Pharmacodynamic Response and Inhibition of Growth of Human Tumor Xenografts by the Novel Histone Deacetylase Inhibitor PXD101

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Abstract
Histone acetylation has a central role in the control of gene expression, influencing transcriptional control of many genes, including tumor suppressor genes. PXD101 is a novel hydroxamate-type inhibitor of histone deacetylase activity that inhibits histone deacetylase activity in HeLa cell extracts with an $IC_{50}$ of 27 nM and induces a concentration-dependent (0.2–5 µM) increase in acetylation of histone H4 in tumor cell lines. PXD101 is cytotoxic in vitro in a number of tumor cell lines with $IC_{50}$ in the range 0.2–3.4 µM as determined by a clonogenic assay and induces apoptosis. Treatment of nude mice bearing human ovarian and colon tumor xenografts with PXD101 (10–40 mg/kg/day i.p.) daily for 7 days causes a significant dose-dependent growth delay with no obvious signs of toxicity to the mice. Growth delay is also observed for xenografts of cisplatin-resistant ovarian tumor cells. A marked increase in acetylation of H4 is detected in blood and tumor of mice 3 h after treatment with PXD101. The inhibition of growth of human tumor xenografts in mice, with no apparent toxicity, suggests that PXD101 has potential as a novel antitumor agent. Furthermore, the ability to measure histone acetylation in blood samples could provide a suitable pharmacodynamic end point to monitor drug activity.

Introduction
Tumor cells are characterized by aberrant gene expression. Although this is often the result of genetic change (1), it also occurs as a consequence of changes in the epigenetic regulation of gene expression (2). In eukaryotic cells, levels of histone acetylation play a pivotal role in chromatin remodeling and the regulation of gene expression. Acetylation levels are thought to result from an equilibrium between the activities of histone acetyltransferase and histone deacetylase enzymes (3). In general, deacetylated histones are associated with inactive nontranscribed DNA (4). Aberrant epigenetic transcriptional repression has been demonstrated in a wide variety of tumor types and involves genes in multiple cellular processes involved in tumorigenic transformation and maintenance of the transformed state (5). Consequently, attention has focused on the development of inhibitors of histone deacetylase enzymes as a novel approach to cancer treatment, and several compounds are now undergoing evaluation in Phase I clinical trials (6).

Generically, HDAC inhibitors have been described as consisting of three parts: (a) a zinc-chelating group; (b) a spacer group, which is generally hydrophobic; and (c) an “enzyme binding” group that confers specificity and is generally aromatic in character (7, 8). All three moieties have been explored in our studies. Starting from the structures of natural product inhibitors, we have designed novel, low molecular weight, achiral, and synthetically accessible inhibitors of histone deacetylase activity. It is known that low molecular weight hydroxamic acid containing molecules, such as trichostatin A, oxamflatin, and SAHA,2 are potent histone deacetylase inhibitors (9–11), and we have concentrated on the hydroxamic acid moiety as the zinc-chelating group because this group confers high levels of potency. PXD101 is the lead compound from this series (12), and here we describe the potent antitumor activity of PXD101 both in vitro against a number of human tumor cell lines and in vivo in human tumor xenografts.

Materials and Methods
Cell Lines. The human ovarian cell line A2780 and cisplatin (A2780/cp70) and doxorubicin (2780AD) resistant derivatives were originally obtained from Dr. R. F. Ozols (Fox Chase Cancer Center, Philadelphia, PA). They were grown in RPMI 1640 supplemented with glutamine (2 mM) and FCS (10%). The human colon (HCT116 and HT29), melanoma (HS852), prostate (PC3), lung (CALU-3), and breast (MCF7) cell lines were obtained from American Type Culture Collection (Rockville, MD). MCF7 was grown in RPMI 1640 and the rest in DMEM supplemented as above. The human non-small cell lung cancer cell line WIL was originally obtained from the Ludwig Institute for Cancer Research (Sutton, United Kingdom) and was grown in DMEM supplemented as above.

2 The abbreviations used are: SAHA, suberoylanilide hydroxamic acid; PARP, poly(ADP-ribose) polymerase.
Cytotoxicity Assay. Drug sensitivity was determined by a clonogenic assay (13). Briefly, cells were plated in 5 ml of medium at a density of \(8 \times 10^4\) cells/25 cm\(^2\) flask and allowed to attach and grow for 48 h. Cells were exposed to drug (five concentrations from 0.016 to 10 \(\mu\)M) for 24 h. The medium was removed, and 1 ml of trypsin/EDTA was added to each flask. Once the cells had detached, 1 ml of medium was added, the cells were resuspended, and those from the control untreated flask were counted. Cells were diluted and plated into 6-cm Petri dishes (three per flask) at a density of 500-2000 cells/dish depending on the cell line. Cells from the drug-treated flasks were diluted and plated as for the control flasks. Dishes were incubated for 10–15 days at 37°C. Cells were washed with PBS, fixed in methanol, and stained with crystal violet, and colonies that contained \(\geq 50\) cells counted. Sensitivity is expressed as the IC\(_{50}\) (mean \(\pm\) SE of three experiments) defined as the concentration of drug required to reduce the number of colonies to 50% of that of the control untreated cells.

Histone Deacetylase Activity. Subconfluent cultures were harvested and washed twice in ice cold PBS and pelleted by centrifugation at 2000 \(\times\) g for 5 min. The cell pellet was resuspended in two volumes of lysis buffer [60 mM Tris buffer (pH 7.4) containing 30% glycerol and 450 mM NaCl] and lysed by three freeze (dry ice) thaw (30°C water bath) cycles. Cell debris was removed by centrifugation at 12,000 \(\times\) g for 5 min, and the supernatant was stored at –80°C.

Histone H4 peptide (sequence SGRGKGGKGLGKG-GAKRHRK corresponding to the 20 NH\(_2\)-terminal residues) was acetylated by a recombinant protein containing the p300-aminotransminase-thymidine domain of p300, using \([\text{H}]\)Acetyl CoA as a source of acetyl. H4 peptide (100 \(\mu\)g) was mixed with p300 in a final volume of 300 \(\mu\)l of lysis buffer [50 mM Tris HCl (pH 8.0), 5% glycerol, 50 mM KCl, and 0.1 mM EDTA], 1 mM DTT, 1 mM 4-(2-aminoethyl) benzensulfonylfluoride, 1 \(\times\) complete protease inhibitors (Amersham Pharmacia Biotech), 50 \(\mu\)l of purified p300, and 1.85 \(\mu\)M \([\text{H}]\)Acetyl CoA (Amersham Pharmacia Biotech; 4.50Ci/mmol) in a final volume of 300 \(\mu\)l and incubated at 37°C for 45 min. The p300 protein was removed by incubation with 20 \(\mu\)l of Ni-agarose beads (Qiagen) on ice for 1 h on ice, samples were centrifuged at 12,000 \(\times\) g for 5 min at 4°C in an Eppendorf centrifuge. The supernatant was transferred to a tube containing 1 ml of acetone, incubated overnight at –20°C, and then centrifuged as before. The pellet was air dried and then resuspended in 50 \(\mu\)l of water.

Tissue samples were homogenized in ice cold lysis buffer and processed as above. For blood samples, red cells were lysed by the addition of three volumes of cell lysis solution (Promega). After incubation for 10 min at room temperature, samples were centrifuged at 2000 \(\times\) g for 10 min. Histones were isolated from the white cell pellet as described above.

Proteins (5 \(\mu\)g) were separated by the NuPage electrophoresis system (Invitrogen) on 10% Bis-Tris gels with MES SDS running buffer. The “Novex Xcell II” blotting apparatus (Invitrogen) was used to transfer proteins onto Immobilon polyvinylidene difluoride membrane (Millipore). The membrane was blocked for 1 h in Tris-buffered saline containing 0.02% Tween 20 and 5% powdered milk and then incubated overnight at 4°C with the primary antibody [antiglycosylated histone H3 (Lys 9 and 14) or H4 (Lys 5, 8, 12, and 16)] from Upstate Biotechnologies. The membrane was then washed and incubated for 1 h at room temperature with the secondary antibody (goat antirabbit horseradish peroxidase; Amersham). After washing, protein bands were visualized by enhanced chemiluminescence (ECL, Amersham). All samples were analyzed on two separate gels to exclude loading variations.

PARP Cleavage and Induction of p21\(^{Cip1/WAF1}\). Cells were plated at a density of \(10^5\) cells in a 25-cm\(^2\) flask and allowed to attach and grow for 48 h. Drug was added at a range of concentrations for 24 h. Both adherent cells and those in the medium were harvested and washed twice with ice cold PBS. They were resuspended in 200 \(\mu\)l of lysis buffer [50 mM HEPES (pH 7.0), 250 mM NaCl, and 0.5% NP-40] supplemented with protease inhibitors (Complete from Roche Diagnostics Ltd., Lewes, United Kingdom) and incubated on ice for 20 min. Samples were centrifuged at 12,000 \(\times\) g for 5 min at 4°C to remove debris.

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Proteins were separated on 4–12% Bis-Tris gels with 4-morpholinepropanesulfonic acid SDS running buffer and processed as above. The primary antibody was either anti-PARP (PharMingen from BD Biosciences) or anti-Cip1/WAF1 (Transduction Laboratories from BD Biosciences), and the secondary antibody was sheep antimouse horseradish peroxidase (Amersham).

Animal Studies. Animal studies were carried out under an appropriate United Kingdom Home Office Project License, and all work was conformed to the UKCCCR guidelines for the welfare of animals in experimental neoplasia.

For the human tumor xenograft studies, monolayer cultures were harvested with trypsin/EDTA (0.25%/1 mM in PBS) and resuspended in PBS. About 10^7 cells were injected s.c. into the right flank of athymic nude mice (CD1 nu/nu mice from Charles River). After 10–15 days when the mean tumor diameter was ≥0.5 cm, animals were randomized into groups of six for experiments. PXD101 was dissolved in DMSO and then diluted in water to give a final concentration of 10% and was administered i.p. at the times specified. This formulation gave sufficient solubility for doses of ≤40 mg/kg. Mice were weighed daily, and tumor volumes were estimated by caliper measurements assuming spherical geometry (volume = \( \frac{4}{3} \pi r^3 \)). Mice were also observed daily for any changes in behavior or condition according to the Morton and Griffiths scoring system (14). Significant differences between groups were identified by ANOVA, and the significance level of individual differences was determined by Student’s \( t \) test.

The canine pharmacokinetic studies were carried out by Covance Laboratories, Ltd. (Harrogate, United Kingdom). Beagle dogs received an i.v. infusion of PXD101 given at a rate of 2.5 ml/min over 45 min. The drug was formulated in 0.1 M Tris buffer (pH 8.5) containing 10% volume for volume ethanol and 5% polyethylene glycol 200. Blood samples \( n = 10 \) were taken at various times for measurement of PXD101, and a second 3-ml sample was taken for estimation of histone acetylation. Histones were extracted immediately as described above, the pellet was resuspended in water, and samples were stored at −70°C and transferred to the Department of Medical Oncology, Glasgow, in dry ice for analysis by Western blot.

Estimation of Plasma Drug Concentrations. PXD101 was quantified in plasma by liquid chromatography coupled with tandem mass spectrometric detection by Covance Laboratories. Samples were mixed with water:methanol:formic acid (90:10:1) and the internal standard (oxamflatin) and applied to a Waters Oasis MAX 30-mg cartridge using automated solid phase extraction (Gilson 215). Elution was performed with methanol:water:formic acid (90:10:2), and the extract dried and reconstituted in 200 \( \mu l \) of water:acetonitrile:acetic acid (65:35:1) for injection. Samples were analyzed on a Micromass Quattro LC with a Luna 3 \( \mu m \) C18(2) 50 × 3-mm column. The mobile phase was water:acetonitrile:acetic acid (65:35:1), the flow rate was 0.5 ml/min, and the retention time of PXD101 was 1.8 min. Results were acquired and quantified using MassLynx software (versions 3.3 and 3.1).

<table>
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Fig. 1. Structure and histone deacetylase activity \( \mu l \) in HeLa cell extracts for PXD101 and analogues.

Results

Structure Activity Relationship. Within the core sulfonamide template exemplified by PXD101, a number of important structure activity relationship points have been elucidated (Fig. 1). Modifications to the hydroxamic acid, a key zinc-chelating moiety, lead to large decreases in activity. Acid and amide analogues are inactive (e.g., Compound 1), and substitution on the hydroxamic acid nitrogen or oxygen also leads to inactive compounds (e.g., Compound 2). In the central region of the molecule, replacing the cinnamic acid moiety with an alkyl chain leads to a reduction in activity (e.g., Compound 3), and substitution of the sulfonamide nitrogen also reduces activity (e.g., Compound 4). The position of substitution on the cinnamic acid phenol group is important; ortho substitution leads to inactive compounds (e.g., Compound 5). There is greater flexibility in the “enzyme binding group” region of the molecule, where substitutions are tolerated, and larger groups can be introduced (e.g., Compound 6). On the basis of its potent antiproliferative and histone deacetylase inhibitor activity, PXD101 was selected as the lead compound for additional studies.

Histone Acetylation in Ovarian Tumor Cell Lines. Histone acetylation was determined with antibodies specific for acetylated histones H3 and H4 by Western blot of histones isolated from A2780 ovarian tumor cells treated for various times with PXD101 (Fig. 2a). Markedly increased histone acetylation was observed after drug exposure (1 \( \mu M \)) for 30
Antitumor Activity of a Novel HDAC Inhibitor

such as cisplatin (r2 activity to PXD101 and sensitivity to a DNA-damaging agent, in the cell lysate. There was no correlation between sensi-
total HDAC activity of the cell line or inhibition of this activity
on colony size. Sensitivity to PXD101 is not related to the
apoptosis as determined by measurement of PARP cleavage
low fold cross-resistance to PXD101.

doxorubicin (2780AD, p-glycoprotein positive)-resistant de-
Vitro.

PXD101 up to a dose of 40 mg/kg/day. Drug treatment had
tumor cell line HCT116 (Fig. 4 c). For both
tumors, growth delay increased with increasing dose of
PXD101 up to a dose of 40 mg/kg/day. Drug treatment had
no effect on the body weight of the mice (Fig. 4 c).

Activity of PXD101 in Human Tumor Xenografts. Tu-
more-bearing mice were treated i.p. with PXD101 once daily
for 7 days. Significant (P < 0.01) growth delay was observed
at a dose of 10 mg/kg/day in xenografts of A2780 (Fig. 4 a)
and in the cisplatin derivative (A2780/cp70; Fig. 4 c). For both
tumors, growth delay increased with increasing dose of
PXD101 up to a dose of 40 mg/kg/day. Drug treatment had
no effect on the body weight of the mice (Fig. 4 b), and there
were no apparent signs of toxicity to the mice. Growth inhi-
bition was also observed in xenografts of the human colon
tumor cell line HCT116 (Fig. 4 d).

Histone Acetylation in Vivo. Acetylated histone H4 was
detected in peripheral blood mononuclear cells at 1 and 2 h
after a single i.p. injection of PXD101 (40 mg/kg) to A2780
tumor-bearing mice and had returned to baseline levels by
3 h (Fig. 5 a). This effect of PXD101 on histone acetylation
was dose dependent with marked acetylation apparent at
doses of ≥10 mg/kg in both peripheral blood mononuclear
cells (blood) and tumor (Fig. 5 b). Plasma drug concentrations
were determined at 0.5 and 2 h after a single i.p. injection of
PXD101 (20 mg/kg) in mice. At 0.5 h, the mean drug con-
centration was 3.3 ± 0.7 μM (n = 3), and it had decreased to
0.042 ± 0.002 μM by 2 h.

Acetylation of histones H3 and H4 was also determined in
peripheral blood mononuclear cells in canine blood taken at
various times after an i.v. infusion of PXD101 given over 45
min (total dose 50 mg/kg). At the end of the infusion, the
plasma concentration of PXD101 was between 20 and 30
μM (Fig. 5 b). Acetylated histone H4 was detected at
10 min (Fig. 6). For H4, acetylation was maximal
after 60 min and was still elevated at 240 min (a). For H3,
acetylation was maximal at 10 min and returned to basal
levels by 4 h (b).
Discussion

The histone deacetylase inhibitor PXD101 inhibits growth and induces apoptosis in human tumor cell lines in vitro. It inhibits growth of human tumor xenografts in vivo at concentrations that are without apparent toxicity to the mice. Growth inhibition both in vitro and in vivo is associated with a marked increase in the level of acetylation of histone proteins.
PXD101 inhibited histone deacetylase activity in cell lysates with an IC50 in the range 9–100 nM (Table 1). The potency is slightly less than that seen for trichostatin A (Ki 3.4; Ref. 9) but comparable with that reported for other hydroxamate type inhibitors, such as SAHA (IC50 10 nM for HDAC1 and 20 nM for HDAC3; Ref. 15) and oxamflatin (IC50 16 nM; Ref. 10). PXD101 was clearly able to inhibit the deacetylase activity in whole cells as evidenced by the appearance of acetylated histones H3 and H4 within 30 min of drug addition (Fig. 2a). Enzyme inhibition was stable in the presence of drug and maintained for ≥36 h. However, acetylation was reversible as seen by a marked reduction in the level of acetylated histones 1 h after drug removal (Fig. 2b).

PXD101 inhibited the growth of a range of human tumor cell lines in vitro, including ovarian, non-small cell lung, breast, and prostate (Table 1). Sensitivity to PXD101 was not related either to the total histone deacetylase activity of the cell line or the ability of the drug to inhibit the enzyme activity in cell extracts (Table 1). These are crude estimates because they do not distinguish between the different classes of histone deacetylases, but there is no evidence that the histone deacetylase inhibitors currently available exhibit any selectivity between the enzyme classes (16). We do not know the substrate specificity if any of PXD101. There was no correlation between sensitivity to PXD101 and the DNA-damaging agent cisplatin (Table 1), which suggests that in the cell lines examined, cellular factors affecting PXD101 sensitivity are distinct from those affecting cisplatin sensitivity.

The basis of the selective antitumor activity of histone deacetylase inhibitors is not clear. The effects of histone deacetylase inhibitors on gene expression appear to be specific, and trichostatin A has been shown to affect transcription of only ~7% of genes in CACO-2 colon tumor cells (17). Histone deacetylase inhibitors have been reported to induce growth arrest, differentiation, and apoptosis (7), and the effects may depend on the cell line model used (18). Cytotoxic concentrations of PXD101 induced apoptosis as determined by measurement of PARP cleavage in the majority of the cell lines examined (Fig. 3a). Clearly, this is not the only apoptotic pathway induced by PXD101 because PARP cleavage was not detected in PC3 prostate and 2780AD ovarian tumor cells, yet both cell lines were relatively sensitive to growth inhibition by PXD101. Furthermore, these two cell lines did not show PARP cleavage when treated with cytotoxic concentrations of cisplatin.

In addition to induction of apoptosis, treatment of cells with PXD101 resulted in increased expression of the cyclin-dependent kinase inhibitor p21(Cip1/WAF1) (Fig. 3b). The time course of expression of p21(Cip1/WAF1) and induction of apoptosis was similar with both apparent after incubation with drug for between 18 and 24 h (Fig. 3a). p21(Cip1/WAF1) is a negative regulator of growth and thought to be involved in the regulation of a number of processes, including induction of differentiation (19). A number of histone deacetylase inhibitors have been reported to induce expression of p21(Cip1/WAF1) and cell cycle arrest in G1, and this is consistent with the observation that they can induce differentiation in some cell lines (20–22). For HCT116 cells, histone acetylation, induction of p21, and PARP cleavage were apparent at around the IC50 of PXD101 (Fig. 3b). However, for A2780, which is equally sensitive to PXD101, PARP cleavage was only apparent at a PXD101 concentration 10-fold higher than the IC50 (Table 1 and Fig. 3a). This suggested that growth inhibition of A2780 by PXD101 could be explained by cell
cycle arrest rather than induction of apoptosis. However, we did not see any effect on the cell cycle distribution of A2780 cells (measured by fluorescence-activated cell sorter analysis of propidium iodide-stained cells after BrdUrd labeling) when treated with an IC\textsubscript{50} of PXD101 (0.2 \textmu M; data not shown).

PXD101 showed antitumor activity \textit{in vivo} in human tumor xenografts. For xenografts of the human ovarian cell line A2780, there was a clear dose response with activity at a dose of 10 mg/kg daily (Fig. 4a). Daily treatment with PXD101 at \leq 40 mg/kg had no effect on body weight and was without any apparent toxicity to the mice (Fig. 4b). A similar lack of toxicity to mice has been reported for the histone deacetylase inhibitors SAHA (11) and MS-27–275 (23). Antitumor activity of PXD101 was also observed for the cisplatin-resistant derivative of A2780 (A2780/cp70; Fig. 4c), which showed a 5-fold cross-resistance to PXD101 \textit{in vitro}, and for xenografts of the colon cell line HCT116 (Fig. 4d). This is a potentially clinically relevant observation, because xenografts of A2780/cp70 and HCT116 are relatively resistant to current cytotoxic chemotherapeutic drugs, and both are resistant to the maximum tolerated dose of cisplatin (24).

Treatment of tumor-bearing mice with PXD101 resulted in the appearance of acetylated histone H4 in both peripheral blood mononuclear cells and in the tumor (Fig. 5). Histone acetylation in peripheral blood mononuclear cells was apparent between 1 and 2 h after a single i.p. injection and was dose dependent within the range at which antitumor activity was observed. (Fig. 5). This is consistent with the observation that plasma concentrations of PXD101 (3 \mu M 30 min after treatment of mice with PXD101 20 mg/kg) were comparable with those required to detect histone acetylation \textit{in vitro}.

In view of the lack of apparent toxicity associated with inhibition of histone deacetylase activity in mice, it is possible that optimal anticancer activity will not equate with the maximum tolerated dose in the clinic. Phase I trials of the histone deacetylase inhibitors phenylbutyrate (25) and depsipeptide (26) achieved plasma concentrations comparable with those required for activity \textit{in vitro} in cell lines with minimal toxicity to patients. It is therefore important to identify a means of monitoring drug activity in patients, and our observation suggests that measurement of the levels of histone acetylation in peripheral blood mononuclear cells might provide such a measure. Inhibition of tumor growth is associated with a marked increase in histone acetylation in the tumor, and this is mirrored by increased acetylation of histones in peripheral blood mononuclear cells. A detailed study of the changes in acetylation of histones H3 and H4 in peripheral blood mononuclear cells in canine blood demonstrates that this is a reliable and reproducible measurement. Histone acetylation levels are not merely a reflection of the pharmacokinetics of the drug because the kinetics of the changes in acetylation of histones H3 and H4 differ and do not relate to changes in plasma drug concentrations. Although H3 acetylation appears to be maximal by the end of the infusion, H4 acetylation does not reach a maximum until 30–60 min later. In contrast, plasma concentrations are maximal at the end of infusion, followed by a rapid (half-life of \textasciitilde 40 min) decrease in concentration.

In summary, we have shown that the novel histone deacetylase inhibitor PXD101 is active \textit{in vivo} in human tumor xenografts with no obvious toxicity to the mice. Significantly, PXD101 shows activity in cisplatin-resistant human ovarian tumor xenografts. Our observations suggest that PXD101 has potential as a novel antitumor agent. Furthermore, measurement of histone acetylation in blood cells could provide a suitable pharmacodynamic end point to monitor drug activity in patients.

References

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