In more than 70% of patients with ovarian carcinoma, there is evidence of tumor dissemination beyond the ovaries at diagnosis. In these cases, combined treatment with surgery and chemotherapy is necessary. First-line chemotherapy with platinum drugs and taxanes is initially responsive to combinatorial chemotherapy with platinum drugs and taxanes but, in most cases, develop drug resistance. We recently showed that, in vitro, hepatocyte growth factor (HGF) enhances death of human ovarian cancer cell lines treated with cisplatin (CDDP) and paclitaxel. The present study addresses whether in vivo HGF makes ovarian carcinoma cells more responsive to these chemotherapeutics.

**Experimental Design:** Using Lentiviral vectors carrying the HGF transgene, we transduced SK-OV-3 and NIH:OVCAR-3 ovarian carcinoma cell lines to obtain stable autocrine and paracrine HGF receptor activation. In vitro, we assayed growth, motility, invasiveness, and the response to CDDP and paclitaxel of the HGF-secreting bulk unselected cell populations. In vivo, we tested the cytotoxic effects of the drugs versus s.c. tumors formed by the wild-type and HGF-secreting cells in immunocompromised mice. Tumor-bearing mice were treated with CDDP (i.p.) and paclitaxel (i.v.), combined in different schedules and doses.

**Results:** In vitro, HGF-secreting cells did not show altered proliferation rates and survival but were strongly sensitized to the death triggered by CDDP and paclitaxel, alone or in combination. In vivo, we found a therapeutic window in which autocrine/paracrine HGF made tumors sensitive to low doses of the drugs, which were ineffective on their own.

**Conclusions:** These data provide the proof-of-concept that in vivo gene therapy with HGF might be competent in sensitizing ovarian cancer cells to conventional chemotherapy.
HGF and CDDP modulate transcription in ovarian cancer cells; that this transcriptional response is involved in apoptosis regulation; and that the identified genes might be targeted either to increase the efficacy of chemotherapeutics or to revert chemotherapy resistance (3).

Therefore, we conceived a preclinical model to assess if HGF could be used to improve response to chemotherapy in ovarian carcinomas in vivo. This possibility is particularly intriguing, as it is well known that HGF protects normal tissues from the cytotoxic effects of chemotherapeutics (7, 8). Here, we show that locally delivered HGF increases tumor response to the systemic and combined administration of CDDP and paclitaxel.

Materials and Methods

Chemicals and antibodies. Pure recombinant human HGF was purchased from R&D Systems (Minneapolis, MN). Recombinant human HGF was also obtained from culture supernatant of SF-9 cells infected with Baculovirus vector containing the full-size human factor. Recombinant human HGF was titrated in scatter assay as scatter unit (1 scatter unit = 0.2 ng). Cisplatin (CDDP) and paclitaxel were from Bristol-Myers Squibb (Rocky Hill, NJ).

Anti-human Met receptor polyclonal antibody C-12 was from Santa Cruz Biotechnology (Santa Cruz, CA); anti–phosphorylated Tyr1253/MET rabbit polyclonal antibody was from Upstate (Upstate, MA). Biotinylated anti-human HGF goat antibody BAF294 was from R&D Systems. Anti–p38 MAPK and anti–phosphorylated Thr182/Tyr185/p38 MAPK rabbit polyclonal antibodies were from Cell Signaling Technology (Beverly, MA).

Cell lines and apoptosis induction. Cell lines tested were all purchased from the American Type Culture Collection (Manassas, VA) and grown as suggested by the provider in media supplemented with 10% fetal bovine serum (Euroclone, Wetherby, United Kingdom) and 2 mmol/L L-glutamine. Experiments were done on the SK-OV-3 and NIH:OVCAR-3 ovarian carcinoma cell lines, which express the HGF receptor encoded by the MET gene. It is noteworthy that SK-OV-3 ovarian carcinoma cells showed resistance to platinum drugs (9).

Apoptosis was induced by adding to the medium of the cultured cells either CDDP or paclitaxel or control vehicle, alone or in combination, at indicated concentrations for 48 and 72 h.

Flow cytometry analysis of apoptosis induction. Flow cytometry recordings of several independent apoptotic changes were done by a single-tube analysis, as described (2). Briefly, after induction of apoptosis, cells were resuspended in HEPES buffer (10 mmol/L HEPES, 150 mmol/L NaCl, 5 mmol/L CaCl2) and incubated for 15 min at 37°C in FITC-conjugated Annexin V, tetramethylrhodamine methyl ester (200 mmol/mL), and propidium iodide (1 μg/mL) to detect phosphatidylserine exposure on the cell surface, mitochondrial inner membrane electrochemical gradient, and plasma membrane integrity, respectively. Cell morphology changes were analyzed following variations of the forward and side light scatter. Samples were analyzed on a FACSCalibur flow cytometer (Becton Dickinson, San Diego, CA). Data acquisition was done using CellQuest software and data analysis with WinMDI software. FITC-Annexin V (FL1), tetramethylrhodamine methyl ester (FL2), and propidium iodide (FL3) fluorescent signals were displayed as density plot diagrams. These data were shown as arbitrary units of fluorescence on a logarithmic scale. A quadrant was set on the diagram experiment by experiment, and it was kept constant in all the conditions of each experiment to point out the different cell populations. To quantify the degree of mitochondrial depolarization, the geometric mean of the tetramethylrhodamine methyl ester signal was calculated on the histogram window of WinMDI after discriminating apoptotic and nonapoptotic subpopulations with a logical gate tool.

In vitro biological assays. To measure proliferation rate, 1.5 × 10^6 cells were plated in triplicate in 60-mm diameter dishes. Cell viability was evaluated by trypan blue exclusion assay. Scatter assay was done as described (10). Motility and Matrigel invasion assays were done as described (11). Invasion of three-dimensional collagen gel was assayed as described (12). Each experiment was repeated at least three times with identical results.

Western immunoblot analysis. Cytosolic extracts were prepared from cells at 4°C in a buffer containing 1% NP40, 135 mmol/L NaCl, 20 mmol/L Tris-HCl (pH 7.5), 1 mmol/L CaCl2, in the presence of phosphatase and protease inhibitors (1 mmol/L sodium orthovanadate, 1 μg/mL leupeptin, 1 μmol/L pepstatine, 1 mmol/L phenylmethylsulfonyl fluoride, 100 μg/mL soybean trypsin inhibitor). Proteins were separated, blotted, and labeled as described (4). HGF was purified from culture medium of LV-transduced SK-OV-3 cells by metal chelate affinity chromatography as previously described (10). To detect HGF and phosphorylated p38 MAPK in control and LV-transduced SK-OV-3 xenografts, tumor soluble fraction was obtained from dissected frozen samples. The protein fractions were extracted using a buffer containing 20 mmol/L Tris-HCl (pH 7.4), 5 mmol/L EDTA pH 8.0, 10% glycerol, 150 mmol/L NaCl, and 1% Triton X-100, in the presence of phosphatase and protease inhibitors.

Tumorgenesis assay. SK-OV-3 cells, either untransduced or transduced with LVs carrying either a control or the HGF transgene, were injected (3 × 10^6 per mouse) into the right posterior flank of 5- to 6-week-old immunodeficient nude female mice on a Swiss CD-1 background (Charles River Laboratories, Calco, Lecco, Italy), in 200 μL PBS per injection. As also already reported (13), wild-type SK-OV-3 cells formed tumors in nearly 100% of mice and became palpable in 14 days. Chemotherapy of animals was carried out when tumors reached an approximate weight of 100 to 200 mg, 21 to 23 days after cell injection. Mice were then selected and divided in experimental group, each made of at least six mice. Tumor dimensions were evaluated every 2 days using a caliper. Tumor weight was calculated using the formula: \( W = (D \times d^2) / 2 \), where \( D \) is the major tumor axis, and \( d \) is the minor tumor axis and assuming density \( \rho = 1 \text{mg/mm}^3 \) for tumor tissue. CDDP and paclitaxel were injected i.p. and i.v., respectively. The schedules of the drug treatments were as described in the legend to the relevant figure. CDDP and paclitaxel were used. Briefly, tumors were formalin fixed and paraffin embedded using standard protocols for tissue analysis. The other half was snap-frozen in liquid nitrogen and stored at –80°C until the time of protein and RNA isolation. Western blot analysis and reverse transcription-PCR were carried out as above. To detect possible superficial pulmonary metastases, lungs were harvested and stained with black India ink to facilitate scoring of metastatic nodules, and both the surface and dissected samples were inspected under a stereoscopic microscope. All animal procedures were approved by the Ethical Commission of the University of Torino and by the Italian Ministry of Health.

Quantitative reverse transcription-PCR. cDNA was synthesized from 1 μg RNA using MMLV-RT(H-) enzyme (Promega, Madison, WI). Quantitative reverse transcription-PCR was done on a MyIQ Thermal Cycler (Bio-Rad, Hercules, CA); all quantitative PCR mixtures contained 40 ng retrotranscribed RNA, 1× SYBR Green PCR Master Mix (2× Applied, Foster City, CA), and 300 μmol/L of each target specific primer. Forward and reverse primers for each gene are reported elsewhere (3). The expression of each target genes was evaluated using a relative quantitation approach (ΔΔCT method) with cyclophilin A as internal reference, as described (3).

Detection of apoptotic nuclei. To detect apoptotic nuclei in tumor samples, the 4,6-diamidino-2-phenylindole labeling technique was used. Briefly, tumors were formalin fixed and paraffin embedded using standard protocols. Then, DNA of each section was stained with a 1 μg/ml dilution of 4',6-diamidino-2-phenylindole stock solution (Sigma-Aldrich, St. Louis, MO). The preparations were observed under a fluorescence microscope (excitation at wavelength of 352 nm).

Cancer Res 2007;13(7) April 1, 2007 2192

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ELISA. Quantification of HGF in culture medium and tumor extracts was done by sandwich ELISA using a monoclonal anti-HGF antibody for capture (MAB694, 0.25 μg per well) and a biotinylated anti-HGF antibody for detection (BAF294, 0.2 μg per well), both from R&D Systems. Quantification of phosphorylated p38 MAPK in each tumor extract was done by sandwich ELISA using the polyclonal antibody p38 for capture (0.15 μg per well) and anti–phosphorylated p38 for detection (0.15 μg per well) antibodies, which were described above.

**Results**

**Engineering of ovarian cancer cells to continuously produce and secrete biologically active HGF.** We previously showed in vitro that ovarian cancer cells are sensitized to CDDP and paclitaxel when exposed to HGF for at least 24 h before treatment (2–4). The aim of the present work was to assess whether continuous exposure of cells to HGF and local HGF delivery might be used to obtain a comparable effect in vivo. HGF is produced and secreted as an inactive precursor of the approximate Mr of 90 kDa, which is activated after proteolytic cleavage by cell surface–associated proteases, such as the urokinase-type plasminogen activator (14). It can be also activated by serum convertases (15), but its half-life in the blood stream is short (16) due to high instability. Therefore, to test HGF effects onto ovarian carcinoma cells, we engineered cells themselves to produce and secrete the factor.

HGF gene transfer was achieved using lentiviral vectors, developed for human gene therapy for their suitability in transferring transgenes also into non-proliferating cells and to allow sustained and prolonged gene expression, thanks to gene transfer in non-silenced chromatin regions and to the use of an internal promoter included in the transgene cassette (17). The high efficiency of gene transfer allows avoiding clonal selection and assaying the bulk unselected populations, thus mimicking gene therapy protocols working in vivo.

We transduced SK-OV-3 and NIH:OVCAR-3 ovarian carcinoma cell lines, which express the HGF receptor encoded by the MET gene, do not produce endogenous HGF, and are sensitized to both CDDP and paclitaxel by the addition of exogenous pure recombinant HGF (2, 4). We obtained cell lines producing HGF and secreting the factor in the culture medium, as both the precursor and the α chain of the mature and cleaved factor were detectable in the transduced cells (data not shown) and in their culture supernatants (Fig. 1A). After transduction, as expected, the HGF transgene was randomly integrated in the bulk unselected cell populations (data not shown). These data show that we generated polyclonal SK-OV-3 and NIH:OVCAR-3 populations with concurrent autocrine and paracrine HGF circuits.

The MET gene–encoded HGF receptor was activated (i.e., phosphorylated on tyrosine residues) by the HGF produced by the cells themselves (Fig. 1B). The constitutive autocrine/paracrine HGF circuit led not only to phosphorylation on
Tyrosines but also to constitutive down-modulation of the MET receptors (Fig. 1B). A similar down-modulation was not detected in cells transiently stimulated by the exogenous factor. To better appreciate the MET receptor activation, Fig. 1C shows that the relative amount of phosphorylated receptor was greatly increased in cells continuously exposed to HGF. In the latter cells, we also found activation of the p38 MAPK pathway (Fig. 1D), which is necessary and sufficient for the HGF sensitization to drugs (4).

The HGF secreted by transduced ovarian cancer cells was able to trigger the known and specific HGF biological activities (6). In fact, HGF is also known as scatter factor for its ability to dissociate epithelial cell colonies in culture, causing the so-called cell scattering. We found that the supernatant of transduced cells triggered the scattering of Madin-Darby canine kidney cells similar to that obtained by adding exogenous recombinant human HGF (Fig. 1E). The amount of HGF secreted by cells was measured by diluting the supernatant and identifying the lowest dilution, which causes Madin-Darby canine kidney cell scattering, that correspond to the so-called scatter unit. HGF concentration in the supernatant was \( \sim 2.5 \text{ ng/mL} \).

These data show that in ovarian cancer cell lines, the autocrine/paracrine HGF circuit, established by means of LV-mediated cell transduction, activated the MET gene–encoded HGF receptor signaling and was biologically effective.

**Ovarian cancer cells secreting HGF do not proliferate faster, are more motile, and respond better to CDDP and paclitaxel.** We used functional assays to measure the biological outcome of the autocrine/paracrine HGF circuit in SK-OV-3 and NIH:OVCAR-3 cells in vitro. HGF-secreting cells did not show striking modification of morphology (data not shown). HGF secretion did not accelerate proliferation of either cell line (Fig. 2A). We also tested whether the autocrine/paracrine HGF circuit activated cell motility and invasiveness. In particular, we assayed SK-OV-3 cells, as we and others have previously shown that HGF activates the ability of the latter cells to move through porous filters and to invade an artificial basement membrane made of Matrigel (11, 18). Cell motility (data not shown) and invasiveness (Fig. 2B and C) were increased in cells exposed continuously to HGF.

Then, we assayed the apoptotic response of HGF-secreting cells to CDDP and paclitaxel, alone or in combination, using a cyttofluorimetric technique (see Materials and Methods and ref. 2). In response to either drug, both the ovarian cancer cell lines entered the apoptotic program, as assessed by mitochondrial depolarization, phosphatidylserine flipping across the plasma membrane, increase of propidium iodide–positive cells, and increase of cytosol granularity (data not shown). Remarkably, the autocrine/paracrine cell stimulation by HGF did not induce apoptotic changes by itself, but it caused a marked sensitization to the subsequent treatment with either CDDP or paclitaxel, with a net increase of the measured apoptotic features. The simultaneous addition of CDDP and paclitaxel further improved the apoptotic response of both cell lines, even at lower doses.

These data show that the continuous exposure of ovarian cancer cells to HGF did not de-sensitize cells and made them persistently susceptible to drug-induced apoptosis.

**Ovarian cancer cells form s.c. tumors that are cured by high-dose chemotherapy but are promoted by HGF.** To evaluate if...
HGF sensitizes ovarian carcinoma cells to CDDP and paclitaxel also in vivo, we injected wild-type control and HGF-secreting SK-OV-3 s.c. into immunocompromised mice and treated animals carrying palpable tumors with i.p. injection of CDDP and i.v. injection of paclitaxel, to simulate clinically achievable systemic exposures of the tumors.

We first tested onto wild-type control SK-OV-3 cells the effect of decreasing doses of CDDP (20-4 mg/kg) and paclitaxel (80-20 mg/kg) in different schedules (Fig. 3A). We found that the highest doses completely blocked the growth of tumors, whereas the lowest were ineffective (Fig. 3A).

We then compared the growth of HGF-secreting and wild-type tumors and found that autocrine/paracrine HGF circuit promoted tumor growth (Fig. 3B). As HGF is known as a proinvasive and prometastatic factor, we inspected lungs of mice bearing HGF-secreting s.c. tumors: we observed only one lung metastasis in one of the lung out of 19 mice inspected (data not shown). Spontaneous metastases were never detected in mice carrying tumors made of wild-type SK-OV-3 cells.

**Autocrine and paracrine HGF circuit makes ovarian cancer cells more responsive to low-dose chemotherapy.** To test the effectiveness of HGF in sensitizing ovarian carcinoma cells to the combined treatment with CDDP and paclitaxel, mice carrying s.c. tumors, formed by either wild-type or HGF-secreting SK-OV-3 cells, were treated with the lowest and ineffective drug doses tested before. Surprisingly, although the growth of the SK-OV-3 tumors was promoted by HGF, its promoting activity was counteracted by the HGF-mediated sensitization to drugs. At drug doses that allowed tumor growth (see before), HGF-secreting cells responded better than wild-type cells (Fig. 3B). These data show that it was possible to find a therapeutic window in which HGF can increase the efficacy of chemotherapy.

However, one could argue that HGF had therapeutic potential only if it was fully effective at low concentrations and besides promoting tumor growth. We measured the amount of HGF secreted by the bulk, HGF-secreting, SK-OV-3 cell population that gave rise to fast growing s.c. tumors. We found that these cells secreted 1,300 ± 40 ng/mL HGF into the culture supernatant. In the tumors formed by the bulk HGF-secreting SK-OV-3 cell population (Fig. 3A), the HGF concentration ranged from 900 ± 50 to 120 ± 20 ng/mL of the tumor soluble fraction. This variability was not surprising and is likely due to a random selection of cell subclones producing different amounts of HGF, among the bulk LV-transduced population.

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**Fig. 3.** Effect of HGF on the response of s.c. ovarian cancer cell xenografts to chemotherapy. Average tumor weight in each experimental group, as measured starting from the day of s.c. tumor cell injection in mice. Points, mean; bars, SD. Representative of the three to four experiment done. A, effects of CDDP and paclitaxel combined treatment on the growth of wild-type control SK-OV-3 cell xenografts, in different schedules and doses, as indicated. Immunocompromised mice received s.c. cell injection, and when tumors weighed 100 to 200 mg, animals were randomly assigned to four groups of six to eight mice each. Animals in groups 2 and 4 received the indicated total drug doses divided in four injections, administered weekly for 4 wks, whereas animals in group 3 were treated with the indicated total doses divided in five injections, administered daily for 5 d. The differences between groups 1 and 2 versus either group 3 or 4 are statistically significant ($P < 0.01$). B, effect of autocrine/paracrine HGF circuit on tumor growth and response to therapy. Animals received either wild-type control (SK-OV-3) or HGF-secreting (HGF-SK) SK-OV-3 cells and were divided in groups as above. Where indicated, animals received CDDP and paclitaxel treatment as above, at the indicated total doses divided in four injections, administered weekly for 4 wks. The differences between groups 1 and 2 are statistically significant, using Student’s $t$ test ($P < 0.01$). C, effect of autocrine/paracrine HGF circuit on the growth and response to therapy of HGF-secreting SK-OV-3 clone 4. Animals received either wild-type control (SK-OV-3) or HGF-secreting SK-OV-3 cell clone 4 (HGF-SK-4) and were divided in groups as above. Where indicated, animals received CDDP and paclitaxel treatment as above, at the indicated total doses divided in four injections, administered weekly for 4 wks. The differences between groups 1 and 2 are statistically significant, using Student’s $t$ test ($P < 0.01$), whereas those between groups 1 and 3 are not ($P > 0.05$).
Therefore, we cloned the HGF-secreting bulk SK-OV-3 cell population to obtain cells secreting lower and stable amounts of HGF. The HGF_SK-4 clone, which secreted 250 ± 70 ng/mL HGF into the culture medium, formed s.c. tumors growing similarly to those formed by SK-OV-3 cells that did not secrete HGF (Fig. 3C). The growth of tumors formed by HGF_SK-4 cells was fully abrogated by the combined treatment with CDDP and paclitaxel at doses that were ineffective towards tumors formed by wild-type SK-OV-3 cells (Fig. 3C).

The mechanism of tumor cell death in vivo was similar to that we showed in vitro (see above). In the HGF-secreting tumors of animals treated with CDDP and paclitaxel, the number of apoptotic nuclei was increased (Fig. 4A and B). Cell death was associated to an increase of phosphorylated p38 MAPK (Fig. 4C), which we found (4) to be necessary for the HGF sensitization to drugs. In addition, the top differentially expressed transcripts measured in ovarian cancer cells committed to apoptosis by the treatment with HGF and CDDP in vitro (3) are also modulated in tumors sensitized to drugs by the autocrine/paracrine HGF circuit (Fig. 4D).

Altogether, these data provide the proof-of-concept of the efficacy of HGF to sensitize ovarian cancer cells to chemotherapeutics in vivo.

Discussion

HGF is a multifunctional cytokine that controls proliferation, survival, and motility of a variety of tissues, including epithelia, neurons, endothelia, and hematopoietic cells (5, 6). The coordinated orchestration of these activities results in critical morphogenetic processes during embryo development as shown by the lethality of the HGF gene deletion in mice (19, 20). In the adult organism, the physiologic role of HGF is less clarified, although it definitely plays a role in tissue homeostasis and regeneration. Therefore, HGF has been shown to have therapeutic perspectives in preclinical studies of a variety of chronic and acute pathologic conditions, such as myocardial dysfunction (21), liver (22) and kidney injuries (23), tissue fibrosis (24, 25), and inflammatory bowel disease (26). It has been also shown that HGF protects not only normal (7, 27) but also a number of cancer cell lines to death induced by platinum drugs and taxanes (2–4). Here, we show that HGF sensitizes ovarian carcinoma cells to conventional chemotherapy in vivo. These data disclose a new therapeutic potential of HGF, which could be used in cancer in simultaneously enhance chemotherapy and protect normal cells from the undesired toxic effects of chemotherapeutics.

The very same HGF-controlled processes that promote organ development and maintain tissue homeostasis are responsible for the onset of hereditary cancers and promote invasiveness of advanced cancer (5, 6). The HGF receptor, encoded by the MET oncogene, is activated in human cancer by overexpression (30, 31), gene amplification (32, 33), and point mutation (34–36). However, we show here that in tumors formed by ovarian cancer cells, HGF levels that still promote growth make tumors fully controlled by chemotherapeutics. In ovarian cancer, we and others observed that about 70% of ovarian carcinomas express the HGF receptor, encoded by the MET oncogene, and MET expression level increases from 3- to >50-fold in nearly 30% of cases (31, 37). However, expression of either HGF or its MET-encoded receptor has not been associated to either negative or positive prognosis, yet. Therefore, in these tumors, before proposing MET or HGF as
targets for therapy of cancer, HGF enhancement of chemotherapy should be taken into account. HGF and its receptor Met, in fact, are emerging as promising targets, which could be inhibited by the new-generation of drugs, such as small-molecule kinase inhibitors (38, 39), antibodies (40, 41), and HGF antagonists (10, 42).

Our data might also explain conflicting results, which associated an increased expression of HGF or its receptor in tumors to either poor prognosis or to a better patients’ outcome. Patients suffering from MET-expressing breast (43) and bladder (44) carcinomas show poor outcome. Conversely, it has been reported that MET oncogene expression is associated to a more favorable prognosis in carriers of cancers retaining a differentiated phenotype, such as follicular thyroid carcinomas and pancreatic ductal carcinomas at early stage (45, 46). These contradictory conclusions might be explained taking into account also a possible more favorable response to therapy.

The therapeutic potential of HGF in the treatment of chronic and acute tissue injuries has led to the development of promising strategies to obtain HGF delivery in vivo. To allow the persistent expression of HGF, the gene was transferred into muscle tissue using either electroporation (47, 48), or ultrasound delivery (8), or adenoviral vectors (49). Other therapeutic approaches entailed the administration of recombinant HGF i.p. by either direct injection (50) or osmotic pumps releasing constant amount of the factor over the time (51). These models show that exogenous HGF can be made available to tissues. The model reported here show that the chronic and local exposure to HGF is effective in sensitizing ovarian carcinoma cells to drugs in vivo and might be safe, as the response to drugs fully counteract promotion of tumor growth. Altogether, these data reinforce the hypothesis that HGF or HGF derivatives have the potential to be used to improve response to chemotherapy in ovarian carcinoma, a still lethal cancer showing a good short-term curability, thanks to the successful combination of surgery and chemotherapy, but a still poor long-term patient survival.

Acknowledgments

We thank Enzo De Sio, Raffaella Albano, and Solange Tiengue for technical help.

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The Therapeutic Potential of Hepatocyte Growth Factor to Sensitize Ovarian Cancer Cells to Cisplatin and Paclitaxel In vivo

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