadman K, Obrzut T, Luchenko V, Frye R, Robey RW, Turner M, Gardner ER, Figg WD, et al. (2010) Laboratory correlates for a phase II trial of romidepsin in cutaneous and peripheral T-cell lymphoma. *Br J Haematol* **148**:256–267.
- Beckers T, Burkhardt C, Wieland H, Gimmnich P, Ciossek T, Maier T, and Sanders K (2007) Distinct pharmacological properties of second generation HDAC inhibitors with the benzamide or hydroxamate head group. *Int J Cancer* **121**:1138–1148.
- Beleodag (belinostat). (2014) Package insert. Spectrum Pharmaceuticals Inc., Irvine, CA.
- Benoki S, Yoshinari K, Chikada T, Imai J, and Yamazoe Y (2012) Transactivation of ABCG2 through a novel cis-element in the distal promoter by constitutive androstane receptor but not pregnane X receptor in human hepatocytes. *Arch Biochem Biophys* **517**:123–130.
- Berglund L, Björling E, Oksvold P, Fagerberg L, Asplund L, Sztybel CA, Persson A, Ottosson J, Wernérus H, Nilsson P, et al. (2008) A genecentric Human Protein Atlas for expression profiles based on antibodies. *Mol Cell Proteomics* **7**:2019–2027.
- Bircsak KM, Gupta V, Yuen PY, Gorczyca L, Weinberger BI, Vetrano AM, and Aleksunes LM (2016) Genetic and dietary regulation of glyburide efflux by the human placental breast cancer resistance protein transporter. *J Pharmacol Exp Ther* **357**:103–113.
- Björling P, Silverstein RA, Thon G, Caudy A, Grewal S, and Ekwall K (2002) Functional divergence between histone deacetylases in fission yeast by distinct cellular localization and in vivo specificity. *Mol Cell Biol* **22**:2170–2181.
- Boffa LC, Vidali G, Mann RS, and Allfrey VG (1978) Suppression of histone deacetylation in vivo and in vitro by sodium butyrate. *J Biol Chem* **253**:3364–3366.
- Boissinot M, Inman M, Hemphill A, James SR, Gill JH, Selby P, Bowen DT, Grigg R, and Cockrell PN (2012) Induction of differentiation and apoptosis in leukaemic cell lines by the novel benzamide family histone deacetylase 2 and 3 inhibitor MI-192. *Leuk Res* **36**:1304–1310.
- Bradner JE, West N, Grachan ML, Greenberg EF, Haggarty SJ, Warnow T, and Mazitschek R (2010) Chemical phylogenetics of histone deacetylases. *Nat Chem Biol* **6**:238–243.
- Broide RS, Redwine JM, Aftahi N, Young W, Bloom FE, and Winrow CJ (2007) Distribution of histone deacetylases 1–11 in the rat brain. *J Mol Neurosci* **31**:47–58.
- Brown LW (1979) Valproic acid: a new antiepileptic agent. *Am Fam Physician* **19**:166–168.
- Burgess A, Ruefli A, Beamish H, Warren R, Saunders N, Johnstone R, and Gabrieli B (2004) Histone deacetylase inhibitors specifically kill nonproliferating tumour cells. *Oncogene* **23**:6693–6701.
- Bürlir RW, Luckhurst CA, Aziz O, Matthews KL, Yates D, Lyons KA, Beconi M, McAllister G, Breccia P, Stott AJ, et al. (2013) Design, synthesis, and biological evaluation of potent and selective class IIa histone deacetylase (HDAC) inhibitors as a potential therapy for Huntington's disease. *J Med Chem* **56**:9934–9954.
- Butler LM, Agus DB, Scher HI, Higgins B, Rose A, Cordon-Cardo C, Thaler HT, Rifkind RA, Marks PA, and Richon VM (2000) Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses the growth of prostate cancer cells in vitro and in vivo. *Cancer Res* **60**:5165–5170.
- Campbell PK, Zong Y, Yang S, Zhou S, Rubnitz JE, and Sorrentino BP (2011) Identification of a novel, tissue-specific ABCG2 promoter expressed in pediatric acute megakaryoblastic leukemia. *Leuk Res* **35**:1321–1329.
- Candido EP, Reeves R, and Davie JR (1978) Sodium butyrate inhibits histone deacetylation in cultured cells. *Cell* **14**:105–113.
- Caron H, van Schaik B, van der Mee M, Baas F, Riggins G, van Sluis P, Hermus MC, van Asperen R, Boon K, Voûte PA, et al. (2001) The human transcriptome map: clustering of highly expressed genes in chromosomal domains. *Science* **291**:1289–1292.
- Cary PD, Crane-Robinson C, Bradbury EM, and Dixon GH (1982) Effect of acetylation on the binding of N-terminal peptides of histone H4 to DNA. *Eur J Biochem* **127**:137–143.
- Cerveny L, Svecova L, Anzenbacherova E, Vrzal R, Staud F, Dvorak Z, Ulrichova J, Anzenbacher P, and Pavek P (2007) Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways. *Drug Metab Dispos* **35**:1032–1041.
- Chan GN, Saldivia V, Yang Y, Pang H, de Lannoy I, and Bendayan R (2013a) In vivo induction of P-glycoprotein expression at the mouse blood-brain barrier: an intracerebral microdialysis study. *J Neurochem* **127**:342–352.
- Chan YY, Kalpana S, Chang WC, Chang WC, and Chen BK (2013b) Expression of aryl hydrocarbon receptor nuclear translocator enhances cisplatin resistance by upregulating MDR1 expression in cancer cells. *Mol Pharmacol* **84**:591–602.
- Chen CJ, Chin JY, Ueda K, Clark DP, Pastan I, Gottesman MM, and Roninson IB (1986) Internal duplication and homology with bacterial transport proteins in the mdr1 (P-glycoprotein) gene from multidrug-resistant human cells. *Cell* **47**:381–389.
- Chen PS, Peng GS, Li G, Yang S, Wu X, Wang CC, Wilson B, Lu RB, Gean PW, Chuang DM, et al. (2006) Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurotrophic factors from astrocytes. *Mol Psychiatry* **11**:1116–1125.
- Chen Y, Agarwal S, Shaik NM, Chen C, Yang Z, and Elmquist WF (2009) P-glycoprotein and breast cancer resistance protein influence brain distribution of dasatinib. *J Pharmacol Exp Ther* **330**:956–963.
- Chikamatsu K, Ishii H, Murata T, Sakakura K, Shino M, Toyoda M, Takahashi K, and Masuyama K (2013) Alteration of cancer stem cell-like phenotype by histone deacetylase inhibitors in squamous cell carcinoma of the head and neck. *Cancer Sci* **104**:1468–1475.
- Chin KV, Ueda K, Pastan I, and Gottesman MM (1992) Modulation of activity of the promoter of the human MDR1 gene by Ras and p53. *Science* **255**:459–462.
- Choi JH, Kwon HJ, Yoon BI, Kim JH, Han SU, Joo HJ, and Kim DY (2001) Expression profile of histone deacetylase 1 in gastric cancer tissues. *Jpn J Cancer Res* **92**:1300–1304.
- Choi SA, Kwak PA, Park CK, Wang KC, Phi JH, Lee JY, Lee CS, Lee JH, and Kim SK (2017) A novel histone deacetylase inhibitor, CKD5, has potent anti-cancer effects in glioblastoma. *Oncotarget* **8**:9123–9133.
- Chou CJ, Herman D, and Gottesfeld JM (2008) Pimelic diphenylamide 106 is a slow, tight-binding inhibitor of class I histone deacetylases. *J Biol Chem* **283**:35402–35409.
- Clarke AS, Lowell JE, Jacobson SJ, and Pillus L (1999) Esa1p is an essential histone acetyltransferase required for cell cycle progression. *Mol Cell Biol* **19**:2515–2526.
- Cohen D, Piekarz RL, Hsu SI, DePinho RA, Carrasco N, and Horwitz SB (1991) Structural and functional analysis of the mouse mdr1b gene promoter. *J Biol Chem* **266**:2239–2244.
- Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, Howitz KT, Gorospe M, de Cabo R, and Sinclair DA (2004) Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* **305**:390–392.
- Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, Caballero D, Borchmann P, Morschhauser F, Wilhelm M, et al. (2012) Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* **30**:631–636.
- Cooray HC, Blackmore CG, Maskell L, and Barrand MA (2002) Localisation of breast cancer resistance protein in microvessel endothelium of human brain. *Neuroreport* **13**:2059–2063.

- Cornford EM, Diep CP, and Pardridge WM (1985) Blood-brain barrier transport of valproic acid. *J Neurochem* **44**:1541–1550.
- Cornwell MM (1990) The human multidrug resistance gene: sequences upstream and downstream of the initiation site influence transcription. *Cell Growth Differ* **1**:607–615.
- Cornwell MM (1991) Molecular biology of P-glycoprotein. *Cancer Treat Res* **57**:37–56.
- Cornwell MM and Smith DE (1993) SP1 activates the MDR1 promoter through one of two distinct G-rich regions that modulate promoter activity. *J Biol Chem* **268**:19505–19511.
- Covington HE III, Maze I, LaPlant QC, Vialou VF, Ohnishi YN, Berton O, Fass DM, Renthal W, Rush AJ III, Wu EY, et al. (2009) Antidepressant actions of histone deacetylase inhibitors. *J Neurosci* **29**:11451–11460.
- Cress WD and Seto E (2000) Histone deacetylases, transcriptional control, and cancer. *J Cell Physiol* **184**:1–16.
- Darkin-Rattray SJ, Gurnett AM, Myers RW, Dulski PM, Crumley TM, Allocco JJ, Cannova C, Meinke PT, Colletti SL, Bednarek MA, et al. (1996) Apicidin: a novel antiparasitic agent that inhibits parasite histone deacetylase. *Proc Natl Acad Sci USA* **93**:13143–13147.
- Daschner PJ, Ciolino HP, Plouzek CA, and Yeh GC (1999) Increased AP-1 activity in drug resistant human breast cancer MCF-7 cells. *Breast Cancer Res Treat* **53**:229–240.
- Davis T, Kennedy C, Chiew YE, Clarke CL, and deFazio A (2000) Histone deacetylase inhibitors decrease proliferation and modulate cell cycle gene expression in normal mammary epithelial cells. *Clin Cancer Res* **6**:4334–4342.
- Deng L, Lin-Lee YC, Claret FX, and Kuo MT (2001) 2-acetylaminofluorene up-regulates rat mdr1b expression through generating reactive oxygen species that activate NF-kappa B pathway. *J Biol Chem* **276**:413–420.
- Denison MS, Fisher JM, and Whitlock JP Jr (1988) Inducible, receptor-dependent protein-DNA interactions at a dioxin-responsive transcriptional enhancer. *Proc Natl Acad Sci USA* **85**:2528–2532.
- Depakote (divalproex sodium). (1983) Package insert. AbbVie Inc., North Chicago, IL.
- Deroanne CF, Bonjean K, Servotte S, Devy L, Colige A, Clausse N, Blacher S, Verdin E, Foidart JM, Nussgens BV, et al. (2002) Histone deacetylases inhibitors as anti-angiogenic agents altering vascular endothelial growth factor signaling. *Oncogene* **21**:427–436.
- de Ruijter AJ, van Gennip AH, Caron HN, Kemp S, and van Kuilenburg AB (2003) Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J* **370**:737–749.
- Devault A and Gros P (1990) Two members of the mouse mdr gene family confer multidrug resistance with overlapping but distinct drug specificities. *Mol Cell Biol* **10**:1652–1663.
- Do TM, Noel-Hudson MS, Ribes S, Besengez C, Smirnova M, Cisternino S, Buysse M, Calon F, Chimini G, Chacun H, et al. (2012) ABCG2- and ABCG4-mediated efflux of amyloid- β peptide 1–40 at the mouse blood-brain barrier. *J Alzheimers Dis* **30**:155–166.
- Dressel U, Bailey PJ, Wang SC, Downes M, Evans RM, and Muscat GE (2001) A dynamic role for HDAC7 in MEF2-mediated muscle differentiation. *J Biol Chem* **276**:17007–17013.
- Dryden SC, Nahhas FA, Nowak JE, Goustin AS, and Tainsky MA (2003) Role for human SIRT2 NAD-dependent deacetylase activity in control of mitotic exit in the cell cycle. *Mol Cell Biol* **23**:3173–3185.
- Duan H, Wang C, Zhou K, Wang T, Li Y, Qiu D, Li Q, Zhang Y, and Hua Y (2017a) The effect of histone deacetylase inhibition on the expression of P-glycoprotein in human placental trophoblast cell lines. *Placenta* **49**:37–47.
- Duan H, Zhou K, Zhang Y, Yue P, Wang T, Li Y, Qiu D, Wu J, Hua Y, and Wang C (2017b) HDAC2 was involved in placental P-glycoprotein regulation both in vitro and vivo. *Placenta* **58**:105–114.
- Ee PL, Kamalakaran S, Tonetti D, He X, Ross DD, and Beck WT (2004) Identification of a novel estrogen response element in the breast cancer resistance protein (ABCG2) gene. *Cancer Res* **64**:1247–1251.
- El-Khoury V, Breuzard G, Fourré N, and Dufer J (2007) The histone deacetylase inhibitor trichostatin A downregulates human MDR1 (ABCB1) gene expression by a transcription-dependent mechanism in a drug-resistant small cell lung carcinoma cell line model. *Br J Cancer* **97**:562–573.
- El-Osta A, Kantharidis P, Zalberg JR, and Wolffe AP (2002) Precipitous release of methyl-CpG binding protein 2 and histone deacetylase 1 from the methylated human multidrug resistance gene (MDR1) on activation. *Mol Cell Biol* **22**:1844–1857.
- Enokizono J, Kusuha H, Ose A, Schinkel AH, and Sugiyama Y (2008) Quantitative investigation of the role of breast cancer resistance protein (Bcrp/Abcg2) in limiting brain and testis penetration of xenobiotic compounds. *Drug Metab Dispos* **36**:995–1002.
- Eyal S, Lamb JG, Smith-Yockman M, Yagen B, Fibach E, Altschuler Y, White HS, and Bialer M (2006) The antiepileptic and anticancer agent, valproic acid, induces P-glycoprotein in human tumour cell lines and in rat liver. *Br J Pharmacol* **149**:250–260.
- Eyüpoglu IY, Hahnen E, Tränkle C, Savaskan NE, Siebzehrübl FA, Buslei R, Lemke D, Wick W, Fahlbusch R, and Blümcke I (2006) Experimental therapy of malignant gliomas using the inhibitor of histone deacetylase MS-275. *Mol Cancer Ther* **5**:1248–1255.
- Faraco G, Pancani T, Formentini L, Mascagni P, Fossati G, Leoni F, Moroni F, and Chiarugi A (2006) Pharmacological inhibition of histone deacetylases by suberoylanilide hydroxamic acid specifically alters gene expression and reduces ischemic injury in the mouse brain. *Mol Pharmacol* **70**:1876–1884.
- Farydak (panobinostat). (2015) Package insert. Novartis Pharmaceuticals Corporation, East Hanover, NJ.
- Fiener C (2009) Novel structural insights into class I and II histone deacetylases. *Curr Top Med Chem* **9**:235–240.
- Finnin MS, Donigan JR, Cohen A, Richon VM, Rifkind RA, Marks PA, Breslow R, and Pavletich NP (1999) Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. *Nature* **401**:188–193.
- Fischle W, Dequiedt F, Fillion M, Hendzel MJ, Voelter W, and Verdin E (2001) Human HDAC7 histone deacetylase activity is associated with HDAC3 in vivo. *J Biol Chem* **276**:35826–35835.
- Fischle W, Dequiedt F, Hendzel MJ, Guenther MG, Lazar MA, Voelter W, and Verdin E (2002) Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. *Mol Cell* **9**:45–57.
- Fischle W, Emiliani S, Hendzel MJ, Nagase T, Nomura N, Voelter W, and Verdin E (1999) A new family of human histone deacetylases related to *Saccharomyces cerevisiae* Hda1p. *J Biol Chem* **274**:11713–11720.
- Fojo AT, Ueda K, Slamon DJ, Poplack DG, Gottesman MM, and Pastan I (1987) Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci USA* **84**:265–269.
- Fontán-Lozano A, Romero-Granados R, Troncoso J, Múnera A, Delgado-García JM, and Carrión AM (2008) Histone deacetylase inhibitors improve learning consolidation in young and in KA-induced-neurodegeneration and SAMP-8-mutant mice. *Mol Cell Neurosci* **39**:193–201.
- Francois LN, Gorczyca L, Du J, Bircsak KM, Yen E, Wen X, Tu MJ, Yu AM, Illsley NP, Zamudio S, et al. (2017) Down-regulation of the placental BCRP/ABCG2 transporter in response to hypoxia signaling. *Placenta* **51**:57–63.
- Frommel TO, Coon JS, Tsuruo T, and Roninson IB (1993) Variable effects of sodium butyrate on the expression and function of the MDR1 (P-glycoprotein) gene in colon carcinoma cell lines. *Int J Cancer* **55**:297–302.
- Frye RA (1999) Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem Biophys Res Commun* **260**:273–279.
- Fuchs D, Daniel V, Sadeghi M, Opelz G, and Naujokat C (2010) Salinomycin overcomes ABC transporter-mediated multidrug and apoptosis resistance in human leukemia stem cell-like KG-1a cells. *Biochem Biophys Res Commun* **394**:1098–1104.
- Furumai R, Matsuyama A, Kobashi N, Lee KH, Nishiyama M, Nakajima H, Tanaka A, Komatsu Y, Nishino Y, Yoshida M, et al. (2002) FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. *Cancer Res* **62**:4916–4921.
- Galanis E, Jaecle KA, Maurer MJ, Reid JM, Ames MM, Hardwick JS, Reilly JF, Loboda A, Nebozhyn M, Fantin VR, et al. (2009) Phase II trial of vorinostat in recurrent glioblastoma multiforme: a north central cancer treatment group study. *J Clin Oncol* **27**:2052–2058.
- Gao L, Cueto MA, Asselbergs F, and Atadja P (2002) Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. *J Biol Chem* **277**:25748–25755.
- Garrison PM, Rogers JM, Brackney WR, and Denison MS (2000) Effects of histone deacetylase inhibitors on the Ah receptor gene promoter. *Arch Biochem Biophys* **374**:161–171.
- Geick A, Eichelbaum M, and Burk O (2001) Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. *J Biol Chem* **276**:14581–14587.
- George B, You D, Joy MS, and Aleksunes LM (2017) Xenobiotic transporters and kidney injury. *Adv Drug Deliv Rev* **116**:73–91.
- Gerlach JH, Endicott JA, Juranka PF, Henderson G, Sarangi F, Deuchars KL, and Ling V (1986) Homology between P-glycoprotein and a bacterial haemolysin transport protein suggests a model for multidrug resistance. *Nature* **324**:485–489.
- Giles RH, Peters DJ, and Breuning MH (1998) Conjunction dysfunction: CBP/p300 in human disease. *Trends Genet* **14**:178–183.
- Giri N, Shaik N, Pan G, Terasaki T, Mukai C, Kitagaki S, Miyakoshi N, and Elmquist WF (2008) Investigation of the role of breast cancer resistance protein (Bcrp/Abcg2) on pharmacokinetics and central nervous system penetration of abacavir and zidovudine in the mouse. *Drug Metab Dispos* **36**:1476–1484.
- Glaser KB, Staver MJ, Waring JF, Stender J, Ulrich RG, and 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.
- Gojo I, Tan M, Fang HB, Sadowska M, Lapidus R, Baer MR, Carrier F, Beumer JH, Anyang BN, Srivastava RK, et al. (2013) Translational phase I trial of vorinostat (suberoylanilide hydroxamic acid) combined with cytarabine and etoposide in patients with relapsed, refractory, or high-risk acute myeloid leukemia. *Clin Cancer Res* **19**:1838–1851.
- Goldsmith ME, Madden MJ, Morrow CS, and Cowan KH (1993) A Y-box consensus sequence is required for basal expression of the human multidrug resistance (mdr1) gene. *J Biol Chem* **268**:5856–5860.
- Gómez-Martínez A, García-Morales P, Carrato A, Castro-Galache MD, Soto JL, Carrasco-García E, García-Bautista M, Guaraz P, Ferragut JA, and Saceda M (2007) Post-transcriptional regulation of P-glycoprotein expression in cancer cell lines. *Mol Cancer Res* **5**:641–653.
- Göttlicher M, Minucci S, Zhu P, Krämer OH, Schimpf A, Giavara S, Sleeman JP, Lo Coco F, Nervi C, Pelicci PG, et al. (2001) Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J* **20**:6969–6978.
- Gregoretti IV, Lee YM, and Goodson HV (2004) Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *J Mol Biol* **338**:17–31.
- Grob A, Roussel P, Wright JE, McStay B, Hernandez-Verdun D, and Sirri V (2009) Involvement of SIRT7 in resumption of rDNA transcription at the exit from mitosis. *J Cell Sci* **122**:489–498.
- Gromnicova R, Romero I, and Male D (2012) Transcriptional control of the multi-drug transporter ABCB1 by transcription factor Sp3 in different human tissues. *PLoS One* **7**:e48189.
- Gros P, Croop J, and Housman D (1986a) Mammalian multidrug resistance gene: complete cDNA sequence indicates strong homology to bacterial transport proteins. *Cell* **47**:371–380.
- Gros P, Croop J, Roninson I, Varshavsky A, and Housman DE (1986b) Isolation and characterization of DNA sequences amplified in multidrug-resistant hamster cells. *Proc Natl Acad Sci USA* **83**:337–341.
- Groth A, Rocha W, Verreault A, and Almouzni G (2007) Chromatin challenges during DNA replication and repair. *Cell* **128**:721–733.
- Grozinger CM, Hassig CA, and Schreiber SL (1999) Three proteins define a class of human histone deacetylases related to yeast Hda1p. *Proc Natl Acad Sci USA* **96**:4868–4873.
- Grozinger CM and Schreiber SL (2000) Regulation of histone deacetylase 4 and 5 and transcriptional activity by 14-3-3-dependent cellular localization. *Proc Natl Acad Sci USA* **97**:7835–7840.
- Guardiola AR and Yao TP (2002) Molecular cloning and characterization of a novel histone deacetylase HDAC10. *J Biol Chem* **277**:3350–3356.
- Guay DR (1995) The emerging role of valproate in bipolar disorder and other psychiatric disorders. *Pharmacotherapy* **15**:631–647.
- Guo L, Han A, Bates DL, Cao J, and Chen L (2007) Crystal structure of a conserved N-terminal domain of histone deacetylase 4 reveals functional insights into glutamine-rich domains. *Proc Natl Acad Sci USA* **104**:4297–4302.
- Haberland M, Montgomery RL, and Olson EN (2009) The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet* **10**:32–42.
- Hagis MC, Mostoslavsky R, Hagis KM, Fahie K, Christodoulou DC, Murphy AJ, Valenzuela DM, Yancopoulos GD, Karow M, Blander G, et al. (2006) SIRT4 inhibits glutamate dehydrogenase and opposes the effects of caloric restriction in pancreatic beta cells. *Cell* **126**:941–954.

- Hanson JE, La H, Plise E, Chen YH, Ding X, Hanania T, Sabath EV, Alexandrov V, Brunner D, Leahy E, et al. (2013) SAHA enhances synaptic function and plasticity in vitro but has limited brain availability in vivo and does not impact cognition. *PLoS One* **8**:e69964.
- Harrison BC, Huynh K, Lundgaard GL, Helmske SM, Perryman MB, and McKinsey TA (2010) Protein kinase C-related kinase targets nuclear localization signals in a subset of class IIa histone deacetylases. *FEBS Lett* **584**:1103–1110.
- Harrison IF, Crum WR, Vernon AC, and Dexter DT (2015) Neurorestoration induced by the HDAC inhibitor sodium valproate in the lactacystin model of Parkinson's is associated with histone acetylation and up-regulation of neurotrophic factors. *Br J Pharmacol* **172**:4200–4215.
- Hassig CA, Tong JK, Fleischer TC, Owa T, Grable PG, Ayer DE, and Schreiber SL (1998) A role for histone deacetylase activity in HDAC1-mediated transcriptional repression. *Proc Natl Acad Sci USA* **95**:3519–3524.
- Hauswald S, Duque-Afonso J, Wagner MM, Schertl FM, Lübbert M, Peschel C, Keller U, and Licht T (2009) Histone deacetylase inhibitors induce a very broad, pleiotropic anticancer drug resistance phenotype in acute myeloid leukemia cells by modulation of multiple ABC transporter genes. *Clin Cancer Res* **15**:3705–3715.
- Heinzel T, Lavinsky RM, Mullen TM, Söderstrom M, Laherty CD, Torchia J, Yang WM, Brard G, Ngo SD, Davie JR, et al. (1997) A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. *Nature* **387**:43–48.
- Henriksen U, Fog JU, Litman T, and Gether U (2005) Identification of intra- and intermolecular disulfide bridges in the multidrug resistance transporter ABCG2. *J Biol Chem* **280**:36926–36934.
- Henrique R, Oliveira AI, Costa VL, Baptista T, Martins AT, Morais A, Oliveira J, and Jerónimo C (2013) Epigenetic regulation of MDR1 gene through post-translational histone modifications in prostate cancer. *BMC Genomics* **14**:898.
- Hirschhorn JN, Brown SA, Clark CD, and Winston F (1992) Evidence that SNF2/SWI2 and SNF5 activate transcription in yeast by altering chromatin structure. *Genes Dev* **6**:2288–2298.
- Hockley E, Richon VM, Woodman B, Smith DL, Zhou X, Rosa E, Sathasivam K, Ghazi-Noori S, Mahal A, Lowden PA, et al. (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc Natl Acad Sci USA* **100**:2041–2046.
- Hong L, Schroth GP, Matthews HR, Yau P, and Bradbury EM (1993) Studies of the DNA binding properties of histone H4 amino terminus. Thermal denaturation studies reveal that acetylation markedly reduces the binding constant of the H4 "tail" to DNA. *J Biol Chem* **268**:305–314.
- Hoque MT, Robillard KR, and Bendayan R (2012) Regulation of breast cancer resistant protein by peroxisome proliferator-activated receptor α in human brain microvessel endothelial cells. *Mol Pharmacol* **81**:598–609.
- Hoque MT, Shah A, More V, Miller DS, and Bendayan R (2015) In vivo and ex vivo regulation of breast cancer resistant protein (Bcrp) by peroxisome proliferator-activated receptor alpha (Ppar α) at the blood-brain barrier. *J Neurochem* **135**:1113–1122.
- Howitz KT, Bitterman KJ, Cohen HY, Lammung DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisilewski A, Zhang LL, et al. (2003) Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* **425**:191–196.
- Hsu SI, Cohen D, Kirschner LS, Lothstein L, Hartstein M, and Horwitz SB (1990) Structural analysis of the mouse mdr1a (P-glycoprotein) promoter reveals the basis for differential transcript heterogeneity in multidrug-resistant J774.2 cells. *Mol Cell Biol* **10**:3596–3606.
- Hsu SI, Lothstein L, and Horwitz SB (1989) Differential overexpression of three mdr gene family members in multidrug-resistant J774.2 mouse cells. Evidence that distinct P-glycoprotein precursors are encoded by unique mdr genes. *J Biol Chem* **264**:12053–12062.
- Hu E, Chen Z, Fredrickson T, Zhu Y, Kirkpatrick R, Zhang GF, Johanson K, Sung CM, Liu R, and Winkler J (2000) Cloning and characterization of a novel human class I histone deacetylase that functions as a transcription repressor. *J Biol Chem* **275**:15254–15264.
- Hu E, Dul E, Sung CM, Chen Z, Kirkpatrick R, Zhang GF, Johanson K, Liu R, Lago A, Hofmann G, et al. (2003) Identification of novel isoform-selective inhibitors within class I histone deacetylases. *J Pharmacol Exp Ther* **307**:720–728.
- Hubbert C, Guardiola A, Shao R, Kawaguchi Y, Ito A, Nixon A, Yoshida M, Wang XF, and Yao TP (2002) HDAC6 is a microtubule-associated deacetylase. *Nature* **417**:455–458.
- Huo H, Magro PG, Pietsch EC, Patel BB, and Scotto KW (2010) Histone methyltransferase MLL1 regulates MDR1 transcription and chemoresistance. *Cancer Res* **70**:8726–8735.
- Iizuka M and Stillman B (1999) Histone acetyltransferase HBO1 interacts with the ORC1 subunit of the human initiator protein. *J Biol Chem* **274**:23027–23034.
- Imai S, Armstrong CM, Kaerberlein M, and Guarente L (2000) Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature* **403**:795–800.
- Inoue A and Fujimoto D (1969) Enzymatic deacetylation of histone. *Biochem Biophys Res Commun* **36**:146–150.
- Inoue T, Hiratsuka M, Osaki M, Yamada H, Kishimoto I, Yamaguchi S, Nakano S, Katoh M, Ito H, and Oshimura M (2007) SIRT2, a tubulin deacetylase, acts to block the entry to chromosome condensation in response to mitotic stress. *Oncogene* **26**:945–957.
- Insinga A, Monestiroli S, Ronzoni S, Gelmetti V, Marchesi F, Viale A, Altucci L, Nervi C, Minucci S, and Pelicci PG (2005) Inhibitors of histone deacetylases induce tumor-selective apoptosis through activation of the death receptor pathway. *Nat Med* **11**:71–76.
- Istodax (romidepsin). (2009) Package insert. Celgene Corporation, Summit, NJ.
- Iwahara T, Bonasio R, Narendra V, and Reinberg D (2012) SIRT3 functions in the nucleus in the control of stress-related gene expression. *Mol Cell Biol* **32**:5022–5034.
- Iwai K, Ishikawa K, and Hayashi H (1970) Amino-acid sequence of slightly lysine-rich histone. *Nature* **226**:1056–1058.
- Jackson SM, Manolaidis I, Kowal J, Zechner M, Taylor NMI, Bause M, Bauer S, Bartholomaeus R, Bernhardt G, Koenig B, et al. (2018) Structural basis of small-molecule inhibition of human multidrug transporter ABCG2. *Nat Struct Mol Biol* **25**:333–340.
- Jin S and Scotto KW (1998) Transcriptional regulation of the MDR1 gene by histone acetyltransferase and deacetylase is mediated by NF- κ B. *Mol Cell Biol* **18**:4377–4384.
- Johnson CA, White DA, Lavender JS, O'Neill LP, and Turner BM (2002) Human class I histone deacetylase complexes show enhanced catalytic activity in the presence of ATP and co-immunoprecipitate with the ATP-dependent chaperone protein Hsp70. *J Biol Chem* **277**:9590–9597.
- Johnson RA, Ince TA, and Scotto KW (2001) Transcriptional repression by p53 through direct binding to a novel DNA element. *J Biol Chem* **276**:27716–27720.
- Jones P, Altamura S, De Francesco R, Gallinari P, Lahm A, Neddermann P, Rowley M, Serafini S, and Steinkühler C (2008) Probing the elusive catalytic activity of vertebrate class IIa histone deacetylases. *Bioorg Med Chem Lett* **18**:1814–1819.
- Jonker JW, Buitelaar M, Wagenaar E, Van Der Valk MA, Scheffer GL, Scheper RJ, Plosch T, Kuipers F, Elferink RP, Rosing H, et al. (2002) The breast cancer resistance protein protects against a major chlorophyll-derived dietary phototoxin and protoporphyria. *Proc Natl Acad Sci USA* **99**:15649–15654.
- Jonker JW, Merino G, Musters S, van Herwaarden AE, Bolscher E, Wagenaar E, Mesman E, Dale TC, and Schinkel AH (2005) The breast cancer resistance protein BCRP (ABCG2) concentrates drugs and carcinogenic xenotoxins into milk. *Nat Med* **11**:127–129.
- Juan LJ, Shia WJ, Chen MH, Yang WM, Seto E, Lin YS, and Wu CW (2000) Histone deacetylases specifically down-regulate p53-dependent gene activation. *J Biol Chem* **275**:20436–20443.
- Kaewpiboon C, Srisuttee R, Malilae W, Moon J, Oh S, Jeong HG, Johnston RN, Assavalapsakul W, and Chung YH (2015) Upregulation of Stat1-HDAC4 confers resistance to etoposide through enhanced multidrug resistance 1 expression in human A549 lung cancer cells. *Mol Med Rep* **11**:2315–2321.
- Kao HY, Downes M, Ordentlich P, and Evans RM (2000) Isolation of a novel histone deacetylase reveals that class I and class II deacetylases promote SMRT-mediated repression. *Genes Dev* **14**:55–66.
- Kao HY, Lee CH, Komarov A, Han CC, and Evans RM (2002) Isolation and characterization of mammalian HDAC10, a novel histone deacetylase. *J Biol Chem* **277**:187–193.
- Kawagoe R, Kawagoe H, and Sano K (2002) Valproic acid induces apoptosis in human leukemia cells by stimulating both caspase-dependent and -independent apoptotic signaling pathways. *Leuk Res* **26**:495–502.
- Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, and Yao TP (2003) The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell* **115**:727–738.
- Khan N, Jeffers M, Kumar S, Hackett C, Boldog F, Khramtsov N, Qian X, Mills E, Berghs SC, Carey N, et al. (2008) Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. *Biochem J* **409**:581–589.
- Khunweeraphong N, Stockner T, and Kuchler K (2017) The structure of the human ABC transporter ABCG2 reveals a novel mechanism for drug extrusion. *Sci Rep* **7**:13767.
- Kijima M, Yoshida M, Sugita K, Horinouchi S, and Beppu T (1993) Taxopxin, an antitumor cyclic tetrapeptide, is an irreversible inhibitor of mammalian histone deacetylase. *J Biol Chem* **268**:22429–22435.
- Kilgore M, Miller CA, Fass DM, Hennig KM, Haggarty SJ, Sweatt JD, and Rumbaugh G (2010) Inhibitors of class I histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. *Neuropsychopharmacology* **35**:870–880.
- Kim H, Kim SN, Park YS, Kim NH, Han JW, Lee HY, and Kim YK (2011) HDAC inhibitors downregulate MRP2 expression in multidrug resistant cancer cells: implication for chemosensitization. *Int J Oncol* **38**:807–812.
- Kim HJ, Rowe M, Ren M, Hong JS, Chen PS, and Chuang DM (2007) Histone deacetylase inhibitors exhibit anti-inflammatory and neuroprotective effects in a rat permanent ischemic model of stroke: multiple mechanisms of action. *J Pharmacol Exp Ther* **321**:892–901.
- Kim MS, Kwon HJ, Lee YM, Baek JH, Jang JE, Lee SW, Moon EJ, Kim HS, Lee SK, Chung HY, et al. (2001) Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. *Nat Med* **7**:437–443.
- Kim SN, Kim NH, Lee W, Seo DW, and Kim YK (2009) Histone deacetylase inhibitor induction of P-glycoprotein transcription requires both histone deacetylase 1 dissociation and recruitment of CAAT/enhancer binding protein beta and pCAF to the promoter region. *Mol Cancer Res* **7**:735–744.
- Kim Y, Kim H, and Jeoung D (2015) Tubulin Beta3 serves as a target of HDAC3 and mediates resistance to microtubule-targeting drugs. *Mol Cells* **38**:705–714.
- Kim YK, Kim NH, Hwang JW, Song YJ, Park YS, Seo DW, Lee HY, Choi WS, Han JW, and Kim SN (2008) Histone deacetylase inhibitor apicidin-mediated drug resistance: involvement of P-glycoprotein. *Biochem Biophys Res Commun* **368**:959–964.
- Kiran S, Chatterjee N, Singh S, Kaul SC, Wadhwa R, and Ramakrishna G (2013) Intracellular distribution of human SIRT7 and mapping of the nuclear/nucleolar localization signal. *FEBS J* **280**:3451–3466.
- Klaassen CD and Aleksunes LM (2010) Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol Rev* **62**:1–96.
- Koch-Weser J and Browne TR (1980) Drug therapy: valproic acid. *N Engl J Med* **302**:661–666.
- Kontopoulos E, Parvin JD, and Feany MB (2006) Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. *Hum Mol Genet* **15**:3012–3023.
- Krishnamurthy P, Ross DD, Nakanishi T, Bailey-Dell K, Zhou S, Mercer KE, Sarkadi B, Sorrentino BP, and Schuetz JD (2004) The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J Biol Chem* **279**:24218–24225.
- Kruhlak MJ, Hendzel MJ, Fischle W, Bertos NR, Hameed S, Yang XJ, Verdin E, and Bazett-Jones DP (2001) Regulation of global acetylation in mitosis through loss of histone acetyltransferases and deacetylases from chromatin. *J Biol Chem* **276**:38307–38319.
- Kullak-Ublick GA and Becker MB (2003) Regulation of drug and bile salt transporters in liver and intestine. *Drug Metab Rev* **35**:305–317.
- Kummar S, Gutierrez M, Gardner ER, Donovan E, Hwang K, Chung EJ, Lee MJ, Maynard K, Kalnitskiy M, Chen A, et al. (2007) Phase I trial of MS-275, a histone deacetylase inhibitor, administered weekly in refractory solid tumors and lymphoid malignancies. *Clin Cancer Res* **13**:5411–5417.
- Kuo MH, Brownell JE, Sobel RE, Ranalli TA, Cook RG, Edmondson DG, Roth SY, and Allis CD (1996) Transcription-linked acetylation by Gcn5p of histones H3 and H4 at specific lysines. *Nature* **383**:269–272.
- Kuo MH, Zhou J, Jambeck P, Churchill ME, and Allis CD (1998) Histone acetyltransferase activity of yeast Gcn5p is required for the activation of target genes in vivo. *Genes Dev* **12**:627–639.
- Kusaczuk M, Krętoski R, Stypułkowska A, and Cechowska-Pasko M (2016) Molecular and cellular effects of a novel hydroxamate-based HDAC inhibitor - belinostat - in glioblastoma cell lines: a preliminary report. *Invest New Drugs* **34**:552–564.
- Kwon HJ, Kim MS, Kim MJ, Nakajima H, and Kim KW (2002) Histone deacetylase inhibitor FK228 inhibits tumor angiogenesis. *Int J Cancer* **97**:290–296.
- Laherty CD, Yang WM, Sun JM, Davie JR, Seto E, and Eisenman RN (1997) Histone deacetylases associated with the mSin3 corepressor mediate mad transcriptional repression. *Cell* **89**:349–356.

- Lahn A, Paolini C, Pallaoro M, Nardi MC, Jones P, Neddermann P, Sambucini S, Bottomley MJ, Lo Surdo P, Carfi A, et al. (2007) Unraveling the hidden catalytic activity of vertebrate class IIa histone deacetylases. *Proc Natl Acad Sci USA* **104**:17335–17340.
- Landry J, Slama JT, and Sternglanz R (2000a) Role of NAD(+) in the deacetylase activity of the SIR2-like proteins. *Biochem Biophys Res Commun* **278**:685–690.
- Landry J, Sutton A, Tafrov ST, Heller RC, Stebbins J, Pillus L, and Sternglanz R (2000b) The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. *Proc Natl Acad Sci USA* **97**:5807–5811.
- Lankas GR, Wise LD, Cartwright ME, Pippert T, and Umbenhauer DR (1998) Placental P-glycoprotein deficiency enhances susceptibility to chemically induced birth defects in mice. *Reprod Toxicol* **12**:457–463.
- Laubach JP, Moreau P, San-Miguel JF, and Richardson PG (2015) Panobinostat for the treatment of multiple myeloma. *Clin Cancer Res* **21**:4767–4773.
- Lautz TB, Jie C, Clark S, Naiditch JA, Jafari N, Qiu YY, Zheng X, Chu F, and Madonna MB (2012) The effect of vorinostat on the development of resistance to doxorubicin in neuroblastoma. *PLoS One* **7**:e40816.
- Lecureur V, Thottassery JV, Sun D, Schuetz EG, Lahti J, Zambetti GP, and Schuetz JD (2001) Mdr1b facilitates p53-mediated cell death and p53 is required for Mdr1b upregulation in vivo. *Oncogene* **20**:303–313.
- Lee DY, Hayes JJ, Pruss D, and Wolffe AP (1993) A positive role for histone acetylation in transcription factor access to nucleosomal DNA. *Cell* **72**:73–84.
- Lee HZ, Kwitkowski VE, Del Valle PL, Ricci MS, Saber H, Habtemariam BA, Bullock J, Bloomquist E, Li Shen Y, Chen XH, et al. (2015) FDA approval: belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. *Clin Cancer Res* **21**:2666–2670.
- Lee TB, Park JH, Min YD, Kim KJ, and Choi CH (2008) Epigenetic mechanisms involved in differential MDR1 mRNA expression between gastric and colon cancer cell lines and rationales for clinical chemotherapy. *BMC Gastroenterol* **8**:33.
- Lehrmann H, Pritchard LL, and Harel-Bellan A (2002) Histone acetyltransferases and deacetylases in the control of cell proliferation and differentiation. *Adv Cancer Res* **86**:41–65.
- Levchenko A, Mehta BM, Niu X, Kang G, Villafania L, Way D, Polycarpe D, Sadelain M, and Larson SM (2005) Intercellular transfer of P-glycoprotein mediates acquired multidrug resistance in tumor cells. *Proc Natl Acad Sci USA* **102**:1933–1938.
- Lewis JR (1978) Valproic acid (Depakene). A new anticonvulsant agent. *JAMA* **240**:2190–2192.
- Li W, Nagaraja S, Delcuve GP, Hendzel MJ, and Davie JR (1993) Effects of histone acetylation, ubiquitination and variants on nucleosome stability. *Biochem J* **296**:737–744.
- Li Y, Peng L, and Seto E (2015) Histone deacetylase 10 regulates the cell cycle G2/M phase transition via a novel Let-7-HMGA2-cyclin A2 pathway. *Mol Cell Biol* **35**:3547–3565.
- Lin Y, Bircsak KM, Gorczyca L, Wen X, and Aleksunes LM (2017) Regulation of the placental BCRP transporter by PPAR gamma. *J Biochem Mol Toxicol* **31**.
- Liu Z, Tong Y, Liu Y, Liu H, Li C, Zhao Y, and Zhang Y (2014) Effects of suberoylanilide hydroxamic acid (SAHA) combined with paclitaxel (PTX) on paclitaxel-resistant ovarian cancer cells and insights into the underlying mechanisms. *Cancer Cell Int* **14**:112.
- López-Rodas G, Brosch G, Georgieva EI, Sendra R, Franco L, and Loidl P (1993) Histone deacetylase. A key enzyme for the binding of regulatory proteins to chromatin. *FEBS Lett* **317**:175–180.
- Lu Q, Yang YT, Chen CS, Davis M, Byrd JC, Etherton MR, Umar A, and Chen CS (2004) Zn2+-chelating motif-tethered short-chain fatty acids as a novel class of histone deacetylase inhibitors. *J Med Chem* **47**:467–474.
- Lucio-Eterovic AK, Cortez MA, Valera ET, Motta FJ, Queiroz RG, Machado HR, Carloti CG Jr, Neder L, Scrideli CA, and Tone LG (2008) Differential expression of 12 histone deacetylase (HDAC) genes in astrocytomas and normal brain tissue: class II and IV are hyporepressed in glioblastomas. *BMC Cancer* **8**:243.
- Madden MJ, Morrow CS, Nakagawa M, Goldsmith ME, Fairchild CR, and Cowan KH (1993) Identification of 5' and 3' sequences involved in the regulation of transcription of the human mdr1 gene in vivo. *J Biol Chem* **268**:8290–8297.
- Maliepaard M, Scheffer GL, Faneyte IF, van Gastelen MA, Pijnenborg AC, Schinkel AH, van De Vijver MJ, Scheper RJ, and Schellens JH (2001) Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues. *Cancer Res* **61**:3458–3464.
- Mao Q (2008) BCRP/ABCG2 in the placenta: expression, function and regulation. *Pharm Res* **25**:1244–1255.
- Mao Q and Unadkat JD (2015) Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport—an update. *AAPS J* **17**:65–82.
- Massart C, Poirier C, Fergelot P, Fardel O, and Gibassier J (2005) Effect of sodium butyrate on doxorubicin resistance and expression of multidrug resistance genes in thyroid carcinoma cells. *Anticancer Drugs* **16**:255–261.
- Mathieu MC, Lapierre I, Brault K, and Raymond M (2001) Aromatic hydrocarbon receptor (AhR). AhR nuclear translocator- and p53-mediated induction of the murine multidrug resistance mdr1 gene by 3-methylcholanthrene and benzo(a)pyrene in hepatoma cells. *J Biol Chem* **276**:4819–4827.
- Matsuyama A, Shimazu T, Sumida Y, Saito A, Yoshimatsu Y, Seigneurin-Berny D, Osada H, Komatsu Y, Nishino N, Khochbin S, et al. (2002) In vivo destabilization of dynamic microtubules by HDAC6-mediated deacetylation. *EMBO J* **21**:6820–6831.
- McKinsey TA, Zhang CL, Lu J, and Olson EN (2000a) Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation. *Nature* **408**:106–111.
- McKinsey TA, Zhang CL, and Olson EN (2000b) Activation of the myocyte enhancer factor-2 transcription factor by calcium/calmodulin-dependent protein kinase-stimulated binding of 14-3-3 to histone deacetylase 5. *Proc Natl Acad Sci USA* **97**:14400–14405.
- McKnight GS, Hager L, and Palmiter RD (1980) Butyrate and related inhibitors of histone deacetylase block the induction of egg white genes by steroid hormones. *Cell* **22**:469–477.
- Michishita E, Park JY, Burneski JM, Barrett JC, and Horikawa I (2005) Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol Biol Cell* **16**:4623–4635.
- Miller DS (2010) Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. *Trends Pharmacol Sci* **31**:246–254.
- Miller TA, Witter DJ, and Belvedere S (2003) Histone deacetylase inhibitors. *J Med Chem* **46**:5097–5116.
- Monga V, Swami U, Tanas M, Bossler A, Mott SL, Smith BJ, and Milhem M (2018) A phase I/II study targeting angiogenesis using bevacizumab combined with chemotherapy and a histone deacetylase inhibitor (valproic acid) in advanced sarcomas. *Cancers (Basel)* **10**.
- Montgomery RL, Davis CA, Potthoff MJ, Haberland M, Fielitz J, Qi X, Hill JA, Richardson JA, and Olson EN (2007) Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. *Genes Dev* **21**:1790–1802.
- Morrow CS, Nakagawa M, Goldsmith ME, Madden MJ, and Cowan KH (1994) Reversible transcriptional activation of mdr1 by sodium butyrate treatment of human colon cancer cells. *J Biol Chem* **269**:10739–10746.
- Mostoslavsky R, Chua KF, Lombard DB, Pang WW, Fischer MR, Gellon L, Liu P, Mostoslavsky G, Franco S, Murphy MM, et al. (2006) Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell* **124**:315–329.
- Motta MC, Divecha N, Lemieux M, Kamel C, Chen D, Gu W, Bultsma Y, McBurney M, and Guarente L (2004) Mammalian SIRT1 represses forkhead transcription factors. *Cell* **116**:551–563.
- Moynihan KA, Grimm AA, Plueger MM, Bernal-Mizrachi E, Ford E, Cras-Méneur C, Permutt MA, and Imai S (2005) Increased dosage of mammalian Sir2 in pancreatic beta cells enhances glucose-stimulated insulin secretion in mice. *Cell Metab* **2**:105–117.
- Murata T, Kurokawa R, Krones A, Tatsumi K, Ishii M, Taki T, Masuno M, Ohashi H, Yanagisawa M, Rosenfeld MG, et al. (2001) Defect of histone acetyltransferase activity of the nuclear transcriptional coactivator CBP in Rubinstein-Taybi syndrome. *Hum Mol Genet* **10**:1071–1076.
- Murray IA, Patterson AD, and Perdew GH (2014) Aryl hydrocarbon receptor ligands in cancer: friend and foe. *Nat Rev Cancer* **14**:801–814.
- Nakagawa T, Lomb DJ, Haigis MC, and Guarente L (2009) SIRT5 Deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. *Cell* **137**:560–570.
- Nakajima H, Kim YB, Terano H, Yoshida M, and Horinouchi S (1998) FR901228, a potent antitumor antibiotic, is a novel histone deacetylase inhibitor. *Exp Cell Res* **241**:126–133.
- Nakamura Y, Ogura M, Tanaka D, and Inagaki N (2008) Localization of mouse mitochondrial SIRT proteins: shift of SIRT3 to nucleus by co-expression with SIRT5. *Biochem Biophys Res Commun* **366**:174–179.
- Nakata S, Yoshida T, Horinaka M, Shiraishi T, Wakada M, and Sakai T (2004) Histone deacetylase inhibitors upregulate death receptor 5/TRAIL-R2 and sensitize apoptosis induced by TRAIL/APO2-L in human malignant tumor cells. *Oncogene* **23**:6261–6271.
- Nasrin N, Wu X, Fortier E, Feng Y, Bare' OC, Chen S, Ren X, Wu Z, Streeter RS, and Bordone L (2010) SIRT4 regulates fatty acid oxidation and mitochondrial gene expression in liver and muscle cells. *J Biol Chem* **285**:31995–32002.
- Natarajan K, Xie Y, Nakanishi T, Beck WT, Bauer KS, and Ross DD (2011) Identification and characterization of the major alternative promoter regulating Bcrp1/Abcg2 expression in the mouse intestine. *Biochim Biophys Acta* **1809**:295–305.
- Noack A, Noack S, Buettner M, Naim HY, and Löscher W (2016) Intercellular transfer of P-glycoprotein in human blood-brain barrier endothelial cells is increased by histone deacetylase inhibitors. *Sci Rep* **6**:29253.
- North BJ, Marshall BL, Borra MT, Denu JM, and Verdin E (2003) The human Sir2 ortholog, SIRT2, is an NAD+-dependent tubulin deacetylase. *Mol Cell* **11**:437–444.
- North BJ and Verdin E (2004) Sirtuins: Sir2-related NAD-dependent protein deacetylases. *Genome Biol* **5**:224.
- Odenike O, Halpern A, Godley LA, Madzo J, Karrison T, Green M, Fulton N, Mattison RJ, Yee KW, Bennett M, et al. (2015) A phase I and pharmacodynamic study of the histone deacetylase inhibitor belinostat plus azacitidine in advanced myeloid neoplasia. *Invest New Drugs* **33**:371–379.
- Odenike OM, Alkan S, Sher D, Godwin JE, Huo D, Brandt SJ, Green M, Xie J, Zhang Y, Vesole DH, et al. (2008) Histone deacetylase inhibitor romidepsin has differential activity in core binding factor acute myeloid leukemia. *Clin Cancer Res* **14**:7095–7101.
- Ogryzko VV, Schiltz RL, Russanova V, Howard BH, and Nakatani Y (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. *Cell* **87**:953–959.
- Ogura M, Takatori T, Sugimoto Y, and Tsuruo T (1991) Identification and characterization of three DNA-binding proteins on the promoter of the human MDR1 gene in drug-sensitive and -resistant cells. *Jpn J Cancer Res* **82**:1151–1159.
- Onyango P, Celic I, McCaffery JM, Boeke JD, and Feinberg AP (2002) SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. *Proc Natl Acad Sci USA* **99**:13653–13658.
- Pan G, Giri N, and Elmquist WF (2007) Abcg2/Bcrp1 mediates the polarized transport of anti-retroviral nucleosides abacavir and zidovudine. *Drug Metab Dispos* **35**:1165–1173.
- Park H, Kim Y, Park D, and Jeoung D (2014) Nuclear localization signal domain of HDAC3 is necessary and sufficient for the expression regulation of MDR1. *BMB Rep* **47**:342–347.
- Park JH, Jung Y, Kim TY, Kim SG, Jong HS, Lee JW, Kim DK, Lee JS, Kim NK, Kim TY, et al. (2004) Class I histone deacetylase-selective novel synthetic inhibitors potently inhibit human tumor proliferation. *Clin Cancer Res* **10**:5271–5281.
- Pasvanis S, Tremblay S, and Dumais N (2012) High sodium butyrate levels induce MDR1 activation in colorectal cells: impact of 15-deoxy-Δ(12,14)-prostaglandin J(2) on the resistance to saquinavir. *Biochem Biophys Res Commun* **418**:609–615.
- Pavek P and Smutny T (2014) Nuclear receptors in regulation of biotransformation enzymes and drug transporters in the placental barrier. *Drug Metab Rev* **46**:19–32.
- Peart MJ, Tainton KM, Ruefli AA, Dear AE, Sedelies KA, O'Reilly LA, Waterhouse NJ, Trapani JA, and Johnston RW (2003) Novel mechanisms of apoptosis induced by histone deacetylase inhibitors. *Cancer Res* **63**:4460–4471.
- Petrie K, Guidex F, Howell L, Healy L, Waxman S, Greaves M, and Zelent A (2003) The histone deacetylase 9 gene encodes multiple protein isoforms. *J Biol Chem* **278**:16059–16072.
- Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ, et al. (1995) Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature* **376**:348–351.
- Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, and Klein PS (2001) Histone deacetylase is a direct target for valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem* **276**:36734–36741.
- Plumb JA, Finn PW, Williams RJ, Bandara MJ, Romero MR, Watkins CJ, La Thangue NB, and Brown R (2003) Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. *Mol Cancer Ther* **2**:721–728.
- Pogo BG, Allfrey VG, and Mirsky AE (1966) RNA synthesis and histone acetylation during the course of gene activation in lymphocytes. *Proc Natl Acad Sci USA* **55**:805–812.
- Pollex E, Lubetsky A, and Koren G (2008) The role of placental breast cancer resistance protein in the efflux of glyburide across the human placenta. *Placenta* **29**:743–747.

- Pontén F, Jirstrom K, and Uhlen M (2008) The Human Protein Atlas—a tool for pathology. *J Pathol* **216**:387–393.
- Poole RM (2014) Belinostat: first global approval. *Drugs* **74**:1543–1554.
- Puerta C, Hernández F, López-Alarcón L, and Palacián E (1995) Acetylation of histone H2A.H2B dimers facilitates transcription. *Biochem Biophys Res Commun* **210**:409–416.
- Pugh BF and Tjian R (1991) Transcription from a TATA-less promoter requires a multisubunit TFIID complex. *Genes Dev* **5**:1935–1945.
- Qi X, Hosoi T, Okuma Y, Kaneko M, and Nomura Y (2004) Sodium 4-phenylbutyrate protects against cerebral ischemic injury. *Mol Pharmacol* **66**:899–908.
- Qian DZ, Kato Y, Shabbeer S, Wei Y, Verheul HM, Salumbides B, Sanni T, Atadja P, and Pili R (2006) Targeting tumor angiogenesis with histone deacetylase inhibitors: the hydroxamic acid derivative LBH589. *Clin Cancer Res* **12**:634–642.
- Qing H, He G, Ly PT, Fox CJ, Staufenbiel M, Cai F, Zhang Z, Wei S, Sun X, Chen CH, et al. (2008) Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. *J Exp Med* **205**:2781–2789.
- Rabindran SK, He H, Singh M, Brown E, Collins KI, Annable T, and Greenberger LM (1998) Reversal of a novel multidrug resistance mechanism in human colon carcinoma cells by fumitremogin C. *Cancer Res* **58**:5850–5858.
- Raymond M and Gros P (1989) Mammalian multidrug-resistance gene: correlation of exon organization with structural domains and duplication of an ancestral gene. *Proc Natl Acad Sci USA* **86**:6488–6492.
- Raymond M and Gros P (1990) Cell-specific activity of cis-acting regulatory elements in the promoter of the mouse multidrug resistance gene mdr1. *Mol Cell Biol* **10**:6036–6040.
- Richon VM, Emiliani S, Verdin E, Webb Y, Breslow R, Rifkind RA, and Marks PA (1998) A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. *Proc Natl Acad Sci USA* **95**:3003–3007.
- Richon VM, Sandhoff TW, Rifkind RA, and Marks PA (2000) Histone deacetylase inhibitor selectively induces p21WAF1 expression and gene-associated histone acetylation. *Proc Natl Acad Sci USA* **97**:10014–10019.
- Riggs MG, Whittaker RG, Neumann JR, and Ingram VM (1977) n-Butyrate causes histone modification in HeLa and Friend erythroleukemia cells. *Nature* **268**:462–464.
- Robey RW, Zhan Z, Piekarz RL, Kayastha GL, Fojo T, and Bates SE (2006) Increased MDR1 expression in normal and malignant peripheral blood mononuclear cells obtained from patients receiving desipeptide (FR901228, FK228, NSC630176). *Clin Cancer Res* **12**:1547–1555.
- Roninson IB, Chin JE, Choi KG, Gros P, Housman DE, Fojo A, Shen DW, Gottesman MM, and Pastan I (1986) Isolation of human mdr DNA sequences amplified in multidrug-resistant KB carcinoma cells. *Proc Natl Acad Sci USA* **83**:4538–4542.
- Rubinchik-Stem M, Shmuel M, and Eyal S (2015) Antiepileptic drugs alter the expression of placental carriers: an in vitro study in a human placental cell line. *Epilepsia* **56**:1023–1032.
- Rundlett SE, Carmen AA, Kobayashi R, Baykinn S, Turner BM, and Grunstein M (1996) HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. *Proc Natl Acad Sci USA* **93**:14503–14508.
- Ryan QC, Headlee D, Acharya M, Sparreboom A, Trepel JB, Ye J, Figg WD, Hwang K, Chung EJ, Murgo A, et al. (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.
- Rybouchkin A, Kato Y, and Tsunoda Y (2006) Role of histone acetylation in reprogramming of somatic nuclei following nuclear transfer. *Biol Reprod* **74**:1083–1089.
- Sadhasivam S, Chidambaram V, Zhang X, Ganderi A, Esslinger H, Zhang K, Martin LJ, and McAuliffe J (2015) Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. *Pharmacogenomics J* **15**:119–126.
- Sampath J, Sun D, Kidd VJ, Grenet J, Gandhi A, Shapiro LH, Wang Q, Zambetti GP, and Schuetz JD (2001) Mutant p53 cooperates with ETS and selectively up-regulates human MDR1 not MRP1. *J Biol Chem* **276**:39359–39367.
- Schech AJ, Shah P, Yu S, Sabnis GJ, Goloubeva O, Rosenblatt P, Kazi A, Chumsri S, and Brodie A (2015) Histone deacetylase inhibitor entinostat in combination with a retinoid downregulates HER2 and reduces the tumor initiating cell population in aromatase inhibitor-resistant breast cancer. *Breast Cancer Res Treat* **152**:499–508.
- Scher MB, Vaquero A, and Reinberg D (2007) SirT3 is a nuclear NAD⁺-dependent histone deacetylase that translocates to the mitochondria upon cellular stress. *Genes Dev* **21**:920–928.
- Schinkel AH (1999) P-Glycoprotein, a gatekeeper in the blood-brain barrier. *Adv Drug Deliv Rev* **36**:179–194.
- Schinkel AH, Mayer U, Wagenaar E, Mol CA, van Deemter L, Smit JJ, van der Valk MA, Voordouw AC, Spits H, van Tellingen O, et al. (1997) Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins. *Proc Natl Acad Sci USA* **94**:4028–4033.
- Schmitt HM, Schlamp CL, and Nickells RW (2016) Role of HDACs in optic nerve damage-induced nuclear atrophy of retinal ganglion cells. *Neurosci Lett* **625**:11–15.
- Scotti KW (2003) Transcriptional regulation of ABC drug transporters. *Oncogene* **22**:7496–7511.
- Seelig A and Landwojtowicz E (2000) Structure-activity relationship of P-glycoprotein substrates and modifiers. *Eur J Pharm Sci* **12**:31–40.
- Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, and Kurdastani SK (2005) Global histone modification patterns predict risk of prostate cancer recurrence. *Nature* **435**:1262–1266.
- Sharom FJ (2006) Shedding light on drug transport: structure and function of the P-glycoprotein multidrug transporter (ABCB1). *Biochem Cell Biol* **84**:979–992.
- Sharom FJ (2008) ABC multidrug transporters: structure, function and role in chemoresistance. *Pharmacogenomics* **9**:105–127.
- Shin BS, Bullitta JB, Balthasar JP, Kim M, Choi Y, and Yoo SD (2011) Prediction of human pharmacokinetics and tissue distribution of apicidin, a potent histone deacetylase inhibitor, by physiologically based pharmacokinetic modeling. *Cancer Chemother Pharmacol* **68**:465–475.
- Sike A, Nagy E, Vedelek B, Pusztai D, Szerényi P, Venetianer A, and Boros IM (2014) mRNA levels of related Abcb genes change opposite to each other upon histone deacetylase inhibition in drug-resistant rat hepatoma cells. *PLoS One* **9**:e84915.
- Simonini MV, Camargo LM, Dong E, Maloku E, Veldic M, Costa E, and 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.
- Sinn DI, Kim SJ, Chu K, Jung KH, Lee ST, Song EC, Kim JM, Park DK, Kun Lee S, Kim M, et al. (2007) Valproic acid-mediated neuroprotection in intracerebral hemorrhage via histone deacetylase inhibition and transcriptional activation. *Neurobiol Dis* **26**:464–472.
- Sommer A, Hilfenhaus S, Menkel A, Kremmer E, Seiser C, Loidl P, and Lüscher B (1997) Cell growth inhibition by the Mad/Max complex through recruitment of histone deacetylase activity. *Curr Biol* **7**:357–365.
- Southwood CM, Peppi M, Dryden S, Tainsky MA, and Gow A (2007) Microtubule deacetylases, SirT2 and HDAC6, in the nervous system. *Neurochem Res* **32**:187–195.
- Sparreboom A, van Asperen J, Mayer U, Schinkel AH, Smit JW, Meijer DK, Borst P, Noolen WJ, Beijnen JH, and van Tellingen O (1997) Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. *Proc Natl Acad Sci USA* **94**:2031–2035.
- St-Pierre MV, Serrano MA, Macias RI, Dubs U, Hoechli M, Lauper U, Meier PJ, and Marin JJ (2000) Expression of members of the multidrug resistance protein family in human term placenta. *Am J Physiol Regul Integr Comp Physiol* **279**:R1495–R1503.
- Sugo N, Oshiro H, Takemura M, Kobayashi T, Kohno Y, Uesaka N, Song WJ, and Yamamoto N (2010) Nucleocytoplasmic translocation of HDAC9 regulates gene expression and dendritic growth in developing cortical neurons. *Eur J Neurosci* **31**:1521–1532.
- Sun ZW and Allis CD (2002) Ubiquitination of histone H2B regulates H3 methylation and gene silencing in yeast. *Nature* **418**:104–108.
- Sundseth R, MacDonald G, Ting J, and King AC (1997) DNA elements recognizing NF-Y and Sp1 regulate the human multidrug-resistance gene promoter. *Mol Pharmacol* **51**:963–971.
- Sung MT and Dixon GH (1970) Modification of histones during spermiogenesis in trout: a molecular mechanism for altering histone binding to DNA. *Proc Natl Acad Sci USA* **67**:1616–1623.
- Susanto J, Lin YH, Chen YN, Shen CR, Yan YT, Tsai ST, Chen CH, and Shen CN (2008) Porphyrin homeostasis maintained by ABCG2 regulates self-renewal of embryonic stem cells. *PLoS One* **3**:e4023.
- Suzuki T, Ando T, Tsuchiya K, Fukazawa N, Saito A, Mariko Y, Yamashita T, and Nakanishi O (1999) Synthesis and histone deacetylase inhibitory activity of new benzamide derivatives. *J Med Chem* **42**:3001–3003.
- Suzuki T, Uchida H, Takeuchi H, Nakajima S, Nomura K, Tanabe A, Yagi G, Watanabe K, and Kashima H (2009) Augmentation of atypical antipsychotics with valproic acid. An open-label study for most difficult patients with schizophrenia. *Hum Psychopharmacol* **24**:628–638.
- Szatmari I, Vámosi G, Brazda P, Balint BL, Benko S, Széles L, Jeney V, Orzveg-Laczka C, Szántó A, Barta E, et al. (2006) Peroxisome proliferator-activated receptor gamma-regulated ABCG2 expression confers cytoprotection to human dendritic cells. *J Biol Chem* **281**:23812–23823.
- Tabe Y, Konopleva M, Contractor R, Munsell M, Schober WD, Jin L, Tsutsumi-Ishii Y, Nagaoka I, Igari J, and Andreeff M (2006) Up-regulation of MDR1 and induction of doxorubicin resistance by histone deacetylase inhibitor desipeptide (FK228) and ATRA in acute promyelocytic leukemia cells. *Blood* **107**:1546–1554.
- Takizawa D, Kakizaki S, Horiguchi N, Tojima H, Yamazaki Y, Ichikawa T, Sato K, and Mori M (2010) Histone deacetylase inhibitors induce cytochrome P450 2B by activating nuclear receptor constitutive androstane receptor. *Drug Metab Dispos* **38**:1493–1498.
- Tan KP, Wang B, Yang M, Boutros PC, Macaulay J, Xu H, Chuang AI, Kosuge K, Yamamoto M, Takahashi S, et al. (2010) Aryl hydrocarbon receptor is a transcriptional activator of the human breast cancer resistance protein (BCRP/ABCG2). *Mol Pharmacol* **78**:175–185.
- Tanaka Y, Slitt AL, Leazer TM, Maher JM, and Klaassen CD (2005) Tissue distribution and hormonal regulation of the breast cancer resistance protein (Bcrp/Abcg2) in rats and mice. *Biochem Biophys Res Commun* **326**:181–187.
- Tanno M, Sakamoto J, Miura T, Shimamoto K, and Horio Y (2007) Nucleocytoplasmic shuttling of the NAD⁺-dependent histone deacetylase SIRT1. *J Biol Chem* **282**:6823–6832.
- Tanny JC, Dowd GJ, Huang J, Hilz H, and Moazed D (1999) An enzymatic activity in the yeast Sir2 protein that is essential for gene silencing. *Cell* **99**:735–745.
- Taunton J, Hassig CA, and Schreiber SL (1996) A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. *Science* **272**:408–411.
- Taylor NMI, Manolaidis I, Jackson SM, Kowal J, Stahlberg H, and Locher KP (2017) Structure of the human multidrug transporter ABCG2. *Nature* **546**:504–509.
- Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, and Willingham MC (1987) Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proc Natl Acad Sci USA* **84**:7735–7738.
- Thompson CA (2006) Vorinostat approved for rare lymphoma. *Am J Health Syst Pharm* **63**:2168.
- Thottassery JV, Zambetti GP, Arimori K, Schuetz EG, and Schuetz JD (1997) p53-dependent regulation of MDR1 gene expression causes selective resistance to chemotherapeutic agents. *Proc Natl Acad Sci USA* **94**:11037–11042.
- Thul PJ, Åkesson L, Wiking M, Mahdessian D, Geladaki A, Ait Blal H, Alm T, Asplund A, Björk L, Breckels LM, et al. (2017) A subcellular map of the human proteome. *Science* **356**.
- Timmermann S, Lehmann H, Polesskaya A, and Harel-Bellan A (2001) Histone acetylation and disease. *Cell Mol Life Sci* **58**:728–736.
- To KK, Polgar O, Huff LM, Morisaki K, and Bates SE (2008) Histone modifications at the ABCG2 promoter following treatment with histone deacetylase inhibitor mirror those in multidrug-resistant cells. *Mol Cancer Res* **6**:151–164.
- To KK, Robey R, Zhan Z, Bangiolio L, and Bates SE (2011) Upregulation of ABCG2 by romidepsin via the aryl hydrocarbon receptor pathway. *Mol Cancer Res* **9**:516–527.
- Tomiyasu H, Goto-Koshino Y, Fujino Y, Ohno K, and Tsujimoto H (2014) Epigenetic regulation of the ABCB1 gene in drug-sensitive and drug-resistant lymphoid tumour cell lines obtained from canine patients. *Vet J* **199**:103–109.
- Toth M, Boros IM, and Balint E (2012) Elevated level of lysine 9-acetylated histone H3 at the MDR1 promoter in multidrug-resistant cells. *Cancer Sci* **103**:659–669.
- Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, and Nestler EJ (2006) Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* **9**:519–525.
- Ueda K, Clark DP, Chen CJ, Roninson IB, Gottesman MM, and Pastan I (1987a) The human multidrug resistance (mdr1) gene. cDNA cloning and transcription initiation. *J Biol Chem* **262**:505–508.
- Ueda K, Cornwell MM, Gottesman MM, Pastan I, Roninson IB, Ling V, and Riordan JR (1986) The mdr1 gene, responsible for multidrug-resistance, codes for P-glycoprotein. *Biochem Biophys Res Commun* **141**:956–962.
- Ueda K, Pastan I, and Gottesman MM (1987b) Isolation and sequence of the promoter region of the human multidrug-resistance (P-glycoprotein) gene. *J Biol Chem* **262**:17432–17436.
- Uhlén M, Björling E, Agatón C, Szgyarto CA, Amin B, Andersen E, Andersson AC, Angelidou P, Asplund A, Asplund C, et al. (2005) A human protein atlas for normal and cancer tissues based on antibody proteomics. *Mol Cell Proteomics* **4**:1920–1932.

- Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, et al. (2015) Proteomics. Tissue-based map of the human proteome. *Science* **347**:1260419.
- Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M, Zwahlen M, Kampf C, Wester K, Hober S, et al. (2010) Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol* **28**:1248–1250.
- Uhlen M, Zhang C, Lee S, Sjöstedt E, Fagerberg L, Bidkhorji G, Benfeitas R, Arif M, Liu Z, Edfors F, et al. (2017) A pathology atlas of the human cancer transcriptome. *Science* **357**.
- Ungerstedt JS, Sowa Y, Xu WS, Shao Y, Dokmanovic M, Perez G, Ngo L, Holmgren A, Jiang X, and Marks PA (2005) Role of thioredoxin in the response of normal and transformed cells to histone deacetylase inhibitors. *Proc Natl Acad Sci USA* **102**:673–678.
- USFDA (1978) Valproic acid and sodium valproate approved for use in epilepsy. *FDA Drug Bull* **8**:14–15.
- van der Blik AM, Kooiman PM, Schneider C, and Borst P (1988) Sequence of mdr3 cDNA encoding a human P-glycoprotein. *Gene* **71**:401–411.
- Valdez BC, Li Y, Murray D, Brammer JE, Liu Y, Hosang C, Nieto Y, Champlin RE, and Andersson BS (2016) Differential effects of histone deacetylase inhibitors on cellular drug transporters and their implications for using epigenetic modifiers in combination chemotherapy. *Oncotarget* **7**:63829–63838.
- van Groenigen M, Valentijn LJ, and Baas F (1993) Identification of a functional initiator sequence in the human MDR1 promoter. *Biochim Biophys Acta* **1172**:138–146.
- Van Lint C, Emiliani S, Ott M, and Verdin E (1996) Transcriptional activation and chromatin remodeling of the HIV-1 promoter in response to histone acetylation. *EMBO J* **15**:1112–1120.
- Vannini A, Volpari C, Filocamo G, Casavola EC, Brunetti M, Renzoni D, Chakravarty P, Paolini C, De Francesco R, Gallinari P, et al. (2004) Crystal structure of a eukaryotic zinc-dependent histone deacetylase, human HDAC8, complexed with a hydroxamic acid inhibitor. *Proc Natl Acad Sci USA* **101**:15064–15069.
- Vaziri H, Dessain SK, Ng Eaton E, Imai SI, Frye RA, Pandita TK, Guarente L, and Weinberg RA (2001) hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. *Cell* **107**:149–159.
- Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, Attner MA, Cabrera SM, McDonough CB, Brindle PK, Abel T, et al. (2007) Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB/CPB-dependent transcriptional activation. *J Neurosci* **27**:6128–6140.
- Verdel A, Curtet S, Brocard MP, Rousseaux S, Lemerrier C, Yoshida M, and Khochbin S (2000) Active maintenance of mHDA2/mHDA6 histone-deacetylase in the cytoplasm. *Curr Biol* **10**:747–749.
- Vidali G, Boffa LC, Bradbury EM, and Allfrey VG (1978) Butyrate suppression of histone deacetylation leads to accumulation of multiacetylated forms of histones H3 and H4 and increased DNase I sensitivity of the associated DNA sequences. *Proc Natl Acad Sci USA* **75**:2239–2243.
- Wakabayashi K, Nakagawa H, Adachi T, Kii I, Kobatake E, Kudo A, and Ishikawa T (2006) Identification of cysteine residues critically involved in homodimer formation and protein expression of human ATP-binding cassette transporter ABCG2: a new approach using the flip recombinase system. *J Exp Ther Oncol* **5**:205–222.
- Waltregny D, De Leval L, Glénisson W, Ly Tran S, North BJ, Bellahçène A, Weidle U, Verdin E, and Castronovo V (2004) Expression of histone deacetylase 8, a class I histone deacetylase, is restricted to cells showing smooth muscle differentiation in normal human tissues. *Am J Pathol* **165**:553–564.
- Wang AH, Bertos NR, Vezmar M, Pelletier N, Crosato M, Heng HH, Th'ng J, Han J, and Yang XJ (1999) HDAC4, a human histone deacetylase related to yeast HDA1, is a transcriptional co-repressor. *Mol Cell Biol* **19**:7816–7827.
- Wang AH and Yang XJ (2001) Histone deacetylase 4 possesses intrinsic nuclear import and export signals. *Mol Cell Biol* **21**:5992–6005.
- Wang DF, Helquist P, Wiech NL, and 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.
- Wang H, Chi CH, Zhang Y, Shi B, Jia R, and Wang BJ (2019) Effects of histone deacetylase inhibitors on ATP-binding cassette transporters in lung cancer A549 and colorectal cancer HCT116 cells. *Oncol Lett* **18**:63–71.
- Wang H, Lee EW, Zhou L, Leung PC, Ross DD, Unadkat JD, and Mao Q (2008) Progesterone receptor (PR) isoforms PRA and PRB differentially regulate expression of the breast cancer resistance protein in human placental choriocarcinoma BeWo cells. *Mol Pharmacol* **73**:845–854.
- Wang L, Liu L, and Berger SL (1998) Critical residues for histone acetylation by Gcn5, functioning in Ada and SAGA complexes, are also required for transcriptional function in vivo. *Genes Dev* **12**:640–653.
- Wang L, Mizzen C, Ying C, Candau R, Barlev N, Brownell J, Allis CD, and Berger SL (1997) Histone acetyltransferase activity is conserved between yeast and human GCN5 and is required for complementation of growth and transcriptional activation. *Mol Cell Biol* **17**:519–527.
- Wang RB, Kuo CL, Lien LL, and Lien EJ (2003) Structure-activity relationship: analyses of p-glycoprotein substrates and inhibitors. *J Clin Pharm Ther* **28**:203–228.
- Wang W, Bodles-Brakhop AM, and Barger SW (2016) A role for P-glycoprotein in clearance of Alzheimer amyloid β -peptide from the brain. *Curr Alzheimer Res* **13**:615–620.
- Wang X, Wu X, Wang C, Zhang W, Ouyang Y, Yu Y, and He Z (2010) Transcriptional suppression of breast cancer resistance protein (BCRP) by wild-type p53 through the NF-kappaB pathway in MCF-7 cells. *FEBS Lett* **584**:3392–3397.
- Wen YD, Perissi V, Staszewski LM, Yang WM, Krones A, Glass CK, Rosenfeld MG, and Seto E (2000) The histone deacetylase-3 complex contains nuclear receptor corepressors. *Proc Natl Acad Sci USA* **97**:7202–7207.
- Wu X, Chen PS, Dallas S, Wilson B, Block ML, Wang CC, Kinyamu H, Lu N, Gao X, Leng Y, et al. (2008) Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons. *Int J Neuropsychopharmacol* **11**:1123–1134.
- Wu Y, Starzinski-Powitz A, and Guo SW (2007) Trichostatin A, a histone deacetylase inhibitor, attenuates invasiveness and reactivates E-cadherin expression in immortalized endometrial cells. *Reprod Sci* **14**:374–382.
- Xiao JJ, Huang Y, Dai Z, Sadée W, Chen J, Liu S, Marcucci G, Byrd J, Covey JM, Wright J, et al. (2005) Chemoresistance to depsipeptide FK228 [(E)-(1S,4S,10S,21R)-7-(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]-tricos-16-ene-3,6,9,22-pentane] is mediated by reversible MDR1 induction in human cancer cell lines. *J Pharmacol Exp Ther* **314**:467–475.
- Xie R, Hammarlund-Udenaes M, de Boer AG, and de Lange EC (1999) The role of P-glycoprotein in blood-brain barrier transport of morphine: transcorical microdialysis studies in mdr1a (-/-) and mdr1a (+/+) mice. *Br J Pharmacol* **128**:563–568.
- Xu WS, Parmigiani RB, and Marks PA (2007) Histone deacetylase inhibitors: molecular mechanisms of action. *Oncogene* **26**:5541–5552.
- Xu Y, Jiang Z, Yin P, Li Q, and Liu J (2012) Role for class I histone deacetylases in multidrug resistance. *Exp Cell Res* **318**:177–186.
- Xuan AG, Pan XB, Wei P, Ji WD, Zhang WJ, Liu JH, Hong LP, Chen WL, and Long DH (2015) Valproic acid alleviates memory deficits and attenuates amyloid- β deposition in transgenic mouse model of Alzheimer's disease. *Mol Neurobiol* **51**:300–312.
- Yamasaki Y, Kobayashi K, and Chiba K (2018) Effect of pregnenolone 16 α -carbonitrile on the expression of P-glycoprotein in the intestine, brain and liver of mice. *Biol Pharm Bull* **41**:972–977.
- Yan JK, Gong ZZ, Zhang T, and Cai W (2017) Sodium butyrate attenuates soybean oil-based lipid emulsion-induced increase in intestinal permeability of lipopolysaccharide by modulation of P-glycoprotein in Caco-2 cells. *Biochem Biophys Res Commun* **482**:791–795.
- Yang LP (2011) Romidepsin in the treatment of T-cell lymphoma. *Drugs* **71**:1469–1480.
- Yang WM, Tsai SC, Wen YD, Fejer G, and Seto E (2002) Functional domains of histone deacetylase-3. *J Biol Chem* **277**:9447–9454.
- Yang XJ, Ogrzyk VV, Nishikawa J, Howard BH, and Nakatani Y (1996) A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. *Nature* **382**:319–324.
- Yatouji S, El-Khoury V, Trentesaux C, Trussardi-Regnier A, Benabid R, Bontems F, and Dufer J (2007) Differential modulation of nuclear texture, histone acetylation, and MDR1 gene expression in human drug-sensitive and -resistant OV1 cell lines. *Int J Oncol* **30**:1003–1009.
- Ye P, Xing H, Lou F, Wang K, Pan Q, Zhou X, Gong L, and Li D (2016) Histone deacetylase 2 regulates doxorubicin (Dox) sensitivity of colorectal cancer cells by targeting ABCB1 transcription. *Cancer Chemother Pharmacol* **77**:613–621.
- Yoshida M, Kijima M, Akita M, and Beppu T (1990) Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. *J Biol Chem* **265**:17174–17179.
- You D, Shin HM, Mossaad F, Richardson JR, and Aleksunes LM (2019a) Brain region-specific regulation of histone acetylation and efflux transporters in mice. *J Biochem Mol Toxicol* DOI: 10.1002/jbt.22318 [published ahead of print].
- You D, Wen X, Gorczyca L, Morris A, Richardson JR, and Aleksunes LM (2019b) Increased MDR1 transporter expression in human brain endothelial cells through enhanced histone acetylation and activation of aryl hydrocarbon receptor signaling. *Mol Neurobiol* **56**:6986–7002.
- Zhang W, Bone JR, Edmondson DG, Turner BM, and Roth SY (1998) Essential and redundant functions of histone acetylation revealed by mutation of target lysines and loss of the Gcn5p acetyltransferase. *EMBO J* **17**:3155–3167.
- Zhang W, Xiong H, Callaghan D, Liu H, Jones A, Pei K, Fatehi D, Brunette E, and Stanimirovic D (2013) Blood-brain barrier transport of amyloid beta peptides in efflux pump knock-out animals evaluated by in vivo optical imaging. *Fluids Barriers CNS* **10**:13.
- Zhang Y, Kwon S, Yamaguchi T, Cubizolles F, Rousseaux S, Kneissel M, Cao C, Li N, Cheng HL, Chua K, et al. (2008) Mice lacking histone deacetylase 6 have hyperacetylated tubulin but are viable and develop normally. *Mol Cell Biol* **28**:1688–1701.
- Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A, and Reinberg D (1999) Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. *Genes Dev* **13**:1924–1935.
- Zhang Z, Wang Y, Chen J, Tan Q, Xie C, Li C, Zhan W, and Wang M (2016) Silencing of histone deacetylase 2 suppresses malignancy for proliferation, migration, and invasion of glioblastoma cells and enhances temozolomide sensitivity. *Cancer Chemother Pharmacol* **78**:1289–1296.
- Zhang ZY and Schlusener HJ (2013) Oral administration of histone deacetylase inhibitor MS-275 ameliorates neuroinflammation and cerebral amyloidosis and improves behavior in a mouse model. *J Neuropathol Exp Neurol* **72**:178–185.
- Zhao G, Wang G, Bai H, Li T, Gong F, Yang H, Wen J, and Wang W (2017) Targeted inhibition of HDAC8 increases the doxorubicin sensitivity of neuroblastoma cells via up regulation of miR-137. *Eur J Pharmacol* **802**:20–26.
- Zhao L, Bin S, He HL, Yang JM, Pu YC, Gao CH, Wang H, and Wang BL (2018) Sodium butyrate increases P-gp expression in lung cancer by upregulation of STAT3 and mRNA stabilization of ABCB1. *Anticancer Drugs* **29**:227–233.
- Zhou L, Narahariseti SB, Wang H, Unadkat JD, Hebert MF, and Mao Q (2008) The breast cancer resistance protein (Bcrp1/Abcg2) limits fetal distribution of glyburide in the pregnant mouse: an Obstetric-Fetal Pharmacology Research Unit Network and University of Washington Specialized Center of Research Study. *Mol Pharmacol* **73**:949–959.
- Zhou R, Wu J, Tang X, Wei X, Ju C, Zhang F, Sun J, Shuai D, Zhang Z, Liu Q, et al. (2018) Histone deacetylase inhibitor AR-42 inhibits breast cancer cell growth and demonstrates a synergistic effect in combination with 5-FU. *Oncol Lett* **16**:1967–1974.
- Zolinda (vorinostat). (2006) Package insert. Merck & Co, Kenilworth, NJ.

Address correspondence to: Dr. Lauren M. Aleksunes, Department of Pharmacology and Toxicology, Rutgers University, 170 Frelinghuysen Road, Piscataway, NJ 08854. E-mail: aleksunes@ehs.rutgers.edu