Anticancer Efficacy of Magainin2 and Analogue Peptides

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ABSTRACT

Linear helical channel-forming peptides structurally similar to the Xenopus-derived antibiotic, Magainin2-amide, were synthesized. Because activity resides in the physicochemical properties of the peptides, an all-o-amino acid as well as an all-l-amino acid sequence were tested for anticancer activity. In vitro activity against carcinoma cells and in vivo efficacy against four murine ascites tumors were determined. The novel peptides proved to have enhanced potency in vitro and in vivo as compared to the parent compound. The 50% inhibitory concentrations against A549 cells for the all-o, the all-l, and Magainin2 were 6, 10, and 110 μg/ml, respectively. All three peptides had activity against P388 leukemia, S180 ascites, and a spontaneous ovarian tumor when injected i.p. Increase in life span of over 100% was produced for the analogues in the latter two models. The maximally effective concentrations for the analogues were 20 to 25 mg/kg while Magainin2 required 50—60 mg/kg for in vivo efficacy. The all-o-amino acid peptide, MSI-238, proved as effective as doxorubicin at a more advanced stage of the ovarian tumor and this activity may be attributed to its resistance to proteolytic degradation. Therefore, this class of amphipilic α-helical cationic peptides has potential in the peritoneal treatment of ovarian cancer.

INTRODUCTION

Magainins are among the growing list of naturally occurring, membrane active peptides with antimicrobial activity (1). Antibiotic peptides may represent a first line of defense against infection, a system which has apparently been conserved throughout evolutionary history (2). In the last decade, peptides of similar nature have been identified in species from moth to humans (see Ref. 3 for a review). Based on the naturally occurring sequences, analogues with increased antimicrobial potency but retaining lack of hemolytic activity have been developed (3—6). In vitro, certain magainin analogues were toxic to neoplastic cells at concentrations lower than required to lyse peripheral blood lymphocytes, normal fibroblasts, or erythrocytes (7, 8).

The mechanism of cell killing by magainin and its analogues resides in the unique structural features of these linear peptides, which interact avidly with membranes rich in acidic phospholipids (9—11). Interaction with lipid bilayers induces this class of peptide to form a secondary structure, an amphiphilic α-helix, characterized by a characteristically high polarity between the ionic and hydrophobic face (12). Evidence suggests that the peptide molecules assemble to form ion permeable channels in membranes (12, 13) ultimately leading to cell death (7, 11, 14). In contrast to the L-enantiomers, the peptides configured from all-o-amino acids form left-handed helices (15, 16). They retain antimicrobial activities equivalent to the all-L structures, supporting the hypothesis that magainins act through self-association within a membrane rather than through interaction with a chiral center, such as a receptor or enzyme (15, 16). Furthermore, the o-amino acid enantiomers are not sensitive to proteolytic cleavage (16), a property that has been suggested to be favorable for the development of these peptides as therapeutic agents (6, 15, 16). Currently, chemotherapy for breast, small cell lung, and ovarian cancers using combination protocols with either platinum complexes or natural products such as the epipodophyllotoxins (VP-16), vincristine, and anthracyclins (doxorubicin) show incomplete response rates which are probably related to the development of drug resistance. The taxane ring compounds, taxol and taxotere, have recently advanced to clinical testing. However, novel (17) and classical (18) multidrug resistance mechanisms to these new agents have already been described. The use of cytolytic peptides in cancer treatment has the advantage that they are not affected by the multidrug resistance phenotype (7, 19, 20).

In addition, because of their rapid and direct mechanism of cell killing (6), magainin-like peptides have application in the treatment of human ovarian cancer, a disease which begins and remains largely confined to the peritoneal space. Intraperitoneal therapy for ovarian cancer remains under consideration for treatment (21, 22). Cytolytic peptides therefore are candidates for intercavitary therapy of ovarian and other localized cancers.

In the present study, we have assessed Magainin2 and two magainin analogues for in vivo anticancer activity. The analogue sequence was designed to enhance the amphiphilic α-helical structure and decrease the susceptibility to proteolytic degradation (Table 1). Magainin analogue, MSI-136, exhibiting potent cytotoxicity in vitro against numerous tumor cell lines, was compared to the corresponding peptide composed of all-o-amino acids, MSI-238. We report here the in vivo efficacy against four murine peritoneal ascites tumors: two highly invasive leukemias (L1210 and P388); an ascites form of a sarcoma (S180); and a murine ovarian teratoma (SOT).

MATERIALS AND METHODS

Peptide Synthesis and Purification. The synthesis of peptides was carried out by solid phase methodology (12) either on an ABI-431 peptide synthesizer using the tert-butyloxy carbonyl group for α-amino protection or on a Milligen 9050 PepSynthesizer using the Fmoc group for α-amino protection. When tert-butyloxy carbonyl protection was used for the synthesis, the side chain protecting groups were: o-chlorobenzyloxycarbonyl for epsilon-NH2 groups of lysine; benzyl for serine and glutamic acid; and benzyloxymethyl for histidine. The final deblocking step was carried out with liquid hydrofluoric acid. When Fmoc protection was used, peptide amide linker (5-[(4-Fmoc-aminomethyl)-3′-dimethoxy-phenoxy] valeric acid) resin was used for the preparation of COOH-terminal amides. The side chain protecting groups were: butyloxycarbonyl for lysine; tert-butyloxycarbonyl for serine and glutamic acid; and p-methoxy-2,3,6-trimethyl benzene sulfonyl for arginine. The final deblocking step was carried out with a mixture of 95% trifluoroacetic acid, 2.5% phenol, and 2.5% methanesulfonic acid.

The cleaved free peptides were desalted on a reversed phase HPLC column. Purification to >95% purity was by preparative reversed-phase HPLC using gradient elution. As needed, peptides were also purified by weak cation exchange HPLC, using a NaCl gradient and pooling desired fractions followed by conversion to the acetate form and lyophilization.

Drugs and Chemicals. Unless otherwise noted, all reagents, drugs, and chemicals for biological experiments were purchased from Sigma (St. Louis, MO).

In Vitro Toxicity. The analogues were screened for absolute and relative toxicity using the MTT assay (23) on either Ehrlich ascites tumor cells (American Type Culture Collection CCL77) or a human adenocarcinoma, A549 (American Type Culture Collection CCL185). Briefly, cells were seeded at 5—10,000/well in 96-well microtiter plates in complete medium, either Dul-
becco's modified Eagle's medium or RPMI 1640 with 10% fetal bovine serum for EAT or A549, respectively. After the cells had attached, 20 μl of diluted peptide solution in normal saline were transferred to the well to give final concentrations ranging from 1.5 to 100 μg/ml. Following a 48-h incubation with peptide, 100 μg MTT (sterile-filtered in 50 μl of phosphate-buffered saline plus 10% glucose) were added to each well. Four h later, all but 30 μl of medium plus MTT solution was removed mechanically from the wells and 150 μl of dimethyl sulfoxide were added to dissolve the formazan crystals. The plates were gently agitated for 15–30 min and the absorbance read using a DynaTech MR5000 plate reader at 570 nm. Four replicates/point were used and fractional survival relative to untreated control wells in each plate were calculated as previously described (23). The IC_{50} values were calculated from curves fitted through eight points.

**In Vivo Toxicity.** Preliminary dose-ranging studies on peptide acute toxicity for i.p. injection of peptides used 20–22 g male CF-1 mice (Charles River Laboratories, Wilmington, MA) monitored for at least 2 weeks. The LD_{50} doses for Magainin2, MSI-136, and MSI-238 were 80, 40, and 35 mg/kg, respectively. The maximum tolerated doses were usually 75–77% of the LD_{50} dose.

**In Vivo Efficacy.** To test the ability of peptide to increase life span of tumor-bearing mice, the peptides were dissolved in saline and administered as single daily injections in a volume of not more than 0.5 ml to mice previously given injections of the tumor cell lines described below. The ILS was calculated as the percentage increase of treated versus control mice using either the mean or median day of death of the treated mice divided by the mean or median day of death of saline treated mice and subtracting 100%.

**Murine Tumor Models.** National Cancer Institute lines of L1210 and P388D1 tumor cell lines were maintained (not more than 10 passages) by weekly transfer into DBA/2 mice (Charles River Laboratories). The L1210 were passaged i.p. at 1 × 10^6 cells/mouse and the P388 at 1 × 10^5 cells/mouse in 0.1 ml sterile saline. For efficacy testing, BDF1 males (Charles River Laboratories) were used.

The ascites form of the sarcoma line S180 was acquired from the National Cancer Institute Tumor Repository, Frederick, MD. The tumor was passaged through CD-1 (Charles River Laboratories) mice 3 times before initiating an efficacy experiment. Seven days after the tumor cells had been injected, ascites cells from a single animal were harvested and used for the injections of the experimental groups i.p. with 1 × 10^6 cells.

The SOT cell line was first described by Fekete and Ferrigno (24). The model was characterized with respect to its sensitivity to standard chemotherapeutic agents (25) and found to be most sensitive to doxorubicin (Adriamycin; Adria Labs, Columbus, OH), which was chosen for the positive control in these experiments. Ascites cells were maintained by serial i.p. transfer of 1 × 10^6 cells in female C3HHeB/FeJ mice (Jackson Laboratories, Bar Harbor, ME) every 10 to 14 days. Testing was performed in the same strain of mouse.

**Histopathology.** Normal and mice bearing SOT tumor were given either 20 mg/kg of MSI-136 or MSI-238, or 5 mg/kg doxorubicin on day 2 and 5 after i.p. injection of 1 × 10^6 tumor cells. The mice were sacrificed on day 18, the day of death of the first untreated tumor bearing mouse. Two drug controls and three tumor-bearing and drug-treated mice from each group were evaluated by gross anatomical and microscopic histopathological analyses (Dawson Research Consulting Co., Orlando, FL).

**In Vivo/ex Vivo Cytotoxicity.** One week prior to the experiment, BDF1 mice were given injections of 1 × 10^6 P388 tumor cells. The experiment consisted of i.p. injection of peptides and removal of ascites fluid from these mice after 1 h. The total cell count/ml of ascites fluid and fraction of cells taking up trypan blue was than analyzed by hemocytometer counting for each individual.

**RESULTS**

**In Vitro Toxicity.** The magainin analogues, MSI-238 and MSI-136, were found to have much lower IC_{50} values than the parent, Magainin2, for both the EAT cells and the human lung adenocarcinoma line (A549) (Fig. 1, A and B). The shape of the dose-response curves also varied for the different peptides. MSI-238, the all-D-amino acid peptide, displayed an almost all-or-none or threshold phenomenon at a concentration of 4–8 μg/ml of peptide. MSI-238 was more potent than MSI-136 and both were more cytotoxic than the parent compound, Magainin2, by an order of magnitude (IC_{50}, 6.10 and 110 μg/ml, respectively).

**In Vivo/ex Vivo Assay.** To demonstrate the kinetics of in vivo tumor cell destruction, the following experiment was devised. BDF1 mice with advanced leukemia were used (day 7 following i.p. injection of 1 × 10^6 388 cells). One h after i.p. injection of MSI-238, peritoneal fluid was withdrawn from each mouse. Fig. 2 shows the results of the cell counts and trypan blue assay of the cells contained in that fluid. Fluid withdrawn from mice which had been given injections of MSI-238 contained an average of 1.2 (SD = 0.9) and the saline-injected controls had 4.1 (SD = 1.6) × 10^6 P388 cells/ml. Of the cell population in the MSI-238 treated mice, 13–72% (32; SD = 28%) took up trypan blue while less than 7% (5; SD = 2%) of the cells from saline-treated mice did so. If all trypan blue-positive cells are assumed to be dead or dying, the combined decrease in absolute cell number and increase in percentage of dead cells represents a reduction in tumor cells of over 80% in the peritoneal cavity after a single injection of MSI-238.

**Murine Leukemias.** Initial experiments using mice bearing i.p. wild-type L1210 or P388 tumors investigated a variety of dosing schedules for peptide administration. In mice with P388 but not L1210, treatment with either MSI-136 or MSI-238 produced an increase in life span of 30 to 40% over untreated mice compared to the known chemotherapeutic cisplatin which increased the life span of P388-bearing mice by 160–200%.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>Magainin2</td>
<td>GIGFLHAKKFGAFVGEIMNS-NH,</td>
</tr>
<tr>
<td>MSI-136</td>
<td>GIGFLHAKKFGAFVGEIMNS-NH,</td>
</tr>
<tr>
<td>MSI-238</td>
<td>GIGFLHAKKFGFAKFKIKKNI-NH,</td>
</tr>
</tbody>
</table>
decreased organomegaly (data not shown). Efficacy against the L1210 tumor was consistent with the recorded body weights and a possible sparing of the tumor cell concentration and ability of the cells to exclude trypan blue was quantitated using hemocytometer counts.

Table 2: Effect of peptides on survival time of mice with ascites tumors

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Dose (mg/kg/day)</th>
<th>Mean survival time in days</th>
<th>ILS (%)</th>
<th>Median survival time in days</th>
<th>ILS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magainin2</td>
<td>36</td>
<td>12.3 (10.0)</td>
<td>23</td>
<td>15 (13)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>13.3 (10.0)</td>
<td>33</td>
<td>18 (13)</td>
<td>38</td>
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<tr>
<td></td>
<td>60</td>
<td>11.5 (10.0)</td>
<td>15</td>
<td>19 (13)</td>
<td>46</td>
</tr>
<tr>
<td>MSI-136</td>
<td>15</td>
<td>11.2 (10.0)</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>13.3 (10.0)</td>
<td>33</td>
<td>19 (14)</td>
<td>36</td>
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<tr>
<td></td>
<td>25</td>
<td>11.5 (10.0)</td>
<td>15</td>
<td>24 (14)</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>12.3 (9.4)</td>
<td>31</td>
<td>22 (13)</td>
<td>69</td>
</tr>
<tr>
<td>MSI-238</td>
<td>10</td>
<td>10.5 (10.0)</td>
<td>5</td>
<td>19 (14)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>11.3 (10.0)</td>
<td>13</td>
<td>30 (14)</td>
<td>114</td>
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<td></td>
<td>25</td>
<td>12.3 (9.4)</td>
<td>31</td>
<td>20 (14)</td>
<td>43</td>
</tr>
</tbody>
</table>

Achievement of efficacy in the P388 model required that treatments begin on the same day or day after the tumor cells were injected and several bolus treatments at near maximally tolerated doses. Table 2 lists representative values for the various doses of Magainin2, MSI-136, and MSI-238 all given at the stated dose each day: 1, 4, and 7. A further increase in life span, to 45%, could be achieved with 25 mg/kg MSI-238 given two or three times i.p. when treatment began on the same day as the tumor cells were implanted. Daily doses of 12.5 mg/kg for 6 days beginning day 1 was not better than 3 bolus injections on days 1, 4, and 7 (data not shown). A combination of i.p. and i.v. dosing did not prove significantly better than a multiple i.p. only dosing schedule.

Gross observation of mice treated with peptides compared to the saline-treated controls indicated a reduction in ascites fluid volume consistent with the recorded body weights and a possible sparing of liver, spleen, and lymph node invasion by tumor cells as evidenced by decreased organomegaly (data not shown). Efficacy against the L1210 tumor could not be demonstrated by an increase in survival time but body weight and soft tissue appearance also suggested amelioration of the tumor progression (data not shown).

S180 Tumor. The peptides produced much greater ILS against the S180 tumor, which has limited invasiveness (Table 2). Life span could be extended by as much as 100% after a single i.p. injection 1 day following peritoneal injection of $1 \times 10^6$ tumor cells. The untreated mice succumb to tumor burden in an average of 16.5 days (median, 14 days) while treatment with MSI-238 produced long-term survival, defined as mice living over 3 times longer than the median survival time of the controls. Both MSI-136 and MSI-238, given at 20–25 mg/kg, produced long-term survivors in these experiments. Magainin2 did not prove to increase survival time above 50% even at the maximum tolerated dose, 60 mg/kg.

For both MSI-136 and MSI-238 a maximally effective dose was achieved at about 60% of the estimated LD$_{50}$ (see "Materials and Methods"). In this model which uses Swiss (CD-1) mice, MSI-136 was found to be more effective at 25 mg/kg when compared to a 30 mg/kg dose. MSI-238 was less effective at 25 mg/kg than at 20 mg/kg. These differences were not due to early deaths caused by acute toxicity but rather may be attributed to sublethal toxicity to the host. MSI-238 was also tested against S180 ascites using a daily injection schedule, 10 mg/kg on days 1–5, and produced 93% ILS (data not shown).

SOT Model. Effectiveness against the murine ovarian teratoma by Magainin2 and the analogues was also in the range of 100% ILS. Mice given i.p. injections of peptides once or twice, on day 2 or days 2 and 5, respectively, were protected against ascites tumor growth as effectively as mice treated with the control, doxorubicin. Body weight records (Fig. 3A) showed that the accumulation of ascites fluid was delayed at least 20 days in mice treated once with peptides or with doxorubicin, whereas untreated mice began to accumulate fluid 5–7 days after the tumor cells were implanted. Body weights for animals treated twice with peptides showed an even longer delay in weight gain with the mice rarely accumulating ascites fluid (data not shown). In the experiment shown (Fig. 3, A and B), the untreated mice succumb to the tumor burden at 19–23 days with massive fluid accumulation as evidenced by the almost doubling of body weight. In the peptide-treated groups, the accumulation of ascites fluid was de-
layed and survival time extended by more than 50%. Using the median day of death for the group (3 of 6 animals dead) as an endpoint, the ILS produced by a single injection of MSI-136 was 52%, and by it was MSI-238 67%, while a single treatment with doxorubicin increased the life span in this experiment by 133% (Fig. 3B). A second experiment which included a single i.p. treatment of SOT tumor on day 2 using MSI-238 or doxorubicin gave ILS of 115 and 76%, respectively, demonstrating that the peptide reproducibly prolongs life span through decrease in tumor burden and amelioration of ascites formation.

Table 3 shows that in the SOT-bearing mice, when a second peptide injection was given on day 5 (in addition to dosing on day 2), MSI-136 increased ILS to 81 or 100%. MSI-238 given in two equivalent bolus injections gave more variable but always positive results which was partially due to the variation in control group survival time (Table 3). Magainin2 was also shown to increase the life span of the mice but at 2–3 times the dose required for the analogues and at a level which exhibited some toxicity. The dose was reduced from 60 to 50 mg/kg for the second injection because a greater than 10% weight loss was observed in the mice after the first injection.

Dosing regimens designed to show whether peptides could block ascites formation and increase survival of actively growing tumor cells were tested. If single dose therapy was withheld until 3, 5, or 7 days post-tumor cell injection no effect on tumor progression was seen (data not shown). However, daily dosing with 10 mg/kg of MSI-238 from day 5 through 9 was as effective as 5 daily doses of 2.5 mg/kg of doxorubicin (Fig. 4A and B). MSI-136 given at the same times and level as MSI-238 was without effect on either body weight gain (Fig. 4A) or survival time (Fig. 4B).

Histopathology. The presence and distribution of SOT tumor cells in mice treated with MSI-238, MSI-136, or doxorubicin were compared to mice given injections of saline 18 days after initiation of the tumor (the day of death of the first tumor-bearing mouse given a saline injection). Deleterious effects of the agents themselves were assessed in non-tumor-bearing mice treated using the same schedule.

In the saline-treated group active SOT growth on the peritoneum of all three mice was noted and invasion of the diaphragmatic muscle tissue (Fig. 5A) and/or lymphatics was seen in two out of three animals. Tumor cell colonization and hyperplasia of the mesenteric lymph nodes were observed in two out of three mice given saline. In mice treated with MSI-136, only degenerating SOT cells were present on the peritoneum of the diaphragm (Fig. 5C) and only one of three had slight invasion of the lymphatics and muscle of the diaphragm. MSI-238-treated mice exhibited similar histopathology to those treated with MSI-136 except that one of three had active SOT cell growth on and invasion of the muscle of the diaphragm (Fig. 5B). Untoward effects of the two peptides were evidenced by adhesion of the liver to adjacent organs (diaphragm, stomach, and duodenum). In the doxorubicin-treated tumor-bearing mice, SOT cells had infiltrated the diaphragm in one of the three mice and all had scarring and regeneration of the skeletal muscle of the diaphragm (Fig. 5D). Mesenteric lymph node hyperplasia was also noted in one doxorubicin-treated mouse.

The histopathological evaluation suggested that MSI-136 (20 mg/kg) was as effective, and MSI-238 almost as effective as doxorubicin (5 mg/kg) in preventing peritoneal SOT colonization and diaphragmatic invasion.

DISCUSSION

We have demonstrated that Magainin2 and two more potent analogues, a unique sequence synthesized in either all-L- or all-D- amino acid form, are capable of significantly reducing local disease. In the murine leukemias, L1210 and P388, soft tissue invasion was diminished and an increase in survival was demonstrated against P388 tumor. The most dramatic results were seen against a sarcoma and ovarian teratoma, where the survival time of tumor-bearing mice could be doubled.

The difference in efficacy for peptides administered to mice carrying leukemia as opposed to a sarcoma (S180) or teratoma (SOT) remains to be explained. Both L1210 and P388 leukemia cells invade the central nervous system as early as 4 days after cells are injected into the peritoneum and the animals die as a result of widespread tissue damage rather than primarily due to suffocation, which occurs from bulky ascites produced in the ovarian cancer model (26). Thus, the compartmentation of tumor cells in extraperitoneal tissues, inaccessible to peptide, may explain the enhanced prolongation of survival and attainment of long-term survivors in the S180 and SOT but not the leukemia models.

In the P388 model, we demonstrated here a greater than 80% reduction of tumor cells in the peritoneal ascites occurring within 1 h after a single administration of MSI-238. According to the relationship
between drug-induced kill of leukemic cells and the percentage increase in host life span laid down by Skipper et al. (27), a 1-log reduction in cells on day 1 will produce a 23% ILS. To increase the life span by 45%, using a schedule of 3 injections given every 3 days, at least 80% of the total host leukemia cell population must have been killed at each injection regardless of location. Thus, the rapid cytolytic effect seen in P388 ascites fluid ex vivo correlates with overall increase in survival observed.

Using similar logical and historical data for the SOT model, the delay in ascites formation and increase in survival time produced by a single injection of peptide correlate with 99.9% (3 logs) of the tumor cells having been eliminated when compared to survival for various inoculum cell numbers (28). The all-ω-amino acid peptides, Magainin2 or MSI-136, were effective if provided relatively early after tumor cells were injected. The demonstration that MSI-238 could prevent ascites formation in animals withheld treatment as long as 5 days after tumor cells were injected i.p. suggests that this peptide was capable of destroying tumor cells already invading lymphatic tissue. That the tumor cells had obstructed the lymphatics was demonstrated by Feldman et al. (26), who showed, using the SOT model, that labeled erythrocytes injected i.p. were completely prevented from reaching the abdominal organs. This local toxicity may possibly be overcome by changes in formulation or by coadministration of a weak anion or anionic lipid.4 As with other cancer therapeutics where efficacious doses may overlap deleterious doses, scheduling and methods of administration must be explored. In toxicology testing, related peptides have been found to be neither mutagenic or teratogenic.3 Thus, if used in cancer therapy cytolytic peptides, because of their unique mechanism of action and corresponding spectrum of cellular effects, may be expected to synergize with existing therapeutics in a manner which would neither elicit multidrug resistance mechanisms nor enhance genotoxic processes in normal tissues.

In conclusion, cytotoxic magainin-like analogues, composed of either all-ω- or all-ω-amino acids, were shown to have antitumor cell activity in vitro and in vivo by a mechanism which appears to be related to short duration non-receptor-driven contact with target cell membranes. The problem of proteolytic degradation of the agents has been solved by construction of the all-ω-amino acid analogue. The further development of these agents as therapeutic entities is in progress. Preliminary data showing efficacy in the human ovarian tumor xenograft model, OvCar-3, have been achieved with an analogue of Magainin2 (31).

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3 M. A. Baker and W. L. Maloy, unpublished data.

4 M. A. Baker and M. Zaslolf, unpublished observation.

5 A. Weber and L. S. Jacob, unpublished data.
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