776C was calculated from the ratio (F) of FU IC50 without 776C divided by FU IC50 with 776C. 776C was not cytotoxic to any of the cell lines tested. On CAL51 cell line, expressing a high basal DPD activity, FU enhancement by 776C was a saturable phenomenon related to the 776C concentration; the inhibition of DPD increased between 10^{-12} to 10^{-6} M of 776C. For the following studies, 776C was tested at 10^{-6} M. FU IC50 varied from 15 to 7770 μM among cell lines (median 390 μM). Basal DPD activity ranged from not detectable (< 1 pmol/min/mg prot) to 320 pmol/min/mg prot among cell lines (median 53 pmol/min/mg prot). For the 12 cell lines tested, the mean F ranged from 0.7 (no enhancement of FU cytotoxicity by 776C) up to 5.2 and was significantly related to the basal DPD activity: the greater the DPD activity, the greater the FU enhancement factor (Spearman rank correlation, $P = 0.019$). Enhancement of FU cytotoxicity by 776C occurred only in the 6 cell lines expressing the greatest basal DPD activity (> 50 pmol/min/mg prot, F ranging between 1.7 and 5.2), whereas 776C did not modify FU cytotoxicity in the remaining cell lines expressing the lowest DPD activity (< 50 pmol/min/mg prot, F ranging between 0.7 and 1.4); F was significantly different between these 2 groups of cell lines ($P = 0.005$). These results justify clinical trials with DPD inhibitors like 776C.

131 POSTER

CLINICAL RELEVANCE OF P-GLYCOPROTEIN-RELATED RESISTANCE IN PATIENTS WITH ACUTE LEUKEMIA

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Between 1989 and 1994 P-gp expression was prospectively studied in mononuclear bone marrow cells of 304 (221 AML; 83 ALL) acute leukemia patients. In 282 patients P-gp was investigated before and after therapy and in 22 patients only before therapy: 148 AML patients with AML-6 protocol (EORTC), containing daunorubicin, vincristine and conventional-dose cytarabine (ara-C), and 63 AML patients were treated with intermediate-dose ara-C plus amsacrine. Further 71 ALL patients were treated according to a German standard polychemotherapy protocol (BMFT04/1989). For AML patients with P-gp overexpression at primary diagnosis or early relapse/refractoriness, the predictive values for nonresponse to AML-6 protocol were 90% and 94% respectively, while late-relapsed AML patients with P-gp overexpression had a significantly ($P < 0.05$) lower predictive value of 73% for nonresponse. Additionally, in refractory and late-relapsed P-gp-overexpressing AML patients treated with intermediate-dose ara-C plus amsacrine the predictive values for nonresponse were 44% and 38%, respectively, significantly ($P < 0.05$) lower as compared to AML-6 protocol-treated refractory or late-relapsed AML patients. In P-gp-overexpressing treated ALL patients the predictive values of 50% and 55% for nonresponse were calculated at primary diagnosis and late relapse, respectively. P-gp overexpression is a common phenomenon in AML patients and has an inverse influence on AML-6 treatment outcome.

132 POSTER

MRP GENE EXPRESSION IN COLORECTAL CARCINOMAS

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To determine the clinically important mechanisms of multidrug resistance, we studied the expression of the MRP gene in primary colorectal carcinomas (N = 75). MRP RNA was determined by RT-PCR. MRP RNA was detected in 62 (83%) tumor specimens. The expression was independent of size and localization of the primary tumor, lymph node involvement, tumor stage and the survival durations of the patients. However, MRP gene expression correlated with MDR1 gene expression. In conclusion, the frequent expression of the MRP gene suggests its importance as a drug resistance gene in colorectal carcinomas. (Supported by Austrian Science Foundation.)

133 POSTER

EFFECT OF PACLITAXEL ON THE UPTAKE OF CIPROFLOXACIN AND OFLOXACIN BY HUMAN NEUTROPHILS

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Ciprofloxacin (CPLX) and ofloxacin (OFLX) are antimicrobial agents which concentrate and remain active within phagocytic cells. We have evaluated by a fluorometric assay the effect of paclitaxel in comparison with methotrexate, doxorubicin, Cis-platinum and etopoxide on the intracellular penetration of CPLX and OFLX in human neutrophils. The preincubation of cells for 30 min at 35°C with therapeutical concentrations of these antineoplastic agents yielded the following cellular to extracellular concentration ratio values (C/E) for CPLX and OFLX (at 20 min; 35°C; extracellular concentration: 5 mg/l).

		C/E	
Antineoplastic	**mg/l**	**CPLX**	**OFLX**
None		4.7 ± 1.2	4.6 ± 0.9
Paclitaxel	5	4.8 ± 1.0	4.3 ± 0.4
Methotrexate	10	5.1 ± 1.2	4.4 ± 0.7
Doxorubicin	1	14.3 ± 1.4	4.6 ± 1.1
Cis-Platinum	10	4.7 ± 1.6	3.7 ± 0.5
Etopoxide	10	5.5 ± 1.0	4.8 ± 1.3

Similar results were obtained when other extracellular concentrations of the antineoplastic agents were used. It is concluded that paclitaxel and the other drugs evaluated did not affect the intracellular penetration of quinolone antimicrobial agents.

134 POSTER

ENHANCED TUMOR RADIOIMMUNOTARGETING OF CHIMERIC ^{125}I-BR96-BIOTIN IN A SYNGENEIC RAT TUMOR MODEL USING WHOLE BLOOD EXTRACORPOREAL IMMUNOADSORPTION (ECIA)

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Chimeric BR 96 is a human IgG1 isotype with a high tumor selectivity for most human carcinomas of breast, lung, ovary, and gastrointestinal tract. The rapid internalization into tumor cells is another important feature for BR96. The aim of the study was to investigate if whole blood ECIA has an influence on tumor and normal tissue radioimmunotargeting.

Material and methods.: 30 BN-male rats inoculated intramuscularly (IM) and beneath liver- or kidney capsule (SR) with syngeneic rat colon carcinomas, expressing Ly Ag, were investigated. The rats were injected i.v. with 3.5–4.5 MBq of ^{125}I-BR96-biotin. ECIA of whole blood, using avidin-gel adsorption column, was performed 12 h after injection of Mab. *Results:* After completion of ECIA, whole body radioactivity was reduced by 48–62%, and plasma activity (%/g) by 85%. After finish of ECIA, the uptake in the liver-, SR-, and IM-tumors decreased by only 11, 23 and 13%, respectively, whereas the uptake in normal tissues was considerably diminished. T(umor)/bone marrow, T/liver, T/kidney and T/lung uptake ratios were enhanced in all 3 tumor models by a factor varying from 2.2 to 4.2. The uptake of Mab in Liver and IM-tumor was enhanced by increasing amount of Mab injected. *Conclusion:* ^{125}I-BR96-biotin proved high tumor-to-normal tissue ratios, which were even more enhanced by ECIA of whole blood.

135 POSTER

PHARMACOKINETICS AND PHARMACODYNAMICS OF TENIPOSIDE (VM26) COADMINISTERED WITH CYCLOSPORIN A (CSA) IN PATIENTS WITH METASTATIC RENAL CELL CANCER (RCC)

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Background: Chemosensitizers could alter the pharmacokinetics (PK) and pharmacodynamics (PD) of antineoplastic drugs. It was previously demonstrated that CsA modifies PK and PD of etoposide, an analog of VM26, but the effect of CsA on VM26 has not been clarified yet.

Methods: Thirteen patients with RCC in progression after standard therapy were accrued. Demographics: median age 61 years (range 44–75), male:female 9/4, median WHO P.S. 2 (range 1–3). The patients