when it was administered during the time period that tumor IFP was lowered by PGE1. In contrast, the same dose of 5-FU alone did not influence tumor growth, apoptotic index or carcinoma cell mass. The combination therapy with PGE1 and 5-FU lacked significant anti-tumor activity when administered at sufficiently separated time points. Neither blood vessel density nor the level of leukocyte infiltration were changed after treatment with 5-FU and PGE1. Thus, reduced tumor IFP enabled increased delivery and treatment efficacy of the low molecular weight cytostatic 5-FU in solid tumors as assessed by tumor growth retardation and tumor morphology. These effects did not depend on an immune response nor on changes in the tumor vasculature. In conclusion, we provide for the first time direct evidence that reducing IFP in experimental solid tumors increases the delivery and efficacy of a low molecular weight cytostatic. This concept is an important approach to increase efficacy of anti-cancer drug in solid tumors.

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Phase I/II Study of CT-2103 (Xyotax) in patients with recurrent ovarian cancer

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CT-2103, a polymer-bound form of paclitaxel, shows selective distribution to tumors and is soluble in aqueous solution. CT-2103 preferentially exposes normal organs to conjugated paclitaxel, which does not bind tubulin, thus minimizing systemic toxicity. In an open-label, multicenter phase I/II study, ovarian cancer patients (pts) who have failed primary therapy with paclitaxel/platinum are receiving a paclitaxel-equivalent dose of CT-2103 175 mg/m^2 as a 10-min IV infusion every 21 days. NCI CTC (version 2) and RECIST criteria are being used to assess toxicity and efficacy, respectively. Eighty-eight pts have received from 1 to 9+ cycles. Efficacy data for 43 and safety for all 88 are available; 29 pts are still receiving treatment. Patients range in age from 33 to 81 yr. Median number (range) of prior regimens received was 2 (1-7) in platinum-sensitive (PSens) pts, 4 (1-9) in platinum-resistant (PRes) pts, and 6 (2-9) in platinum-refractory (PRef) pts. In 22 PSens pts, 5 had PR and 8 had SD, with overall disease control achieved in 59% of these pts. In 21 PRes/Ref pts, 1 had PR and 8 had SD, with overall disease control achieved in 43% of these pts. PSens pts had median progression-free survival (PFS) of 3.3 mo; PRes/Ref pts had similar PFS of 3.1 mo. To date, six patients have died. No Grade 4 drug-related toxicity or treatment-related death has been reported, and growth factors for hematologic support have not been required. The majority of patients did not require premedications; 8 pts have required pretreatment in subsequent cycles for Grade 1-2 hypersensitivity. Three pts progressed from Grade 1 or 2 neuropathy at baseline to persistent Grade 3 neuropathy, and minimal hair thinning occurred in 5 pts, but no alopecia has occurred. CT-2103 is well tolerated in these patients with recurrent ovarian cancer and shows antitumor activity across all categories of chemotherapy sensitivity and resistance. Further studies of CT-2103 include (1) a phase II trial in patients with recurrent ovarian cancer conducted by the GOG and (2) a randomized, comparative phase III trial of CT-2103/carboplatin vs paclitaxel/carboplatin in patients with newly diagnosed ovarian cancer. (Supported by Cell Therapeutics, Inc.)

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Evaluation *in vivo* of new agents for drug-resistant ovarian and breast carcinomas

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Therapeutic resistance to Taxol is a major issue in a number of cancers, particularly breast and ovarian carcinoma. This resistance is multifactorial, including P-gp170-linked MDR and over-expression of HER-2/neu. We evaluated the efficacy of a paclitaxel-poly(L-Glu) copolymer (PGA-TXL) in a human ovarian carcinoma orthotopic xenograft model which reflects resistance to Taxol (HEY); we also evaluated PGA-TXL as well as a liposomal (SUV) formulation of dimethyl-sphingosine (L-DMSP; which induces apoptosis in a broad spectrum of tumor cell lines *in vitro*) in an orthotopic human breast adenocarcinoma model that over-expresses HER-2/neu (MDA-361). In the ovarian model, early treatment (Day 2 post-implantation) with multiple-dose MTD Taxol (10 mg/kg) i.p. achieved slight improvement in survival, but was not curative. However, treatment with a single dose (180 mg/kg, paclitaxel equivalents) of PGA-TXL i.p. markedly improved survival and induced some apparent cures. The higher tumor burden present on Day 7 rendered this model resistant to MTD Taxol administration at this time, but still responsive to PGA-TXL. For the breast model, treatment on Day 7 post-implantation, before tumors were palpable, with PGA-TXL resulted in subsequent tumor growth delay, regression, or even apparent cure. Treatment at this time with a multiple-dose MTD regimen of L-DMSP (4.5 mg DMSP/dose) i.p., caused a delay in or reduced subsequent tumor growth, but was not curative. When administered later after tumors grew to 5-6 mm diameter, PGA-TXL still caused tumor growth delay, but no cures were observed; administration of L-DMSP at this later time was not efficacious We conclude that formulation of paclitaxel with this poly(L-Glu) backbone substantially enhanced its potency, and rendered it active in drug-resistant human ovarian and breast models. Further, we conclude that DMSP as a liposomal formulation has some efficacy against this HER-2/neu over-expressing breast model: however, only when the tumor burden is low. (Supported in part by DOD grants BC980420, BC991113 and OC000036 to JK).

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Phase II Study of first-line chemotherapy using CT-2103 in patients with Non-Small-Cell Lung Cancer who are > or = 70 years of age or who have PS = 2

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Xyotax (CT-2103), a polymer-bound form of paclitaxel, shows selective distribution to tumors. Xyotax is soluble in aqueous solution and exposes normal organs to conjugated paclitaxel, which does not bind to tubulin, thus minimizing overall toxicity. Xyotax showed enhanced efficacy compared with paclitaxel/Cremophor in syngeneic and xenogeneic *in vivo* tumor models of lung tumors (data on file, CTI). An open-label, multicenter phase II study is currently under way in chemotherapy-naïve patients with non-small-cell lung cancer who are at least 70 years of age or who are 18 to 69 years of age and have ECOG PS = 2. Patients are receiving a paclitaxel-equivalent dose of Xyotax 175 mg/m^2 in a 10-min IV infusion every 21 days for 6 cycles. Dose reductions for defined toxicities are allowed. NCI CTC (version 2) are used for safety assessments. RECIST criteria are used for efficacy assessments, which are done after every second cycle. Thirty patients have been treated. Preliminary unmonitored data are available. The median age is 77 yr (range, 49-90 yr). Thirty-three percent of patients have PS=2. Thirteen patients (43%) achieved disease control (PR or SD). Nine patients completed the full course (6 cycles) of therapy. With a median follow-up of 6 months, median progression-free survival has not been reached. Twenty-four patients are alive. Treatment was well tolerated. One patient experience drug-related Grade 4 neuropathy and discontinued for disease-related symptom deterioration. One patient was hospitalized for drug-related fever. No other drug-related serious adverse events have been reported to date. The study will continue until an additional 30 patients have been treated.

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Development of MMPs specific peg-peptide-doxorubicin conjugates based on angiogenesis

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Introduction: Matrix metalloproteinases (MMPs) secreted from cancer cells play important roles during the tumor progression. They degrade extracellular matrix (ECM) mainly composed of collagen and facilitate tumor invasion and metastasis. Based on these phenomena, we designed type IV collagenases, MMP-2 and MMP-9, specific PEG-peptide-doxorubicin conjugates formed as micelle in aqueous system (Fig. 1).