clearance resulted in a dose proportional area under the concentration-time curve (AUC) 3× higher in the CI infusion schedule versus the short infusion studies. Sequential CT and FDG PET scans were acquired to assess the effects of rHu-Endo on tumor blood flow and tumor glucose metabolism, respectively. At the 60 and 120 mg/m^2/d dose levels, a substantial decrease in FDG metabolism was observed; while blood flow estimated by first pass metabolism did not significantly change over a 28 day period. Prior to starting rHu-Endo, one patient had two FDG PET scans over a 28 day period. During this drug-free period, blood flow to analyze metastatic lesions increased by 41% from baseline. Following two cycles of rHu-Endo, blood flow decreased by 47% from baseline. This trial is currently accruing patients at the higher dose levels.

Dose Level (mg/m^2/day)	Cycle 1 Mean CI (ml/min/m^2)	Single Day Mean AUC (mg/ml·min)	Cycle 1 Mean AUC (mg/ml·min)	Cycle 1 Mean Est. Css (mcg/ml)
30(n=6)	135.9 ± 77.1	0.26 ± 0.10	7.11 ± 2.63	0.16 ± 0.07
60(n=5)	131.1 ± 12.8	0.46 ± 0.04	12.45 ± 1.19	0.32 ± 0.03
120(n=5)	114.0 ± 25.9	1.10 ± 0.24	29.57 ± 6.43	0.76 ± 0.17

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Structure-growth regulatory potency relationship investigation of TIMP-1 (tissue inhibitor of metalloproteinases) C-terminal domain fragments

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Although TIMP-1 is widely known as a common matrix metalloproteinase (MMP) inhibitor, originally it was identified as a growth factor and is able to stimulate the growth of certain cell lines. It is noteworthy that TIMP-1 looses its growth stimulatory activity upon complex formation through its C-terminal domain with proMMP-9, but reduction and alkylation does not affect it. Assuming the importance of the C-terminal domain sequences in the growth stimulatory activity, peptide fragments related to this domain were synthesized and subjected for studies on SAR. In resting MCF-7 cell cultures TIMP peptides at the early treatment period induced higher DNA content without augmenting cell population, and at later non-apoptotic type of cell death was observed. The abolishment of DNA content elevation in the presence of EGF may indicate the participation of a cell surface receptor in the action of the peptides. TIMP peptides increased MMP-2, but reduced MMP-9 production in the HT-1080 cell cultures. The above data indicate that in growth factor deprived circumstances C-terminal fragments of TIMP-1 cause cell death and modulate the equilibrium between MMP-2 and MMP-9. No conclusion can be drawn from the SAR investigations for the presence of a well defined active center in the TIMP-1 C-terminal domain, it may rather be supposed that pharmacophores at different positions of the molecule are involved in the growth modulating activity of TIMP-1.

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Radiation and the endothelium: the importance and the modulatory effects of VEGF, bFGF, alphavbeta3 and the extracellular matrix components on ionizing radiation-induced endothelial cell damage

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In recent decades, radiation research primarily concentrated on the cancer cell compartment. Much less is known about the effect of ionizing radiation on the endothelial cell compartment and the complex interaction between the tumor and its microenvironment, which includes the ECM, cytokines, integrins and endothelial cells. Here we report that ionizing radiation is a potent antiangiogenic agent that inhibits endothelial cell survival, proliferation, tube formation and invasion. VEGF and bFGF were able to reduce the sensitivity of endothelial cells to radiation-induced damage, and this radioresistance could be reversed by the receptor tyrosine kinase inhibitors SU5416 and SU6668. Endothelial cells were found to be more sensitive to ionizing radiation than PC3 prostate cancer cells. IR upregulated VEGF and bFGF in PC3 cells and, interestingly, VEGFR2 and the integrin alphavbeta3 in endothelial cells. In a co-culture system, irradiation of the prostate cancer cells enhanced endothelial cell invasiveness through a Matrigel matrix. Because of the observed upregulation of alphaVβ3, we explored the modulatory role of ECM components on endothelial cell proliferation, plating efficiency and clonogenic survival. We observed that fibronectin and collagen I increased endothelial cell proliferation and survival without significantly affecting radiosensitivity. In contrast, laminin enhanced intrinsic radiosensitivity. Together these findings form the basis of a complex model of multifactorial communication between the tumor and its microenvironment that is modulated by ionizing radiation. This model may help us to better understand how tumors protect their microvasculature from radiation-induced damage. Simultaneously, our results rationalize concurrent administration of angiogenesis inhibitors and radiotherapy in cancer treatment.

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The alpha-v beta-3 antagonist S-247 inhibits the growth of primary renal tumor and spontaneous lung metastases in the RENCA model

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Tumor angiogenesis is a multistep process requiring migration, attachment and survival of endothelial cells. The integrin receptors play an essential role in tumor angiogenesis. Integrin receptor antagonists have been shown to inhibit tumor progression and metastases in preclinical models, and are currently in clinical development. In this study we assessed the effects of the alpha-v beta-3 (avb3) integrin antagonist S-247 in a murine model of renal tumor and spontaneous lung metastases. Murine syngeneic renal cell carcinoma cells (RENCA) were injected orthotopically into the renal capsule of Balb/c female mice. On day 4, animals were randomly assigned to control group and the experimental group. S-247 100 mg/kg in saline solution was administered by gavage twice a day. On day 22 all mice were sacrificed, and primary kidney tumors and lung metastases were analyzed. S-247 induced 49-68% inhibition of the primary tumor as compared to control ($p<0.01$). S-247 treated mice developed also significantly fewer spontaneous lung metastases than controls (up to 98% inhibition of microscopic lung colonies; controls 65; S-247 1.6; $p<0.01$). Preliminary immunohistochemical staining for CD31 and smooth muscle actin showed a reduction of microvessel and pericyte density in the in primary tumors of S-247 treated mice. Studies to evaluate the therapeutic effect of S-247 on established lung metastases in an "intervention" model are in progress. Imaging PET studies will be presented at the meeting. In conclusion, the avb3 integrin antagonist S-247 demonstrates significant anti-tumor and anti-metastatic activity in a murine model for renal cell cancer. Agents such as integrin receptor antagonists may represent an effective treatment in patients with renal cell carcinoma.

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A phase I study of the heparanase inhibitor PI-88 given subcutaneously (sq) in patients (pts) with advanced solid malignancies

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Heparan sulfates of the extracellular matrix (ECM) bind and sequester proangiogenic growth factors (GFs), such as bFGF and VEGF. Heparanase, which is overexpressed in many cancers, facilitates tissue remodeling and GF release from the ECM, and thereby promotes angiogenesis. PI-88 is a highly sulfated oligosaccharide that interferes with GF binding to heparan sulfates and inhibits heparanase. PI-88 inhibits both angiogenesis in the chick CAM assay, and tumor growth and metastasis in murine syngeneic and human xenograft tumor models. This ongoing phase I study is designed to evaluate the safety, pharmacokinetic (PK) behavior, and biological effects of PI-88 (80-250 mg) when given SQ on days 1-4 and 15-19 of a 28-day cycle to pts with advanced cancer. Dexamethasone 20 mg PO is given on days -1, 1, 14, and 15 for prophylaxis against immune-mediated thrombocytopenia. The rationale for this regimen included the convenience of SQ administration, as well as the possible identification of a distinct toxicity profile from that associated with prolonged intravenous administration. Thus far, 18 pts (median age 60 [range 19-77]; median PS 1) have received 40 courses (crs, range 1-11). Toxicities have included bruising at injection sites (gr 1, 36 crs), pain at known tumor sites (gr 1-2, 12 crs; gr 3, 2 crs), fatigue (gr 1-2, 13 crs), and peripheral neuropathy (gr 1-2, 4 crs). Two SAEs have occurred (pneumonia, second malignancy); neither is considered related to study drug. All