

radiotherapy can result. As a first step toward conformal chemotherapy, we have developed a 3D-imaging method to quantitatively map local drug concentrations in solid tumors.

Methods: Distribution patterns in dermal murine solid tumors (SCCVII, RIF-1, and pancreatic cancer xenografts) were examined after intratumoral injection of radiolabeled 5-FU in either an aqueous solution or a gel formulation at injection-volume to tumor-volume ratios of 1:50 to 1:3. Autoradiograms and photomicrographs of tumor cryosections were analyzed using NIH Image software to obtain isodose curves. Autoradiograms were digitally combined to reconstruct the tumor in 3D. Drug concentration in any specific location was determined by digital resectioning of the reconstructed tumor image.

Results: ^{14}C -5-FU administered in a simple aqueous solution was rapidly distributed throughout the tumor (3–19 mM, at 2 min, depending on dose volume) and cleared quickly (0.2–3.4 mM at 1 h). ^{14}C -5-FU administered in the gel was distributed through 60–80% of the tumor at 2 min (21–111 mM) and through 80–100% of the tumor at 1–2 h (8–13 mM). Distribution pattern varied with tumor tissue and formulation. Isodose curves were concentric after administration of 5-FU gel. Concentrations depended on dose volume and decreased exponentially as a function of distance from the margin of the gel. Overall exposure (extent $\times$ concentration $\times$ time) was severalfold higher using the gel formulation than that using the solution.

Conclusion: This 3D mapping technique may enhance our ability to predict local drug exposure in solid tumors and contribute to the development of conformal chemotherapy for local tumor control.

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POSTER

Activation of immune effector cell cytolytic activity by the alkaloid derivate Ukrain (NSC 631570)

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Purpose: To investigate the possible modulation of immune effector cells' cytolytic activities by the alkaloid thiophosphoric acid derivative Ukrain (NSC 631570).

Methods: The cytolytic activity of alloimmunized spleen lymphocytes and peritoneal macrophages (PM) from tumor bearing animals was investigated in vitro by ^{51}Cr release assays in the presence of various concentrations of Ukrain in the CML assays.

Results: The cytolytic activity of freshly isolated spleen lymphocytes from P815 (H-2) alloimmunized C57B1/6 mice, which had no significant endogenous cytolytic activity, i.e. 2.0% specific ^{51}Cr release, were found to increase their lytic activity to 65% in the presence of 1.2 M of Ukrain. The in vitro CML investigations were carried out at E/T = 5:1 for 3.5 hrs. The effects of Ukrain on the cytolytic activity of PM of Balb/c bearing syngeneic D1-DMBA-3 tumors were also assayed in vitro. Results showed that Ukrain at 2.5 M activated the cytolytic activity of macrophages from 0% to 13% specific lysis of syngeneic tumor cells. Moreover, in vivo studies with Balb/c mice bearing syngeneic mammary adenocarcinomas showed that Ukrain had a significant inhibition of tumor growth and progression.

Conclusions: Ukrain was found to activate the cytolytic activity of spleen lymphocytes as well as anergic macrophages obtained from mice bearing syngeneic tumors. It indicates that this compound functions as a biologic response modifier (BRM). This conclusion is further supported by the finding that Ukrain reduced significantly the growth rate of established mammary adenocarcinomas without any observable side effects.

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POSTER

Schedule-dependent myelotoxicity induced in vitro by the new marine derived minor groove interacting agent ecteinascidin 743

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Purpose: To evaluate the toxicity on human hematopoietic progenitor cells of the marine derived anticancer compound ecteinascidin 743 (ET 743) at different schedules of exposure.

Methods: Human umbilical cord blood derived progenitors were incubated with ET 743 for 1 h, 24 h and 1 h daily $\times$ 5, then plated in clonogenic assays. The growth of erythroid (CFC-E and BFU-E) and myeloid colonies (GM-CFC) was scored after 7 days (more differentiated progenitors) and 14 days (earlier progenitors).

Results: The concentration of drug inhibiting the growth of 70% of the colonies (ID70) for each schedule was (median and range):

	ID70 (ng/ml)		
	1 hour	24 hours	1 hour daily $\times$ 5
GM-CFC d7	6 (1–13)	0.8 (0.3–3.2)	1.6 (1.2–2.0)
GM-CFC d14	12 (7.5–13)	2.5 (1–9)	3.0 (2.2–3.6)
CFC-E d7	5 (2.5–12)	1 (0.5–3.3)	2.2 (1–2.5)
BFU-E d14	9.5 (4–12.5)	1.4 (0.5–9)	2.4 (1.5–2.6)

Conclusions: Erythroid and myeloid progenitors are equally sensitive to the drug, while early progenitors are more resistant than the differentiated ones. The 1 h daily $\times$ 5 treatment is 3–4 times more toxic than 1 h exposure, suggesting that the toxicity might be schedule dependent, while the 24 hours exposure seems to be less myelotoxic.

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POSTER

Tumor uptake of MTX-albumin conjugates in rats

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Following our observation that albumin turnover in rodent tumors is markedly increased, we present evidence that albumin can be employed for targeting methotrexate (MTX) into tumors. The discrepancy in the molecular weight of MTX (454 Da) and albumin (67000 Da) tempted to load multiple drug molecules on one carrier molecule.

Methods and Results: We will show that only a loading rate of approx. 1 mol of the cytostatic drug MTX per mol of albumin offers optimal conditions for targeting residualizingly radiolabeled methotrexate-albumin conjugates into rodent tumors (W-256 carcinosarcoma). Conjugates bearing 5, 7, 10, and 20 molecules of MTX showed signs for albumin denaturation. These conjugates, tagged with a residualizing radiolabel, were efficiently trapped by the liver before reaching the tumor tissue. Competition experiments with maleylated bovine serum albumin and fucoidan revealed that the group of scavenger receptors present on the cells of the liver monocyte macrophage system were involved in this process.

Conclusion: We chose the MTX-albumin conjugate, derivatized only at a molar ratio of approx. 1:1, for further preclinical and clinical studies. This conjugate showed the best tumor targeting properties, low liver uptake rates, and a very long biological half life.

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POSTER

High effectiveness of combined treatments of paclitaxel (TX) and 4'-epi-doxorubicin (EP) in a murine tumour: A preclinical study

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Purpose: The optimization of schedule of combined TX and EP administration on the growth of a murine mammary carcinoma was studied.

Methods: For the experiments tumour was transplanted into the right hind foot of female hybrid (C3D2F1) mice. Drugs were delivered i.p. TX was administered in single doses from 15 to 75 mg/kg b.w. and EP was administered from 9 to 24 mg/kg b.w.. Results were analyzed in terms of Tumour Growth Delay (TGD).

Results: TGD's, in the combined administration, show an effect at least additive in all the tested protocols. Quasi-simultaneous delivery has shown at the higher doses a non tolerable toxicity, that is acceptable with a time interval of 24 h between treatments. The best result, both in terms of effectiveness and tolerability, was obtained delivering TX 45 mg/kg 24 h before EP 15 mg/kg (with a TGD of 22.6 days). The superadditive effect clearly shown by divergent linear regression curves was also obtained after quasi simultaneous treatment TX in different doses and EP 9 mg/kg.

Conclusion: The performed experiments have shown the high effectiveness of the combination of the two drugs and the importance of the delivery protocols.