Antitumor Activity of P-4055 (Elaidic Acid-Cytarabine) Compared to Cytarabine in Metastatic and s.c. Human Tumor Xenograft Models

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ABSTRACT

The antineoplastic efficacy of P-4055, a 5'-elaidic acid (C18:1, unsaturated fatty acid) ester of cytarabine, a nucleoside antimetabolite frequently used in the treatment of hematological malignancies, was examined in several in vivo models for human cancer.

In initial dose-finding studies in nude mice, the efficacy of P-4055 was highest when using schedules with repeated daily doses. In a Raji Burkitt's lymphoma xenograft model in nude rats, the control cytarabine- and saline-treated animals (five in each group) had a mean survival time of 13.2 days, whereas treatment with P-4055 resulted in three of five long-time survivors (70 days). In a systemic Raji leukemia model in nude mice, 8 of 10 of the P-4055-treated animals survived (>90 days), compared with none of the cytarabine-treated animals (mean survival time, 34.2 days).

In s.c. xenograft models, the effects of maximum tolerated doses of P-4055 and cytarabine, given in four weekly cycles of daily bolus i.v. injections for 5 subsequent days, against seven tumors (three melanomas, one lung adenocarcinoma, one breast cancer, and two osteogenic sarcomas) were investigated. P-4055 induced partial or complete tumor regression in the lung carcinoma, as well as of all three malignant melanomas. In two of the melanomas the activity was highly superior to that of cytarabine, and both P-4055 and cytarabine were, in general, more effective than several clinically established drugs previously tested in the same tumor models. In in vitro studies, inhibitors of nucleoside carrier-dependant transport, nitrobenzylmercaptopurine riboside and dipridamol, reduced strongly the cellular sensitivity to cytarabine, but not to P-4055, indicating that P-4055 uses an alternative/additional mechanism of internalization into the cell compared with cytarabine. The results explain, at least in part, the observed differences between the two compounds in in vivo efficacy, and together the data strongly support the evaluation of P-4055 in clinical studies.

INTRODUCTION

Cytarabine, a nucleoside analogue of deoxyxycytidine, is frequently used in the treatment of hematological cancers. Its antitumor activity is well proven in leukemias (acute myelogenic leukemia and acute lymphoblastic leukemia) and lymphomas, but not in solid tumors (1). The efficacy of cytarabine is heavily dependent on dose and schedule because of its short biological half-life. This is due to a rapid deamination into uracil arabinoside by the ubiquitous enzyme cytidine deaminase, which is found at highest concentrations in the intestine, liver, and kidneys (2). Recently developed deoxynucleoside analogues are finding an expanding application in cancer chemotherapy, leading to a renewed interest in the use of such antimetabolites also against solid tumors (3).

We have tested a novel approach to improve the efficacy of antimetabolites by constructing ester derivatives of cytarabine and fatty acids designed with the aim of increasing cellular uptake of cytarabine and/or delaying its metabolic deamination and clearance. In vitro testing in murine and human tumor cell lines revealed differential cytotoxic properties of various conjugates of cytarabine and fatty acids, with chain-lengths varying from 16–22 C-atoms and with 0–3 double bonds. The fatty acids were linked to the sugar moiety of cytarabine at the 5'-OH position, and of 11 derivatives tested, P-4055 was found to be the most promising one (4, 5). P-4055 is the 5'-elaidic acid (C18:1trans, unsaturated fatty acid) ester of cytarabine. We studied its antitumor potential in vivo in human tumor models in nude mice and rats and in vitro in several tumor cell lines in the presence or absence of nucleoside carrier inhibitors.

MATERIALS AND METHODS

Animals. Female BALB/c nude (nu/nu) mice, 5–8 weeks of age at the start of the experiment, and Rowett nude (Han/hrnu) rats, 4 weeks of age, were used. The animals were maintained under specific pathogen-free conditions, and food and water were supplied ad libitum. Housing and all procedures involving animals were performed according to protocols approved by the animal care and use committee, in compliance with the National Committee for Animal Experiments guidelines on animal welfare.

Mice were anesthetized with 5 mg/10 g propanidid (Sombrevin; Gedeon Richter Ltd., Budapest, Hungary), given i.p. during tumor tissue implantation, and rats were anesthetized with 0.3 ml/100 g of a mixture with equal parts of fentanyl/luanislon (Hypnorm; Janssen, Beerse, Belgium) and midazolam (Dormicum; Roche, Basel, Switzerland) during surgical procedures.

Tumor Models. Initially, a leptomeningeal carcinomatosis model in nude rats, including the malignant lymphoma cell lines Raji (6) and Molt-4 (7, 8), was established. Cells (1 × 106) were injected into the spinal fluid in c.m. of nude rats, 4–5 weeks of age.

A systemic leukemia model in nude mice (9, 10) was established by i.v. injection of 1 × 106 Raji cells.

The solid tumor xenograft panel consisted of three malignant melanomas (LOX, THX, and HHMSX; Refs. 11–16), one breast carcinoma (MDA-MB 435; Ref. 17), one non-small cell lung adenocarcinoma (EKVX; Refs. 15 and 16), and two osteogenic sarcomas (KPDX and OHS; Refs. 18–20).

Evaluation of s.c. Tumor Growth. Tumor pieces, about 2 × 2 × 2 mm3, were implanted into each flank of female nude mice. The tumors were allowed to grow to a mean diameter of about 6 mm before the start of treatment (day 0). Each group consisted of at least six tumors in five animals, randomized in a size-matched manner.

At the start of treatment, the minimum tumor diameter was 4 mm, equivalent to a volume of 32 mm3. If a mouse died within 2 weeks after the final injection, this was considered toxic death, and the animal was excluded from the study. Treatment causing more than 10% body weight loss, compared with controls, was considered not evaluable for antitumor efficacy. The drug effects were calculated from growth curves constructed on the basis of median RTVs, where the calculated volume at any day X, based on two perpendicular measurements of the tumor twice weekly, was divided by the tumor volume at the start of treatment (day 0; Refs. 15, 21, 22). Tumor volume was calculated according to the formula: tumor volume = 0.5 × length × width2; and median RTVs were used for construction of growth curves and to calculate treatment efficacy (Table 1; Ref. 15). The time to reach one or two TD times (TD50 and TD90) was calculated for each individual tumor, and the mean values in each
The optimal i. d. doses of P-4055 and cytarabine were found to be 20–30 mg/kg and 100–200 mg/kg, respectively, depending on the frequency of dosing. In inhibiting tumor growth, schedules comprising repeated daily injections were clearly favorable over schedules with weekly or every 2nd-day injec-

RESULTS

Doses and Schedules in Rats. Initial treatment of leptomeningeal lymphomas in rats indicated a clear relationship between the response and the number of times the daily bolus dose was repeated, both for P-4055 and cytarabine given at equitoxic or equimolar doses. No cumulative toxicity was observed when a once daily dose, in a 40-μl volume, was given for 4 subsequent days after cell injection.

Doses and Schedules in Mice. The optimal i. p. doses of P-4055 and cytarabine were found to be 20–30 mg/kg and 100–200 mg/kg, respectively, depending on the frequency of dosing. In inhibiting tumor growth, schedules comprising repeated daily injections were clearly favorable over schedules with weekly or every 2nd-day injec-

Table 1 Antitumor effects of P-4055 (25 mg/kg) and cytarabine (100 mg/kg) in human tumor xenografts i.p., days 0–4, 7–11, 14–18, and 21–25

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Drug</th>
<th>Number of tumors</th>
<th>Body weight loss (%)</th>
<th>Toxicity</th>
<th>TD200</th>
<th>TD400</th>
<th>T/C%</th>
<th>SGD200</th>
<th>SGD400</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>LOX (malignant melanoma)</td>
<td>Control</td>
<td>11</td>
<td>0/7</td>
<td>2.0</td>
<td>4.0</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++++</td>
</tr>
<tr>
<td>P-4055</td>
<td>11</td>
<td>2.9</td>
<td>0/7</td>
<td>36.5</td>
<td>38.5</td>
<td>2.8</td>
<td>17.3</td>
<td>8.6</td>
<td>-</td>
<td>++++</td>
</tr>
<tr>
<td>Cytarabine</td>
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<td>2.5</td>
<td>0/7</td>
<td>2.5</td>
<td>4.5</td>
<td>76.5</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>THX (malignant melanoma)</td>
<td>Control</td>
<td>9</td>
<td>0/6</td>
<td>&gt;70.0</td>
<td>&gt;70.0</td>
<td>6.6</td>
<td>&gt;22.3</td>
<td>&gt;22.3</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>P-4055</td>
<td>10</td>
<td>2.9</td>
<td>0/6</td>
<td>&gt;70.0</td>
<td>&gt;70.0</td>
<td>8.6</td>
<td>&gt;9.0</td>
<td>&gt;9.0</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>10</td>
<td>0</td>
<td>0/6</td>
<td>&gt;70.0</td>
<td>&gt;70.0</td>
<td>8.6</td>
<td>&gt;9.0</td>
<td>&gt;9.0</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>HHMSX (malignant melanoma)</td>
<td>Control</td>
<td>9</td>
<td>0/6</td>
<td>7.0</td>
<td>17.0</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td>P-4055</td>
<td>6</td>
<td>12.1</td>
<td>1/6</td>
<td>46.5</td>
<td>50.0</td>
<td>11.0</td>
<td>5.6</td>
<td>1.9</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>7</td>
<td>13.4</td>
<td>1/6</td>
<td>16.5</td>
<td>27.0</td>
<td>38.3</td>
<td>1.4</td>
<td>0.6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>EKXX (lung adenocarcinoma)</td>
<td>Control</td>
<td>6</td>
<td>0/5</td>
<td>15.0</td>
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<td>+</td>
</tr>
<tr>
<td>P-4055</td>
<td>6</td>
<td>5.3</td>
<td>0/5</td>
<td>&gt;100.0</td>
<td>&gt;100.0</td>
<td>1.9</td>
<td>&gt;5.7</td>
<td>&gt;2.7</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>6</td>
<td>2.3</td>
<td>0/5</td>
<td>&gt;100.0</td>
<td>&gt;100.0</td>
<td>1.0</td>
<td>&gt;5.7</td>
<td>&gt;2.7</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>MDA-MB 435 (breast cancer)</td>
<td>Control</td>
<td>11</td>
<td>0/9</td>
<td>13.0</td>
<td>24.0</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>P-4055</td>
<td>7</td>
<td>7.1</td>
<td>2/9</td>
<td>12.0</td>
<td>30.0</td>
<td>44.6</td>
<td>0.1</td>
<td>0.3</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>7</td>
<td>8.0</td>
<td>2/8</td>
<td>14.0</td>
<td>29.0</td>
<td>51.3</td>
<td>0.1</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KPDX (osteogenic sarcoma)</td>
<td>Control</td>
<td>9</td>
<td>0/7</td>
<td>5.0</td>
<td>11.0</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P-4055</td>
<td>8</td>
<td>1.3</td>
<td>0/8</td>
<td>5.5</td>
<td>14.5</td>
<td>81.4</td>
<td>0.6</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>OHS (osteogenic sarcoma)</td>
<td>Control</td>
<td>9</td>
<td>0/8</td>
<td>3.5</td>
<td>15.0</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P-4055</td>
<td>9</td>
<td>1.3</td>
<td>0/8</td>
<td>5.5</td>
<td>14.5</td>
<td>81.4</td>
<td>0.6</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Footnotes:

1) TDS of test and control groups were defined as the period (days) required to reach a median RTV value of 200 or 400.
2) Growth inhibition at a particular day was assessed by dividing the median RTV of treated group of animals with the median RTV of the control group, at the same day: T/C% ＝ (RTV treated/RTV control) × 100%.
3) A SGD was calculated as follows: SGD ＝ (TD treated-TD control)/TD control.
4) Efficacy as defined by: (+) T/C <50% or SGD >1.0; + T/C <<50% and SGD >1.0; + + T/C <40% and SGD >1.5; ++ T/C <25% and SGD >2.0; +++ T/C <10% and SGD >3.0. Based on the experience with the model used, a T/C% value of <50% and a SGD value of >1.0 were defined as minimum criteria for antitumor activity.
EFFECTS OF P-4055 ON s.c. AND METASTATIC HUMAN TUMORS

Activity in Leptomeningeal Carcinomatosis Models. After i.v. injection of $1 \times 10^6$ Raji cells, the mice developed paralysis as a result of systemic growth of tumor cells after a mean latency of 40 days (range, 34–48) in the control group ($n = 10$; one survivor). The i.p. drug doses were 25 mg/kg P-4055 and 100 mg/kg cytarabine, given on days 7–11, 14–18, 21–25, and 28–32 after cell injection ($n = 10$ in both groups). A highly significant increase ($P < 0.001$, Kruskal-Wallis test) in survival was observed for the P-4055-treated group, with 8 of 10 animals living more than 80 days after the start of treatment, compared with none of the cytarabine-treated animals (mean survival time, 34.2 days; Fig. 2B).

Antitumor Activity in s.c. Models. In Table 1, the effects of the drugs in inhibiting the growth of solid tumor xenografts are summarized, using the described activity criteria. Partial or complete tumor regression of the lung carcinoma and all three malignant melanomas was obtained after treatment with P-4055. In two of the melanomas, the effect was much stronger than that of cytarabine.

Thus, pronounced regression of the P-4055-treated LOX tumors was observed with 2 of the 11 tumors seemingly eradicated. All tumors started, however, to regrow 7–10 days after the end of treatment (Fig. 3A). Cytarabine did not affect tumor growth, and all of the animals had to be sacrificed on day 16 after the start of treatment, as was the case for the untreated control animals. The optimal T/C% (RTV treated/RTV control) × 100% values were 2.8 for the P-4055 and 76.5 for the cytarabine group (Table 1). The calculated SGD over one doubling time (SGD_200) was 17.3 and 0.3 for P-4055 and cytarabine, respectively.

For the THX malignant melanoma, the latency from tumor implantation until the start of treatment was 19 days. As shown in Fig. 3B, both drugs were highly active, and 5 (P-4055) and 3 (cytarabine) of 10 tumors disappeared and showed no regrowth within 116 days after the start of treatment.

Like LOX, the melanotic HHMSX xenograft line was highly sensitive to P-4055 and moderately sensitive to cytarabine ($P < 0.001$; Fig. 3C), with T/C% values of 11 and 38.3 and SGD_200 of 5.6 and 1.4 (Table 1). One death among six animals was observed in each group. This might be caused by a combination of drug toxicity and cachexia, which is known to appear in mice carrying this tumor, reflected in a weight loss of 9.2% in the control group. The rather slowly growing and generally resistant EKVX non-small cell lung cancer was also highly responsive to both P-4055 and cytarabine, with regression of the tumors from the start of treatment, although none of the tumors disappeared completely (Fig. 3D). TD_200 was not reached within more than 100 days, resulting in SGD of >5.7 for both drugs (Table 1). The optimal T/C% values were 1.9 and 1.0 for P-4055 and cytarabine, respectively.

In the MDA-MB 435 breast carcinoma and the osteogenic sarcoma
KPDX and OHS models, P-4055 and cytarabine were both inactive, except from a marginal effect, against MDA-MB 435 (Table 1).

**Effects of Nucleoside Transport Inhibitors in Vitro.** In attempts to elucidate mechanisms underlying the differential activity of P-4055 and cytarabine in vivo, we examined how nucleoside transport carrier inhibitors could influence their antiproliferative capacity in vitro. The effects of the two compounds on murine L1210 and human CEM, Molt-4, Molt-4/clone 8, and THX cells were evaluated in the presence or absence of NBMPR and dipyridamol at subtoxic concentrations (100 μM and 4 μg/ml, respectively).

The IC_{50} values of cytarabine and P-4055 ranged from <0.001 μM to 1.0 μM, depending on the tumor cell line. Importantly, in all cases, the presence of the transport inhibitors (NBMPR or dipyridamol) partially reversed the cytostatic activity of cytarabine, but not that of P-4055. Whereas in L1210 cells the inhibitory effect of cytarabine on cell proliferation was reduced 3–4-fold by NBMPR and dipyridamol, the values were as high as 12–50-fold, 7–26-fold, and 40–75-fold in CEM, Molt-4/clone 8, and THX cell cultures, respectively (Table 2). In striking contrast, neither NBMPR nor dipyridamol could significantly reverse the cytostatic activity of P-4055 (Table 2).

**Table 2. Effects of nucleoside transport inhibition on the in vitro cytotoxic effect of cytarabine and P-4055.**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Nucleoside transport inhibitor</th>
<th>Cytarabine IC_{50}(μM)</th>
<th>P-4055 IC_{50}(μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1210</td>
<td>As such</td>
<td>0.04 ± 0.009</td>
<td>0.04 ± 0.001</td>
</tr>
<tr>
<td></td>
<td>+ NBMPR</td>
<td>0.12 ± 0.01</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>+ Dipyridamol <em>a</em></td>
<td>0.16 ± 0.01</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>CEM</td>
<td>As such</td>
<td>0.04 ± 0.006</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>+ NBMPR</td>
<td>0.49 ± 0.05</td>
<td>0.06 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>+ Dipyridamol <em>b</em></td>
<td>1.9 ± 0.15</td>
<td>0.09 ± 0.008</td>
</tr>
<tr>
<td>Molt-4</td>
<td>As such</td>
<td>0.0001 ± 0.00002</td>
<td>0.0009 ± 0.00002</td>
</tr>
<tr>
<td></td>
<td>+ NBMPR</td>
<td>4.35 ± 1.53</td>
<td>0.036 ± 0.014</td>
</tr>
<tr>
<td></td>
<td>+ Dipyridamole</td>
<td>2.82 ± 0.18</td>
<td>0.038 ± 0.005</td>
</tr>
<tr>
<td>Molt-4/clone 8</td>
<td>As such</td>
<td>1.00 ± 0.12</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>+ NBMPR</td>
<td>7.65 ± 0.75</td>
<td>0.038 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>+ Dipyridamole</td>
<td>25.6 ± 5.4</td>
<td>0.076 ± 0.003</td>
</tr>
<tr>
<td>THX</td>
<td>As such</td>
<td>0.32 ± 0.18</td>
<td>0.23 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>+ NBMPR</td>
<td>12.6 ± 0.55</td>
<td>0.072 ± 0.039</td>
</tr>
<tr>
<td></td>
<td>+ Dipyridamole</td>
<td>23.5 ± 6.3</td>
<td>0.17 ± 0.05</td>
</tr>
</tbody>
</table>

_a_ NBMPR was used at a subtoxic concentration of 100 μM.

_b_ Dipyridamole was used at a subtoxic concentration of 4 μg/ml.
diprydamol had any appreciable influence on the cytostatic activity of P-4055 in any of the cell lines, except in Molt-4 cells, where the activity decreased 40–43-fold, compared with >43,000- to >28,000-fold for cytarabine.

**DISCUSSION**

In a number of in vivo human tumor models, P-4055, a novel conjugate of cytarabine and elaidic acid, was superior in antitumor activity compared with its parent compound cytarabine. Differential activity was seen in several experimental metastasis and s.c. models in nude mice and rats, including models for leptomeningeal carcinomatosis and systemic leukemia, as well as two of the four s.c. xenografts that responded to these drugs. Because no differences in effects were found in some of the models, the observed selectivity may reflect tumor-associated differences in cellular uptake and/or metabolism of the compounds.

Hardly any data have been reported on cytarabine having an effect against solid tumors in the clinic (1, 25–27), and part of our findings with P-4055 and cytarabine were, therefore, surprising. However, another nucleoside analogue of deoxycytidine 2',2' difluorodeoxycytidine (dFdC, gemcitabine) has proven effective in the treatment of nonhematological tumors, both preclinically and in clinical trials in patients with lung, ovarian, breast, and pancreatic cancers (3, 28, 29), indicating that deoxycytidine analogues possess a potential for a wider spectrum of activity than leukemias and lymphomas. This might be dependent on optimal scheduling of the treatment.

Because of the rapid inactivation of cytarabine by cytidine deaminase, and its phase-dependent tumor cell killing, the drug is usually administered to patients as a continuous infusion of 100–200 mg/m² for 5–10 days. An alternative high-dose regimen for patients with refractory forms of acute leukemia is to use 2–3 g/m², given as a 2-h infusion twice daily for 6 days; but, it is not clear to us whether similar dosages and schedules have been tested in patients with solid cancer.

P-4055 was synthesized with the aim of reducing the deamination of cytarabine, possibly lowering the clearance, and increasing the intracellular level of the drug in tumor cells. The results obtained here suggest that, in part, this goal may have been reached. When calculated at a molar level of active nucleoside, the results were obtained at an 8-fold lower dose of cytarabine in the form of P-4055. After testing different doses and schedules to establish the MTD at an 8-fold lower dose of cytarabine, possibly lowering the clearance, and increasing the intracellular level of the drug in tumor cells. The results obtained here suggest that, in part, this goal may have been reached. When calculated at a molar level of active nucleoside, the results were obtained at an 8-fold lower dose of cytarabine in the form of P-4055.

When cytarabine is administered by continuous i.v. infusion to patients, it distributes rapidly into total body water with concentration in the CSF reaching 50% of simultaneous plasma levels after 2 h. P-4055 has in this study proven effective against lymphomas growing in the CNS compartment. However, because the models used here were examined with bolus injections given intracereally to directly reach the CSF, the efficacy of systemic P-4055 treatment against metastases to the CNS is not yet determined.

In conclusion, P-4055 is a new analogue of cytarabine, with a different or at least an additional mechanism of transport into the cell. The compound was active against experimental human lymphomas growing systemically or in the CNS of nude mice and rats, as well as against solid human tumor xenografts growing s.c. in immunodeficient mice. The superior and differential activity compared with cytarabine suggests that P-4055 might be effective also in the treatment of solid tumors in the clinical setting.

**REFERENCES**

9. Ghetie, M. A., Tucker, K., Richardson, J., Uhr, J. W., and Vivetta, E. S. Eradication of minimal disease in severe combined immunodeficient mice with disseminated


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