human integrin, inhibited the growth of established tumors by approximately 40%, confirming that inhibition of integrin alpha5beta1 can slow tumor growth by impeding angiogenesis in vivo. Importantly, targeting of both host vasculature and tumor integrin using 339.1 and volociximab together resulted in additive efficacy in multiple xenograft models, suggesting that in the clinic, volociximab may exert both anti-angiogenic and direct anti-tumor cell activity in vivo.

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Hsp90 inhibitor synergistically potentiates the growth inhibitory and pro-apoptotic effects of SN-38 in gastric carcinoma cells

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Background: Gastric cancer is the second most frequent cancer in the world. To date, we have few effective chemotherapeutic agents against it. A representative Hsp90 inhibitor, 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) is a new anticancer agent for solid tumor currently in clinical trials. The aim of the current study was to determine the effects of combination treatment of 17-DMAG and CPT-11 on gastric cancer lines and investigate the mechanism responsible for this enhancement of CPT-11-induced cytotoxicity by 17-DMAG.
Methods: Human gastric cancer cells MKN-1, MKN-7 and MKN-45 were treated with 17-DMAG and SN-38, an active metabolite of CPT-11, alone and in combination, and their effect on growth and cell cycle distribution was evaluated using tetrazolium-based colorimetric assay (MTT) and flowcytometory, respectively. The possible synergism was analysed using median drug effect analysis resulting in combination indexes (CI), in which CI < 0.9 indicates synergism, CI = 0.9–1.1 indicates additivity and CI > 1.1 indicates antagonism when the two drugs were added in a 1:1 IC(50)-based molar ratio. Apoptosis was monitored by flow cytometrical analysis, DNA ladder fragmentation analysis and biochemical markers of apoptosis.
Results: We demonstrated that MKN45 (poorly differentiated adeno-carcinoma line) is sensitive to 17-DMAG, with an average IC (50) of 196.9+72.0 nmol/L although MKN1 (adeno-squamouscarcinoma line) and MKN7 (highly differentiated adenocarcinoma line) are less sensitive with an average IC (50) of 1309.7+275.2 and 2316.6+688.2 nmol/L respectively. Combination of 17-DMAG and SN-38 significantly induced cell death, and synergistically inhibited proliferative activity of all three cell lines. It resulted in enhanced accumulations of the sub-G1 phase population, occurrence of DNA fragmentation and a pronounced increase of active caspase-3, 8, 9 and poly (ADP) ribose polymerase cleavage.
Conclusion: These data suggest 17-DMAG could potentiate the cytotoxic effects of CPT-11 chemotherapy in patients with gastric cancer and underscore the need for rational design of human clinical trials.

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Doxorubicin cardiotoxicity and effectiveness in MCF-7 breast cancer cells could be mediated by polyprenol

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Background: Doxorubicin (Dox) is an important and effective anticancer drug widely used for the treatment of various types of cancer but its clinical use is limited by dose-dependent cardiotoxicity. The investigations reveals that Dox toxicity and multidrug resistance (MDR) correlates with concentration of P-glycoprotein (P-gp) in plasma membrane. Poliprenol (Pol) have been proved to be a rate limiting factor in membrane glycoprotein synthesis in Dolichyl Phosphate Cycle (DPC). The purpose of this study was to investigate the role of Pol in cardiotoxicity Dox and its effectivness in MDR MCF-7 breast cancer cells.
Methods: Pol concentration in the culture medium with neonatal rat ventricular myocytes (NRVM) made up 10^{-3}–10^{-8} M. Cell viability was evaluated. Breast cancer cell lines, MCF-7 and MCF-7 cells with induced resistance to Doxorubicin (MCF-7/ADR) were used. Pol concentration in the culture medium made up 10^{-2}–10^{-6} M. MDR1 expression was assessed by an immunohistochemical technique. Intermediates of DPC and Pgp fractions were analysed by HPLC methods.
Results: Pol in concentration 10^{-5}–10^{-6} M could increase the viability of NRVM that were treated with Dox. Pol in concentration 10^{-2}–10^{-3} M induced apoptosis in MCF-7/ADR cells within 3–4 hours. It is confirmed that plasmatic membranes of MCF-7 cells contain 5.6–6.4% of P-gp (the total protein amount) as a resistance marker. Resistant MCF-7/ADR cells differ from sensitive ones MCF-7 in Pgp content by 10–12 times. The study showed 8.5-fold DPC intermediates decrease in MCF-7/ADR cells. The investigations demonstrate that the situation can be changed by treatment with Pol. The DPC concentration in MCF-7/ADR cells was returned to the normal level. It is established that Pol in the concentration 10^{-4} M aid 7–9-fold reducing P-gp in membranes of MCF-7/ADR cells. The MCF-7/ADR cells cultivation in medium with Pol proceeded to give lowered P-gp content in membranes no over 0.4–0.6%, which amount was consistent with the level of Pgp in MCF-7 cells. NRVM cells cultivation in medium with Pol proceeded to give P-gp content in membranes about 18–2.5%, which amount could reduce the toxicity concentration of Dox in myocytes.
Conclusions: These results indicate that noncontrollable accumulation of P-gp, which cause MDR and Dox cardiotoxicity can be overcomed using stimulation of DPC with Pol, which provides a DPC substitute in regulation of P-gp. Pol is a promising new drug which clinical usage can open up possibilities to tackling the problem of cardiotoxicity and resistance in breast cancer chemotherapy.

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Ectopic expression of PIK3CD in human cancer cell lines and human lung carcinoma

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Class I phosphoinositide-3-kinase (PI3K) consists of four isoforms of the catalytic subunit, p110a, -β, -d and -? generated from the gene PIK3CA, -B, -D and -G, respectively. These isoforms show different tissue distribution and some specific and indispensable functions in various biological pathways such as development, inflammation and cancer. In human cancers, frequent genomic amplification, over expression and gain-of-function mutations of PIK3CA were reported, which suggests its oncogenic potential. However, the connections of other three isoforms containing PIK3CD to human cancers remain unclear. We previously established a panel of 39 human cancer cell lines (JFCR39). JFCR39 has been well characterized in the profiles of gene expression [1], protein expression [2] and sensitivity to various types of pathway inhibitors including PI3K inhibitors [3]. Therefore, JFCR39 is considered to be a good model for studying the PI3K pathway and its implication in cancer. To get more information on non-a isoforms in human cancers, we herein have established an absolute-quantification system of all four isoforms by real-time RT-PCR using isoform-specific primers. This system revealed that, in JFCR39, not only PIK3CA or -B but also PIK3CD was expressed ubiquitously, while PIK3CG expression was restricted in several cell lines. PIK3CD expression was confirmed by semi-quantitative RT-PCR technique and by sequencing the resulting PCR products. Next we examined 30 human lung carcinoma tissues for the expression of the four isoforms and revealed that PIK3CD, not only PIK3CA or -B, was also expressed in most of the cases, while PIK3CG was expressed only in several cases. It has been considered that PIK3CD is expressed predominantly in leukocytes. However, by measuring the expression of all four isoforms at a time, we demonstrated for the first time the ectopic expression of PIK3CD in human cancer cell lines as well as in clinical specimens of lung carcinoma. Biological implications of the ectopic PIK3CD expression remain to be solved.

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Effects of a neutrophil elastase inhibitor on the reduction of radiation pneumonitis

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Background: As the cause of radiation-induced lung injury, experimental studies have shown that the immediate release of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 after lung irradiation is closely related with lung toxicity. The increase in these cytokines activates neutrophils, resulting in an accumulation of the activated neutrophils in the lung and the release of elastase. Neutrophil elastase (NE) is deeply involved in the non-specific phylaxis of neutrophils. When neutrophils are activated by stimulation, NE is released from the granules to the extracellular, thereby accelerating permeability of the vascular endothelial