

Answer 1:

### Bibliographic Information

**Nonviral Nanoscale-Based Delivery of Antisense Oligonucleotides Targeted to Hypoxia-Inducible Factor 1 $\alpha$  Enhances the Efficacy of Chemotherapy in Drug-Resistant Tumor.** Wang, Yang; Saad, Maha; Pakunlu, Refika I.; Khandare, Jayant J.; Garbuzenko, Olga B.; Vetcher, Alexandre A.; Soldatenkov, Viatcheslav A.; Pozharov, Vitaly P.; Minko, Tamara. Department of Pharmaceutics, Rutgers, Rutgers The State University of New Jersey, Piscataway, NJ, USA. *Clinical Cancer Research* (2008), 14(11), 3607-3616. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:143409 AN 2008:678357 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**PURPOSE:** To enhance the efficacy of cancer treatment, we propose a complex approach: simultaneous delivery to the tumor of a chemotherapeutic agent and a suppressor of hypoxia-inducible factor 1 $\alpha$  (HIF1A). **Exptl. Design:** The novel complex liposomal drug delivery system was developed and evaluated *in vitro* and *in vivo* on nude mice bearing xenografts of multidrug-resistant human ovarian carcinoma. The proposed novel complex drug delivery system consists of liposomes as a nanocarrier, a traditional anticancer drug (doxorubicin) as a cell death inducer, and antisense oligonucleotides targeted to HIF1A mRNA as a suppressor of cellular resistance and angiogenesis. **RESULTS:** The system effectively delivers active ingredients into tumor cells, multiplies the cell death signal initiated by doxorubicin, and inhibits cellular defensive mechanisms and angiogenesis by down-regulating BCL2, HSP90, and vascular endothelial growth factor proteins. This, in turn, activates caspases, promotes apoptosis, necrosis, and tumor shrinkage. The proposed novel complex multipronged approach enhances the efficiency of chemotherapy. **CONCLUSIONS:** The proposed combination therapy prevents the development of resistance in cancer cells, and thus, increases the efficacy of chemotherapy to an extent that cannot be achieved by individual components applied sep. It could form the foundation for a novel type of cancer therapy based on simultaneous delivery of an anticancer drug and a suppressor of HIF1A.

Answer 2:

### Bibliographic Information

**Epidermal Growth Factor Receptor Blockade in Combination with Conventional Chemotherapy Inhibits Soft Tissue Sarcoma Cell Growth *in vitro* and *In vivo*.** Ren, Wenhong; Korchin, Borys; Zhu, Quan-Sheng; Wei, Caimiao; Dicker, Adam; Heymach, John; Lazar, Alexander; Pollock, Raphael E.; Lev, Dina. Departments of Surgical Oncology, Cancer Biology, Medical Oncology, and Pathology and Division of Quantitative Sciences, University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2008), 14(9), 2785-2795. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:549995 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**PURPOSE:** The epidermal growth factor receptor (EGFR) is highly expressed in many human soft tissue sarcomas (STS). However, EGFR blockade has not apparently been used for human STS therapy; therefore, we examd. the *in vitro* and *in vivo* effects and the underlying mechanisms before considering EGFR blockade as a therapy for STS patients. **Exptl. Design:** Human STS tissues and cell lines were used to study EGFR expression and activation. Western blot anal. was used to evaluate effects of EGFR activation on downstream signaling. Cell culture assays were used to assess the effect of EGF stimulation as well as EGFR blockade (using an EGFR tyrosine kinase inhibitor, Iressa; AstraZeneca) on STS cell growth, apoptosis, and chemosensitivity. An *in vivo* study (HT1080 human fibrosarcoma cell line in nude/nude mice: Iressa, doxorubicin, Iressa + doxorubicin, vehicle) was used to examine tumor growth; pEGFR, proliferating cell nuclear antigen, and terminal deoxyribonucleotide transferase-mediated nick-end labeling staining helped assess the effect of therapy *in vivo* on STS EGFR activation, proliferation, and apoptosis. **RESULTS:** EGFR was expressed and activated in STS cell lines and tumors, probably due to ligand binding rather than EGFR mutation. Stimulation caused activation of AKT and mitogen-activated protein kinase pathways. EGFR blockade inhibited these effects and also caused increased apoptosis, a p53-independent G0-G1 cell cycle arrest, and decreased cyclin D1 expression. *In vivo*, Iressa + doxorubicin had markedly synergistic anti-STs effects. **CONCLUSION:** EGFR blockade combined with conventional chemotherapy results in anti-human STS activity *in vitro* and *in vivo*, suggesting the possibility that combining these synergistic treatments will improve anti-STs therapy.

Answer 3:

### Bibliographic Information

**Preclinical Toxicity, Toxicokinetics, and Antitumoral Efficacy Studies of DTS-201, a Tumor-Selective Peptidic Prodrug of Doxorubicin.** Ravel, Denis; Dubois, Vincent; Quinonero, Jerome; Meyer-Losic, Florence; Delord, JeanPierre; Rochaix, Philippe; Nicolazzi, Celine; Ribes, Fabien; Mazerolles, Catherine; Assouly, Elise; Vialatte, Karine; Hor, Ines; Kearsley, Jonathan; Trouet, Andre. Diatos S.A., Paris, Fr. *Clinical Cancer Research* (2008), 14(4), 1258-1265. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:199454 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**PURPOSE:** There is a clear clin. need for cytotoxic drugs with a lower systemic toxicity. DTS-201 (CPI-0004Na) is a peptidic prodrug of doxorubicin that shows an improved therapeutic index in exptl. models. The purpose of the current study was to complete its preclin. characterization before initiation of phase I clin. trials. **Exptl. Design:** The preclin. development program consisted of a detailed assessment of the general and cardiac toxicity profiles of DTS-201 in mice, rats, and dogs, together with mass balance and antitumoral efficacy studies in rodents. Neprilysin and thimet oligopeptidase expression, two enzymic activators of DTS-201, was also characterized in human breast and prostate tumor biopsies. **RESULTS:** The target organs of DTS-201 toxicity in rodents and dogs are typically those of doxorubicin, albeit at much higher doses. Importantly, chronic treatment with DTS-201 proved to be significantly less cardiotoxic than with doxorubicin at doses up to 8-fold higher in rats. The mass balance study showed that [14C] DTS-201 does not accumulate in the body after i.v. administration. The improved therapeutic index of DTS-201 compared with free doxorubicin was confirmed in three tumor xenograft models of prostate, breast, and lung cancer. Neprilysin and/or thimet oligopeptidase are expressed in all exptl. human tumor types thus far tested as well as in a large majority of human breast and prostate tumor biopsies. **CONCLUSION:** DTS-201 gave promising results in terms of general toxicity, cardiovascular tolerance, and in vivo efficacy in xenograft mouse models compared with free doxorubicin. Taken together, these results and the confirmation of the presence of activating enzymes in human tumor biopsies provide a strong rationale for a phase I clin. study in cancer patients.

Answer 4:

### Bibliographic Information

**STX140 Is Efficacious In vitro and In vivo in Taxane-Resistant Breast Carcinoma Cells.** Newman, Simon P.; Foster, Paul A.; Stengel, Chloe; Day, Joanna M.; Ho, Yaik T.; Judde, Jean-Gabriel; Lassalle, Myriam; Prevost, Gregoire; Leese, Mathew P.; Potter, Barry V. L.; Reed, Michael J.; Purohit, Atul. *Endocrinology and Metabolic Medicine, Faculty of Medicine, Imperial College London, Sterix, Ltd., St Mary's Hospital, London, UK.* *Clinical Cancer Research* (2008), 14(2), 597-606. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:106247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**PURPOSE:** The aim of these studies was to characterize the action of STX140 in a P-glycoprotein-overexpressing tumor cell line both in vitro and in vivo. In addn., its efficacy was detd. against xenografts derived from patients who failed docetaxel therapy. **Exptl. Design:** The effects of STX140, Taxol, and 2-methoxyestradiol (2-MeOE2) on cell proliferation, cell cycle, and apoptosis were assessed in vitro in drug-resistant cells (MCF-7DOX) and the parental cell line (MCF-7WT). Mice bearing an MCF-7DOX tumor on one flank and an MCF-7WT tumor on the other flank were used to assess the in vivo efficacy. Furthermore, the responses to STX140 of three xenografts, derived from drug-resistant patients, were assessed. **RESULTS:** In this study, STX140 caused cell cycle arrest, cyclin B1 induction, and subsequent apoptosis of both MCF-7DOX and MCF-7WT cells. Taxol and 2-MeOE2 were only active in the MCF-7WT parental cell line. Although both STX140 and Taxol inhibited the growth of xenografts derived from MCF-7WT cells, only STX140 inhibited the growth of tumors derived from MCF-7DOX cells. 2-MeOE2 was ineffective at the dose tested against both tumor types. Two out of the three newly derived docetaxel-resistant xenografts, including a metastatic triple-neg. tumor, responded to STX140 but not to docetaxel treatment. **CONCLUSIONS:** STX140 shows excellent efficacy in both MCF-7WT and MCF-7DOX breast cancer xenograft models, in contrast to Taxol and 2-MeOE2. The clin. potential of STX140 was further highlighted by the efficacy seen in

xenografts recently derived from patients who had failed on taxane therapy.

Answer 5:

#### **Bibliographic Information**

**Synergistic antileukemic effects between ABT-869 and chemotherapy involve downregulation of cell cycle-regulated genes and c-Mos-mediated MAPK pathway.** Zhou, J.; Pan, M.; Xie, Z.; Loh, S.-L.; Bi, C.; Tai, Y.-C.; Lilly, M.; Lim, Y.-P.; Han, J.-H.; Glaser, K. B.; Albert, D. H.; Davidsen, S. K.; Chen, C.-S. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. *Leukemia* (2008), 22(1), 138-146. Publisher: Nature Publishing Group, CODEN: LEUKED ISSN: 0887-6924. Journal written in English. CAN 149:118833 AN 2008:64902 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Internal tandem duplications (ITDs) of fms-like tyrosine kinase 3 (FLT3) receptor play an important role in the pathogenesis of acute myeloid leukemia (AML) and represent an attractive therapeutic target. ABT-869 has demonstrated potent effects in AML cells with FLT3-ITDs. Here, we provide further evidence that ABT-869 treatment significantly downregulates cyclins D and E but increases the expression of p21 and p27. ABT-869 induces apoptosis through downregulation of Bcl-xL and upregulation of BAK, BID and BAD. We also evaluate the combinations of ABT-869 and chemotherapy. ABT-869 demonstrates significant sequence-dependent synergism with cytarabine and doxorubicin in cell lines and primary leukemia samples. The optimal combination was validated in MV4-11 xenografts. Low-d. array anal. revealed the synergistic interaction involved in downregulation of cell cycle and mitogen-activated protein kinase pathway genes. CCND1 and c-Mos were the most significantly inhibited targets on both transcriptional and translational levels. Treatment with short hairpin RNAs targeting either CCND1 or c-Mos further sensitized MV4-11 cells to ABT-869. These findings suggest that specific pathway genes were further targeted by adding chemotherapy and support the rationale of combination therapy. Thus, a clin. trial using sequence-dependent combination therapy with ABT-869 in AML is warranted.

Answer 6:

#### **Bibliographic Information**

**INO-1001, a novel inhibitor of poly(ADP-ribose) polymerase, enhances tumor response to doxorubicin.** Mason, Kathryn A.; Valdecanas, David; Hunter, Nancy R.; Milas, Luka. Department of Experimental Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *Investigational New Drugs* (2008), 26(1), 1-5. Publisher: Springer, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 148:486493 AN 2008:52293 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Poly(ADP-ribose) synthetase inhibitor, INO-1001, is known to sensitize cells to radiation in vitro by inhibiting the repair of DNA damage. Recent evidence has suggested that PARP inhibition may also be a way of selectively targeting p53 deficient cancer cells. The present study tested INO-1001 for its in vivo effect on the chemoresponse of two p53 deficient tumors, human breast cancer MDA-MB-231 and murine mammary carcinoma MCA-K. Doxorubicin was used as the DNA damaging agent and tumor growth delay assay was used as the endpoint. Results showed that INO-1001 was highly effective in enhancing the anti-tumor effects of Doxorubicin for both MDA-MB-231 (EF = 1.88) and MCA-K (EF = 1.64). We conclude that PARP inhibitor INO-1001 has high potential for enhancing the anti-tumor effects of chemotherapy agents such as Doxorubicin against p53 deficient breast cancer.

Answer 7:

#### **Bibliographic Information**

**Peptide-Mediated Targeting to Tumor Blood Vessels of Lung Cancer for Drug Delivery.** Lee, Tong-Young; Lin, Chin-Tarn; Kuo, Szu-Yao; Chang, De-Kuan; Wu, Han-Chung. Institute of Pathology, College of Medicine, Natl. Taiwan Univ., Taipei, Taiwan. *Cancer Research* (2007), 67(22), 10958-10965. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 148:112567 AN 2007:1306234 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Antiangiogenesis therapies for the treatment of cancers hold the promise of high efficacy and low toxicity. In vivo phage display was used to identify peptides specifically targeting tumor blood vessels. The peptide SP5-52 recognized tumor neovasculature but not normal blood vessels in severe combined immunodeficiency mice bearing human tumors. Synthetic peptide was shown to inhibit the binding of PC5-52 phage particles to the tumor mass in the competitive inhibition assay. Several selected phage clones displayed the consensus motif, proline-serine-proline, and this motif was crucial for peptide binding to the tumor neovasculature. SP5-52 peptides also bound vascular endothelial growth factor-stimulated human umbilical vein endothelial cells and blood vessels of human lung cancer surgical specimens. Furthermore, this targeting phage was shown to home to tumor tissues from eight different types of human tumor xenografts following in vivo phage display expts. An SP5-52 peptide-linked liposome carrying doxorubicin enhanced the therapeutic efficacy of the drug, markedly decreased tumor blood vessels, and resulted in higher survival rates of human lung and oral cancer-bearing xenograft mice. The current study indicates that ligand-targeted therapy offers improved therapeutic effects over conventional anticancer drug therapy, and that the peptide SP5-52 specifically targets tumor neovasculature and is a good candidate for targeted drug delivery to solid tumors.

Answer 8:

#### Bibliographic Information

**Fever-range whole body hyperthermia increases the number of perfused tumor blood vessels and therapeutic efficacy of liposomally encapsulated doxorubicin.** Xu, Yan; Choi, Jason; Hylander, Bonnie; Sen, Arindam; Evans, Sharon S.; Kraybill, William G.; Repasky, Elizabeth A. Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. *International Journal of Hyperthermia* (2007), 23(6), 513-527. Publisher: Informa Healthcare, CODEN: IJHYEQ ISSN: 0265-6736. Journal written in English. CAN 148:205637 AN 2007:1188863 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Purpose: Two major questions were addressed: (1) Can fever-range whole body hyperthermia (FR-WBH) affect the no. of perfused tumor blood vessels. (2) Can pre-treatment with FR-WBH improve accumulation or anti-tumor efficacy of doxorubicin or DOXIL (liposomal doxorubicin). Materials and methods: Perfused blood vessels were visualized by i.v. injection of the fluorescent dye (DiOC7(3)) and the no. of labeled vessels in tumors and normal organs of unheated mice and those previously heated to 39.5°C for 6 h were compared. Using three animal tumor models (one syngeneic murine model and two human tumor xenografts in SCID mice) we also compared tumor growth and amt. of intratumoral doxorubicin (given as free drug or as DOXIL) in control mice or those given pre-treatment with FR-WBH. Results: FR-WBH had no effect on the no. of CD-31 labeled blood vessels. However, in tumors, but not in normal organs of the same animals, FR-WBH resulted in a significant increase in those blood vessels which could take up dye over a prolonged period of time after heating. There was also an increase in DOXIL uptake in the tumors of mice given FR-WBH prior to drug injection as well as enhanced therapeutic efficacy in all three tumor models. Conclusions: FR-WBH increases the no. of perfused blood vessels in tumors over a prolonged period following FR-WBH and thus may be useful for improving tumor targeting of cancer therapeutics. We discuss these data in relation to long-conserved thermoregulatory features in normal vasculature, which may be deficient in tumor vasculature.

Answer 9:

#### Bibliographic Information

**The effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 in human breast cancer xenograft (MCF-7) transplanted in nude mice.** Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Lv, Ya-lei; Wang, Shu-qin.

Department of Medical Oncology, The 4th Hospital of Hebei Medical University, Shijiazhuang, Peop. Rep. China. Linchuang Zhongliuxue Zazhi (2007), 12(3), 173-176. Publisher: Institution of Chinese Clinical Oncology Journal, CODEN: LZZIA5 ISSN: 1009-0460. Journal written in Chinese. CAN 148:205626 AN 2007:1152600 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The objective of the paper is to investigate the effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 of breast cancer, to assess the relationships between chemotherapy and two markers, and to evaluate the value of them to predict the response of chemotherapy. Forty-eight nude mice models of human breast cancer xenograft (MCF-7) were established, and then were randomly divided into control and 5 chemotherapy groups (each group, n = 8). Among 5 chemotherapy groups, mice were treated i.p. or orally by 5 chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) resp. at two-thirds LD10 (dose lethal to 10% of the mice). Control animals were administered i.p. with normal saline. The pathol. feature of transplanted tumor was studied by HE stain, and the expression of Bcl-2 and PCNA was studied by SP immunohistochem. method. The expression of PCNA in 5 chemotherapy group was significantly lower than that of control ( $P < 0.05$ ), and the expression of PCNA in NP, TP and Xeloda groups was significantly lower than that of CMF and CAF groups ( $P < 0.05$ ). Moreover, the expression of PCNA was significantly correlated with pathol. therapeutic response ( $P = 0.001$ ). The expression of Bcl-2 in CAF, NP, TP, Xeloda groups was significantly higher than that of control ( $P < 0.05$ ). Moreover, the expression of Bcl-2 in TP group was significantly higher than that of CMF and CAF groups ( $P < 0.05$ ). The expression of Bcl-2 was not significantly correlated with the pathol. therapeutic response ( $P = 0.093$ ). Chemotherapy can increase the expression of PCNA, and decrease the expression of Bcl-2. Different chemotherapy regimens have different effects on PCNA and Bcl-2. PCNA can become a factor to evaluate the response to chemotherapy, and become possibly the prospective factor of chemoselect.

Answer 10:

### Bibliographic Information

#### **AZD6244 and doxorubicin induce growth suppression and apoptosis in mouse models of hepatocellular carcinoma.**

Huynh, Hung; Chow, Pierce K. H.; Soo, Khee-Chee. Laboratory of Molecular Endocrinology, Division of Cellular and Molecular Research, National Cancer Centre, Singapore General Hospital, Singapore, Singapore. Molecular Cancer Therapeutics (2007), 6(9), 2468-2476. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:397879 AN 2007:1043804 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with no effective treatment for most individuals who succumb to this neoplasm. We report that treatment of primary HCC cells with the mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase 1/2 inhibitor AZD6244 (ARRY-142886) plus doxorubicin led to synergistic growth inhibition and apoptosis. In vivo administration of AZD6244, doxorubicin, or the combination of AZD6244 and doxorubicin in mice bearing 5-1318 HCC xenografts resulted in approx.  $52\% \pm 15\%$ ,  $12\% \pm 9\%$ , and  $76\% \pm 7\%$  growth inhibition, resp. AZD6244-inhibited tumor growth was assocd. with increased apoptosis, inactivation of ERK1/2, inhibition of cell proliferation, and down-regulation of cell cycle regulators, including cyclin D1, cdc-2, cyclin-dependent kinases 2 and 4, cyclin B1, and c-Myc. The AZD6244-doxorubicin combined protocol not only promoted apoptosis but also induced a synergistic effect not seen in single-agent-treated tumors, including increased expression of the p130 RB tumor suppressor gene. Our study provides a strong rationale for clin. investigation of combination therapy with the mitogen-activated protein/ERK kinase 1/2 inhibitor AZD6244 and doxorubicin in patients with HCC.

Answer 11:

### Bibliographic Information

**Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy.** Rapoport, Natalya; Gao, Zhonggao; Kennedy, Anne. Department of Bioengineering, University of Utah, Salt Lake City, UT, USA. Journal of the National Cancer Institute (2007), 99(14), 1095-1106. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874.

Journal written in English. CAN 147:330028 AN 2007:946574 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Drug delivery in polymeric micelles combined with tumor irradiation by ultrasound results in effective drug targeting, but this technique requires prior tumor imaging. A technology that combined ultrasound imaging with ultrasound-mediated nanoparticle-based targeted chemotherapy could therefore have important applications in cancer treatment. Mixtures of drug-loaded polymeric micelles and perfluoropentane (PFP) nano/microbubbles stabilized by the same biodegradable block copolymer were prepared. Size distribution of nanoparticles was measured by dynamic light scattering. Cavitation activity (oscillation, growth, and collapse of microbubbles) under ultrasound was assessed based on the changes in micelle/microbubble volume ratios. The effect of the nano/microbubbles on the ultrasound-mediated cellular uptake of doxorubicin (Dox) in MDA MB231 breast tumors in vitro and in vivo (in mice bearing xenograft tumors) was determined by flow cytometry. Statistical tests were two-sided. Phase state and nanoparticle sizes were sensitive to the copolymer/perfluorocarbon volume ratio. At physiological temperatures, nanodroplets converted into nano/microbubbles. Doxorubicin was localized in the microbubble walls formed by the block copolymer. Upon intravenous injection into mice, Dox-loaded micelles and nanobubbles extravasated selectively into the tumor interstitium, where the nanobubbles coalesced to produce microbubbles with a strong, durable ultrasound contrast. Doxorubicin was strongly retained in the microbubbles but released in response to therapeutic ultrasound. Microbubbles cavitated under the action of tumor-directed ultrasound, which enhanced intracellular Dox uptake by tumor cells in vitro to a statistically significant extent relative to that observed with unsonicated microbubbles (drug uptake ratio = 4.60; 95% confidence interval [CI] = 1.70 to 12.47;  $P = .017$ ) and unsonicated micelles (drug uptake ratio = 7.97; 95% CI = 3.72 to 17.08;  $P = .0032$ ) and resulted in tumor regression in the mouse model.

Multifunctional nanoparticles that are tumor-targeted drug carriers, long-lasting ultrasound contrast agents, and enhancers of ultrasound-mediated drug delivery have been developed and deserve further exploration as cancer therapeutics.

Answer 12:

### Bibliographic Information

**Predicting the active doses in humans from animal studies: a novel approach in oncology.** Rocchetti, M.; Simeoni, M.; Pesenti, E.; De Nicolao, G.; Poggesi, I. Preclinical Development, Nerviano Medical Sciences, Nerviano, Italy. *European Journal of Cancer* (2007), 43(12), 1862-1868. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:461695 AN 2007:895461 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The success rate of clinical drug development is significantly lower in oncology than in other therapeutic areas. Predicting the activity of new compounds in humans from preclinical data could substantially reduce the number of failures. A novel approach for predicting the expected active doses in humans from the first animal studies is presented here. The method relies upon a PK/PD model of tumor growth inhibition in xenografts, which provides parameters describing the potency of the tested compounds. Anticancer drugs, currently used in the clinic, were evaluated in xenograft models and their potency parameters were established. A good correlation was obtained between these parameters and the exposures sustained at the therapeutically relevant dosing regimens. Based on the corresponding regression equation and the potency parameters established in the first preclinical studies, the therapeutically active concentrations of new compounds can be established. An early knowledge of level of exposure or doses to be reached in humans will improve the risk evaluation and decision making processes in anticancer drug development.

Answer 13:

### Bibliographic Information

**The synergistic inhibitory effect of somatostatin-doxorubicin co-treatment on gallbladder carcinoma.** Li, Ji-Yu; Quan, Zhi-Wei; Zhang, Qiang; Liu, Jian-Wen. Department of General Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China. *BMC Cancer* (2007), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. <http://www.biomedcentral.com/content/pdf/1471-2407-7-125.pdf> Journal; Online Computer File written in

English. CAN 147:203198 AN 2007:774848 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Gallbladder cancer is the most common biliary tract malignancy and carries a very poor prognosis. Somatostatin was recently shown to play an important role in the development of various tumors. In the current study, we evaluated the effect of doxorubicin on the chemosensitivity of gallbladder cancer cells and xenograft growth after treatment with somatostatin. Twenty-four hours after somatostatin treatment, doxorubicin was gradually added and the growth curve of gallbladder cancer cells was detd. Exponential-phase gallbladder cancer cells were treated with doxorubicin or co-treated with doxorubicin and somastatin and the resp. IC50 values were detd. In addn., the inhibitory effect on the growth of gallbladder cancer xenograft on nude mice was evaluated using the same treatments as those described above. Treatment of gallbladder cancer cells with somatostatin led to a block in the cell cycle at the S phase. Growth inhibition of gallbladder cancer cells by doxorubicin was concn.-dependent ( $P < 0.05$ ). However, upon co-treatment with doxorubicin and somatostatin, the IC50 value significantly decreased as compared to that of cells treated with doxorubicin alone ( $P < 0.05$ ). Interestingly, treatment with either doxorubicin or somatostatin did not significantly inhibit xenograft growth on nude mice, in contrast to a co-treatment with both drugs ( $P < 0.05$ ). Somatostatin most likely sensitizes the chemotherapeutic effect and diminishes the cytotoxicity of doxorubicin in a gallbladder cancer cell line and in mouse gallbladder cancer xenografts.

Answer 14:

### Bibliographic Information

**Determination of the optimal combination chemotherapy regimen for treatment of platinum-resistant ovarian cancer in nude mouse model.** Saucier, Jenifer M.; Yu, Jiang; Gaikwad, Anjali; Coleman, Robert L.; Wolf, Judith K.; Smith, Judith A. Department of Gynecologic Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. Journal of Oncology Pharmacy Practice (2007), 13(1), 39-45. Publisher: Sage Publications Ltd., CODEN: JOPPFI ISSN: 1078-1552. Journal written in English. CAN 147:157549 AN 2007:740310 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Objective: The primary objective of this study was to evaluate the potential to increase the in vivo activity of liposomal doxorubicin when administered in combination with other chemotherapeutic agents such as topotecan, docetaxel, gemcitabine, capecitabine, or celecoxib in an ovarian cancer xenograft mouse model to identify new treatment options for recurrent platinum-sensitive/resistant ovarian cancer. Methods: This was a five-arm study in two xenograft ovarian cancer mouse models, ES-2 (platinum-sensitive), and OVCAR3 (platinum-resistant), to evaluate the combination of liposomal doxorubicin with the common chemotherapeutic agents. Each cell line had five mice for each treatment arm, five vehicle control mice, and five liposomal doxorubicin alone control mice. Expts. were done in duplicate. Results: The percentage tumor redn. ranged from 52% to 74.1% for the single-agent treatment arms. Tumor growth inhibition and regression (response) was improved on the combination treatment arms ranging from 76.1% to 100%. We obsd. increased activity in the liposomal doxorubicin plus topotecan arm, with a 27.3% improvement in response, compared with either agent alone. Conclusions: The addn. of liposomal doxorubicin demonstrated increased antitumor activity compared with either agent used alone. The most active combination treatment arm was liposomal doxorubicin with topotecan which is consistent with recent clin. study reports of enhanced activity with the combination of topoisomerase I and topoisomerase II agents. Addnl. studies are warranted to evaluate the efficacy and safety to optimize the combination of liposomal doxorubicin and topotecan for the treatment of recurrent or refractory ovarian cancer.

Answer 15:

### Bibliographic Information

**Chemotherapeutic treatment of xenograft Spirocerca lupi-associated sarcoma in a murine model.** Stettner, Noa; Ranen, Eyal; Dank, Gillian; Lavy, Eran; Brenner, Ori; Harmelin, Alon. Department of Veterinary Resources, Weizmann Institute of Science, Rehovot, Israel. Comparative Medicine (2007), 57(3), 267-271. Publisher: American Association for Laboratory Animal Science, CODEN: COMEFT ISSN: 1532-0820. Journal written in English. CAN 147:63680 AN 2007:699937 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

To date, data are not available concerning the effectiveness of chemotherapy in the treatment of *Spirocera lupi*-assocd. esophageal sarcomas. In the present study, we compared the effectiveness of 4 chemotherapeutic agents against *S. lupi*-assocd. osteosarcoma, using a xenograft murine model created in our lab. Samples of xenografted osteosarcoma were inoculated s.c. into 5 groups (n = 10 each) of 6-wk-old male and female NOD/SCID mice. Tumor-bearing mice were divided into treatment and control groups. The treatment groups were injected with either pegylated liposomal doxorubicin (6 mg/kg, i.v., n = 9), doxorubicin (6 mg/kg, i.v., n = 8), carboplatin (60 mg/kg, i.p., repeated twice at 1-wk intervals for a total of 2 doses, n = 9), or cisplatin (6 mg/kg, i.p., n = 8). The control group was injected with buffered saline (n = 9). Tumor size was detd. by caliper measurements. Compared with the control group, the pegylated liposomal doxorubicin- and doxorubicin-treated groups, but not the carboplatin or cisplatin groups, showed significant inhibition of tumor growth. Our results indicate that doxorubicin-based drugs are effective against *S. lupi*-assocd. sarcomas in a mouse xenograft model. Because it is less toxic than doxorubicin, pegylated liposomal doxorubicin is likely the drug of choice for treatment of *S. lupi*-assocd. sarcomas. We suggest that combination of doxorubicin or its pegylated form with surgical excision will improve the prognosis of dogs with this disease.

Answer 16:

**Bibliographic Information**

**Monoclonal antibody 2C5-modified doxorubicin-loaded liposomes with significantly enhanced therapeutic activity against intracranial human brain U-87 MG tumor xenografts in nude mice.** Gupta, Bhawna; Torchilin, Vladimir P. Department of Pharmaceutical Sciences and Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, USA. *Cancer Immunology Immunotherapy* (2007), 56(8), 1215-1223. Publisher: Springer, CODEN: CIIMDN ISSN: 0340-7004. Journal written in English. CAN 147:263125 AN 2007:530727 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Liposomes, modified with monoclonal antibodies, are suitable carriers for targeted delivery of chemotherapeutic drugs into brain tumors. Here, we investigate the therapeutic efficacy of monoclonal anticancer antibody 2C5-modified long-circulating liposomes (LCL) loaded with doxorubicin (2C5-DoxLCL) for the treatment of U-87 MG human brain tumors in an intracranial model in nude mice. In vitro, 2C5-DoxLCL is significantly more effective in killing the U-87 MG tumor cells than Doxil (com. doxorubicin-loaded PEGylated LCL) or DoxLCL modified with a non-specific IgG. 2C5-immunoliposomes also demonstrate a significantly higher accumulation in U-87 MG tumors compared to all controls in a s.c. model. The treatment of intracranial U-87 MG brain tumors in nude mice with 2C5-DoxLCL provides a significant therapeutic benefit over control formulations, substantially reducing the tumor size and almost doubling the survival time. Thus, monoclonal antibody 2C5-modified LCL can specifically target the anticancer drugs to brain tumors, leading to improved therapeutic treatment of brain tumor in an intracranial model, in vivo.

Answer 17:

**Bibliographic Information**

**Effects of various chemotherapy regimens on the expression of PCNA and growth of human breast cancer xenograft (MCF-7) in nude mice.** Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Wang, Jun-ling; Yan, Xia; Zhang, Xiang-hong. Department of Medical Oncology, 4th Hospital, Hebei Medical University, Shijiazhuang Hebei, Peop. Rep. China. *Zhongguo Aizheng Zazhi* (2007), 17(2), 139-143. Publisher: Fudan Daxue Fushu Zhongliu Yiyuan, CODEN: ZAZHAF ISSN: 1007-3639. Journal written in Chinese. CAN 147:86596 AN 2007:395164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Although standardized therapy has been widely adapted in clin. practice and results are being improved, effective protocols for truly individualized chemotherapy is still lacking. The anti-tumor activity of different combination regimens on human breast cancer xenograft (MCF-7) transplanted in nude mice and their impacts on the expression of PCNA were investigated, and to evaluate the

value of PCNA as predictive factors for the res. 88 Nude mice with human breast cancer xenograft (MCF-7) were randomly divided into control and 10 chemotherapy groups, and 8 mice were assigned into each group. Among 5 chemotherapy groups, they were treated either i.p. or orally by 5 different combinations of chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) at one-third of LD10 dosage, and another 5 chemotherapy groups were treated at two-third. Control animals were given normal saline i.p. The body wt. of nude mice and transplanted tumor growth were recorded on a regular basis, and tumor growth inhibition was calcd. The pathol. features of the transplanted tumor were studied under the microscope before and after treatment. The expression of PCNA was evaluated by SP immunohistochem. method and flow cytometry. The results show that body wt. and tumor wt. of nude mice treated by two-third LD10 dosage of various chemotherapy combinations were significantly lower than that in the control ( $P < 0.05$ ), and the inhibition rate of tumor growth for the groups we. The results showed that the two-third LD10 dosage of chemotherapy could reflect the anti-tumor effect of various combinations chemotherapy better and more accurately, so this dosage was used for the next study. The expression at PCNA by immunohistochem. studies shows that the expression of PCNA in every chemotherapy group was significantly lower than that of the control ( $P < 0.05$ ).

Moreover, the expressions of PCNA in NP group was significantly lower than that of CMF, CAF, TP and Xeloda group ( $P < 0.05$ ), while TP and Xeloda group was significantly lower than that of CMF and CAF group ( $P < 0.05$ ). FCM anal. shows that FI value of PCNA in every chemotherapy group was significantly lower than that of the control ( $P < 0.05$ ). FI value of PCNA in TP and Xeloda group was significantly lower than that of CMF and CAF group ( $P < 0.05$ ), while NP group a significantly lower than that of CMF group ( $P < 0.05$ ). Relationship between PCNA expression and pathol. response shows that the expression of PCNA was pos. correlated with pathol. therapeutic response of transplanted breast carcinoma ( $r = 0.540$ ,  $P < 0.05$ ). It was concluded that in vivo chemosensitivity testing with two third LD10 dosage of various combinations of chemotherapy cancer could somewhat predict the clin. situations. All of various chemotherapy regimens can decrease the expression of PCNA in breast cancer. The expression of PCNA could perhaps serve as the factor to judge the response to chemotherapy, and play a role in the selection of the kind of chemotherapy to be used in the clinic.

Answer 18:

### Bibliographic Information

**Role of human longevity assurance gene 1 and C18-ceramide in chemotherapy-induced cell death in human head and neck squamous cell carcinomas.** Senkal, Can E.; Ponnusamy, Suriyan; Rossi, Michael J.; Bialewski, Jacek; Sinha, Debijyati; Jiang, James C.; Jazwinski, S. Michal; Hannun, Yusuf A.; Ogretmen, Besim. Departments of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston, SC, USA. *Molecular Cancer Therapeutics* (2007), 6(2), 712-722. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:414436 AN 2007:181853 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In this study, quant. isobologram studies showed that treatment with gemcitabine and doxorubicin, known inducers of ceramide generation, in combination, supra-additively inhibited the growth of human UM-SCC-22A cells in situ. Then, possible involvement of the human homolog of yeast longevity assurance gene 1 (LASS1)/C18-ceramide in chemotherapy-induced cell death in these cells was examd. Gemcitabine/doxorubicin combination treatment resulted in the elevation of mRNA and protein levels of LASS1 and not LASS2-6, which was consistent with a 3.5-fold increase in the endogenous (dihydro)ceramide synthase activity of LASS1 for the generation of C18-ceramide. Importantly, the overexpression of LASS1 (both human and mouse homologs) enhanced the growth-inhibitory effects of gemcitabine/doxorubicin with a concomitant induction of caspase-3 activation. In reciprocal expts., partial inhibition of human LASS1 expression using small interfering RNA (siRNA) prevented cell death by about 50% in response to gemcitabine/doxorubicin. In addn., LASS1, and not LASS5, siRNA modulated the activation of caspase-3 and caspase-9, but not caspase-8, in response to this combination. Treatment with gemcitabine/doxorubicin in combination also resulted in a significant suppression of the head and neck squamous cell carcinoma (HNSCC) tumor growth in severe combined immunodeficiency mice bearing the UM-SCC-22A xenografts. More interestingly, anal. of endogenous ceramide levels in these tumors by liq. chromatog./mass spectroscopy showed that only the levels of C18-ceramide, the main product of LASS1, were elevated significantly (about 7-fold) in response to gemcitabine/doxorubicin when compared with controls. In conclusion, these data suggest an important role for LASS1/C18-ceramide in gemcitabine/doxorubicin-induced cell death via the activation of caspase-9/3 in HNSCC.

Answer 19:

**Bibliographic Information**

**Protectors against doxorubicin-induced cardiotoxicity: flavonoids.** Bast, A.; Kaiserova, H.; Hartog, G. J. M.; Haenen, G. R. M. M.; Vijgh, W. J. F. Department of Pharmacology and Toxicology, Faculty of Medicine, Maastricht University, Maastricht, Neth. *Cell Biology and Toxicology* (2007), 23(1), 39-47. Publisher: Springer, CODEN: CBTOE2 ISSN: 0742-2091. Journal written in English. CAN 146:266654 AN 2006:1293193 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Doxorubicin is a widely used anthracycline anticancer agent. Its use may cause cardiomyopathy: in fact, the development of cumulative dose-related cardiotoxicity forms the major limitation of clin. doxorubicin use. We therefore searched for protective agents that combine iron-chelating and oxygen radical-scavenging properties. Moreover, any novel protector should not interfere with the cytostatic activity of doxorubicin. After extensive *in vitro* screening we found that flavonoids could serve this purpose. In particular 7-mono-hydroxyethylrutoside almost completely protected against the neg. inotropic action of doxorubicin in the elec. paced mouse left atrium model. *In vivo* it gave full protection at 500 mg/kg i.p. against the doxorubicin-induced ST-interval lengthening in the ECG. Moreover, this protector did not influence the antitumor effect of doxorubicin either *in vitro* using the human ovarian cell lines A2780 and OVCAR-3 and the human breast cancer cell line MCF-7 or *in vivo* in A2780 and OVCAR-3 s.c. xenografts in nude mice. Comparison of various iron chelators suggest that iron, in contrast to the general assumption, might not play a crucial role in the oxidative stress-induced toxicity of doxorubicin. Moreover, incubation of vascular endothelial cells with doxorubicin produced overexpression of adhesion mols., which could be inhibited by 7-mono-hydroxyethylrutoside. From a study in human volunteers, we conclude that an i.v. dose of 1500 mg/m<sup>2</sup> of 7-mono-hydroxyethylrutoside is feasible and is safe to be investigated as protection against doxorubicin-induced cardiotoxicity.

Answer 20:

**Bibliographic Information**

**Selective and effective cytotoxicity of folic acid-conjugated cholesteryl pullulan hydrogel nanoparticles complexed with doxorubicin in *in vitro* and *in vivo* studies.** Hidaka, Masaaki; Kanematsu, Takashi; Ushio, Kazutoshi; Sunamoto, Junzo. Department of Transplantation and Digestive Surgery, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki City, Japan. *Journal of Bioactive and Compatible Polymers* (2006), 21(6), 591-602. Publisher: Sage Publications Ltd., CODEN: JBCPEV ISSN: 0883-9115. Journal written in English. CAN 146:107159 AN 2006:1238761 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

We previously reported that cholesteryl pullulan (CHP) derivs. were effective carriers drug delivery systems in targeting cancer cells. We have now synthesized folic acid-conjugated CHP hydrogel nanoparticles (FA-CHP). FA-CHP complexed with the anticancer drug doxorubicin (DOX) show a higher cytotoxicity than CHP complexed with DOX in *in vitro* studies. The expression of a folate receptor (FR) is elevated in many cancers; in this case, confocal image anal. revealed that FA-CHP complexed with DOX exhibited greater cellular uptake than CHP complexed with DOX in human epidermal carcinoma (KB) cells over-expressing surface FR. *In vivo* studies showed that the increase of tumor vol. in a nude mice xenograft model was significantly suppressed. Accordingly, FA-CHP may be an effective vehicle for the delivery of anticancer drugs and has a potential application in the treatment of over-expressing FR solid tumor cells.

Answer 21:

**Bibliographic Information**

**Anticancer effects of amooranin in human colon carcinoma cell line *in vitro* and in nude mice xenografts.** Ramachandran, Cheppail; Nair, P. K. Raveendran; Alamo, Arturo; Cochrane, Curtis Bruce; Escalon, Enrique; Melnick, Steven J. Research Institute, Division of Hematology/Oncology, Miami Children's Hospital, Miami, FL, USA. *International Journal of Cancer* (2006), 119(10),

2443-2454. Publisher: Wiley-Liss, Inc., CODEN: IJCNAA ISSN: 0020-7136. Journal written in English. CAN 145:369467 AN 2006:1086257 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Amooranin (AMR), a natural triterpenoid drug isolated and characterized from *Amoora rohituka* stem bark, is cytotoxic to SW620 human colon carcinoma cell line with an IC<sub>50</sub> value of 2.9 µg/mL. This novel compd. caused depolarization of mitochondrial membrane and decrease of membrane potential, indicating initial signal of apoptosis induction. The percentage of cells with decreased mitochondrial potential ranged from 7.4% at 1 µg/mL to 60.5% at 100 µg/mL AMR. Flow cytometric anal. of apoptosis using Annexin-V-FITC staining showed that the percentage of apoptotic cells ranged from 7.5% at 1 µg/mL to 59.2% at 100 µg/mL AMR. AMR-induced apoptosis was accompanied by redistribution of cytochrome c from mitochondria to cytosol as well as down regulation of Bcl-2 and Bcl-XL proteins in a dose-dependent manner. SW620 human colon carcinoma xenograft mice treated with AMR showed significant redn. in tumor growth rates compared to saline- and doxorubicin-treated groups. The redn. in tumor growth rate was better in xenografts treated with 2 mg/kg AMR than 5 and 10 mg/kg treated mice. The anal. of global gene expression changes induced by AMR in xenograft tumors by microarray hybridization revealed that several genes involved in energy pathways, transport, apoptosis, immune response, nucleic acid metab., protein metab., cell growth and/or maintenance, signal transduction and cell communication, were affected by this natural cancer drug. These results suggest that the anticancer properties of AMR in SW620 human colon carcinoma cell line are mediated through its effects on functional genomics, targeting the apoptotic process.

Answer 22:

### Bibliographic Information

**Vascular Endothelial Growth Factor Overexpression by Soft Tissue Sarcoma Cells: Implications for Tumor Growth, Metastasis, and Chemoresistance.** Zhang, Lianglin; Hannay, Jonathan A. F.; Liu, Juehui; Das, Parimal; Zhan, Maocheng; Nguyen, Theresa; Hicklin, Daniel J.; Yu, Dihua; Pollock, Raphael E.; Lev, Dina. Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Cancer Research* (2006), 66(17), 8770-8778. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 145:289897 AN 2006:899230 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

To better elucidate the role of vascular endothelial growth factor (VEGF)<sub>165</sub> in soft tissue sarcoma (STS) growth, metastasis, and chemoresistance, we generated stably transfected human STS cell lines with VEGF<sub>165</sub> to study the effect of VEGF<sub>165</sub> on STS cells in vitro and the effect of culture medium from these cells on human umbilical vascular endothelial cells. Severe combined immunodeficient mice bearing xenografts of transfected cell lines were used to assess the effect of VEGF overexpression and the effect of VEGF receptor (VEGFR) 2 inhibition on STS growth, metastasis, and response to doxorubicin. VEGF<sub>165</sub>-transfected xenografts formed highly vascular tumors with shorter latency, accelerated growth, enhanced chemoresistance, and increased incidence of pulmonary metastases. Blockade of VEGFR2 signaling using DC101 anti-VEGFR2 monoclonal antibody enhanced doxorubicin chemoresponse; this combined biochemotherapy inhibited tumor growth and decreased pulmonary metastases without overt toxicity. Combined therapy reduced microvessel counts while increasing vessel maturation index. VEGF overexpression did not affect on the sarcoma cells per se; however, conditioned medium from VEGF transfectants caused increased endothelial cell proliferation, migration, and chemoresistance. Addn. of DC101 induced endothelial cell sensitivity to doxorubicin and suppressed the activity of matrix metalloproteinases secreted by endothelial cells. We therefore conclude that VEGF is a crit. determinant of STS growth and metastasis and that STS chemoresistance, in our model, is a process induced by the interplay between STS cells and tumor-assocd. endothelial cells. STS growth and metastasis can be interrupted by combined low-dose doxorubicin and anti-VEGFR2, a strategy that attacks STS-assocd. endothelial cells. In the future, such therapeutic approaches may be useful in treating STS before the development of clin. apparent metastases.

Answer 23:

### Bibliographic Information

**Potentiation of the antitumoral activity of gemcitabine and paclitaxel in combination on human breast cancer cells.** Zupi, Gabriella; Scarsella, Marco; D'Angelo, Carmen; Biroccio, Annamaria; Paoletti, Giancarlo; Lopez, Massimo; Leonetti, Carlo. Experimental Chemotherapy Laboratory, Regina Elena Cancer Institute, Rome, Italy. *Cancer Biology & Therapy* (2005), 4(8), 866-871. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:347983 AN 2006:480435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The purpose of this study was to evaluate the antitumoral activity of different gemcitabine-based combination on an exptl. model of human breast cancer, in order to identify the most effective treatment and to provide a rationale for clin. investigations. To this end, CG5 breast cancer cells were treated in vitro with gemcitabine followed by epirubicin, doxorubicin, docetaxel or paclitaxel. The reversed sequence was also investigated. Results, analyzed by multiple drug effect/combination index (CI) isobologram, demonstrated that the combination gemcitabine/paclitaxel was the most active showing synergism with a CI of about 0.5 in the two sequences employed. Moreover, the synergistic interaction of gemcitabine and paclitaxel was correlated to a block of the cells in the G0/G1 compartment of cell cycle and to an increase of apoptotic cells compared to each drug. Based on these evidences, the antitumoral efficacy of gemcitabine/paclitaxel combination has been studied in vivo. Mice bearing CG5 human breast xenografts treated with paclitaxel and gemcitabine in combination showed a significant higher inhibition of tumor growth (.apprx.70%) compared to that with either agent alone (25%). In conclusion, this study suggests that paclitaxel is the most promising agent for combination protocols with gemcitabine and supports the use of gemcitabine/paclitaxel combination in the clin. management of advanced breast cancer.

Answer 24:

#### Bibliographic Information

**In vivo antitumor efficacy and cardiotoxicity of novel anthracycline ID6105 (11-hydroxy-aclacinomycin X, Hyrubicin).** Ryu, Jung Su; Lee, Hong Sub; Hong, Young-Soo; Lee, Jung Joon; Sohn, Uy Dong; Kim, Tae Yong. Laboratory of Microbiology, Il-dong Pharmaceutical Co., Ltd., Gyonggi-Do, S. Korea. *Cancer Chemotherapy and Pharmacology* (2006), 57(6), 811-818. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:305835 AN 2006:331404 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Hybrid biosynthetic approach produced a new anthracycline ID6105 (11-hydroxyaclacinomycin X, Hyrubicin), which has potent antitumor activities against a broad range of cancer cell lines. Like other anthracyclines, ID6105 has the inhibitory effects on DNA synthesis as well as topoisomerase II. As preclin. studies of ID6105, we investigated ID6105's efficacy on human tumors, and cardiotoxicity. In human tumor xenografts, the ID6105's antitumor effects were greater than other anticancer drugs. ID6105 induced tumor regression in Hep G2 human hepatoma model, and slowed down the tumor growth rates in several tumor models. Doxorubicin-refractory tumors such as PC-3, DU-145, and CX-1 were sensitive to ID6105, and the growth of EKVX, lung cancer, which did not respond to paclitaxel, was also inhibited by ID6105, but tumor mass in CFP, MCF7, and HCT-15 was not reduced by ID6105. The cardiotoxicity of ID6105 has also been assessed in rats. ID6105 did not induce any remarkable histopathol. changes in hearts, and its lipid peroxidn. in rat cardiac muscles did not occur as much as doxorubicin, indicating that the cardiotoxicity of ID6105 is remarkably lower than that of doxorubicin. Taking all into account, our results suggest that ID6105 would be a promising candidate for a novel anthracycline chemotherapeutic agent.

Answer 25:

#### Bibliographic Information

**Determining doxorubicin concentration in nude mice xenograft by fluorescence spectrometry.** Liang, Yongju; Wu, Xingping; Shi, Zhi; Ding, Yan; Chen, Liming; Wang, Xiuwen; Yang, Xiaoping; Fu, Liwu. Cancer Center, Sun Yat-Sen University, Guangzhou, Guangdong Province, Peop. Rep. China. *Zhongguo Linchuang Yaolixue Zazhi* (2005), 21(4), 296-298. Publisher: Beijing Yike

Daxue, Linchuang Yaoli Yanjiuso, CODEN: ZLYZE9 ISSN: 1001-6821. Journal written in Chinese. CAN 145:39784 AN 2006:328043 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The model of the nude mice xenograft with human tumor cells KB and KBv 200 was established. Three hours after injection of different Dox concn. by tail vein the mice were killed, and the xenograft tissues were extd., mashed and resuspended in HCl 0.3 mol·L<sup>-1</sup> in 60% ethanol. Following centrifugation, the supernatant was removed and assayed spectrofluorometrically at  $\lambda_{ex}$  470 nm and  $\lambda_{ex}$  590 nm. The concn. of Dox was calcd. by the std. curve of Dox. The intra-day and inter-day RSD was <6.4% and 5.7% resp. The recovery of Dox from tumor tissues was > 75.9%. The concn. of Dox in KB nude mice xenograft tissues was 2.53-4.54 times of KBv 200. This method is simple, rapid, sensitive and of excellent precision, so suitable for Dox pharmacokinetic studies in xenograft.

Answer 26:

#### Bibliographic Information

**Targeted bioavailability of drugs by triggered release from liposomes.** Ponce, Ana M.; Wright, Alex; Dewhirst, Mark W.; Needham, David. Department of Biomedical Engineering and Department of Mechanical Engineering and Materials Science, Duke University, Durham, NC, USA. *Future Lipidology* (2006), 1(1), 25-34. Publisher: Future Medicine Ltd., CODEN: FLUIBL ISSN: 1746-0875. Journal; General Review written in English. CAN 145:255625 AN 2006:325322 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A review. The temp.-sensitive liposome is now in Phase I human clin. trials. This review will provide an update, recapping earlier work and presenting new data that show unexpected mechanistic features that make this triggered-release system an emerging new paradigm for local drug delivery.

Answer 27:

#### Bibliographic Information

**Accelerator mass spectrometry allows for cellular quantification of doxorubicin at femtomolar concentrations.** DeGregorio, M. W.; Dingley, K. H.; Wurz, G. T.; Ubick, E.; Turteltaub, K. W. Department of Internal Medicine, Division of Hematology and Oncology, Cancer Center, University of California, Davis, Sacramento, CA, USA. *Cancer Chemotherapy and Pharmacology* (2006), 57(3), 335-342. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 144:381285 AN 2006:271794 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Accelerator mass spectrometry (AMS) is a highly sensitive anal. methodol. used to quantify the content of radioisotopes, such as <sup>14</sup>C, in a sample. The primary goals of this work were to demonstrate the utility of AMS in detg. total cellular [<sup>14</sup>C]anthracycline concns. following administration of doxorubicin (DOX) and to develop a sensitive assay that is superior to high performance liq. chromatog. (HPLC) for the quantification of [<sup>14</sup>C]anthracycline at the tumor level. In order to validate the sensitivity of AMS vs. HPLC with fluorescence detection, we performed three studies comparing the cellular accumulation of DOX: one in vitro cell line study, and two in vivo xenograft mouse studies. Using AMS, we quantified cellular [<sup>14</sup>C]anthracycline content up to 4 h following in vitro exposure at concns. ranging from 0.2 pg/mL (345 fM) to 2 µg/mL (3.45 µM) [<sup>14</sup>C]DOX. The results of this study show that, compared to std. fluorescence-based HPLC, the AMS method was over five orders of magnitude more sensitive. Two in vivo studies compared the sensitivity of AMS to HPLC using a nude mouse xenograft model in which breast cancer cells were implanted s.c. After sufficiently large tumors formed, [<sup>14</sup>C]DOX was administered i.v. at two dose levels. Addnl., we tested the AMS method in a nude mouse xenograft model of multidrug resistance (MDR) in which each mouse was implanted with both wild type and MDR+ cells on

opposite flanks. The results of the second and third studies showed that [<sup>14</sup>C]anthracycline concns. were significantly higher in the wild type tumors compared to the MDR+ tumors, consistent with the MDR model. Although this method does not discriminate between parent drug and metabolites, the extreme sensitivity of AMS should facilitate similar studies in humans to establish target site drug delivery and to potentially det. the optimal treatment dose and regimen.

Answer 28:

#### Bibliographic Information

**Discovery and structure-based design of benzodiazepinedione inhibitors of the HDM2:p53 complex.** Grasberger, Bruce L.; Lu, Tianbao; Marugan, Juan Jose; Parks, Daniel J.; Schubert, Carsten; Koblisch, Holly K.; Cummings, Maxwell D.; Leonard, Kristi A.; Raboisson, Pierre; Milkiewicz, Karen L.; Calvo, Raul R.; LaFrance, Louis V.; Donatelli, Robert R.; Maguire, Diane; Carver, Theodore E.; Lattanze, Jennifer; Franks, Carol F.; Zhao, Shuyuan; Ramachandren, Kannan; Deckman, Ingrid C.; Maroney, Anna C. Johnson & Johnson Pharmaceutical Research & Development LLC, Exton, PA, USA. Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006 (2006), MEDI-230. Publisher: American Chemical Society, Washington, D. C CODEN: 69HYEC Conference; Meeting Abstract; Computer Optical Disk written in English. AN 2006:248382 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

HDM2 binds to an  $\alpha$ -helical transactivation domain of p53, inhibiting its tumor suppressive functions. We have used a miniaturized thermal denaturation assay to screen chem. libraries and discover a novel series of benzodiazepinediones that bind to HDM2 and inhibit its assocn. with p53. The X-ray crystal structure of benzodiazepinedione inhibitors bound to HDM2 reveals their  $\alpha$ -helix mimetic properties. This structural information was used in the design and synthesis of compds. with improved cellular activity that, in combination with doxorubicin, decrease tumor growth in a mouse xenograft.

Answer 29:

#### Bibliographic Information

**Anti-cancer effects of bortezomib against chemoresistant neuroblastoma cell lines in vitro and in vivo.** Michaelis, Martin; Fichtner, Iduna; Behrens, Diana; Haider, Wolfram; Rothweiler, Florian; Mack, Andreas; Cinatl, Jaroslav; Doerr, Hans Wilhelm; Cinatl, Jindrich, Jr. Institut fuer Medizinische Virologie, Klinikum der Johann Wolfgang Goethe-Universitaet, Frankfurt am Main, Germany. International Journal of Oncology (2006), 28(2), 439-446. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:95897 AN 2006:150396 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The proteasome inhibitor bortezomib (Velcade) was recently approved for the treatment of therapy-refractive multiple myeloma and is under investigation for numerous other types of cancer. A phase I clin. trial in pediatric patients resulted in tolerable toxicity. Since the emergence of chemoresistance represents one of the major drawbacks in cancer therapy, we investigated the influence of bortezomib on multi-drug resistant human neuroblastoma cell lines characterized by P-glycoprotein expression and p53 mutation. Nanomolar concns. of bortezomib inhibited the cell cycle and induced apoptosis in chemosensitive as well as in chemoresistant cell lines. In vivo growth of chemosensitive and chemoresistant neuroblastoma cell lines was inhibited to a similar extent. In addn., bortezomib inhibited vessel formation in neuroblastoma xenografts. These findings and the favorable toxicity profile of bortezomib in children make it reasonable to further pursue addnl. development of the drug for the treatment of neuroblastoma and other pediatric solid tumors.

Answer 30:

#### Bibliographic Information

**Antitumor activity of doxorubicin encapsulated in hexadecylphosphocholine (HePC) liposomes against human xenografts on scid mice.** Papagiannaros, A.; Hatziantoniou, S.; Lelong-Rebel, I. H.; Papaioannou, G. Th.; Dimas, K.; Demetzos, C. Department of Pharmaceutical Technology, School of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece. *In Vivo* (2006), 20(1), 129-135. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 145:39908 AN 2006:114726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Doxorubicin was encapsulated into liposomes composed of hexadecylphosphocholine:egg yolk phosphatidylcholine:stearylamine (HePC:EPC:SA) 10:10:0.1 (molar ratio) (1) and EPC:SA 10:0.1 (molar ratio) (2). Liposomal formulations 1 and 2, as well as free doxorubicin and free HePC, were tested in vitro against HCT116 human colon cancer cell lines and peripheral blood mononuclear cells (PBMCs) obtained from healthy donors, using the sulforodamine B assay. The activity of doxorubicin was retained or slightly improved when entrapped into liposomes 1 and 2, while liposomal formulation 1 incorporating doxorubicin was found to be less toxic against normal cells. The liposomes were tested in vivo against human colon cancer xenografts in scid mice. The antitumor activities of liposomes 1 and 2 were statistically similar to that of free doxorubicin, but their toxicity was significantly lower. Based on these results, the combination of HePC and doxorubicin in one liposomal formulation may be justified for further evaluation.

Answer 31:

#### Bibliographic Information

**Optimal classes of chemotherapeutic agents sensitized by specific small-molecule inhibitors of Akt in vitro and in vivo.**

Shi, Yan; Liu, Xuesong; Han, Edward K.; Guan, Ran; Shoemaker, Alexander R.; Oleksijew, Anatol; Woods, Keith W.; Fisher, John P.; Klinghofer, Vered; Lasko, Loren; McGonigal, Thomas; Li, Qun; Rosenberg, Saul H.; Giranda, Vincent L.; Luo, Yan. Departments of R47S, Abbott Laboratories, Abbott Park, IL, USA. *Neoplasia* (Ann Arbor, MI, United States) (2005), 7(11), 992-1000. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 145:444 AN 2006:84249 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Akt is a serine/threonine kinase that transduces survival signals from survival/growth factors. Deregulation and signal imbalance in cancer cells make them prone to apoptosis. Upregulation or activation of Akt to aid the survival of cancer cells is a common theme in human malignancies. We have developed small-mol. Akt inhibitors that are potent and specific. These Akt inhibitors can inhibit Akt activity and block phosphorylation by Akt on multiple downstream targets in cells. Synergy in apoptosis induction was obsd. when Akt inhibitors were combined with doxorubicin or camptothecin. Akt inhibitor-induced enhancement of topoisomerase inhibitor cytotoxicity was also evident in long-term cell survival assay. Synergy with paclitaxel in apoptosis induction was evident in cells pretreated with paclitaxel, and enhancement of tumor delay by paclitaxel was demonstrated through cotreatment with Akt inhibitor Compd. A (A-443654). Combination with other classes of chemotherapeutic agents did not yield any enhancement of cytotoxicity. These findings provide important guidance in selecting appropriate classes of chemotherapeutic agents for combination with Akt inhibitors in cancer treatment.

Answer 32:

#### Bibliographic Information

**Cetuximab and Irinotecan Interact Synergistically to Inhibit the Growth of Orthotopic Anaplastic Thyroid Carcinoma Xenografts in Nude Mice.**

Kim, Seungwon; Prichard, Christopher N.; Younes, Maher N.; Yazici, Yasemin D.; Jasser, Samar A.; Bekele, B. Nebiyou; Myers, Jeffrey N. Departments of Head and Neck Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2006), 12(2), 600-607. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 145:55478 AN 2006:63632 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Purpose:** Anaplastic thyroid carcinoma (ATC) remains one of the most lethal known human cancers. Targeted mol. therapy with cetuximab, a monoclonal antibody against epidermal growth factor receptor, offers new treatment potentials for patient with ATC. Cetuximab has also been reported to have synergistic effects when combined with irinotecan, a topoisomerase inhibitor. Therefore, we hypothesized that cetuximab and irinotecan would be effective in inhibiting the growth and progression of ATC in a murine orthotopic model. **Exptl. Design:** The in vitro antiproliferative effects of cetuximab and irinotecan on ATC cell line ARO were examd. We also studied the in vivo effects of cetuximab and irinotecan on the growth, invasion, and metastasis of orthotopic ATC tumors in nude mice. The in vivo antitumor efficacy of cetuximab/irinotecan combination was also compared with that of doxorubicin. **Results:** Cetuximab alone did not show any antiproliferative or proapoptotic effect on this cell line. However, when combined with irinotecan, cetuximab potentiated the in vitro antiproliferative and proapoptotic effect of irinotecan. Cetuximab, irinotecan, and cetuximab/irinotecan combination resulted in 77%, 79%, and 93% in vivo inhibition of tumor growth, resp. Incidences of lymph node metastasis, laryngeal invasion, and tumor microvessel d. were also significantly decreased in these treatment groups. Furthermore, the cetuximab/irinotecan combination was significantly more effective than doxorubicin in inhibiting the growth of orthotopic ATC xenografts. **Conclusions:** Combination therapy with cetuximab/irinotecan inhibits the growth and progression of orthotopic ATC xenografts in nude mice. Given the lack of curative options for patients with ATC, combination therapy with cetuximab and irinotecan treatment warrants further study.

Answer 33:

**Bibliographic Information**

**The Distribution of the Anticancer Drug Doxorubicin in Relation to Blood Vessels in Solid Tumors.** Primeau, Andrew J.; Rendon, Augusto; Hedley, David; Lilge, Lothar; Tannock, Ian F. Divisions of Applied Molecular Oncology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Can. *Clinical Cancer Research* (2005), 11(24, Pt. 1), 8782-8788. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:460403 AN 2005:1318366 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Purpose:** Anticancer drugs gain access to solid tumors via the circulatory system and must penetrate the tissue to kill cancer cells. Here, we study the distribution of doxorubicin in relation to blood vessels and regions of hypoxia in solid tumors of mice. **Exptl. Design:** The distribution of doxorubicin was quantified by immunofluorescence in relation to blood vessels (recognized by CD31) of murine 16C and EMT6 tumors and human prostate cancer PC-3 xenografts. Hypoxic regions were identified by injection of EF5. **Results:** The concn. of doxorubicin decreases exponentially with distance from tumor blood vessels, decreasing to half its perivascular concn. at a distance of about 40 to 50  $\mu\text{m}$ . The mean distance from blood vessels to regions of hypoxia is 90 to 140  $\mu\text{m}$  in these tumors. Many viable tumor cells are not exposed to detectable concns. of drug following a single injection. **Conclusions:** Limited distribution of doxorubicin in solid tumors is an important and neglected cause of clin. resistance that is amenable to modification. The technique described here can be adapted to studying the distribution of other drugs within solid tumors and the effect of strategies to modify their distribution.

Answer 34:

**Bibliographic Information**

**Urease-induced alkalization of extracellular pH and its antitumor activity in human breast and lung cancers.** Wong, Wah Yau; DeLuca, Carl I.; Tian, Baomin; Wilson, Iain; Molund, Sharon; Warriar, Nalini; Govindan, Manjapra V.; Segal, Donald; Chao, Heman. Sensium Technologies Inc., Edmonton, AB, Can. *Journal of Experimental Therapeutics and Oncology* (2005), 5(2), 93-99. Publisher: Old City Publishing, CODEN: JETOFX ISSN: 1359-4117. Journal written in English. CAN 144:324313 AN 2005:1314419 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Jack bean urease catalyzes the decompn. of urea into ammonia, which in turn increases the pH of the surrounding medium. Based on these two properties, we have investigated the antitumor effects of urease in vitro and in vivo on human lung and breast cancer cell lines either by the enzyme itself or in combination with other chemotherapeutic drugs. First, through the generation of toxic ammonia, urease exerted direct cytotoxicity on A549 and MDA-MB-231 tumor cells with LC50 of 0.22 and 0.45 U/mL, resp. The cytotoxic effects could effectively be blocked using the reversible urease inhibitor acetohydroxamic acid. Complete protection was obsd. at dose  $\geq 2$  mM. In addn., nude mouse xenograft models demonstrated that intratumoral urease injections (1 - 10 U/dose) inhibited A549 and MCF-7 tumor growth in vivo. Second, when combined with weak-base anticancer drugs, urease provided indirect antitumor effects via pH augmentation. Alkalinization of extracellular pH by urease (2 U/mL) and urea ( $\geq 2$  mM) was found to enhance the antitumor efficacy of doxorubicin (50  $\mu$ M) and vinblastine (100  $\mu$ M) significantly.

Answer 35:

### Bibliographic Information

**Targeted therapy against Bcl-2-related proteins in breast cancer cells.** Emi, Manabu; Kim, Ryungsa; Tanabe, Kazuaki; Uchida, Yoko; Toge, Tetsuya. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. *Breast Cancer Research* (2005), 7(6), R940-R952. Publisher: BioMed Central Ltd., CODEN: BRCRFS ISSN: 1465-542X. <http://breast-cancer-research.com/content/pdf/bcr1323.pdf> Journal; Online Computer File written in English. CAN 144:403854 AN 2005:1215059 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Introduction Bcl-2 and Bcl-xL confer resistance to apoptosis, thereby reducing the effectiveness of chemotherapy. We examd. the relationship between the expression of Bcl-2 and Bcl-xL and chemosensitivity of breast cancer cells, with the aim of developing specific targeted therapy. Methods Four human breast cancer cell lines were examd., and the effects of antisense (AS) Bcl-2 and AS Bcl-xL phosphorothioate oligodeoxynucleotides (ODNs) on chemosensitivity were tested in vitro and in vivo. Chemosensitivity was evaluated by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay, and the antitumor effect was assessed in vivo by the success of xenograft transplantation into athymic mice. Results Treatment with AS Bcl-2 and Bcl-xL ODNs resulted in a sequence-specific decrease in protein expression, compared with controls. Treatment of BT-474, ZR-75-1, and MDA-MB-231 cells with AS Bcl-2 increased chemosensitivity to doxorubicin (DOX), mitomycin C (MMC), paclitaxel (TXL), and docetaxel (TXT). Transfection of the Bcl-2 gene into MDA-MB-453 cells decreased sensitivity to DOX and MMC. Treatment of MDA-MB-231, BT-474, and ZR-75-1 cells with AS Bcl-xL increased chemosensitivity to DOX, MMC and taxanes to a smaller extent than AS Bcl-2. This occurred in the setting of increased Bax and cleaved poly(ADP-ribose) polymerase, as well as decreased Bcl-2 and pAkt. AS Bcl-2 ODNs induced splenomegaly in assocn. with increased serum IL-12, which was attenuated by methylation of the CpG motifs of AS Bcl-2; however, methylated CpG failed to negate the increased antitumor effect of AS Bcl-2. Bcl-2 and Bcl-xL, to a smaller extent, are major determinants of chemosensitivity in breast cancer cells. Conclusion Targeted therapy against Bcl-2 protein with the use of AS ODNs might enhance the effects of chemotherapy in patients with breast cancer.

Answer 36:

### Bibliographic Information

**Effects of Exercise Training on Antitumor Efficacy of Doxorubicin in MDA-MB-231 Breast Cancer Xenografts.** Jones, Lee W.; Eves, Neil D.; Courneya, Kerry S.; Chiu, Brian K.; Baracos, Vickie E.; Hanson, John; Johnson, Lorelei; Mackey, John R. Department of Medicine, Duke University Medical Center, Durham, NC, USA. *Clinical Cancer Research* (2005), 11(18), 6695-6698. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:452318 AN 2005:1002329 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Purpose: Exercise is becoming readily accepted as a beneficial adjunct therapy to maintain or enhance quality of life in breast cancer patients undergoing adjuvant chemotherapy. An essential precursor to these studies is to investigate whether exercise modulates the

antitumor efficacy of chemotherapeutic agents. Exptl. Design: Athymic female mice were transplanted with MDA-MB-231 breast xenografts and randomly assigned to one of four groups (n = 21 per group): (a) control, (b) exercise-only, (c) doxorubicin-only, or (d) exercise + doxorubicin. Exercise groups performed progressive treadmill running up to 18 m/min at 0% grade for 45 min, 5 d/wk for 8 wk. Results: Tumor growth delay was significantly longer in the doxorubicin-only and exercise + doxorubicin groups compared with the control (median 42 vs. 25 days, P = 0.0082; 36 vs. 25 days, P = 0.029, resp.) and exercise-only groups (median 42 vs. 25 days, P = 0.029; 36 vs. 25 days, P = 0.080, resp.). There was no significant difference between the doxorubicin-only and exercise + doxorubicin groups (median 42 vs. 36 days, P = 0.33), suggesting that moderate intensity exercise does not significantly influence doxorubicin-induced tumor growth delay. Conclusion: These studies are essential to fully understand the safety and application of exercise as a supportive intervention in cancer control.

Answer 37:

#### Bibliographic Information

**Doxorubicin modulates telomerase activity in Ewing's sarcoma in vitro and in vivo.** Lanvers-Kaminsky, Claudia; Winter, Barbara; Kolling, Susanne; Frodermann, Bernd; Braun, Yvonne; Schaefer, Karl-Ludwig; Diallo, Raihanatou; Koenemann, Stephan; Wai, Daniel; Willich, Normann; Poremba, Christopher; Schuck, Andreas. Department of Paediatric Haematology and Oncology, University Children's Hospital, Germany. *Oncology Reports* (2005), 14(3), 751-758. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 144:16554 AN 2005:995034 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Since most tumors escape replicative senescence by re-activation of the enzyme telomerase, telomerase is a promising target in the treatment of cancer and a promising marker for diagnosis and therapeutic response. We evaluated the effects of doxorubicin, one of the most active drugs in the treatment of Ewing's sarcoma, on telomerase in the human Ewing's sarcoma cell line STA-ET-1 in vitro and in STA-ET-1 xenografts in vivo. Telomerase activity (TA) was examd. by TRAP-assay and real-time PCR. Real-time PCR was also used to quantify the mRNA expression of the catalytic subunit of telomerase (hTERT). In vitro growth inhibition was detd. by the MTT-assay. Tumor xenografts were analyzed for tumor vol., apoptosis, necrosis, and proliferation. Doxorubicin concns. that inhibited in vitro growth of STA-ET-1 by 50% compared to untreated controls ranged between 0.14  $\mu$ M after 24 h and 0.01  $\mu$ M after 72 h. Compared to untreated controls doxorubicin reduced TA in STA-ET-1 at toxic concns., but increased TA at non-toxic concns. In comparison with untreated xenografts, TA was reduced to 65% and hTERT expression dropped to 25% within 72 h in xenografts treated with 17.5 mg/kg doxorubicin i.p.; both recovered to initial values after 264 h. The rate of proliferating cells dropped to 70% within 96 h and increased thereafter. The highest rates of necrosis and apoptosis were seen after 96 h. HTERT expression co-varied significantly with proliferation but not with TA, apoptosis, and necrosis. No correlation was obsd. between TA, proliferation, apoptosis and necrosis. The results suggest doxorubicin induces down regulation of hTERT gene expression that at least in part modulates TA in these tumors.

Answer 38:

#### Bibliographic Information

**In vitro and in vivo reversal of cancer cell multidrug resistance by 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone.** Qian, F.; Ye, C. L.; Wei, D. Z.; Lu, Y. H.; Yang, S. L. State Key Laboratory of Bioreactor Engineering, New World Institute of Biotechnology, East China University of Science and Technology, Shanghai, Peop. Rep. China. *Journal of Chemotherapy* (Firenze, Italy) (2005), 17(3), 309-314. Publisher: E.S.I.F.T. srl, CODEN: JCHEEU ISSN: 1120-009X. Journal written in English. CAN 143:241534 AN 2005:779195 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC) isolated from the buds of *Cleistocalyx operculatus*, was investigated for its reversal effects on cancer cell multidrug resistance. DMC potentiated the cytotoxicity of the chemotherapeutic agent doxorubicin to drug-resistant KB-A1 cells. When 5  $\mu$ M DMC was present simultaneously with doxorubicin, the IC<sub>50</sub> of DOX on KB-A1 cells decreased

from  $13.9 \pm 0.7 \mu\text{g/mL}$  to  $3.6 \pm 0.7 \mu\text{g/mL}$ . A human carcinoma xenograft model was established with the KB-A1 cell line. DMC could sensitize the tumors to doxorubicin as indicated by a considerable redn. in tumor wt. DMC increased the intracellular accumulation of doxorubicin in KB-A1 cells. When KB-A1 cells were exposed to  $10 \mu\text{g/mL}$  doxorubicin combined with 5, 10, 20  $\mu\text{M}$  DMC for 4 h, the intracellular concns. of doxorubicin were increased 1.4-, 1.8-, 3.1-fold, resp., in comparison with doxorubicin alone treatment. All results indicated that DMC had reversal effects on the multidrug resistance phenotype.

Answer 39:

#### Bibliographic Information

**Anti-CD74 Antibody-Doxorubicin Conjugate, IMMU-110, in a Human Multiple Myeloma Xenograft and in Monkeys.** Sapa, Puja; Stein, Rhona; Pickett, Jennifer; Qu, Zhengxing; Govindan, Serengulam V.; Cardillo, Thomas M.; Hansen, Hans J.; Horak, Ivan D.; Griffiths, Gary L.; Goldenberg, David M. Immunomedics, Inc., Morris Plains, NJ, USA. *Clinical Cancer Research* (2005), 11(14), 5257-5264. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:399050 AN 2005:629986 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Purpose: IMMU-110 is a drug immunoconjugate composed of doxorubicin conjugated to the humanized anti-CD74 monoclonal antibody, hLL1, at a doxorubicin/monoclonal antibody ratio of .apprx.8:1 (mol/mol). CD74 is a rapidly internalizing mol. assocd. with HLA-DR, which has high expression by several tumor types. Here, we describe safety evaluations of IMMU-110 in mice and monkeys as well as efficacy studies in a xenograft model of the human multiple myeloma cell line, MC/CAR. Exptl. Design: In vitro binding of IMMU-110 was detd. by a cell-based ELISA and cytotoxicity of IMMU-110 assayed with a tetrazolium assay. Pharmacokinetics and biodistribution of radiolabeled IMMU-110 were examd. in tumor-free BALB/c mice, and the therapeutic effectiveness was evaluated in severe combined immunodeficient mice bearing MC/CAR cells. Acute toxicity of IMMU-110 was studied in CD74-pos. cynomolgus monkeys (*Macaca fascicularis*). Results: In vitro, IMMU-110 specifically binds to CD74 and is cytotoxic against MC/CAR cells. In vivo, IMMU-110 displayed a pharmacokinetic and biodistribution profile identical to that of unconjugated hLL1 monoclonal antibody, except for higher kidney uptake. Treatment with a single dose of IMMU-110 as low as 50  $\mu\text{g}$  antibody/mouse (or 1.4  $\mu\text{g}$  doxorubicin/mouse), 5 days postinjection of the multiple myeloma cells, resulted in cure of most mice. In mice, no host toxicity of IMMU-110 was obsd. at the highest protein dose tested (125 mg/kg). In cynomolgus monkeys, bone marrow toxicity was obsd. at 30 and 90 mg/kg doses. Conclusions: The excellent safety and efficacy profile of IMMU-110 supports clin. testing of this immunoconjugate in the treatment of CD74-pos. B-cell malignancies.

Answer 40:

#### Bibliographic Information

**Efficient elimination of B-lineage lymphomas by anti-CD20-auristatin conjugates. [Erratum to document cited in CA142:273558].** Law, Che-Leung; Cervený, Charles G.; Gordon, Kristine A.; Klussman, Kerry; Mixan, Bruce J.; Chace, Dana F.; Meyer, Damon L.; Doronina, Svetlana O.; Siegall, Clay B.; Francisco, Joseph A.; Senter, Peter D.; Wahl, Alan F. Seattle Genetics, Inc., Bothell, WA, USA. *Clinical Cancer Research* (2005), 11(10), 3969. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:339085 AN 2005:604390 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Figure 6 lacked symbol legends; the correct figure is given.

Answer 41:

#### Bibliographic Information

**Desferal inhibits breast tumor growth and does not interfere with the tumoricidal activity of doxorubicin.** Hoke, Eileen M.; Maylock, Caroline A.; Shacter, Emily. Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. *Free Radical Biology & Medicine* (2005), 39(3), 403-411. Publisher: Elsevier, CODEN: FRBMEH ISSN: 0891-5849. Journal written in English. CAN 143:241492 AN 2005:581712 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Desferal is a clin. approved iron chelator used to treat iron overload. Doxorubicin is an anthracycline cancer chemotherapy drug used in the treatment of breast cancer. It can undergo redox cycling in the presence of iron to produce reactive oxygen species. The oxidant-generating activity of doxorubicin is thought to be responsible for the cardiotoxic side effects of the drug, but it is unclear whether it is also required for its antitumor activity. To test whether an iron-chelating antioxidant would interfere with the tumor-killing activity of doxorubicin, nude mice were transplanted with xenografts of human breast cancer MDA-MB 231 cells and then treated with doxorubicin and/or desferal. Not only did desferal not interfere with the antitumor activity of doxorubicin, it inhibited tumor growth on its own. In vitro studies confirmed that desferal inhibits breast tumor growth. However, it did not induce apoptosis, nor did it induce cell cycle arrest. Instead, desferal caused cytostasis, apparently through iron depletion. The cytostatic activity of desferal was partially ameliorated by pretreatment with iron-satd. transferrin, and transferrin receptor expression on breast cancer cells nearly doubled after exposure to desferal. In contrast to its effect on tumor cells, desferal did not inhibit growth of normal breast epithelial cells. The data indicate that the antitumor activity of doxorubicin is not dependent on iron-mediated ROS prodn. Furthermore, desferal may have utility as an adjunctive chemotherapy due to its ability to inhibit breast tumor growth and cardiotoxic side effects without compromising the tumor-killing activity of an anthracycline chemotherapy drug.

Answer 42:

#### Bibliographic Information

**Hyaluronidase induces a transcapillary pressure gradient and improves the distribution and uptake of liposomal doxorubicin (Caelyx) in human osteosarcoma xenografts.** Eikenes, L.; Tari, M.; Tufto, I.; Bruland, O. S.; de Lange Davies, C. Department of Physics, The Norwegian University of Science and Technology, Trondheim, Norway. *British Journal of Cancer* (2005), 93(1), 81-88. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 144:163615 AN 2005:579155 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Liposomal drug delivery enhances the tumor selective localization and may improve the uptake compared to free drug. However, the drug distribution within the tumor tissue may still be heterogeneous. Degrdn. of the extracellular matrix is assumed to improve the uptake and penetration of drugs. The effect of the ECM-degrading enzyme hyaluronidase on interstitial fluid pressure and microvascular pressure were measured in human osteosarcoma xenografts by the wick-in-needle and micropipette technique, resp. The tumor uptake and distribution of liposomal doxorubicin were studied on tumor sections by confocal laser scanning microscopy. The drugs were injected i.v. 1 h after the hyaluronidase pretreatment. Intratumoral injection of hyaluronidase reduced interstitial fluid pressure in a nonlinear dose-dependent manner. Maximum interstitial fluid pressure redn. of approx. 50% was found after injection of 1500 U hyaluronidase. Neither intratumoral nor i.v. injection of hyaluronidase induced any changes in the microvascular pressure. Thus, hyaluronidase induced a transcapillary pressure gradient, resulting in a four-fold increase in the tumor uptake and improving the distribution of the liposomal doxorubicin. Hyaluronidase reduces a major barrier for drug delivery by inducing a transcapillary pressure gradient, and administration of hyaluronidase adjuvant with liposomal doxorubicin may thus improve the therapeutic outcome.

Answer 43:

#### Bibliographic Information

**Trastuzumab and Liposomal Doxorubicin in the Treatment of MCF-7 Xenograft Tumor-Bearing Mice: Combination Does Not Affect Drug Serum Levels.** Waterhouse, Dawn N.; Denyssevych, Tetyana; Hudon, Norma; Chia, Stephen; Gelmon, Karen A.; Bally, Marcel B. BC Cancer Agency, USA. *Pharmaceutical Research* (2005), 22(6), 915-922. Publisher: Springer, CODEN:

PHREEB ISSN: 0724-8741. Journal written in English. CAN 143:241449 AN 2005:506482 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose** We assessed the combination of doxorubicin or liposomal doxorubicin with trastuzumab for alterations in peak serum drug levels, as these agents are increasingly being paired in the treatment of aggressive breast cancer. We hypothesized that trastuzumab would exhibit a slower rate of elimination from the serum when in combination with liposomal doxorubicin based on the known effects of liposomal doxorubicin on phagocytic cells of the mononuclear phagocyte system (MPS), which are responsible in part for the uptake and degrdn. of antibodies. **Methods** Doxorubicin and trastuzumab serum levels were assessed following injection of free doxorubicin, liposomal doxorubicin, or trastuzumab into female RAG2-M mice bearing s.c. MCF-7HER-2 tumors. The effects of combination drug treatment on tumor growth were compared to single-agent treatment. **Results** Peak serum trastuzumab levels were not altered as a result of addn. of doxorubicin therapy, nor were doxorubicin levels altered over 24 h as a result of coadministration of trastuzumab. Liposomal doxorubicin administration did result in serum doxorubicin levels 200- to 1000-fold higher than with injection of free doxorubicin. **Conclusions** For the specific combination of trastuzumab with doxorubicin, either in free or liposomal form, coadministered in mice, there was no impact of one drug on the other in terms of peak serum drug levels or efficacy.

Answer 44:

### Bibliographic Information

**Specific occlusion of murine and human tumor vasculature by VCAM-1-targeted recombinant fusion proteins.** Dienst, Ariane; Grunow, Andrea; Unruh, Maike; Rabausch, Berit; Noer, Jacques E.; Fries, Jochen W. U.; Gottstein, Claudia. Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany. *Journal of the National Cancer Institute* (2005), 97(10), 733-747. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 143:265160 AN 2005:440036 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The tumor vasculature is increasingly recognized as a target for cancer therapy. The authors developed and evaluated recombinant fusion proteins targeting the coagulation-inducing protein sol. tissue factor (sTF) to the luminal tumor endothelial antigen vascular cell adhesion mol. 1 (VCAM-1, CD106). The authors generated fusion proteins consisting of sTF fused to antibody fragments directed against mouse or human VCAM-1 and characterized them in vitro by flow cytometry, surface plasmon resonance, and two-stage coagulation assays. Their therapeutic effects were tested in three human xenograft tumor models: L540rec Hodgkin lymphoma, Colo677 small-cell lung carcinoma, and Colo677/HDMEC small-cell lung carcinoma with human vasculature. Toxicity was analyzed by histol. examn. of organs and detn. of lab. blood parameters. The fusion proteins bound VCAM-1 with nanomolar affinities and had the same coagulation activity as an sTF std. Xenograft tumor-bearing mice treated with fusion protein (FP) alone or in combination with lipopolysaccharide (FP/L) or doxorubicin (FP/D) exhibited tumor-selective necrosis (L540rec tumors: 74% tumor necrosis [95% confidence interval {CI} = 55% to 93%] with FP/L vs. 13% tumor necrosis [95% CI = 4% to 22%] with vehicle; Colo677 tumors: 26% [95% CI = 16% to 36%] with FP vs. 8% [95% CI = 2% to 14%] with vehicle); tumor growth delay (Colo677/HDMEC: mean tumor wts. after 3 days = 42 mg in FP-treated mice vs. 71 mg in vehicle-treated mice, difference = 29 mg, 95% CI = 8 to 100, Mann-Whitney); and some tumor regressions (one of seven FP-treated Colo677 tumor-bearing mice and two of seven FP/D-treated mice). The fusion protein was well tolerated. Recombinant tissue factor-based fusion proteins directed against an intraluminal tumor endothelial cell marker induce tumor-selective intravascular coagulation, tumor tissue necrosis, and tumor growth delay.

Answer 45:

### Bibliographic Information

**Matrix metalloproteinase-activated doxorubicin prodrugs inhibit HT1080 xenograft growth better than doxorubicin with less toxicity.** Albright, Charles F.; Graciani, Nilsa; Han, Wei; Yue, Eddy; Stein, Ross; Lai, Zhihong; Diamond, Melody; Dowling, Randine; Grimminger, Lisa; Zhang, Shu-Yun; Behrens, Davette; Musselman, Amy; Bruckner, Robert; Zhang, Mingzhu; Jiang, Xiang; Hu, Daniel;

Higley, Anne; DiMeo, Susan; Rafalski, Maria; Mandlekar, Sandya; Car, Bruce; Yeleswaram, Swamy; Stern, Andrew; Copeland, Robert A.; Combs, Andrew; Seitz, Steve P.; Trainor, George L.; Taub, Rebecca; Huang, Pearl; Oliff, Allen. Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA. *Molecular Cancer Therapeutics* (2005), 4(5), 751-760. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 143:186276 AN 2005:418732 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Matrix metalloproteinase (MMP)-activated prodrugs were formed by coupling MMP-cleavable peptides to doxorubicin. The resulting conjugates were excellent in vitro substrates for MMP-2, -9, and -14. HT1080, a fibrosarcoma cell line, was used as a model system to test these prodrugs because these cells, like tumor stromal fibroblasts, expressed several MMPs. In cultured HT1080 cells, simple MMP-cleavable peptides were primarily metabolized by neprilysin, a membrane-bound metalloproteinase. MMP-selective metab. in cultured HT1080 cells was obtained by designing conjugates that were good MMP substrates but poor neprilysin substrates. To det. how conjugates were metabolized in animals, MMP-selective conjugates were given to mice with HT1080 xenografts and the distribution of doxorubicin was detd. These studies showed that MMP-selective conjugates were preferentially metabolized in HT1080 xenografts, relative to heart and plasma, leading to 10-fold increases in the tumor/heart ratio of doxorubicin. The doxorubicin deposited by a MMP-selective prodrug, compd. 6, was more effective than doxorubicin at reducing HT1080 xenograft growth. In particular, compd. 6 cured 8 of 10 mice with HT1080 xenografts at doses below the max. tolerated dose, whereas doxorubicin cured 2 of 20 mice at its max. tolerated dose. Compd. 6 was less toxic than doxorubicin at this efficacious dose because mice treated with compd. 6 had no detectable changes in body wt. or reticulocytes, a marker for marrow toxicity. Hence, MMP-activated doxorubicin prodrugs have a much higher therapeutic index than doxorubicin using HT1080 xenografts as a preclin. model.

Answer 46:

### Bibliographic Information

**Role of lipid peroxidation and antioxidant enzymes in omega 3 fatty acids induced suppression of breast cancer xenograft growth in mice.** Hardman, W. Elaine; Munoz, Jesus, Jr.; Cameron, Ivan L. Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA. *Cancer Cell International* (2002), 2 No pp. given. Publisher: BioMed Central Ltd., CODEN: CCIACC ISSN: 1475-2867. <http://www.cancerci.com/content/pdf/1475-2867-2-10.pdf> Journal; Online Computer File written in English. CAN 143:132445 AN 2005:342170 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Background: Supplementing mice with high levels of dietary n-3 polyunsatd. fatty acids (PUFAs) increases the n-3 PUFAs in cell membranes, increases the susceptibility of the cells for lipid peroxidn. (LPO) and decreases the growth rate of mammary and other tumors. However, the results of an earlier study indicated that a factor in addn. to LPO was involved in the redn. in tumor growth in n-3 PUFAs fed mice. Athymic mice bearing MDA-MB-231 human breast carcinoma xenografts, were fed fish oil conc. (FOC) or control diets, with and without supplemental Vitamin E (2000 IU /kg diet) and were sacrificed both before and after doxorubicin (DOX) treatment to evaluate factors involved in tumor growth suppression. Results: Prior to DOX, basal LPO in the tumor of 3% FOC fed mice was slightly higher than in the control fed mice and was decreased in mice consuming FOC with vitamin E. Vitamin E suppressed the DOX induced increase in LPO in the tumors of control mice, however, vitamin E was not sufficient to suppress a DOX induced increase in LPO in the tumors of FOC fed mice. The mean growth rate of tumors of FOC fed mice was significantly less than the mean growth rate of the tumors of control mice. Multiple regression analyses indicated that suppression of glutathione peroxidase (GPX) activity by FOC prior to DOX therapy was more important than increased LPO as an explanation of tumor growth suppression. Tumor induced cachexia was decreased in mice consuming FOC. Conclusions: It appears that the increased sensitivity to DOX was related to an FOC induced redn. in GPX activity. FOC reduced tumor induced cachexia.

Answer 47:

### Bibliographic Information

**Doxorubicin increases the effectiveness of Apo2L/TRAIL for tumor growth inhibition of prostate cancer xenografts.**

El-Zawahry, Ahmed M.; McKillop, John; Voelkel-Johnson, Christina. Department of Microbiology & Immunology, Medical University of South Carolina, Charleston, SC, USA. BMC Cancer (2005), 5 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. <http://www.biomedcentral.com/content/pdf/1471-2407-5-2.pdf> Journal; Online Computer File written in English. CAN 142:366922 AN 2005:138988 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Background** Prostate cancer is a significant health problem among American men. Treatment strategies for androgen-independent cancer are currently not available. Tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) is a death receptor ligand that can induce apoptosis in a variety of cancer cell lines, including androgen-independent PC3 prostate carcinoma cells. In vitro, TRAIL-mediated apoptosis of prostate cancer cell lines can be enhanced by doxorubicin and correlates with the downregulation of the anti-apoptotic protein c-FLIP. This study evaluated the effects of doxorubicin on c-FLIP expression and tumor growth in combination with Apo2L/TRAIL in a xenograft model. **Methods** In vitro cytotoxic effects of TRAIL were measured using a MTS-based viability assay. For in vivo studies, PC3 prostate carcinoma cells were grown s.c. in athymic nude mice and tumor growth was measured following treatment with doxorubicin and/or Apo2L/TRAIL. C-FLIP expression was detd. by western blot anal. Apoptosis in xenografts was detected using TUNEL. Statistical anal. was performed using the student t-test. **Results** In vitro expts. show that PC3 cells are partially susceptible to Apo2L/TRAIL and that susceptibility is enhanced by doxorubicin. In mice, doxorubicin did not significantly affect the growth of PC3 xenografts but reduced c-FLIP expression in tumors. Expression of c-FLIP in mouse heart was decreased only at the high doxorubicin concn. (8 mg/kg). Combination of doxorubicin with Apo2L/TRAIL resulted in more apoptotic cell death and tumor growth inhibition than Apo2L/TRAIL alone. **Conclusions** Combination of doxorubicin and Apo2L/TRAIL is more effective in growth inhibition of PC3 xenografts in vivo than either agent alone and could present a novel treatment strategy against hormone-refractory prostate cancer. The intracellular mechanism by which doxorubicin enhances the effect of Apo2L/TRAIL on PC3 xenografts may be by reducing expression of c-FLIP.

Answer 48:

**Bibliographic Information****Oral Silibinin Inhibits Lung Tumor Growth in Athymic Nude Mice and Forms a Novel Chemocombination with Doxorubicin Targeting Nuclear Factor  $\kappa$ B-Mediated Inducible Chemoresistance.**

Singh, Rana P.; Mallikarjuna, G. U.; Sharma, Girish; Dhanalakshmi, Sivanandhan; Tyagi, Anil K.; Chan, Daniel C. F.; Agarwal, Chapla; Agarwal, Rajesh. Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO, USA. Clinical Cancer Research (2004), 10(24), 8641-8647. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 142:423170 AN 2004:1150200 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The acute and cumulative dose-related toxicity and drug resistance, mediated via nuclear factor  $\kappa$ B (NF $\kappa$ B), of anthracycline anticancer drugs pose a major problem in cancer chemotherapy. Here, we report that oral silibinin (a flavanone) suppresses human non-small-cell lung carcinoma A549 xenograft growth ( $P = 0.003$ ) and enhances the therapeutic response ( $P < 0.05$ ) of doxorubicin in athymic BALB/c nu/nu mice together with a strong prevention of doxorubicin-caused adverse health effects. Immunohistochem. analyses of tumors showed that silibinin and doxorubicin decrease ( $P < 0.001$ ) proliferation index and vasculature and increase ( $P < 0.001$ ) apoptosis; these effects were further enhanced ( $P < 0.001$ ) in combination treatment. Pharmacol. dose of silibinin (60  $\mu$ mol/L) achieved in animal study was biol. effective ( $P < 0.01$  to 0.001, growth inhibition and apoptosis) in vitro in A549 cell culture together with an increased efficacy ( $P < 0.05$  to 0.001) in doxorubicin (25 nmol/L) combination. Furthermore, doxorubicin increased NF $\kappa$ B DNA binding activity as one of the possible mechanisms for chemoresistance in A549 cells, which was inhibited by silibinin in combination treatment. Consistent with this, silibinin inhibited doxorubicin-caused increased translocation of p65 and p50 from cytosol to nucleus. Silibinin also inhibited cyclooxygenase-2, an NF $\kappa$ B target, in doxorubicin combination. These findings suggest that silibinin inhibits in vivo lung tumor growth and reduces systemic toxicity of doxorubicin with an enhanced therapeutic efficacy most likely via an inhibition of doxorubicin-induced chemoresistance involving NF $\kappa$ B signaling.

Answer 49:

**Bibliographic Information**

**Reversal of multidrug resistance of cancer through inhibition of P-glycoprotein by 5-bromotetrandrine.** Jin, Jing; Wang, Feng-Peng; Wei, Huailing; Liu, Gengtao. Department of Pharmacology, University of Cambridge, Cambridge, UK. *Cancer Chemotherapy and Pharmacology* (2005), 55(2), 179-188. Publisher: Springer GmbH, CODEN: CCFDZ ISSN: 0344-5704. Journal written in English. CAN 142:253974 AN 2004:1053627 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Purpose:** The present study aimed to evaluate the MDR reversal activity of bromotetrandrine (BrTet), a bromized deriv. of tetrandrine (Tet), in vitro and in vivo. **Methods:** Drug sensitivity was detd. using the MTT assay. The in vivo effect of Tet was investigated using nude mice grafted with sensitive and resistant KB human epidermoid cancer cells. Doxorubicin (Dox) accumulation was analyzed by fluorospectrophotometry and the protein and mRNA levels of P-glycoprotein (P-gp) were detd. by immunocytochem. and RT-PCR, resp. **Results:** BrTet at 0.25, 0.5 and 1  $\mu$ M reversed Dox resistance in MDR human breast cancer MCF-7/Dox cells dose-dependently and its potency was greater than that of Tet at the same concns. BrTet reversed vincristine (VCR), Dox and paclitaxel resistance in MDR human oral epidermoid carcinoma KBv200 cells as well as innate VCR and Dox resistance in human hepatocellular carcinoma Bel7402 cells. However, BrTet showed no effect on the IC50 values of the above-mentioned anticancer drugs in sensitive MCF-7 and KB cells. No reversal effect of BrTet on the cytotoxicity of 5-fluorouracil and cisplatin, non-P-gp substrates, was obsd. In nude mice bearing KBv200 xenografts on the left flank and KB xenografts on the right flank, i.p. injection of 5 mg/kg and 10 mg/kg BrTet significantly enhanced the antitumor activity of Dox against KBv200 xenografts with inhibitory rates of 33.0 and 39.2, while Dox alone inhibited the growth of KBv200 xenografts by only 11.6. No enhancement by BrTet was seen in KB xenografts. Moreover, BrTet at 5 mg/kg reversed paclitaxel resistance in KBv200 xenografts. Fluorospectrophotometric assay showed that BrTet significantly increased the intracellular accumulation of Dox in MCF-7/Dox cells in a dose-dependent manner. BrTet also inhibited the overexpression of P-gp in MCF-7/Dox cells, but had no effect on *mdr1* expression. **Conclusions:** BrTet showed significant MDR reversal activity in vitro and in vivo.

Its activity may be related to the inhibition of P-gp overexpression and the increase in intracellular accumulation of anticancer drugs. BrTet may be a promising MDR modulator for eventual assessment in the clinic.

Answer 50:

**Bibliographic Information**

**Efficient elimination of B-lineage lymphomas by anti-CD20-auristatin conjugates.** Law, Che-Leung; Cervený, Charles G.; Gordon, Kristine A.; Klussman, Kerry; Mixan, Bruce J.; Chace, Dana F.; Meyer, Damon L.; Doronina, Svetlana O.; Siegall, Clay B.; Francisco, Joseph A.; Senter, Peter D.; Wahl, Alan F. Seattle Genetics, Inc., Bothell, WA, USA. *Clinical Cancer Research* (2004), 10(23), 7842-7851. Publisher: American Association for Cancer Research, CODEN: CCFR4 ISSN: 1078-0432. Journal written in English. CAN 142:273558 AN 2004:1048126 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The anti-CD20 antibody rituximab is useful in the treatment of certain B-cell malignancies, most notably non-Hodgkin's lymphoma. Its efficacy has been increased when used in combination with chemotherapy, yet anti-CD20 monoclonal antibodies (mAbs) directly conjugated with drugs such as doxorubicin (Dox) have failed to deliver drug or to demonstrate antitumor activity. We have produced anti-CD20 antibody-drug conjugates that possess potent antitumor activity by using the anti-mitotic agent, monomethyl auristatin E (MMAE), linked via the lysosomally cleavable dipeptide, valine-citrulline (vc). Two anti-CD20 conjugates, rituximab-vcMMAE and 1F5-vcMMAE, were selectively cytotoxic against CD20+ B-lymphoma cell lines, with IC50 values ranging from 50 ng/mL to 1  $\mu$ g/mL. Unlike rituximab, which showed diffuse surface localization, rituximab-vcMMAE capped and was internalized within 4 h after binding to CD20+ B cells. Internalization of rituximab-vcMMAE was followed by rapid G2-M phase arrest and onset of apoptosis. Anti-CD20 antibody-drug conjugates prepd. with Dox were internalized and localized as with rituximab-vcMMAE, yet these were not effective for drug delivery (IC50 > 50  $\mu$ g/mL). Consistent with in vitro activity, rituximab-vcMMAE showed antitumor efficacy in xenograft models of CD20-pos. lymphoma at doses where rituximab or rituximab-Dox conjugates were ineffective. These data indicate that

anti-CD20-based antibody-drug conjugates are effective antitumor agents when prepd. with a stable, enzyme-cleavable peptide linkage to highly potent cytotoxic agents such as MMAE.

Answer 51:

#### **Bibliographic Information**

**Human osteosarcoma xenografts and their sensitivity to chemotherapy.** Bruheim, Skjalg; Bruland, Oyvind S.; Breistol, Knut; Maeldandsmo, Gunhild M.; Fodstad, Oystein. Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway. Pathology Oncology Research (2004), 10(3), 133-141. Publisher: Aranyi Lajos Foundation, CODEN: POREFR ISSN: 1219-4956. Journal written in English. CAN 142:253924 AN 2004:1018322 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Despite the increased survival rates of osteosarcoma patients attributed to adjuvant chemotherapy, at least one third of the patients still die due to their disease. Further improvements in the management of osteosarcoma may rely on a more individualized treatment strategy, as well as on the introduction of new drugs. To aid in the preclin. evaluation of new candidate substances against osteosarcoma, we have established 11 human osteosarcoma xenograft lines and characterized them with regard to response to five different ref. drugs. Doxorubicin, cisplatin methotrexate, ifosfamide and lomustine were effective in 3/11, 3/11, 1/10, 5/11 and 4/11 of the xenografts, resp. Five xenografts were resistant to all compds. tested. We also assessed the mRNA expression levels of the xenografts for the O6-Methylguanine DNA Methyltransferase (MGMT), DNA topoisomerase II- (Topo II)- $\alpha$ , Gluthathione-S-transferase (GST)- $\pi$ , Multidrug-resistance related protein (MRP) 1 and Multidrug-resistance (MDR) 1 genes. There was an inverse correlation between the transcript levels of GST- $\pi$  and doxorubicin growth inhibition ( $r = -0.66$ ;  $p < 0.05$ ), and between the transcript levels of MGMT and the effect of lomustine ( $r = -0.72$ ;  $p < 0.01$ ), whereas the expression of MRP1 and cisplatin growth inhibition was pos. correlated ( $r = 0.82$ ;  $p < 0.005$ ). This panel of xenografts should constitute a good tool for pharmacol. and mol. studies in osteosarcoma.

Answer 52:

#### **Bibliographic Information**

**Folate-receptor-targeted delivery of doxorubicin nano-aggregates stabilized by doxorubicin-PEG-folate conjugate.** Yoo, Hyuk Sang; Park, Tae Gwan. Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, S. Korea. Journal of Controlled Release (2004), 100(2), 247-256. Publisher: Elsevier B.V., CODEN: JCREEC ISSN: 0168-3659. Journal written in English. CAN 142:341598 AN 2004:967899 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

For folate-receptor-targeted anti-cancer therapy, doxorubicin aggregates in a nano-scale size were produced employing doxorubicin-polyethylene glycol-folate (DOX-PEG-FOL) conjugate. Doxorubicin and folate were resp. conjugated to  $\alpha$ - and  $\omega$ -terminal end group of a PEG chain. The conjugates assisted to form doxorubicin nano-aggregates with an av. size of 200 nm in diam. when combined with an excess amt. of deprotonated doxorubicin in an aq. phase. Hydrophobically deprotonated doxorubicin mols. were aggregated within the core, while the DOX-PEG-FOL conjugates stabilized the aggregates with exposing folate moieties on the surface. The doxorubicin nano-aggregates showed a greater extent of intracellular uptake against folate-receptor-pos. cancer cells than folate-receptor-neg. cells, indicating that the cellular uptake occurred via a folate-receptor-mediated endocytosis mechanism. They also exhibited more potent cytotoxic effect on KB cells than free doxorubicin. In a human tumor xenograft nude mouse model, folate-targeted doxorubicin nano-aggregates significantly reduced the tumor vol. compared to non-targeted doxorubicin aggregates or free doxorubicin. These results suggested that folate-targeted doxorubicin nano-aggregates could be a potentially useful delivery system for folate-receptor-pos. cancer cells.

Answer 53:

**Bibliographic Information**

**Fluoxetine inhibits multidrug resistance extrusion pumps and enhances responses to chemotherapy in syngeneic and in human xenograft mouse tumor models.** Peer, Dan; Dekel, Yaron; Melikhov, Dina; Margalit, Rimona. Department of Biochemistry, the George S. Wise Life Science Faculty, Tel Aviv University, Tel Aviv-Jaffa, Israel. *Cancer Research* (2004), 64(20), 7562-7569. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:343083 AN 2004:858494 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Multidrug resistance (MDR) operated by extrusion pumps such as P-glycoprotein and multidrug-resistance-assocd.-proteins, is a major reason for poor responses and failures in cancer chemotherapy. MDR modulators (chemosensitizers) were found among drugs approved for noncancer indications and their derivs. Yet toxicity, adverse effects, and poor soly. at doses required for MDR reversal prevent their clin. application. Among newly designed chemosensitizers, some still suffer from toxicity and adverse effects, whereas others progressed to clin. trials. Diversities among tumors and among MDR pumps indicate a need for several clin. approved MDR modulators. Here we report for the first time that fluoxetine (Prozac), the well-known antidepressant, is a highly effective chemosensitizer. In vitro, fluoxetine enhanced (10- to 100-fold) cytotoxicity of anticancer drugs (doxorubicin, mitomycin C, vinblastine, and paclitaxel) in drug-resistant but not in drug-sensitive cells (5 and 3 lines, resp.). Fluoxetine increased drug accumulation within MDR-cells and inhibited drug efflux from those cells. In vivo, fluoxetine enhanced doxorubicin accumulation within tumors (12-fold) with unaltered pharmacokinetics. In four resistant mouse tumor models of both syngeneic and human xenograft, combination treatment of fluoxetine and doxorubicin generated substantial ( $P < 0.001$ ) improvements in tumor responses and in survivals (2- to 3-fold). Moreover, fluoxetine reversed MDR at doses that are well below its human safety limits, free of the severe dose-related toxicity, adverse effects, and poor soly. that are obstacles to other chemosensitizers. This low-dose range, together with the findings reported here, indicate that fluoxetine has a high potential to join the arsenal of MDR reversal agents that may reach the clinic.

Answer 54:

**Bibliographic Information**

**The Experimental Antitumor Agents Phortress and Doxorubicin are Equiactive Against Human-Derived Breast Carcinoma Xenograft Models.** Fichtner, Iduna; Monks, Anne; Hose, Curtis; Stevens, Malcolm F. G.; Bradshaw, Tracey D. Max-Delbrueck Center for Molecular Medicine, Experimental Pharmacology, Berlin, Germany. *Breast Cancer Research and Treatment* (2004), 87(1), 97-107. Publisher: Kluwer Academic Publishers, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 142:348246 AN 2004:757951 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Phortress (the dihydrochloride salt of the lysylamide prodrug of 2-(4-amino-3-methylphenyl)-5-fluoro-benzothiazole (5F 203)) is an exptl. antitumor agent with potent and selective activity against human-derived carcinomas of breast, ovarian and renal origin. The mechanism of action of Phortress is distinct from all classes of chemotherapeutic agents currently in the clinic, and involves metabolic activation by cytochrome P 450 (CYP) 1A1 to electrophilic species, which generate DNA adducts in sensitive tumors only. In the present study, the antitumor efficacy of Phortress has been compared with that of doxorubicin (Dox) in nine human-derived mammary carcinoma xenograft models, cultivated s.c. in the flanks of nude mice. In addn., cyp1a1 mRNA expression was measured in tumors of control and treated animals. Phortress compared favorably with Dox: significant activity, independent of estrogen receptor (ER) status, was established in 7/9 xenografts; in one xenograft model, Phortress elicited superior antitumor activity; no model demonstrated complete resistance to Phortress. In accordance with this observation, all xenografts available for examn. (8) displayed clear induction of cyp1a1 expression upon treatment of mice with Phortress whereas Dox failed to induce cyp1a1 expression in all models. Prolonged viability of tumor fragments, recovered for treatment ex vivo could not be sustained; thus correlations between tumor cells' response to Phortress and cyp1a1 or cyp1b1 inducibility following 5F 203 treatment could not be detd. with confidence.

Answer 55:

**Bibliographic Information**

**Tumor-targeted hyaluronan nanoliposomes increase the antitumor activity of liposomal doxorubicin in syngeneic and human xenograft mouse tumor models.** Peer, Dan; Margalit, Rimona. Department of Biochemistry, The George S. Wise, Life Science Faculty, Tel-Aviv University, Tel Aviv-Jaffa, Israel. Neoplasia (Ann Arbor, MI, United States) (2004), 6(4), 343-353. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 142:162299 AN 2004:671689 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Naturally occurring high-Mr hyaluronan, bound to the surface of nanoliposomes (denoted targeted hyaluronan liposomes, or tHA-LIP), is a candidate for active targeting to tumors, many of which overexpress the hyaluronan receptors CD44 and RHAMM. The surface-bound hyaluronan also provides a hydrophilic coat that, similar to polyethylene glycol, may promote long-term circulation. We recently reported the successful targeting of mitomycin C, mediated by tHA-LIP, in tumor-bearing syngeneic mice. Hypothesizing that this targeting is carrier-specific, rather than drug-specific, we report here studies with doxorubicin (DXR)-loaded tHA-LIP, in syngeneic and human xenograft models. Saline, free DXR, DXR-loaded nontargeted liposomes (nt-LIP), and Doxil served as controls. The tHA-LIP were long-circulating, more than all controls, in healthy and tumor-bearing (C57BL/6/B16F10.9; BALB/c/C-26) mice. Mediated by tHA-LIP, DXR accumulation in tumor-bearing lungs was 30-, 6.7-, and 3.5-fold higher than free DXR, nt-LIP, and Doxil, resp. Key indicators of therapeutic responses-tumor progression, metastatic burden, and survival-were superior ( $P < .001$ ) in animals receiving DXR-loaded tHA-LIP compared with controls, in tumor-bearing syngeneic mice (BDF1/P388/ADR ascites, C57BL/6/B16F10.9 lung metastasis, and BALB/c/C-26 solid tumors), and in nude mice bearing PANC-1 solid tumors. In conclusion, tHA-LIP, performing as tumor-targeted carriers, have the potential to join the arsenal of carrier-formulated anticancer drugs.

Answer 56:

**Bibliographic Information**

**Increased anti-tumour efficacy of doxorubicin when combined with sulindac in a xenograft model of an MRP-1-positive human lung cancer.** O'Connor, Robert; Heenan, Mary; Connolly, Lisa; Larkin, Annemarie; Clynes, Martin. The National Institute for Cellular Biotechnology, Dublin City University, Dublin 9, Ire. Anticancer Research (2004), 24(2A), 457-464. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 141:420145 AN 2004:483282 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Background: A no. of cellular proteins, including P-glycoprotein (P-gp) and Multiple drug Resistance Protein (MRP-1), act as drug efflux pumps and are important in the resistance of many cancers to chemotherapy. We previously reported that a small no. of NSAIDs could inhibit the activity of MRP-1. Materials and Methods: We chose sulindac as a candidate agent for further investigation as it has the most favorable efficacy and toxicity profile of the agents available for a potential specific MRP-1 inhibitor. NCI H460 cells expressed MRP-1 protein (by Western blot) and also the toxicity of doxorubicin (a substrate of MRP-1) could be potentiated in this line using non-toxic concns. of the MRP-1 substrate/inhibitor sulindac. These cells were implanted in nude mice and the animals divided into various groups which were administered doxorubicin and/or sulindac. Results: Sulindac was shown to significantly potentiate the tumor growth inhibitor activity of doxorubicin in this MRP-1-overexpressing human tumor xenograft model. Conclusion: Sulindac may be clin. useful as an inhibitor of the MRP-1 cancer resistance mechanism.

Answer 57:

**Bibliographic Information**

**Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing compounds against human tumor xenografts.** Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Pharmacology and Therapeutics,

Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2004), 10(7), 2561-2569. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:360262 AN 2004:290939 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Studies were carried out in athymic nude mice bearing human squamous cell carcinoma of the head and neck (FaDu and A253) and colon carcinoma (HCT-8 and HT-29) xenografts to evaluate the potential role of selenium-contg. compds. as selective modulators of the toxicity and antitumor activity of selected anticancer drugs with particular emphasis on irinotecan, a topoisomerase I poison. Antitumor activity and toxicity were evaluated using nontoxic doses (0.2 mg/mouse/day) and schedule (14-28 days) of the selenium-contg. compds., 5-methylselenocysteine and seleno-L-methionine, administered orally to nude mice daily for 7 days before i.v. administration of anticancer drugs, with continued selenium treatment for 7-21 days, depending on anticancer drugs under evaluation. Several doses of anticancer drugs were used, including the max. tolerated dose (MTD) and toxic doses. Although many chemotherapeutic agents were evaluated for toxicity protection by selenium, data on antitumor activity were primarily obtained using the MTD, 2 x MTD, and 3 x MTD of weekly x4 schedule of irinotecan. Selenium was highly protective against toxicity induced by a variety of chemotherapeutic agents. Furthermore, selenium increased significantly the cure rate of xenografts bearing human tumors that are sensitive (HCT-8 and FaDu) and resistant (HT-29 and A253) to irinotecan. The high cure rate (100%) was achieved in nude mice bearing HCT-8 and FaDu xenografts treated with the MTD of irinotecan (100 mg/kg/wk x 4) when combined with selenium. Administration of higher doses of irinotecan (200 and 300 mg/kg/wk x 4) was required to achieve high cure rate for HT-29 and A253 xenografts. Administration of these higher doses was possible due to selective protection of normal tissues by selenium. Thus, the use of selenium as selective modulator of the therapeutic efficacy of anticancer drugs is new and novel.

We demonstrated that selenium is a highly effective modulator of the therapeutic efficacy and selectivity of anticancer drugs in nude mice bearing human tumor xenografts of colon carcinoma and squamous cell carcinoma of the head and neck. The obsd. in vivo synergic interaction is highly dependent on the schedule of selenium.

Answer 58:

### Bibliographic Information

#### **Radiation Improves the Distribution and Uptake of Liposomal Doxorubicin (Caelyx) in Human Osteosarcoma Xenografts.**

Davies, Catharina de L.; Lundstrom, Lisa M.; Frengen, Jomar; Eikenes, Live; Bruland, Oyvind S.; Kaalhus, Olav; Hjelstuen, Mari H. B.; Brekken, Christian. Department of Physics, The Norwegian University of Science and Technology, Trondheim, Norway. Cancer Research (2004), 64(2), 547-553. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 140:141797 AN 2004:64193 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Liposomal drug delivery appears to improve the antitumor effect and reduce toxicity compared with the free drug. The therapeutic index may be improved further by combining cytotoxic drugs and radiotherapy. Successful therapy requires that the cytotoxic agents reach the tumor cells. Therefore, we studied tumor growth and the microdistribution of liposomal doxorubicin (Caelyx) with and without addnl. ionizing radiation in human osteosarcoma xenografts in athymic mice. Caelyx was injected i.v. 1 day before single or fractionated radiotherapy. Both chemoirradn. regimens induced significant tumor growth delays and worked synergistically. Confocal laser scanning microscopy showed that intact liposomes were located in close proximity to endothelial cells, and the distribution of released doxorubicin was heterogeneous. Before radiotherapy, hardly any doxorubicin was localized in the central parts of the tumor. Radiotherapy increased the tumor uptake of doxorubicin by a factor of two to four, with drug being redistributed farther from the vessels in the tumor periphery and located around vessels in the central parts of the tumor. Colocalization of doxorubicin and hypoxic cells showed no distribution of drug into hypoxic areas. Dynamic contrast-enhanced magnetic resonance imaging (MRI) 1 day before the injection of Caelyx and 2 days after treatment start showed that the combined treatment reduced the vascular vol. and the vascular transfer rate of the MRI tracer. The results show that chemoirradn. with Caelyx induces synergistic treatment effects. Improved intratumoral drug uptake and distribution are responsible to some extent for the enhanced antitumor effect.

Answer 59:

**Bibliographic Information**

**Lecithinized copper,zinc-superoxide dismutase as a protector against doxorubicin-induced cardiotoxicity in mice.** den Hartog, Gertjan J. M.; Haenen, Guido R. M. M.; Boven, Epie; van der Vijgh, Wim J. F.; Bast, Aalt. Department of Pharmacology and Toxicology, University Maastricht, Maastricht, Neth. Toxicology and Applied Pharmacology (2004), 194(2), 180-188. Publisher: Elsevier Science, CODEN: TXAPA9 ISSN: 0041-008X. Journal written in English. CAN 140:297016 AN 2004:49820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Prod. of superoxide radicals from doxorubicin is widely accepted to be the cause of the cardiotoxicity induced by this antitumor agent. Pretreatment with superoxide dismutase could improve the therapeutic application. Aim of the present study was to det. whether lecithinized superoxide dismutase (PC-SOD) can serve as a cardioprotective drug during doxorubicin treatment. The protective potential of PC-SOD on doxorubicin-induced cardiotoxicity was investigated in BALB/c mice. The possible influence of PC-SOD on the antitumor activity of doxorubicin was investigated in vitro as well as in vivo. Mice were treated i.v. with doxorubicin (4 mg/kg-1) or doxorubicin and PC-SOD (5000, 20 000 or 80 000 U/kg-1) weekly  $\times$  6 and appropriate controls were included. Cardiotoxicity was monitored for 8 wk by ECG measurement. The influence of PC-SOD on the antitumor activity of doxorubicin was evaluated in three human malignant cell lines. Nude mice bearing OVCAR-3 human ovarian cancer xenografts were treated i.v. with doxorubicin (8 mg/kg-1) alone or preceded by PC-SOD 20 000 or 80 000 U/kg-1 weekly  $\times$  2 and appropriate controls were included. PC-SOD prevented doxorubicin-induced cardiotoxicity already at 5000 U/kg-1 whereas 20 000 and 80 000 U/kg-1 were equally protective. No toxicity was obsd. in mice treated with PC-SOD. PC-SOD did not interfere with the antiproliferative effects of doxorubicin in vitro. In vivo, PC-SOD had no neg. effect on the inhibition of xenograft growth induced by doxorubicin. It can be concluded that PC-SOD protects the heart, but not the tumor against doxorubicin. These data suggest that PC-SOD may be a suitable cardioprotector during doxorubicin treatment.

Answer 60:

**Bibliographic Information**

**Combining doxorubicin and liposomal anti-HER-2/NEU antisense oligodeoxynucleotides to treat HER-2/NEU-expressing MDA-MB-435 breast tumor model.** Waterhouse, Dawn N.; Gelmon, Karen A.; Masin, Dana; Bally, Marcel B. Department of Advanced Therapeutics, British Columbia Cancer Research Centre, Vancouver, BC, Can. Journal of Experimental Therapeutics and Oncology (2003), 3(5), 261-271. Publisher: Blackwell Publishing, Inc., CODEN: JETOFX ISSN: 1359-4117. Journal written in English. CAN 141:586 AN 2004:29111 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

This study assessed the in vivo therapeutic activity of an antisense mol. targeted against HER-2/neu mRNA. Antisense activity was evaluated in female SCID/Rag2m mice bearing s.c. tumors derived from HER-2/neu-transfected MDA-MB-435 (MDA-MB-435HER2) cells, a transfected line derived from the human breast cancer MDA-MB-435 cell line. Animals were treated with free or liposome-encapsulated antisense. The area under the curve (AUC<sub>0-24h</sub>) of the liposomal formulated antisense was demonstrated to be more than 30-fold greater than that of free antisense following i.v. administration. Efficacy was detd. by assessing changes in tumor growth rate as well as by an immunohistol. end-point evaluating HER-2/neu expression. HER-2/neu protein expression was reduced in mice bearing HER-2/neu-transfected MDA-MB-435 tumors when treated with liposomal antisense. However, tumors in these mice grew at a faster rate than the control, a result that was interpreted to be a consequence of selection of a more rapidly proliferating HER-2/neu-neg. subpopulation of cells. Effective control of the MDA-MB-435HER2 tumors was achieved when antisense treatment was combined with doxorubicin. Tumors derived from animals treated with the combination of doxorubicin and the liposomal antisense against HER-2/neu exhibited no detectable levels of HER-2/neu expression. Antisense targeted against HER-2/neu mRNA was effective in reducing or eliminating HER-2/neu protein expression, and when combined with doxorubicin treatment was efficacious in the treatment of mice bearing HER-2/neu-overexpressing human xenograft tumors.

Answer 61:

**Bibliographic Information****Cure of SCID mice bearing human B-lymphoma xenografts by an anti-CD74 antibody-anthracycline drug conjugate.**

Griffiths, Gary L.; Mattes, M. Jules; Stein, Rhona; Govindan, Serengulam V.; Horak, Ivan D.; Hansen, Hans J.; Goldenberg, David M. Immunomedics, Inc., Morris Plains, NJ, USA. *Clinical Cancer Research* (2003), 9(17), 6567-6571. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:116586 AN 2003:1009884 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The purpose of this research was to test the therapeutic efficacy of an anthracycline-antibody conjugate for the treatment of human B-cell lymphoma in a preclin. animal model. Doxorubicin (dox) conjugates of the murine and humanized versions of the anti B-cell antibody LL1, targeting CD74, were prepd., along with a nonspecific control dox-antibody conjugate, targeting carcinoembryonic antigen. Antibody conjugates carried approx. 8 - 10 drug mols. attached site-specifically at thiols of reduced interchain disulfide bonds. Conjugates were tested, initially in vitro, and then for therapeutic efficacy in a systemic model, using a lethal i.v. dose of Raji cells in SCID mice. Dox-LL1 conjugates were shown to be stable and 3-fold more effective in vitro against the human B-cell Burkitt's lymphoma line, Raji, compared with the nonspecific control conjugate that did not target CD74 or B cells. When SCID mice were given an i.v. dose of 2.5 million Raji cells, they would die of disseminated disease within 15-25 days postinjection. A single dose of dox-LL1 conjugate, 117-350 µg, given 5 days to 14 (advanced disease) days after injection of the Raji cells resulted in cure of most animals out to 180 days after injection of the cells, whereas animals in treatment control groups were not cured. The dose of dox-LL1 found useful in this work corresponds with a significantly lower drug dose than reported previously with other drug-antibody conjugates. CD74 appears to be a uniquely useful target antigen for delivery of drugs, effecting cures of animals with single, low doses of conjugate.

Answer 62:

**Bibliographic Information****Vascular Damage and Anti-angiogenic Effects of Tumor Vessel-Targeted Liposomal Chemotherapy.**

Pastorino, Fabio; Brignole, Chiara; Marimpietri, Danilo; Cilli, Michele; Gambini, Claudio; Ribatti, Domenico; Longhi, Renato; Allen, Theresa M.; Corti, Angelo; Ponzoni, Mirco. Laboratory of Oncology, Differentiation Therapy Unit, G. Gaslini Children's Hospital, Genoa, Italy. *Cancer Research* (2003), 63(21), 7400-7409. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 140:138927 AN 2003:885666 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The poor selective toxicity of chemotherapeutic anticancer drugs leads to dose-limiting side effects that compromise clin. outcome. Solid tumors recruit new blood vessels to support tumor growth, and unique epitopes expressed on tumor endothelial cells can function as targets for the anti-angiogenic therapy of cancer. An NGR peptide that targets aminopeptidase N, a marker of angiogenic endothelial cells, was coupled to the surface of liposomal doxorubicin (NGR-SL[DXR]) and was used to treat orthotopic neuroblastoma (NB) xenografts in SCID mice. Pharmacokinetic studies indicated that liposomes coupled to NGR peptide had long-circulating profiles in blood. Their uptake into NB tumor was time dependent, being at least 10 times higher than that of nontargeted liposomes (SL[DXR]) after 24 h, with DXR spreading outside the blood vessels and into the tumors. No uptake was obsd. into tumors of mice treated with the mismatched peptide ARA-targeted SL[DXR]. Tumor-specific DXR uptake was completely blocked when mice were coinjected with a 50-fold molar excess of the sol. NGR peptide. Adrenal tumor-bearing mice treated with 2 mg/kg/wk/x3 of NGR-SL[DXR] partly outlived the control mice ( $P < 0.001$ ), whereas doses  $> 3$  mg/kg/wk/x3 were toxic. Histopathol. anal. of cryosections taken from treated mice revealed pronounced destruction of the tumor vasculature with a marked decreased in vessel d. Double staining of tumors with terminal deoxynucleotidyl transferase-mediated nick end labeling and antifactor VIII antibody or antihuman NB demonstrated endothelial cell apoptosis in the vasculature, as well as increased tumor cell apoptosis. Moreover, mice injected with 3 mg/kg/wk/x3 of NGR-SL[DXR] displayed rapid tumor regression, as well as inhibition of metastases growth ( $P = 0.0002$ ). One day after the third treatment, four of six mice showed no evidence of tumors, and the two others showed a  $>80\%$  redn. in tumor mass and a  $>90\%$  suppression of blood vessel d. ( $P < 0.01$ ).

In contrast, mice treated with ARA-SL[DXR] formed large well-vascularized tumors. Finally, a metronomic administration

of NGR-SL[DXR] (1 mg/kg/every other 2 days x 9) induced complete tumor eradication in all animals ( $P < 0.0001$ ). Our strategy markedly enhanced the therapeutic index of DXR and enabled metronomic administration of therapeutic doses. A dual mechanism of action is proposed: indirect tumor cell kill via the destruction of tumor endothelium by NGR-targeted liposomes and direct tumor cell kill via localization of liposomal DXR to the tumor interstitial space. This combined strategy has the potential to overcome some major limitations of conventional chemotherapy.

Answer 63:

#### Bibliographic Information

**Preclinical evaluation of targeted cytotoxic luteinizing hormone-releasing hormone analogue AN-152 in androgen-sensitive and insensitive prostate cancers.** Letsch, Markus; Schally, Andrew V.; Szepeshazi, Karoly; Halmos, Gabor; Nagy, Attila.

Department of Medicine, Veterans Affairs Medical Center and Section of Experimental Medicine, and Cancer Institute, Polypeptide, Endocrine, Tulane University School of Medicine, New Orleans, LA, USA. *Clinical Cancer Research* (2003), 9(12), 4505-4513. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 140:157704 AN 2003:800245 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

To improve conventional chemotherapy, the authors developed cytotoxic analogs of LH-releasing hormone (LH-RH), which can be targeted to prostate cancers expressing LH-RH receptors. In view of pending clin. trials on cytotoxic LH-RH analog AN-152, contg. doxorubicin (DOX) linked to [D-Lys6]-LH-RH, the authors investigated the effects of AN-152 on tumor growth of s.c. implanted androgen-sensitive LNCaP and MDA-PCa-2b prostate cancers, as well as androgen-independent C4-2 prostate cancers xenografted into the tibiae of nude mice. In the C4-2 study, serum prostate-specific antigen (PSA) levels were also measured. LH-RH receptors were analyzed by reverse transcription-PCR and ligand competition assay. The authors also evaluated whether AN-152 can affect mRNA expression of human epidermal growth factor receptor and HER-2 and -3 oncogenes. After 32 days of treatment with AN-152, the growth of LNCaP cancers in castrated nude mice was strongly inhibited by 83% vs. intact controls and 62% vs. castrated controls. In animals bearing MDA-PCa-2b prostate cancers, therapy with AN-152 for 25 days resulted in a 69% inhibition of tumor growth (vs. controls) and was more effective than equimolar doses of DOX or microcapsules of LH-RH agonist Decapeptyl. In nude mice bearing intraosseous C4-2 prostate cancers, treatment with AN-152 decreased serum PSA levels to 10.3 ng/mL from 24.8 ng/mL in controls, whereas DOX had no effect on PSA. The inhibitory effects of AN-152 on C4-2 tumors was accompanied by an increase in apoptosis and a decrease in tumor proliferation. Binding sites for LH-RH and the expression of mRNA for LH-RH receptors were found on s.c. C4-2 and MDA-PCa-2b tumors. The inhibition of MDA-PCa-2b tumors by AN-152 was assocd. with a significant decrease in mRNA expression for epidermal growth factor receptor, HER-2, and 3. The authors' findings suggest that cytotoxic analog AN-152 could be considered for therapeutic trials in patients with advanced prostate carcinoma.

Answer 64:

#### Bibliographic Information

**In vivo antitumor activity of S16020, a topoisomerase II inhibitor, and doxorubicin against human brain tumor xenografts.**

Vassal, Gilles; Merlin, Jean-Louis; Terrier-Lacombe, Marie-Jose; Grill, Jacques; Parker, Fabrice; Sainte-Rose, Christian; Aubert, Genevieve; Morizet, Jackie; Sevenet, Nicolas; Poullain, Marie-Gwenaelle; Lucas, Catherine; Kalifa, Chantal. *Pharmacology and New Treatments of Cancers, Institut Gustave-Roussy, Villejuif, Fr.* *Cancer Chemotherapy and Pharmacology* (2003), 51(5), 385-394. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 140:104537 AN 2003:347901 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

New active drugs are needed for the treatment of primary brain tumors in both children and adults. S16020 is a cytotoxic olivacine deriv. that inhibits topoisomerase II. The aim of the study was to det. its antitumor activity in athymic mice bearing s.c. medulloblastoma (IGRM33, 34, 57) and glioblastoma (IGRG88, 93, 121) xenografts treated at an advanced stage of tumor growth in

comparison with that of doxorubicin. Animals were randomly assigned to receive i.v. S16020 or doxorubicin weekly for three consecutive weeks. The optimal dose was 80 mg/kg per wk. S16020 demonstrated a significant antitumor activity in two out of three medulloblastoma xenografts. IGRM57 xenografts were highly sensitive with 100% tumor regressions and a tumor growth delay (TGD) of 102 days, while one of eight IGRM34 xenografts showed a partial regression with a TGD of 16 days. Doxorubicin was significantly more active than S16020 in these two models. IGRM33, a model established from a tumor in relapse after chemotherapy and radiotherapy, was refractory to both drugs. S16020 demonstrated a significant antitumor activity in the three glioblastoma xenografts evaluated. The wild-type p53 IGRG93 xenograft was highly sensitive with 100% tumor regressions and a TGD of 54 days. IGRG121 (wt p53) and IGRG88 (mutant p53) were moderately sensitive with TGDs of 33 and 23 days, resp. Doxorubicin showed greater activity in two of these models. All six xenografts exhibited low expression of *mdr1* as quantitated by RT-PCR, and no correlation was found with the activity of either drug. Conversely, a low activity of the two drugs was significantly assocd. with a high expression of MRP1 in medulloblastomas. Finally, no relationship was obsd. between drug sensitivity to either drug and expression of their target, topoisomerase II $\alpha$ . In conclusion, S16020 and doxorubicin showed significant antitumor activity in brain tumor xenografts treated at an advanced stage of tumor growth. Their activity was related to MRP1 expression in medulloblastomas.

Answer 65:

### Bibliographic Information

**Antitumor activity of doxorubicin in combination with docetaxel against human breast cancer xenografts.** Egawa, Tomohisa; Kubota, Tetsuro; Suto, Akihiko; Otani, Yoshihide; Furukawa, Toshiharu; Saikawa, Yoshiro; Watanabe, Masahiko; Kumai, Koichiro; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Shinjuku-ku, Tokyo, Japan. *In Vivo* (2003), 17(1), 23-28. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 139:285841 AN 2003:271051 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In this study we assessed the in vivo antitumor activity of combined docetaxel (DOCE) and doxorubicin (DXR) treatment using 2 human breast carcinoma cell xenografts (R-27 and MX-1) in the nude mouse model. The transplanted tumors were allowed to reach exponential growth, whereupon 10 or 40 mg DOCE per kg alone (i.p.), 8 mg DXR per kg alone (iv), or 10 mg/kg DOCE (i.p.) and 8 mg/kg of DXR (iv), in the sequence of DOCE followed by DXR, were administered. The in vivo antitumor activity of combined DOCE and DXR was synergistic against R-27 and additive against MX-1. P-glycoprotein (P-gp) was detected immunohistochem., and was highly expressed in R-27, but not in MX-1. In conclusion, DOCE may increase the antitumor activity of DXR against P-gp-pos. breast cancer xenografts, such that the DOCE and DXR combination may be a useful treatment in clin. breast cancer.

Answer 66:

### Bibliographic Information

**The Celsion adaptive thermodynamic therapy (TDT) drug delivery system for treating deep-seated cancer.** Fenn, Alan J. Massachusetts Institute of Technology, USA. *Drug Delivery Technology* (2002), 2(7), 74-79. Publisher: Drug Delivery Technology LLC, CODEN: DDTRAW ISSN: 1537-2898. Journal; General Review written in English. CAN 139:57693 AN 2002:881793 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A review and discussion. The delivery of therapeutic amts. of infused chemotherapy to solid tumors deep in the body is often limited by toxic effects on healthy body tissues. Elevated cell tissue temp. (hyperthermia) is known to produce an improved response for malignant tumors in humans when applied in combination with chemotherapy. Recent preclin. thermotherapy studies have demonstrated improved targeting and effectiveness of doxorubicin when the chemotherapy is encapsulated and delivered by lysolipid-contg. thermosensitive Liposomes to human squamous cell carcinoma xenograft line (FaDu) tumors heated in mice. Radiofrequency (RF) phased array applicators surrounding the body have been used in attempting to heat deep tumors. However, studies in external RF phased array thermotherapy have shown the difficulty of localizing RF energy deposition in malignant tissue

deep within the human body without damaging superficial healthy tissue due to hot spots. Improvements in RF energy deposition are achieved when the RF phased array is controlled by an adaptive algorithm to focus the RF energy in the tumor and tumor margins, while the superficial RF fields are nullified. The combination of external adaptive-phased array thermotherapy and thermosensitive liposomes for targeted drug delivery is referred to as thermodyn. therapy (TDT). This article discusses Celsion Corporation's progress in developing a clin. thermodyn. therapy cancer treatment system based on a novel noninvasive RF adaptive phased array system to safely heat deep-seated tumors and effect drug release from thermosensitive liposomes.

Answer 67:

#### **Bibliographic Information**

**Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells.** Grunwald, Viktor; DeGraffenried, Linda; Russel, Douglas; Friedrichs, William E.; Ray, Ratna B.; Hidalgo, Manuel. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA. *Cancer Research* (2002), 62(21), 6141-6145. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 138:362269 AN 2002:859511 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Phosphatase and tensin homolog deleted from chromosome 10 (PTEN) is a lipid phosphatase with putative tumor suppressing abilities, which is frequently mutated in prostate cancer. Loss of PTEN leads to constitutive activation of the phosphatidylinositol 3'-kinase/serine-threonine kinase (Akt) signal transduction pathway and has been assocd. with resistance to chemotherapy. This study aimed to det. the effects of PTEN status and treatment with rapamycin, an inhibitor of mTOR, in the response of prostate cancer cell lines to doxorubicin. The DU-145 PTEN-pos. cell line was significantly more susceptible to the antiproliferative effects of doxorubicin as compared with the PTEN-neg. PC-3 cell line. Transfection of PTEN into the PC3 cells decreased the activation of Akt and the downstream mTOR-regulated 70-kDa S6 (p70s6k) kinase and reversed the resistance to doxorubicin in these cells, indicating that changes in PTEN status/Akt activation modulate the cellular response to doxorubicin. Treatment of PC-3 PTEN-neg. cells with rapamycin inhibited 70-kDa S6 kinase and increased the proliferative response of these cells to doxorubicin, so that it was comparable with the responses of PTEN-pos. DU-145 cells and the PC-3-transfected cells. Furthermore, treatment of mice bearing the PTEN-neg. PC-3 prostate cancer xenografts with CCI-779, an ester of rapamycin in clin. development combined with doxorubicin, inhibited the growth of the doxorubicin-resistant PC-3 tumors confirming the observations in vitro. Thus, rapamycin and CCI-779, by interacting with downstream intermediates in the phosphatidylinositol 3'-kinase/Akt signaling pathway, reverse the resistance to doxorubicin conferred by PTEN mutation/Akt activation. These results provide the rationale to explore in clin. trials whether these agents increase the response to chemotherapy of patients with PTEN-neg./Akt active cancers.

Answer 68:

#### **Bibliographic Information**

**Antitumor effects of the cytotoxic luteinizing hormone-releasing hormone analog AN-152 on human endometrial and ovarian cancers xenografted into nude mice.** Grundker, Carsten; Volker, Peter; Griesinger, Frank; Ramaswamy, Annette; Nagy, Attila; Schally, Andrew V.; Emons, Gunter. Department of Gynecology, Georg-August-University, Göttingen, Germany. *American Journal of Obstetrics and Gynecology* (2002), 187(3), 528-537. Publisher: Mosby, Inc., CODEN: AJOGAH ISSN: 0002-9378. Journal written in English. CAN 138:66891 AN 2002:815965 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Most human endometrial and ovarian cancers express receptors for LH-releasing hormone. These receptors can be used for targeted chemotherapy with cytotoxic LH-releasing hormone analogs such as AN-152, in which doxorubicin is linked to [D-Lys6]LH-releasing hormone. The antitumor effects of doxorubicin and AN-152 were assessed in vivo in human LH-releasing hormone receptor-pos. HEC-1B endometrial cancers and NIH:OVCAR-3 ovarian cancers and in the LH-releasing hormone receptor-neg. SK-OV-3 ovarian line. Nude mice bearing these tumors s.c. were injected i.v. with saline soln. (control), AN-152, or doxorubicin at equimolar doses.

LH-releasing hormone receptor expression in tumors and specimens of human reproductive (n = 5) and nonreproductive (n = 15) normal tissues and in hematopoietic stem cells were analyzed with reverse transcriptase-polymerase chain reaction and radioligand binding assay. The tumor vols. of LH-releasing hormone receptor-pos. HEC-1B and NIH:OVCAR-3 cancers were reduced significantly (P <.001) 1 wk after treatment with AN-152 at 700 nmol/20 g or at 300 nmol/20 g. No toxic side effects were obsd. Treatment with doxorubicin arrested tumor growth but did not reduce tumor vol. Doxorubicin at 700 nmol/20 g caused a high mortality rate and at 300 nmol/20 g (B.7 mg/kg) caused a loss of body wt., but no deaths occurred. The growth of LH-releasing hormone receptor-neg. SK-OV-3 cancers was not affected by AN-152. Normal human nonreproductive tissues, hematopoietic stem cells, and vaginal tissue did not express LH-releasing hormone receptors, but LH-releasing hormone receptors were found in the ovary, fallopian tube, cervix, endometrium, and myometrium. Targeted chemotherapeutic LH-releasing hormone analog AN-152 is more effective and less toxic than cytotoxic radical doxorubicin on LH-releasing hormone receptor-pos. tumors. AN-152 could be considered for targeted chemotherapy in patients with ovarian or endometrial cancers.

Answer 69:

### **Bibliographic Information**

#### **Therapeutic efficacy of anti-ErbB2 immunoliposomes targeted by a phage antibody selected for cellular endocytosis.**

Nielsen, Ulrik B.; Kirpotin, Dmitri B.; Pickering, Edward M.; Hong, Keelung; Park, John W.; Refaat Shalaby, M.; Shao, Yi; Benz, Christopher C.; Marks, James D. Department of Anesthesia and Pharmaceutical Chemistry, University of California, San Francisco, CA, USA. *Biochimica et Biophysica Acta, Molecular Cell Research* (2002), 1591(1-3), 109-118. Publisher: Elsevier B.V., CODEN: BBAMCO ISSN: 0167-4889. Journal written in English. CAN 137:215473 AN 2002:634870 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Many targeted cancer therapies require endocytosis of the targeting mol. and delivery of the therapeutic agent to the interior of the tumor cell. To generate single chain Fv (scFv) antibodies capable of triggering receptor-mediated endocytosis, we previously developed a method to directly select phage antibodies for internalization by recovering infectious phage from the cytoplasm of the target cell. Using this methodol., we reported the selection of a panel of scFv that were internalized into breast cancer cells from a nonimmune phage library. For this work, an immunotherapeutic was generated from one of these scFv (F5), which bound to ErbB2 (HER2/neu). The F5 scFv was reengineered with a C-terminal cysteine, expressed at high levels in *Escherichia coli*, and coupled to sterically stabilized liposomes. F5 anti-ErbB2 immunoliposomes were immunoreactive as detd. by surface plasmon resonance (SPR) and were avidly internalized by ErbB2-expressing tumor cell lines in proportion to the levels of ErbB2 expression. F5-scFv targeted liposomes contg. doxorubicin had antitumor activity and produced significant redn. in tumor size in xenografted mice compared to nontargeted liposomes contg. doxorubicin. This strategy should be applicable to generate immunotherapeutics for other malignancies by selecting phage antibodies for internalization into other tumor types and using the scFv to target liposomes or other nanoparticles.

Answer 70:

### **Bibliographic Information**

**pH and chemotherapy.** Raghunand, Natarajan; Gillies, Robert J. Cancer Center Division, University of Arizona Health Sciences Center, Tucson, AZ, USA. *Novartis Foundation Symposium* (2001), 240(Tumour Microenvironment), 199-211. Publisher: John Wiley & Sons Ltd., CODEN: NFSYF7 ISSN: 1528-2511. Journal; General Review written in English. CAN 138:49226 AN 2002:454752 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

A review. In vivo pH measurements by magnetic resonance spectroscopy reveal the presence of large regions of acidic extracellular pH in tumors, with the intracellular pH being maintained in the neutral-to-alk. range. This acid-outside plasmalemmal pH gradient acts to exclude weak base drugs such as the anthracyclines and vinca alkaloids, a behavior that is predicted by the decrease in octanol-water partition coeffs. of Mitoxantrone and doxorubicin with decreasing soln. pH. This pH gradient can be reduced or eliminated in mouse

models of breast cancer by systemic treatment with sodium bicarbonate. The authors have demonstrated tumor alkalization following chronic ad libitum administration of NaHCO<sub>3</sub> and acute i.p. administration of NaHCO<sub>3</sub> to tumor-bearing mice. Chronic treatment of tumor-bearing SCID mice with NaHCO<sub>3</sub> results in an enhancement in MCF-7 tumor xenograft response to doxorubicin. I.p. administration of NaHCO<sub>3</sub> to tumor-bearing C3H/Hen mice prior to treatment with Mitoxantrone results in a >4.5-fold increase in cell-kill in the syngeneic C3H mammary tumor model. Most combination chemotherapy regimens include  $\geq 1$  weak base drug. Apparently, agents such as sodium bicarbonate, Carbicarb, and the diuretic furosemide - which are known to induce metabolic alkalosis in humans - may be useful in enhancing the efficacy of these treatment regimens in humans.

Answer 71:

### Bibliographic Information

**Enhanced antitumor activity of combined pretargeted radioimmunotherapy and paclitaxel in medullary thyroid cancer xenograft.** Kraeber-Bodere, Françoise; Sai-Maurel, Catherine; Campion, Loïc; Faivre-Chauvet, Alain; Mirallie, Eric; Chérel, Michel; Supiot, Stéphane; Barbet, Jacques; Chatal, Jean-François; Thedrez, Philippe. Regional Cancer Center, Institut National de la Santé et de la Recherche Médicale Research Unit 463, CEA, Nantes, Fr. *Molecular Cancer Therapeutics* (2002), 1(4), 267-274. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 137:72777 AN 2002:230852 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A significant antitumor effect assocd. with moderate toxicity was obtained previously with anti-carcinoembryonic antigen  $\times$  anti-diethylene-triaminepentaacetic acid (DTPA)-indium F6-734 bispecific antibody and iodine-131-labeled DTPA-indium bivalent hapten in an animal model of medullary thyroid cancer (MTC). The purpose of this study was to det. whether the cytotoxic agents doxorubicin and paclitaxel, also known as radiosensitizers, improve efficacy of pre-targeted radioimmunotherapy (RIT) in exptl. MTC. Nude mice bearing TT MTC xenograft were treated with F6-734 and iodine-131-labeled DTPA-indium bivalent hapten injected 48 h apart with or without doxorubicin or paclitaxel. The max. tolerated dose (MTD) of RIT was 92.5 MBq (as detd. previously) and that of doxorubicin and paclitaxel 200 and 1000  $\mu$ g, resp. A control group received no treatment. Animal wt., hematotoxicity, tumor vol., and serum calcitonin were monitored for 5 mo. Tumor growth inhibition induced by drugs alone, RIT alone, or combined therapy was characterized by measuring relative tumor vol. 20, 40, and 60 days after treatment to detect additivity or synergism. Mean tumor vol. doubling time (MTVDT) was 13 $\pm$ 4 days in the control group, 15 $\pm$ 8 days in the group treated with the MTD of doxorubicin, and 32 $\pm$ 13 days in the group treated with the MTD of paclitaxel. After RIT alone at 92.5 MBq, MTVDT was 86 $\pm$ 22 days. After RIT at 74 MBq (80% of MTD), MTVDT was 56 $\pm$ 10 days. MTVDT was not significantly different from this value after RIT plus doxorubicin, 60 $\pm$ 16 days (65 and 100% of the resp. single-agent MTDs). Combination of RIT with paclitaxel (65 and 100% of the resp. single-agent MTDs) prolonged the suppression of tumor growth. One complete response was obsd., and MTVDT was 114 $\pm$ 44 days. This value was significantly longer than the value obtained with RIT alone at 74 MBq ( $P < 0.05$ ) or with RIT combined with doxorubicin ( $P < 0.02$ ). The change in serum calcitonin levels paralleled those in tumor vol. Anal.

of dose-response curves at days 20 and 40 showed additivity between RIT and paclitaxel, and anal. at day 60 suggested a synergistic effect. In conclusion, addn. of doxorubicin did not improve RIT efficacy, whereas paclitaxel improved RIT efficacy significantly without increasing toxicity.

Answer 72:

### Bibliographic Information

**The multidrug resistance of tumour cells was reversed by tetrandrine in vitro and in xenografts derived from human breast adenocarcinoma MCF-7/adr cells.** Fu, L. W.; Zhang, Y. M.; Liang, Y. J.; Yang, X. P.; Pan, Q. C. Cancer Center, Sun Yat-Sen University of Medical Sciences, Canton, Peop. Rep. China. *European Journal of Cancer* (2002), 38(3), 418-426. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 137:226258 AN 2002:89030 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Multidrug resistance (MDR) is one of the main obstacles limiting the efficacy of chemotherapy treatment of tumors. One of the main causes of MDR is linked to the over-expression of P-glycoprotein (P-gp). This study aimed to characterize tetrandrine (Tet), a potent inhibitor of P-gp mediated MDR. Cytotoxicity was detd. by the tetrazolium (MTT) assay. A MCF-7/adr cell xenograft model was established to investigate the effect of Tet on reversing MDR in vivo. Mechanistic expts. were conducted to examine the uptake, efflux and accumulation of doxorubicin (Dox) and Fura-2, and to assess lipid membrane fluidity. Tet potentiated the cytotoxicity of Dox; a 20.4-fold reversal of resistance was achieved in the presence of 2.5  $\mu\text{mol/L}$  of Tet. Accumulation and efflux studies with the P-gp substrates, Dox and Fura-2, demonstrated that Tet inhibited the P-gp-mediated drug efflux. In addn., Tet lowered cell membrane fluidity in a concn.-dependent manner. In mice bearing the MDR MCF-7/adr cell xenografts, co-administration of Tet potentiated the antitumor activity of doxorubicin without a significant increase in toxicity. Tet was an extremely potent MDR modulator both in vitro and in vivo, without apparently enhancing the toxicity of the co-administered drugs. Hence, Tet holds great promise as a MDR modulator for the treatment of P-gp-mediated MDR cancers.

Answer 73:

### Bibliographic Information

**Combining radioimmunotherapy and chemotherapy for treatment of medullary thyroid carcinoma: Effectiveness of dacarbazine.** Stein, Rhona; Chen, Susan; Reed, Linda; Richel, Heidi; Goldenberg, David M. Garden State Cancer Center, Belleville, NJ, USA. *Cancer (New York, NY, United States)* (2002), 94(1), 51-61. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 136:259269 AN 2002:57632 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Background.** To enhance the efficacy of chemotherapy for medullary thyroid carcinoma (MTC), we evaluated the effect of combining radioimmunotherapy (RAIT) with 90Y-anticarcinoembryonic antigen (CEA) monoclonal antibody MN-14 and chemotherapy in nude mice bearing human MTC xenografts. A preliminary study evaluated doxorubicin, dacarbazine (DTIC), cyclophosphamide, and vincristine, singly and in combination, for their effect on the growth of MTC xenografts (TT) in nude mice. Given individually, DTIC yielded the most effective tumor growth inhibition, delaying the mean time to doubling from 1 wk for untreated tumor-bearing mice to 7.5 wk. Administering either the 4 drugs in combination or a 2-drug combination comprised of doxorubicin and DTIC significantly improved the efficacy compared with any single drug alone, increasing the mean doubling time to 10-12 wk. **Methods.** Drug doses were selected to conform to the doses of each drug given clin. For the combined modality therapy, administration of 90Y-labeled anti-CEA monoclonal antibody MN-14 to nude mice bearing established TT tumors was followed by various chemotherapy regimens initiated 24 h after RAIT. Chemotherapy protocols combined with RAIT included doxorubicin or DTIC alone and in combination, and the doxorubicin, DTIC, cyclophosphamide, and vincristine 4-drug protocol. Tumor vols. were measured weekly, and toxicity was evaluated by measuring blood counts and body wt. **Results.** Combinations of RAIT and chemotherapy with DTIC or RAIT and chemotherapy with the drug combinations were found to augment the antitumor effects of RAIT or chemotherapy alone, without a significant increase in toxicity. The mean tumor vol. doubling times were increased up to 100% compared with the results of chemotherapy alone. No significant differences in tumor growth were obsd. between the RAIT plus DTIC protocol and the RAIT plus two- or four-drug protocols. **Conclusions.**

The superiority of the combined modality treatment argues for the integration of RAIT into chemotherapeutic regimens for MTC treatment. Clin. trials are needed to assess these principles in MTC patients.

Answer 74:

### Bibliographic Information

**Inhibition of in vivo proliferation of MDA-PCa-2b human prostate cancer by a targeted cytotoxic analog of luteinizing hormone-releasing hormone AN-207.** Plonowski, Artur; Schally, Andrew V.; Nagy, Attila; Groot, Kate; Krupa, Magdalena; Navone, Nora M.; Logothetis, Christopher. Veterans Administration Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, USA. *Cancer Letters (Shannon, Ireland)* (2002), 176(1), 57-63. Publisher: Elsevier Science Ireland Ltd., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 136:257507 AN 2002:41282 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The efficacy of therapy with targeted cytotoxic LH-releasing hormone (LHRH) analog AN-207 consisting of superactive doxorubicin deriv. AN-201 linked to carrier [D-Lys6]LH-RH was evaluated in vivo in nude mice bearing xenografts of MDA-PCa-2b prostate cancer line. AN-207 was administered i.v. at 200 nmol/kg on day 1 and at 150 nmol/kg on day 14. After 4 wk of treatment with AN-207, tumor growth was inhibited as shown by a 63% decrease in tumor vol. and a 55% redn. in tumor wt., compared with controls. None of the animals died after administration of AN-207 at the total dose of 350 nmol/kg, and at the end of the expt. the body wts. of mice given AN-207 did not differ significantly from controls. A single injection of cytotoxic radical AN-201 at 200 nmol/kg resulted in 43% mortality. In the surviving mice, AN-201 caused a 50% inhibition in tumor vol. and a 27% redn. in tumor wt., which were non-significant, as compared to the controls. After 4 wk, serum prostate-specific antigen concns. in mice treated with AN-207 were 65% lower than those in controls, while in animals given AN-201 the redn. in serum prostate-specific antigen was only 40% (NS). The expression of mRNA for LHRH receptors was detected by reverse transcriptase polymerase chain reaction (RT-PCR) in MDA-PCa-2b tumors. The present study indicates that chemotherapy targeted to LHRH receptors on tumors inhibits growth of MDA-PCa-2B prostate cancers representative of human carcinoma disseminated to the bone and progressing despite androgen withdrawal.

Answer 75:

**Bibliographic Information**

**Pharmacokinetics of Bcl-2 antisense oligonucleotide (G3139) combined with doxorubicin in SCID mice bearing human breast cancer solid tumor xenografts.** Lopes de Menezes, Daniel E.; Mayer, Lawrence D. Department of Advanced Therapeutics, B.C. Cancer Research Centre, Vancouver, BC, Can. Cancer Chemotherapy and Pharmacology (2002), 49(1), 57-68. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 137:272796 AN 2001:914696 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The aim was to evaluate the pharmacokinetic (PK) properties of Bcl-2 antisense oligodeoxynucleotide G3139 when combined with the anthracycline anticancer drug doxorubicin (DOX) in a model of MDA435/LCC6 human breast cancer in severely compromised immunodeficient (SCID) mice. An orthotopic model of MDA435/LCC6 solid breast tumors was developed by bilateral implantation of passaged cells in female SCID-RAG2 mice. The G3139 plasma profile was compared for two common routes of administration (i.v. or i.p.) in single and multiple dose treatment regimens of 5 mg/kg G3139 alone or with simultaneous DOX (5 mg/kg) administration. At selected times, plasma and major organs were assayed for [<sup>3</sup>H]G3139 using scintillation counting and DOX detd. using HPLC. The mol. integrity of G3139 was analyzed using SDS-PAGE. The PKs of G3139 and DOX were evaluated using a two-compartment model. G3139 administered i.v. at 5 mg/kg revealed a biexponential plasma concn.-time curve with a C<sub>max</sub> of 99.9 μg/mL and elimination half-lives of 0.03 h and 9.8 h, resp., which resulted in an area under the concn.-time curve (AUC) of 15.9 μg·h/mL. G3139 administered i.p. showed a plasma absorption, distribution and elimination profile typical of this route of administration, characterized by half-lives of 0.03 h, 0.2 h and 8.9 h, resp. and a C<sub>max</sub> of 8.6 μg/mL. Based on AUC comparisons, the bioavailability of G3139 injected i.p. was 84% compared to i.v. administration. Subtle changes were obsd. in G3139 PKs after three prior i.p. doses of G3139. Specifically, a sixfold slower absorption rate, lower C<sub>max</sub> (6.9 μg/mL), increased T<sub>max</sub> (0.2 h), and an AUC of 17.4 μg·h/mL were obsd., consistent with concns. approaching satn. levels in tissue sites to which G3139 distributes. Coadministration of DOX had significant effects on the PK properties of G3139, manifested by an increased C<sub>max</sub> (11.2 μg/mL), higher AUC (19.7 μg·h/mL), and ninefold lower plasma clearance for single-dose G3139 administration.

G3139 in plasma remained largely intact (<17% degraded in plasma over 4 h), and increased plasma protein assocn. occurred as a function of time. G3139 was detected in both healthy and tumor tissue after i.v. and i.p. administration. The highest tissue levels of G3139 were obsd. in the kidneys (40 μg/g), and low levels (<2 μg/g) were detected in lung, heart and muscle. The rate of accumulation of G3139 in organs was dependent upon G3139 levels in plasma and the presence of coadministered DOX. Significant accumulation of G3139 was obsd. in solid tumors, with peak levels of approx. 5 μg G3139/g tumor, and approx. a two- to threefold tumor/muscle AUC ratio. The kinetics of G3139 accumulation in tumor tissue increased with increasing circulating G3139 concn. The tissue distribution properties of DOX were also altered in the presence of coadministered G3139: in the presence of G3139, tumor exposure to DOX increased two- to threefold without alteration in plasma DOX PKs. These findings indicate that drug-drug interactions between G3139 and DOX are modest and favorable in that elevated tumor DOX levels are achieved without compromising G3139 tumor uptake or significantly altering plasma drug concns.

Answer 76:

**Bibliographic Information**

**Targeting Stealth liposomes in a murine model of human small cell lung cancer.** Moreira, Joao N.; Gaspar, Rogerio; Allen, Theresa M. Department of Pharmacology, University of Alberta, Edmonton, AB, Can. *Biochimica et Biophysica Acta, Biomembranes* (2001), 1515(2), 167-176. Publisher: Elsevier B.V., CODEN: BBBMBS ISSN: 0005-2736. Journal written in English. CAN 137:129663 AN 2001:856895 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Tumor accumulation and therapeutic activity of Stealth liposomes loaded with doxorubicin (DXR) were examd. in Balb/c nude mice xenografts inoculated s.c. with the human small cell lung cancer (SCLC) cell line, H69. Mice were treated with non-targeted liposomes (SL) or liposomes targeted with antagonist G coupled to the liposome surface (SLG). SLG showed 30-44-fold higher binding to H69 cells harvested from H69 xenografts than SL. At 48 and 72 h post injection, tumor accumulation of [<sup>125</sup>I]tyraminylinulin-contg. liposomes was shown to be dependent on liposome size but independent of the presence of the targeting ligand. Maximum tumor uptake of either SLG or SL ranged from 2 to 4% of injected dose/g of tissue. In therapeutic studies, mice received three weekly injections of 3 or 6 mg free DXR/kg or 3 or 10 mg liposomal DXR/kg at initial tumor vols. of either 7 or 33 mm<sup>3</sup>. The therapeutic efficacy of DXR-contg. SL or SLG was significantly improved over free DXR, but SLG did not improve anti-tumor efficacy relative to SL. Stealth liposomes contg. DXR have potential as a therapy against human SCLC tumors.

Answer 77:

**Bibliographic Information**

**Experimental chemotherapy against canine mammary cancer xenograft in SCID mice and prediction of its clinical effect.** Yamashita, Atsuko; Maruo, Kohji; Suzuki, Kaoru; Shiota, Kinji; Kobayashi, Kimio; Hioki, Kyoji. Department of Veterinary Surgery, Tokyo University of Agriculture and Technology, Tokyo, Japan. *Journal of Veterinary Medical Science* (2001), 63(8), 831-836. Publisher: Japanese Society of Veterinary Science, CODEN: JVMSEQ ISSN: 0916-7250. Journal written in English. CAN 136:379575 AN 2001:706827 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The effectiveness of 6 antitumor agents was evaluated for a canine mammary gland tumor (CMG-6) serially transplanted into mice with severe combined immunodeficiency. CMG-6, a solid carcinoma, was s.c. transplanted into immunodeficient mice, and 6 antitumor agents were given i.v. as a single injection. The min. EDs (MEDs; mg/kg) in mice were: cyclophosphamide (CPM) 65, doxorubicin (DXR) 6, cisplatin (CDDP) 5, vincristine (VCR) 1.6, vinblastine (VLB) >5.5, 5-fluorouracil (5-FU) 105. The clin. effects of the drugs were predicted based on the ratio of the area under the curve (AUC) in dogs given a clin. dose (AUC dog) to the AUC of mice given a MED (AUC mouse) from published refs. The AUC ratios were: CPM 2.24, DXR 0.19, CDDP 1.20, VCR 0.04, VLB <1.24 and 5-FU 1.15. The drugs having a value of >1.0 for the AUC dog/AUC mouse ratio were CPM, CDDP and 5-FU, suggesting that they might be effective in the original dogs with CMG-6. Combination chemotherapy using clin. equiv. doses of CDDP and CPM, which had the two highest values of the AUC dog/AUC mouse ratio in single-agent therapy, had addnl. effects as compared to the effectiveness of the single agents against CMG-6.

Answer 78:

**Bibliographic Information**

**Targeting of doxorubicin to ES-2 human ovarian cancers in nude mice by linking to an analog of luteinizing hormone-releasing hormone improves its effectiveness.** Arencibia, Jose M.; Schally, Andrew V.; Krupa, Magdalena; Bajo, Ana M.; Nagy, Attila; Szepeshazi, Karoly; Plonowski, Artur. Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center and Section of Experimental Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, LA, USA. *International Journal of Oncology* (2001), 19(3), 571-577. Publisher: International Journal of Oncology, CODEN: IJONES ISSN:

1019-6439. Journal written in English. CAN 136:334856 AN 2001:660074 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Receptors for LH-releasing hormone (LHRH), expressed by ovarian cancers, can be used for targeting chemotherapeutic compds. more selectively to these tumors. The authors investigated the effects of cytotoxic LHRH analog AN-152, consisting of doxorubicin (DOX)-14-O-hemiglutarate linked to the  $\epsilon$ -amino group of [D-Lys6]LHRH, on the growth of LHRH receptor-pos. ES-2 human ovarian cancer line xenografted into nude mice. A single injection of AN-152, at a dose of 345 nmol/20 g body wt., caused a 34.5% redn. in tumor growth after 28 days, while its cytotoxic moiety DOX was inactive at the same dose. Since the overexpression of certain growth factors and/or their receptors, such as vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and HER-2/neu, as well as various oncogenes like c-fos and c-jun, is assocd. with unfavorable prognosis and contributes to progressive growth of ovarian carcinomas, their mRNA levels were analyzed by RT-PCR. Treatment with AN-152 significantly reduced the expression of EGFR, VEGF, c-fos and c-jun, to 49, 48, 55, and 58% resp., compared to controls. HER-2/neu mRNA expression was also decreased to non-detectable levels. Conversely, DOX decreased non-significantly the expression levels for EGFR by 32, VEGF 35, both c-fos and c-jun approx. 20 and HER-2/neu by only 15%. In conclusion, cytotoxic LHRH analog AN-152 could be considered for chemotherapy of ovarian cancers expressing LHRH receptors.

Answer 79:

### Bibliographic Information

#### **Three percent dietary fish oil concentrate increased efficacy of doxorubicin against MDA-MB 231 breast cancer xenografts.**

Hardman, W. Elaine; Avula, C. P. Reddy; Fernandes, Gabriel; Cameron, Ivan L. Departments of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. *Clinical Cancer Research* (2001), 7(7), 2041-2049. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 136:272764 AN 2001:572692 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Omega 3 polyunsatd. fatty acids (the type of fat found in fish oil) have been used to kill or slow the growth of cancer cells in culture and in animal models and to increase the effectiveness of cancer chemotherapeutic drugs. An AIN-76 diet contg. 5% corn oil (CO) was modified to contain 3% wt./wt. fish oil conc. (FOC) and 2% CO to test whether a clin. applicable amt. of FOC is beneficial during doxorubicin (DOX) treatment of cancer xenografts in mice. Compared with the diet contg. 5% CO, consumption of FOC increased omega 3 polyunsatd. fatty acids and lipid peroxidn. in tumor and liver, significantly decreased the ratio of glutathione peroxidase activity to superoxide dismutase activity (a putative indicator of increased oxidative stress) in tumor but not in the liver, and significantly decreased the tumor-growth rate. The decreased glutathione peroxidase:superoxide dismutase ratio, indicating an altered redox state, in the tumor of FOC-fed mice was significantly correlated with decreased tumor-growth rate. Assay of the body wt. change, blood cell counts, and no. of micronuclei in peripheral erythrocytes indicated that the toxicity of DOX to the host mouse was not increased in mice fed FOC. Thus, a small amt. of FOC increased the effectiveness of DOX but did not increase the toxicity of DOX to the host mouse. These pos. results justify clin. testing of FOC in conjunction with cancer chemotherapy.

Answer 80:

### Bibliographic Information

#### **Combination chemotherapy and photodynamic therapy of targetable N-(2-hydroxypropyl)methacrylamide copolymer-doxorubicin/mesochlorin e6-OV-TL 16 antibody immunoconjugates.**

Shiah, J.-G.; Sun, Y.; Kopeckova, P.; Peterson, C. M.; Straight, R. C.; Kopecek, J. Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, USA. *Journal of Controlled Release* (2001), 74(1-3), 249-253. Publisher: Elsevier Science Ireland Ltd., CODEN: JCREEC ISSN: 0168-3659. Journal written in English. CAN 136:345603 AN 2001:572422 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The aim of this study was to evaluate the combination chemotherapy and photodynamic therapy of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound doxorubicin (DOX) and mesochlorin e6 (Mce6) targeted with an OV-TL 16 monoclonal antibody (P-DOX-Ab and P-Mce6-Ab, resp.) in nude mice bearing human ovarian OVCAR-3 carcinoma xenografts. P-DOX-Ab and P-Mce6-Ab were synthesized by first conjugating DOX or Mce6 to an HPMA copolymer precursor (Mw=21000), then reacting with OV-TL 16 antibody. The immunoconjugates were purified by size exclusion chromatog. on Superose 6 column and analyzed. The Mce6 concn. in tissues was detd. by a fluorescence assay. Eighteen hours after administration, the tumors received a light dose of 220 J/cm<sup>2</sup> from a KTP 650-nm dye-laser. P-DOX-Ab and P-Mce6-Ab had polymer:drug:protein wt. ratios of 32:3:62 and 26:2:72, corresponding to polymer:drug:protein mol. ratios of approx. 4:14:1 and 3:8:1, resp. The biodistribution results indicated that the percentage of total administered dose of Mce6 in tumors reached approx. 1% for the nontargeted conjugate at 18 h after administration, while that of P-Mce6-Ab was approx. 13 times higher. Nude mice bearing OVCAR-3 xenografts that received one i.v. dose of P-DOX-Ab (2.2 mg/kg DOX equiv.) and P-Mce6-Ab (1.5 mg/kg Mce6 equivalent) with light irradiation achieved a xenograft cure rate of more than 60%. The incorporation of OV-TL 16 antibody dramatically enhanced the accumulation in tumors with a concomitant increase in the therapeutic efficacy of P-DOX-Ab and P-Mce6-Ab in combination therapy, which may probably be attributed to both antibody targeting and enhanced permeability and retention (EPR) effects.

Answer 81:

**Bibliographic Information**

**In vivo antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumor xenograft models including several lung and gastric tumors.** Sato, Y.; Kashimoto, S.; MacDonald, J. R.; Nakano, K. Discovery Research Laboratories, Department of Pharmacology II, Dainippon Pharmaceutical Co., Ltd., Suita, Osaka, Japan. *European Journal of Cancer* (2001), 37(11), 1419-1428. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 136:288614 AN 2001:483139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The in vivo antitumor efficacy of MGI-114 (a semisynthetic analog of the cytotoxic sesquiterpenoid illudins) was examined in a panel of human tumor xenografts in mice, consisting mainly of human lung and gastric tumors, and compared with that of other antitumor drugs (irinotecan, paclitaxel, cisplatin, doxorubicin, vindesine, etoposide and 5-fluorouracil). When different administration schedules were compared, daily administration of MGI-114 was more effective than intermittent administrations. In human tumor xenograft models of nasopharyngeal, breast and colon carcinoma and melanoma, MGI-114 exerted a strong antitumor activity, with complete tumor regression occurring. Moreover, in four human lung and three gastric tumor xenografts, MGI-114 had a strong antitumor activity, with complete tumor regression occurring in some cases. The antitumor efficacy of MGI-114 was generally higher than or equiv. to that of irinotecan and paclitaxel. These results support the potential utility of MGI-114 in the treatment of a variety of human solid tumors.

Answer 82:

**Bibliographic Information**

**Frederine, a new and promising protector against doxorubicin-induced cardiotoxicity.** van Acker, Frederique A. A.; Boven, Epie; Kramer, Klaas; Haenen, Guido R. M. M.; Bast, Aalt; van der Vijgh, Wim J. F. Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, Neth. *Clinical Cancer Research* (2001), 7(5), 1378-1384. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 136:193761 AN 2001:433613 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The flavonoid 7-monohydroxyethylrutoside (mono-HER) can protect against doxorubicin-induced cardiotoxicity. A drawback of monoHER therapy would be the relatively high dose needed to obtain complete protection (500 mg/kg in mice). Therefore, we

synthesized a series of new compds. with improved antioxidant properties. After characterization of antioxidant activity, cardioprotection in vitro, and possible toxic properties in hepatocytes, we selected Frederine for addnl. investigations in vivo. In the present study, it was found that this compd. did not induce wt. loss or (gross) organ changes in mice in a treatment schedule of 170 mg/kg i.p., 5 times/wk during 2 wk. We recorded the ECG telemetrically in mice during and 2 wk after the combined treatment with doxorubicin (4 mg/kg, i.v.) and 5 times Frederine (68 mg/kg, i.p.; equimolar to 100 mg/kg monoHER) for 6 wk. Complete protection against doxorubicin-induced cardiotoxicity was found, indicating that Frederine is at least 5 times more potent than monoHER. Frederine did not have a neg. influence on the antiproliferative effects of doxorubicin on A2780, OVCAR-3, and MCF-7 cells in vitro and on OVCAR-3 xenografts grown in nude mice when administered 5 min before doxorubicin (8 mg/kg i.v.) and 4 days thereafter with an interval of 24 h. It can be concluded that we succeeded in designing a better cardioprotector than monoHER. Therefore, Frederine merits further investigation as a possible protector against doxorubicin-induced cardiotoxicity in cancer patients.

Answer 83:

### Bibliographic Information

**HER2/neu antisense targeting of human breast carcinoma.** Roh, Haeri; Pippin, James A.; Green, Douglas W.; Boswell, Craig B.; Hirose, Christopher T.; Mokadam, Nahush; Drebin, Jeffrey A. Department of Surgery, Washington University School of Medicine, Saint Louis, MO, USA. *Oncogene* (2000), 19(53), 6138-6143. Publisher: Nature Publishing Group, CODEN: ONCNES ISSN: 0950-9232. Journal written in English. CAN 134:216951 AN 2001:158250 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Overexpression of the HER2/neu oncogene is obsd. in approx. 30% of human breast carcinoma specimens. HER2/neu overexpression is a neg. prognostic factor in breast cancer patients. Cancer cells that overexpress HER2/neu may also be less sensitive to chemotherapy. In order to further define mechanisms by which HER2/neu overexpression drives neoplastic cell growth and chemoresistance, antisense oligonucleotides (ODNs) have been utilized to selectively down-regulate HER2/neu expression in human breast cancer cells. Such antisense ODNs suppress HER2/neu mRNA and protein levels in a dose-dependent, sequence-specific manner. Down-regulation of HER2/neu expression in HER2/neu overexpressing breast cancer cells inhibits cell cycle progression in G0/G1 and results in apoptotic cell death. In tissue culture studies, combined treatment of HER2/neu overexpressing breast cancer cells with HER2/neu antisense ODNs and conventional chemotherapeutic agents results in synergistic inhibition of cancer cell growth and activation of apoptotic cell death mechanisms. These studies have been extended to demonstrate synergistic antitumor effects following systemic treatment with antisense ODNs plus doxorubicin in nude mice bearing human breast carcinoma xenografts. Collectively these findings demonstrate that HER2/neu overexpression stimulates anti-apoptotic cell survival mechanisms and suggest that HER2/neu antisense ODNs may be of use in cancer therapeutics.

Answer 84:

### Bibliographic Information

**Cardioprotective effects of zofenopril, a new angiotensin-converting enzyme inhibitor, on doxorubicin-induced cardiotoxicity in the rat.** Sacco, G.; Bigioni, M.; Evangelista, S.; Goso, C.; Manzini, S.; Maggi, C. A. Department of Pharmacology, Menarini Ricerche, Rome, Italy. *European Journal of Pharmacology* (2001), 414(1), 71-78. Publisher: Elsevier Science B.V., CODEN: EJPHAZ ISSN: 0014-2999. Journal written in English. CAN 134:361161 AN 2001:147273 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

We have studied the effect of zofenopril, a new angiotensin-converting enzyme inhibitor in preventing cardiac injury induced by chronic doxorubicin treatment in rats. Cardiac function was assessed by measuring changes in ECG tracings, hemodynamics and cardiac responses in vivo to isoprenaline, 4 wk after suspension of doxorubicin treatment, in vehicle-treated rats and in animals receiving zofenopril (15 mg/kg/os/day) alone, doxorubicin (1.5 mg/kg i.v. once a week for 5 wk) or zofenopril+doxorubicin treatment. Doxorubicin

induced a significant lengthening of the Q<sub>α</sub>T interval, which was completely prevented by zofenopril treatment. The cardiac pos. inotropic effect induced by i.v. isoprenaline was selectively depressed by doxorubicin (no changes in chronotropic responses) and this adverse effect of doxorubicin was also prevented in zofenopril+doxorubicin pretreated rats. Doxorubicin induced a significant increase in relative heart wt., which was likewise prevented in zofenopril+doxorubicin treated rats. In sep. expts., zofenopril did not interfere with the antitumor activity of doxorubicin (inhibition of tumor growth in nude mice xenografted with A2780 human tumor line). In conclusion, the oral administration of zofenopril is able to significantly ameliorate, up to 4 wk after the end of doxorubicin administration, doxorubicin-induced cardiotoxicity without affecting the antitumor activity of this anthracycline.

Answer 85:

#### **Bibliographic Information**

##### **PSA-specific and non-PSA-specific conversion of a PSA-targeted peptide conjugate of doxorubicin to its active metabolites.**

Wong, Bradley K.; Defeo-Jones, Deborah; Jones, Raymond E.; Garsky, Victor M.; Feng, Dong-Mei; Oliff, Allen; Chiba, Masato; Ellis, Joan D.; Lin, Jiunn H. Drug Metabolism, Merck Research Laboratories, West Point, PA, USA. Drug Metabolism and Disposition (2001), 29(3), 313-318. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: DMSAI ISSN: 0090-9556. Journal written in English. CAN 134:320505 AN 2001:146172 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Tumor-selective delivery of doxorubicin by a prostate-specific antigen (PSA)-targeted peptide conjugate prodrug of doxorubicin was demonstrated in a nude mouse xenograft model of human prostate cancer. The prodrug (referred to as doxorubicin conjugate) contains doxorubicin linked to a seven-amino acid peptide conjugate that was designed to increase delivery of doxorubicin to tumor sites through the hydrolytic properties of PSA, which prostate tumors express in high amts. Following i.p. administration of the doxorubicin conjugate to mice, tumor exposure to doxorubicin was increased 2.5-fold as compared with that achieved after an equimolar dose of doxorubicin itself. However, in heart tissue, the site of clin. dose-limiting toxicity, doxorubicin concns. obsd. after administration of doxorubicin conjugate were substantially lower than those in mice that received doxorubicin itself. While the prodrug provided selective delivery of doxorubicin to tumor tissue, there was substantial non-PSA-specific formation of doxorubicin in lab. animals, a factor that would limit the extent of therapeutic gain of the prodrug. Following i.v. administration to mice, rats, dogs, and monkeys, about one-third of the dose was metabolized to doxorubicin. In tumor-bearing mice, the fraction of the dose metabolized to doxorubicin appeared even higher. This is likely the result of conjugate conversion to doxorubicin by both PSA-specific (in tumor) and non-PSA-specific proteolytic activities. In vitro studies provided further support for the PSA specificity of metab.; LNCaP cells mediated rapid metab. of the conjugate, while DuPRO-1 cells, which are deficient in PSA, were incapable of metab.

Answer 86:

#### **Bibliographic Information**

##### **Pegylated liposome-encapsulated doxorubicin and cisplatin enhance the effect of radiotherapy in a tumor xenograft model.**

Harrington, Kevin J.; Rowlinson-Busza, Gail; Syrigos, Konstantinos N.; Vile, Richard G.; Uster, Paul S.; Peters, A. Michael; Stewart, J. Simon W. Imperial Cancer Research Fund, Oncology Unit Imperial College of Science, Technology and Medicine, Hammersmith Hospital, London, UK. Clinical Cancer Research (2000), 6(12), 4939-4949. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 135:118855 AN 2001:83384 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Concomitant chemotherapy and radiotherapy (CCRT) has recently been shown to improve treatment outcome in a range of solid tumors. Pegylated liposomes have the potential to target drugs directly to tumors and may increase the efficacy and reduce the toxicity of CCRT by selectively delivering radiosensitizing agents to tumor, as opposed to normal, tissues. In these studies, we have assessed CCRT using pegylated liposome encapsulated doxorubicin (PLED) and pegylated liposome encapsulated cisplatin (PLEC) against KB head and neck cancer xenograft tumors in nude mice. The addn. of low-dose (2 mg/kg) PLED (P < 0.001) and PLEC (P <

0.001) significantly increased the effect of 4.5 Gy, but not 9 Gy, single-fraction radiotherapy (SFRT). Both PLED and PLEC were significantly more effective than their unencapsulated counterparts in increasing the effect of SFRT. In addn., PLED ( $P < 0.001$ ) and PLEC ( $P < 0.05$ ) significantly increased the effect of fractionated radiotherapy (9 Gy in 3 fractions) in two different dosing schedules (2 mg/kg single dose or three sequential doses of 0.67 mg/kg). Unencapsulated diethylenetriaminepentaacetic acid and pegylated liposomal diethylenetriaminepentaacetic acid were used as controls to test the effect of the liposome vehicle and showed no interaction with 4.5 Gy or 9 Gy SFRT ( $P > 0.1$ ). CCRT was well-tolerated, with no evidence of increased local or systemic toxicity, as compared with radiotherapy alone. This study is the first to demonstrate the value of pegylated liposomes as vehicles for the delivery of radiosensitizing drugs in CCRT strategies.

Answer 87:

#### Bibliographic Information

**Biodistribution and antitumor efficacy of long-circulating N-(2-hydroxypropyl)methacrylamide copolymer-doxorubicin conjugates in nude mice.** Shiah, J.-G.; Dvorak, M.; Kopeckova, P.; Sun, Y.; Peterson, C. M.; Kopecek, J. Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD, University of Utah, Salt Lake City, UT, USA. *European Journal of Cancer* (2001), 37(1), 131-139. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 135:116668 AN 2001:73751 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The aim of this study was to evaluate the influence of the mol. wt. of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-doxorubicin (DOX) conjugates (P-DOX) on biodistribution and therapeutic efficacy in nu/nu mice bearing human ovarian carcinoma OVCAR-3 xenografts. Copolymn. of HPMA, a polymerizable deriv. of DOX (N-methacryloylglycylphenylalanylleucylglycyl doxorubicin) and a newly designed crosslinking agent, N<sub>2</sub>,N<sub>5</sub>-bis(N-methacryloylglycylphenylalanyl-leucylglycyl)ornithine Me ester monomers resulted in novel, high mol. wt, branched, water-sol. P-DOX contg. lysosomally degradable oligopeptide sequences as crosslinks and side-chains terminated in DOX. Four conjugates with mol. wt of 22, 160, 895 and 1230 kDa were prepd. The results indicated that the half-life in blood and the elimination rate from the tumor were up to 28 times longer and 25 times slower, resp., for P-DOX (mol. wt=1230 kDa) than for free DOX. Treatment with P-DOX (mol. wt $\geq$ 160 kDa) inhibited tumor growth more efficiently than that of 22 kDa P-DOX or free DOX ( $P < 0.02$ ) at a 2.2 mg/kg DOX equiv. dose. In conclusion, the administration of long circulating P-DOX resulted in enhanced tumor accumulation with a concomitant increase in therapeutic efficacy.

Answer 88:

#### Bibliographic Information

**Antibody targeting of doxorubicin-loaded liposomes suppresses the growth and metastatic spread of established human lung tumor xenografts in severe combined immunodeficient mice.** Sugano, Masahiko; Egilmez, Nejat K.; Yokota, Sandra J.; Chen, Fang-An; Harding, Jennifer; Huang, Shi Kun; Bankert, Richard B. Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. *Cancer Research* (2000), 60(24), 6942-6949. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 134:246973 AN 2001:34705 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

$\beta$ 1 Integrins, expressed on the cell surface of human non-small cell lung carcinomas, are used here as a target for the selective delivery of anti-cancer drug-loaded liposomes. Fab' fragments of a monoclonal antibody specific for human  $\beta$ 1 integrins were conjugated to sterically stabilized liposomes. Confocal microscopy of  $\beta$ 1 integrin-pos. lung tumor cells incubated with fluorescently labeled anti- $\beta$ 1 Fab immunoliposomes revealed a tumor-specific binding and efficient internalization of the liposomes into the tumor cells. The ability of these liposomes to deliver cytotoxic drugs to the tumor and kill these cells was demonstrated in vitro by incubating tumor cells with doxorubicin-loaded anti- $\beta$ 1 Fab' immunoliposomes. The drug-loaded immunoliposomes were >30-fold more cytotoxic to the tumor cells than drug-loaded liposomes without antibody, nonspecific Fab' control immunoliposomes with drug or

immunoliposomes without drug. The therapeutic efficacy of doxorubicin-loaded immunoliposomes was also evaluated in a metastatic human lung tumor xenograft/severe combined immunodeficient (SCID) mouse model. SCID mice that received i.v. injections of human lung tumor cells developed primary tumor nodules in the lung that subsequently metastasized to the liver and adrenal gland. Treatment of SCID mice bearing established lung tumor xenografts with doxorubicin-loaded anti- $\beta$ 1 Fab immunoliposomes resulted in a significant suppression of tumor growth (monitored periodically by quantifying serum levels of a tumor marker), whereas tumors grew progressively in mice treated with control formulations. In addn. to suppressing the growth of the primary lung tumor nodules, the immunoliposomes prevented the metastatic spread of the tumor to the liver and adrenal glands and increased the median survival time of the tumor-bearing mice. We conclude that Fab' immunoliposomes directed to tumor-assocd. integrins represent a potentially viable approach clin.

for the selective delivery of drugs to solid tumors and may be useful in preventing the metastatic spread of lung cancer.

Answer 89:

### Bibliographic Information

**Role of caspases in cellular signal transduction pathways of apoptosis induced by free and HPMA copolymer-bound doxorubicin.** Minko, T.; Kopeckova, P.; Kopecek, J. Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, USA. Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000), 27th 71-72. Publisher: Controlled Release Society, Inc., CODEN: PCRMEY ISSN: 1022-0178. Journal written in English. CAN 134:202472 AN 2000:671832 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Caspases are the mol. instigators of apoptosis. Recently, it has been shown that treatment of human ovarian carcinoma cells and mice xenografts by N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound doxorubicin (P(GFLG)-DOX) more significantly induced cell death and demonstrated different apoptosis signaling pathways when compared with free doxorubicin (DOX). Specifically, it was found that P(GFLG)-DOX inhibited drug detoxification and other cellular defensive mechanisms. The main pathways involved in apoptosis induction by P(GFLG)-DOX include the DNA damage produced by DOX directly or through c-fos/c-jun pathways; p53 gene-dependent central cell death signal; alteration of mitochondrial homeostasis, release of cytochrome c into the cytosol and Apaf-1 mediated activation of caspase-9 (C-9). It was hypothesized that caspase-9 might trigger other caspase activation events finally resulting in addnl. DNA damage and cell death. To verify the hypothesis, the role of caspases in signaling pathways of apoptosis induced by free DOX and P(GFLG)-DOX was investigated. P(GFLG)-DOX effectively induced apoptosis by more significant activation of C9-C3 and C9-C7 signaling pathways when compared with free DOX, and triggering an addnl. C9-C3-C6 pathway and the C9-C3-C6-C8-C9 feedback loop.

Answer 90:

### Bibliographic Information

**Enhanced therapeutic efficacy of Bcl-2 antisense oligonucleotide G3139 combined with sterically-stabilized liposomal doxorubicin.** Lopes de Menezes, D.; Hudon, N.; McIntosh, N.; Mayer, L. Department of Advanced Therapeutics, B. C. Cancer Agency, BC, Can. Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000), 27th 31-32. Publisher: Controlled Release Society, Inc., CODEN: PCRMEY ISSN: 1022-0178. Journal written in English. CAN 134:216881 AN 2000:671795 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A study was conducted to characterize the mol. and pharmacol. effects of Bcl-2 antisense oligonucleotide G3139 alone and in combination with free doxorubicin or sterically-stabilized doxorubicin in a Bcl-2-expressing human breast solid tumor (MDA435/LCC6) xenograft model in SCID mice. In addn., these two doxorubicin formulations combined with G3139 were used to investigate the effect drug pharmacodistribution may have on antitumor activity. Results suggest that addnl. benefits of Bcl-2 antisense oligonucleotides may be obtained when combined with liposomal formulations of anticancer drugs such as doxorubicin.

Answer 91:

#### Bibliographic Information

**Effects of mitomycin C and carboplatin pretreatment on multidrug resistance-associated P-glycoprotein expression and on subsequent suppression of tumor growth by doxorubicin and paclitaxel in human metastatic breast cancer-xenografted nude mice.** Ihnat, Michael A.; Nervi, Angela M.; Anthony, Stephen P.; Kaltreider, Ronald C.; Warren, Amy J.; Pesce, Carrie A.; Davis, Stacey A.; Lariviere, Jean P.; Hamilton, Joshua W. Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, USA. *Oncology Research* (1999), 11(7), 303-310. Publisher: Cognizant Communication Corp., CODEN: ONREE8 ISSN: 0965-0407. Journal written in English. CAN 133:344264 AN 2000:517393 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Mitomycin C and carboplatin each suppressed cell P-glycoprotein levels in human MDA-MB-435 cells xenografted as solid tumors into the lateral mammary fat pads of female nude mice, with a similar time course as had previously been obsd. in cell culture. Pretreatment of the mice with mitomycin C or carboplatin 48-72 h prior to receiving either doxorubicin or paclitaxel caused a greater redn. of tumor growth rate than did either of the latter agents alone or given simultaneously. These data suggest that a combination chemotherapy regimen consisting of a DNA crosslinking agent given to modulate the multidrug-resistant phenotype, followed by a 2nd cytotoxic agent, may be an effective treatment for human patients with de novo or late-stage-acquired multidrug-resistant malignancies.

Answer 92:

#### Bibliographic Information

**Mdr1 promoter-driven tumor necrosis factor- $\alpha$  expression for a chemotherapy-controllable combined in vivo gene therapy and chemotherapy of tumors.** Walther, Wolfgang; Stein, Ulrike; Fichtner, Iduna; Alexander, Mark; Shoemaker, Robert H.; Schlag, Peter M. Max-Delbrück-Center for Molecular Medicine, Berlin, Germany. *Cancer Gene Therapy* (2000), 7(6), 893-900. Publisher: Nature America Inc., CODEN: CGTHEG ISSN: 0929-1903. Journal written in English. CAN 133:175967 AN 2000:466621 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Cancer gene therapy approaches are often designed as single-agent treatments; however, greater therapeutic effect might be obtained if combined with an established conventional treatment regimen such as chemotherapy. In this context, conditional promoters are useful tools, because they may be induced by therapeutic modalities. The human multidrug resistance gene (*mdr1*) promoter is inducible by cytostatic drugs and can be employed for the chemotherapy-regulated expression of therapeutic genes. In this in vivo study, the human *mdr1* promoter fragment (-207 to +158) was used for drug-inducible expression of human tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in the vector construct pM3mdr-p-hTNF. The single doxorubicin and vincristine treatment of nude mice xenografted with pM3mdr-p-hTNF-transduced MCF-7 mammary tumors resulted in drug-induced and time-dependent elevation of intratumoral TNF- $\alpha$  expression at the mRNA and protein level. The highest drug induction was achieved at 2 days after drug application, as reflected by a max. 25-fold increase in TNF- $\alpha$  secretion in the tumor. This drug-induced TNF- $\alpha$  expression is more effective in inhibiting tumor growth compared with the growth of tumors transduced with constitutively TNF- $\alpha$ -expressing vectors in combination with chemotherapy.

Answer 93:

#### Bibliographic Information

**The influence of cytotoxicity of macromolecules and of VEGF gene modulated vascular permeability on the enhanced permeability and retention effect in resistant solid tumors.** Minko, Tamara; Kopeckova, Pavla; Pozharov, Vitaliy; Jensen, Keith D.; Kopecek, Jindrich. Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT,

USA. Pharmaceutical Research (2000), 17(5), 505-514. Publisher: Kluwer Academic/Plenum Publishers, CODEN: PHREEB ISSN: 0724-8741. Journal written in English. CAN 133:187662 AN 2000:445977 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

To study the influence of cytotoxicity of macromols., VEGF gene expression, and vascular permeability on the enhanced permeability and retention (EPR) effect. Mice bearing xenografts of A2780 multidrug resistant human ovarian carcinoma were treated by free doxorubicin (DOX) and N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-bound DOX (P(GFLG)-DOX), Texas Red (P-TR), and FITC (P-FITC). Antitumor activity, drug distribution in tumor, vascular permeability, VEGF gene expression, and DNA fragmentation were studied. The accumulation of free DOX led to the VEGF gene overexpression and increased the vascular permeability, which in turn enhanced the drug accumulation in the same location. This pos. feedback loop led to a highly inhomogeneous distribution of the drug within the tumor. In contrast, P(GFLG)-DOX down-regulated the VEGF gene and decreased vascular permeability. This neg. feedback seemed to prevent addnl. drug accumulation in dead necrotic tissue, resulting in a more uniform drug distribution and enhanced the antitumor activity P(GFLG)-DOX. The EPR effect significantly differed for macromols. contg. DOX when compared to macromols. without drug. The cytotoxicity of P(GFLG)-DOX amplified the EPR effect, led to a more homogeneous distribution of the drug, increased the av. drug concn. in tumor and augmented its efficacy.

Answer 94:

### Bibliographic Information

**Plasma Escherichia coli  $\beta$ -galactosidase as a marker of tumor burden and response to experimental anti-neoplastic therapy in nude mice xenografted with lacZ transduced human tumor cells.** Holst-Hansen, Claus; Stephens, Ross Wentworth; Johannessen, Bente Egholm; Jensen, Peter Buhl; Brunner, Nils. The Finsen Laboratory, Copenhagen University Hospital, Copenhagen, Den. Laboratory Investigation (2000), 80(5), 719-724. Publisher: Lippincott Williams & Wilkins, CODEN: LAINAW ISSN: 0023-6837. Journal written in English. CAN 134:53377 AN 2000:415073 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Genetic labeling of tumor cells with the Escherichia coli lacZ reporter gene, encoding the enzyme  $\beta$ -galactosidase, is widely used for histochem. detection of micrometastases in mice. Recently, we have developed a novel, highly sensitive and specific immunocapture chemiluminescence assay for the quantitation of E. coli  $\beta$ -galactosidase. This assay achieved a detection limit of 0.01 mU of E. coli  $\beta$ -galactosidase per mL, and 97% signal recovery of purified enzyme added to mouse plasma. LacZ transduced MDA-MB-231 BAG human breast cancer cells grown in vitro released sol.  $\beta$ -galactosidase into the culture medium, and the concn. found correlated with cell d. Growth of the same cells in nude mice produced readily measurable levels of E. coli  $\beta$ -galactosidase enzyme activity in host plasma and a highly significant correlation could be demonstrated between the size of primary tumor xenografts and the host plasma level of E. coli  $\beta$ -galactosidase activity. When mice bearing MDA-MB-231 BAG tumor xenografts were treated i.v. with a single injection of doxorubicin (5 mg/kg), the mean tumor vol. after 16 days was reduced 4-fold in the group of doxorubicin-treated mice compared with saline-treated control mice, and the mean level of plasma E. coli  $\beta$ -galactosidase was correspondingly reduced 3.8-fold in the doxorubicin-treated mice compared with control mice. Sensitive and specific measurement of sol. E. coli  $\beta$ -galactosidase in blood, using an immunocapture chemiluminescence assay, thus provides objective assessment of tumor burden in mice xenografted with lacZ transduced human tumors. This assay may have important applications as a tool for detg. the efficacy of new exptl. anti-tumor agents.

Answer 95:

### Bibliographic Information

**Discovery and characterization of OC144-093, a novel inhibitor of P-glycoprotein-mediated multidrug resistance.** Newman, Michael J.; Rodarte, Jennifer C.; Benbatoul, Khalid D.; Romano, Suzanne J.; Zhang, Chengzhi; Krane, Sonja; Moran, Edmund J.; Uyeda, Roy T.; Dixon, Ross; Guns, Emma S.; Mayer, Lawrence D. Ontogen Corporation, Carlsbad, CA, USA. Cancer Research

(2000), 60(11), 2964-2972. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 133:187741 AN 2000:397650 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

OC144-093 is a novel substituted diarylimidazole (Mr 495) generated using the OntoBLOCK system, a solid-phase combinatorial chem. technol., in combination with high-throughput cell-based screening. OC144-093 reversed multidrug resistance (MDR) to doxorubicin, paclitaxel, and vinblastine in human lymphoma, breast, ovarian, uterine, and colorectal carcinoma cell lines expressing P-glycoprotein (P-gp) with an av. EC50 of 0.032  $\mu$ M. Inhibition of MDR by OC144-093 was reversible, but the effect persisted for at least 12 h after removal of compd. from the culture medium. OC144-093 had no effect on the response to cytotoxic agents by cells in vitro lacking P-gp expression or expressing a multidrug resistance-assocd. protein (MRP-1). OC144-093 was not cytotoxic by itself against 15 normal, nontransformed, or tumor cell lines, regardless of P-gp status, with an av. cytostatic IC50 of >60  $\mu$ M. OC144-093 blocked the binding of [3H]azidopine to P-gp and inhibited P-gp ATPase activity. The compd. was >50% p.o. bioavailable in rodents and dogs and did not alter the plasma pharmacokinetics of i.v.-administered paclitaxel. OC144-093 increased the life span of doxorubicin-treated mice engrafted with MDR P388 leukemia cells by >100% and significantly enhanced the in vivo antitumor activity of paclitaxel in MDR human breast and colon carcinoma xenograft models, without a significant increase in doxorubicin or paclitaxel toxicity. The results demonstrate that OC144-093 is an orally active, potent, and nontoxic inhibitor of P-gp-mediated multidrug resistance that exhibits all of the desired properties for treatment of P-gp-mediated MDR, as well as for prevention of MDR prior to selection and/or induction of refractory disease.

Answer 96:

#### Bibliographic Information

**Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents.** Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 97:

#### Bibliographic Information

**Significant increase in antitumor potency of doxorubicin HCl by its encapsulation in pegylated liposomes.** Colbern, Gail T.; Hiller, Alan J.; Musterer, Randy S.; Pegg, Erik; Henderson, I. Craig; Working, Peter K. ALZA Corporation, Mountain View, CA, USA. Journal of Liposome Research (1999), 9(4), 523-538. Publisher: Marcel Dekker, Inc., CODEN: JLREE7 ISSN: 0898-2104. Journal written in English. CAN 132:303071 AN 2000:40446 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Pegylated liposomal doxorubicin (PL-DOX or Doxil) is currently being used in the clinic to treat solid tumors in humans (ovarian and breast cancer and Kaposi's sarcoma). Previous preclin. studies comparing the antitumor activity of nonliposomal doxorubicin and PL-DOX have shown that PL-DOX has significantly greater antitumor activity at equiv. doses, but these studies have not reported the degree of increase in antitumor potency assocd. with liposome encapsulation at lower doses of PL-DOX. The studies presented here were designed to det. the dose of PL-DOX that produces the same antitumor activity as the max. tolerated dose (MTD) of nonliposomal doxorubicin. Conventional mice were inoculated with Lewis lung or C26 colon cells, and nude mice were inoculated with BT474 or MCF7 human breast cancer cells. Tumor-bearing mice were treated with nonliposomal doxorubicin at the MTD or with PL-DOX at the same or lower doses. As in previously published studies, PL-DOX had significantly greater antitumor activity than nonliposomal doxorubicin at the same dose levels. In Lewis Lung and C26 Colon carcinoma, antitumor activity of nonliposomal doxorubicin (9 mg/kg, the MTD for conventional mice) was equiv. to antitumor activity of PL-DOX at 2 mg/kg, a 4.5-fold increase in antitumor potency. In human breast cancer xenografts (BT474 and MCF7) in nude mice, antitumor activity of nonliposomal doxorubicin (4 mg/kg, the MTD for nude mice) was equiv. to PL-DOX at 2 mg/kg, a 2-fold increase in potency. Based on results of these studies, the potency of PL-DOX is increased from 2- to 4.5-fold compared to nonliposomal doxorubicin.

Answer 98:

### Bibliographic Information

#### **Enhanced antitumor activity of paclitaxel in combination with the anticarcinoma immunoconjugate BR96-doxorubicin.**

Trail, Pamela A.; Willner, David; Bianchi, Albert B.; Henderson, Arris J.; TrailSmith, Mark D.; Girit, Emel; Lasch, Shirley; Hellstrom, Ingegerd; Hellstrom, Karl Erik. Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA. *Clinical Cancer Research* (1999), 5(11), 3632-3638. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 132:260199 AN 1999:809348 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Combined therapy of athymic rats or mice bearing human tumor xenografts with an anticarcinoma immunoconjugate, BR96-doxorubicin, and the cytotoxic drug paclitaxel resulted in a significant increase in antitumor activity over that of either agent alone. Synergistic activity was seen at doses of BR96-doxorubicin that were minimally active as a single agent. A dramatic increase in regression rates was seen when a regimen that combined BR96-doxorubicin and paclitaxel was used to treat both paclitaxel-sensitive and paclitaxel-insensitive carcinomas. Combined therapy resulted in increased antitumor activity against lung, colon, and breast tumors xenografted in athymic mice and large, paclitaxel-insensitive colon tumors xenografted in athymic rats that also express the Lewis target antigen in normal tissues.

Answer 99:

### Bibliographic Information

#### **Efficacy of treatment of colon, lung and breast human carcinoma xenografts with: doxorubicin, cisplatin, irinotecan or topotecan.**

Hardman, W. Elaine; Moyer, Mary Pat; Cameron, Ivan L. Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. *Anticancer Research* (1999), 19(3B), 2269-2274. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 132:117206 AN 1999:654636 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Given that human cancer xenografts tend to retain chemosensitivities similar to the cancerous tissue of origin, human carcinoma xenografts grown in nude mice were tested for sensitivity to 4 drug protocols: doxorubicin at 5 mg/kg, i.v., every 5 days; irinotecan at 60 mg/kg, i.v., every 4 days; cisplatin at 5 mg/kg, i.p., every 7 days; and topotecan at 1.5 mg/kg, orally, on 5 of 7 days. The irinotecan and doxorubicin protocols either halted or caused significant regression of the breast cancer cell lines (MCF7, MDA-MB 231 and T47D). None of the protocols tested resulted in significant regression of the lung cancer xenografts (H460, A549 and H226) although both irinotecan and doxorubicin did halt growth of the H226 xenograft. The ability of the irinotecan treatment to cause

regression of xenograft size in all 3 colon cancer cell lines (SW620, COLO205 and HT29) justifies further clin. trials of irinotecan as an esp. promising drug for the treatment of colon cancer.

Answer 100:

### **Bibliographic Information**

**Evaluation of amrubicin with a 5 day administration schedule in a mouse model.** Noguchi, Toshihiro; Ichii, Shinji; Morisada, Shinya; Yamaoka, Takashi; Yanagi, Yoshikazu. Research Center, Sumitomo Pharmaceuticals Co., Ltd., Japan. Gan to Kagaku Ryoho (1999), 26(9), 1305-1312. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 132:117202 AN 1999:634563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

It was reported that amrubicin hydrochloride (9-aminoanthracycline; SM-5887), showed a higher therapeutic activity than doxorubicin against human tumor xenografts implanted into nude mice with a single treatment schedule. In order to find a more effective treatment schedule, the efficacy, toxicity and pharmacokinetic properties with a 5 consecutive day treatment schedule were investigated. The total amt. of the max. tolerated dose and tumor growth inhibiting activity with a 5 day schedule was found to be higher than with a single administration. High levels of amrubicinol, the active metabolite of amrubicin, was detected in the tumor tissue. It was thus assumed that the improved efficacy with the 5-day schedule resulted from the high accumulation of amrubicinol. Bone marrow suppression at the MTD with the 5 day schedule was severer than with a single dose, but recovery was rapid, similar to that following a single dose. In conclusion, it was demonstrated that a 5 day treatment schedule was more effective than a single administration.

Answer 101:

### **Bibliographic Information**

**MTA (LY231514) in combination treatment regimens using human tumor xenografts and the EMT-6 murine mammary carcinoma.** Teicher, Beverly A.; Alvarez, Enrique; Liu, Pocheng; Lu, Ku; Menon, Krishna; Dempsey, Jack; Schultz, Richard M. Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, USA. Seminars in Oncology (1999), 26(2, Suppl. 6), 55-62. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 131:125026 AN 1999:290814 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

An important component in the development of a new anticancer drug is an understanding of its potential for inclusion in combination treatment regimens. LY231514, a multitargeted antifolate (MTA), was tested in combination with cisplatin, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, doxorubicin, LY329201 (a glycinamide ribonucleotide formyl-transferase [GARFT] inhibitor), and fractionated radiation therapy in vivo using EMT-6 mammary carcinoma, human HCT 116 colon carcinoma, and human H460 non-small cell lung carcinoma grown as xenografts in nude mice. Isobologram methodol. was used to det. the additivity or synergy of the combination regimens. MTA administered with cisplatin, paclitaxel, docetaxel, or fractionated radiation therapy produced additive to greater than additive tumor response by tumor cell survival assay and tumor growth delay. While an additive tumor response was obsd. when MTA was administered with methotrexate, synergistic tumor responses were seen when MTA was administered with the GARFT inhibitor, LY329201, or with the topoisomerase I inhibitor, irinotecan. MTA was administered in combination with full doses of each anticancer agent studied, with no evidence of increased toxicity resulting from the combination.

Answer 102:

### **Bibliographic Information**

**Targeting of drugs to solid tumors using anti-HER2 immunoliposomes.** Papahadjopoulos, Demetrios; Kirpotin, Dmitri B.; Park, John W.; Hong, Keelung; Shao, Yi; Shalaby, Refaat; Colbern, Gail; Benz, Christopher C. California Pacific Medical Center Research Institute, San Francisco, CA, USA. *Journal of Liposome Research* (1998), 8(4), 425-442. Publisher: Marcel Dekker, Inc., CODEN: JLREE7 ISSN: 0898-2104. Journal; General Review written in English. CAN 130:231718 AN 1999:17476 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A review with 76 refs. Cancer therapy would clearly benefit from a carrier system capable of intracellular delivery of systemically administered drugs to cancer cells in solid tumors. Sterically stabilized immunoliposomes specific to the cells expressing HER2 protooncogene (anti-HER2 SIL), were designed by conjugating Fab' fragments of a recombinant humanized anti-HER2 MAb to the distal termini of poly(ethylene glycol) chains on the surface of unilamellar liposomes (size 90-100 nm) of phosphatidylcholine, cholesterol, and poly(ethylene glycol)-derivatized phosphatidylethanolamine. Anti-HER2 SIL avidly and specifically bound to cultured HER2-overexpressing cancer cells (8,000-23,000 vesicles per cell) and became endocytosed ( $k_e = 0.022-0.033 \text{ min.}^{-1}$ ) via the coated pit pathway. Anti-HER2 SIL showed prolonged circulation lifetime in rats (blood MRT approx. 24 h) and significantly increased antitumor activity of encapsulated doxorubicin against HER2-overexpressing human breast cancer xenografts in nude mice. Although the accumulation of anti-HER2 SIL in HER2-overexpressing tumor xenografts was not increased over that of non-targeted sterically stabilized liposomes (SL), microscopic examn. revealed abundance of anti-HER2 SIL in the interstitial spaces, as well as within the cytoplasm of cancer cells, while identical liposomes lacking anti-HER2 Fab' were located predominantly within tumor-resident macrophages. Anti-HER2 SIL, a targeted vehicle capable of in vivo intracellular delivery of substances to HER2-overexpressing solid cancers, enhances the potential for tumor targeting and opens new avenues for better treatment of cancer.

Answer 103:

#### Bibliographic Information

**Tumor-selective distribution of an active metabolite of the 9-aminoanthracycline amrubicin.** Noguchi, Toshihiro; Ichii, Shinji; Morisada, Shinya; Yamaoka, Takashi; Yanagi, Yoshikazu. Research Center, Sumitomo Pharmaceuticals Co., Ltd., Osaka, Japan. *Japanese Journal of Cancer Research* (1998), 89(10), 1061-1066. Publisher: Japanese Cancer Association, CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 130:90041 AN 1998:727094 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The disposition and metab. of amrubicin in human-tumor-xenograft-bearing mice were studied in comparison with those of doxorubicin. Amrubicinol, a 13-hydroxy metabolite of amrubicin, which is 10-100-fold more cytotoxic than amrubicin, was detected as a major metabolite in blood and tissues, and aglycons of amrubicin were also detected. A pharmacokinetic study revealed that amrubicin had a smaller distribution vol. and a shorter half-life than doxorubicin. In several normal tissues, the levels of amrubicin and amrubicinol were lower than those of doxorubicin. In contrast, the tumor levels of amrubicinol in the mice treated with amrubicin were higher than those of doxorubicin in the mice treated with that drug, in tumors that are sensitive to amrubicin. The results suggest that the potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors.

Answer 104:

#### Bibliographic Information

**The antitumor activity of the prodrug N-L-leucyldoxorubicin and its parent compound doxorubicin in human tumor xenografts.** Breistol, K.; Hendriks, H. R.; Berger, D. P.; Langdon, S. P.; Fiebig, H. H.; Fodstad, O. The Norwegian Radium Hospital, Norway. *European Journal of Cancer* (1998), 34(10), 1602-1606. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 130:75865 AN 1998:680806 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The antitumor activity of the investigational agent N-L-leucyldoxorubicin (Leu-DOX) was compared with that of doxorubicin (DOX) in human tumor xenografts growing s.c. in athymic nude mice. Leu-DOX was developed as a prodrug of DOX, and may be converted into the clin. active parent compd. by hydrolytic enzymes present in or on tumor cells. It has been suggested that a better therapeutic index with a reduced cardiac toxicity and higher efficacy might be obtained. Both compds. were administered i.v. weekly for 2 wk, each at max. tolerated doses of 8 mg/kg and 28 mg/kg for DOX and Leu-DOX, resp. The panel of xenografts represented three different tumor types. Leu-DOX showed antitumor activity, defined as tumor growth inhibition > 50% and specific growth delay > 1.0, in 10 of the 16 tumors, including two of five breast, five of seven small cell and three of four non-small cell lung carcinomas. In comparison, DOX was active in one breast, four small cell lung and two lung adenocarcinoma xenografts. In all the DOX sensitive lung tumors, Leu-DOX showed higher efficacy than the parent compd. Based on the results of the present study, and since phase I clin. trials with Leu-DOX have already been performed, phase II clin. evaluation of Leu-DOX in patients with breast and lung cancer is recommended.

Answer 105:

**Bibliographic Information**

**Chemosensitivity of human pancreatic cancer cell lines serially transplanted in nude mouse.** Tomikawa, Moriaki; Kubota, Tetsuro; Takahashi, Shin; Matsuzaki, Shinjiro Wilson; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. *Anticancer Research* (1998), 18(2A), 1059-1062. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 129:156567 AN 1998:396377 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Pancreatic cancer frequently recurs or metastasizes even after apparently curative surgical resection. Because of a low, five-year survival rate after radical surgery, multi-modal adjuvant treatment must be used to prevent recurrence of systemic spread. The effectiveness of the exptl. cancer chemotherapy of mitomycin C (MMC), cisplatin (DDP), doxorubicin (DXR) and 5-fluorouracil (5-FU) was evaluated in three human pancreatic cancer xenografts serially transplanted in nude mice. When the effects of these agents were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay, only MMC and DDP were effective on PAN-3-JCK, a poorly differentiated adenocarcinoma. When PAN-12-JCK, a moderately differentiated adenocarcinoma, was used an in vitro assessment of combined chemotherapy of MMC and DDP, a synergistic combination effect was obsd. Three xenografts were transplanted s.c. into nude mice and the max. tolerated doses of these agents were administered i.p. or i.v. (DXR). MMC showed pos. antitumor activity on PAN-3-JCK and PAN-12-JCK, and 5-FU was effective on PAN-12-JCK. These results reflect the low sensitivity of clin. pancreatic cancer to conventionally available antitumor agents, and suggest the possible synergistic combination antitumor activity of MMC and DDP.

Answer 106:

**Bibliographic Information**

**Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model.** Arap, Wadih; Pasqualini, Renata; Ruosillahti, Erkki. *Cancer Res. Cent., Burnham Inst., La Jolla, CA, USA. Science* (Washington, D. C.) (1998), 279(5349), 377-380. Publisher: American Association for the Advancement of Science, CODEN: SCIEAS ISSN: 0036-8075. Journal written in English. CAN 128:200637 AN 1998:63909 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

In vivo selection of phage display libraries was used to isolate peptides that home specifically to tumor blood vessels. When coupled to the anticancer drug doxorubicin, two of these peptides - one contg. an  $\alpha v$  integrin-binding Arg-Gly-Asp motif and the other an Asn-Gly-Arg motif - enhanced the efficacy of the drug against human breast cancer xenografts in nude mice and also reduced its toxicity. These results indicate that it may be possible to develop targeted chemotherapy strategies that are based on selective

expression of receptors in tumor vasculature.

Answer 107:

### **Bibliographic Information**

**Targeting of liposomes to solid tumors: the case of sterically stabilized anti-HER2 immunoliposomes.** Kirpotin, Dmitri B.; Park, John W.; Hong, Keelung; Shao, Yi; Shalaby, Refaat; Colbern, Gail; Benz, Christopher C.; Papahadjopoulos, Demetrios. Department of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, CA, USA. *Journal of Liposome Research* (1997), 7(4), 391-417. Publisher: Marcel Dekker, Inc., CODEN: JLREE7 ISSN: 0898-2104. Journal; General Review written in English. CAN 128:123357 AN 1998:50484 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

A review with 74 refs. Novel therapies for cancer call for a carrier capable of intracellular delivery of systemically administered drugs to cancer cells in solid tumors. Such carrier, sterically stabilized immunoliposomes specific to the cells expressing HER2 protooncogene (anti-HER2 SSL), was designed by conjugating Fab' fragments of a recombinant humanized anti-HER2 MAb to the distal termini of poly(ethylene glycol) chains on the surface of unilamellar liposomes (size 90-100 nm) of phosphatidylcholine, cholesterol, and poly(ethylene glycol)-derivatized phosphatidylethanolamine. Anti-HER2 SSL avidly and specifically bound to cultured HER2-overexpressing cancer cells (8,000-23,000 vesicles per cell) and became endocytosed ( $k_e=0.022-0.033 \text{ min.}^{-1}$ ) via the coated pit pathway. AntiHER2 SSL showed prolonged circulation lifetime in rats (blood MRT approx. 24 h) and significantly increased antitumor activity of encapsulated doxorubicin against HER2-overexpressing human breast cancer xenografts in nude mice. Although the accumulation of anti-HER2 SSL in HER2-overexpressing tumor xenografts was not increased over that of non-targeted SSL, microscopic examn. revealed abundance of anti-HER2 SSL in the interstitial spaces, as well as within the cytoplasm of cancer cells, while identical liposomes lacking anti-HER2 Fab' were located predominantly within tumor-resident macrophages. Anti-HER2 SSL, a targeted vehicle capable of in vivo intracellular delivery of substances to HER2-overexpressing solid cancers, enhances the potential for tumor targeting and opens new avenues for better treatment of cancer.

Answer 108:

### **Bibliographic Information**

**Expression of CD44 standard and isoforms in human breast cancer xenografts and shedding of soluble forms into serum of nude mice.** Fichtner, I.; Dehmel, A.; Naundorf, H.; Finke, L. H. Max-Delbrück-Center of Molecular Medicine, Berlin, Germany. *Anticancer Research* (1997), 17(5A), 3633-3645. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 128:113538 AN 1998:49734 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Std. CD44 (CD44s) and variant isoforms (CD44v) are expressed on different malignant cells and tissues. Their upregulation has been implicated, in the progression and metastasis of malignomas (sic). In this work, the authors addressed the question of whether these mol. are also expressed on xenografted human breast carcinomas and if certain expression patterns are correlated with biol. parameters like tumor size, hormone receptor status, histol., growth rate, chemoresistance, and microenvironment. Addnl., the authors were interested in the shedding of sol. CD44 (sCD44) into the blood circulation of tumor-bearing nude mice. The human breast carcinomas MCF-7, MCF-7/ADR, 4296 and MDA-MB435, 4134 and 4151 were transplanted s.c. or into the mammary fat pad (mfp.) of nude mice. The expression of the CD44s and -v6 and -v9 isoforms was detd. at different time points on tissue samples by immunohistochem. or RT-PCR employing human-specific antibodies or primers, resp. The serum concn. of CD44s and -v6 was measured by human specific ELISAs. All tumors expressed CD44s. The lowest level was obsd. in the MCF-7 cancer. The CD44v6 and -v9 sequences and epitopes were distinctly expressed in MCF-7/ADR, MDA-MB435, 4134, 4151 and 4296, whereas MCF-7 lacked these isoforms. The highest serum concn. of the v6 isoform was detected in mice bearing the tumor 4296 with a high tendency for lymphogenic metastasis. The serum levels of sCD44 were in 5/6 xenografts linearly correlated with the tumor size. Interestingly, there was a remarkable difference between the two sublines MCF-7 and MCF-7/ADR: both the tissue and serum levels of CD44

isoforms indicated that the development of multidrug resistance is accompanied by an alteration in the expression of membrane proteins discussed to be involved in metastasis. There was no relation of tissue expression with the transplantation site and the hormone receptor status of the tumor lines.

CD44s and its variant isoforms are expressed in human xenotransplanted breast cancers in very different levels and patterns. The highest expression in the tumor 4296 is related to lymphogenic metastasis, whereas the absence of isoforms in the model MCF-7 is related to non-metastatic behavior. CD44 is shed into the serum and can be used for monitoring of tumor growth.

Answer 109:

### Bibliographic Information

**Improved treatment of medullary thyroid cancer in a nude mouse model by combined radioimmunochemotherapy: doxorubicin potentiates the therapeutic efficacy of radiolabeled antibodies in a radioresistant tumor type.** Behr, Thomas M.; Wulst, Erik; Radetzky, Sven; Blumenthal, Rosalyn D.; Dunn, Robert M.; Gratz, Stefan; Rave-Frank, Margret; Schmidberger, Heinz; Raue, Friedhelm; Becker, Wolfgang. Department of Nuclear Medicine, Georg-August-University, Göttingen, Germany. *Cancer Research* (1997), 57(23), 5309-5319. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 128:99359 AN 1997:775899 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Whereas in advanced metastatic medullary thyroid cancer (MTC), a variety of chemotherapeutic regimens have achieved only limited success clin., more recently, radioimmunotherapy (RIT) with <sup>131</sup>I-labeled anti-carcinoembryonic antigen (CEA) monoclonal antibodies (MAbs) has shown promising results. The aims of this study were to compare, in an animal model, the therapeutic efficacy of RIT to clin. used "std." chemotherapeutic regimens and to evaluate whether combination strategies of both modalities may be feasible and may help to improve therapeutic results in this rather radioresistant tumor type. Nude mice, bearing s.c. xenografts of the human MTC cell line, TT, were treated either with the <sup>131</sup>I-labeled anti-CEA MAb, F023C5 IgG, or were administered chemotherapeutic regimens that had shown promising results in patients with metastatic MTC (doxorubicin and cisplatinum monotherapy, combinations of both agents, and a 5-fluorouracil/dacarbazine/streptozotocin scheme). Control groups were left untreated or were injected with an irrelevant radiolabeled antibody at equitoxic dose levels. The max. tolerated dose (MTD) of each agent was detd. Combinations of chemotherapy and RIT were evaluated as well. Toxicity and tumor growth were monitored at weekly intervals. From the chemotherapeutic agents and schemes tested, doxorubicin monotherapy was the most effective; combination therapies did not result in an increased antitumor efficacy, but they did result in more severe toxicity. At equitoxic doses, no significant difference was found between the therapeutic efficacy of doxorubicin and that of RIT. Myelotoxicity was dose limiting with radiolabeled MAbs (MTD, 600  $\mu$ Ci), as well as with chemotherapeutic regimens contg. alkylating agents (cisplatinum, dacarbazine, or streptozotocin). At its MTD (200  $\mu$ g), doxorubicin caused only mild myelotoxicity, and despite signs of cardiac toxicity, gastrointestinal side effects were dose limiting.

Accordingly, bone marrow transplantation (BMT) enabled dose intensification with RIT (MTD with BMT, 1100  $\mu$ Ci), which led to further increased antitumor efficacy, whereas BMT was unable to increase the MTD of doxorubicin. Due to the complementarity of toxic side effects but an anticipated synergism of antitumor efficacy, combinations of RIT with doxorubicin were tested. Administrations of 500  $\mu$ Ci of <sup>131</sup>I-labeled anti-CEA and, 48 h later, 200  $\mu$ g of doxorubicin (i.e., 83 and 100% of the resp. single-agent MTDs), were the highest doses that did not result in an increased lethality; with bone marrow support, 1000  $\mu$ Ci of <sup>131</sup>I-labeled anti-CEA could be combined with 200  $\mu$ g of doxorubicin (i.e., 90 and 100% of the individual MTDs). Therapeutic results of this combined radioimmunochemotherapy were superior to equitoxic monotherapy with either agent, and indication for synergistic antitumor effects is given. At its resp. MTD, radioimmunochemotherapy led to a 36% cure rate if it was given without bone marrow support and to a 85% permanent cure rate if it was given with bone marrow support. The animal model, as presented in this study, seems to be useful for the preclin. testing of therapeutic agents for the systemic treatment of MTC. At equitoxic doses, RIT with radiolabeled anti-CEA antibodies seems to be equally as effective as chemotherapy with doxorubicin. Combination of RIT and doxorubicin chemotherapy seems to have synergistic therapeutic efficacy, which may be due to a radiosensitizing effect of doxorubicin.

Answer 110:

### Bibliographic Information

**Clinical efficacy and prospects for use of pegylated liposomal doxorubicin in the treatment of ovarian and breast cancers.**

Muggia, Franco M. New York University Medical Center, NY, USA. *Drugs* (1997), 54(Suppl. 4, Disease Management of Solid Tumours and the Emerging Role of Pegylated Liposomal Doxorubicin), 22-29. Publisher: Adis, CODEN: DRUGAY ISSN: 0012-6667. Journal; General Review written in English. CAN 128:43234 AN 1997:738395 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

A review with 44 refs. There is an urgent need for more active and better tolerated chemotherapy regimens for the treatment of advanced breast and ovarian cancers. Current therapeutic strategies in these malignancies include the use of moderately effective initial regimens that are usually accepted by patients. Tolerability considerations are esp. important in the development of palliative regimens: retreatment for persistent or hormone-resistant disease must include quality-of-life analyses. Pegylated liposomal doxorubicin (PLD) has demonstrated a better therapeutic index than free doxorubicin in murine solid tumors and human tumor xenografts in nude mice. In early clin. studies in patients with refractory ovarian cancer, PLD has produced high response rates (26%) and gratifyingly long response durations (8 to 21 + months after onset of therapy). Less mature data also suggest that PLD is active against breast cancer. Information from these same clin. studies confirms the marked redn. in several toxicities assocd. with free doxorubicin, including nausea and vomiting, myelosuppression and cardiotoxicity. Alopecia is also markedly diminished. On the other hand, mucosal and skin toxicities appear to be more common with PLD. PLD therefore offers the prospect of retaining activity, together with attenuated acute toxicity. In addn. to facilitating the development of palliative regimens with better tolerability, the drug may lend itself to effective integration of chemotherapy with loco-regional therapies, utilisation in "maintenance" regimens that are assocd. with an acceptable quality of life for the patient, and the avoidance of long term toxicities assocd. with treatment. Moreover, addnl. study of PLD in combination with other drugs and modalities may extend the use of the drug beyond palliation to the development of combination regimens with other drugs at conventional doses, and high doses with G-CSF support.

Answer 111:

**Bibliographic Information****Monohydroxyethylrutoside, a dose-dependent cardioprotective agent, does not affect the antitumor activity of doxorubicin.**

Van Acker, Saskia A. B. E.; Boven, Epie; Kuiper, Karin; Van Den Berg, Dirk-Jan; Grimbergen, Joop A.; Kramer, Klaas; Bast, Aalt; Van Der Vijgh, Wim J. F. Leiden Amsterdam Center for Drug Research, Division of Molecular Pharmacology, Department of Pharmacochemistry, Faculty of Chemistry, Vrije Universiteit, Amsterdam, Neth. *Clinical Cancer Research* (1997), 3(10), 1747-1754. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 127:326495 AN 1997:695950 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The cumulative dose-related cardiotoxicity of doxorubicin is believed to be caused by the prodn. of oxygen-free radicals. 7-Monohydroxyethylrutoside (monoHER), a semisynthetic flavonoid and powerful antioxidant, was investigated with respect to the prevention of doxorubicin-induced cardiotoxicity in mice and to its influence on the antitumor activity of doxorubicin in vitro and in vivo. Nontumor-bearing mice were equipped with a telemeter in the peritoneal cavity. They were given six weekly doses of 4 mg/kg doxorubicin i.v., alone or in combination with either 100 or 250 mg/kg monoHER i.p., 1 h prior to doxorubicin administration and for the following 4 days. Cardiotoxic effects were measured from ECG changes up to 2 wk after treatment. Protection against cardiotoxicity was found to be dose dependent, with 53 and 75% protection, resp., as calcd. from the redn. in the increase in the ST interval. MonoHER and several other flavonoids with good antioxidant properties were tested for their antiproliferative effects in the absence or the presence of doxorubicin in A2780 and OVCAR-3 human ovarian cancer cells and MCF-7 human breast cancer cells in vitro. Some flavonoids were directly toxic at 50 and 100  $\mu$ M, whereas others, including monoHER, did not influence the antiproliferative effects of doxorubicin at these concns. The influence of monoHER was further tested on the growth-inhibitory effect of 8 mg/kg doxorubicin i.v., given twice with an interval of 1 wk in A2780 and OVCAR-3 cells that were grown as s.c. xenografts in nude mice. MonoHER, administered 1 h before doxorubicin in a dose schedule of 500 mg/kg i.p. 2 or 5 days per wk, was not toxic and did not decrease the antitumor activity of doxorubicin. It can be concluded that monoHER showed a dose-dependent protection against chronic cardiotoxicity and did not influence the antitumor activity of doxorubicin in vitro or in vivo.

Answer 112:

### **Bibliographic Information**

**Tumor blood flow influences combined radiation and doxorubicin treatments.** Durand, Ralph E.; LePard, Nancy E. Medical Biophysics Department, British Columbia Cancer Research Centre, 601 West 10th Avenue, Vancouver, B.C. V5Z 1L3, Can. *Radiotherapy and Oncology* (1997), 42(2), 171-179. Publisher: Elsevier, CODEN: RAONDT ISSN: 0167-8140. Journal written in English. CAN 126:260978 AN 1997:191485 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Doxorubicin is usually an effective radiosensitizer in vitro, but in vivo reports have been more variable. We have examd. potential explanations for those observations by comprehensively evaluating doxorubicin and x-ray treatments in xenografted human tumors, and in conventional mice with syngeneic tumors. Nude or SCID mice bearing the SiHa cervical squamous cell carcinoma or WiDr colon adenocarcinoma were studied, as were C3H/HeN animals with SCCVII tumors. Nude or SCID mice bearing the SiHa cervical squamous cell carcinoma or WiDr colon adenocarcinoma were studied, as were C3H/HeN animals with SCCVII tumors. Assays included a clonogenic assay in combination with cell sorting, laser Doppler flowmetry, and the dual staining mismatch technique. Doxorubicin decreased tumor blood flow in all tumor systems, in a dose-dependent fashion with each assay. This resulted in increased tumor hypoxia and decreased response to radiation when inappropriate treatment sequences were employed. However, significant variability from animal to animal was noted. To the extent that these results can be extrapolated to human tumor treatments, we conclude that unless compelling evidence suggests that a tumor will be exceedingly sensitive to the drug, the potential effects of doxorubicin on tumor blood flow contraindicate its administration immediately prior to irradiation.

Answer 113:

### **Bibliographic Information**

**The biological effects of C225, a chimeric monoclonal antibody to the EGFR, on human prostate carcinoma.** Prewett, Marie; Rockwell, Patricia; Rockwell, R. F.; Giorgio, Nicholas A.; Mendelsohn, John; Scher, Howard I.; Goldstein, Neil I. Department of Immunology, ImClone Systems Incorporated, New York, NY, USA. *Journal of Immunotherapy with Emphasis on Tumor Immunology* (1996), 19(6), 419-427. Publisher: Lippincott-Raven, CODEN: JIEIEZ ISSN: 1067-5582. Journal written in English. CAN 126:210800 AN 1997:180450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

For prostate cancer, a correlation exists between overexpression of the epidermal growth factor receptor (EGFR) and poor clinical prognosis. In addition, late-stage metastatic disease is characterized by a change from a paracrine to an autocrine mode of expression for TGF- $\alpha$ , the ligand for the EGFR. These observations suggest that activation of the EGFR may be important for the growth of prostatic carcinoma in situ, and blockade of the receptor-ligand interaction may offer a means of therapeutic intervention for this disease. The authors describe the biological effects of a chimeric anti-EGFR monoclonal antibody, C225, on several human prostate tumor cell lines in culture and the tumor inhibitory properties of the antibody for the treatment of human prostate carcinoma xenografts in nude mice. In vitro analysis of the EGFR from androgen-responsive and independent prostatic carcinoma cell lines revealed that C225 blocked EGF-induced receptor activation and induced internalization of the receptor. In vivo, a treatment regimen of C225 alone or antibody plus doxorubicin significantly inhibited tumor progression of well-established DU145 and PC-3 xenografts in nude mice. These results suggest that C225 may have utility for the treatment of human prostate carcinoma in a clinical setting.

Answer 114:

### **Bibliographic Information**

**Doxorubicin encapsulated in sterically stabilized liposomes is superior to free drug or drug-containing conventional liposomes at suppressing growth and metastases of human lung tumor xenografts.** Sakakibara, Takashi; Chen, Fang-An;

Kida, Hisashi; Kunieda, Katsuyuki; Cuenca, Rosa E.; Martin, F. J.; Bankert, Richard B. Dep. Mol. Immunol., Roswell Park Cancer Inst., Buffalo, NY, USA. *Cancer Research* (1996), 56(16), 3743-3746. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 125:204366 AN 1996:506718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Liposomes contg. polyethylene glycol-derivatized phospholipids are able to evade the reticuloendothelial system and thereby remain in circulating for prolonged periods. The authors report here that doxorubicin encapsulated in these sterically stabilized liposomes (S-DOX) suppresses the growth of established human lung tumor xenografts in severe combined immunodeficient (SCID) mice and inhibits the spontaneous metastases of these tumors. The enhanced therapeutic efficacy of S-DOX compared to free doxorubicin was demonstrated in two independent human/mouse models. In the first model, S-DOX inhibited the growth of a human non-small cell lung tumor xenograft established orthotopically in the lungs of SCID mice. Treatment of these mice with S-DOX, but not with free drug, suppressed the growth of the tumor in the lung, prevented metastasis from the lung, and enhanced survival percentage. In another model, the human lung tumor is engrafted into the gonadal fat pad of SCID mice. Human tumor xenografts grow floridly in this site of engraftment, and the tumor spreads from this primary site into the peritoneal cavity and subsequently reaches the liver and lung. In this model, free drug suppressed the growth of the primary tumor but had no effect upon the subsequent spread of the tumor into the peritoneal cavity, liver, and lung. In contrast, treatment of the tumor-bearing mice with S-DOX (but not with doxorubicin in conventional liposomes) suppressed the tumor spread to the peritoneal cavity, completely arrested metastasis to the liver and lung, and suppressed the growth of the primary tumor xenograft. This report provides the first evidence that antitumor drugs delivered by sterically stabilized liposomes can arrest the metastasis of human tumor xenografts.

Answer 115:

### Bibliographic Information

**Altered cell cycle distribution and cyclin-CDK protein expression in A431 epidermoid carcinoma cells treated with doxorubicin and a chimeric monoclonal antibody to the epidermal growth factor receptor.** Prewett, Marie; Rockwell, Patricia; Rose, Caroline; Zuklys, Kazys; Goldstein, Neil I. *Immunology/Monoclonal Antibody*, ImClone Systems, Inc., New York, NY, USA. *Molecular and Cellular Differentiation* (1996), 4(2), 167-186. Publisher: CRC, CODEN: MCDIEL ISSN: 1065-3074. Journal written in English. CAN 125:185087 AN 1996:492466 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

C225, a chimeric monoclonal antibody recognizing the epidermal growth factor receptor (EGFR), can eliminate established A431 (human epidermoid carcinoma) xenografts in nude mice alone or in combination with DNA-damaging drugs such as doxorubicin. This report examines the in vitro effects of combining doxorubicin with C225 on cell cycle distribution and the temporal expression of several important cellular and cell cycle-assocd. proteins, including the EGFR, p53, pRb, cyclins D1 and B, Cdk4, and Cdc2. Doxorubicin induced a G2/M arrest in A431 cells 24 h following treatment with the drug. At 72 h, the cell cycle distribution for cells treated with doxorubicin plus C225 showed an increase in a hypodiploid (<2n) peak that was suggestive of apoptosis. Morphol. changes for cells in the combination group included enlarged cell mass, extensive vacuolization, and the presence of multiple micronuclei. The combination regimen was also found to inhibit cell proliferation to a greater extent than seen for treatment with the individual agents. By 72 h, expression levels of p53, pRb, and EGFR were lower in cells treated with doxorubicin plus C225 and receptor activation (defined by phosphorylation) was substantially decreased in the combination group. Down-regulation of the protein expression levels of cyclin D, Cdk4, and Cdc2 was also obsd. in cells treated with doxorubicin plus C225. In the case of Cdc2, the relative expression of the higher mol. wt. (hyperphosphorylated) or inactive form of this mol. was increased, whereas the opposite was obsd. in both the control and single agent groups. These data suggest a putative model for the therapeutic effects of doxorubicin and C225 on the growth of solid tumors obsd. in preclin. animal models.

Answer 116:

### Bibliographic Information

**Establishment and serial quantification of intrahepatic xenografts of human hepatocellular carcinoma in severe combined immunodeficiency mice, and development of therapeutic strategies to overcome multidrug resistance.** Leveille-Webster, Cynthia R.; Arias, Irwin A. School Medicine, Tufts University, Boston, MA, USA. *Clinical Cancer Research* (1996), 2(4), 695-706. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 124:332166 AN 1996:261680 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A murine model in which to study multiple drug resistance in human hepatocellular carcinoma was developed. PRF/PLC/5 hepatoma cells (Alex 0) and an induced multidrug resistant clone (Alex 0.5) were injected intrasplenically into severe combined immunodeficiency mice. In 70% of injected mice, hepatoma cells engrafted in the liver and grew as intrahepatic metastasis. Since Alex cells contain an integrated hepatitis B virus genome and secrete hepatitis B surface antigen (HBsAg), the serum HBsAg concn. in tumor-bearing mice was used to quantitate tumor burden. Tumor wet wt. detd. at necropsy was directly proportional to the serum HBsAg concn. In Alex 0 cells, IC50s for doxorubicin, vinblastine, and cis-platinum were 0.35  $\mu\text{M}$ , 0.029  $\mu\text{M}$ , and 3.70  $\mu\text{M}$ , resp. Alex 0.5 cells were 25-, 14-, and 1.4-fold more resistant to doxorubicin, vinblastine, and cis-platinum, resp. Immunoblotting of Alex 0 cell membranes with an anti-P-glycoprotein antibody (C219) revealed small amts. of P-glycoprotein, whereas Alex 0.5 membranes overexpressed the protein. Concurrent exposure to verapamil (10  $\mu\text{M}$ ) sensitized both cell lines to the cytotoxic action of vinblastine and doxorubicin but had no effect on the cytotoxicity of cis-platinum. Mice bearing intrahepatic xenografts derived from Alex 0 and 0.5 cells had no response to treatment with i.v. vinblastine or doxorubicin, as was anticipated from in vitro drug testing. Addn. of verapamil to vinblastine treatment did not improve the success of in vivo chemotherapy. Immunotherapy with a human anti-P-glycoprotein antibody (MRK16) suppressed the in vivo growth of tumors derived from both cell lines. The effect was most pronounced in mice bearing Alex 0.5 tumors. Immunoblotting of tumors which initially responded to MRK16 therapy, but subsequently relapsed, revealed a marked decrease in P-glycoprotein expression when compared to results in tumors that were untreated or treated with vinblastine or control antibody.

In summary, we have developed an intrahepatic tumor xenograft model of human hepatocellular carcinoma in mice that permits noninvasive serial quantification of tumor burden by detn. of serum HBsAg levels and demonstrated a pos. response to immunotherapy with anti-P-glycoprotein antibodies.

Answer 117:

### Bibliographic Information

**Synthesis and bioactivity of anthracycline disaccharides.** Animati, F.; Arcamone, F.; Berettoni, B.; Cipollone, A.; Franciotti, M.; Lombardi, P.; Monteagudo, E. Department Chemistry, Pomezia, Italy. *Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28 (1996)*, CARB-013. Publisher: American Chemical Society, Washington, D. C CODEN: 62PIAJ Conference; Meeting Abstract written in English. AN 1996:217454 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Disaccharide anthracyclines of the daunorubicin and idarubicin series, in which the daunosamine moiety is sepd. from the aglycon by either a 2-deoxy-L-rhamnose or a 2-deoxy-L-fucose residue, are obtained following a convergent synthetic procedure from the appropriate disaccharide units and daunomycinone or 4-demethoxydaunomycinone. The synthesis of such compds. has provided insight on the configurational requirements for bioactivity of the first sugar residue, and opened the way to a new class of antitumor anthracyclines. Hence, the first doxorubicin disaccharide analog ever reported has been synthesised starting from 14-acetoxy-4-demethoxydaunomycinone, 2-deoxy-L-fucose and L-daunosamine. The new compd. exhibits, according to our experience, unprecedented activity when compared with doxorubicin in different human gynecol. and lung cancer xenografts in athymic mice (G. Pratesi et al., Comm. at the 9th NCI-EORTC Symposium on New Drugs in Cancer Therapy, Mar. 12-15, 1996, Amsterdam).

Answer 118:

### Bibliographic Information

**PAK-104P, a pyridine analog, reverses paclitaxel and doxorubicin resistance in cell lines and nude mice bearing xenografts that overexpress the multidrug resistance protein.** Vanhoefer, Udo; Cao, Shousong; Minderman, Hans; Toth, Karoly; Scheper, Rik J.; Slovak, Marilyn L.; Rustum, Youcef M. Dep. Exptl. Therapeutics, Roswell Park Cancer Inst., Buffalo, NY, USA. *Clinical Cancer Research* (1996), 2(2), 369-77. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 124:278265 AN 1996:182914 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Multidrug resistance (MDR) is considered multifactorial and has been assocd. with overexpression of the multidrug resistance protein (MRP). However, effective compds. for reversal of MRP-related MDR are limited. In the present study, the modulatory activity of the novel pyridine analog PAK-104P on MRP-mediated resistance to doxorubicin and paclitaxel was investigated in two doxorubicin-selected human tumor cell lines [HT1080/DR4 (sarcoma) and HL60/ADR (leukemia)] and compared with the nonimmunosuppressive cyclosporine analog PSC-833. In cell lines HT1080/DR4 (MRP/lung resistance-related protein phenotype) and HL60/ADR (MRP phenotype), doxorubicin resistance was significantly higher (250-fold and 180-fold, resp.) than that to paclitaxel (6-fold and 9-fold, resp.). With noncytotoxic concns. of PAK-104P (1 and 5  $\mu$ M), the reversal of doxorubicin resistance was significant but partial in HT1080/DR4 and HL60/ADR cells (dose-modifying factor for 5.0  $\mu$ M PAK-104P, 25.0 and 31.2, resp.), whereas complete reversal of paclitaxel resistance was achieved in HL60/ADR cells. In contrast, PSC-833 modulation of doxorubicin and paclitaxel resistance was modest. Cellular drug uptake and retention studies by flow cytometry anal. demonstrated that PAK-104P was effective in restoring cellular doxorubicin concns. in resistant cells to levels comparable to those obtained in parental cells. In athymic nude mice, PAK-104P significantly potentiated the therapeutic efficacy of doxorubicin and paclitaxel against resistant HT1080/DR4 xenografts. Of significance is that the max. tolerated doses of doxorubicin and paclitaxel were administered in combination with PAK-104P, documenting improvement in the therapeutic index of these agents. In addn. to reversing P-glycoprotein-mediated MDR, the pyridine analog PAK-104P provides an example of an effective in vivo modulator of MRP-mediated MDR.

Answer 119:

#### Bibliographic Information

**Severe combined immunodeficiency (SCID) mouse modeling of P-glycoprotein chemosensitization in multidrug-resistant human myeloma xenografts.** Bellamy, William T.; Odeleye, Abiodun; Huizenga, Elizabeth; Dalton, William S.; Weinstein, Ronald S.; Grogan, Thomas M. School Medicine, University Arizona, Tucson, AZ, USA. *Clinical Cancer Research* (1995), 1(12), 1563-70. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 124:164575 AN 1996:68123 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

We have established a reproducible in vivo model of human multiple myeloma in the severe combined immunodeficiency (SCID) mouse using both the drug-sensitive 8226/S human myeloma cell line and the P-glycoprotein-expressing multidrug-resistant 8226/C1N subline. As demonstrated previously, the SCID mouse is well suited as a model for myeloma because: (a) human SCID xenografts are readily attained; (b) human myeloma xenografts are readily detected by their Ig secretion; and (c) differential therapy effects in drug-sensitive vs. drug-resistant cell lines are readily demonstrable by monitoring mouse urinary human Ig output. In the current study, we have utilized this model to evaluate the in vivo efficacy of chemomodulators of P-glycoprotein-related multidrug resistance. In our initial expts., doxorubicin alone was effective in treating the 8226/S human myeloma xenografts but had no effect on the drug-resistant 8226/C1N xenografts, in the absence of the chemosensitizing agent verapamil. In subsequent expts., the combination of verapamil and doxorubicin resulted in both a decrease in human  $\lambda$  light chain urinary excretion and an increase in survival of those animals bearing the 8226/C1N tumor. The median survival time of animals injected with 8226/C1N cells and subsequently treated with doxorubicin was  $48.6 \pm 7$  days, which compared to a survival of  $89.6 \pm 18$  days in animals receiving the 8226/S cell line and treated with doxorubicin alone ( $P < 0.001$ ). When verapamil was added to the treatment regimen of those animals bearing the 8226/C1N xenografts, there was a 179% increase in their life span ( $P < 0.001$ ), which corresponded with the obsd. decreased light chain in the urine. In animals receiving multiple courses of chemotherapy, an attenuated response to verapamil and doxorubicin was obsd., in a manner analogous to the clin. setting of human drug-resistant myeloma escape from chemosensitivity.

The SCID human myeloma xenograft model thus offers a means of evaluating the in vivo efficacy and potential toxicities of new therapeutic approaches directed against P-glycoprotein in multidrug-resistant human myeloma.

Answer 120:

### Bibliographic Information

**Intratumoral chemotherapy with a sustained-release drug delivery system inhibits growth of human pancreatic cancer xenografts.** Smith, Jill P.; Stock, Elizabeth; Orenberg, Elaine K.; Yu, Ning Y.; Kanekal, Sarathchandra; Brown, Dennis M. Dep. Medicine, Pennsylvania State Univ., Hershey, PA, USA. *Anti-Cancer Drugs* (1995), 6(6), 717-26. Publisher: Rapid Science Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 124:135020 AN 1996:49697 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

This study provides the first evidence that treatment of human pancreatic adenocarcinoma is markedly improved by the intratumoral administration of chemotherapeutic agents in a novel drug delivery system. The effect of chemotherapeutic agents delivered in a sustained-release, protein-based, injectable gel was evaluated on the growth of human pancreatic adenocarcinoma cell line, BxPC-3. In vitro chemosensitivity of BxPC-3 cells exposed for 24 or 72 h to fluorouracil (0.01-5 mM), cisplatin or doxorubicin (0.1-50  $\mu$ M) and floxuridine, vinblastine, mitomycin or paclitaxel (1.0-100  $\mu$ M) was compared with that of untreated cells. In vitro chemosensitivity was also studied with fluorouracil and mitomycin in the poorly differentiated PANC-1, human pancreatic cancer cell line. Survival was detd. after 7-10 days. All drugs decreased cell growth in a dose dependent fashion. The efficacy of fluorouracil, cisplatin and doxorubicin increased with prolonged exposure, rendering these drugs most appropriate for a sustained-release prepn. For in vivo studies, athymic nude mice bearing BxPC-3 xenografts were treated either with fluorouracil, cisplatin or doxorubicin in the therapeutic injectable gel contg. epinephrine or with vehicle alone administered intratumorally on days 1 and 4. After 28 days, the mice were sacrificed and tumors dissected and weighed. Tumors in mice treated with the injectable gel decreased in size by 72-79% compared with tumors in untreated controls and tumors treated with vehicle alone. Intratumoral injection of drug soln. and i.p. injection of drug in the injectable gel did not change tumor size compared with controls. In a drug-retention study, mice were injected intratumorally with [<sup>3</sup>H]fluorouracil either in the injectable gel or in soln. Sustained radioactivity was obsd. in tumors injected with the gel, and, conversely, greater radioactivity was detected in the liver and kidneys in mice receiving the radiolabeled soln.

These results suggest that the therapeutic injectable gel chemotherapy, when given intratumorally, may improve tumor response with less systemic toxicity in comparison with conventional systemic chemotherapy.

Answer 121:

### Bibliographic Information

**Adding a reverser (verapamil) to combined chemotherapy overrides resistance in small cell lung cancer xenografts.** Arvelo, F.; Poupon, M. F.; Bichat, F.; Grossin, F.; Bourgeois, Y.; Jacrot, M.; Bastian, G.; Le Chevalier, T. CNRS, Institut Curie, Paris, Fr. *European Journal of Cancer, Part A* (1995), 31A(11), 1862-8. Publisher: Elsevier, CODEN: EJCTEA Journal written in English. CAN 124:134977 AN 1996:39796 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Small cell lung carcinomas (SCLC) are characterized by chemosensitivity to diverse antitumoral compds. However, responses are transitory and relapses are commonly obsd. The authors examd. the ability of verapamil, a reverser of P-glycoprotein (Pgp)-related resistance, to improve the efficacy of CyCAV combined chemotherapy (Cy, cyclophosphamide (CPA); C, cisplatin (CDDP); A, doxorubicin (ADM); V, etoposide (VP16)), as currently administered to SCLC patients at Institute Gustave-Roussy, France, and adapted to the treatment of nude mice implanted with these tumors. Although Pgp encoded by the MDR1 (multidrug resistance) gene is not the only mechanism for multidrug resistance (MDR), and not all drugs included in this regimen are recognized by Pgp, the authors anticipated a therapeutic benefit. Four different SCLC lines, expressing the MDR1 gene and recently grafted into nude mice, were used. SCLC-75, SCLC-6 and SCLC-41 originated from untreated patients, and SCLC-74T was derived from a patient treated with a combination of ADM, CPA and VP16. SCLC-41T and SCLC-6T tumors were used after having undergone, resp., five and nine cycles of in vivo passage and CyCAV treatment of the tumor-bearing nude mice, to reinforce their chemoresistance. The efficacy of the CyCAV regimen, assocd. with or without verapamil (given 24 h before CyCAV on days 1-5), was tested on the growth of these SCLC.

Verapamil (25 mg/kg) improved the antitumor effect of CyCAV in mice bearing SCLC-6T, SCLC-41T and SCLC-75 tumors, although toxicity was obsd. Verapamil modestly delayed the plasma clearance of ADM. Two daily injections of 10 mg/kg of verapamil, administered at a 3 h interval, proved to be effective, whereas the same total dose administered as a bolus was not. These results indicate that the assocn. of some reversers of MDR, including drugs possibly interacting with Pgp, might potentiate SCLC combined chemotherapy.

Answer 122:

#### Bibliographic Information

##### **Anti-B4-blocked ricin synergizes with doxorubicin and etoposide on multidrug-resistant and drug-sensitive tumors.**

O'Connor, Rosemary; Liu, Changnian; Ferris, Cynthia A.; Guild, Braydon C.; Teicher, Beverly A.; Corvi, Christopher; Liu, Yimao; Arceci, Robert J.; Goldmacher, Victor S.; et al. Dana-Farber Cancer Inst., Boston, MA, USA. *Blood* (1995), 86(11), 4286-94. Publisher: Saunders, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 124:45029 AN 1995:972819 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Anti-B4-blocked ricin (anti-B4-bR) is an immunotoxin directed against CD19-pos. cells that is currently being tested in several B-cell leukemia/lymphoma clin. trials. To explore the possibility of using anti-B4-bR in combination with chemotherapy protocols, the authors investigated the in vitro and in vivo cytotoxic effects of combining it with doxorubicin or etoposide using the lymphoma cell line Namalwa and a P-glycoprotein-expressing cell line, Namalwa/mdr-1, obtained by retroviral infection of Namalwa cells with the mdr-1 gene. Namalwa/mdr-1 cells were slightly more sensitive to anti-B4-bR than Namalwa cells; IC37 values were approx. 4 pmol/L and 8 pmol/L, resp. When anti-B4-bR was combined simultaneously with doxorubicin or etoposide, additive to supra-additive killing of Namalwa and Namalwa/mdr-1 cells was obsd. In xenografts of Namalwa/mdr-1 cells in severe combined immunodeficiency (SCID) mice, doxorubicin and etoposide at their max. tolerated doses (3 mg/kg  $\times$  3 or 15 mg/kg  $\times$  3) showed no therapeutic effect. However, treatment with 5 daily bolus injections of anti-B4-bR (50  $\mu$ g/kg) followed by treatment with doxorubicin or etoposide significantly increased the life span of the mice by 129% and 115%, resp. After treatment with anti-B4-bR, the Namalwa/mdr-1 population expressed lower levels of P-glycoprotein, and this decrease may account for the synergistic action of the drug combinations. These results suggest that anti-B4-bR could be used to good effect in combination with current treatment regimens and further hint at a promising role for this immunotoxin in treatment of disease at the minimal residual disease stage, where cells may be resistant to chemotherapy.

Answer 123:

#### Bibliographic Information

**Antitumor activity of CC49-doxorubicin immunoconjugates.** Johnson, D. A.; Briggs, S. L.; Gutowski, M. C.; Barton, R. Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, USA. *Anticancer Research* (1995), 15(4), 1387-93. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 123:329439 AN 1995:866011 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The TAG72 reactive monoclonal antibody CC49 was conjugated to doxorubicin with a malonate linker. The immunoconjugate, designated CC49-BAMME-CH-DOX, was approx. a log less potent than unconjugated doxorubicin in an in vitro cytotoxicity assay. Immunoreactivity of the antibody was fully retained. When evaluated in a nude mouse xenograft model with the antigen pos. LS174T human colorectal tumor target, CC49-BAMME-CH-DOX and free doxorubicin had similar tumor suppressive activities. The immunoconjugate was clearly less toxic, however, as measured by wt. loss and deaths. When evaluated in an NIH:OVCAR-3 human ovarian carcinoma xenograft model, CC49-BAMME-CH-DOX was superior at prolonging survival in comparison to free doxorubicin, unmodified CC49, and a non tumor binding doxorubicin immunoconjugate. These results indicate that targeting of doxorubicin with the CC49 antibody can improve the toxicity and/or the potency of the drug, depending on the tumor target being evaluated.

CC49-Doxorubicin immunoconjugates should be considered for clin. evaluation.

Answer 124:

### Bibliographic Information

**A novel one-step tumor-selective prodrug activation system.** Bosslet, K.; Czech, J.; Hoffmann, D. Research Laboratories, Behringwerke AG, Marburg, Germany. *Tumor Targeting* (1995), 1(1), 45-50. Publisher: Chapman & Hall, CODEN: TUTAF9 ISSN: 1351-8488. Journal written in English. CAN 123:187842 AN 1995:729602 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Using enzyme histochem. methods, it was obsd. that lysosomal  $\beta$ -glucuronidase is liberated in necrotic tumor areas as functionally active enzyme. Injection of a hydrophilic nontoxic prodrug [N-(4- $\beta$ -glucuronyl-3-nitrobenzyloxycarbonyl)-doxorubicin] at a dose of  $3 \times 250$  mg kg<sup>-1</sup> into nude mice bearing necrotic human tumor xenografts, resulted in tumor-therapeutic effects superior to chemotherapy ( $p = 0.0022$ ) using doxorubicin. Marginal therapeutic effects were obsd. if non-necrotic small human tumor xenografts were treated with the prodrug under the same conditions ( $p = 0.22$ ). These studies support the hypothesis that human lysosomal  $\beta$ -glucuronidase accessible to the prodrug in necrotic tumor cells enzymically activates the prodrug intratumorally so that high concns. of doxorubicin are generated and are responsible for the superior tumor-therapeutic effects. Thus, a tumor-selective prodrug monotherapy for the treatment of necrotic human tumors seems to be feasible if appropriate hydrophilic prodrugs are applied.

Answer 125:

### Bibliographic Information

**Relationship between tumor response and the ratio of nucleotide triphosphates to inorganic phosphate in small cell lung cancer xenografts.** Kristjansen, Paul E.G.; Kristensen, Claus A.; Spang-Thomsen, Mogens; Quistorff, Bjoern. Department of Oncology, Rigshospitalet-Finsen Institute, Copenhagen, Den. *International Journal of Oncology* (1995), 7(1), 127-31. CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 123:187838 AN 1995:674798 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

We examd. whether grossly similar tumor responses, obtained by different therapies, induce similar patterns of change in the ratios of nucleotide triphosphate (NTP) to inorg. phosphate (Pi) in two human tumor lines, derived from the tumor of the same patient. The tumor responses were induced by doxorubicin 10 mg/kg i.p. or 5 Gy X-radiation in the human small cell lung cancer (SCLC) lines 54A and 54B, grown as xenografts in athymic nude mice. In vivo <sup>31</sup>P magnetic resonance spectroscopy of tumors was performed pretherapeutically, and on days 1, 4, 8, and 15 following therapy, in a 4.7 T magnet. Individual NTP/Pi ratios were calcd. relative to the pretherapeutic values, and treated (n=28) vs. controls (n=28) were compared. In both tumor lines, doxorubicin induced a significant drop in NTP/Pi at day 1. In 54A tumors 5 Gy induced a significant increase in NTP/Pi, whereas no difference between the NTP/Pi of irradiated and controls was found in 54B tumors. Thus three distinct NTP/Pi patterns were obsd. in tumors during response to therapy: (i) A decrease, (ii) an increase, and (iii) no change. Our findings indicate that changes in this ratio do not correlate independently with tumor response in the SCLC sublines 54A and 54B.

Answer 126:

### Bibliographic Information

**Development of anti-p185HER2 immunoliposomes for cancer therapy.** Park, J. W.; Hong, K.; Carter, P.; Asgari, H.; Guo, L. Y.; Keller, G. A.; Wirth, C.; Shalaby, R.; Kotts, C.; et al. Dep. of Medicine, Univ. of California, San Francisco, CA, USA. *Proceedings of the National Academy of Sciences of the United States of America* (1995), 92(5), 1327-31. Publisher: National

Academy of Sciences, CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 122:196817 AN 1995:411739  
CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The product of the HER2 protooncogene, p185HER2, represents an attractive target for cancer immunotherapies. We have prepared anti-p185HER2 immunoliposomes in which Fab' fragments of a humanized anti-p185HER2 monoclonal antibody with antiproliferative properties (rhuMab-HER2) were conjugated to either conventional or sterically stabilized liposomes. These immunoliposomes bind specifically to p185HER2 immunoliposomes is comparable to that of free rhuMabHER2-Fab' or the intact antibody. Empty immunoliposomes inhibit the culture growth of p185HER2-overexpressing breast cancer cells, and this antiproliferative effect is superior to that of free rhuMabHER2-Fab', indicating that liposomal anchoring of these anti-p185HER2 Fab' fragments enhances their biological activity. Efficient internalization of anti-p185HER2 immunoliposomes, demonstrated by light and electron microscopy, occurs by receptor-mediated endocytosis via the coated pit pathway and also possibly by membrane fusion. Doxorubicin-loaded anti-p185HER2 immunoliposomes are markedly and specifically cytotoxic against p185HER2-overexpressing tumor cells in vitro. Anti-p185HER2 immunoliposomes administered in vivo in Scid mice bearing human breast tumor (BT-474) xenografts can deliver doxorubicin to tumors. These results indicate that anti-p185HER2 immunoliposomes are a promising therapeutic vehicle for the treatment of p185HER2-overexpressing human cancers.

Answer 127:

### Bibliographic Information

**Immunotherapy and chemotherapy in anaplastic thyroid carcinoma - an experimental study.** Wenisch, H. J. C.; Mueller, B.; Bergmann, L.; Fortmeyer, H. P.; Encke, A. Departments Surgery, Johann Wolfgang Goethe University, Frankfurt/Main, Germany. Contributions to Oncology (1994), 46(CYTOKINES IN CANCER THERAPY), 99-104. CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 122:103640 AN 1995:290995 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The growth-reducing effects of interferons in comparison and in combination with doxorubicin in several anaplastic carcinoma xenografts in mice were studied. The best results were obtained with interferon- $\alpha$ 2b (10,000 IU s.c. 3x/wk combined with doxorubicin 3.25 ng/kg 1x/wk).

Answer 128:

### Bibliographic Information

**Modulation of tumor hypoxia by conventional chemotherapeutic agents.** Durand, Ralph E.; LePard, Nancy E. Medical Biophysics Dept., B.C. Cancer Research Centre, Vancouver, BC, Can. International Journal of Radiation Oncology, Biology, Physics (1994), 29(3), 481-6. CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 121:195401 AN 1994:595401 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

We have evaluated the capacity of a no. of common cancer chemotherapeutic drugs to modulate the oxygenation of human tumor xenografts growing in murine hosts. Considerable effort has been expended on developing methods to radiosensitize hypoxic cells, or to selectively kill them with appropriate chems. Another approach, suggested by our ongoing studies with spheroids in vitro, is to modify tumor oxygenation by physiol. means. The feasibility of this approach is illustrated in this article using human tumor xenografts in mice treated with doxorubicin or mitomycin C plus radiation. The therapeutic potential of the combination treatments has been assessed using fluorescence-activated cell sorting techniques to isolate and differentially study hypoxic vs. aerobic cell subpopulations from the xenografts. Addnl., drug-induced changes in blood flow have been quantified at the macroscopic level with

laser Doppler flowmetry, and at the microregional level with image anal. techniques. At doses which produced only modest amts. of tumor cell killing, doxorubicin and mitomycin C markedly altered tumor blood flow in all tumor types examd., and with all assays used. Common anti-cancer agents may find new use as blood flow modifiers for combined modality treatments, in addn. to their conventional use as "pure" cytotoxins.

Answer 129:

#### **Bibliographic Information**

**Predictability of clinical response to anticancer agents in human cancer xenografts.** Tsukamoto, Fumine. Med. Sch., Osaka Univ., Suita, Japan. Osaka Daigaku Igaku Zasshi (1994), 46(4), 251-61. CODEN: ODIZAK ISSN: 0369-710X. Journal written in Japanese. CAN 121:124753 AN 1994:524753 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Nude mouse transplanted human tumors retained original sensitivity to antitumor drugs, and was useful in secondary screening for the sensitivity to tumor chemotherapy. Fresh tumor tissues were transplanted and maintained in nude mice in 77 cases (tried: 247 cases), and sensitivity of the transplanted tumors to chemotherapy was compared between human therapy and in nude mice using regimen used clin. in 17 cases with 21 expts. (stomach, breast, colon, pancreas, esophagus, melanoma). Tested drugs were adriamycin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, doxifluoridine, epirubicin, 5-fluorouracil, M-83 (a mitomycin C deriv.), mitomycin C, tegafur, and UFT. Chemotherapy in nude mice was effective in 6 expts., which coincided with clin. results in 5 cases. The ineffective 15 cases in nude mice coincided with the clin. results in all cases.

Answer 130:

#### **Bibliographic Information**

**Tumor-selective prodrug activation by fusion protein-mediated catalysis.** Bosslet, Klaus; Czech, Joerg; Hoffmann, Dieter. Res. Lab., Behringwerke AG, Marburg, Germany. Cancer Research (1994), 54(8), 2151-9. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 121:26372 AN 1994:426372 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

A two component system, consisting of a fusion protein and an appropriate prodrug, suited to perform selective tumor therapy in vivo is presented. The fusion protein, due to its humanized carcinoembryonic antigen-specific variable region, specifically binds to carcinoembryonic antigen-expressing tumors and has an enzymic activity comparable to that of human  $\beta$ -glucuronidase. The prodrug is a nontoxic glucuronide-spacer deriv. of doxorubicin decomp. to doxorubicin by enzymic deglucuronidation. In vivo studies in nude mice bearing human carcinoembryonic antigen-expressing tumor xenografts revealed that 7 days after injection of 20 mg/kg fusion protein a high specificity ratio (>100:1) was obtained between tumor and plasma or tumor and normal tissues. Injection of 250 mg/kg of prodrug at day 7 resulted in tumor therapeutic effects superior to those of conventional chemotherapy without any detectable toxicity. These superior therapeutic effects which were obsd. using established human tumor xenografts can be explained by the approx. 4-12-fold higher doxorubicin concns. found in tumors of mice treated with fusion protein and prodrug than in those treated with the maximal tolerable dose of drug alone. The nondetectable toxicity in the animals treated with fusion protein and prodrug is probably caused by up to 5-fold lower drug concns. in normal tissues compared to the animals treated with doxorubicin. Thus, a more tumor-selective therapy, resulting in stronger therapeutic effects and reduced toxicity seems to be possible by the appropriate use of the humanized nontoxic fusion protein and the nontoxic prodrug.

Answer 131:

#### **Bibliographic Information**

**Similarity of serum - tumor pharmacokinetics of antitumor agents in man and nude mice.** Kubota, Tetsuro; Inoue, So; Furukawa, Toshihuru; Ishibiki, Kyuya; Kitajima, Masaki; Kawamura, Eiji; Hoffman, Robert M. Sch. Med., Keio Univ., Tokyo, Japan. *Anticancer Research* (1993), 13(5A), 1481-4. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 120:315103 AN 1994:315103 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A pharmacokinetic comparison was made between nude mice and human gastric cancer patients. This comparison is important in order to optimize the human tumor xenograft - nude mouse system as a screening panel for potential antitumor agents. In this report, mitomycin C (MMC), doxorubicin (DXR), 5-fluorouracil (5-FU) and cisplatin (DDP) were administered to nude mice bearing human tumor s.c. xenografts in max. tolerated doses and to patients with gastric cancer at conventional doses. The concns. of antitumor agents in serum and tumor were detected by bioassay for MMC and 5-FU, by high performance liq. chromatog. for DXR, and by at. absorption method for DDP. Peak drug concns. in the serum (C<sub>max</sub>) of mice and humans correlated well with statistical significance (R = 0.999, P < 0.0001). When C<sub>max</sub> and drug concns. in the tumor (T) of mice and human were compared with each other to evaluate the uptake of drugs into the tumor from the serum and calcd. as T/C<sub>max</sub>, similar results were obsd. for the same agent with statistical significance (r = 0.990, p < 0.02). These results indicate that the human tumor xenograft - nude mouse system and humans are essentially similar pharmacodynamically, which further validates the use of this system to evaluate potential antitumor agents.

Answer 132:

#### Bibliographic Information

**Antitumor effects of doxorubicin in combination with anti-epidermal growth factor receptor monoclonal antibodies.**

Baselga, Jose; Norton, Larry; Masui, Hideo; Pandiella, Atanasio; Coplan, Keren; Miller, Wilson H. Jr.; Mendelsohn, John. Med. Coll., Cornell ??, Ithaca, NY, USA. *Journal of the National Cancer Institute* (1993), 85(16), 1327-33. CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 120:95063 AN 1994:95063 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A variety of human tumors frequently express high levels of epidermal growth factor (EGF) receptor and its ligand, transforming growth factor  $\alpha$  (TGF- $\alpha$ ), which in some tumors is assocd. with poor prognosis. Monoclonal antibodies (MAbs) that block the binding of TGF- $\alpha$  or EGF to the receptor can inhibit proliferation of tumor cells that express the receptor. Studies suggest that these MAbs may enhance the antitumor effects of chemotherapy. The authors' purpose was to study, in vitro and in vivo, the antitumor effects of doxorubicin in combination with anti-EGF receptor MAbs against tumor cells expressing high levels of EGF receptor. The authors' goal was to achieve max. initial cytoredn. with high-dose doxorubicin in assocn. with prolonged blockade of EGF receptor with MAbs. Anti-EGF receptor MAbs 528 (isotype IgG2a) and 225 (isotype IgG1) were used in combination with doxorubicin against cells from human A431 squamous cell carcinoma and human MDA-468 breast adenocarcinoma. Both A431 and MDA-468 cells express high levels of EGF receptors and TGF- $\alpha$ . Cultured cells were treated with doxorubicin (range, 0-10 nM) in the presence or absence of MAb 528 or 225 (range, 0-30 nM). At 48 h, doxorubicin-contg. medium was removed, and treatment with antibody was continued for 5 days, when cell proliferation assays were performed. The activity of the agents and the combinations against well-established xenografts in BALB/c nude mice was also studied. In nude mice, doxorubicin was given at doses of 50-100  $\mu$ g/20 g body wt. on 2 successive days, and MAbs 528 and 225 were given at a dose range of 0-2 mg i.p. twice a week. MAbs 528 and 225 both enhanced the antitumor effects of doxorubicin against A431 and MDA-468 tumor cells, producing additive growth suppression in cell cultures. MAb 528 increased the antitumor effects of doxorubicin by 32%-42%, and similar results were obtained with MAb 225.

In BALB/c athymic mice, the treatment of well-established xenografts with either doxorubicin or anti-EGF receptor MAb alone temporarily inhibited growth, but the combination of both agents substantially enhanced antitumor activity over that of doxorubicin alone in A431 and MDA-468 cell xenografts. The combination treatment of mice bearing A431 xenografts resulted in tumor eradication of 40%-100% in the surviving mice in several independent expts. The enhanced antitumor activity was dose dependent. The authors' results suggest that anti-EGF receptor MAbs substantially enhance the effects of doxorubicin against well-established xenografts of tumor cells expressing high levels of EGF receptors. Clin. trials with anti-EGF receptor MAbs are being conducted, and trials with anti-EGF receptor MAbs combined with doxorubicin are planned.

Answer 133:

**Bibliographic Information**

**Arrest of human lung tumor xenograft growth in severe combined immunodeficient mice using doxorubicin encapsulated in sterically stabilized liposomes.** Williams, Scott S.; Alosco, Thomas R.; Mayhew, Eric; Lasic, Danilo D.; Martin, Frank J.; Bankert, Richard B. Dep. Mol. Immunol., Roswell Oral Cancer Inst., Buffalo, NY, USA. *Cancer Research* (1993), 53(17), 3964-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 120:195 AN 1994:195 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Incorporation of polyethylene glycol-derivatized phospholipids into liposomes results in carriers that can enhance the therapeutic efficacy of encapsulated drugs by imparting the ability to evade the reticuloendothelial system and remain in the circulation for prolonged periods. In this study, doxorubicin encapsulated in these sterically stabilized liposomes (S-DOX) is shown to completely arrest the growth of human lung tumor xenografts in severe combined immunodeficient (scid) mice. Doxorubicin administered at equiv. doses as free drug or encapsulated into conventional liposomes was ineffective at completely arresting the growth of this human tumor, although a decrease in tumor growth rate compared to untreated controls was obsd. Scid mice were more susceptible to the toxic effects of doxorubicin than were immunocompetent C.B-17 control mice, a characteristic that is likely to result from the deficit in DNA repair mechanisms previously identified in scid mice. However, doxorubicin toxicity in scid mice could be minimized while maintaining the antitumor activity of doxorubicin encapsulated in sterically stabilized liposomes by administering the drug in multiple weekly injections at low doses. This report provides the first evidence that antitumor drugs delivered in sterically stabilized liposomes are more effective at arresting the growth of human tumors than are conventional delivery systems. In addn., the scid mouse is presented as a viable model in which to study novel chemotherapeutic approaches to the treatment of human cancer.

Answer 134:

**Bibliographic Information**

**An in vivo model of human multidrug-resistant multiple myeloma in SCID mice.** Bellamy, William T.; Odeleye, Abiodun; Finley, Paul; Huizenga, Beth; Dalton, William S.; Weinstein, Ronald S.; Hersh, Evan M.; Grogan, Thomas M. *Coll. Med., Univ. Arizona, Tucson, AZ, USA. American Journal of Pathology* (1993), 142(3), 691-7. CODEN: AJPAA4 ISSN: 0002-9440. Journal written in English. CAN 118:247099 AN 1993:247099 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The authors have established a reproducible in vivo model of human multiple myeloma in the severe combined immunodeficient (SCID) mouse using both the RPMI 8226 human myeloma cell line and the P-glycoprotein-expressing multidrug-resistant 8226/C1N subline. SCID mice 5 to 8 wk of age were injected i.p. with either 8226 drug-sensitive or P-glycoprotein-expressing multidrug-resistant myeloma cells (8226/C1N). Tumors were detected within 5 days after injection by the presence of human lambda light chain excretion in the mouse urine. Growth of the tumor was obsd. primarily in the abdominal cavity with spread to the abdominal organs. The anti-neoplastic agent doxorubicin was effective in treating the drug-sensitive 8226 human-SCID xenografts but had no effect on the multi-drug-resistant 8226/C1N human-SCID xenografts. In the 8226-sensitive xenografts, treatment with doxorubicin resulted in a sharp decline in the concn. of human lambda light chain being excreted in the mouse urine. This correlated with an increased survival of the drug-treated animals. This correlated with an increased survival of the drug-treated animals. This mouse model offers an in vivo means of evaluating efficacy and toxicity of new therapeutic approaches, including development of chemosensitizers directed against P-glycoprotein in multidrug-resistant myelomas.

Answer 135:

**Bibliographic Information**

**Toxicity of 3'-deamino-3'-(3-cyano-4-morpholinyl) doxorubicin and doxorubicin in nude mice bearing human tumor**

**xenografts.** Ford, C. H. J.; Richardson, V. J.; Pushpanathan, C.; Ali, S. K. Fac. Med., Mem. Univ., St. John's, NF, Can. Anticancer Research (1991), 11(5), 1855-62. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 116:165675 AN 1992:165675 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The toxicity of the intensely potent anthracycline 3'-deamino-3'-(3-cyano-4-morpholinyl)doxorubicin (MRA-CN) was evaluated in nude mice bearing human colonic cancer xenografts. In addn. to dose related toxicity manifested as wt. loss and effects on the haematol. profile, evidence of cardiotoxicity with MRA-CN was obtained which has not been reported previously. Even a single dose of 0.012 mg kg<sup>-1</sup> could induce significant myocardial changes as seen by electron microscopy. Nude mice bearing human tumor xenografts may offer a very sensitive model for the evaluation of anthracycline induced cardiomyopathy. In view of the potential of MRA-CN in cancer treatment, these results need to be confirmed and extended.

Answer 136:

#### Bibliographic Information

**The relationship between cytotoxic drug exposure and tumor cell kill, in vitro and in vivo.** Kerr, D. J.; Smart, H. I. Beatson Oncol. Cent., Belvidere Hosp., Glasgow, UK. In Vivo (1991), 5(4), 385-8. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 116:75824 AN 1992:75824 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Doxorubicin has been shown to be more effective against MGH-U1 bladder carcinoma cells grown in monolayer than spheroid. In vitro clonogenic cell survival curves have been replotted against the area under the concn.-time curve (AUC) for drug exposure and fitted to a Hill plot to derive the parameters E max (max. possible cell kill) and C50 (drug exposure resulting in half the max. cell kill). The plasma AUC following i.p. administration of doxorubicin to nude mice was measured using a sensitive and specific HPLC assay and combined with the in vitro cell survival parameters to predict the clonogenic cell survival in MGH-U1 xenografts. The Hill parameters from the spheroid model are better predictors of xenograft clonogenic cell survival than the monolayer parameters. It is possible to predict clonogenic cell survival in solid tumors on the basis of the pharmacokinetics of cytotoxic drug exposure, using a math. model based on clonogenic cell kill in vitro.

Answer 137:

#### Bibliographic Information

**Biochemical and pharmacological characterization of MCE-7 drug-sensitive and AdrR multidrug-resistant human breast tumor xenografts in athymic nude mice.** Mimnaugh, Edward G.; Fairchild, Craig R.; Fruehauf, John P.; Sinha, Birandra K. Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, USA. Biochemical Pharmacology (1991), 42(2), 391-402. CODEN: BCPA6 ISSN: 0006-2952. Journal written in English. CAN 115:126588 AN 1991:526588 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The phenotypic expression of multidrug resistance by the doxorubicin-selected AdrR human breast tumor cell line is assocd. with overexpression of plasma membrane P-170 glycoprotein and increased cytosolic selenium-dependent GSH-peroxidase activity relative to the parental MCF-7 wild-type line (WT). To det. whether doxorubicin resistance by AdrR cells persists in vivo, and to further investigate the possibility of biochem. differences between WT and AdrR cells persists in vivo, and to further investigate the possibility of biochem. differences between WT and AdrR solid tumors, both tumor cell lines were grown as s.c. xenografts in athymic nude mice. Tumorigenicity depended upon cell inoculation burden, and tumor incidence was similar for both cell lines (>80% tumor takes at 107 cells/mouse) at 14 days, provided 17 $\beta$ -estradiol was supplied to the animals bearing the WT tumors. However, the growth

rate for the AdrR xenografts was only about half of the WT xenografts. Doxorubicin (2-8 mg/kg, i.p., injected weekly) significantly diminished the growth of the WT tumors, but AdrR solid tumors failed to respond to doxorubicin. The accumulation of <sup>14</sup>C-labeled doxorubicin was 2-fold greater in WT xenografts than in AdrR, although there were no differences in host organ drug levels in mice bearing either type of tumors. Membrane P-170 glycoprotein mRNA was detected by slot-blot anal. in AdrR tumors, but not in WT. ESR 5,5-dimethylpyrroline-N-oxide-spin-trapping expts. with microsomes and mitochondria from WT and AdrR xenografts demonstrated a 2-fold greater oxygen radical (superoxide and hydroxyl) formation from activated doxorubicin with WT xenografts compared to AdrR. Selenium-dependent glutathione (GSH)-peroxidase, superoxide dismutase and GSH-S-arytransferase activities in AdrR xenografts were elevated relative to WT.

Although the activities of the latter two enzymes were similar to those measured in both tumor cell lines, GSH-peroxidase activities were elevated 70-fold (WT) and 10-fold (AdrR) in xenografts compared to tumor cells. In contrast, in both WT and AdrR solid tumors in vivo, catalase, NAD(P)H-oxidoreductases, and glutathione disulfide (GSSG)-reductase activities, and GSH and GSSG levels were not markedly different, and were essentially the same as in cells in vitro. Like the MDR cells in culture, AdrR tumor xenografts were extremely resistant to doxorubicin and retained most of the characteristics of the altered phenotype. These results suggest that WT and AdrR breast tumor xenografts provide a useful model for the study of biochem. and pharmacol. mechanisms of drug resistance by solid tumors in vivo.

Answer 138:

### Bibliographic Information

#### **Studies on chemotherapy for adenocarcinoma of the uterine cervix using xenografts transplanted in nude mice.**

Yamagishi, Masaji. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. Nippon Sanka Fujinka Gakkai Zasshi (1991), 43(2), 165-72. CODEN: NISFAY ISSN: 0300-9165. Journal written in Japanese. CAN 115:341 AN 1991:400341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Adenocarcinoma of the human uterine cervix was successively transplanted into nude mice and the effects of chemotherapy on adenocarcinoma of uterine cervix were investigated in this transplanted tumor. First, it was confirmed that both the original tumor and the transplanted tumor were apparently histol. the same as adenocarcinoma of the uterine cervix (endocervical type). And the transplanted tumor was shown to have the features of adenocarcinoma by an electron microscope. The doubling time of the transplanted tumor was 9.2 days. For the chemotherapy study, first the therapeutic effects of 11 kinds of agents were screened by single-agent chemotherapy applied to the transplanted tumor. From the results of this series, 6 regimens for multi-agent chemotherapy were tried on the transplanted tumor. The effects of the chemotherapy were evaluated following Battelle Columbus Labs. Protocol and histopathol. The relative regression rates for the tumors treated with mitomycin C (MMC) + cyclophosphamide (CPM) and MMC + CPM + methotrexate (MTX) were 72.99 and 80.9% (Tn/To = 0.84), resp. The results suggest that the combinations of MMC + CPM or MMC + CPM + MTX are regimens that are possibly effective on the adenocarcinoma of human uterine cervix and are worth be trying clin.

Answer 139:

### Bibliographic Information

**Differential efficacy of flavone acetic acid against liver versus lung metastases in a human tumor xenograft.** Pratesi, G.; Manzotti, C.; Tortoreto, M.; Audisio, R. A.; Zunino, F. Div. Exp. Oncol. B, Ist. Naz. Stud. Cura Tumori, Milan, Italy. British Journal of Cancer (1991), 63(1), 71-4. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 114:156741 AN 1991:156741 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A human ovarian carcinoma, IGROV-1, was xenografted into different sites (i.p., s.c., i.v., and intrasplenically) in nude athymic female mice to investigate the pattern of antitumor efficacy of flavone acetic acid (FAA) and compare it to that of doxorubicin and

cisplatin, two established cytotoxic drugs. Ascitic and lung-growing tumors totally failed to respond to FAA, whereas s.c. and liver-growing tumors were significantly growth inhibited. This pattern of activity differs from that achieved by the two conventional cytotoxic drugs, which were active against the IGROV-1 tumor growing in all of the tested sites. These studies indicate that cytotoxicity is not the major determinant of FAA antitumor efficacy even against human tumor xenografts. Moreover, the dramatic difference between the sensitivity of lung and liver tumor colonies demonstrates the great importance of the site of tumor growth for FAA efficacy.

Answer 140:

#### **Bibliographic Information**

**Comparative cytotoxic effect of anthracycline antibiotics on heterotransplants of human breast cancer cells cultivated in diffusion chambers in vivo.** Krutova, T. V.; Korman, D. B.; Batomunkueva, T. V. Inst. Khim. Fiz., Moscow, USSR. *Antibiotiki i Khimioterapiya* (1989), 34(11), 849-52. CODEN: ANKHEW ISSN: 0235-2990. Journal written in Russian. CAN 112:229409 AN 1990:229409 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The cytotoxic activity of doxorubicin, daunomycin, carminomycin, and ruboxyl against 50 human breast cancer heterotransplants was studied in diffusion chambers implanted in mice. The effect was estd. autoradiog. on the 6th or the 7th day of the cultivation after the drug administration in the max. tolerance doses. The tumors were considered sensitive when the labeling index of their transplants after the treatment was reduced by  $\geq 50\%$ . The no. of the tumors sensitive to all the drugs was 72-80%. Nineteen tumors were sensitive to 4 antibiotics. Fourteen and 8 tumors were sensitive to 3 and 2 antibiotics, resp., and only 1 tumor was sensitive to 1 drug. The sensitivity significantly correlated with the initial labeling index of the primary tumors and their heterotransplants. Thus, daunomycin and ruboxyl possessed a high cytotoxic activity close to that of doxorubicin and carminomycin and might be recommended for clin. trails in the treatment of patients with breast cancer.

Answer 141:

#### **Bibliographic Information**

**Tissue concentrations of doxorubicin in animal models with engrafted intraocular tumors.** White, Les; Chan, Kenneth K.; Barrientos, Alfonso; Gomer, Charles J.; Murphree, A. Linn; Benedict, William F. Child. Leuk. Cancer Res. Unit, Prince Wales Child. Hosp., Randwick, Australia. *In Vivo* (1989), 3(5), 315-17. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 112:229356 AN 1990:229356 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The role of chemotherapy in the management of retinoblastoma remains unclear. In order to evaluate the responsiveness to conventional or exptl. agents, a xenograft model had been developed, where human retinoblastoma is heterotransplanted to the anterior chambers of nude mouse eyes. Because doxorubicin had been found to be ineffective in therapeutic studies utilizing the model, expts. were conducted to evaluate the concn. of the drug in tissues, including intraocular engrafted tumor. The presence of doxorubicin was demonstrated in xenograft contg. mouse eyes as well as in tumors of a comparable rabbit model. Distribution in extraocular tissues was consistent with previously published data. It is concluded that failure of response to doxorubicin in the xenograft model is not explained by lack of tumor penetration by the drug.

Answer 142:

#### **Bibliographic Information**

**Therapy-induced drug resistance in a human leukemia line (LALW-2). A clinically relevant model.** White, Les; Haber,

Michelle; Brian, Michael J.; Norris, Murray D.; Trickett, Annette; Sosula, Leo; Tiley, Campbell; Stewart, Bernard W. Child. Leukaemia Cancer Res. Unit, Prince of Wales Child. Hospital, Sydney, Australia. Cancer (New York, NY, United States) (1989), 63(11), 2103-10. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 111:50044 AN 1989:450044 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A human leukemic T-cell line, LALW-2, established by xenografting in nude mice, has been maintained through 14 serial passages. The cells display consistent morphol. features, immunophenotype, and karyotypic aberrations (including an 11;14 translocation) and exhibit rearrangement of the T-cell receptor  $\beta$ -chain gene. The growth rate of LALW-2 xenografts was differentially affected by drugs administered to host mice, the cells being resistant to cytotoxic agents (particularly methotrexate and doxorubicin) used in treatment of the donor patient. In short-term in vitro culture, LALW-2 cells exhibited extreme resistance to methotrexate and were also resistant to vincristine, vinblastine, dactinomycin, and doxorubicin. The findings differ from those obtained with lab.-derived methotrexate or multidrug-resistant cell lines. The response of LALW-2 cells, in both the nude mouse model and in vitro, is consistent with acquisition of drug-resistance as a result of clin. treatment.

Answer 143:

#### Bibliographic Information

**Inhibition of human tumor growth in nude mice by a conjugate of doxorubicin with monoclonal antibodies to epidermal growth factor receptor.** Aboud-Pirak, Esther; Hurwitz, Esther; Bellot, Françoise; Schlessinger, Joseph; Sela, Michael. Dep. Chem. Immunol., Weizmann Inst. Science, Rehovot, Israel. Proceedings of the National Academy of Sciences of the United States of America (1989), 86(10), 3778-81. CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 111:12429 AN 1989:412429 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Monoclonal antibodies that recognize the extracellular domain of the epidermal growth factor receptor (mAb108) were conjugated with doxorubicin through a dextran bridge. Several antibody-drug conjugates, contg. different amts. of doxorubicin, retained binding capacity to human epidermoid carcinoma (KB) cells overexpressing epidermal growth factor receptors. A slight decrease in drug cytotoxicity was seen in in vitro test, as detd. either by inhibition of thymidine incorporation into cells or by redn. in the no. and size of KB-cell colonies. Yet, when tested in vivo against KB tumor xenografted into nude mice, the antiepidermal growth factor-receptor drug conjugates with high drug-substitution levels were more effective than free doxorubicin, antibody alone, mixt. of dextran-doxorubicin and antibody, or drug conjugated with irrelevant antibody. When the labile covalent bonds linking antibody to dextran bridge were stabilized by redn., the therapeutic efficacy of the conjugate was markedly decreased. Thus, antibodies against the extracellular domain of the epidermal growth factor can deliver doxorubicin specifically and efficiently to tumor sites that express high receptor levels exerting a specific antitumor effect.

Answer 144:

#### Bibliographic Information

**Recombinant human tumor necrosis factor alone and with chemotherapeutic agents. Effect on nude mouse-supported human bladder cancer heterografts.** Das, Anurag K.; Walther, Philip J.; Buckley, Niall J.; Poulton, Susan H. M. Sch. Med., Duke Univ., Durham, NC, USA. Archives of Surgery (Chicago, IL, United States) (1989), 124(1), 107-10. CODEN: ARSUAX ISSN: 0004-0010. Journal written in English. CAN 110:112847 AN 1989:112847 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The effect of recombinant human tumor necrosis factor (rhTNF) alone and in combination with cisplatin, etoposide, doxorubicin, or

dactinomycin on the growth of heterotransplants of human bladder transitional cell carcinoma was studied using a modified subrenal capsule assay in athymic nude mice. Only etoposide potentiated rhTNF cytotoxicity; no increase in host toxicity was noted. Variably enhanced toxic side effects were seen with other combinations. Thus, rhTNF combined with etoposide may have potential clinically exploitable therapeutic synergism in the treatment of advanced bladder cancer.

Answer 145:

### **Bibliographic Information**

**Antitumor activity of doxorubicin-monoclonal antibody conjugate on human bladder cancer.** Yu, Dah Shyong; Chu, T. Ming; Yeh, Ming Yang; Chang, Sun Yran; Ma, Cheng Ping; Han, Shou Hwa. Dep. Diagn. Immunol. Res. Biochem., Roswell Park Mem. Inst., Buffalo, NY, USA. Journal of Urology (Hagerstown, MD, United States) (1988), 140(2), 415-21. CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 109:142131 AN 1988:542131 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Doxorubicin (adriamycin) was conjugated via the dextran bridge method to a murine IgG3 monoclonal antibody, 1G3.10, directed against human bladder cancer. The drug-antibody conjugate, prepared from using 25% oxidized dextran as the linker, retained essentially the original immunological activity of the antibody using ELISA as tested against an antigen-positive target cell line (TSGH-8301), which has been shown to express an antigen recognized by the monoclonal antibody 1G3.10. The antitumor effect of the conjugate in vitro was evaluated by its inhibition on <sup>3</sup>H-uridine incorporation into the established human bladder cancer cells. The conjugate exhibited a significantly higher cytotoxicity on target TSGH-8301 cells than that by a control antibody-doxorubicin conjugate prepared identically from an irrelevant mouse IgG3 monoclonal antibody. No apparently different cytotoxicity was detected on control antigen-negative bladder tumor cells of J82 between these two drug-antibody conjugates. Verapamil, a calcium channel blocker, enhanced the in vitro cytotoxicity of doxorubicin-1G3.10 monoclonal antibody conjugate. Results obtained from in vivo evaluation using xenografted target TSGH-8301 bladder tumor indicated that the 1G3.10 monoclonal antibody conjugate containing doxorubicin injected 4x, i.p., significantly inhibited TSGH-8301 bladder tumor growth in nude mice, whereas free monoclonal antibody, free drug and the mixture of both showed only moderate inhibition of tumor growth as compared to the untreated control. Verapamil also enhanced in vivo antitumor activity of the conjugate. There was no side effect (weight loss) detected on the conjugate-treated mice. Results obtained from in vivo evaluation using xenografted control J82 bladder tumor showed no specific antitumor activity as exhibited by doxorubicin-1G3.10 monoclonal antibody conjugate in comparison with free drug, mixture of drug and antibody without conjugation, or doxorubicin conjugated to the irrelevant antibody.

These results suggested that doxorubicin conjugated with bladder tumor associated monoclonal antibody could be useful as a potentially cytotoxic agent in immunochemotherapy of human bladder cancer.

Answer 146:

### **Bibliographic Information**

**Doxorubicin conjugated with a monoclonal antibody directed to a human melanoma-associated proteoglycan suppresses the growth of established tumor xenografts in nude mice.** Yang, Hsin Ming; Reisfeld, Ralph A. Dep. Immunol., Scripps Clin. and Res. Found., La Jolla, CA, USA. Proceedings of the National Academy of Sciences of the United States of America (1988), 85(4), 1189-93. CODEN: PNASA6 ISSN: 0027-8424. Journal written in English. CAN 108:137791 AN 1988:137791 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### **Abstract**

Doxorubicin (I) was covalently conjugated to a monoclonal antibody (mAb), 9.2.27 (IgG2a), which recognizes a chondroitin sulfate proteoglycan expressed preferentially on the surface of human melanoma cells. Immunoconjugates with a molar ratio of I to mAb ranging from 2:1 to 10:1 were obtained by coupling the drug via an acid-sensitive linker, cis-aconitic anhydride. The immunoreactivity of mAb 9.2.27 was well retained after conjugation. I-mAb 9.2.27 conjugates were 2 orders of magnitude more potent in killing tumor

cells in vitro (IC<sub>50</sub> = 0.1 μM) than free drug targeted to drug receptors. Most significantly, I-mAb 9.2.27 immunoconjugates specifically suppressed the growth of established tumors in vivo and prolonged the life-span of tumor-bearing nude mice. This suppression of melanoma growth achieved by the immunoconjugate was both tumor and antibody specific. A biodistribution study indicated that I-mAb 9.2.27 conjugates delivered at least 4-fold more I (3.7% total injected dose per g of tumor) as compared to free I alone (0.8% total injected dose per g of tumor) in tumor-bearing nude mice 48 h postinjection. The tumor-suppressive effects of I-mAb 9.2.27 conjugates are even more remarkable since free I did not suppress tumor growth in vivo and also because this drug per se is quite ineffective for the treatment of human melanoma.

Answer 147:

#### **Bibliographic Information**

##### **Sensitivity to antineoplastic agents of squamous cell carcinoma of the uterine cervix xenografted into nude mice.**

Kawabata, Masakiyo; Hosokawa, Hitoshi; Kato, Kiyoshi; Izumi, Rikuichi. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. *Gan to Kagaku Ryoho* (1987), 14(11), 3058-63. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 108:68479 AN 1988:68479 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The efficacies of 5 antineoplastic agents (cisplatin, mitomycin, doxorubicin, 5-fluorouracil, and bleomycin) were tested against carcinoma of the human uterine cervix xenografted into nude mice in order to search for effective combination chemotherapy. The responses to cisplatin and mitomycin were the highest. Thus, combination chemotherapies involving cisplatin and mitomycin are recommended for the treatment of squamous cell carcinoma of the uterine cervix.

Answer 148:

#### **Bibliographic Information**

##### **Antitumor effect of kzasumycin B on experimental tumors.**

Yoshida, Eisaku; Komiyama, Kanki; Naito, Kyozo; Watanabe, Yoshinori; Takamiya, Keiko; Okura, Akira; Funaiishi, Kohtarou; Kawamura, Kenji; Funayama, Shinji; Umezawa, Iwao. Explor. Res. Lab., Banyu Pharm. Co., Ltd., Tokyo, Japan. *Journal of Antibiotics* (1987), 40(11), 1596-604. CODEN: JANTAJ ISSN: 0021-8820. Journal written in English. CAN 108:15969 AN 1988:15969 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Kzasumycin B showed a broad antitumor spectrum both in vitro and in vivo. The 50%-inhibitory concn. for the growth of tumor cells was .apprx.1 ng/mL at 72-h exposure in vitro. I.p. injection of the antibiotic was effective in inhibiting the growth of murine tumors S180, P388, EL-4, and B16. It was also against doxorubicin-resistant P388, hepatic metastases of L5178Y-ML, pulmonary metastases of 3LL, and human mammary cancer MX-1 xenografted in nude mice. However, the activity of kzasumycin B toward L1210 or human lung cancer LX-1 was weaker. The effects of kzasumycins B and A were essentially equiv. The ED range and toxicity were markedly dependent on the tumor lines tested and the regimen used. The max. tolerated dose in mice with s.c. tumors was much higher than that in mice bearing ascitic leukemia as P388. Although intermittent administration could greatly reduce the cumulative toxicity of the drug, the therapeutic effect was similar with both successive and intermittent administration schedules.

Answer 149:

#### **Bibliographic Information**

##### **Efficacy of anticancer agents in vitro and in vivo using cultured human endometrial carcinoma cells. Study of therapeutic index.**

Yasui, Yoshie. Sch. Med., Nagoya City Univ., Nagoya, Japan. *Nippon Sanka Fujinka Gakkai Zasshi* (1987), 39(2), 303-6. CODEN: NISFAY ISSN: 0300-9165. Journal written in English. CAN 106:188338 AN 1987:188338 CAPLUS

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### Abstract

Employing the new cell line, NUE-1, which was derived from cells of ascites in a woman with endometrial carcinoma, the sensitivity test for anticancer agents was carried out in culture and xenografts in nude mice. Anticancer activity in vitro was evaluated by counting surviving cells, and the therapeutic index was expressed by LD50 for mice/MLD90 (90% mean LD) in vitro. NUE-1 cells were inoculated s.c. in BALB/c nude mice, and then tumors serially transplanted were used as materials. Anticancer agents (adriamycin (ADM) [23214-92-8], cisplatinum [15663-27-1], chromomycin A3 [7059-24-7], carbazilquinone [24279-91-2], and mitomycin C [50-07-7]) at 1/3 LD50 dosage for mice were administered i.p. on a schedule of 3 doses for every 4 days. The results were as follows: (a) the therapeutic index of ADM was highest at 5-19 times the others; (b) in vivo, ADM demonstrated chemotherapeutic effectiveness, whereas the others had no significant effect; and (c) there was a close correlation between the therapeutic index and in vivo anticancer effect using nude mice.

Answer 150:

### Bibliographic Information

**Targeted therapy of human tumor xenografts in nude mice with pullulan-coated liposomes containing adriamycin.** Hirota, Masaki; Fukushima, Kiyoyasu; Hiratani, Kazuhito; Kawano, Kenji; Oka, Mikio; Tomonaga, Akimitsu; Saitoh, Atsushi; Hara, Kohei; Sato, Toshinori; Sunamoto, Junzo. Sch. Med., Nagasaki Univ., Nagasaki, Japan. Gan to Kagaku Ryoho (1986), 13(9), 2875-8. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 106:12526 AN 1987:12526 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In nude mice implanted with human PC-9 lung cancer xenografts, the antitumor effect of pullulan [9057-02-7]-coated liposomes encapsulating IgM (immunoliposomes) and adriamycin [23214-92-8] was better than that of liposomes encapsulating adriamycin only. In tumor-bearing nude mice following i.v. injection of 125I-labeled IgM, the image of the tumor was clearly shown by scintigraphy. The distribution of 14C-labeled immunoliposomes was the highest in the liver and spleen, followed by the kidneys, tumor, lungs, intestine, muscle, and heart.

Answer 151:

### Bibliographic Information

**Xenografts in pharmacologically immunosuppressed mice as a model to test the chemotherapeutic sensitivity of human tumors.** Floersheim, G. L.; Bieri, A.; Chioldetti, Nicole. Zent. Lehre Forsch., Kantonssp., Basel, Switz. International Journal of Cancer (1986), 37(1), 109-14. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 104:81665 AN 1986:81665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A human tumor xenograft model using pharmacol. immunosuppressed mice was assessed for its suitability to test preclinically the sensitivity of colorectal carcinomas, bone sarcomas and melanomas against anticancer agents. Beside ionizing radiation, 14 cytotoxic drugs including 5-fluorouracil (5-FU) [51-21-8], dimethylmyleran (DMM) [55-93-6], cytosine arabinoside [147-94-4], cyclophosphamide [50-18-0], melphalan [148-82-3], mitomycin C [50-07-7], adriamycin [23214-92-8], bleomycin [11056-06-7], etoposide [33419-42-0], vinblastine [865-21-4], cisplatin [15663-27-1], procarbazine [671-16-9], DTIC [4342-03-4], and BCNU [154-93-8] were assayed. Ionizing radiation, 5-FU and DMM were also applied at LDs followed by bone-marrow rescue high-dose therapy. Four colon carcinomas responded poorly to most of the agents but one tumor displayed marked sensitivity to BCNU. LDs of radiation, 5-FU and DMM and cyclophosphamide and by an osteosarcoma to the latter drug. No strong effects were seen against melanomas. LDs of DMM induced

the best regression of one colon carcinoma. In general, the superiority of high-dose therapy for solid human tumors compared to maximally tolerated doses was demonstrated. Individual carcinomas of the same type displayed different drug sensitivity.

Answer 152:

#### **Bibliographic Information**

**Experimental chemotherapy of human carcinomas serially transplanted into nude mice.** Kubota, Tetsuro; Asanuma, F.; Tsuyuki, K.; Kurihara, H.; Inada, T.; Ishibiki, K.; Abe, O. Dep. Surg., Keio Univ., Tokyo, Japan. Editor(s): Spitz, K. H.; Karrer, K. Proc. Int. Congr. Chemother., 13th (1983), 18 291/55-291/59. Publisher: Verlag H. Egermann, Vienna, Austria CODEN: 53XPA8 Conference written in English. CAN 104:14592 AN 1986:14592 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

In nude mice transplanted with human carcinomas, most gastrointestinal carcinomas were suppressed by mitomycin C [50-07-7] and were insensitive to cyclophosphamide (CPA) [50-18-0], whereas 2 breast carcinomas and 1 hemangiosarcoma were markedly suppressed by CPA, suggesting that the chemosensitivities of these tumors were different. No differences were found in chemosensitivity between the gastric and colon carcinomas. No correlations were obsd. between the histol. differentiations of the carcinomas and the chemosensitivity to mitomycin C, adriamycin [23214-92-8], aclarubicin [57576-44-0], and CPA. However, the growth-rate of the tumors correlated with the chemosensitivity to mitomycin C and aclarubicin, i.e., the rapid-growing tumors were more sensitive than the slow-growing tumors to the drugs.

Answer 153:

#### **Bibliographic Information**

**Studies on the activity of cytostatic drug therapy on human thyroid carcinomas xenotransplanted into athymic nude mice.** Wenisch, H. J. C.; Wagner, R. H.; Schumm, P. M.; Encke, A. Abt. Allg.- Abdominalchir., Johann Wolfgang Goethe-Univ., Frankfurt/Main, Fed. Rep. Ger. Chirurgisches Forum fuer Experimentelle und Klinische Forschung (1985), 123-6. CODEN: CFEKA7 ISSN: 0303-6227. Journal written in German. CAN 103:64494 AN 1985:464494 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

I.v. administration of doxorubicin (I) [23214-92-8] once a wk to athymic nude mice with xenotransplanted human anaplastic thyroid carcinomas significantly decreased the tumor size and wt. when compared to untreated tumor-bearing controls. Combined therapy with I and cyclophosphamide [50-18-0] further reduced tumor size and wt.; however, these changes were not significant when compared to those obsd. with I alone.

Answer 154:

#### **Bibliographic Information**

**Cytotoxicity of adriamycin in MGH-U1 cells grown as monolayer cultures, spheroids, and xenografts in immune-deprived mice.** Erlichman, C.; Vidgen, D. Dep. Med. Pharmacol., Univ. Toronto, Toronto, ON, Can. Cancer Research (1984), 44(11), 5369-75. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 101:222230 AN 1984:622230 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The cytotoxic activity of Adriamycin [23214-92-8] was examd. in the MGH-U1 human bladder carcinoma line, grown as monolayer culture, as spheroids, and as xenografts in immune-deprived mice. The MGH-U1 cells grown as spheroids were much more resistant to Adriamycin (concn. of drug resulting in 37% cell survival, 4.5  $\mu\text{g}/\text{mL}$ ) than when treated as monolayer cultures (concn. of drug resulting in 37% cell survival, 0.9  $\mu\text{g}/\text{mL}$ ). Adriamycin fluorescence was demonstrated only in the outer two layers of cells forming the spheroids, suggesting that limited drug penetration is an important factor in the resistance of spheroids to adriamycin. Sequential trypsinization of spheroids with 750  $\mu\text{m}$  in diam. allowed us to det. the cytotoxic effects of Adriamycin in MGH-U1 cells derived from different depths of the spheroid. Cells near the surface of the spheroid had a survival similar to those of exponentially growing monolayer cells treated with Adriamycin. Cells located in the middle of the viable rim were more resistant to Adriamycin, and those found near the necrotic center were most resistant to Adriamycin. The effects of Adriamycin treatment on spheroid growth delay were detd., also. In spite of a small cytotoxic effect on the clonogenic fraction of cells in MGH-U1 spheroids, the growth delay effect of Adriamycin in intact spheroids was marked. This observation is consistent with Adriamycin killing primarily the cells in the outer layers of the spheroid, where most of the proliferation in the spheroid occurs. In vivo treatment of MGH-U1 xenografts with adriamycin followed by assessment of cell survival in vitro showed min. evidence of cytotoxicity, consistent with the poor drug penetration obsd. in the spheroid model. These studies suggest that: (a) adriamycin penetrates poorly into solid tissues; (b) in vitro clonogenic survival following adriamycin exposure of a cell suspension may predict falsely for drug sensitivity to chemotherapy; (c) a small decrease in clonogenic survival can be translated into a long growth delay but, ultimately, the tumor regrows because some clonogenic cells are spared; and (d) for adriamycin, the spheroid model more closely parallels the in vivo effects than does monolayer culture. The use of the spheroid model for the study of adriamycin cytotoxicity gives further insight into the action of this drug in solid tumors.

Answer 155:

#### Bibliographic Information

##### **Increased cytotoxic effects of various anticancer drugs by $\alpha$ -interferon (HLBI) on human tumor xenografts in nude mice.**

Nosoh, Yoshihiro; Yoshinaka, Ken; Yamaguchi, Masahiro; Tani, Tadanori; Toge, Tetsuya; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1984), 11(8), 1623-8. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 101:163319 AN 1984:563319 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The effect of 7 anticancer agents in combination with interferon on gastric cancer and malignant melanoma of human transplanted s.c. in nude mice was studied. Of the 7 drugs, mitomycin C [50-07-7] and adriamycin [23214-92-8] showed the greatest inhibition of tumor growth in combination with interferon.

Answer 156:

#### Bibliographic Information

##### **Childhood rhabdomyosarcoma xenografts: responses to DNA-interacting agents and agents used in current clinical therapy.**

Houghton, Janet A.; Cook, Ruby L.; Lutz, Pamela J.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. European Journal of Cancer & Clinical Oncology (1984), 20(7), 955-60. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 101:163109 AN 1984:563109 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

A lab. model of childhood rhabdomyosarcoma (RMS) has been used to evaluate cytotoxic agents used in current clin. protocols, and DNA-reacting agents that have had either limited or no evaluation in this histiotype. Seven lines of RMS each derived from a different patient were grown as xenografts in immune-deprived mice, six of these being from specimens derived from previously untreated patients. Of the conventional agents, vincristine [57-22-7] was the most effective. Of the other agents evaluated [L-phenylalanine

mustard (L-PAM) [148-82-3], cis-dichlorodiammineplatinum (cis-DDP) [15663-27-1], mitomycin C [50-07-7] and 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) [4342-03-4]], L-PAM caused complete regressions in six of seven lines, including those resistant to cyclophosphamide [50-18-0]. DTIC had marked activity in five tumors, and mitomycin C in three lines. Cyclophosphamide was active in five tumors, although efficacy was less marked in two lines in comparison to DTIC and mitomycin C.

Answer 157:

#### **Bibliographic Information**

**Effect of five antineoplastic agents on tumor xenografts with different growth rates.** Mattern, Juergen; Wayss, Klaus; Volm, Manfred. Dep. Exp. Pathol., German Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. JNCI, Journal of the National Cancer Institute (1984), 72(6), 1335-9. CODEN: JJIND8 ISSN: 0198-0157. Journal written in English. CAN 101:103754 AN 1984:503754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The effects of cyclophosphamide (Cy) [50-18-0], doxorubicin (Dx) [23214-92-8], cisplatin (DDP) [15663-27-1], melphalan (L-PAM) [148-82-3], and vincristine (VCR) [57-22-7] on various human and animal tumor lines with different growth rates, growing as xenografts in NMRI (nu/nu) mice, were studied. Two types of response were obsd.: For Cy and Dx, the response of the xenografts was neg. correlated with tumor vol. doubling time (TD), indicating that rapidly growing tumors were more sensitive to these drugs than were slowly growing tumors. For DDP, L-PAM, and VCR, the effects were pos. correlated with the TD, indicating that slowly growing tumors were more sensitive to these drugs than rapidly growing tumors. The data are discussed in relation to the effects of the drugs on proliferating and nonproliferating cells obtained with other cell lines.

Answer 158:

#### **Bibliographic Information**

**Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice and predictability to clinical response of anticancer agents.** Fujita, M.; Fujita, F.; Taguchi, T. Dep. Oncol. Surg., Osaka Univ., Osaka, Japan. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 311-15. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:103450 AN 1984:503450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The effectiveness of 13 drugs against 14 lines of human gastrointestinal and breast cancers xenografted in nude mice was studied. Despite identical origins of organ and similarities in histol. types, degrees of differentiation, and growth rate, each line of cancer demonstrated different spectra of sensitivity to various agents. The effectiveness of various chemotherapeutic agents against human gastric cancer xenografts in nude mice was compared with the clin. effects of these drugs in clin. trials and phase II studies. The results indicated that the nude mouse-human cancer system would be useful in preclin. secondary screening.

Answer 159:

#### **Bibliographic Information**

**The use of athymic mice in the screening of new anthracycline derivatives.** Giuliani, Fernando C.; Kaplan, Nathan O. Farmitalia Carlo Erba Res. Cent., Milan, Italy. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 374-8. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:32720 AN 1984:432720 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The antineoplastic action of several anthracyclines (doxorubicin [23214-92-8], 4'-epidoxorubicin [56420-45-2], 4-demethoxydoxorubicin [64314-52-9], 4-demethoxydaunorubicin [58957-92-9], and 4-demethoxy-4'-epidoxorubicin [62348-68-9]) against human tumors transplanted in nude athymic mice is discussed; for 4'-epidoxorubicin, the results are compared with data obtained from preliminary Phase I clin. trials. No conclusive assertion can be made about the clin. predictivity of new anthracyclines based on the human tumor xenograft-nude mouse screening model; a good correlation was, however, obtained between the clin. and animal studies for doxorubicin.

Answer 160:

**Bibliographic Information**

**Renal cell carcinoma - xenotransplantation into immuno-suppressed mice.** Kopper, L.; Magyarosy, E.; Nagy, P.; Lapis, K.; Szamel, I.; Eckhardt, S.; Csata, S.; Wabrosch, G.; Repassy, D. 1st Inst. Pathol. Exp. Cancer Res., Semmelweis Med. Univ., Budapest, Hung. *Oncology* (1984), 41(1), 19-24. CODEN: ONCOBS ISSN: 0030-2414. Journal written in English. CAN 100:150726 AN 1984:150726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Twenty one human renal cell carcinomas (RCC) were xenotransplanted into artificially immunosuppressed mice. Four tumors grew successfully retaining some characteristics of the primary tumors (according to morphol. and karyotype anal.), but losing metastatic capacity. One of the serially transplantable tumors (HT 40) with hyperdiploid cellular DNA content and estrogen receptor positivity failed to respond to the single maximally tolerated dose of several cytotoxic agents.

Answer 161:

**Bibliographic Information**

**Optical fiber fluoroprobes in clinical analysis.** Sepaniak, Michael J.; Tromberg, Bruce J.; Eastham, Jerome F. Dep. Chem., Univ. Tennessee, Knoxville, TN, USA. *Clinical Chemistry* (Washington, DC, United States) (1983), 29(9), 1678-82. CODEN: CLCHAU ISSN: 0009-9147. Journal written in English. CAN 99:151627 AN 1983:551627 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Quartz optical fibers and laser excitation were used in developing single-fiber fluoroprobes, for measuring mol. fluorescence in minute vols. of body fluids. The anal. capabilities of these fluoroprobes are illustrated and discussed. Limits of detection for the antitumor drug doxorubicin [23214-92-8] are .apprx.10<sup>-7</sup> mol/L, by either conventional fluorescence or sequentially excited fluorescence modes of detection. The results of preliminary in vivo measurements of doxorubicin in the interstitial fluids of human tumors (heterotransplanted in immune-deficient lab. mice) are reported.

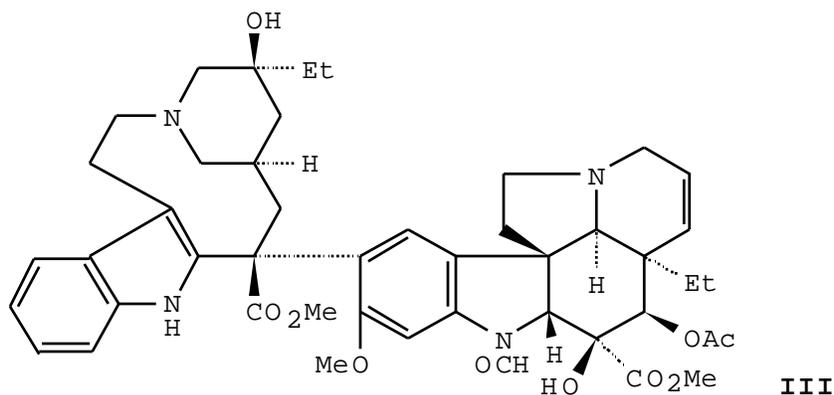
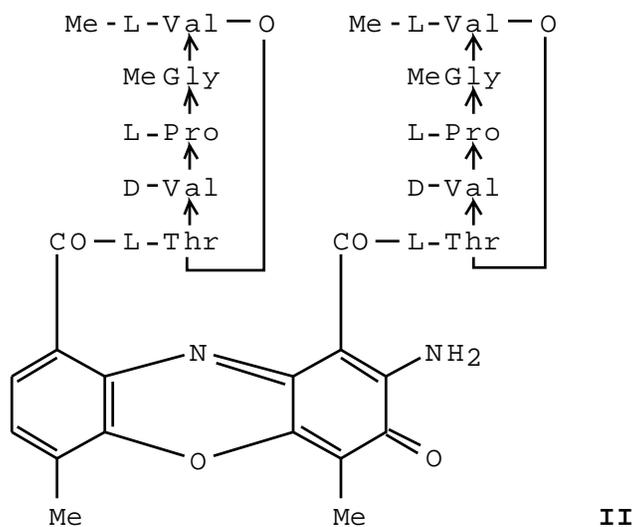
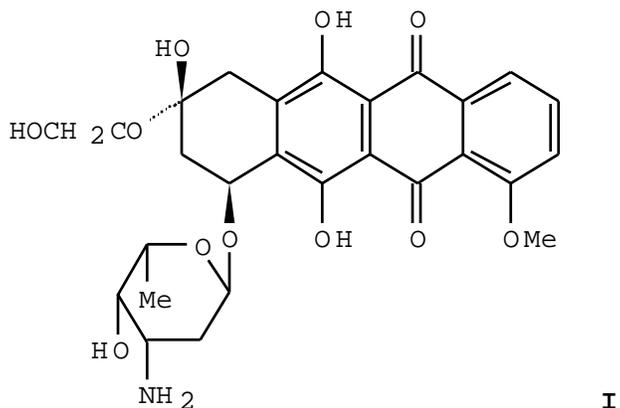
Answer 162:

**Bibliographic Information**

**Chemotherapeutic response in xenografts: inter- and intra-tumor heterogeneity.** Houghton, Peter J.; Houghton, Janet A. Dep. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. *UCLA Symposia on Molecular and Cellular Biology, New Series* (1983), 4(Ration. Basis Chemother.), 61-9. CODEN: USMBD6 ISSN: 0735-9543. Journal written in English. CAN 98:209649 AN 1983:209649 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The sensitivity of 5 lines of rhabdomyosarcoma, each derived from a different child and grown as xenografts in mice, was examd. to doxorubicin (I) [23214-92-8] actinomycin D (II) [50-76-0] and vincristine (III) [57-22-7]. Resistance de novo to 1 agent was not assocd. necessarily with cross resistance. Development of resistance to vincristine in situ was examd. Resistant lines were derived only from 2 tumor lines which showed a slight sensitivity to vincristine initially. Apparently, the initial tumor response is detd. by subpopulations of cells having different intrinsic sensitivity to vincristine.

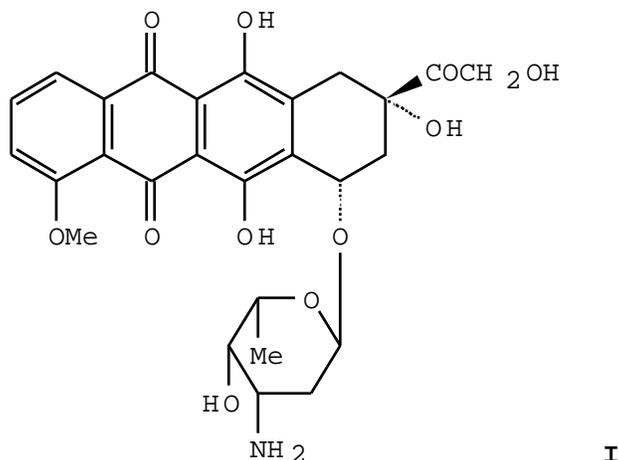


**Bibliographic Information**

**In vitro responses of nude mouse-xenografted human colon carcinomas exposed to doxorubicin derivatives in tissue culture and in the mouse.** Zirvi, Karimullah A.; Van der Bosch, Juergen; Kaplan, Nathan O. Dep. Chem., Univ. California, La Jolla, CA, USA. Cancer Research (1982), 42(9), 3793-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 98:27415 AN 1983:27415 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

In vitro responses of 4 xenografted human colon tumors (T183, T219, T245, and T348) to various doses of 4'-deoxydoxorubicin (I) [63521-85-7] were investigated. The individual tumors showed marked differences in drug responsiveness, ranging from high sensitivity at low doses (T219; 125 ng/mL) to very low sensitivity at high doses (T245; 4000 ng/mL). The sensitivity ranking deduced from these in vitro expts. correlates well with the ranking deduced earlier from in vivo drug treatments of transplants of these tumors in the nude mouse. The effect of in vitro drug treatment (4'-deoxydoxorubicin; 250 ng/mL; 1-h incubation) on the in vivo growth of one of the tumors, T219, in nude mice was investigated. Growth of the tumor in nude mice was markedly delayed by pretreatments in vitro with 4'-deoxydoxorubicin. Furthermore, in vitro responsiveness of the T219 tumor was investigated following in vivo and in vitro treatment of the tumor with 4'-deoxydoxorubicin. Both of the pretreatments produced very similar decreases in drug responsiveness to all of the doxorubicin derivs. tested (4'-deoxydoxorubicin, , 4'-O-methyldoxorubicin [77121-90-5], 4'-epidoxorubicin [56420-45-2], 4-demethoxydoxorubicin [64314-52-9], and N-trifluoroacetyldoxorubicin-14-valerate [56124-62-0]).



Answer 164:

**Bibliographic Information**

**New method for evaluating the effect of experimental chemotherapy on human xenografts in nude mice: use of lactate dehydrogenase isozyme.** Hayata, Satoshi; Fujita, Masahide; Nakano, Yosuke; Kumagai, Michihiko; Hakozaiki, Michinori; Taguchi, Tetsuo. Res. Inst. Microbial Dis., Osaka Univ., Osaka, Japan. Editor(s): Periti, Piero; Gialdroni Grassi, Giuliana. Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Meeting Date 1981, 2 1283-4. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 48HGAR Conference written in English. CAN 97:174303 AN 1982:574303 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Monitoring human lactate dehydrogenase (I) [9001-60-9] isozyme 5 during chemotherapy in the nude mouse was more sensitive than conventional methods for evaluation of treatment. In H-55 (gastric) and H-62 (breast) tumors, good correlation between tumor vols.

and human I were obsd. and the coeffs. were 0.686 and 0.803, resp. H-81 gastric cancer was very sensitive to TA-077 [70189-62-7] (100 mg/kg, weekly). S.c. tumor decreased after treatment and almost disappeared at the termination of the expt. Human I also decreased, and this decrease was greater than that obsd. for tumor size. The I isozyme method was more sensitive than the measurement of tumor size. In the ascitic tumor (Br-13 breast cancer) system, the effect of drugs was easily detd. by the human I level.

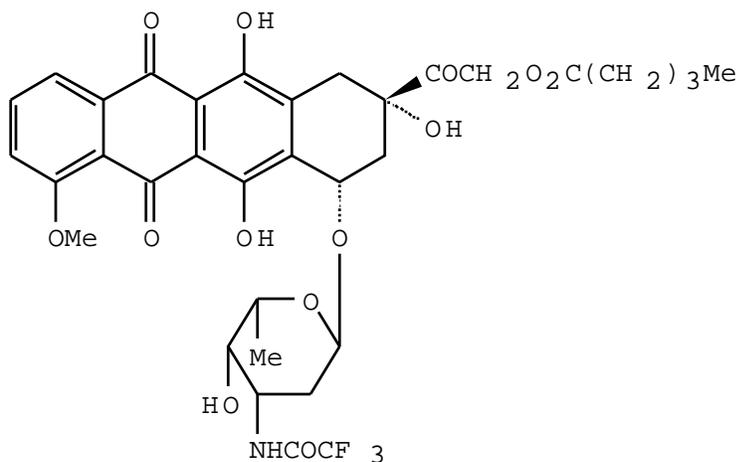
Answer 165:

### Bibliographic Information

**Comparative antineoplastic activity of N-trifluoroacetyl adriamycin-14-valerate and doxorubicin against human tumors xenografted into athymic mice.** Giuliani, Fernando C.; Zirvi, Karimullah A.; Kaplan, Nathan O.; Goldin, Abraham. Cancer Cent., Univ. California, La Jolla, CA, USA. Editor(s): Periti, Piero; Gialdroni Grassi, Giuliana. Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Meeting Date 1981, 2 1435-6. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 48HGAR Conference written in English. CAN 97:138243 AN 1982:538243 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

AD-32 (N-Trifluoroacetyl adriamycin-14-valerate)(I) [56124-62-0] exerted an antitumor effect against human tumors sensitive to doxorubicin [23214-92-8] transplanted in nude mice when it was administered at doses 10 times higher than those of doxorubicin. However, under these exptl. conditions, the antitumor activity of I against the human solid tumors was not superior to that of doxorubicin.



Answer 166:

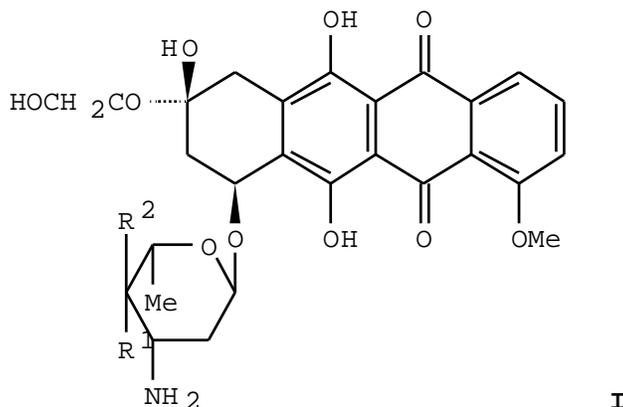
### Bibliographic Information

**Effect of 4'-doxorubicin analogs on heterotransplantation of human tumors in congenitally athymic mice.** Giuliani, Fernando C.; Coirin, Antonio K.; Rice, M. Rene; Kaplan, Nathan O. Cancer Cent., Univ. California, La Jolla, CA, USA. Cancer Treatment Reports (1981), 65(11-12), 1063-75. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 96:45961 AN 1982:45961 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The antitumor activity of three new doxorubicin (DX) derivs. I (R1 = H or OMe and R2 = H or OH) with less cardiotoxicity than the parent compd. I (R1 = OH and R2 = H) was tested against several human tumors representative of some of the major classes of

human cancer. The tested DX derivs., modified on the 4' position of the amino sugar, were 4'-epiDX [56420-45-2], 4'-deoxyDX [63521-85-7], and 4'-O-methylDX [77121-90-5]. Fourteen human tumors (3 breast tumors, 3 lung tumors, 3 melanomas, 2 ovarian tumors, 1 prostate tumor, 1 sarcoma, and 1 larynx tumor) serially transplanted in athymic mice were used to screen the antineoplastic activity of the 4'-DX derivs. BALB/c nude mice were treated i.v. with equitoxic doses of each as a single agent ( $\leq$  LD10) on a weekly basis for 3-4 wk, starting when the tumor became relatively large. 4'-EpiDX, which has a higher threshold limit of cardiac toxicity in man, was active against breast, lung (epidermoid and oat cell carcinoma), prostate, and ovarian tumors. This drug showed particularly good activity against melanomas. 4'-DeoxyDX was active against breast and prostate tumors, whereas 4'-O-methylDX was active against breast and ovarian tumors and possibly sarcoma.



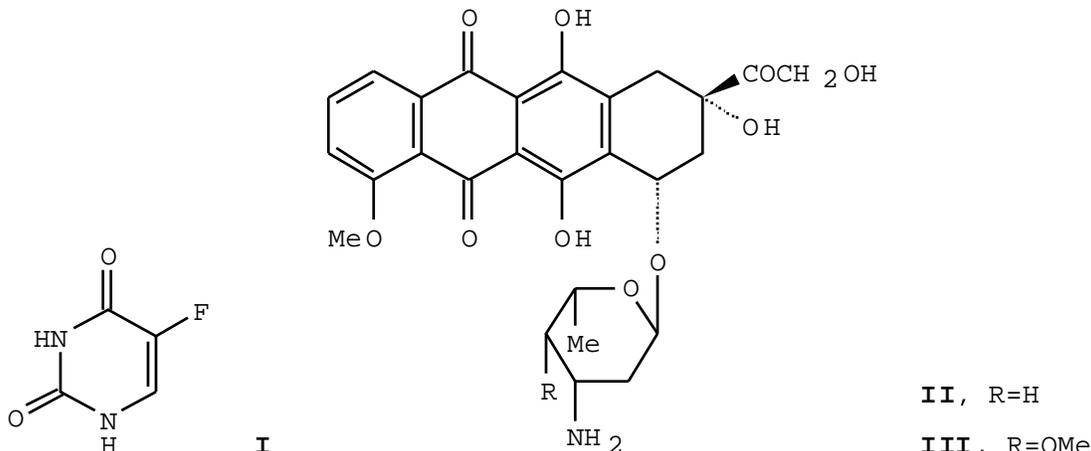
Answer 167:

### Bibliographic Information

**Chemotherapy of human colorectal tumor xenografts in athymic mice with clinically active drugs: 5-fluorouracil and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Comparison with doxorubicin derivatives: 4'-deoxydoxorubicin and 4'-O-methyl-doxorubicin.** Giuliani, Fernando C.; Zirvi, Karimullah A.; Kaplan, Nathan O.; Goldin, Abraham. Cancer Cent., Univ. California, La Jolla, CA, USA. International Journal of Cancer (1981), 27(1), 5-13. CODEN: IJCNW ISSN: 0020-7136. Journal written in English. CAN 94:185489 AN 1981:185489 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The effects of single-agent therapy with 2 clin. useful drugs 5-fluorouracil (5-FU)(I) [51-21-8] and BCNU [154-93-8], against human colorectal tumors (rectum T 157 and T 348, lung metastasis T 84, lymph-node metastasis T 245, colon, T 183, T 219, T 347, T 362 and T 380) transplanted and passed serially in athymic (nude) mice were studied. In addn., chemosensitivity of the tumors to 5-FU and BCNU was compared with the chemosensitivity of the tumors to 2 new doxorubicin analogs, 4'-deoxydoxorubicin (II) [63521-85-7] and 4'-O-methyl-doxorubicin (III) [77121-90-5]. BALB/c nude mice were treated i.v. on a weekly basis for 3-4 wk, starting when the tumor vol. became relatively large (advanced stage of tumor treatment). All the tumors showed a 90-100% take rate and stable growth. In these expts., 77% of the colorectal tumors were biol. sensitive to the treatment with 5-FU, but the percentage of statistically significant sensitive tumors was 22%, which is in good agreement with the clin. data reported in the literature (21%). In patients, BCNU has been reported to give up 13% response. In contrast, a 33% statistically significant response rate was found in our panel of colorectal tumors. The difference could be related to the higher tolerance of nude mice to certain drugs, including BCNU. Apparently, the 2 new doxorubicin derivs., 4'-deoxydoxorubicin and 4'-O-methyl-doxorubicin, should be more active in the patient than both of the clin. used drugs, 5-FU and BCNU. Furthermore, there is a good correlation between the results obtained in the exptl. system (human tumor/nude mouse) and in human patients with the active drugs, 5-FU and BCNU.



Answer 168:

### Bibliographic Information

**Chemotherapy of human breast-carcinoma xenografts.** Bailey, M. J.; Gazet, J. C.; Smith, I. E.; Steel, G. G. *Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer* (1980), 42(4), 530-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 94:95754 AN 1981:95754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Sensitivities were varied for 5 lines of human breast carcinoma xenografts, grown and passaged in immune-suppressed mice, to cyclophosphamide [50-18-0], methotrexate [59-05-2], 5-fluorouracil [51-21-8], adriamycin [23214-92-8], vincristine [57-22-7], and melphalan [148-82-3], alone and in combination. The most effective single agent or combination differed for each tumor. This system may be useful for testing new cytotoxic agents and predicting clin. chemotherapy response.

Answer 169:

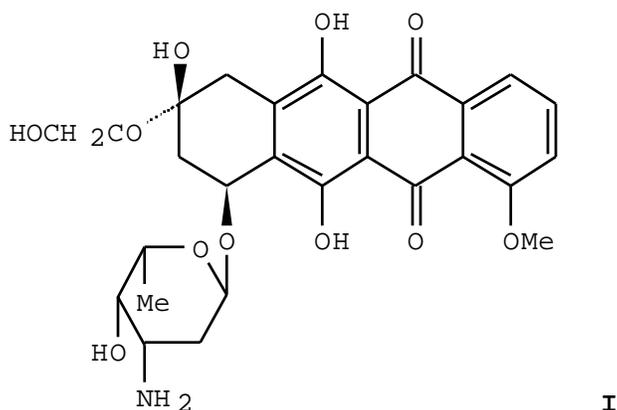
### Bibliographic Information

**Therapeutic response of human tumor xenografts in athymic mice to doxorubicin.** Giuliani, Fernando C.; Zirvi, Karimullah A.; Kaplan, Nathan O. *Cancer Cent., Univ. California, La Jolla, CA, USA. Cancer Research* (1981), 41(1), 325-35. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 94:76748 AN 1981:76748 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In order to establish the usefulness of the human tumor-nude mouse system as a predictive screen for anticancer agents, 17 tumors (3 breast, 3 colon, 3 lung, 3 melanoma, 2 ovary, 1 prostate, 1 sarcoma, and 1 larynx), serially transplantable in athymic mice, were used to study antitumor activity of doxorubicin (I) [23214-92-8]. BALB/c nude mice were treated i.v. on a weekly basis for 3 to 4 wk, starting when the tumor vol. became relatively large (advanced stage of tumor treatment). All the tumors except lung tumor T 293 showed a 90 to 100% take rate and stable growth. Doxorubicin, at dose levels of 6 and 10 mg/kg/injection i.v. every week for 3 wk, showed significant activity against all of the three breast tumors studied. As was expected on the basis of clin. data, doxorubicin showed no antitumor activity against the 3 different colon tumors. In the case of lung tumors, statistically significant activities against oat cell carcinoma T 293 and epidermoid carcinoma T 222 were obsd. In contradiction to clin. data, doxorubicin was found to have significant activity against various melanomas studied and slight but not statistically significant activity against ovarian tumor T 17.

Exptl. results obtained using doxorubicin against prostate, sarcoma, and larynx tumors also parallel the reported clin. data.



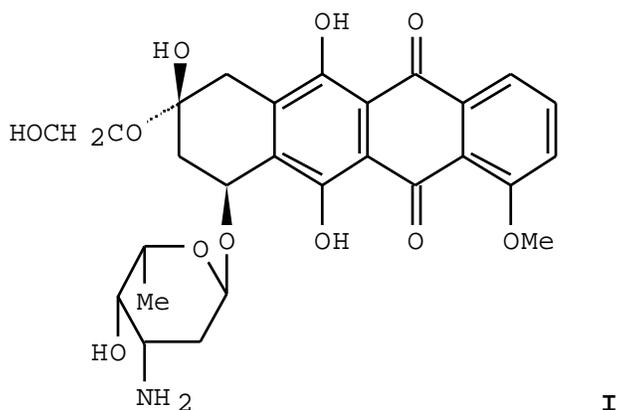
Answer 170:

### Bibliographic Information

**New doxorubicin analogs active against doxorubicin-resistant colon tumor xenografts in the nude mouse.** Giuliani, Fernando C.; Kaplan, Nathan O. Cancer Cent., Univ. California, La Jolla, CA, USA. *Cancer Research* (1980), 40(12), 4682-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 94:76695 AN 1981:76695 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The antitumor activity of doxorubicin (I) [23214-92-8] and 3 new derivs. modified on the position 4' of the amino sugar were tested against human colon tumors and rectal tumors (from different patients) and xenografted into nude mice. The drugs tested were 4'-epidoxorubicin [56420-45-2]; 4'-deoxydoxorubicin [63521-85-7], and 4'-O-methyldoxorubicin [68102-52-3]. Mice were treated i.v. on a weekly basis for 3 to 4 wk, starting when the tumors were well established. No statistically significant effect was obsd. against the tumors tested with I and 4'-epidoxorubicin. 4'-Deoxydoxorubicin was active against all the colon tumors tested, and 4'-O-methyldoxorubicin was active against 4 of 5 colon tumors tested. Overall, the activity of 4'-O-methyldoxorubicin was less than that of 4'-deoxydoxorubicin against the colon carcinomas tested. Neither analog was active against the 2 rectal carcinomas tested. Apparently, the modifications in the chem. structure of I can alter the biol. properties and thus create new drugs varying in activity against different human tumors; the 2 derivs., 4'-deoxydoxorubicin and 4'-O-methyldoxorubicin, appear to be good candidates for clin. trial against colon carcinoma; and the nude mice system can offer a great potential for identification of new anthracycline analogs and new anticancer agents.



Answer 171:

**Bibliographic Information**

**Detecting doxorubicin concentration in KBv200 and KB cell xenografts in nude mice by high-performance liquid chromatography.** Deng Wen-Jing; Zeng Zhao-Lei; Liang Yong-Ju; Dai Chun-Ling; Zhang Jian-Ye; Fu Li-Wu State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, 510060, PR China Ai zheng = Aizheng = Chinese journal of cancer (2008), 27(4), 364-8. Journal code: 9424852. ISSN:1000-467X. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Chinese. PubMed ID 18423121 AN 2008263229 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

**BACKGROUND & OBJECTIVE:** Doxorubicin (Dox) is one of the most commonly used chemotherapeutic drugs. Drug concentrations in tumor tissue can predict the drug's efficacy better than that in serum do. This study was to detect and compare the concentration of Dox in KBv200 and KB cell xenografts in nude mice by high-performance liquid chromatography (HPLC). **METHODS:** Tumor models in nude mice were established with KB cells (drug-sensitive) and KBv200 cells (multidrug-resistant). Dox was injected via the tail vein. The concentration of Dox in tumor tissue was detected by HPLC at 1, 3 and 5 h after injection. A Hypersil reversed-phase BDS C18 column (250 mm x 4.6 mm, ID 5 microm) and mobile phases that were composed of acetonitrile and 0.02 mol/L KH<sub>2</sub>PO<sub>4</sub> (1/2.4, V/V, pH 3.9) at a flow rate of 1.0 mL/min were used for setting a fluorescence detector (excitation wave length was 480 nm; emission wave length was 580 nm). **RESULTS:** Under the condition of HPLC, the calibration curve of Dox concentration in tumor tissue was linear within a range of 29.3-7 500 ng/g ( $r=0.9998$ ). The limit of detection in tumor tissue was 14 ng/g. At the concentration of 3 750, 468.8 and 117.2 ng/g, extraction recovery were (99.35+/-7.65)%, (99.79+/-5.73)% and (103.67+/-6.76)%, respectively, method recovery were (91.89+/-7.03)%, (94.94+/-5.18)% and (100.83+/-5.32)%, respectively. The relative standard deviation (RSD) of the intra-day and inter-day precision were less than 4.2%. At 1, 3, 5 h after Dox injection, the concentrations of Dox were (139.32+/-54.68), (260.00+/-126.11) and (173.26+/-13.88) ng/g in KBv cell xenografts, respectively, and (385.13+/-42.55), (523.38+/-138.84) and (460.75+/-86.85) ng/g in KB cell xenografts, respectively. The Dox concentration was significantly higher in KB cell xenografts than in KBv200 cell xenografts at the same time point ( $P<0.05$ ). **CONCLUSION:** Detected by HPLC, the concentration of Dox is much lower in multidrug-resistant cell xenografts than in sensitive cell xenografts.

Answer 172:

**Bibliographic Information**

**The synergistic inhibitory effect of somatostatin-doxorubicin co-treatment on gallbladder carcinoma.** Li Ji-Yu; Quan Zhi-Wei; Zhang Qiang; Liu Jian-Wen Department of General Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, PR China. lee\_jiyu@hotmail.com <lee\_jiyu@hotmail.com> BMC cancer (2007), 7 125. Journal code: 100967800. E-ISSN:1471-2407. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17617924 AN 2007428208 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

**BACKGROUND:** Gallbladder cancer is the most common biliary tract malignancy and carries a very poor prognosis. Somatostatin was recently shown to play an important role in the development of various tumors. In the current study, we evaluated the effect of doxorubicin on the chemosensitivity of gallbladder cancer cells and xenograft growth after treatment with somatostatin. **METHODS:** Twenty-four hours after somatostatin treatment, doxorubicin was gradually added and the growth curve of gallbladder cancer cells was determined. Exponential-phase gallbladder cancer cells were treated with doxorubicine or co-treated with doxorubicine and somastatine and the respective IC<sub>50</sub> values were determined. In addition, the inhibitory effect on the growth of gallbladder cancer xenograft on nude mice was evaluated using the same treatments as those described above. **RESULTS:** Treatment of gallbladder cancer cells with somatostatin

led to a block in the cell cycle at the S phase. Growth inhibition of gallbladder cancer cells by doxorubicin was concentration-dependent ( $P < 0.05$ ). However, upon co-treatment with doxorubicin and somatostatin, the IC50 value significantly decreased as compared to that of cells treated with doxorubicin alone ( $P < 0.05$ ). Interestingly, treatment with either doxorubicin or somatostatin did not significantly inhibit xenograft growth on nude mice, in contrast to a co-treatment with both drugs ( $P < 0.05$ ). **CONCLUSION:** Somatostatin most likely sensitizes the chemotherapeutic effect and diminishes the cytotoxicity of doxorubicin in a gallbladder cancer cell line and in mouse gallbladder cancer xenografts.

Answer 173:

#### **Bibliographic Information**

**Preclinical in vivo activity of a combination gemcitabine/liposomal doxorubicin against cisplatin-resistant human ovarian cancer (A2780/CDDP).** Gallo D; Fruscella E; Ferlini C; Apollonio P; Mancuso S; Scambia G Department of Obstetrics and Gynaecology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy International journal of gynecological cancer : official journal of the International Gynecological Cancer Society (2006), 16(1), 222-30. Journal code: 9111626. ISSN:1048-891X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16445637 AN 2006061953 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Both gemcitabine and liposomal doxorubicin are antineoplastic drugs with clinical activity in platinum-refractory ovarian cancer. The purpose of this study was to evaluate the antitumor activity of a combination gemcitabine/liposomal doxorubicin administered to athymic mice bearing cisplatin-resistant human ovarian cancer (A2780/CDDP) xenografts. Emphasis was on the use of very low doses of each drug and of different dosing schedules. Data obtained showed that combined treatment with 80 mg/kg gemcitabine and 15 mg/kg liposomal doxorubicin produced a significant enhancement of antitumor activity compared with monotherapy at the same doses of these agents. Noteworthy is the fact that the majority of xenograft-bearing animals receiving the combination therapy demonstrated a complete tumor regression at the end of the study. A similar trend was observed when doses of both drugs were reduced to 20 mg/kg gemcitabine and to 6 mg/kg liposomal doxorubicin. Again, three out of ten mice receiving the combination were tumor free at the end of the study. No significant differences were observed in antitumor activity when comparing the simultaneous vs the consecutive dosing schedule. Remarkably, no additive toxicity was observed in any experimental trials. These data encourage clinical trials to prove the advantages of this combination treatment with respect to the single-agent chemotherapy in platinum-refractory ovarian cancer patients.

Answer 174:

#### **Bibliographic Information**

**Doxorubicin increases the effectiveness of Apo2L/TRAIL for tumor growth inhibition of prostate cancer xenografts.** El-Zawahry Ahmed; McKillop John; Voelkel-Johnson Christina Department of Microbiology & Immunology, Medical University of South Carolina, Charleston, SC, USA. elzawaha@musc.edu <elzawaha@musc.edu> BMC cancer (2005), 5 2. Journal code: 100967800. E-ISSN:1471-2407. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15638938 AN 2005049408 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**BACKGROUND:** Prostate cancer is a significant health problem among American men. Treatment strategies for androgen-independent cancer are currently not available. Tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) is a death receptor ligand that can induce apoptosis in a variety of cancer cell lines, including

androgen-independent PC3 prostate carcinoma cells. In vitro, TRAIL-mediated apoptosis of prostate cancer cell lines can be enhanced by doxorubicin and correlates with the downregulation of the anti-apoptotic protein c-FLIP. This study evaluated the effects of doxorubicin on c-FLIP expression and tumor growth in combination with Apo2L/TRAIL in a xenograft model. **METHODS:** In vitro cytotoxic effects of TRAIL were measured using a MTS-based viability assay. For in vivo studies, PC3 prostate carcinoma cells were grown subcutaneously in athymic nude mice and tumor growth was measured following treatment with doxorubicin and/or Apo2L/TRAIL. c-FLIP expression was determined by western blot analysis. Apoptosis in xenografts was detected using TUNEL. Statistical analysis was performed using the student t-test. **RESULTS:** In vitro experiments show that PC3 cells are partially susceptible to Apo2L/TRAIL and that susceptibility is enhanced by doxorubicin. In mice, doxorubicin did not significantly affect the growth of PC3 xenografts but reduced c-FLIP expression in tumors. Expression of c-FLIP in mouse heart was decreased only at the high doxorubicin concentration (8 mg/kg). Combination of doxorubicin with Apo2L/TRAIL resulted in more apoptotic cell death and tumor growth inhibition than Apo2L/TRAIL alone. **CONCLUSIONS:** Combination of doxorubicin and Apo2L/TRAIL is more effective in growth inhibition of PC3 xenografts in vivo than either agent alone and could present a novel treatment strategy against hormone-refractory prostate cancer. The intracellular mechanism by which doxorubicin enhances the effect of Apo2L/TRAIL on PC3 xenografts may be by reducing expression of c-FLIP.

Answer 175:

#### **Bibliographic Information**

**Synergistic antitumor effects of HER2/neu antisense oligodeoxynucleotides and conventional chemotherapeutic agents.** Roh H; Hirose C B; Boswell C B; Pippin J A; Drebin J A Department of Surgery, Washington University School of Medicine, St Louis, MO 63110, USA Surgery (1999), 126(2), 413-21. Journal code: 0417347. ISSN:0039-6060. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 10455915 AN 1999384857 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**BACKGROUND:** The HER2/neu oncogene is overexpressed in a substantial fraction of human tumors. HER2/neu overexpressing tumors may be intrinsically resistant to chemotherapy. The present study examined the ability of antisense-mediated downregulation of HER2/neu expression to enhance the antitumor effects of conventional chemotherapeutic agents against human tumor cells that overexpress HER2/neu. **METHODS:** The effects of HER2/neu antisense oligodeoxynucleotides (ODNs) on the growth inhibitory and proapoptotic activity of several distinct chemotherapeutic agents were examined in vitro. In vivo effects of HER2/neu antisense ODNs in combination with doxorubicin hydrochloride were assessed by examining the growth of human tumor xenografts implanted into nude mice. **RESULTS:** The proliferation of tumor cell lines that overexpress HER2/neu was inhibited by antisense ODNs in combination with conventional chemotherapeutic agents in an additive or synergistic fashion. Such combination therapy also demonstrated synergistic activation of apoptosis. HER2/neu antisense ODNs in combination with doxorubicin hydrochloride demonstrated synergistic antitumor effects in vivo as well. **CONCLUSIONS:** Downregulation of HER2/neu expression can enhance the sensitivity of human cancer cells, which overexpress HER2/neu to the cytotoxic effects of chemotherapy. Antisense ODNs targeting the HER2/neu gene may play a role in cancer therapy.

Answer 176:

#### **Bibliographic Information**

**Comparative antitumor efficacy of docetaxel and paclitaxel in nude mice bearing human tumor xenografts that overexpress the multidrug resistance protein (MRP).** Comment in: Ann Oncol. 1997 Dec;8(12):1183-4. PubMed ID: 9496382 Vanhoefer U; Cao S; Harstrick A; Seeber S; Rustum Y M Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen, Germany Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (1997), 8(12), 1221-8. Journal code: 9007735. ISSN:0923-7534. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written

in English. PubMed ID 9496387 AN 1998157472 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

**BACKGROUND:** Multidrug resistance has been associated with expression of the multidrug resistance protein (MRP). Recently, MRP-expression has been detected in human tumor samples of patients with breast cancer and non-small-cell lung cancer. Since taxoids are the most active drugs in the treatment of both tumor entities, the antitumor efficacies of paclitaxel and docetaxel were compared in nude mice bearing human tumor xenografts that express MRP. **MATERIALS AND METHODS:** Athymic nude mice (nu/nu) bearing tumor xenografts of parental human sarcoma HT1080 or MRP-expressing HT1080/DR4 cells (as confirmed by Northern blot analysis) were treated with the maximum tolerated doses (MTD) of doxorubicin ([Dx] 10 mg/kg i.v. push), paclitaxel ([PC] 50 mg/kg three-hour i.v. infusion), or docetaxel ([DC] 40 mg/kg three-hour i.v. infusion). In vitro, the activity of doxorubicin, paclitaxel and docetaxel was evaluated by the sulphorhodamine B (SRB) assay using the pyridine analogue PAK-104P (5 microM), a potent inhibitor of MRP-function. **RESULTS:** At their MTDs both taxoids showed significant activity against MRP-negative HT1080 xenografts with response rates of 80% (40% CR) for PC and 100% (60% CR) for DC. In contrast, DC was significantly more active than PC in nude mice bearing doxorubicin resistant MRP-expressing HT1080/DR4 tumor xenografts (overall response rates: 100% (60% CR) for DC; 10% (0% CR) for PC; 0% for Dx). Since treatment of mice with the MTD of PC or DC yielded similar overall toxicity (maximum weight loss for HT1080: PC 8.6 +/- 2.2%; DC 7.5 +/- 2.2% and for HT1080/DR4: PC 11.6 +/- 3.0%; DC 7.6 +/- 1.8%, respectively), these results demonstrate the increase in the therapeutic index for docetaxel against MRP-expressing tumors. In vitro, HT1080/DR4 cells were 270-fold, 6.4-fold and 2.8-fold more resistant than parental cells to doxorubicin, PC and DC, respectively. Pyridine analogue PAK-104P completely restored drug sensitivity to PC and DC, while no effect of PAK-104P on parental HT1080 cells was observed.

**CONCLUSIONS:** Both taxoids, when given at their MTDs, showed significant efficacy against parental HT1080 tumor xenografts. However, docetaxel at its MTD was significantly more active against MRP-expressing tumor xenografts than paclitaxel. Furthermore, in vitro resistance of HT1080/DR4 cells was higher for PC (6.4-fold) than for DC (2.8-fold). Since PAK-104P completely restored sensitivity to both taxoids, the observed resistance appears to be related to MRP. These data suggest, that docetaxel is not as readily transported by MRP as paclitaxel leading to an increased therapeutic ratio in MRP-expressing tumors in vivo. Therefore, docetaxel may have therapeutic advantages in the clinical treatment of MRP-expressing tumors.

Answer 177:

### Bibliographic Information

**Chemotherapy of human carcinoma xenografts during pulsed magnetic field exposure.** Hannan C J Jr; Liang Y; Allison J D; Pantazis C G; Searle J R Radiology Department, Medical College of Georgia, Augusta 30912 Anticancer research (1994), 14(4A), 1521-4. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7979179 AN 95069897 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

Immune deficient mice growing xenografts of HT-29 or A-431 cell lines were treated with cisplatin, carboplatin or doxorubicin in combination with one hour of wholebody pulsed magnetic field (PMF) exposure (calculated peak field 5.2 mTesla, with an average field strength of 0.525 mTeslarms; pulses rose for 120 microseconds and then abruptly fell to neutral, and were repeated at a rate of 250 pulses per second). At 24 days, the mice in each experiment were found to have significantly ( $p < 0.05$ , ANOVA) different tumor sizes among groups. The smallest mean tumor volume was consistently found in the drug+PMF group. With A-431 tumors, the cisplatin+PMF group (T) was significantly smaller, 52% [1-(100T/C)], than the cisplatin alone group (C). In HT-29 tumors, those treated with carboplatin+PMF had the smallest tumor volume at just 34% of the carboplatin-alone group. In HT-29 tumors, the doxorubicin+PMF group was 35% of the doxorubicin alone group.

Answer 178:

### Bibliographic Information

**Drug- and radiation-induced resistance in a human neurogenic sarcoma xenografted in nude mice.** Budach W; Budach V; Scheulen M E; Stuschke M; Chaborski P Department of Radiation Oncology, Essen University, Federal Republic of Germany Cancer chemotherapy and pharmacology (1993), 31 Suppl 2 S169-73. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8453692 AN 93201652 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

The in vivo development of radiation- and doxorubicin-induced resistance was studied in a chemosensitive and radiosensitive human neurogenic sarcoma (Essen neuroectodermal tumor line 2) xenografted in nude mice. Dose-response curves were generated for the parent tumor line, and growth delay (GD) and specific growth delay (SGD) were the study end points. An intravenous injection of doxorubicin at 10 mg/kg, the lethal dose for 10% of the study population (LD10) in nude mice, and a single dose of 12 Gy radiation were determined to be isoeffective and were thus maintained for all subsequent treatments. For the induction of resistance to both treatment modalities, regrowing tumors were transplanted into successive generations of nude mice and retreated. This procedure was repeated 13 and 9 times, respectively, for the doxorubicin and radiation treatments. The response was monitored in all passages. As compared with the parent tumor line, a 50% decrease in SGD was observed following 3.9 and 8.5 treatments with doxorubicin and radiation, respectively. Following four treatments with doxorubicin, SGD in tumors crossed over to radiation therapy declined by 50%. Radiation therapy, on the other hand, caused significant reductions in GD and SGD in tumors that were subsequently exposed to doxorubicin, but it did not induce a 50% decline in response. Overexpression of P-170-glycoprotein was not observed for either treatment modality. The data suggest that treatment with doxorubicin or radiation can potentially induce resistance to subsequent continued or crossover treatment and that this resistance develops gradually. The lack of P-170-glycoprotein over-expression in the resistant cell lines indicates the existence of alternative pathways that may lead to resistance.

Answer 179:

### Bibliographic Information

**Reversal of Vinca alkaloid resistance by anti-P-glycoprotein monoclonal antibody HYB-241 in a human tumor xenograft.** Rittmann-Grauer L S; Yong M A; Sanders V; Mackensen D G Hybritech Incorporated, San Diego, California 92121 Cancer research (1992), 52(7), 1810-6. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1348013 AN 92200392 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

A panel of monoclonal antibodies (MAbs) to P-glycoprotein was developed by immunization of mice with multidrug-resistant human neuroepithelioma and neuroblastoma cells. All the anti-P-glycoprotein MAbs reacted with the extracellular portion of P-glycoprotein. The MAbs were examined for their ability to enhance accumulation of actinomycin D, vincristine, vinblastine, and doxorubicin in the human mdr1 transfectant cell line, BRO/pFRmdr1.6. HYB-241, an IgG1 anti-P-glycoprotein MAb, was the most effective modulator, increasing actinomycin D levels in the transfectant line by 6-fold, vincristine by 2-fold, and vinblastine levels by 3-fold. None of the MAbs were capable of modifying the accumulation of doxorubicin. HYB-241 lowered the 50% inhibitory concentration values of actinomycin D by 11-fold, vincristine by 6-fold, and vinblastine by 2-fold. No effect on the 50% inhibitory concentration values of doxorubicin or gramicidin were seen. <sup>111</sup>In-labeled HYB-241 localized in human tumor xenografts of BRO/pFRmdr1.6 in nude mice (25% injected dose/g at 120 h). Mice with established drug-resistant xenografts were treated with antibody 24 h prior to the injection of Vinca alkaloid at concentrations known to be non-growth inhibitory. The addition of HYB-241 at 25 mg/kg per injection prior to drug resulted in a significant inhibition of growth of this drug-resistant tumor.

Answer 180:

### Bibliographic Information

**Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine).** Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Koderu Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

**BACKGROUND:** Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. These findings suggest that MST-16 has a mode of cytotoxic activity different from that of other antitumor agents. **PURPOSE:** The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). **METHODS:** As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m<sup>2</sup> a day for 5-7 days at intervals of 2-3 weeks. **RESULTS:** Response consisted of one complete remission and seven partial remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. **CONCLUSIONS:** MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. **IMPLICATIONS:** Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.