samples from patients with AML, ALL, CML and CLL topo II alpha and beta activities were detected with high sensitivity. Neither topo II alpha nor topo II beta activity correlates with sensitivity to anthracyclines or podophyllotoxines but a high correlation with cellular sensitivity to anthracyclines and the alpha/beta ratio was found. With the methods presented clinical studies can be performed with patient material either fresh or frozen and the selective activities of topo II inhibiting drugs on either the alpha or the beta isoenzyme can be illustrated.

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A new methodology for determination of anthracycline intracellular active concentration in sensitive and multidrug resistant cells

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It is the quantity of anthracyclines (Anth) bound to DNA (active intracellular Anth concentration) rather than total drug intracellular content that correlates with sensitivity of tumor cells to the drugs and in most cases characterizes the level of multidrug resistance (MDR). Common biochemical methods which involve extraction and cell destruction are not accurate enough to determine this parameter. This study develops a new methodology which allows accurate determination of this parameter during short-time incubation of the drug with living cells. The methodology uses a DNA-specific fluorescent dye Hoechst 33258 whose fluorescence increases many times after binding to DNA. The approach is based on possible competition between the Hoechst and Anth for binding to DNA. It has been found that after addition of Anth DNA-bound Hoechst fluorescence decreases proportionally to Anth intracellular active concentration bound to DNA. Using the approach described here the difference between active intracellular concentration of various Anths (including polymer-bound drug complexes) and the detected MDR level in different resistant variants of tumor cell lines and tumor cells growing *in vivo* has been detected even at a low MDR level. The methodology has also been used for screening modifiers that increase active intracellular Anth concentration and thereby reduce cell resistance to Anths and MDR in general. It was found that panangin has such activity and increases Anth active concentration in resistant cells.

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Preclinical studies: reversal

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An *in vivo* model of chemosensitization of multidrug resistant human myeloma cell line in SCID mice

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A reproducible *in vivo* model of human multiple myeloma has been established in the SCID mouse using both the drug-sensitive 8226/S human myeloma cell line and the P-glycoprotein-expressing multidrug resistant 8226/C1N subline.[1] The SCID mouse is well suited as a model for myeloma because: (1) human–SCID xenografts are readily attained; (2) tumor cells are readily detected by their immunoglobulin secretion; and (3) differential therapy effects in drug-sensitive versus drug-resistant cell lines are readily demonstrable. In the current study this model has been utilized to evaluate its ability to ascertain the *in vivo* efficacy of chemomodulators of the P-gp. The initial evaluation of chemosensitizers in this model has been performed using verapamil. Doxorubicin alone was effective in treating the 8226/S xenografts but had no effect on 8226/C1N xenografts in the absence of verapamil. The combination of verapamil and doxorubicin resulted in both a decrease in human lambda light chain excretion and an increase in survival of those animals bearing the 8226/C1N tumor. Several animals were treated with multiple courses of the combination of doxorubicin and verapamil and tissues harvested to study the immunophenotype of those cells surviving this treatment in order to determine whether there was a clonal change from the initial population of cells injected. The SCID–human xenograft model offers both an *in vivo* means of evaluating the efficacy and toxicities of new therapeutic approaches including development of chemosensitizers directed against P-gp as well as a model in which to study those cells which escape the effects of chemosensitization.

1. Bellamy *et al. Am J Pathol* 1993; 142: 691.

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Selective inhibition of hepatic P-glycoprotein mediated excretion by SDZ PSC 833 and dexniguldipin

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The apical membrane of liver cells accomplishes the biliary excretion of various organic compounds: (1) as in tumor