Introduction

The cytosolic thioredoxin reductase system is composed of thioredoxin-1 and thioredoxin reductase-1 reductase, which catalyzes the NADPH-dependent reduction of thioredoxin-1. Thioredoxin reductase-1 is an important regulator of cancer cell growth and survival (1, 2). Thioredoxin-1 acting with peroxiredoxin-1 is an antioxidant that scavenges H$_2$O$_2$ (3). Thioredoxins are also able to reduce buried oxidized thiol residues in proteins (4) and regulate the activity of redox-sensitive transcription factors, including p53 (5), nuclear factor-κB (6), the glucocorticoid receptor (7), activator protein-1 (8), hypoxia-inducible factor-1 (HIF-1; ref. 9), Sp1 (10), and Nrf2 (11). Thioredoxin-1 also binds and inhibits the activity of the apoptosis-inducing proteins, apoptosis signal-regulating kinase-1 (12) and, the tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (13), thus inhibiting apoptosis. Thioredoxin-1 is overexpressed in many human tumors (14–17) where it is associated with increased cell proliferation, decreased apoptosis, and decreased patient survival (18). Thioredoxin-1 is overexpressed in many human tumors (14–17) where it is associated with increased cell proliferation, decreased apoptosis, and decreased patient survival (18).

Molecular pharmacology and antitumor activity of palmarumycin-based inhibitors of thioredoxin reductase

Garth Powis,1 Peter Wipf,2 Stephen M. Lynch,2 Anne Birmingham,3 and D. Lynn Kirkpatrick4

1Department of Experimental Therapeutics, M.D. Anderson Cancer Center, Houston, Texas; 2Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania; 3Arizona Cancer Center; and 4ProlX Pharmaceuticals, Tucson, Arizona

Abstract

The cytosolic thioredoxin redox system composed of thioredoxin-1 and the NADPH-dependent thioredoxin reductase-1 reductase is an important regulator of cell growth and survival. Thioredoxin-1 is overexpressed in many human tumors where it is associated with increased cell proliferation, decreased apoptosis, and decreased patient survival. We hypothesized that thioredoxin reductase-1 provides a target to inhibit the activity of overexpressed thioredoxin-1 for the development of novel anticancer agents. We found that the naphthoquinone spiroketal fungal metabolite palmarumycin CP1 is a potent inhibitor of thioredoxin reductase-1, but attempts to exploit the activity of palmarumycin CP1 analogues as antitumor agents in vivo were hampered by their insolubility. We have therefore developed PX-916, a water-soluble produg of a palmarumycin CP1 analogue. PX-916 rapidly releases the parent compound at physiologic pH and in plasma but is stable at acid pH, allowing its i.v. administration. PX-916 is a potent inhibitor of purified human thioredoxin reductase-1 and of thioredoxin reductase-1 activity in cells and tumor xenografts when given to mice and inhibits the downstream targets of thioredoxin-1 signaling, hypoxia-inducible factor-1α, and vascular endothelial growth factor in tumors. PX-916 showed excellent antitumor activity against several animal tumor models with some cures. Thus, the study shows that water-soluble inhibitors of thioredoxin reductase-1, such as PX-916, can block thioredoxin-1 signaling in tumors producing marked inhibition of tumor growth. [Mol Cancer Ther 2006; 5(3):630–6]
thioredoxin reductase-1 (28). There are reports that levels of thioredoxin reductase-1 are increased by epidermal growth factor (29) and hypoxia (30) in cancer cells, although tumors show only moderately increased levels of thioredoxin reductase-1 (23, 30).

We have identified the naphthoquinone spiroketal fungal metabolite palmarumycin CP1 as a potent inhibitor of thioredoxin reductase-1, but attempts to exploit the activity of palmarumycin CP1 analogues as antitumor agents in vivo were hampered by their insolubility (31). We have recently reported the synthesis of a series of water-soluble palmarumycin CP1 analogue prodrugs (32). We now report the molecular pharmacology and antitumor activity of one of these prodrugs in cancer cells and in human tumor xenografts.

Materials and Methods

Materials

The palmarumycin CP1 analogues PX-911, PX-916, and PX-960 (Fig. 1) were synthesized as described previously (31, 32). PX-916 was dissolved at 3 mg/mL in 5% ethanol, 10 mmol/L sodium phosphate (pH 4.0) for i.p. and oral administration and in 5% ethanol, 0.9% NaCl, 10 mmol/L sodium phosphate (pH 4.0) for i.v. administration and used within 30 minutes. Human placental thioredoxin reductase-1, specific activity 33 μmol NADPH oxidized/min/mg protein at room temperature, was prepared as described previously (33). Human recombinant thioredoxin-1 was prepared as described previously (34). Mouse monoclonal anti-human HIF-1α antibody was purchased from Transduction Laboratories (Lexington, KY), and rabbit polyclonal anti-human vascular endothelial growth factor (VEGF) was from Santa Cruz Biotechnology (Santa Cruz, CA). Immunohistochemistry for tumor HIF-1α and VEGF was done as described previously (35).

Table 1. Inhibition of thioredoxin reductase-1 and cell growth by palmarumycin CP1 analogues

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition of human thioredoxin reductase-1 IC50 (μmol/L)</th>
<th>Inhibition of MCF-7 breast cancer cell growth IC50 (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmarumycin CP1</td>
<td>0.35</td>
<td>1.0</td>
</tr>
<tr>
<td>PX-911</td>
<td>3.2</td>
<td>9.2</td>
</tr>
<tr>
<td>PX-916</td>
<td>0.28</td>
<td>3.1</td>
</tr>
<tr>
<td>PX-960</td>
<td>0.27</td>
<td>4.1</td>
</tr>
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</table>

Figure 2. Inhibition of cellular and tumor thioredoxin reductase by PX-916. MCF-7 human breast cancer cells grown in medium containing 1 μmol/L selenium for 7 d were treated with PX-916 and cellular thioredoxin reductase activity was measured. A, time course of the inhibition of thioredoxin reductase on exposure to 1 μmol/L PX-916. B, concentration dependence of the inhibition of thioredoxin reductase on exposure to various concentrations of PX-916 for 17 h. Points, mean of three determinations; bars, SE. *, P < 0.05; **, P < 0.01, compared with control. C, MCF-7 human breast cancer xenografts were grown in female scid mice implanted with 90-d 17α-estradiol slow release pellets until they were ~300 mm3. The mice were given a single dose of PX-916 (25 mg/kg i.v.) and tumors were harvested at various times. Thioredoxin reductase activity was measured in tumor homogenates. Points, mean of three mice at each time point; bars, SE. **, P < 0.01, compared with pretreatment value.
A673 human rhabdomyosarcoma cells were provided by Dr. Peter Houghton (St. Jude Children’s Hospital, Memphis, TN). SHP-77 human small cell lung cancer cells and MCF-7 human breast cancer cells were obtained from the American Tissue Type Collection (Manassas, VA). All cells were tested to be Mycoplasma free using a PCR ELISA kit (Roche Diagnostics, Inc., Indianapolis, IN) and grown in 95% humidified air with 5% CO2 at 37°C in McCoy’s 5A medium supplemented with 10% fetal bovine serum. For studies of effects of the palmarumycin CP1 analogues on cellular thioredoxin reductase activity, MCF-7 human breast cancer cells were grown in medium containing 1 μmol/L selenium for 7 days, which increased cellular thioredoxin reductase activity by ~5-fold as reported previously (36).

Figure 3. Antitumor activity of PX-916. A. Female Beige nude mice were inoculated s.c. with 10⁷ A673 rhabdomyosarcoma cells. When tumors were 100 mm³ on day 8 (arrow), dosing was begun with vehicle alone (C) or 30 mg/kg/d i.p. PX-916 for five doses (▲). Points, mean of six mice per group; bars, SE. B, Female scid mice were inoculated s.c. with 10⁷ SHP-77 human small cell lung cancer cells. When tumors were 150 mm³ on day 17 (arrow), dosing was begun with vehicle alone (C), 10 mg/kg/d i.v. PX-916 for eight doses (▲), or 25 mg/kg/d i.v. PX-916 for five doses (▲). Points, mean of eight mice per group; bars, SE. C, Female scid mice implanted 1 d previously with a 90-d 17β-estradiol slow release pellet were inoculated s.c. with 10⁷ MCF-7 human breast cancer cells. When tumors were 175 mm³ on day 8 (arrow), dosing was begun with vehicle alone (C), 22.5 mg/kg/d i.v. PX-916 for five doses (▲), 27.5 mg/kg/d i.v. PX-916 every other day for five doses (▲), and 22.5 mg/kg/d orally PX-916 for five doses (▲). Points, mean of eight mice per group; bars, SE.

Figure 4. Inhibition of tumor HIF-1α, VEGF, and thioredoxin reductase by repeated administration of PX-916. Female scid mice implanted 1 d previously with a 90-d 17β-estradiol slow release pellet were inoculated s.c. with 10⁷ MCF-7 human breast cancer cells. When the tumors were 300 mm³, vehicle or 25 mg/kg/d PX-916 was given i.v. for five doses. Twenty-four hours later, the tumors were removed and stained by immunohistochemistry for HIF-1α and VEGF (A) or assayed for thioredoxin reductase activity (B). Columns, mean of four mice; bars, SE. *, P < 0.05.
Thioredoxin Reductase-1 Assay
Thioredoxin reductase-1 activity was measured as the NADPH-dependent colorimetric reduction of dinitrothiobenzoate as described previously (37). Thioredoxin reductase-1, NADPH, and palmarumycin CP1 analogues were incubated for 15 minutes before adding dinitrothiobenzoate. Thioredoxin reductase activity in cell lysates was measured as the thioredoxin-1-dependent reduction of insulin by NADPH as described previously (37). Thioredoxin reductase activity in tumor tissue homogenates was measured also as described previously (24).

Antitumor Studies
A673 rhabdomyosarcoma, SHP-77 small cell lung cancer, or MCF-7 breast cancer cells (10⁷) in log cell growth were injected s.c. in 0.1 mL PBS into the flanks of female nude Beige mice (A673 cells) or female severe combined immunodeficient (scid) mice (SHP-77 and MCF-7 cells). Female mice that were to receive the estrogen-dependent MCF-7 breast cancer cell line were implanted s.c. in the back with a 90-day 17β-estradiol release pellet (Innovative Research of America, Sarasota, FL) a day before the tumor cells. The animals were weighed weekly and tumor diameters were measured twice weekly at right angles (d_short and d_long) with electronic calipers and converted to volume by the formula: volume = [(d_short)² x (d_long)] / 2; ref. 38. When the tumors reached volumes between 100 and 170 mm³, the mice were stratified into groups of eight animals having approximately equal mean tumor volumes and administration of PX-916 was started. When the tumor volume reached ≥2,000 mm³ or became necrotic, the animals were euthanized. Tumor growth rate was calculated from the linear portion of the least-squares regression of the cube root of the tumor volume. One-way ANOVA using the General Linear Model (39) was used to test for the effect of treatment on tumor growth rate.

Toxicity Studies
PX-916 was given i.v. at 25 mg/kg/d for 5 days to female scid mice. The mice were killed 24 hours after the last dose and changes in body weight from the start of the study, blood lymphocyte, neutrophil, RBC and platelet counts, and aspartate aminotransferase and alanine aminotransferase were measured. In separate studies, the maximum tolerated dose was determined as the dose that caused 4 g body weight loss or death of at least one of three animals.

Pharmacodynamic Studies
MCF-7 breast cancer cells (10⁷) were injected s.c. into the flanks of female scid mice previously implanted 1 day earlier with a 90-day 17β-estradiol release pellet and tumors were allowed to grow to ~300 mm³. Mice were given a single i.v. dose of 25 mg/kg PX-916 or vehicle alone. Mice were killed at various times and the tumors were removed and immediately frozen in liquid N₂ for the thioredoxin reductase assay. In a separate study, female scid mice with 300 mm³ MCF-7 tumor xenografts were treated with 25 mg/kg/d i.v. PX-916 or vehicle alone for 5 days. Twenty-four hours after the last dose, the tumors were removed and fixed for immunohistochemistry or frozen for the thioredoxin reductase assay.

Pharmacokinetic Studies
Male C57Bl/6 mice were given PX-916 i.v. at 25 mg/kg. The mice were killed at various times, blood was collected into heparinized tubes, and plasma was prepared. Plasma (0.2 mL) was immediately mixed with an equal volume of 0.25 mol/L sodium phosphate (pH 4.0) and extracted for 1 hour by inversion with 4 mL ethyl acetate. After centrifugation, the organic layer (3.8 mL) was removed and evaporated under N₂ and the residue was dried on a lyophilizer. Chromatographic separation was achieved with a Waters Symmetry C-18 3.9 × 150 mm column (Waters, Milford, PA) with a mobile phase of 0.1% trifluoroacetic acid in 60% methanol at a flow rate of L/min with detection at 254 nm. For the assay, the sample residue was dissolved in 100 µL mobile phase and centrifuged at 15,000 × g for 5 minutes at 4°C. The limit of detection of the assay for all the compounds from 0.2 mL mouse plasma was 0.1 µg/mL.

Results
Stability
PX-916 was stable as a stock solution in ethanol at room temperature with a half-life of >5 days. However, in 0.1 mol/L sodium phosphate, PX-916 showed pH-dependent degradation with a half-life of 37 hours at pH 4.0, 1 hour at pH 7.0, and ~1 hour at pH 10.0 (data not shown). Therefore, PX-916 was used as a stock solution in ethanol for in vitro studies and made fresh in vehicle (pH 4.0) for in vivo studies.

Inhibition of Thioredoxin Reductase-1
PX-916 was a potent inhibitor of purified human thioredoxin reductase-1 with an IC₅₀ of 0.28 µmol/L, which is similar to that of palmarumycin CP1 (Table 1). However, unlike palmarumycin CP1, which is almost insoluble in aqueous medium, PX-916 is soluble with a maximum solubility in water of ~10 mg/mL. Based on the observation that PX-916 was rapidly converted to PX-960 in aqueous solution, we measured the ability of PX-960 to inhibit purified human thioredoxin reductase-1 and found it to be similar to that of PX-916 (Table 1). PX-916 was a selective inhibitor of human thioredoxin reductase-1 compared with two other NADPH-dependent reductases with an IC₅₀ for human glutathione reductase of >50 µmol/L (>200-fold selectivity for thioredoxin reductase-1) and 29.2 µmol/L for human cytochrome P450 reductase (104-fold selectivity for thioredoxin reductase).

In vitro Activity
Cell growth inhibition of MCF-7 human breast cancer cells by palmarumycin CP1, PX-916, and PX-960 occurred at similar concentrations of 1 to 3 µmol/L (Table 1). When MCF-7 cells were exposed to 1 µmol/L PX-916, there was a time-dependent inhibition of cellular thioredoxin reductase that was maximum at 24 hours (Fig. 2A). The IC₅₀ for inhibition of cellular thioredoxin reductase by PX-916 was 0.25 µmol/L and maximum inhibition occurred at 0.5 µmol/L (Fig. 2B). Thus,
inhibition of purified human thioredoxin reductase-1, MCF-7 cellular thioredoxin reductase, and cell growth inhibition of MCF-7 cells occurred at about the same concentration of PX-916.

**In vivo Inhibition of Tumor Thioredoxin Reductase and Antitumor Activity**

A single i.v. dose of PX-916 of 25 mg/kg inhibited MCF-7 human tumor xenograft thioredoxin reductase-1 up to 60% at 24 hours and the inhibition was maintained for at least 48 hours (Fig. 2C). The growth of A673 human rhabdomyosarcoma xenografts (mean ± SE, n = 6 mice) was decreased from 153 ± 35 mm³/d in the vehicle control group to 5 ± 3 mm³/d for 5 days after dosing with PX-916 at 30 mg/kg/d i.p. for five doses (97% inhibition; *P* < 0.01; Fig. 3A). PX-916 given i.v. also showed good antitumor activity against the SHP-77 small cell lung cancer with a decrease in tumor growth rate 5 days after the end of dosing (mean ± SE, n = 8 mice) from 150 ± 48 mm³/d in the vehicle control group to 27 ± 14 mm³/d when given at 25 mg/kg/d i.v. for five doses (82% inhibition; *P* < 0.05; Fig. 3B). In this study, three of eight mice had no histologically detectable tumor when the study was terminated on day 42. When PX-916 was given i.v. at 10 mg/kg/d i.v. for eight doses, tumor growth was decreased to only 91 ± 24 mm³/d (39% inhibition; *P* < 0.05) by 5 days after the end of dosing. The growth of MCF-7 human breast cancer xenografts was decreased 5 days after the end of dosing from 47 ± 10 mm³/d in the vehicle control group to 22 ± 4 mm³/d by PX-916 at 25 mg/kg/d i.v. for five doses (52% inhibition; *P* < 0.05), 22 ± 8 mm³/d by PX-916 at 27.5 mg/kg i.v. every other day for five doses (52% inhibition; *P* < 0.05), and 18.5 ± 8 mm³/d by PX-916 at 27.5 mg/kg/d orally for five doses (62% inhibition; *P* < 0.05; Fig. 3C).

**Tumor HIF-1α and VEGF**

Levels of the HIF-1α transcription factor and its downstream target VEGF are increased by thioredoxin-1 expression (9). We therefore examined the effect of PX-916 administration on tumor HIF-1α and VEGF levels (Fig. 4A). Twenty-four hours after the last dose of five daily doses of PX-916 of 25 mg/kg, there was a decrease in MCF-7 xenograft staining for both HIF-1α and VEGF. At the same time, levels of tumor thioredoxin reductase activity were decreased by 75% (Fig. 4B).

**Toxicity**

The maximum tolerated single i.v. dose of PX-916 to female scid mice was 50 mg/kg, and the mice tolerated five daily doses of PX-916 of 30 mg/kg i.v. The major toxicities observed 24 hours after five daily doses of PX-916 of 25 mg/kg i.v. were neutropenia and thrombocytopenia, with no increase in plasma liver enzymes and no significant weight loss (Table 2). No other gross toxicities were observed.

**Discussion**

Thioredoxin-1 is overexpressed in many human tumors (14–17) where it is associated with increased cell proliferation, decreased apoptosis (18), and decreased patient survival (19, 20). The redox activity of thioredoxin-1 is necessary for its biological effects in stimulating cancer cell growth and inhibiting apoptosis (12, 13, 34). Although thioredoxin reductase-1 is necessary for the reduction of thioredoxin-1, its levels are only moderately increased in tumors (23, 30). We hypothesized that preventing the reduction of thioredoxin-1 by inhibiting tumor thioredoxin reductase-1 could be a critical point at which to block the redox-dependent biological effects of thioredoxin-1 leading to inhibition of tumor growth.

We have reported previously that palmarumycin CP1 and some of its analogues are potent inhibitors of thioredoxin reductase-1 (31). However, all prior compounds were very insoluble and could not be given to animals. PX-916 was synthesized as a water-soluble prodrug of the palmarumycin CP1 derivative PX-960 and was found to retain the ability to inhibit purified thioredoxin reductase-1 with an IC₅₀ of 0.28 μmol/L. PX-916 also inhibited thioredoxin reductase-1 activity in MCF-7 human breast cancer cells with an IC₅₀ of 0.25 μmol/L and was an inhibitor of MCF-7 cell growth with an IC₅₀ of 3.1 μmol/L. As with other reported inhibitors of thioredoxin reductase-1 (40), PX-916 was an NADPH and time dependent, apparently irreversible inhibitor of thioredoxin

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose (mg/kg)</th>
<th>ΔBody weight (g)</th>
<th>Alanine aminotransferase (units/L)</th>
<th>Aspartate aminotransferase (units/L)</th>
<th>WBC (K/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25</td>
<td>−1.2 ± 1.5</td>
<td>30.3 ± 10</td>
<td>154.1 ± 62.4</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>QD × 5 i.v.</td>
<td>25</td>
<td>−0.6 ± 0.3</td>
<td>39.8 ± 12.8</td>
<td>166.9 ± 29.8</td>
<td>1.3 ± 0.6*</td>
</tr>
</tbody>
</table>

**NOTE:** PX-916 was given to female scid mice at 25 mg/kg/d i.v. for 5 days, and mice were killed 24 hours after the last dose. There were four mice per group (mean ± SE).

*P* < 0.05.
Neutrophils, and have been reported, including lipoic acid, ascorbyl free nonspecific enzyme, and other potential natural substrates noted previously, thioredoxin reductase-1 is a relatively reductase-1 might affect other pathways in the cell. As thioredoxin-1 redox signaling. Inhibition of thioredoxin-1 inhibitor (41). MCF-7 tumor xenografts in angiogenesis (9), and this effect was reversed by a VEGF formation, associated with an increase in tumor growth was inhibited as long as the drug was given. Significant antitumor activity was not seen following oral administration at doses that gave i.v. antitumor activity. We have reported previously that thioredoxin-1 acts by a redox mechanism to increase HIF-1α levels and VEGF formation, associated with an increase in tumor angiogenesis (9), and this effect was reversed by a thioredoxin-1 inhibitor (41). MCF-7 tumor xenografts in mice treated with PX-916 showed a decrease in tumor HIF-1α and VEGF presumably due to the inhibition of thioredoxin-1 redox signaling. Inhibition of thioredoxin reductase-1 might affect other pathways in the cell. As noted previously, thioredoxin reductase-1 is a relatively nonspecific enzyme, and other potential natural substrates have been reported, including lipoic acid, ascorbyl free radicals, and 5-nitrosoglutathione (21, 42). A recent study using small interfering RNA to knockdown thioredoxin reductase-1 expression and microarray analysis showed surprisingly few changes in gene expression, only 8 of 20,000 genes on the array, possibly because thioredoxin reductase-1 activity was only decreased 43% by the treatment (27). The genes that did change, leukotriene B4 12-hydroxydehydrogenase, ubiquitin D, differentiation-enhancing factor, fibronectin 1, apolipoprotein 3, prosaposin, choline/ethanolamine phosphotransferase, and IFN-α-inducible protein, give little clue to the pathways affected by thioredoxin reductase-1.

Several anticancer agents have been reported to inhibit thioredoxin reductase-1, including alkylating agents and platinum agents (40), the polyphenol curcumin (43), the porphyrin gadolinium macrocycle, motexafin gadolinium (22), and the quinol NSC 706704 (44). It remains to be determined whether concentrations of any of these compounds that inhibit tumor thioredoxin reductase-1 can be obtained in vivo, and most of these agents have other mechanisms that are more likely than thioredoxin reductase-1 inhibition to account for their antitumor activity.

Although this work has focused on the antitumor consequences of the inhibition of thioredoxin reductase, there are several other diseases where thioredoxin reductase is thought to play a pathophysiologic role, such as diabetic neuropathy, rheumatoid arthritis, Sjogren’s syndrome, AIDS, and reperfusion injury (1, 2, 42). Thioredoxin reductase inhibitors may have therapeutic benefits in these conditions as well as in cancer.

In summary, we have shown that PX-916, a water-soluble prodruk of a palmarumycin CP1 analogue, rapidly releases the parent compound at physiologic pH and in plasma but is stable at acid pH, allowing its i.v. administration. PX-916 is a potent inhibitor of purified human thioredoxin reductase-1 and of thioredoxin reductase activity in cells and tumor xenografts when given to mice. PX-916 exhibited antitumor activity against several animal tumor models, with some cures, and blocked the expression of the downstream targets of thioredoxin-1 signaling, HIF-1α and VEGF, in the tumors.

Table 2. Toxicity of PX-916 in scid mice (Cont’d)

<table>
<thead>
<tr>
<th>Neutrophils (K/μL)</th>
<th>Lymphocytes (K/μL)</th>
<th>Monocytes (K/μL)</th>
<th>RBC (mol/L/μL)</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelets (K/μL)</th>
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</thead>
<tbody>
<tr>
<td>2.5 ± 0.5</td>
<td>0.4 ± 0.1</td>
<td>0.11 ± 0.05</td>
<td>9.4 ± 0.5</td>
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</tr>
<tr>
<td>0.9 ± 0.3*</td>
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<td>0.005 ± 0.01</td>
<td>8.9 ± 0.4</td>
<td>14.9 ± 0.4</td>
<td>436 ± 142*</td>
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</tbody>
</table>

References


Molecular Cancer Therapeutics

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