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Histone Deacetylase Inhibitors as Therapeutic Agents for Cancer Therapy: Drug Metabolism and Pharmacokinetic Properties

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1. Introduction

The processes of absorption (A), distribution (D), metabolism (M) and excretion (E) (collectively referred as ADME) determine the pharmacokinetics (PK) of a compound. Lack of optimum PK is one of the major reasons for compounds to fail in the clinic resulting in high attrition rates. In the beginning of 1990, 39% of the drugs failed in the clinic due to poor PK emphasizing its importance in drug development (Waterbeemd and Gifford, 2003). In 1988, a study of the pharmaceutical companies in UK showed that non-optimal PK was one of the major reasons (~40%) for termination of drugs in development (Prentis et al., 1988). In the last two decades this number dropped to ~ 10% (Yengi et al., 2007). The main reasons for this significant drop in the number of compounds failing for PK reasons can be attributed to the following: a) application of concepts of drug metabolism and PK to design compounds in medicinal chemistry programs (Smith et al., 1996); b) development of *in vitro* ADME assays that are predictive of *in vivo* behavior (PK) of drugs (Obach et al., 1997; Venkatakrishnan et al.,2003; Pelkonen and Raunio, 2005; Thompson,2000; Fagerholm, 2007); c) use of the Lipinski rule of 5 to design oral drugs (Lipinski, 2000); d) development of computer programs to predict the human PK parameters and profiles based on *in vitro* ADME properties of drugs (Jamei et al., 2009); e) PK/PD correlation studies in preclinical setting and f) high throughput screening of ADME properties in *in vitro* and *in vivo* assays for hundreds of compounds in the lead identification to lead optimization stages of drug discovery. The consequence of all the above mentioned developments in ADME have resulted in the frontloading of non-drug like compounds early in drug discovery and ultimately reducing the attrition rates of compounds in the clinic.

Histone acetylases (HATs) and Histone deacetylases (HDACs) are enzymes that carry out acetylation and deacetylation, respectively, of histone proteins (Minucci and Pelicci, 2006). Histone proteins form a complex with DNA called as nucleosomes, which are the structural units of chromatin. The interplay of HATs and HDACs activities regulate the structure of chromatin and control gene expression. The aberrant expression of HDACs has been linked to the pathogenesis of cancer (Minucci and Pelicci, 2006). Histone deacetylase inhibitors

(HDACi) are an emerging class of therapeutic agents that induce tumor cell cytostasis, differentiation and apoptosis in various hematologic and solid malignancies (Mercurio et al., 2010; Stimson et al., 2009). They are known to exert their anti-tumor activity by inhibiting the HDACs, which play an important role in controlling gene expression by chromatin remodeling, that affect cell cycle and survival pathways (Stimson et al., 2009). Inhibitors of histone deacetylases (HDACi) also show promising anti-inflammatory properties as demonstrated in a number of animal and cellular models of inflammatory diseases and for diabetes (Christensen et al., 2011). The HDACi Zolinza (Vorinostat/ Suberolyanilide hydroxamic acid [SAHA]) and Romidepsin (FK228) have been approved by the FDA (United States Food and Drug Administration) for the treatment of cutaneous T cell Lymphoma (CTCL) (Mann et al., 2007, Grant et al.,2010) and for peripheral T cell lymphoma (PTCL)(http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022393s004ltr.pdf) as such demonstrating clinical "proof-of-principle" for this class of compounds.

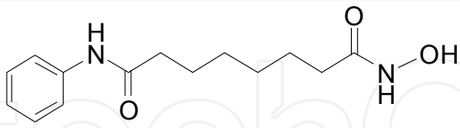
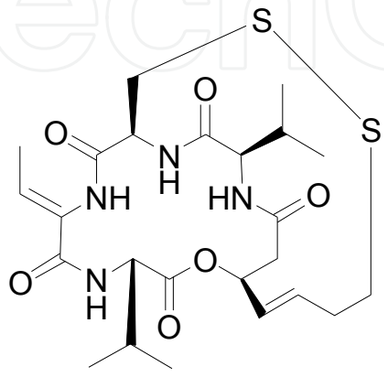
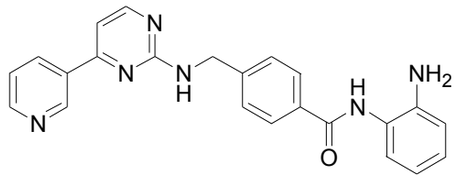
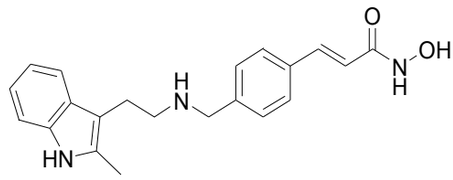
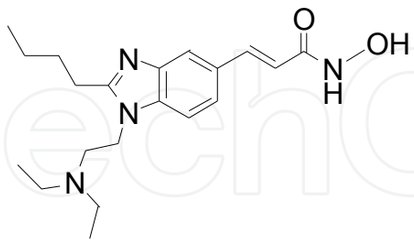
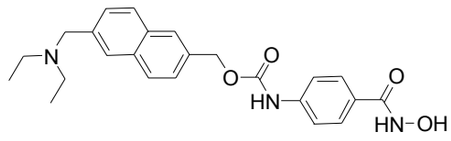
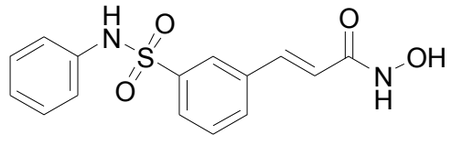
Four groups of HDAC inhibitors have been characterized: (i) short chain fatty acids (e.g., Sodium butyrate and phenylbutyrate), (ii) cyclic tetrapeptides (e.g., Depsipeptide and Trapoxin), (iii) benzamides (e.g. MGCD0103 (Mocetinostat), Cl-994 and MS-275 (Entinostat)), and (iv) hydroxamic acids (e.g., SAHA [Vorinostat/Zolinza]), LBH589 (Panabinostat), SB939 (Pracinostat), ITF2357 (Givinostat), PXD101 etc). Table 1 shows compounds that are currently in different stages of clinical development.

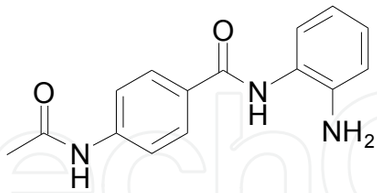
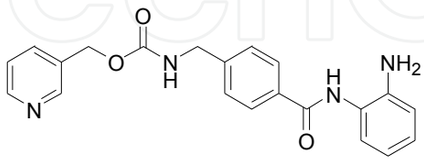
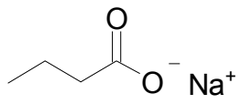
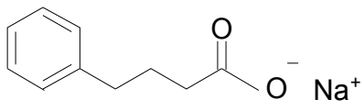
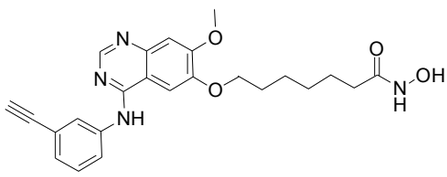
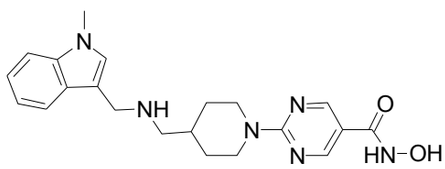
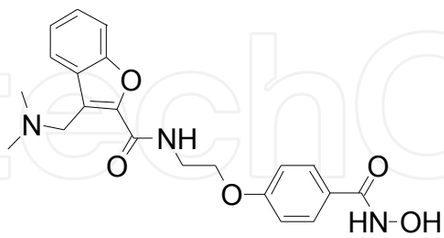
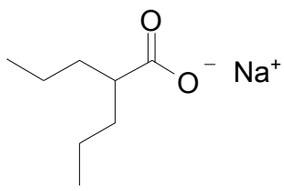
The clinical progress that has been made by hydroxamic acid derivatives as HDAC inhibitors is of particular interest because they are usually considered as non-druggable and are down-prioritized in lead identification campaigns attributing to their poor physicochemical and ADME properties. SB939 (Pracinostat) is a potent HDACi that was discovered and developed at S*BIO (Wang et al., 2011; Novotny-Diermayr et al, 2011) to overcome some of the ADME and PK/PD (Pharmacokinetic/Pharmacodynamic) limitations of the current HDACi. The pharmacokinetics and drug metabolism aspects of the four classes of HDACi have not been reviewed extensively. In this article, we review the pharmacokinetic and drug metabolism properties of SB939 and the preclinical and clinical ADME aspects of other HDAC inhibitors in the clinic.

2. Short chain fatty acids

2.1 Sodium butyrate (SB)

Sodium butyrate is a short chain fatty acid inhibitor of HDAC enzymes that is in phase 2 clinical trials. The PK of SB in preclinical species was characterized by poor bioavailability, short $t_{1/2}$ (< 5 min in mice and rabbits), leading to challenges in oral administration (Coradini et al, 1999; Daniel P et al, 1989). Butyrate was found to be transported by via a carrier mediated transport system MCT1 in Caco-2 cells suggesting that the absorption of SB might be saturable (Stein et al., 2000). SB has been reported to significantly increase the cytochrome P450 3A4 (CYP3A4) activity in Caco-2 cells transfected with CYP3A4 (Cummins et al; 2001) and induce P glycoprotein (PgP) *in vivo* (Machavaram et al., 2000). Due to its low potency very high doses were required to achieve pharmacological concentrations in animals and humans (Kim and Bae, 2011). In PK studies in mice and rats, SB showed rapid clearance (CL) with non-linear PK resulting from the high doses (up to 5 g/kg in mice), based on which the authors indicated that high doses would be problematic in humans (Egorin et al., 1999). In a clinical pharmacology study in leukemia patients, where SB was administered as continuous intravenous (IV) infusions (at a dose of 500 mg/kg/day) over a

Compound name	Structure	Class	Stage of clinical development*
Vorinostat (ZOLINZA™)		Hydroxamic Acid	Approved (2006)
Romidepsin (Istodax)		Cyclic peptide	Approved (2009)
MGCD0103 (Mocetinostat)		Benzamide	Phase 2
LBH589 (Panabinostat)		Hydroxamic Acid	Phase 2
SB939 (Pracinostat)		Hydroxamic Acid	Phase 2
ITF2357 (Givinostat)		Hydroxamic Acid	Phase 2
PXD101 (Belinostat)		Hydroxamic Acid	Phase 2

Compound name	Structure	Class	Stage of clinical development*
CI994 (Tacedinaline)		Benzamide	Phase 2
MS-275 (Entinostat)		Benzamide	Phase 2
Sodium Butyrate		Short chain fatty acid	Phase 2
Sodium Phenylbutyrate		Short chain fatty acid	Phase 2
CUDC-101		Hydroxamic acid	Phase 1
JNJ-26481585		Hydroxamic acid	Phase 1
CRA 24781 (PCI-24781)		Hydroxamic acid	Phase 1
Sodium Valproate		Short chain fatty acid	Phase 2

*Reference from http://www.fda.gov

Table 1. HDAC inhibitors in clinical development

10 day period, SB declined rapidly post infusion with a very short $t_{1/2}$ (~ 6 min), with high systemic clearance (CL~5 L/h/kg) and low volume of distribution (V_d =0.74 L/kg) (Miller et al., 1987). The amount of unchanged SB in urine was minimal suggesting that SB's clearance was primarily by metabolism. The authors concluded that the lack of efficacy of SB in the leukemic patients was due to its low plasma levels and very short $t_{1/2}$ (Miller et al., 1987).

2.2 Sodium phenyl butyrate (PB)

Sodium phenyl butyrate (PB) is an aromatic fatty acid HDACi, with low potency of 0.5 mM that is in phase 2 trials for cancer. PB (Buphenyl) has already been approved by the FDA for patients with hyperammonemia (Gilbert et al., 2001).

In a phase 1 study in patients with solid tumors, the PK of PB was characterized by rapid absorption (time of peak concentration [t_{max}] ~1.8 h), dose proportional increase in oral exposures between doses of 9 and 36 g/day, a short $t_{1/2}$ of 1 h, with mean absolute oral bioavailability (F) of 78% (Gilbert et al., 2001). In the same study, the major circulating metabolites of PB were phenylacetate (PA) and phenyacetylglutamine (PG), the exposures of which were 46-66% and 70-100% respectively of PB, suggesting extensive metabolic clearance of PB in humans. The highest percentage of patients that showed stable disease was from the 36 g/day cohort, in which the time above 0.5 mM was ~ 4.0 h (Gilbert et al., 2001). In another phase 1 study in patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML), where PB was dosed as IV infusions, PB showed non-linear PK between 125 and 500 mg/kg/day, with PA and PG being formed as major metabolites (Gore et al., 2001). The low potency of PB requires very high doses in humans, leading to non-linear kinetics, thus making it a less attractive chemotherapeutic agent. In another phase 1 study, where PB was evaluated as continuous IV infusions (120 h) in solid tumors, the PK of PB was best described by saturable elimination, and PG was the major metabolite found in urine which was indicative of extensive metabolic clearance of PB in humans (Carducci et al., 2001). In the same study the plasma clearance (CL) of PB increased during the infusion period in some patients at higher dose levels. In a dose escalation oral study of PB in patients with glioma, who also received anticonvulsants concomitantly, the mean CL of PB was significantly higher than in solid tumor patients, and the possible reason was attributed to the induction of cytochrome P450 (CYP450) enzymes by anticonvulsants (Phuphanich et al., 2005). Thus it appears that the CYP450 metabolism might play a significant role in clearance of PB in humans.

2.3 Sodium valproate

Sodium valproate is a short chain fatty acid that is currently in phase 1 and 2 clinical trials in patients with solid tumors and hematological malignancies (Federico and Bagella, 2011). Sodium valproate (Depakote) has been previously approved for use in epilepsy patients and is in medical use for the last 3 decades (Federico and Bagella, 2011). It is a moderately potent inhibitor of class 1 HDAC enzymes with promising antitumor effects *in vitro* and *in vivo*. The human ADME of sodium valproate is characterized by a) high plasma protein binding (PPB) of 90 % with concentration dependent PPB; b) weak inhibitor of some CYP450, epoxide hydrolase and glucoronosyl transferases; c) entirely metabolized by the liver via glucoronidation and β-oxidation pathways with less than 3% of unchanged parent drug found in the urine; d) minimum drug-drug interaction (DDI) potential with CYP450 inhibitors as CYP450 mediated oxidation is a minor pathway ; e) high absolute oral bioavailability (90%); f) mean terminal half-life of 9-16 h (Depakote prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label).

3. Cyclic tetrapeptides

3.1 Romidepsin (FK228, depsipeptide, ISTODAX™)

Romidepsin is a bicyclic peptide that was isolated as a secondary metabolite from a naturally occurring soil bacterium, and found to be a potent anti-tumor agent *in vitro* and *in vivo* (Ueda et al., 1994) and subsequently found to be a potent HDACi. It was approved by the FDA for treatment of patients with refractory CTCL (Mercurio et al., 2010). Romidepsin is a high molecular weight drug (Mw ~ 541), highly lipophilic, and insoluble in water, necessitating intraperitoneal and subcutaneous administrations in pharmacology studies (Ueda et al., 1994). The *in vitro* PPB of Romidepsin to human plasma was 92-94 % over a concentration of 50-1000 ng/mL, indicating high binding (http://www.accessdata.fda). Romidepsin is a substrate of PgP and MRP1 (Xiao et al., 2005). Depsipeptide was extensively metabolized by human liver microsomes, leading to the formation of at least 10 different metabolites, and was found to be primarily metabolized by CYP3A4 *in vitro* (Shiraga et al., 2005). Among the metabolites formed, mono-oxidation, di-oxidation, reduction of disulfide metabolites and two unidentified metabolites were the major metabolites in humans (http://www.accessdata.fda). It did not seem to inhibit any of the major human CYP450 enzymes *in vitro*, and there are no reports on its effect on the induction of human CYP450s (http://www.accessdata.fda). The preclinical PK of depsipeptide was characterized by high systemic CL and long $t_{1/2}$ (~ 6.0 h) in mice (Graham et al., 2006). In rats, the volume of distribution at steady state (V_{ss}) was very high (100 L/kg) and systemic CL was high (~ 49 L/h/kg), $t_{1/2}$ was short (18 min), and had poor oral bioavailability (F= ~ 2-11%) (Li and Chan, 2000). The low F in rats may be could be due to high first-pass effect, poor solubility and PgP efflux. Systemic CL (~1.8 L/h/kg) and $t_{1/2}$ (205 min) were moderate in nonhuman primates (Berg et al., 2004). In a radiolabelled mass-balance study in rats with FK228, approximately 98% of the dose was recovered in excreta with ~ 79% of the dose in the feces, and biliary clearance appeared to be the main clearance mechanism (http://www.accessdata.fda; Shiraga et al., 2005). Unchanged FK228 accounted for 3% of the dose, with > 30 metabolites detected in bile, indicating extensive metabolism of FK228 (Shiraga et al., 2005). The clinical PK of Romidepsin was characterized by low V_{ss} (54 L), low CL (20 L/h), and a short $t_{1/2}$ (~ 3.5 h) (http://www.accessdata.fda; Woo et al., 2009). The intra-patient variability was moderate to high (30-80%) and the inter-patient variability was high (50-70%) (http://www.accessdata.fda;). Despite the high inter-patient variability the AUC and C_{max} increased dose proportionally (http://www.accessdata.fda).

Romidepsin is the only HDACi that seems to be a PgP substrate. Romidepsin induced PgP expression in the HCT15 tumor cell line and conferred resistance to its action (Xiao et al., 2005). A possibility of correlation between PgP induction and the poor response rate of Romidepsin in cancer patients has been proposed (Xiao et al., 2005).

4. Benzamides

4.1 Mocetinostat (MGCD0103)

Mocetinostat (MGCD0103), an aminophenyl benzamide, is a potent inhibitor of HDAC 1, 2, and 3 enzymes and has recently completed Phase 2 clinical trials (Mercurio et al., 2010). It is a small molecule (Mw~396) and moderately lipophilic (LogP=2.6). There is no information available on its permeability, microsomal stability, metabolism, plasma protein binding, CYP450 inhibition and induction. In preclinical PK studies in mice, rat and dog,

Mocetinostat showed moderate V_{ss} (0.35 -0.91 L/kg), moderate to high CL (1.7 to 4.3 L/h/kg), short $t_{1/2}$ (0.6-1.3 h), with F ranging between low (mice =12%), moderate (rat=47%) and low-high (dogs=1-92%) (Zhou et al., 2008). In preclinical PK and PD studies, where the dihydrobromo salt of Mocetinostat was used, the dosing formulations required acidification and cosolvent addition indicating solubility issues (Zhou et al, 2008).
In a phase 1 study in patients with leukemia, the oral PK of Mocetinostat was characterized by rapid absorption (t_{max} = 0.5-1.2 h), mean elimination $t_{1/2}$ of 7-11 h, and a dose related increase in peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) between 20 and 60 mg/m² and tended to plateau at higher doses (Garcia-Manero et al., 2011). Based on the lack of accumulation upon repeated dosing, it was suggested that induction or inhibition of drug elimination was unlikely in humans (Le Tourneau and Siu, 2008).

4.2 CI994 (N-acetyldinaline)

CI994 (N-acetlydinaline), belonging to the benzamide class, is a HDACi with promising antitumor activities in preclinical xenograft models, and subsequently progressed to phase 1 2 clinical trials (Richards et al., 2006). CI994, a small molecule (MW=269.3) and with poor aqueous solubility, was developed as an acetylated analogue of Dinaline (GOE-1734), which, also showed equivalent antitumor activity (LoRusso et al., 1996). CI994 was eventually identified as an active metabolite of Dinaline (LoRusso et al., 1996). Limited data is available on its *in vitro* ADME. It showed low PPB in mice (20%) (Foster et al., 1997). In an oral PK and metabolism study in mice, where CI-994 was dosed once daily at 50 mg/kg for 14 days, it showed moderately rapid absorption (t_{max}= 30-45 min), 2 compartment disposition with a terminal $t_{1/2}$ on day 1 (9.4 h) being longer than on day 14 (3.4 h), and oral CL ranging between 0.42 (Day 1) -0.52 (day 14) ml/min (Foster et al., 1997). High amounts of unchanged drug (42-58% of dose) were found in the urine with minimal amounts in fecal samples, suggesting that renal clearance was a major clearance pathway for CI-994. Low amounts of Dinaline were found in urine and feces indicating that *in vivo* conversion of CI-994 to Dinaline were not significant. In rhesus monkeys, the PK of CI-994 was characterized by low volume of distribution (V_d) (0.3 L/kg) and CL (0.05 L/h/kg), a moderate $t_{1/2}$ (7.4 h), and high brain penetration (Riva et al., 2000). The oral bioavailability of CI-994 in preclinical species was 100% (Riva et al., 2000). In a phase 1 study in cancer patients following oral dosing (5-15 mg/m²), CI-994 showed rapid absorption (t_{max} 0.7-1.6 h), oral CL ranging between ~30-48 ml/min/m²), dose proportional increases in C_{max} and AUC, and moderately long $t_{1/2}$ (7.4-14 h) (Prakash et al., 2001). In the same study, no food effects were observed on the oral PK of CI-994.

4.3 Entinostat (MS-275)

Entinostat (MS-275) is a small molecule, synthetic benzamide that is currently in phase 2 trials (Mercurio et al., 2010). It is moderately lipophilic (LogD= 1.79), with moderate plasma protein binding (fraction unbound [f_u] ranged between 0.375 to 0.439 in preclinical species, and 0.188 in humans) (Hooker et al., 2010; Acharya et al., 2006). In preclinical pharmacology studies, the t_{max} of Entinostat ranged between 30-40 minutes with a $t_{1/2}$ of ~ 1 h in rats, mice and dogs, and the oral bioavailability was high (F~ 85%) (Ryan et al., 2005). In a radiolabeled tissue distribution and brain penetration study in baboons, radioactivity was cleared both by renal and biliary systems, and showed poor brain penetration (Hooker et al,

2010). The authors concluded that PgP mediated efflux was probably not the main mechanism for the poor brain penetration.
The clinical PK of Entinostat, in cancer patients, was characterized by variable absorption rates (t_{max} ranged between 0.5 to 60 h), a mean terminal elimination half-life of ~ 52 h, low oral clearance (CL/F=17.4 L/h/m^2), nearly dose proportional increase in exposures with dose (range 2-12 mg/m^2), and with substantial interpatient variability (Ryan et al., 2005). The nearly 50 fold longer $t_{1/2}$ in humans was not predicted based on the preclinical PK (Ryan et al., 2005). The possible reasons for the extended $t_{1/2}$ in humans were attributed to entero-hepatic recirculation and higher binding to human plasma proteins to some extent (Ryan et al., 2005). In an *in vitro* study, no metabolites could be detected after incubation of MS-275 in human liver microsomes, indicating that hepatic metabolism was a minor pathway of elimination in humans (Acharya et al., 2006).

5. Hydroxamic acids

5.1 Vorinostat (suberoylanilide hydroxamic acid [SAHA], ZOLINZA™)

Vorinostat (SAHA, ZOLINZA™), belonging to the hydroxamic acid class, was the first HDACi to be clinically approved for the treatment of refractory cutaneous T-cell lymphoma (Mann et al., 2007). Vorinostat (M_w=264) is poorly soluble in aqueous solutions ~ 191 µg/mL [~0.7 mM] (Cai et al., 2010), has a pKa of 9.2 and a LogP ~1.0 (http://www.accessdata.fda). It was moderately permeable in Caco-2 cell permeability assays (~ 2 X 10^{-6} cm/sec), based on which, and its poor solubility, it was classified as a Biopharmaceutical Classification System (BCS) class 4 drug (http://www.accessdata.fda). It displayed low to moderate binding to plasma proteins, with mean PPB of 71.3, 62.5, 43.6, 32.4, and 31.1 % in human, rabbit, dog, rat and mouse plasma, respectively (http://www.accessdata.fda). The mean blood-to-plasma partition ratio was 1.2, 0.7, and 2.0 in rat, dog and human blood, respectively (http://www.accessdata.fda). In *in vitro* metabolism studies, using S9 and liver microsomal fractions from rat, dog and humans, the major metabolic pathway was *O*-glucoronidation of Vorinostat in all the 3 species, and a minor pathway was the hydrolysis of parent to 8-anilino-8-oxooctanoic acid (8-AOO) (http://www.accessdata.fda). In metabolism studies with hepatocytes from rat, dog and humans, the major metabolites formed in all the 3 species were 4-anilino-4-oxobutanoic acid (4-AOB, β-oxidation product) and 8-AOO (hydrolysis). In dog hepatocytes, the *O*-glucoronide was also a major metabolite, with human hepatocytes generating small amounts of it (http://www.accessdata.fda). The CYP450 enzymes were not responsible for the biotransformation of Vorinostat (http://www.accessdata.fda).
In preclinical studies in rats and dogs (Sandhu et al., 2007), the PK of Vorinostat was characterized by high systemic CL (7.8 and 3.3 L/h/kg in dog (> liver blood flow of ~ 1.9 L/h/kg) and rat (=liver blood flow of 3.3 L/h/kg), respectively), low to moderate V_{ss} (1.6 and 0.6 L/kg in dog and rat respectively), short half-lives (12 min in dog and rat), and poor oral bioavailability (11 % and ~ 2% in dog and rat, respectively). The *O*-glucoronide and 4-AOB metabolites of Vorinostat were detected in significant levels in both the species following oral dosing (AUC ratio of *O*-glucoronide to Vorinostat was ~ 1.0 and 2.3 in dog and rat, respectively; and the AUC ratio of 4-AOB to Vorinostat was 10 and 23 in dog and rat, respectively). In excretion studies with radiolabeled Vorinostat, 89-91% and 68-81% of the total dose was recovered in urine of rat and dog, respectively. The major metabolites in rat urine (over a period of 24 h) were acetaminophen-O-sulfate (~16-19%), 4-AOB (47-48%),

6-anilino-oxohexanoic acid (6-AOB) (~10-14%), O-glucoronide in trace amounts, and the parent accounting for 0.7- 5%. In dog urine, the major metabolites found were 4-AOB (31-34%), ortho-hydroxyaniline O-sulfate (17-21%), with minor amounts of the O-glucoronide and carnitine esters of 6-AOH and 8-AOO. Thus, Vorinostat was primarily cleared by metabolism and renally excreted in rat and dog. The data suggest that the low bioavailability of Vorinostat in rat and dog was due to a high first-pass effect and not due to absorption since the > 90% of the dose was recovered in urine, indicative of high intestinal absorption (fraction of dose absorbed [F_a]=0.8-1.0) (Sandhu et al., 2007).

Vorinostat did not inhibit any of the major human CYP450 enzymes (http://www.accessdata.fda). It did not significantly induce CYP1A2, 2B6, 2C9, 2C19 and 3A4 in freshly cultured human hepatocytes, although the induction activity of 2C9 and 2C19 were suppressed at the highest concentration (http://www.accessdata.fda).

In the first clinical trial in cancer patients Vorinostat was administered intravenously as a 2 h infusion (Kelly et al., 2003). The intravenous route was chosen due to predictions of poor oral bioavailability based on its preclinical ADME properties (Kelly et al., 2003). In a subsequent phase 1 trial, Vorinostat was dosed orally in patients with advanced cancer in which the oral PK was also characterized (Kelly et al., 2005). Vorinostat showed dose proportional increase in C_{max} and AUC following single oral doses of 100, 400 and 600 mg, with the average terminal $t_{1/2}$ ranging between ~ 92 to 127 minutes, median t_{max} ranging between 53 to 150 minutes, and an absolute oral bioavailability of 43%. No apparent changes were observed in PK following multiple oral dosing. The $t_{1/2}$ following oral dosing was longer than the $t_{1/2}$ observed after i.v. dosing (range of ~35-42 min), suggesting that the elimination of Vorinostat was absorption rate limited (Kelly et al., 2005). In another study investigating the PK of Vorinostat, at 400 mg, and its major metabolites in cancer patients, the mean serum exposures of the O-glucoronide and 4-AOB were 3-4 fold and 10-to-13 fold higher, respectively, than that of Vorinostat (Rubin et al., 2006). In the same study, up to 18% and 36% of the O-glucoronide and 4-AOB, respectively, were recovered in urine, with the parent accounting for < 1 % of the total dose, clearly indicating that Vorinostat was cleared primarily by metabolism in humans, and that the O-glucoronide and 4-AOB were the major metabolites. The main enzymes responsible for the formation of the O-glucoronide were identified as the UDP-glucoronosyltransferases (UGTs), such as the UGTs 2B17 and 1A9, which are expressed in the liver, and the extrahepatic UGTs 1A8 and 1A10 (Balliet et al.,2009). UGT2B17 was one of the major enzymes contributing to the formation of the O-glucoronide of Vorinostat in humans (Balliet et al., 2009). Since UGTs are known to show extensive polymorphism, including UGT2B17, they have been associated with the variable PK and response of Vorinostat in patients (Balliet et al., 2009).

There have been no reports on allometric scaling or the predictions of human PK based on preclinical ADME data so far.

5.2 Panabinostat (LBH589)

Panabinostat (LBH589) is a cinnamic hydroxamic acid and a potent pan HDAC inhibitor that is currently in phase 2 clinical trials (Mercurio et al., 2010). Very little information is available on its preclinical ADME characteristics. It showed poor oral bioavailability in rodents (F=6% in rats) and moderate F in dogs (33-50%) (Konsoula et al, 2009).

Like SAHA, Panabinostat was first tried as an intravenous formulation in the phase 1 clinical trials (Giles et al., 2006). In that study, LBH589 showed dose proportional increase in

C_{max} and AUC between 4.8 and 14 mg/m^2, with the terminal half-life ranging between 8-16 h. The V_{ss} and CL were not reported. The oral PK of Panabinostat was characterized by rapid absorption (t_{max} =1-1.5 h), linear increase in dose between 20 and 80 mg and the terminal $t_{1/2}$ ranged between 16-17 h (Prince et al, 2009). In an oral mass-balance study in patients with advanced cancer, following a single oral dose of 20 mg of ^{14}C radioactively labeled Panabinostat, 87% of the administered dose was recovered in the excreta, with unchanged drug accounting for <3% of the administered dose in the feces, suggesting good oral absorption and extensive metabolism (Clive et al, 2006). The major circulating metabolites were glucoronidation products of Panabinostat, in addition to hydrolysis and reduction products. Thus, it appears that there is no single major metabolic pathway for the elimination of Panabinostat in humans. CYP3A4 does not significantly contribute to the elimination of Panabinostat in humans (DeJonge et al, 2009). Human PK data suggest that Panabinostat is a permeable drug and the poor bioavailability in preclinical rodents could be due high first-pass and poor solubility.

5.3 Givinostat (ITF2357)

Givinostat (ITF2357) is a pan HDAC inhibitor, belonging to the hydroxamic acid class that is currently in phase 2 trials for many hematological malignancies (Mercurio et al., 2010). Preclinical ADME information is either limited or qualitative for Givinostat. Metabolism was the primary clearance mechanism in preclinical species like rats, dogs, rabbits and monkeys, with excretion being biliary or renal (Furlan et al, 2011). In a phase 1 study in healthy volunteers, the oral PK of Givinostat was characterized by rapid absorption, dose proportional increases in C_{max} and AUC upon single and multiple oral dosing, and the terminal half-life ranged between 5-7 h (Furlan et al, 2011). Two major circulating metabolites of Givinostat, a carboxylate and an amide formed due to oxidation and reduction of the hydroxamic acid group, were detected at significant levels in plasma.

5.4 Belinostat (PXD101)

Belinostat (PXD101) is a hydroxamic acid class potent pan HDAC inhibitor that is currently in phase 2 clinical trials (Mercurio et al., 2010). It is a small molecule (Mw 318) and sparingly soluble in aqueous solutions (Urbinati et al., 2010). Preclinical ADME information on Belinostat is limited. Preclinical pharmacodynamic studies in mice (Plumb et al., 2003) and PK studies in non-human primates (Warren et al 2008) have been performed using IV administrations, suggesting that Belinostat may have poor solubility and bioavailability issues. However, in dogs an oral bioavailability of 30-35% was reported (Steele et al, 2011). In rhesus monkeys, clearance was rapid (425 mL/min/m^2) with a $t_{1/2}$ of 1.0 h (Warren et al 2008). In a PK/PD study in mice following IV dosing at 200 mg/kg, Belinostat declined rapidly in plasma (ca $t_{1/2}$ ~ 0.4 h), suggesting high systemic clearance (Marquard et al 2008). In the same study a correlation was observed between tumor concentrations and histone 4 acetylation levels indicating that Belinostat penetrated solid tumors.

In a phase 1 clinical study in patients with solid tumors, where Belinostat was administered as a 30 min IV infusion, its PK was characterized by dose proportional increase in AUC and C_{max}, and a short $t_{1/2}$ (0.45 to 0.79 h) (Steele et al., 2008). The oral PK of Belinostat following a 1000 mg/m^2 dose in patients with solid tumors, was characterized by mean t_{max} of 1.9 h (although the oral concentration-time profile showed a flat absorption phase), with a mean

$t_{1/2}$ of 1.5 h (Steele et al, 2011). High variability was observed in oral clearance (39-71%) due to which dose proportionality analysis was not attempted. The oral $t_{1/2}$ was longer than that of the IV, which was attributed to a slow absorption rate (Steele et al., 2011). Oral bioavailability ranged between low to moderate (20-50%) in patients with advanced solid tumors (Kelly et al., 2007). Although a correlation between H4 acetylation and concentrations was observed following oral dosing at 1000 mg/m² (Steele et al., 2011), recent phase 2 trials have employed IV dosing of Belinostat (Cashen et al., 2011). In another Phase 1 study, where the metabolism of Belinostat was studied in patients with hepatocellular carcinoma, five metabolites were identified (Wang et al, 2010). Glucoronidation was the most significant pathway of metabolism, and the methylated and amide (reduction of hydroxamic acid) products were also detected. The acid and N-glucoside forms of Belinostat were found as minor metabolites. In an *in vitro* assay using 12 isoforms forms of human UGTs, Belinostat was mainly cleared by UGT1A1 (Wang et al., 2010). The data taken together suggest that Belinostat was primarily cleared by phase 2 metabolism, involving UGT1A1, in humans.

5.5 CUDC-101

CUDC-101 is a small molecule (Mw 434.5) hydroxamic acid HDACi, synthesized by incorporating the hydroxamic acid group into the epidermal growth factor receptor (EGFR) pharmacophore, that exhibited antiproliferative effects *in vitro* and *in vivo* (Cai et al., 2010; Lai et al, 2010). The preclinical ADME of CUDC-101 is not available (Cai et al., 2010). The fact that CUDC-101 was dosed IV in the preclinical efficacy studies suggests that it may have had poor oral bioavailability (Cai et al., 2010). CUDC-101 is currently in phase 1 trials (Cai et al., 2010)

5.6 JNJ-26481585

JNJ-26481585 is a second-generation, small molecule hydroxamic acid based potent pan-HDACi that is currently in phase 1 trials (Mercurio et al., 2010). The preclinical ADME information for this compound is minimal. JNJ-26481585 has been shown to undergo extensive first-pass metabolism resulting in poor oral bioavailability in rodents, due to which it had to be dosed intraperitoneally (IP) in xenograft models (Arts et al., 2009). In a phase 1 oral PK/PD study in solid tumor patients, the exposures of JNJ-26481585 (dosed *q.d.* in 3 weekly cycles) increased dose proportionally between 2 and 12 mg (Postel-Vinay et al., 2009). In the same study promising antitumor activity was observed indicating orally active exposures were achieved in humans.

5.7 CRA-024781(PCI-24781)

CRA-024781(PCI-24781) is a small molecule, hydroxamic based pan HDACi that is currently in phase 1 trials (Mercurio et al., 2010). In preclinical murine models of efficacy, its PK was characterized by a very short $t_{1/2}$ (~ 7 min), very high CL (~ 18 L/h/kg) and high V_{ss} (~ 9 l/kg) (Buggy et al., 2006). It was administered intravenously at high doses of up to 200 mg/kg in the efficacy models, most probably owing to poor oral bioavailability and high CL (Buggy et al, 2006). In a phase 1 study in patients with solid tumors, where PCI-24781was dosed as a 2 h IV infusion, the mean elimination $t_{1/2}$ was ~ 6 h, high CL and moderately high V_{ss}, low oral bioavailability of 28%, with the carboxylic acid and amide metabolites formed at ~ 60 % of the parent (Undevia et al., 2008).

5.8 Pracinostat (SB939)

Pracinostat (SB939) is a hydroxamic acid based potent HDACi that is in multiple phase 2 clinical trials (http://clinicaltrials.gov/ct2/results?term=Sb939) in patients with solid tumors and hematological malignancies. Since the clinically advanced hydroxamic acid HDACi (Zolinza, Panabinostat and Belinostat) had ADME liabilities, such as poor solubility and oral bioavailability, we sought to identify a candidate that would achieve pharmacologically active exposures in humans when dosed orally. Pracinostat is a small molecule (Mw 359) moderately lipophilic base ($LogD_{7.4}$ =2.1) with high aqueous solubility (>100 mg/mL in water for the HCl salt of SB939) and high permeability with low efflux which indicated that Pracinostat would show high intestinal absorption *in vivo* (Wang et al., 2011). Based on its solubility and permeability Pracinostat was categorized as a BCS class 1 compound (S*BIO Data files). In preclinical PK studies Pracinostat showed higher oral bioavailability in mice (F=34%) and dogs (F=65%), than Zolinza, Panabinostat and Belinostat (table 2). The superior efficacy of Pracinostat, over Zolinza and Belinostat, when dosed orally in murine xenograft models was consistent its improved PK profile (Novotny-Diermayr et al., 2011). Pracinostat was found to selectively accumulate in tumors which correlated well with increased and prolonged acetylation levels in tumor which, in turn correlated with high tumor growth inhibition in mice (Novotny-Diermayr et al., 2011).

Preclinical ADME of Pracinostat was characterized by: a) in *in vitro* liver microsomal stability studies, Pracinostat was most stable in human and dog, moderate in mouse, and least stable in rat; b) uniform PPB of 84-94% in preclinical species and humans; c) was metabolized mainly by human CYP3A4 and 1A2; d) did not inhibit the major human CYPs except moderate inhibition of 2C19 (~ 6 μM); e) lack of significant induction of human CYP3A4 and 1A2 *in vitro*; f) metabolite identification studies using liver microsomes showed the formation of *N*-deethylation and bis-*N*-deethylation as major metabolites in addition to minor oxidative products; g) a glucoronidation product of SB939 was found as the major metabolite in rat urine following oral dosing; h) PK: high systemic clearance of 9.2, 4.5 and 1.5 L/h/kg in mice, rat and dog, respectively and high volume of distribution (V_{ss} ranged between 1.7 to 4.2 L/kg) in preclinical species; i) moderate F in mice and dogs and poor in rats (Jayaraman et al., 2011). In PK/PD studies in HCT116 xenograft models, studying the relationship between tumor growth inhibition and the PK/PD indices such as $AUC/IC_{50,HCT116}$, $C_{max}/ IC_{50,HCT116}$, and time above $IC_{50,HCT116}$, Pracinostat was found to have the highest PK/PD ratios for all the three PK/PD parameters when compared to Vorinostat, Panabinostat and Belinostat (figure 1) (Jayaraman et al., 2009).

Pracinostat showed linear allometric relationships for V_{ss} and CL in preclinical species. Prediction of human PK parameters using allometry indicated oral exposures would be achieved in humans with an acceptable $t_{1/2}$ which, was subsequently found to be consistent with the observed data from cancer patients (Jayaraman et al., 2011). The human PK of Pracinostat was simulated with the Simcyp ADME simulator (Jamei et al., 2009) using the physico-chemical and *in vitro* ADME data. The simulated PK profiles were in good agreement with the observed mean data, and the mean oral clearance and AUCs were predicted reasonably well (within 2 fold of observed data) (Jayaraman et al., 2011). Furthermore, simulations of drug-drug interactions (DDI) of Pracinostat in humans with the potent CYP3A inhibitor and inducers, ketoconazole and rifampicin, respectively, and with omeprazole (substrate of 2C19) showed lack of potential DDI at the clinically relevant dose of 60 mg (Jayaraman et al., 2011).

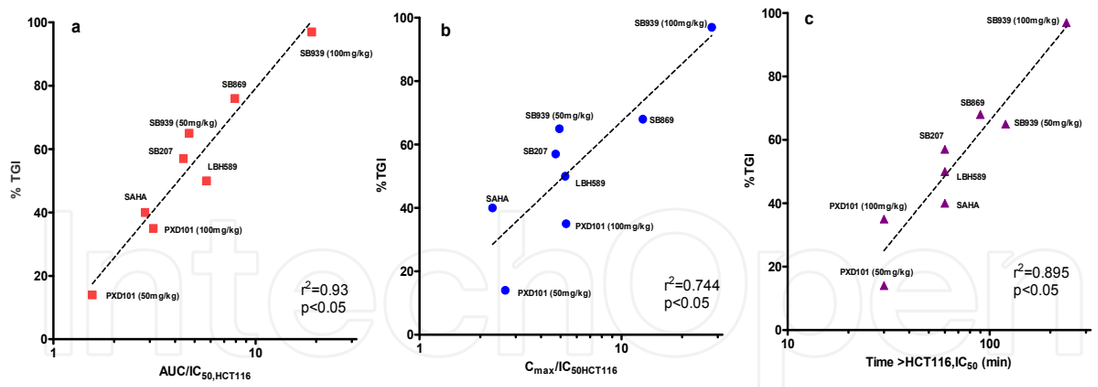


Fig. 1. The relationship between tumor growth inhibition (%TGI) and PK/PD parameters for HDACi in the murine HCT116 xenograft model (Jayaraman et al., 2009). a) AUC/$IC_{50, HCT116}$; b) C_{max}/ $IC_{50, HCT116}$; c) time above $IC_{50, HCT116}$.

Parameter	mice				dog	
	Pracinostat (SB939)	Vorinostat (SAHA)	Belinostat (PXD101)	Panabinostat (LBH589)	Pracinostat (SB939)	Vorinostat (SAHA)
C_{max}(ng/mL)	2632	501	489	116	1537	35
t_{max}(h)	0.17	0.5	0.17	0.17	0.8	0.7
$t_{1/2}$(h)	2.4	0.75	1.3	2.9	4.1	0.2
$AUC_{0\text{-inf}}$ (ng.h/mL)	1841	619	287	126	4481	55
F (%)	34	8.3	6.7	4.6	65	2

Table 2. Comparison of preclinical pharmacokinetics of Pracinostat with that of other advanced hydroxamic acid HDACi.

In the first phase 1 study in patients with solid tumors, Pracinostat showed rapid absorption (t_{max} = 0.9-2 h), dose proportional increase in C_{max} and AUC between 10 and 60 mg doses, a mean terminal $t_{1/2}$ of ~ 7 h, and lack of significant accumulation on repeated dosing (Yong et al, 2011). In the same study, pharmacologically active concentrations were achieved at the starting dose of 10 mg, and a dose dependent increase in histone acetylation was observed. At the 60 mg dose high acetylation levels was observed in all patients indicating sustained target inhibition, and two of the patients experienced prolonged disease stabilization. The clinical PK of Pracinostat was superior to the other hydroxamic acid HDACi in the clinic (table 3). The high aqueous solubility, permeability, good oral bioavailability and predictable human PK of Pracinostat contributed to obtaining active exposures in the clinic when dosed orally, which was in contrast to the intravenous dosing of Zolinza, Panabinostat and Belinostat in the initial clinical trials. The terminal $t_{1/2}$ of Pracinostat was longer than that of Zolinza and Belinostat, and shorter than Panabinostat.

In summary, the superior preclinical ADME of Pracinostat over Zolinza, Panabinostat and Belinostat was translated into the clinic.

Parameter	Pracinostat (SB939)*	Vorinostat (SAHA)#	Panabinostat (LBH589)%	Belinostat (PXD101)$
Dosage regimen	thrice weekly	once daily	thrice weekly	once daily
Recommended Dose (mg)	60	400	20	250
$t_{1/2}$(h)	7-9	0.8-3.9	16	1.5
AUC_{0-inf}(ng.h/mL)	1226(3.4μM)	1716 (6.5 μM)	183(0.54 μM)	2767 (8.7 μM)
Remarks	Orally active exposures achieved at FTIM&. Best-in-class profile.	FTIM dose was given IV due to poor F in preclinical species.	FTIM dose was given IV due to poor F in preclinical species. Limited exposure.	FTIM dose was given IV due to poor F in preclinical species. Poor PK/PD

* Yong et al., 2011
# Rubin et al., 2006
% Prince et al., 2009
$ Steele et al., 2011
& first time in Man

Table 3. Comparison of oral clinical pharmacokinetics of Pracinostat with hydroxamic acid HDAC inhibitors

6. Conclusions

The clinical use of the less potent short chain fatty acid HDACi (PB, SP and sodium valproate) in cancer patients was limited by the requirement of high doses and short half-life. The cyclic peptide drug Depsipeptide had to be administered intravenously because of poor solubility and oral bioavailability. The most clinically advanced hydroxamic acid HDACi such as Zolinza, Belinostat and Panabinostat were initially administered IV in patients owing to their poor solubility and oral bioavailability in preclinical species. Formulations were subsequently developed for oral administration. We succeeded in designing the hydroxamic acid pan HDACi Pracinostat (SB939) which had high solubility and permeability, with superior preclinical ADME and PK/PD properties when compared to the other hydroxamic acid HDACi, which subsequently helped to achieve pharmacologically active exposures upon oral dosing in cancer patients.

7. References

[1] van de Waterbeemd H and Gifford E. 2003. ADMET IN SILICO MODELLING: TOWARDS PREDICTION PARADISE? *Nat Rev Drug Disc* 2:192-204

[2] Prentis RA, Lis Y and Walker SR. 1988 Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964-1985). *Br. J. Clin. Pharmacol*. 25: 387-396
[3] Yengi LG, Leung L, and Kao J. 2007. The evolving role of drug metabolism in drug discovery and development. *Pharm Res*. 24(5): 842-858
[4] Smith DA., Jones BC, and Walker DK.1996. Design of drugs involving the concepts and theories of drug metabolism and pharmacokinetics. *Med Res Rev*. 16(3):243-266
[5] Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, Rance DJ, Wastall P.1997. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *J Pharmacol Exp Ther* 283(1):46-58.
[6] Venkatakrishnan K, von Moltke LL, Obach RS, Greenblatt DJ. 2003. Drug metabolism and drug interactions: application and clinical value of in vitro models. *Curr Drug Metab*. 4(5):423-59.
[7] Pelkonen O and Raunio H. 2005. In vitro screening of drug metabolism during drug development: can we trust the predictions? *Expert Opin Drug Metab Toxicol* 1(1):49-59
[8] Thompson TN. 2000. Early ADME in support of drug discovery: the role of metabolic stability studies. *Curr Drug Metab* 1(3): 215-241
[9] Fagerholm U .2007. Prediction of human pharmacokinetics-gastrointestinal absorption. *J Pharm Pharmacol* 59:905-916
[10] Lipinski CA. 2000. Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol and Toxicol Meth* 44: 235- 249
[11] Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A.2009. The Simcyp population-based ADME simulator. *Expert Opin Drug Metab Toxicol* 5(2):211-223
[12] Minucci S and Pelicci PG. 2006. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat. Rev. Cancer* 6(1):38-51
[13] Mercurio C, Minucci S, and Pelicci PG. 2010. Histone deacetylases and epigenetic therapies of hematological malignancies. *Pharmacol Res*. 62(1):18-34.
[14] Stimson L, Wood V, Khan O, Fotheringham S, and La Thangue NB. 2009. HDAC inhibitor-based therapies and haematological malignancy. *Ann Oncol*. 20(8):1293-302.
[15] Christensen DP, Dahllöf M, Lundh M, Rasmussen DN, Nielsen MD, Billestrup N, Grunnet LG, Mandrup-Poulsen T. 2011. HDAC inhibition as a novel treatment for diabetes mellitus. *Mol Med*. doi: 10.2119/molmed.2011.00021
[16] Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. 2007. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist*. 12(10):1247-52.
[17] Grant C, Rahman F, Piekarz R, Peer C, Frye R, Robey RW, Gardner ER, Figg WD, Bates SE. 2010. Romidepsin: a new therapy for cutaneous T-cell lymphoma and a potential therapy for solid tumors. *Expert Rev Anticancer Ther*. 10(7):997-1008.
[18] Wang H, Yu N, Chen D, Lee KC, Lye PL, Chang JW, Deng W, Ng MC, Lu T, Khoo ML, Poulsen A, Sangthongpitag K, Wu X, Hu C, Goh KC, Wang X, Fang L, Goh KL, Khng HH, Goh SK, Yeo P, Liu X, Bonday Z, Wood JM, Dymock BW, Kantharaj E, Sun ET. 2011. Discovery of (2E)-3-{2-Butyl-1-[2- (diethylamino)ethyl]-1H-benzimidazol-5-yl}-Nhydroxyacrylamide (SB939), an Orally Active Histone Deacetylase Inhibitor with a Superior Preclinical Profile. *J Med Chem* in press.
[19] Novotny-Diermayr V, Sangthongpitag K, Hu CY, Wu X, Sausgruber N, Yeo P, Greicius G, Pettersson S, Liang AL, Loh YK, Bonday Z, Goh KC, Hentze H, Hart S, Wang H,

Ethirajulu K, Wood JM. 2010. SB939, a novel potent and orally active histone deacetylase inhibitor with high tumor exposure and efficacy in mouse models of colorectal cancer. *Mol Cancer Ther*. 9(3):642-52.

[20] Coradini D, Pellizzaro C, Miglierini G, Daidone MG, Perbellini A. 1999. Hyaluronic acid as drug delivery for sodium butyrate: improvement of the anti-proliferative activity on a breast-cancer cell line. *Int J Cancer*.81(3):411-6.

[21] Daniel P, Brazier M, Cerutti I, Pieri F, Tardivel I, Desmet G, Baillet J, Chany C. 1989. Pharmacokinetic study of butyric acid administered in vivo as sodium and arginine butyrate salts. *Clin Chim Acta*. 181(3):255-63.

[22] Stein J, Zores M, Schröder O. 2000. Short-chain fatty acid (SCFA) uptake into Caco-2 cells by a pH-dependent and carrier mediated transport mechanism. *Eur J Nutr.* 39(3):121-5.

[23] Cummins CL, Mangravite LM, Benet LZ. 2000. Characterizing the expression of CYP3A4 and efflux transporters (P-gp, MRP1, and MRP2) in CYP3A4-transfected Caco-2 cells after induction with sodium butyrate and the phorbol ester 12-O-tetradecanoylphorbol-13-acetate. *Pharm Res*. 18(8):1102-9.

[24] Machavaram KK, Gundu J, Yamsani MR. 2000. Effect of various cytochrome P450 3A and P-glycoprotein modulators on the biliary clearance of bromosulphaphthalein in male wistar rats. *Pharmazie.* 59(12):957-60.

[25] Hyun-Jung Kim and Suk-Chul Bae. 2011. Histone deacetylase inhibitors: molecular mechanisms of action and clinical trials as anti-cancer drugs. *Am J Transl Res* 3(2): 166–179

[26] Egorin MJ, Yuan ZM, Sentz DL, Plaisance K, Eiseman JL. 1999. Plasma pharmacokinetics of butyrate after intravenous administration of sodium butyrate or oral administration of tributyrin or sodium butyrate to mice and rats. *Cancer Chemother Pharmacol*.43(6):445-53.

[27] Miller AA, Kurschel E, Osieka R, Schmidt CG. 1987. Clinical pharmacology of sodium butyrate in patients with acute leukemia. *Eur J Cancer Clin Oncol*. 23(9):1283-7

[28] Gilbert J, Baker SD, Bowling MK, Grochow L, Figg WD, Zabelina Y, Donehower RC, Carducci MA. 2001. A phase I dose escalation and bioavailability study of oral sodium phenylbutyrate in patients with refractory solid tumor malignancies. *Clin Cancer Res*. 7(8):2292-300.

[29] Gore SD, Weng LJ, Zhai S, Figg WD, Donehower RC, Dover GJ, Grever M, Griffin CA, Grochow LB, Rowinsky EK, Zabalena Y, Hawkins AL, Burks K, Miller CB. 2001. Impact of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syndromes and acute myeloid leukemia. *Clin Cancer Res*. 7(8):2330-9.

[30] Carducci MA, Gilbert J, Bowling MK, Noe D, Eisenberger MA, Sinibaldi V, Zabelina Y, Chen TL, Grochow LB, Donehower RC. 2001. A Phase I clinical and pharmacological evaluation of sodium phenylbutyrate on an 120-h infusion schedule. *Clin Cancer Res*. 7(10):3047-55.

[31] Phuphanich S, Baker SD, Grossman SA, Carson KA, Gilbert MR, Fisher JD, Carducci MA. 2005. Oral sodium phenylbutyrate in patients with recurrent malignant gliomas: a dose escalation and pharmacologic study. *Neuro Oncol*. 7(2):177-82.

[32] Federico M and Bagella L. 2011. Histone deacetylase inhibitors in the treatment of hematological malignancies and solid tumors. *J Biomed Biotechnol*. 2011:475641

[33] http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/018723s039lbl.pdf

[34] Ueda H, Nakajima H, Hori Y, Fujita T, Nishimura M, Goto T, and Okuhara M. 1994. FR901228, a novel antitumor bicyclic depsipeptide produced by Chromobacterium

violaceum No. 968. I. Taxonomy, fermentation, isolation, physico-chemical and biological properties, and antitumor activity. *J Antibiot (Tokyo)*. 47(3):301-10.

[35] Xiao JJ, Foraker AB, Swaan PW, Liu S, Huang Y, Dai Z, Chen J, Sadée W, Byrd J, Marcucci G, and Chan KK. 2005. Efflux of depsipeptide FK228 (FR901228, NSC-630176) is mediated by P-glycoprotein and multidrug resistance-associated protein 1. *J Pharmacol Exp Ther.* 313(1):268-76

[36] Shiraga T, Tozuka Z, Ishimura R, Kawamura A, and Kagayama A. 2005. Identification of cytochrome P450 enzymes involved in the metabolism of FK228, a potent histone deacetylase inhibitor, in human liver microsomes. *Biol Pharm Bull*. 28(1):124-9.

[37] Graham C, Tucker C, Creech J, Favours E, Billups CA, Liu T, Fouladi M, Freeman BB 3rd, Stewart CF, and Houghton PJ. 2006. Evaluation of the antitumor efficacy, pharmacokinetics, and pharmacodynamics of the histone deacetylase inhibitor depsipeptide in childhood cancer models in vivo. *Clin Cancer Res*. 12(1):223-34.

[38] Li Z, and Chan KK. C.2000. A subnanogram API LC/MS/MS quantitation method for depsipeptide FR901228 and its preclinical pharmacokinetics. *J Pharm Biomed Anal.* 22(1):33-44.

[39] Berg SL, Stone J, Xiao JJ, Chan KK, Nuchtern J, Dauser R, McGuffey L, Thompson P, and Blaney SM. 2004. Plasma and cerebrospinal fluid pharmacokinetics of depsipeptide (FR901228) in nonhuman primates. *Cancer Chemother Pharmacol*. 54(1):85-8.

[40] Woo S, Gardner ER, Chen X, Ockers SB, Baum CE, Sissung TM, Price DK, Frye R, Piekarz RL, Bates SE, Figg WD. 2009. Population pharmacokinetics of romidepsin in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma. *Clin Cancer Res.* 15(4):1496-503.

[41] Zhou N, Moradei O, Raeppel S, Leit S, Frechette S, Gaudette F, Paquin I, Bernstein N, Bouchain G, Vaisburg A, Jin Z, Gillespie J, Wang J, Fournel M, Yan PT, Trachy-Bourget MC, Kalita A, Lu A, Rahil J, MacLeod AR, Li Z, Besterman JM, Delorme D. 2008. Discovery of N-(2-aminophenyl)-4-[(4-pyridin-3-ylpyrimidin-2-ylamino) methyl]benzamide (MGCD0103), an orally active histone deacetylase inhibitor. *J Med Chem.* 51(14):4072-5.

[42]Garcia-Manero G, Assouline S, Cortes J, Estrov Z, Kantarjian H, Yang H, Newsome WM, Miller WH Jr, Rousseau C, Kalita A, Bonfils C, Dubay M, Patterson TA, Li Z, Besterman JM, Reid G, Laille E, Martell RE, and Minden M. 2011. Phase 1 study of the oral isotype specific histone deacetylase inhibitor MGCD0103 in leukemia. *Blood*. 112(4):981-9.

[43] Le Tourneau C and Siu LL. 2008. Promising antitumor activity with MGCD0103, a novel isotype-selective histone deacetylase inhibitor. *Expert Opin Investig Drugs.* 17(8):1247-54.

[44] Richards DA, Boehm KA, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, Grove W, Macdonald K, Gulyas S, Clark M, Dasse KD. 2006. Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study. *Ann Oncol*. 17(7):1096-102.

[45] LoRusso PM, Demchik L, Foster B, Knight J, Bissery MC, Polin LM, Leopold WR 3rd, Corbett TH. 1996. Preclinical antitumor activity of CI-994. *Invest New Drugs*. 14(4):349-56.

[46] Foster BJ, Jones L, Wiegand R, LoRusso PM, Corbett TH. 1997. Preclinical pharmacokinetic, antitumor and toxicity studies with CI-994 (correction of CL-994) (N-acetyldinaline). *Invest New Drugs*. 15(3):187-94.

[47] Riva L, Blaney SM, Dauser R, Nuchtern JG, Durfee J, McGuffey L, Berg SL. 2000. Pharmacokinetics and cerebrospinal fluid penetration of CI-994 (N-acetyldinaline) in the nonhuman primate. *Clin Cancer Res.* 6(3):994-7.

[48] Prakash S, Foster BJ, Meyer M, Wozniak A, Heilbrun LK, Flaherty L, Zalupski M, Radulovic L, Valdivieso M, LoRusso PM. 2001. Chronic oral administration of CI-994: a phase 1 study. *Invest New Drugs*. 19(1):1-11.

[49] Hooker JM, Kim SW, Alexoff D, Xu Y, Shea C, Reid A, Volkow N, Fowler JS.2010. Histone deacetylase inhibitor, MS-275, exhibits poor brain penetration: PK studies of [C]MS-275 using Positron Emission Tomography. *ACS Chem Neurosci*. 1(1):65-73.

[50] Acharya MR, Sparreboom A, Sausville EA, Conley BA, Doroshow JH, Venitz J, Figg WD. 2006. Interspecies differences in plasma protein binding of MS-275, a novel histone deacetylase inhibitor. *Cancer Chemother Pharmacol*. 57(3):275-81.

[51] Ryan QC, Headlee D, Acharya M, Sparreboom A, Trepel JB, Ye J, Figg WD, Hwang K, Chung EJ, Murgo A, Melillo G, Elsayed Y, Monga M, Kalnitskiy M, Zwiebel J, Sausville EA. 2005. Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma. *J Clin Oncol*. 23(17):3912-22.

[52] Acharya MR, Karp JE, Sausville EA, Hwang K, Ryan Q, Gojo I, Venitz J, Figg WD, Sparreboom A. 2006. Factors affecting the pharmacokinetic profile of MS-275, a novel histone deacetylase inhibitor, in patients with cancer. *Invest New Drugs*. 24(5):367-75.

[53] Cai YY, Yap CW, Wang Z, Ho PC, Chan SY, Ng KY, Ge ZG, Lin HS. 2010. Solubilization of vorinostat by cyclodextrins. *J Clin Pharm Ther*. 35(5):521-6

[54] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Drug Details

[55] Sandhu P, Andrews PA, Baker MP, Koeplinger KA, Soli ED, Miller T, and Baillie TA .2007. Disposition of vorinostat, a novel histone deacetylase inhibitor and anticancer agent, in preclinical species. *Drug Metab Lett* 1(2):153-61.

[56] Kelly WK, Richon VM, O'Connor O, Curley T, MacGregor-Curtelli B, Tong W, Klang M, Schwartz L, Richardson S, Rosa E, Drobnjak M, Cordon-Cordo C, Chiao JH, Rifkind R, Marks PA, Scher H. 2003. Phase I clinical trial of histone deacetylase inhibitor: suberoylanilide hydroxamic acid administered intravenously. *Clin Cancer Res.* 9:3578-88.

[57] Kelly WK, O'Connor OA, Krug LM, Chiao JH, Heaney M, Curley T, MacGregore-Cortelli B, Tong W, Secrist JP, Schwartz L, Richardson S, Chu E, Olgac S, Marks PA, Scher H, Richon VM. 2005. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. *J Clin Oncol*. 23(17):3923-31.

[58] Rubin EH, Agrawal NG, Friedman EJ, Scott P, Mazina KE, Sun L, Du L, Ricker JL, Frankel SR, Gottesdiener KM, Wagner JA, Iwamoto M. 2006. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res*. 12(23):7039-45.

[59] Balliet RM, Chen G, Gallagher CJ, Dellinger RW, Sun D, and Lazarus P.2009. Characterization of UGTs active against SAHA and association between SAHA glucuronidation activity phenotype with UGT genotype. *Cancer Res*. 69(7):2981-9.

[60] Konsoula Z, Cao H, Velena A, and Jung M. 2009. Pharmacokinetics-pharmacodynamics and antitumor activity of mercaptoacetamide-based histone deacetylase inhibitors. *Mol Cancer Ther*. 8(10):2844-51.

[61] Giles F, Fischer T, Cortes J, Garcia-Manero G, Beck J, Ravandi F, Masson E, Rae P, Laird G, Sharma S, Kantarjian H, Dugan M, Albitar M, and Bhalla K. 2006. A phase I study of intravenous LBH589, a novel cinnamic hydroxamic acid analogue histone deacetylase inhibitor, in patients with refractory hematologic malignancies. *Clin Cancer Res.* 12(15):4628-35

[62] Prince HM, Bishton MJ, Johnstone RW. 2009. Panobinostat (LBH589): a potent pan-deacetylase inhibitor with promising activity against hematologic and solid tumors. *Future Oncol*. 5(5):601-12.

[63] Clive S, Woo MM, Stewart M, Nydam T, Hirawat S, and Kagan M. 2009. Elucidation of the metabolic and elimination pathways of panabinostat (LBH589) using [^{14}C]-panabinostat. *J Clin Oncol*. ASCO Annual Meeting Proceedings. 27(15S). Abstract number 2549.

[64] M. DeJonge, M. M. Woo, D. Van der Biessen, P. Hamberg, S. Sharma, L. C. Chen, N. Myke, L. Zhao, S. Hirawat, J. 2009. drug interaction study between ketoconazole and panobinostat (LBH589), an orally active histone deacetylase inhibitor, in patients with advanced cancer. *J Clin Oncol*. ASCO Annual Meeting Proceedings. 27(15S). Abstract number 2501.

[65] Furlan A, Monzani V, Reznikov LL, Leoni F, Fossati G, Modena D, Mascagni P, Dinarello CA. 2011. Pharmacokinetics, Safety and Inducible Cytokine Responses during a Phase 1 Trial of the Oral Histone Deacetylase Inhibitor ITF2357 (givinostat). *Mol Med.*. doi: 10.2119/molmed.2011.00020

[66] Urbinati G, Marsaud V, Plassat V, Fattal E, Lesieur S, Renoir JM. 2010. Liposomes loaded with histone deacetylase inhibitors for breast cancer therapy. *Int J Pharm*. 397(1-2):184-93

[67] Plumb JA, Finn PW, Williams RJ, Bandara MJ, Romero MR, Watkins CJ, La Thangue NB, Brown R. 2003. Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. *Mol Cancer Ther*. 2(8):721-8.

[68] Warren KE, McCully C, Dvinge H, Tjørnelund J, Sehested M, Lichenstein HS, Balis FM. 2008. Plasma and cerebrospinal fluid pharmacokinetics of the histone deacetylase inhibitor, belinostat (PXD101), in non-human primates. *Cancer Chemother Pharmacol*. 62(3):433-7.

[69] Steele NL, Plumb JA, Vidal L, Tjørnelund J, Knoblauch P, Buhl-Jensen P, Molife R, Brown R, de Bono JS, Evans TR. 2011. Pharmacokinetic and pharmacodynamic properties of an oral formulation of the histone deacetylase inhibitor Belinostat (PXD101). *Cancer Chemother Pharmacol*. 67(6):1273-9.

[70] Marquard L, Petersen KD, Persson M, Hoff KD, Jensen PB, Sehested M. 2008. Monitoring the effect of belinostat in solid tumors by H4 acetylation. *APMIS*. 116(5):382-92.

[71] Steele NL, Plumb JA, Vidal L, Tjørnelund J, Knoblauch P, Rasmussen A, Ooi CE, Buhl-Jensen P, Brown R, Evans TR, DeBono JS. 2008. A phase 1 pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. *Clin Cancer Res*. 14(3):804-10.

[72] Kelly WK, Yap T, Lee J, Lassen U, Crowley E, Clarke A, Hawthorne T, Buhl-Jensen P, and de Bono J. 2007. A phase I study of oral belinostat (PXD101) in patients with advanced solid tumors. *J Clin Oncol* 25(18S), ASCO Annual Meeting Proceedings. Abstract 14092

[73] Cashen A, Juckett M, Jumonville A, Litzow M, Flynn PJ, Eckardt J, Laplant B, Laumann K, Erlichman C, Dipersio J. 2011. Phase II study of the histone deacetylase inhibitor belinostat (PXD101) for the treatment of myelodysplastic syndrome (MDS). *Ann Hematol*. May 3. [Epub ahead of print]

[74] Wang L, Goh BC, Lwin TW, Lee H, S Chan SL, Lim RS, Chan AT, and Yeo W. 2010. Phase I pharmacokinetics and metabolic pathway of belinostat in patients with hepatocellular carcinoma. *J Clin Oncol* 28(15S), ASCO Annual Meeting Proceedings. Abstract 2585

[75] Cai X, Zhai HX, Wang J, Forrester J, Qu H, Yin L, Lai CJ, Bao R, Qian C. 2010. Discovery of 7-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide (CUDC-101) as a potent multi-acting HDAC, EGFR, and HER2 inhibitor for the treatment of cancer. *J Med Chem*. 53(5):2000-9.

[76] Lai CJ, Bao R, Tao X, Wang J, Atoyan R, Qu H, Wang DG, Yin L, Samson M, Forrester J, Zifcak B, Xu GX, DellaRocca S, Zhai HX, Cai X, Munger WE, Keegan M, Pepicelli CV, Qian C. 2010. CUDC-101, a multitargeted inhibitor of histone deacetylase, epidermal growth factor receptor, and human epidermal growth factor receptor 2, exerts potent anticancer activity. *Cancer Res*. 70(9):3647-56

[77] Arts J, King P, Mariën A, Floren W, Beliën A, Janssen L, Pilatte I, Roux B, Decrane L, Gilissen R, Hickson I, Vreys V, Cox E, Bol K, Talloen W, Goris I, Andries L, Du Jardin M, Janicot M, Page M, van Emelen K, Angibaud P. 2009. JNJ-26481585, a novel "second-generation" oral histone deacetylase inhibitor, shows broad-spectrum preclinical antitumoral activity. *Clin Cancer Res*. 15(22):6841-51

[78] Postel-Vinay S, Kristeleit R, Fong P, Venugopal B, Crawford D, Van Beÿsterveldt L, Fourneau N, Hellemans P, Evans J, and De-Bono J. 2009. Preliminary results of an open-label phase I pharmacokinetic/pharmacodynamic study of JNJ26481585: Early evidence of antitumor activity. *J Clin Oncol* 27, 2009 (abstract e13504)

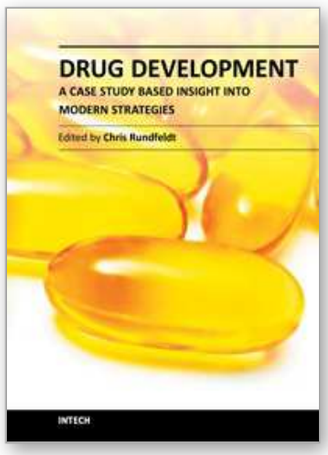
[79] Buggy JJ, Cao ZA, Bass KE, Verner E, Balasubramanian S, Liu L, Schultz BE, Young PR, Dalrymple SA. 2006. CRA-024781: a novel synthetic inhibitor of histone deacetylase enzymes with antitumor activity in vitro and in vivo. *Mol Cancer Ther*. 5(5):1309-17.

[80] Undevia SD, Janisch L, Schilsky RL, Loury D, Balasubramanian S, Mani C, Sirisawad M, Buggy JJ, Miller RA, and Ratain MJ. 2008. Phase I study of the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of the histone deacetylase inhibitor (HDACi) PCI-24781. *J Clin Oncol* 26: (abstr 14514)

[81] Jayaraman R, Pilla Reddy V, Khalid Pasha M, Wang H, Sangthongpitag K, Yeo P, Hu C, Wu X, Xin L, Goh E, New L, and Ethirajulu K. 2011. Preclinical Metabolism and Disposition of SB939(Pracinostat), an Orally Active Histone Deacetylase (HDAC) Inhibitor, and Prediction of Human Pharmacokinetics. Drug Metab Dispos. doi: 10.1124/dmd.111.04155

[82] Yong WP, Goh BC, Soo RA, Toh HC, Ethirajulu K, Wood J, Novotny-Diermayr V, Lee SC, Yeo WL, Chan D, Lim D, Seah E, Lim R, and Zhu J .2011. Phase 1 and pharmacodynamic study of an orally administered novel inhibitor of histone deacetylases, SB939, in patients with refractory solid malignancies. *Ann Oncol* doi: 10.1093/annonc/mdq784 In press.

[83] Jayaraman R, Khalid Pasha M, Yeo P, Sangthongpitag K, Wang H, Hentze H, Novotny-Diermayr V, Wood J and Ethirajulu K. 2009. Pharmacokinetic/Pharmacodynamic (PK/PD) relationships of novel HDAC inhibitors in an HCT-116 mouse xenograft tumor model. *AACR*: 100th Annual Meeting, Abstract no 2924



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This book represents a case study based overview of many different aspects of drug development, ranging from target identification and characterization to chemical optimization for efficacy and safety, as well as bioproduction of natural products utilizing for example lichen. In the last section, special aspects of the formal drug development process are discussed. Since drug development is a highly complex multidisciplinary process, case studies are an excellent tool to obtain insight in this field. While each chapter gives specific insight and may be read as an independent source of information, the whole book represents a unique collection of different facets giving insight in the complexity of drug development.

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