

Answer 1:

### Bibliographic Information

**Impaired p53 function leads to centrosome amplification, acquired ER $\alpha$  phenotypic heterogeneity and distant metastases in breast cancer MCF-7 xenografts.** D'Assoro, A. B.; Busby, R.; Acu, I. D.; Quatraro, C.; Reinholz, M. M.; Farrugia, D. J.; Schroeder, M. A.; Allen, C.; Stivala, F.; Galanis, E.; Salisbury, J. L. Department of Biochemistry and Molecular Biology, Tumor Biology Program, Mayo Clinic College of Medicine, Rochester, MN, USA. *Oncogene* (2008), 27(28), 3901-3911. Publisher: Nature Publishing Group, CODEN: ONCNES ISSN: 0950-9232. Journal written in English. AN 2008:767404 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In this study, we establish an MCF-7 xenograft model that mimics the progression of human breast carcinomas typified by loss of p53 integrity, development of centrosome amplification, acquired estrogen receptor (ER $\alpha$ ) heterogeneity, overexpression of Mdm2 and metastatic spread from the primary tumor to distant organs. MCF-7 cells with abrogated p53 function (vMCF-7Dnp53) maintained nuclear ER $\alpha$  expression and normal centrosome characteristics in vitro. However, following mitogen stimulation, they developed centrosome amplification and a higher frequency of aberrant mitotic spindles. Centrosome amplification was dependent on cdk2/cyclin activity since treatment with the small mol. inhibitor SU9516 suppressed centriole reduplication. In contrast to the parental MCF-7 cells, when introduced into nude mice as xenografts, tumors derived from the vMCF-7Dnp53 cell line developed a strikingly altered phenotype characterized by increased tumor growth, higher tumor histopathol. grade, centrosome amplification, loss of nuclear ER $\alpha$  expression, increased expression of Mdm-2 oncoprotein and resistance to the antiestrogen tamoxifen. Importantly, while MCF-7 xenografts did not develop distant metastases, primary tumors derived from vMCF-7Dnp53 cells gave rise to lung metastases. Taken together, these observations indicate that abrogation of p53 function and consequent deregulation of the G1/S cell cycle transition leads to centrosome amplification responsible for breast cancer progression. *Oncogene* (2008) 27, 3901-3911; doi:10.1038/onc.2008.18; published online 11 Feb. 2008.

Answer 2:

### Bibliographic Information

**A Proteomic Analysis of the Plasma Glycoproteins of a MCF-7 Mouse Xenograft: A Model System for the Detection of Tumor Markers.** Orazine, Christina I.; Hincapie, Marina; Hancock, William S.; Hattersley, Maureen; Hanke, Jeff H. Barnett Institute, Northeastern University, Boston, MA, USA. *Journal of Proteome Research* (2008), 7(4), 1542-1554. Publisher: American Chemical Society, CODEN: JPROBS ISSN: 1535-3893. Journal written in English. CAN 148:373530 AN 2008:321889 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

In this study, the authors report a plasma proteomic anal. of a mouse MCF7 xenograft, using a novel platform named M-LAC (multilectin affinity chromatog.), to identify putative serum biomarkers of tumor presence and response to therapy. The use of the M-LAC platform enabled the authors to focus on secreted proteins as well as remove interference from serum albumin and other nonglycosylated proteins. The study focused on the MCF7 human xenograft tumor model which enabled the authors to distinguish tumor proteins (human peptide sequences) from host-derived murine proteins, potentially discriminating tumor- vs. supporting tissue-derived markers. A large set of murine proteins was identified in this study, including several signaling mol. such as EGFR, interleukin-6 receptor, protein-kinase C, and phosphatidylinositol kinase which changed in plasma levels relative to tumor-free animals. The authors also detected in the samples with maximal tumor growth a no. of human tumor-derived proteins linked to cell signaling, immune response, and transcriptional regulation. This is the first report where tumor-derived peptides could be detected in the serum of a xenograft model. The authors conclude that the M-LAC approach may be used to detect plasma proteins of potential biol. significance in tumor-bearing animals and warrants further study in terms of increasing the sensitivity of the method for the characterization of low level tumor markers and to explore the applicability of these markers for human studies.

Answer 3:

**Bibliographic Information**

**Enhancement of the antitumor activity of tamoxifen and anastrozole by the farnesyltransferase inhibitor lonafarnib (SCH66336).** Liu, Gongjie; Marrinan, Cindy H.; Taylor, Stacey A.; Black, Stuart; Basso, Andrea D.; Kirschmeier, Paul; Robert Bishop, W.; Liu, Ming; Long, Brian J. Department of Biological Research - Oncology, Schering-Plough Research Institute, Kenilworth, NJ, USA. *Anti-Cancer Drugs* (2007), 18(8), 923-931. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 147:203228 AN 2007:833451 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Lonafarnib is an orally bioavailable farnesyltransferase inhibitor. Originally developed to block the membrane localization of Ras, subsequent work suggested that farnesyltransferase inhibitors mediate their antitumor activities by altering the biol. activities of addnl. farnesylated proteins. Breast tumor models that express wild-type Ras have been shown to be sensitive to farnesyltransferase inhibitors. We have detd. the effects of combining lonafarnib with the antiestrogen 4-hydroxy tamoxifen on hormone-dependent breast cancer cell lines in vitro. The effects of combining lonafarnib with tamoxifen or the aromatase inhibitor anastrozole on the growth of two different MCF-7 breast tumor xenograft models were also evaluated. In four of five human breast cancer cell lines, lonafarnib enhanced the antiproliferative effects of 4-hydroxy tamoxifen. The combination prevented MCF-7 cells from transitioning through the G1 to S phase of the cell cycle and augmented apoptosis. This was assocd. with reduced expression of E2F-1 and a redn. in hyperphosphorylated retinoblastoma protein. Lonafarnib plus 4-hydroxy tamoxifen also inhibited the mammalian target of rapamycin signal transduction pathway. In nude mice bearing parental MCF-7 or aromatase-transfected MCF-7Ca breast tumor xenografts, lonafarnib enhanced the antitumor activity of both tamoxifen and anastrozole. These studies indicate that lonafarnib enhances the efficacy of endocrine agents clin. used for treating hormone-dependent breast cancer.

Answer 4:

**Bibliographic Information**

**An  $\alpha$ -fetoprotein-derived peptide reduces the uterine hyperplasia and increases the antitumor effect of tamoxifen.** Andersen, T. T.; Georgekutty, J.; DeFreest, L. A.; Amaratunga, G.; Narendran, A.; Lemanski, N.; Jacobson, H. I.; Bennett, J. A. Center for Cardiovascular Sciences, Albany Medical College, Albany, NY, USA. *British Journal of Cancer* (2007), 97(3), 327-333. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 149:143292 AN 2007:830349 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Tamoxifen (Tam) is effective for the treatment and prevention of breast cancer. However, it has toxic drawbacks and has limited-duration utility because, over time, human tumors become refractory to Tam. Recently, a new nontoxic peptide,  $\alpha$ -fetoprotein-derived peptide (AFPep) has been proposed for the treatment and prevention of breast cancer. The purpose of this paper is to det. whether combining AFPep with Tam would increase efficacy and reduce toxicity in exptl. models of breast cancer. Low doses of AFPep and Tam were more effective in combination than either agent alone against breast cancer growth in cell culture, in tumor-xenografted mice, and in carcinogen-exposed rats.  $\alpha$ -Fetoprotein-derived peptide interfered with Tam-induced uterine hyperplasia in immature mice, and showed no toxic effects. Unlike Tam, AFPep did not inhibit binding of estradiol (E2) to estrogen receptor (ER). Thus, these two agents utilize different mechanisms to interfere with ER functionality, yet work cooperatively to reduce breast cancer growth and alleviate Tam's troubling toxicity of uterine hyperplasia and appear to be a rational combination for the treatment of ER-pos. breast cancer.

Answer 5:

**Bibliographic Information**

**Treatment of human epidermal growth factor receptor 2-overexpressing breast cancer xenografts with multiagent HER-targeted therapy.** Arpino, Grazia; Gutierrez, Carolina; Weiss, Heidi; Rimawi, Mothaffar; Massarweh, Suleiman; Bharwani, Lavina; De Placido, Sabino; Osborne, C. Kent; Schiff, Rachel. Breast Center and the Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA. *Journal of the National Cancer Institute* (2007), 99(9), 694-705. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 148:393927 AN 2007:652807 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Human epidermal growth factor receptor 2 (HER2) is a member of the HER signaling pathway. HER inhibitors partially block HER signaling and tumor growth in preclin. breast cancer models. We investigated whether blockade of all HER homo- and heterodimer pairs by combined treatment with several inhibitors could more effectively inhibit tumor growth in such models. Mice carrying xenograft tumors of HER2-overexpressing MCF7/HER2-18 (HER2-transfected) or BT474 (HER2-amplified) cells were treated with estrogen supplementation or estrogen withdrawal, alone or combined with tamoxifen. One to three HER inhibitors (pertuzumab, trastuzumab, or gefitinib) could also be added ( $n \geq 8$  mice per group). Tumor vols., HER signaling, and tumor cell proliferation and apoptosis were assessed. Results were analyzed with the t test or Wilcoxon rank sum test and survival anal. methods. All statistical tests were two-sided. Median time to tumor progression was 21 days for mice receiving estrogen and 28 days for mice receiving estrogen and pertuzumab (difference = 7 days;  $P = .001$ ; hazard ratio [HR] of progression in mice receiving estrogen and pertuzumab vs. mice receiving estrogen = 0.27, 95% confidence interval [CI] = 0.09 to 0.77). Addn. of gefitinib and trastuzumab to estrogen and pertuzumab increased this time to 49 days (difference = 21 days;  $P = .004$ ; HR of progression = 0.28, 95% CI = 0.10 to 0.76). MCF7/HER2-18 tumors disappeared completely and did not progress (for  $\geq 189$  days) after combination treatment with pertuzumab, trastuzumab, and gefitinib plus tamoxifen (19 of 20 mice) or plus estrogen withdrawal (14 of 15 mice). Both combination treatments induced apoptosis and blocked HER signaling and proliferation in tumor cells better than any single agent or dual combination. All BT474 tumors treated with pertuzumab, trastuzumab, and gefitinib disappeared rapidly, regardless of endocrine therapy, and no tumor progression was obsd. for 232 days.

Combined treatment with gefitinib, trastuzumab, and pertuzumab to block signals from all HER homo- and heterodimers inhibited growth of HER2-overexpressing xenografts statistically significantly better than single agents and dual combinations.

Answer 6:

### Bibliographic Information

**Role for HER2/neu and HER3 in fulvestrant-resistant breast cancer.** Osipo, Clodia; Meeke, Kathleen; Cheng, Dong; Weichel, Alyssa; Bertucci, Anne; Liu, Hong; Jordan, V. Craig. Department of Pathology, Oncology Institute, Cardinal Bernadin Cancer Center, Loyola University Medical Center, Maywood, IL, USA. *International Journal of Oncology* (2007), 30(2), 509-520. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 146:308719 AN 2007:198897 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Tamoxifen resistance is common for estrogen receptor  $\alpha$  (ER $\alpha$ ) pos. breast cancer. Second-line therapies include aromatase inhibitors or fulvestrant. We have shown previously that fulvestrant reversed 17 $\beta$ -estradiol-induced tumor regression of tamoxifen-stimulated MCF-7 xenografts (MCF-7TAMLT) treated for >5 years with tamoxifen in athymic mice and paradoxically stimulated growth. We investigated mechanisms responsible for growth by fulvestrant in the presence of physiol. estradiol and therapeutic strategies in vivo. The results demonstrated that only estradiol increased expression of the estrogen-responsive genes, c-myc, igf-1, cathepsin D, and pS2 mRNAs, in MCF-7E2 and MCF-7TAMLT tumors. Tamoxifen or fulvestrant decreased the estradiol-induced increase of these mRNAs in both tumor models. However, tyrosine-phosphorylated HER2/neu, HER3, phospho-extracellular-regulated kinase-1/2 (ERK-1/2), and phospho-glycogen synthetase kinase 3 $\alpha$  (GSK3 $\alpha$ ) and  $\beta$  proteins were increased in MCF-7TAMLT tumors treated with fulvestrant compared to estradiol, control, or tamoxifen. Phospho-HER2/neu interacted with HER3 protein in MCF-7TAMLT tumors. In order to det. whether the functional interaction of HER2/neu with HER3 is crit. for growth of fulvestrant-stimulated MCF-7TAMLT tumors, pertuzumab (an antibody that blocks HER2/neu-HER3 interaction) was used in an in vivo xenograft growth assay. Only growth of fulvestrant-treated MCF-7TAMLT xenografts was decreased significantly by 37.2% in response to pertuzumab ( $P = 0.004$ ).

Pertuzumab specifically decreased the interaction of HER2/neu protein with HER3 in fulvestrant-stimulated MCF-7TAMLT tumors. These results suggested growth of MCF-7TAMLT tumors by tamoxifen or fulvestrant is potentially independent of ER $\alpha$  transcriptional activity as evidenced by lack of induction of four estrogen-responsive genes. The results suggested that growth of MCF-7TAMLT tumors treated with fulvestrant in the presence of physiol.

estradiol is in part mediated through enhanced signaling from the HER2/neu-HER3 pathway as pertuzumab partially inhibited growth and the interaction of HER2/neu with HER3 in vivo.

Answer 7:

### Bibliographic Information

**The combination of green tea and tamoxifen is effective against breast cancer.** Sartippour, Maryam R.; Pietras, Richard; Marquez-Garban, Diana C.; Chen, Hsiao-Wang; Heber, David; Henning, Susanne M.; Sartippour, Guilan; Zhang, Liping; Lu, Ming; Weinberg, Olga; Rao, Jian Yu; Brooks, Mai N. Department of Surgery, University of California, Los Angeles, CA, USA. *Carcinogenesis* (2006), 27(12), 2424-2433. Publisher: Oxford University Press, CODEN: CRNGDP ISSN: 0143-3334. Journal written in English. CAN 146:74844 AN 2006:1273078 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Epidemiol. data have suggested that green tea may prevent breast cancer. Studies in our lab. have provided evidence that green tea ext. inhibits breast cancer growth by a direct anti-proliferative effect on the tumor cells, as well as by indirect suppressive effects on the tumor-assocd. endothelial cells. In this study, we asked whether concurrent administration of green tea may add to the anti-tumor effects of std. breast cancer therapy. We obsd. that green tea increased the inhibitory effect of tamoxifen on the proliferation of the ER (estrogen receptor)-pos. MCF-7, ZR75, T47D human breast cancer cells in vitro. This combination regimen was also more potent than either agent alone at increasing cell apoptosis. In animal expts., mice treated with both green tea and tamoxifen had the smallest MCF-7 xenograft tumor size, and the highest levels of apoptosis in tumor tissue, as compared with either agent administered alone. Moreover, the suppression of angiogenesis in vivo correlated with larger areas of necrosis and lower tumor blood vessel d. in treated xenografts. Green tea decreased levels of ER- $\alpha$  in tumors both in vitro and in vivo. We also obsd. that green tea blocked ER-dependent transcription, as well as estradiol-induced phosphorylation and nuclear localization of mitogen-activated protein kinase. To our knowledge, this study is the 1st to show the interaction of green tea with the ER pathway, as well as provide mechanistic evidence that the combination of green tea and tamoxifen is more potent than either agent alone in suppressing breast cancer growth. These results may lead to future improvements in breast cancer treatment and prevention.

Answer 8:

### Bibliographic Information

**Effects of polyphyllin D, a steroidal saponin in Paris polyphylla, in growth inhibition of human breast cancer cells and in xenograft.** Lee, Mei-Sze; Yuet-Wa, Judy Chan; Kong, Siu-Kai; Yu, Biao; Eng-Choon, Vincent Ooi; Nai-Ching, Henry Wong; Chung-Wai, Thomas Mak; Fung, Kwok-Pui. Department of Biochemistry, The Chinese University of Hong Kong, Shatin, Peop. Rep. China. *Cancer Biology & Therapy* (2005), 4(11), 1248-1254. Publisher: Landes Bioscience, CODEN: CBTA AO ISSN: 1538-4047. Journal written in English. CAN 145:369388 AN 2006:495271 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Paris polyphylla is a traditional Chinese Medical herb that has been used in treating cancer for thousands of year. Without studies on the anticancer effects of Paris polyphylla being initiated before, we have first studied the component of Paris polyphylla and have spotted out a steroidal saponin, polyphyllin D. As long as the chem. structure and the improved synthesis of polyphyllin D were ascertained, both in vitro to in vivo studies were performed. It was found that treatment of MCF-7 and MDA-MB-231 cells with polyphyllin D resulted in the inhibition of viability and induction of apoptosis in a dose-dependent manner, with an IC<sub>50</sub> of 5  $\mu$ M and 2.5  $\mu$ M, resp., after 48 h of incubations. Apoptosis of MCF-7 and MDA-MB-231 cells by polyphyllin D was evidenced by the occurrence of DNA fragmentation, formation of a hypodiploid peak in the cell cycle anal., phosphatidyl-serine externalization and a late loss of

membrane integrity. Mechanistically, polyphyllin D dissipates the mitochondrial membrane potential, induces a down regulation of anti-apoptotic Bcl-2 expression and an up-regulation of pro-apoptotic Bax expression, and activates caspase-9. These results suggest that polyphyllin D elicits apoptosis through mitochondria dysfunction. In vivo study demonstrated that daily administration of polyphyllin D (2.73 mg/kg body wt.) through i.v. injection for ten days in nude mice bearing MCF-7 cells effectively reduced tumor growth for 50% in terms of tumor wt. and size, given no significant toxicity in heart and liver to the host. All these findings provide novel insights that polyphyllin D could serve as a candidate in breast cancer treatment.

Answer 9:

#### **Bibliographic Information**

**Signal therapy of breast cancers by the HDAC inhibitor FK228 that blocks the activation of PAK1 and abrogates the tamoxifen-resistance.** Hirokawa, Yumiko; Arnold, Melissa; Nakajima, Hidenori; Zalcborg, John; Maruta, Hiroshi. Ludwig Institute for Cancer Research, Parkville/Melbourne, Australia. *Cancer Biology & Therapy* (2005), 4(9), 956-960. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:369375 AN 2006:487207 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

PAK1, a Rac/CDC42-dependent Ser/Thr kinase, is required for both neurofibromatosis (NF) and RAS transformation in vivo. FK228, a histone deacetylase (HDAC) inhibitor, activates a very specific set of genes such as the tumor suppressor WAF1, an inhibitor of cyclin-dependent kinases (CDKs), and suppresses the growth of these tumors. In addn., this drug downregulates cyclin D1, which is upregulated by RAS through PAK1, in breast cancers. In this study, we demonstrate that FK228 at 0.1-1 nM significantly reduces the kinase activity of PAK1 in these cells, without affecting the protein level of PAK1. Interestingly, estrogen receptor (ER) and PAK1 mutually activate each other in breast cancers. Here we provide an evidence suggesting that breast cancers require PAK1 for their estrogen-dependent growth. Moreover, the treatment with FK228 strongly inhibits the estrogen-dependent growth of human breast cancers (both tamoxifen-sensitive and resistant cell lines) in vivo, suggesting that FK228 and other anti-PAK1 drugs would be useful for the treatment of breast cancers which become resistant to currently used estrogen antagonists such as tamoxifen.

Answer 10:

#### **Bibliographic Information**

**Accounting for quiescent cells in tumor growth and cancer treatment.** Florian, J. A., Jr.; Eiseman, J. L.; Parker, R. S. Department of Chemical and Petroleum Engineering, University of Pittsburgh School of Engineering, Pittsburgh, PA, USA. *IEE Proceedings: Systems Biology* (2005), 152(4), 185-192. Publisher: Institution of Electrical Engineers, CODEN: IPSBDJ Journal; General Review written in English. CAN 145:158715 AN 2006:182536 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

A review. A four-state cell-cycle model with explicit G1-phase representation, termed the quiescent-cell model (QCM), has been proposed to represent biol. the G1-phase specific effect of the chemotherapeutic tamoxifen. The QCM was used to model untreated and tamoxifen treated tumor xenograft data from the literature with equiv. accuracy to previously developed tumor growth models. Open-loop anal. demonstrated that perturbations to the two newly introduced parameters, kG01 and kG10 significantly altered untreated tumor growth predictions. However, the sensitivity did not carry over to closed-loop simulations, where alterations to kD and kGS proved most significant in detg. overall controller performance. Addnl. mismatch studies comparing controllers designed using the QCM to controllers designed with the Gompertz model and satg.-rate, cell-cycle model returned similar performance for a stepwise tumor redn. case study, but the quiescent-cell controller delivered a more aggressive treatment regimen. More importantly, the Gompertz and satg.-rate, cell-cycle controllers were unable to follow a ref. trajectory when measurement updates were made biweekly, with both controllers returning tamoxifen dose schedules alternating between the max. and min. allowable dose.

Answer 11:

**Bibliographic Information**

**Estradiol regulates different genes in human breast tumor xenografts compared with the identical cells in culture.** Harvell, Djuana M. E.; Richer, Jennifer K.; Allred, D. Craig; Sartorius, Carol A.; Horwitz, Kathryn B. Department of Medicine, University of Colorado Health Sciences Center at Fitzsimonas, Aurora, CO, USA. *Endocrinology* (2006), 147(2), 700-713. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 144:251644 AN 2006:98279 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

In breast cancers, estrogen receptor (ER) levels are highly correlated with response to endocrine therapies. The authors sought to define mechanisms of estrogen (E) signaling in a solid breast tumor model using gene expression profiling. ER+ T47D-Y human breast cancer cells were grown as xenografts in ovariectomized nude mice under four conditions: 17 $\beta$ -estradiol for 8 wk (E); without E for 8 wk (control); E for 7 wk followed by 1 wk of E withdrawal (Ewd); or E for 8 wk plus tamoxifen for the last week. E-regulated genes were defined as those that differed significantly between control and E and/or between E and Ewd or control and Ewd. These protocols generated 188 in vivo E-regulated genes that showed two major patterns of regulation. Approx. 46% returned to basal states after Ewd (class I genes); 53% did not (class II genes). In addn., more than 70% of class II-regulated genes also failed to reverse in response to tamoxifen. These genes may be interesting for the study of hormone-resistance issues. A subset of in vivo E-regulated genes appears on lists of clin. ER discriminator genes. These may be useful therapeutic targets or markers of E activity. Comparison of in vivo E-regulated genes with those regulated in identical cells in vitro after 6 and 24 h of E treatment demonstrate only 11% overlap. This indicates the extent to which gene expression profiles are uniquely dependent on hormone-treatment times and the cellular microenvironment.

Answer 12:

**Bibliographic Information**

**Models of hormone resistance in vitro and in vivo.** Schafer, Jennifer MacGregor; Jordan, V. Craig. Robert H. Lurie Comprehensive Cancer Center, The Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. *Methods in Molecular Medicine* (2006), 120(Breast Cancer Research Protocols), 453-464. Publisher: Humana Press Inc., CODEN: MMMEFN Journal; General Review written in English. CAN 144:362402 AN 2005:1341013 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

A review. Estrogen receptor (ER)-pos. MCF-7 breast cancer cell lines can be used both in vitro and in vivo to create anti-hormone resistance. Estrogen withdrawal in vitro results in spontaneous growth of MCF-7 cells. Similarly, culture in the selective ER modulators (SERMs) tamoxifen and raloxifene, can result in SERM resistance. This form of anti-hormone resistance is evidenced by SERM-stimulated tumor growth in athymic mice. These tumors are transplantable into successive generations of ovariectomized SERM treated mice. However, there is an evolution of drug resistance to anti-hormones. This is evidenced by a change in sensitivity to estrogen. The natural hormone no longer stimulated tumor growth but causes apoptosis and tumor regression.

Answer 13:

**Bibliographic Information**

**In vitro and in vivo Effects of Combination of Trastuzumab (Herceptin) and Tamoxifen in Breast Cancer.** Wang, Chun-Xia; Koay, Debbie C.; Edwards, Andrea; Lu, Zhao; Mor, Gil; Ocal, Idris T.; DiGiovanna, Michael P. Departments of Internal Medicine (Section of Medical Oncology) and Pharmacology, Obstetrics and Gynecology, Pathology, and the Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA. *Breast Cancer Research and Treatment* (2005), 92(3), 251-263. Publisher: Springer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 144:68382 AN 2005:989330 CAPLUS

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### Abstract

Extensive interactions between estrogen receptor  $\alpha$  (ER $\alpha$ ) and HER2 signaling pathways have been described. Using BT-474 human breast cancer cells, we have previously shown that the combination of tamoxifen (TAM) and Herceptin results in strong synergistic growth inhibition, enhancement of G0-G1 cell cycle accumulation, inhibition of HER2 activity and a cytostatic effect without cell death. To further examine the underlying mechanism of synergy, we investigated the effect of this drug combination on ER $\alpha$  function and growth factor downstream signaling. TAM caused a small increase in ER $\alpha$  levels while Herceptin had no effect, and both drugs caused an increase in the level of Ser118-phosphorylated ER $\alpha$ . However, both TAM and Herceptin individually inhibited ER $\alpha$  transcriptional activity, although the combination did not have a greater effect than either single agent. Herceptin inhibited MAPK and Akt activity, while TAM had no effect on these either as a single agent or when added to Herceptin. Using a BALB/c athymic BT-474 in vivo xenograft model, the drug combination (Herceptin 0.3 mg/kg i.p. twice weekly, TAM 1.0 mg/mouse i.p. three times per wk) showed a greater inhibition of tumor growth compared to either single agent. Tumor exts. and fixed sections were examd. at the end of the treatment period for treatment-specific alterations: we noted a paradoxical proliferation-inducing effect of TAM that was reversed by the addn. of Herceptin. Our results indicate that combined targeting of both peptide growth factor receptors and ER $\alpha$  represents a promising breast cancer treatment strategy.

Answer 14:

### Bibliographic Information

**Stimulation of MCF-7 tumor progression in athymic nude mice by 17 $\beta$ -estradiol induces WISP-2/CCN5 expression in xenografts: A novel signaling molecule in hormonal carcinogenesis.** Ray, Gibanananda; Banerjee, Snigdha; Saxena, Neela K.; Campbell, Donald R.; Van Veldhuizen, Peter; Banerjee, Sushanta K. Cancer Research Unit, V.A. Medical Center, University of Missouri, Kansas City, MO, USA. *Oncology Reports* (2005), 13(3), 445-448. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:75716 AN 2005:240503 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

There was 100% solid tumor formation following inoculation of MCF-7 cells. However, MCF-7 tumor progression was significantly greater in the mice exposed to 17 $\beta$ -estradiol (17 $\beta$ -E2) compared to unexposed mice. WISP-2/CCN5 mRNA expression was correspondingly increased in 17 $\beta$ -E2 exposed MCF-7 tumors compared to unexposed xenografts. Moreover, estrogen exposure followed by anti-estrogen tamoxifen treatment drastically inhibited the tumor growth and WISP-2 expression in nude mice. Therefore, the study suggests that higher WISP-2/CCN5 expression by estrogen may be assocd. with the estrogen-induced growth of MCF-7 tumors in vivo. Finally, overexpression of WISP-2/CCN5 may be considered as a prognostic marker of estrogen-sensitive tumor growth.

Answer 15:

### Bibliographic Information

**Poly(ethylene oxide)-modified poly( $\epsilon$ -caprolactone) nanoparticles for targeted delivery of tamoxifen in breast cancer.** Shenoy, Dinesh B.; Amiji, Mansoor M. Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA, USA. *International Journal of Pharmaceutics* (2005), 293(1-2), 261-270. Publisher: Elsevier B.V., CODEN: IJPHDE ISSN: 0378-5173. Journal written in English. CAN 143:253631 AN 2005:230378 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

This study was carried out to evaluate and compare the biodistribution profile of tamoxifen when administered i.v. as a simple soln. or when encapsulated in polymeric nanoparticulate formulations, with or without surface-stabilizing agents. Tamoxifen-loaded, poly(ethylene oxide)-modified poly( $\epsilon$ -caprolactone) (PEO-PCL) nanoparticles were prep'd. by solvent displacement process that allowed in situ surface modification via phys. adsorption of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock polymeric stabilizer (Pluronic). The nanoparticles were characterized for particle size and surface charge. Presence of PEO chains on nanoparticle surface was ascertained by electron spectroscopy for chem. anal. (ESCA). In vivo biodistribution studies were carried out in Nu/Nu athymic mice bearing a human breast carcinoma xenograft, MDA-MB-231 using tritiated [3H]-tamoxifen as radio-marker for quantification. PEO-PCL nanoparticles with an av. diam. of 150-250 nm, having a smooth spherical shape, and a pos. surface charge were obtained with the formulation procedure. About 90% drug encapsulation efficiency was achieved when tamoxifen was loaded at 10% by wt. of the polymer. Aq. wettability, suspendability, and ESCA results showed surface hydrophilization of the PCL nanoparticles by the Pluronics. The primary site of accumulation for the drug-loaded nanoparticles after i.v. administration was the liver, though up to 26% of the total activity could be recovered in tumor at 6 h post-injection for PEO-modified nanoparticles. PEO-PCL nanoparticles exhibited significantly increased level of accumulation of the drug within tumor with time as well as extended their presence in the systemic circulation than the controls (unmodified nanoparticles or the soln. form). Pluronic surfactants (F-68 and F-108) presented simple means for efficient surface modification and stabilization of PCL nanoparticles to achieve preferential tumor-targeting and a circulating drug reservoir for tamoxifen.

Answer 16:

### Bibliographic Information

**Inhibition of mTOR Activity Restores Tamoxifen Response in Breast Cancer Cells with Aberrant Akt Activity.** de Graffenried, Linda A.; Friedrichs, William E.; Russell, Douglas H.; Donzis, Elissa J.; Middleton, Amanda K.; Silva, Jessica M.; Roth, Richard A.; Hidalgo, Manuel. Division of Medical Oncology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. *Clinical Cancer Research* (2004), 10(23), 8059-8067. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:329044 AN 2004:1048151 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The Akt kinase is a serine/threonine protein kinase that has been implicated in mediating a variety of biol. responses. Studies show that high Akt activity in breast carcinoma is assoc'd. with a poor pathophenotype, as well as hormone and chemotherapy resistance. Addnl., high Akt activity is assoc'd. with other features of poor prognosis. Thus, a chemotherapeutic agent directed specifically toward tumors with high Akt activity could prove extremely potent in treating those breast tumors with the most aggressive phenotypes. Several studies have demonstrated that rapamycin, which inhibits mammalian target of rapamycin (mTOR), a downstream target of Akt, sensitizes certain resistant cancer cells to chemotherapeutic agents. This study evaluated the efficacy of mTOR inhibition in the treatment of tamoxifen-resistant breast carcinoma characterized by high Akt activity. We found that MCF-7 breast cancer cell lines expressing a constitutively active Akt are able to proliferate under reduced estrogen conditions and are resistant to the growth inhibitory effects of tamoxifen, both in vitro as well as in vivo in xenograft models. Cotreatment with the mTOR inhibitor rapamycin in vitro, or the ester of rapamycin, CCI-779 (Wyeth) in vivo, inhibited mTOR activity and restored sensitivity to tamoxifen, suggesting that Akt-induced tamoxifen resistance is mediated in part by signaling through the mTOR pathway. Although the mechanism underlying the synergism remains to be understood, the results were assoc'd. with rapamycin's ability to block transcriptional activity mediated by estrogen receptor  $\alpha$ , as assessed by reporter gene assays with estrogen-responsive element luciferase. These data corroborate prior findings indicating that Akt activation induces resistance to tamoxifen in breast cancer cells.

Importantly, these data indicate a novel mechanism for tamoxifen resistance and suggest that blockage of the phosphatidylinositol 3'-kinase/Akt signaling pathway by mTOR inhibition effectively restores the susceptibility of these cells to tamoxifen. These data may have implication for future clin. studies of mTOR inhibition in breast carcinoma.

Answer 17:

### Bibliographic Information

**Reduction of CWR22 prostate tumor xenograft growth by combined tamoxifen-quercetin treatment is associated with**

**inhibition of angiogenesis and cellular proliferation.** Ma, Zeng-Shuan; Huynh, Thanh Hoa; Ng, Chee Pang; Do, Phuc Tien; Nguyen, Thanh Hung; Huynh, Hung. Laboratory of Molecular Endocrinology, Division of Cellular and Molecular Research, National Cancer Center of Singapore, Singapore, Singapore. International Journal of Oncology (2004), 24(5), 1297-1304. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 141:374503 AN 2004:385438 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Combination chemotherapy is increasingly practiced for the treatment of malignant prostate cancers. The aim of this study was to evaluate the in vivo efficacy of combined tamoxifen and quercetin in prostate tumor xenografts. Severe combined immune deficient (SCID) mice inoculated with CWR22 prostate tumor cells were treated with either tamoxifen (10 mg/kg/wk), quercetin (200 mg/kg/day) or combined tamoxifen-quercetin for 28 days. Tamoxifen or quercetin alone exhibited a moderate antitumor activity. Tamoxifen decreased the Ki-67 index by 52.4%, reduced the vascular endothelial growth factor (VEGF) 121 and VEGF165 mRNA by 18.6 and 21.8%, resp., and suppressed the blood vessel formation, while quercetin modulated the expression and phosphorylation of cdc-2 and cyclin B1, and inhibited the Ki-67 index by 66.0%. Combined tamoxifen-quercetin effectively delayed the appearance of tumors, inhibited the final tumor vol. by 73.3% and reduced the endpoint tumor wt. by 67.1% ( $p < 0.05$ ). The Ki-67 index, VEGF121, VEGF165 mRNA and microvessel d. (MVD) were decreased by 66.9, 22.1, 40.1 and 59.0%, resp., by the combined treatment. These findings indicate that tamoxifen inhibits CWR22 prostate tumor by modulating the angiogenesis and its antineoplastic effects can be potentiated by combined use with quercetin.

Answer 18:

### Bibliographic Information

**Therapeutic Strategies Using the Aromatase Inhibitor Letrozole and Tamoxifen in a Breast Cancer Model.** Long, Brian J.; Jelovac, Danijela; Handratta, Venkatesh; Thiantanawat, Apinya; MacPherson, Nicol; Ragaz, Joseph; Goloubeva, Olga G.; Brodie, Angela M. Department of Pharmacology and Experimental Therapeutics, Health Sciences Facility, University of Maryland School of Medicine, Baltimore, MD, USA. Journal of the National Cancer Institute (2004), 96(6), 456-465. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:325248 AN 2004:238191 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Background:** The antiestrogen tamoxifen has potent activity against estrogen receptor-pos. breast cancer, but two nonsteroidal aromatase inhibitors, letrozole and anastrozole, show considerable advantages over tamoxifen with respect to patient survival and tolerability. To det. the optimal way to use letrozole and tamoxifen, we studied their effects on a breast tumor xenograft model, MCF-7Ca, that is responsive to both antiestrogens and aromatase inhibitors. **Methods:** Female ovariectomized BALB/c athymic nude mice carrying xenograft tumors were treated daily s.c. with one of the following first-line therapies for varying durations: no drug (control), tamoxifen (100  $\mu\text{g}/\text{day}$ ) alone, letrozole (10  $\mu\text{g}/\text{day}$ ) alone, both drugs at the same time, or alternating 4-wk courses of each drug (beginning with a course of tamoxifen or beginning with a course of letrozole). Tumor vols. and wts. were estd. using linear mixed-effects models. The time to tumor doubling was calcd., and tumor wts. in the treatment groups were compared, with adjustments for multiple comparisons being made with either Tukey's or Dunnett's procedure. Second-line therapies (with tamoxifen, letrozole, or fulvestrant) were initiated when tumors doubled in size under first-line therapies. All statistical tests were two-sided. **Results:** The times for doubling of tumor vol. were as follows: control, 3-4 wk; tamoxifen alone, 16 wk; tamoxifen alternating with letrozole, 17-18 wk; tamoxifen plus letrozole, 18 wk; letrozole alternating with tamoxifen, 22 wk; letrozole alone, 34 wk. First-line treatment with letrozole was superior to treatment with tamoxifen alone or with the two drugs combined (at week 16, both  $P < .001$ ). Alternating tamoxifen and letrozole and alternating letrozole and tamoxifen were also not as effective as letrozole alone (at week 16,  $P = .002$  and  $P < .001$ , resp.).

Tumors progressing on tamoxifen remained sensitive to second-line therapy with letrozole compared with those remaining on tamoxifen at the end of treatment (week 28,  $P < .001$ ), whereas tumors progressing on letrozole were unaffected by second-line treatment with the antiestrogens tamoxifen or fulvestrant. **Conclusions:** First-line letrozole therapy extends time for tumor progression in this model relative to the other treatment regimens tested. However, further studies are needed to det. the most effective second-line therapy for tumors that progress on letrozole.

Answer 19:

### Bibliographic Information

**Characterization of New Estrogen Receptor Destabilizing Compounds: Effects on Estrogen-Sensitive and Tamoxifen-Resistant Breast Cancer.** Hoffmann, Jens; Bohlmann, Rolf; Heinrich, Nikolaus; Hofmeister, Helmut; Kroll, Joerg; Kuenzer, Hermann; Lichtner, Rosemarie B.; Nishino, Yuki; Parczyk, Karsten; Sauer, Gerhard; Gieschen, Hille; Ulbrich, Hannes-F.; Schneider, Martin R. Research Laboratories of Schering AG, Berlin, Germany. Journal of the National Cancer Institute (2004), 96(3), 210-218. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 141:219128 AN 2004:106785 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Antiestrogens of the selective estrogen receptor modulator (SERM) type, such as tamoxifen, have two major limitations: their mixed agonist and antagonist profile and the development of tumor resistance. We characterized two new pure antiestrogens-ZK-703 and ZK-253-that belong to the class of specific estrogen receptor destabilizers (SERDs), which includes fulvestrant, and compared their activity with that of fulvestrant and tamoxifen. Effects of antiestrogens on the growth of estrogen-dependent breast tumors in vivo were detd. using several mouse xenograft models (including the tamoxifen-sensitive tumors MCF7, T47D, and MV3366 and the tamoxifen-resistant tumors ZR75-1 and MCF7/TAM) and chem. induced (nitrosomethyl urea [NMU] and dimethylbenzanthracene [DMBA]) rat breast cancer models (groups of 10 animals). We detd. the initial response and effects on hormone receptor levels and the time to relapse after treatment (i.e., time to reach a predetd. tumor size threshold). Estrogen receptor (ER) levels were detd. by immunoassay. ZK-703 (administered s.c.) and ZK-253 (administered orally) were more effective than tamoxifen or fulvestrant at inhibiting the growth of ER-pos. breast cancer in all xenograft models. For example, MCF7 tumors relapsed (i.e., reached the size threshold) in 10 wk in mice treated with tamoxifen but in 30 wk in mice treated with ZK-703. ZK-703 and ZK-253 also prevented further tumor progression in tamoxifen-resistant breast cancer models to a similar extent (more than 30 wk in mice with ZR75-1 and MCF7/TAM tumors). In the chem. induced rat breast cancer models, orally administered ZK-703 and ZK-253 caused a nearly complete (>80%) inhibition of tumor growth. ER levels were dramatically reduced in MCF7 tumors after 5 wk of ZK-703 treatment compared with ER levels in vehicle-treated tumors; by contrast, ER levels in tamoxifen-treated tumors were higher than those in control tumors.

ZK-703 and ZK-253 are potent, long-term inhibitors of growth in both tamoxifen-sensitive and tamoxifen-resistant breast cancer models.

Answer 20:

### Bibliographic Information

**Paradoxical Action of Fulvestrant in Estradiol-Induced Regression of Tamoxifen-Stimulated Breast Cancer.** Osipo, Clodia; Gajdos, Csaba; Liu, Hong; Chen, Bin; Jordan, V. Craig. Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. Journal of the National Cancer Institute (2003), 95(21), 1597-1608. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 140:280903 AN 2003:903987 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Background: Long-term tamoxifen treatment of breast cancer can result in tamoxifen-stimulated breast cancer, in which estrogen inhibits tumor growth after tamoxifen withdrawal. The authors investigated the mol. mechanism(s) of estradiol-induced tumor regression by using an in vivo model of tamoxifen-stimulated human breast cancer. Methods: Growth of parental estradiol-stimulated MCF-7E2 and long-term tamoxifen-stimulated MCF-7TAML xenografts in athymic mice was measured during treatment with vehicle, estradiol, estradiol plus tamoxifen, tamoxifen alone, estradiol plus fulvestrant, or fulvestrant alone. Apoptosis was detected by the terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay. Protein expression was assessed by western blot anal. mRNA expression was assessed by real-time reverse transcription-polymerase chain reaction. All statistical tests were two-sided. Results: MCF-7E2 tumor growth was stimulated by estradiol (cross-sectional area at week 13=1.06 Cm<sup>2</sup>, 95% confidence interval [CI] = 0.82 to 1.30 Cm<sup>2</sup>; P<.001) compared with control (0.06 Cm<sup>2</sup>, 95%CI = -0.02 to 0.14 Cm<sup>2</sup>), but

tumor growth was inhibited by tamoxifen or fulvestrant. MCF-7TAMLT tumor growth was stimulated by tamoxifen (cross-sectional area at week 10=0.60 Cm<sup>2</sup>, 95% CI = 0.50 to 0.70 Cm<sup>2</sup>; P<.001) compared with control (0.02 Cm<sup>2</sup>, 95% CI = 0.00 to 0.04 Cm<sup>2</sup>). For MCF-7TAMLT tumors that were initially 0.35 Cm<sup>2</sup>, estradiol-induced regression to 0.18 Cm<sup>2</sup> (95% CI = 0.15 to 0.21 Cm<sup>2</sup>; P<.001), and tamoxifen or estradiol plus fulvestrant enhanced tumor growth to 1.00 Cm<sup>2</sup> (95% CI = 0.88 to 1.22 Cm<sup>2</sup>). Estradiol increased the no. of apoptotic cells in tumors by 23% (95% CI = 20% to 26%; P<.001) compared with all other treatments, decreased estrogen receptor  $\alpha$  (ER $\alpha$ ) protein expression, increased the expression of Fas mRNA and protein, decreased the expression of HER2/neu mRNA and protein and nuclear factor  $\kappa$ B (NF- $\kappa$ B) protein but did not affect Fas ligand protein expression compared with control.

Paradoxically, fulvestrant reversed this effect and stimulated MCF-7TAMLT tumor growth apparently through ER $\alpha$ -mediated regulation of Fas, HER2/neu, and NF- $\kappa$ B. Conclusion: Physiol. levels of estradiol induced regression of tamoxifen-stimulated breast cancer tumors, apparently by inducing the death receptor Fas and suppressing the antiapoptotic/prosurvival factors NF- $\kappa$ B and HER2/neu.

Answer 21:

### Bibliographic Information

**Aromatase inhibitor development and hormone therapy: a perspective.** Brodie, Angela. Department of Pharmacology and Experimental Therapeutics, School of Medicine and Greenbaum Cancer Center, University of Maryland, Baltimore, MD, USA. *Seminars in Oncology* (2003), 30(4, Suppl. 14), 12-22. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 139:374066 AN 2003:891141 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A review. The introduction of aromatase inhibitors as a new class of agents represents a further step in improving breast cancer treatment and possibly in preventing this disease. Although these agents are now used in the first- and second-line treatment of postmenopausal breast cancer, the heterogeneity of patients enrolled in clin. trials prevents a thorough assessment of the effectiveness of potential sequential and combination therapies. Such investigations are more easily performed in the lab., and to this end, a tumor model in nude mice was established to simulate several aspects of the postmenopausal breast cancer patient. This model showed that aromatase inhibitors are more efficient than tamoxifen at reducing tumor vol. Addnl., the combination of an aromatase inhibitor plus tamoxifen does not improve the antiproliferative results obtained with the aromatase inhibitor alone, a finding corroborated in the Arimidex, Tamoxifen Alone or in Combination adjuvant clin. trial. To investigate the effect that potential sequences of treatment have on tumor growth, letrozole was administered in sequence with tamoxifen to nude mice bearing human xenografts. Tumor growth was significantly reduced with the sequence compared with tamoxifen alone. Addnl., when agents were alternated every 4 wk, mice started on letrozole fared better than those started on tamoxifen. Finally, letrozole alone provided the best and most sustained redn. in tumor growth. These expts. suggest the means to evaluate therapeutic combinations in the lab. to guide potential trial designs and provide the best chance of success to the patients who enter these clin. trials.

Answer 22:

### Bibliographic Information

**Mifepristone-induced secretion of transforming growth factor  $\beta$ 1-induced apoptosis in prostate cancer cells.** Liang, Yayun; Eid, Manal A.; El Etreby, Fathy; Lewis, Ronald W.; Kumar, M. Vijay. Section of Urology, Medical College of Georgia, Augusta, GA, USA. *International Journal of Oncology* (2002), 21(6), 1259-1267. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 139:95583 AN 2002:948378 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Successful therapy should induce apoptosis in prostate cancer cells irresp. of their androgen response. We have investigated the possibility of utilizing Mifepristone and Tamoxifen as treatment options for prostate cancer cells. Because preliminary results demonstrated induction of apoptosis by these drugs, the mechanism of induction of apoptosis was investigated. LNCaP-C4 prostate

cancer cells were treated with Mifepristone and/or Tamoxifen. To confirm cytotoxic effects, nude mice with LNCaP-C4 xenografts were treated with Mifepristone and Tamoxifen. Cell viability was assayed using Sulforhodamine B (SRB) assay and DNA fragmentation was measured by ELISA. Culture media from vehicle- and drug-treated cells were collected and secretion of transforming growth factor  $\beta$ 1 (TGF $\beta$ 1) was estd. by ELISA. Role of TGF $\beta$ 1 was confirmed by inhibiting its function using TGF $\beta$ 1 antibody or M6P, which blocked activation of TGF $\beta$ 1. Apoptotic effects were detd. by immunoblots of cytochrome c levels in cytosol and by in vitro colorimetric assay of caspase-3 activity. Results showed that although both drugs induced apoptosis in LNCaP-C4 cells, Mifepristone was more effective. The effects of these drugs on xenografts confirmed in vitro results. It was hypothesized that drug-induced secretion of TGF $\beta$ 1 may be responsible for induction of apoptosis. Neutralization of TGF $\beta$ 1 with an antibody or blocking the activation of TGF $\beta$ 1 by M6P abrogated the effects of Mifepristone and Tamoxifen confirming our hypothesis. Furthermore, treatment with Mifepristone and/or Tamoxifen released cytochrome c into the cytoplasm and induced activity of caspase-3, providing evidence that the drug-stimulated secretion of TGF $\beta$ 1 was responsible for induction of apoptosis in these cells. In conclusion, both Mifepristone and Tamoxifen induced apoptosis mediated through TGF $\beta$ 1. However, no crit. advantage was noted by the addn. of Tamoxifen to Mifepristone treatment.

Answer 23:

### Bibliographic Information

**Different H2 receptor antihistamines dissimilarly retard the growth of xenografted human melanoma cells in immunodeficient mice.** Szincsak, Nora; Hegyesi, Hargita; Hunyadi, Janos; Falus, Andras; Juhasz, Istvan. Department of Dermatology, Debrecen University, Debrecen, Hung. Cell Biology International (2002), 26(9), 833-836. Publisher: Elsevier Science B.V., CODEN: CBIIEV ISSN: 1065-6995. Journal written in English. CAN 138:395544 AN 2002:752132 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Melanoma cells and tissues contain considerable amts. of histamine and express histamine receptors, suggesting the existence of autocrine and paracrine regulation by histamine. Our previous in vitro results suggested that histamine elevates melanoma cell growth through the H2 receptor. In this work we show that in vivo tumor proliferation in immunodeficient mice xenotransplanted with a human melanoma cell line is diminished by cimetidine, an H2 receptor antagonist, if combined with a tamoxifen deriv. acting on cytochrome P 450 mols. (DPPE). Ranitidine, another H2 receptor antagonist, has a weaker inhibitory effect, the kinetics and mechanism of which is probably dissimilar to that of the cimetidine/DPPE mixt.

Answer 24:

### Bibliographic Information

**Cimetidine and a tamoxifen derivate reduce tumor formation in SCID mice xenotransplanted with a human melanoma cell line.** Szincsak, N.; Hegyesi, H.; Hunyadi, J.; Martin, G.; Lazar-Molnar, E.; Kovacs, P.; Rivera, E.; Falus, A.; Juhasz, I. Department of Dermatology, Debrecen University, Debrecen, Hung. Melanoma Research (2002), 12(3), 231-240. Publisher: Lippincott Williams & Wilkins, CODEN: MREEEH ISSN: 0960-8931. Journal written in English. CAN 137:119254 AN 2002:546572 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Histamine is produced by many cells expressing histidine decarboxylase (HDC), the enzyme responsible for the synthesis of histamine. Since melanoma cells and tissue contain relatively large amts. of histamine, the functional significance of histamine was examd. using specific antihistamines in vitro and in vivo in the human melanoma cell line HT168 and severe combined immunodeficiency (SCID) mice. It was shown that the H2 receptor antagonist cimetidine when combined with N, N-diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine-HCl (DPPE), a tamoxifen derivate, inhibits the proliferation of HT168 cells. Furthermore, it is suggested that there is a factor(s) that interferes with the exponential growth of HT168 cells xenografted to immunodeficient mice, and cimetidine and DPPE together significantly influence this factor(s). This combination of antihistamines also

increases the survival of human melanoma-grafted mice. These changes are accompanied by enhanced infiltration of interferon- $\gamma$ -producing mouse macrophages into the tumor tissue. These findings suggest that two different mechanisms are probably acting concordantly: direct inhibition of tumor cell proliferation by the H2 receptor antagonists, and activation of the local immune response characterized by interferon- $\gamma$  prodn. These findings may help to elucidate the possibility of a rationally designed antihistamine strategy in melanoma therapy.

Answer 25:

#### Bibliographic Information

**Comparison of the effects of EM-652 (SCH57068), tamoxifen, toremifene, droloxifene, idoxifene, GW-5638 and raloxifene on the growth of human ZR-75-1 breast tumors in nude mice.** Gutman, Matthien; Couillard, Steeve; Roy, Jenny; Labrie, Fernand; Candas, Bernard; Labrie, Claude. Oncology and Molecular Endocrinology Research Center, Laval University Medical Center and Laval University, Quebec, Can. International Journal of Cancer (2002), 99(2), 273-278. Publisher: Wiley-Liss, Inc., CODEN: IJCNAAW ISSN: 0020-7136. Journal written in English. CAN 137:211088 AN 2002:298816 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

The agonistic and antagonistic effects of EM-652 were compared with those of tamoxifen and 5 other antiestrogens on the growth of ZR-75-1 human breast xenografts in ovariectomized nude mice. During the 23 wk of treatment at a daily oral dose of 50  $\mu$ g, EM-652 was the only compd. that decreased tumor size to below pretreatment values, whereas the other 6 antiestrogens decreased the estrone-stimulated progression rate to lesser extents. Under estrone stimulation, all the groups of animals had >60% of their tumors in the progression stage except for the EM-652-treated group, where only 7% of the tumors progressed. In the absence of estrone stimulation, progression occurred in 60%, 33%, 21% and 12% of the tumors in the tamoxifen-, idoxifene-, toremifene- and raloxifene-treated groups, resp., while only 4% of the tumors progressed in the EM-652-treated group. The agonistic and antagonistic actions of each antiestrogen were also measured on endometrial epithelial cell thickness. The findings indicate that EM-652, in addn. to being the most potent of these antiestrogens on human breast tumor growth, has no agonistic effect in breast and endometrial tissues. Since previous data have shown benefits of EM-652 on bone d. and lipid profile, this compd. could be an ideal candidate for chemoprevention of breast and uterine cancers, while protecting against osteoporosis and cardiovascular disease.

Answer 26:

#### Bibliographic Information

**A peptide derived from  $\alpha$ -fetoprotein prevents the growth of estrogen-dependent human breast cancers sensitive and resistant to tamoxifen.** Bennett, James A.; Mesfin, Fassil B.; Andersen, Thomas T.; Gierthy, John F.; Jacobson, Herbert I. Albany Medical College, Albany, NY, USA. Proceedings of the National Academy of Sciences of the United States of America (2002), 99(4), 2211-2215. Publisher: National Academy of Sciences, CODEN: PNASAA6 ISSN: 0027-8424. Journal written in English. CAN 137:87997 AN 2002:200863 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

An 8-mer peptide (EMTOVNOG) derived from  $\alpha$ -fetoprotein was compared with tamoxifen for activity against growth of human breast cancer xenografts implanted in immune-deficient mice. Both peptide and tamoxifen prevented growth of estrogen-receptor-pos. MCF-7 and T47D human breast cancer xenografts. A subline of MCF-7, made resistant to tamoxifen by a 6-mo exposure to this drug in culture, was found to be resistant to tamoxifen in vivo. Peptide completely prevented the xenograft growth of this tamoxifen-resistant subline of MCF-7. Neither peptide nor tamoxifen was effective in slowing the xenograft growth of the estrogen-receptor-neg. MDA-MB-231 human breast cancer. A worrisome side effect of tamoxifen is its hypertrophic effect on the uterus. In this study, tamoxifen was shown to stimulate the growth of the immature mouse uterus in vivo, and the peptide significantly inhibited tamoxifen's uterotrophic effect. The mechanism of action of peptide is different from that of tamoxifen in that the peptide does not interfere with the binding of [3H]estradiol to the estrogen receptor. In conclusion,  $\alpha$ -fetoprotein-derived peptide appears to be a novel agent that

interferes with the growth of tamoxifen-sensitive as well as tamoxifen-resistant estrogen-receptor-pos. human breast cancers; it inhibits the uterotrophic side effect of tamoxifen and, thus, it may be useful in combination with or in place of tamoxifen for treatment of estrogen-receptor-pos. human breast cancers.

Answer 27:

#### **Bibliographic Information**

**Aromatase inhibitors in breast cancer.** Brodie, Angela. Dept Pharmacology and Experimental Therapeutics, University of Maryland, School of Medicine, Baltimore, MD, USA. *Trends in Endocrinology and Metabolism* (2002), 13(2), 61-65. Publisher: Elsevier Science Ltd., CODEN: TENME4 ISSN: 1043-2760. Journal; General Review written in English. CAN 137:118895 AN 2002:122086 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

A review. Several compds. that selectively inhibit estrogen synthesis via aromatase have been developed. Steroidal substrate analogs, such as formestane and exemestane, inactivate aromatase by binding irreversibly to it. Non-steroidal inhibitors, such as the triazole compds. letrozole and anastrozole, are highly potent, reversible inhibitors with good specificity for aromatase. The intratumoral aromatase model for postmenopausal breast cancer has been used to investigate the efficacy of letrozole, anastrozole and exemestane in combination and sequentially. Combining letrozole or arimidex with tamoxifen or faslodex was not more effective than the aromatase inhibitors alone, but was more effective than tamoxifen alone. Letrozole was superior to and longer lasting than the other agents, suggesting that aromatase inhibitors control tumor growth effectively by inducing greater tumor response and extending treatment time. In addn., aromatase inhibitors can be effective in patients relapsing from tamoxifen. Because two types of aromatase inhibitors are available, steroidal enzyme inactivators and reversible non-steroidal inhibitors in sequential therapy could be useful if resistance to one type develops. Aromatase (estrogen synthesis) inhibitors have been developed. These are more effective than tamoxifen in mouse xenograft models, and current clin. data suggest the inhibitors are likely to improve breast cancer treatment.

Answer 28:

#### **Bibliographic Information**

**Inhibition of erbB receptor (HER) tyrosine kinases as a strategy to abrogate antiestrogen resistance in human breast cancer.** Kurokawa, Hirokazu; Arteaga, Carlos L. Departments of Medicine and Cancer Biology and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. *Clinical Cancer Research* (2001), 7(12, Suppl.), 4436S-4442S. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal; General Review written in English. CAN 137:118875 AN 2002:53817 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

A review. It has been proposed that binding of ligand to the estrogen receptor (ER) releases its assocn. with transcriptional corepressors, allowing the ER to recruit coactivators, which possess histone acetylase activity, and induce transcription of gene promoters contg. estrogen response elements. It has also been proposed that the antiestrogen tamoxifen recruits transcriptional corepressors to the AF-2 region of the hormone-binding domain of the ER, thus blocking ER-mediated transcription. The ER cross-talks with a no. of mitogenic signaling pathways and second messengers, like the epidermal growth factor receptor, the insulin-like growth factor-1 receptor, mitogen-activated protein (MAP) kinase, phosphatidylinositol-3 kinase/Akt, dopamine, and cAMP. Some of these mols. may: (a) support ligand-independent ER transcription; (b) increase the assocn. of ER with coactivators of transcription; and/or (c) reduce the antiestrogen-induced assocn. of ER with corepressors. These events either alone or in combination may result in hormone independence and/or antiestrogen resistance. The authors have examd. whether signaling by HER2/neu (erbB-2) receptor tyrosine kinase, which can induce antiestrogen resistance, can also disrupt the tamoxifen-induced interaction of ER with transcriptional corepressors. Notably, tamoxifen-induced assocn. of ER with the transcriptional corepressors N-CoR or SMRT was reduced in HER2-overexpressing breast tumor cells but not in cells with low HER2 levels. Small mol. inhibitors of the HER2 kinase or MAP extracellular signal-regulated kinase 1/2 or dominant-neg. MAP extracellular signal-regulated kinase 1/2 constructs restored the

inhibitory effect of tamoxifen on both ER-mediated transcription and tumor cell proliferation. Treatment with both tamoxifen and the small mol. HER1/2 kinase inhibitor AG1478 reduced mitogen-activated protein kinase activity and markedly reduced growth of established MCF-7/HER2 xenografts in athymic nude mice.

Similar results have been obtained with ZD1839 ("Iressa"), an epidermal growth factor receptor (HER1) tyrosine kinase inhibitor. Taken together, these data suggest that exogenous inhibitors of the HER-signaling network and other mitogenic pathways can abrogate or delay the emergence of antiestrogen resistance, thus providing an evaluable therapeutic strategy in human breast carcinoma.

Answer 29:

### Bibliographic Information

**Tamoxifen suppresses histologic progression to atypia and DCIS in MCFIOAT xenografts, a model of early human breast cancer.** Visscher, Daniel W.; Nanjia-Makker, Pratima; Heppner, Gloria; Shekhar, P. V. Malathy. Department of Pathology, the Barbara Ann Karmanos Cancer Institute and Wayne State University, Detroit, MI, USA. Breast Cancer Research and Treatment (2001), 65(1), 41-47. Publisher: Kluwer Academic Publishers, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 135:162180 AN 2001:193774 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

This work evaluated the effects of tamoxifen on the growth and progression of MCFIOAT xenografts, an estrogen-responsive model of human breast tumor progression, in which cells are injected orthotopically into the mammary fat pad of female nude mice. Ten wk following implantation, histol. sections of each graft were evaluated microscopically for histol. lesions analogous to human breast tumor progression, graded as simple hyperplasia, complex hyperplasia, atypical hyperplasia, ductal carcinoma in situ (DCIS) and invasive carcinoma. Three of five xenografts in (endocrine-intact) control animals progressed to atypical hyperplasia, one progressed to DCIS and one to invasive carcinoma. The latter two control grafts also contained foci of putative precursor lesions (i.e., atypical hyperplasia and in situ carcinoma). Tamoxifen-supplemented xenografts were uniformly smaller than controls but contained invasive carcinoma in a similar proportion (24%). However, none of these grafts exhibited DCIS, and only one contained atypical hyperplasia. Most grafts in tamoxifen-supplemented animals (10/17, including all four with carcinomas) showed complex hyperplasia, which typically dominated the graft. It is concluded that tamoxifen selectively inhibits the appearance or growth of preinvasive index lesions. Development of malignancy in the absence of such precursors, though, implies selection for alternative histogenetic pathways as a result of endocrine manipulation.

Answer 30:

### Bibliographic Information

**EM-652 (SCH 57068), a third generation SERM (selective estrogen receptor modulator), acting as pure antiestrogen in the mammary gland and endometrium.** Labrie, Claude; Labrie, Fernand; Belanger, Alain; Simard, Jacques; Luo, Shouqi; Martel, Celine. Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL) and Laval University, Quebec, QC, Can. International Congress Series (2000), 1206(Current Knowledge in Reproductive Medicine), 381-397. Publisher: Elsevier Science B.V., CODEN: EXMDA4 ISSN: 0531-5131. Journal; General Review written in English. CAN 134:81010 AN 2000:788988 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A review with 92 refs. Estrogens are well recognized to play the predominant role in breast cancer development and growth and much efforts have been devoted to the blockade of estrogen formation and action. The most widely used therapy of breast cancer which has shown benefits at all stages of the disease is the use of the antiestrogen Tamoxifen. This compd., however, possesses mixed agonist and antagonist activities and major efforts have thus been devoted to the development of compds. having pure antiestrogenic activity in the mammary gland and endometrium. Such a compd. would avoid the problem of stimulation of the endometrium and the risk of endometrial carcinoma. The authors have thus synthesized an orally active nonsteroidal antiestrogen, EM-652 (SCH 57068) and

the prodrug EM-800 (SCH 57050) which are the most potent of the known antiestrogens. EM-800, the prodrug of EM-652, has been shown to prevent the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat, a well-recognized model of human breast cancer. Not only the development, but also the growth of established DMBA-induced mammary carcinoma was inhibited by treatment with EM-800. Uterine size was reduced to castration levels in the groups of animals treated with EM-800. EM-652 was the most potent antiestrogen to inhibit the growth of human breast cancer ZR-75-1, MCF-7 and T-47D cells in vitro when compared with ICI 182780, ICI 164384, hydroxytamoxifen, raloxifene, and Droloxifene. Moreover, EM-652 and EM-800 have no stimulatory effect on the basal levels of cell proliferation in the absence of E2 while hydroxytamoxifen, raloxifene, and Droloxifene have a stimulatory effect on the basal growth of T-47D and ZR-75-1 cells.

When human breast cancer ZR-75-1 xenografts were grown in nude mice, EM-800 led to a complete inhibition of the stimulatory effect of estrogens in ovariectomized mice while tamoxifen was less potent and even stimulated the growth of the tumors in the absence of estrogens thus, illustrating the stimulatory effect of tamoxifen on breast cancer growth. When incubated with human Ishikawa endometrial carcinoma cells, EM-800 had no stimulatory effect on alk. phosphatase activity, an estrogen-sensitive parameter. Raloxifene, Droloxifene, hydroxytoremifene and hydroxytamoxifen, all stimulated to various extents, the activity of this enzyme. The stimulatory effect of all four compds. was blocked by EM-800 thus, confirming their estrogenic activity in human endometrial tissue. When administered to ovariectomized animals, EM-800 prevents bone loss, the effect on bone mineral d., trabecular bone vol., and trabecular sepn. being 5-10 times more potent than that of raloxifene. EM-800 lowers serum cholesterol and triglyceride levels in the rat, as well as in women. The detailed information obtained at the preclin. level with EM-652 or EM-800 indicates that these orally active compds. are highly potent and pure antiestrogens in the mammary gland and endometrium while they prevent bone loss and lower serum cholesterol and triglyceride levels. Preclin. and clin. data clearly suggest the interest of studying this compd. in the neoadjuvant and adjuvant settings and, most importantly, for the prevention of breast and uterine cancer in which settings they should provide addnl. benefits by reducing bone loss and by decreasing serum cholesterol and triglyceride levels.

Answer 31:

#### Bibliographic Information

**Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells.** Kurokawa, Hirokazu; Lenferink, Anne E. G.; Simpson, Jean F.; Pisacane, Paul I.; Sliwkowski, Mark X.; Forbes, James T.; Arteaga, Carlos L. Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA. *Cancer Research* (2000), 60(20), 5887-5894. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 134:80613 AN 2000:780462 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

HER2/neu (erbB-2) overexpression has been causally assocd. with tamoxifen resistance in human breast cancer cells. Forced expression of HER2 in MCF-7 breast cancer cells resulted in mitogen-activated protein kinase (MAPK) hyperactivity and tamoxifen resistance. Inhibition of HER2 and MAPKs with AG1478 and U0126, resp., as well as dominant-neg. MEK-1/2 constructs restored the inhibitory effect of tamoxifen on estrogen receptor (ER)-mediated transcription and cell proliferation. Both AG1478 and U0126 also restored the tamoxifen-mediated assocn. of ER with nuclear receptor corepressor (N-CoR) in the antiestrogen-resistant MCF-7 cells. Treatment with a combination of tamoxifen and a HER2 kinase inhibitor reduced tumor MAPK activity and markedly prevented growth of HER2-overexpressing MCF-7 xenografts in athymic mice. Thus, blockade of HER2 and MAPK signaling may enhance tamoxifen action and abrogate antiestrogen resistance in human breast cancer.

Answer 32:

#### Bibliographic Information

**Development and characterization of a tamoxifen-resistant breast carcinoma xenograft.** Naundorf, H.; Becker, M.; Lykkesfeldt, A. E.; Elbe, B.; Neumann, C.; Buttner, B.; Fichtner, I. Max-Delbruck-Center for Molecular Medicine, Berlin, Germany. *British Journal of Cancer* (2000), 82(11), 1844-1850. Publisher: Harcourt Publishers Ltd., CODEN: BJCAAI ISSN: 0007-0920.

Journal written in English. CAN 133:276515 AN 2000:424850 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A human tamoxifen-resistant mammary carcinoma, MaCa 3366/TAM, originating from a sensitive parental xenograft, 3366, was successfully established by treatment of tumor-bearing nude mice with 1-50 mg tamoxifen/kg for 3 yr during routine passaging. The tumors did not differ significantly in estrogen receptor (ER) and progesterone receptor (PR) positivity; however, when compared with the sensitive tumor line, the mean ER content of the tamoxifen-resistant subline was slightly lower. An ER upregulation following withdrawal of estradiol treatment was obsd. in the parental tumors but not in the resistant xenografts. Following long-term treatment with tamoxifen, the histol. pattern of the breast carcinoma changed. The more differentiated structures apparent after treatment with 17 $\beta$ -estradiol in the original 3366 tumor were not induced in the resistant line. Tamoxifen failed to induce a tumor growth inhibition in comparison to the tamoxifen-sensitive line. Tests with the pure antiestrogen ICI 182 780 revealed cross-resistance. Sequence anal. of the hormone-binding domain of the ER of both lines showed no differences, suggesting that either mutations in other regions of the ER are involved in the tamoxifen-resistance phenotype or that mechanisms outside of this protein induced this phenotype. Estrogen and antiestrogen regulate gene pS2 and cathepsin D expression in the 3366 tumors as in the human breast cancer cell line MCF-7. The resistant 3366/TAM tumors lost this regulation. The established breast cancer xenografts 3366 and 3366/TAM offer the possibility of investigating mechanisms of antiestrogen resistance in an in vivo situation. They can be used to test novel approaches to prevent, or to overcome, this resistance in a clin. related manner.

Answer 33:

### Bibliographic Information

**Estrogen agonistic/antagonistic effects of miproxifene phosphate (TAT-59).** Shibata, Jiro; Toko, Toshiyuki; Saito, Hitoshi; Fujioka, Akio; Sato, Kouji; Hashimoto, Akihiro; Wierzba, Konstanty; Yamada, Yuji. Hanno Research Center, Taiho Pharmaceutical Co., Ltd., Hanno-City, Saitama, Japan. *Cancer Chemotherapy and Pharmacology* (2000), 45(2), 133-141. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 133:202698 AN 2000:60879 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The authors evaluated miproxifene phosphate (TAT-59) to elucidate its efficacy in antiestrogen therapy for breast cancer patients and to assess its tissue-selective estrogenic/antiestrogenic activity. Using DP-TAT-59, a major and active metabolite of TAT-59, an in vitro cell growth inhibition test was performed. Antitumor activity was detd. using TAT-59 against human tumor xenografts of the MCF-7 and the Br-10 cell lines and MCF-7-derived tamoxifen-resistant cell lines, R-27 and FST-1. The antitumor activity of DP-TAT-59 and DM-DP-TAT-59, major metabolites of TAT-59 found in human blood following a TAT-59 dose, was also examd. after i.v. administration to exptl. animals. The residual estrogenic activity of TAT-59, evaluated in terms of bone and lipid metab. in ovariectomized rats, was then compared with that of tamoxifen. DP-TAT-59 inhibited the proliferation of estrogen receptor-pos. MCF-7 and T-47D tumor cells in the presence of 1 nM estradiol. TAT-59, given to mice bearing MCF-7 or Br-10 xenografts, at the dose level of 5 mg/kg, exerted a growth inhibitory effect that was stronger than that of tamoxifen. Moreover, R-27 and FST-1 tumors, which show a resistance to tamoxifen, responded strongly to TAT-59, suggesting that TAT-59 might be effective against tumors resistant to tamoxifen. The metabolites of TAT-59, DP-TAT-59 and DM-DP-TAT-59, showed similar antitumor activity. Both TAT-59 and tamoxifen suppressed the decrease in bone d. and reduced the blood cholesterol levels in ovariectomized rats, suggesting that the estrogenic activity of TAT-59 is comparable to that of tamoxifen. On the basis of the above results, one may expect TAT-59 to become an effective drug in patients with tumors less sensitive to tamoxifen, while its estrogenic activity as detd. by bone and lipid metab. is similar to that of tamoxifen.

Answer 34:

### Bibliographic Information

**Expression of CD44 isoforms in human breast carcinoma xenografts is not influenced by the treatment of mice with**

**cytostatics or (anti-)hormones.** Dehmel, A.; Becker, M.; Lemm, M.; Fichtner, I. Max-Delbrück-Center of Molecular Medicine, Berlin, Germany. *Anticancer Research* (1999), 19(3A), 1977-1987. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 132:120767 AN 1999:654678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

CD44 std. (s) and variant (v) isoforms have been discussed to be implicated in progression and metastasis of different malignomas. For breast carcinomas, the results of different studies are contradictory. These apparent discrepancies suggest that CD44 isoforms are not available on the tumor cell surface, but could be regulated by different endogenous and exogenous factors. Here we report the regulation of CD44 isoforms in xenografted breast cancer cell lines by cytostatics, hormones and antihormones. The human breast cancer models MDA-MB 435, MCF-7, NCI/ADR, 4296, 4151 and 4134 were transplanted into the mammary fat pad of nude mice. When tumors reached a palpable size, animals were treated with farmorubicin, cyclophosphamide, estradiol, tamoxifen or progesterone, resp. At different times after treatment, serum and tumors were taken. The expression of CD44 and its isoforms was detd. by immunohistochem. and RT-PCR, serum levels were measured by human specific ELISA kits. Serum levels of CD44s and v6 varied among the tumors. For 3/6 tumors we found differences between control groups and treated animals. Immunohistochem. results remained unchanged: each tumor showed a specific pattern of CD44 expression, but this pattern did not change when the animals received cytostatics, hormones or antihormones. The same held true for RT-PCR-results. Also, the time of tumor collection had no influence on CD44 expression. Therefore, it can be concluded, that in the xenografted breast cancer cell lines a regulation of CD44 isoforms by farmorubicin, cyclophosphamide, estradiol, progesterone or tamoxifen could not be found, while serum levels were influenced in some cases probably due to tumor cell kill and shedding of surface proteins into blood stream.

Answer 35:

#### Bibliographic Information

**Idoxifene antagonizes estradiol-dependent MCF-7 breast cancer xenograft growth through sustained induction of apoptosis.** Johnston, Stephen R. D.; Boeddinghaus, Irene M.; Riddler, Sharon; Haynes, Ben P.; Hardcastle, Ian R.; Rowlands, Martin; Grimshaw, Rachel; Jarman, Michael; Dowsett, Mitch. Departments of Medicine, The Royal Marsden NHS Trust, London, UK. *Cancer Research* (1999), 59(15), 3646-3651. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 131:295210 AN 1999:514392 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### Abstract

Idoxifene is a novel selective estrogen (E2) receptor (ER) modulator that is currently in clin. development for the treatment of breast cancer. Compared to tamoxifen, idoxifene is metabolically more stable, with a higher relative binding affinity for the ER and reduced agonist activity on breast and uterine cells. Idoxifene also inhibits calmodulin, a calcium-binding protein that is involved in cell signal transduction pathways. In this study, the abilities of idoxifene and tamoxifen to antagonize E2-dependent MCF-7 xenograft growth in oophorectomized athymic mice were compared. The basis for idoxifene's antitumor activity was examd. by comparing the effectiveness of the clin. used trans-isomer (referred to here as idoxifene) with its cis-isomer, which has a 50-fold lower relative binding affinity for ER than idoxifene but similar calmodulin-inhibitory activity. Changes in tumor cell proliferation, apoptosis, and ER-dependent protein expression were studied. Both idoxifene and tamoxifen significantly inhibited E2-dependent tumor growth, whereas cis-idoxifene had little effect. Withdrawal of E2 support induced significant tumor regression due to impaired cell proliferation (Ki-67 score, 9 vs. 51% compared to E2 controls) and induction of apoptosis (3.6 vs. 0.9% compared to E2 controls). Both anti-E2s inhibited cell proliferation and caused a significant 3-fold induction of apoptosis in E2-supported tumors after 1 wk, which was maintained for 3 mo with idoxifene (3.1 vs. 0.48% compared to E2 controls) but decreased back to baseline in tumors treated with tamoxifen (0.69%). In contrast, cis-idoxifene had no effect on either cell proliferation or apoptosis. Both tamoxifen and idoxifene initially induced ER expression, whereas prolonged therapy with tamoxifen significantly reduced progesterone receptor levels. Thus, idoxifene resulted in similar inhibition of E2-dependent MCF-7 xenograft growth compared with tamoxifen, an effect that is mediated via ER rather than through calmodulin.

Sustained induction of apoptosis may contribute to prolonged antagonism of E2-dependent growth, and it occurred to a greater extent following 3 mo of idoxifene, compared to tamoxifen.

Answer 36:

### Bibliographic Information

**EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium.** Labrie, Fernand; Labrie, Claude; Belanger, Alain; Simard, Jacques; Gauthier, Sylvain; Luu-The, Van; Merand, Yves; Giguere, Vincent; Candas, Bernard; Luo, Shouqi; Martel, Celine; Singh, Shankar Mohan; Fournier, Marc; Coquet, Agnes; Richard, Virgile; Charbonneau, Ronald; Charpenet, Gilles; Tremblay, Andre; Tremblay, Gilles; Cusan, Lionel; Veilleux, Raymonde. *Oncology and Molecular Endocrinology Research Center, Centre Hospitalier Universitaire de Quebec (CHUQ), Pavillon CHUL, Department of Medicine, Laval University, Quebec, QC, Can. Journal of Steroid Biochemistry and Molecular Biology* (1999), 69(1-6), 51-84. Publisher: Elsevier Science Ltd., CODEN: JSBBEZ ISSN: 0960-0760. Journal; General Review written in English. CAN 131:208327 AN 1999:437555 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A review, with 224 refs. Breast cancer is the most frequent cancer in women while it is the second cause of cancer death. Estrogens are well recognized to play the predominant role in breast cancer development and growth and much efforts have been devoted to the blockade of estrogen formation and action. The most widely used therapy of breast cancer which has shown benefits at all stages of the disease is the use of the antiestrogen Tamoxifen. This compd., however, possesses mixed agonist and antagonist activity and major efforts have been devoted to the development of compds. having pure antiestrogenic activity in the mammary gland and endometrium. Such a compd. would avoid the problem of stimulation of the endometrium and the risk of endometrial carcinoma. We have thus synthesized an orally active non-steroidal antiestrogen, EM-652 (SCH 57068) and the prodrug EM-800 (SCH57050) which are the most potent of the known antiestrogens. EM-652 is the compd. having the highest affinity for the estrogen receptor, including estradiol. It has higher affinity for the ER than ICI 182780, hydroxytamoxifen, raloxifene, droloxifene and hydroxytoremifene. EM-652 has the most potent inhibitory activity on both ER $\alpha$  and ER $\beta$  compared to any of the other antiestrogens tested. An important aspect of EM-652 is that it inhibits both the AF1 and AF2 functions of both ER $\alpha$  and ER $\beta$  while the inhibitory action of hydroxytamoxifen is limited to AF2, the ligand-dependent function of the estrogen receptors. AF1 activity is constitutive, ligand-independent and is responsible for mediation of the activity of growth factors and of the ras oncogene and MAP-kinase pathway. EM-652 inhibits Ras-induced transcriptional activity of ER $\alpha$  and ER $\beta$  and blocks SRC-1-stimulated activity of the two receptors. EM-652 was also found to block the recruitment of SRC-1 at AF1 of ER $\beta$ , this ligand-independent activation of AF1 being closely related to phosphorylation of the steroid receptors by protein kinase.

Most importantly, the antiestrogen hydroxytamoxifen has no inhibitory effect on the SRC-1-induced ER $\beta$  activity while the pure antiestrogen EM-652 completely abolishes this effect, thus strengthening the need to use pure antiestrogens in breast cancer therapy in order to control all known aspects of ER-regulated gene expression. In fact, the absence of blockade of AF2 by hydroxytamoxifen could explain why the benefits of tamoxifen obsd. up to 5 yr become neg. at longer time intervals and why resistance develops to tamoxifen. EM-800, the prodrug of EM-652, has been shown to prevent the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat, a well-recognized model of human breast cancer. It is of interest that the addn. of dehydroepiandrosterone, a precursor of androgens, to EM-800, led to complete inhibition of tumor development in this model. Not only the development, but also the growth of established DMBA-induced mammary carcinoma was inhibited by treatment with EM-800. An inhibitory effect was also obsd. when medroxyprogesterone was added to treatment with EM-800. Uterine size was reduced to castration levels in the groups of animals treated with EM-800. An almost complete disappearance of estrogen receptors was obsd. in the uterus, vagina and tumors in nude mice treated with EM-800. EM-652 was the most potent antiestrogen to inhibit the growth of human breast cancer ZR-75-1, MCF-7 and T-47D cells in vitro when compared with ICI 182780, ICI 164384, hydroxytamoxifen, and droloxifene. Moreover, EM-652 and EM-800 have no stimulatory effect on the basal levels of cell proliferation in the absence of E2 while hydroxytamoxifen and droloxifene had a stimulatory effect on the basal growth of T-47D and ZR-75-1 cells. EM-652 was also the most potent inhibitor of the percentage of cycling cancer cells.

When human breast cancer ZR-75-1 xenografts were grown in nude mice, EM-800 led to a complete inhibition of the stimulatory effect of estrogens in ovariectomized mice while tamoxifen was less potent and even stimulated the growth of the tumors in the absence of estrogens, thus illustrating the stimulatory effect of tamoxifen on breast cancer growth. When incubated with human Ishikawa endometrial carcinoma cells, EM-800 had no stimulatory effect on alk. phosphatase activity, an estrogen-sensitive parameter. Raloxifene, droloxifene, hydroxytoremifene and hydroxytamoxifen, on the other hand, all stimulated to various extent, the activity of this enzyme. The stimulatory effect of all four compds. was blocked by EM-800, thus confirming their estrogenic activity in human endometrial tissue. When administered to ovariectomized animals, EM-800 prevents bone loss, the effect on bone mineral d., trabecular bone vol., and trabecular

sepn. being 5-10 times more potent than raloxifene. EM-800 lowers serum cholesterol and triglyceride levels in the rat as well as in women. In a Phase II study performed in patients with breast cancer showing failure on tamoxifen, 1 patient had a complete response while 5 patients had a partial response and stable disease for at least three months has been obsd. in an addnl. 13 patients for a total of 19 pos. responses out of 43 evaluable patients (44.2%). No significant secondary effect related to the drug was obsd. A phase 3 international clin. trial is currently being performed in tamoxifen failure patients where EM-800 (SCH 57050) is compared to Arimidex. The detailed information obtained at the preclin. level with EM-652 or EM-800 indicates that these orally active compds. are highly potent and pure antiestrogens in the mammary gland and endometrium while they prevent bone loss and lower serum cholesterol and triglyceride levels. Preclin. and clin. data clearly suggest the interest of studying this compd. in the neoadjuvant and adjuvant settings and, most importantly, for the prevention of breast and uterine cancer in which settings they should provide addnl. benefits on bone and lipids.

Answer 37:

### Bibliographic Information

**Antitumor activity, distribution, and metabolism of 13-cis-retinoic acid as a single agent or in combination with tamoxifen in established human MCF-7 xenografts in mice.** Conley, Barbara A.; Ramsland, Thomas S.; Sentz, Dorothy L.; Wu, Suhlan; Rosen, D. Marc; Wollman, Megan; Eiseman, Julie L. Div. Developmental Therapeutics, Cancer Center, Univ. Maryland, Baltimore, MD, USA. *Cancer Chemotherapy and Pharmacology* (1999), 43(3), 183-197. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 130:217624 AN 1999:191820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The efficacy of 13-cis-retinoic acid (13-CRA) given as a single agent or in combination with tamoxifen (TAM) was detd. in athymic nude mice bearing advanced s.c. MCF-7 human breast cancers. 13-CRA alone was given by gavage at doses ranging from 26.4-200 mg/kg. TAM alone was given by gavage at doses of 7.5, 15, 30, or 60 mg/kg. For combination studies, each dose of TAM was followed 4 h later by 13-CRA at doses of 25, 50, 100, or 200 mg/kg. All treatments began on day 12 and were continued for 3 wk. The median time to 2 doublings recorded for the control and for 13-CRA and TAM given as single agents at the highest dose were 22.2, 29.2, and 54.7 days, resp. In combination, 100 and 200 mg/kg 13-CRA with 7.5 mg/kg TAM resulted in a delay in tumor growth at least as high as that achieved with highest-dose TAM alone, but the effect was not synergistic. Pharmacokinetic anal. of 13-CRA was performed in blood plasma, liver, and tumor from mice bearing 0.5-2.0 g carcinomas following a single dose of 100 mg/kg 13-CRA. Results showed that 13-CRA was metabolized differently in various tissues, but concns. at 13-CRA detected in tumor were in the range reported to be active in vitro. All-trans-retinoic acid (ATRA) concns. were about 5% at the 13-CRA concns. detected in plasma, 68% of those found in liver, and 20% of those found in tumor. 4-Oxo-CRA represented between 2 and 10% of 13-CEA concns. detected in plasma and liver but was not detected in tumor. Furthermore there was no difference in peak plasma 13-CRA concns. found in the same tissues at 30 min after a single dose or after the 8h dose of 100 mg/kg 13-CRA or 13-CRA and TAM. Mean 13-CRA concns. detected in liver and tumor were 50-90% and 16-30% of plasma peak concns., resp. No difference in 4-oxo-CRA concn. was obsd. between the treatment groups. These data suggest that 13-CRA is not effective against established human breast tumor xenografts despite the stability of the pharmacokinetics of 13-CRA and the generation of ATRA as a metabolite. The addn. of 13-CRA to TAM did not improve the efficacy of TAM against these estrogen-receptor-pos. xenografts.

Answer 38:

### Bibliographic Information

**Reversal of tamoxifen resistance of human breast carcinomas in vivo by neutralizing antibodies to transforming growth factor- $\beta$**  Arteaga, Carlos L.; Koli, Katri M.; Dugger, Teresa C.; Clarke, Robert. Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA. *Journal of the National Cancer Institute* (1999), 91(1), 46-53. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 130:291157 AN 1999:59038 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Background:** Overexpression of transforming growth factor (TGF)- $\beta$  has been reported in human breast carcinomas resistant to antiestrogen tamoxifen, but the role of TGF- $\beta$  in this resistant phenotype is unclear. We investigated whether inhibition of TGF- $\beta$ 2, which is overexpressed in LCC2 tamoxifen-resistant human breast cancer cells, could modify antiestrogen resistance. **Methods:** TGF- $\beta$ 2 expression was evaluated in LCC2 cells and tamoxifen-sensitive LCC1 cells by northern blot anal. Secreted TGF- $\beta$  activity was quantified by use of an  $^{125}\text{I}$ -TGF- $\beta$  competitive radioreceptor assay. Sensitivity to tamoxifen was measured in a soft agarose colony-forming assay and in a xenograft model in nude and beige/nude mice. Natural killer (NK) cell cytotoxicity was measured by  $^{51}\text{Cr}$  release from LCC1 and LCC2 cell targets coincubated with human peripheral blood mononuclear cells. Decrease in TGF- $\beta$ 2 expression in LCC2 cells was achieved by treatment with antisense oligodeoxynucleotides and confirmed by TGF- $\beta$ 2 immunoblot anal. **Results and Conclusions:** The proliferative response of LCC2 cells to tamoxifen in vitro was not altered by TGF- $\beta$  neutralizing antibodies. However, established LCC2 tumors in nude mice treated with tamoxifen plus TGF- $\beta$  antibodies failed to grow, whereas tumors treated with tamoxifen plus a control antibody continued to proliferate. This reversal of tamoxifen resistance by TGF- $\beta$  antibodies did not occur in beige/nude mice, which lack NK-cell function, suggesting that immune mechanisms may be involved in the antitumor effects of tamoxifen. Antisense TGF- $\beta$ 2 oligodeoxynucleotides enhanced the NK sensitivity of LCC2 cells in the presence of tamoxifen. Finally, LCC1 tumors were markedly more sensitive to tamoxifen in NK-active than in NK-deficient mice. **Implications:** These data suggest that host NK function mediates, in part, the antitumor effect of tamoxifen and that TGF- $\beta$ 2 may abrogate this mechanism, thus contributing to tamoxifen resistance.

Answer 39:

**Bibliographic Information**

**Comparison of the effects of the antiestrogens EM-800 and tamoxifen on the growth of human breast ZR-75-1 cancer xenografts in nude mice.** Couillard, Steeve; Gutman, Matthieu; Labrie, Claude; Belanger, Alain; Candas, Bernard; Labrie, Fernand. Laboratory of Molecular Endocrinology, Research Center and Laval University, Le Centre Hospitalier de L'universite Laval, Quebec, QC, Can. *Cancer Research* (1998), 58(1), 60-64. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 128:175866 AN 1998:20555 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Although estrone supplementation in ovariectomized (OVX) nude mice bearing ZR-75-1 xenografts caused a 365% increase in av. tumor size during the 4-mo treatment period, administration of the antiestrogen EM-800 at the daily oral doses of 50, 150, or 400  $\mu\text{g}$  completely prevented estrogen-stimulated tumor growth. At the same doses of tamoxifen, tumor size was inhibited to 189, 117, and 120% above pretreatment values. However, when EM-800 (150  $\mu\text{g}/\text{day}$ ) was added to the daily 150- and 400- $\mu\text{g}$  doses of tamoxifen, final tumor size was decreased further to 12 and 38% above pretreatment values, resp. EM-800 (400  $\mu\text{g}$  daily) administered to estrone-supplemented OVX mice caused complete, partial, and stable responses in 11, 22, and 49% of estrone-stimulated tumors, resp., whereas 19% (7 of 37) progressed. At the same dose of tamoxifen, the corresponding responses were 3% (complete response), 3% (partial response), and 25% (no change), whereas 69% (22 of 32) of tumors progressed. In the absence of estrone supplementation, tamoxifen (400  $\mu\text{g}$ ) alone administered to OVX mice stimulated tumor growth to 161% compared with initial size whereas the same dose of EM-800 reduced tumor size by 55%, a value superimposable to that obsd. in OVX control animals. The agonistic effect of tamoxifen is thus illustrated by the observation that 73% of tumors progressed when tamoxifen was administered alone to OVX animals whereas no tumor progressed with EM-800. The present data strongly suggest that at least part of the initial lack of response and resistance to tamoxifen during tamoxifen treatment in women is due to the estrogenic activity of this compd., whereas the new antiestrogen EM-800 exerts pure antagonistic action.

Answer 40:

**Bibliographic Information**

**Tamoxifen-induced apoptosis in ZR-75 breast cancer xenografts antedates tumor regression.** Cameron, D. A.; Ritchie, A. A.; Langdon, S.; Anderson, T. J.; Miller, W. R. I.C.R.F. Medical Oncology Unit, Western General Hospital, Edinburgh, UK. *Breast*

Cancer Research and Treatment (1997), 45(2), 99-107. Publisher: Kluwer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 127:341487 AN 1997:698378 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The ZR-75-1 ER pos. breast cancer cell line, xenografted in female nude mice, has been used to det. the effect of tamoxifen on cell proliferation (as measured by mitosis) and cell death (as evidenced by apoptosis and necrosis). After 2 days treatment, there was a significant rise in apoptosis ( $p < 0.05$ ), whereas a fall in mitosis was not apparent until 7 days ( $p < 0.05$ ). Furthermore there was an increase in the apoptotic: mitotic ratio on day 7 ( $p < 0.05$ ). These changes antedated tumor regression, which did reach not significance until day 14. Tamoxifen did not increase necrosis (which significantly decreased in treated tumors once they had regressed ( $p < 0.01$ )). In contrast, tamoxifen treatment of xenografted MDA-MB-231 ER-neg. breast cancer cells produced no significant effects on growth, apoptosis, or mitosis. This study presents clear evidence for tamoxifen inducing apoptosis in ZR-75-1 xenografts (but not MDA-MB-231 tumors). Since changes in apoptosis and mitosis antedate tumor regression, their assessment may provide the potential by which to predict tumor response to tamoxifen therapy.

Answer 41:

### Bibliographic Information

#### Comparison of estrogen receptor DNA binding in untreated and acquired antiestrogen-resistant human breast tumors.

Johnston, Stephen R. D.; Lu, B.; Dowsett, Mitchell; Liang, X.; Kaufmann, Manfred; Scott, Gary K.; Osborne, C. Kent; Benz, Christopher C. Academic Department of Biochemistry, Royal Marsden Hospital and Institute of Cancer Research, London, UK. Cancer Research (1997), 57(17), 3723-3727. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 127:272366 AN 1997:593453 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Preliminary studies have suggested that measuring the ability of immunoreactive 67-kDa estrogen receptor (ER) to bind DNA and form in vitro complexes with its cognate estrogen response element (ERE) might serve to identify breast tumors most likely to respond to antiestrogens like tamoxifen. Data from two different surveys of untreated primary breast tumors confirmed that only 67% (74 of 111) of ER-pos. tumors express a receptor capable of forming ER-ERE complexes by gel-shift assay, with tumors of lower ER content having significantly reduced ER DNA-binding frequency (56%) relative to those of higher ER content (82%). In contrast to these untreated tumors, a panel of 41 receptor-pos. breast tumors excised after acquiring clin. resistance to tamoxifen during either primary or adjuvant therapy showed a significantly greater ER DNA-binding frequency, with nearly 90% capable of forming ER-ERE complexes. To assess exptl. whether ER DNA-binding function is altered during the development of antiestrogen resistance, nude mouse MCF-7 tumor xenografts were analyzed before and after the acquisition of in vivo resistance to either tamoxifen or a pure steroidal antiestrogen, ICI 182,780. Tamoxifen-resistant MCF-7 tumors retained full expression of 67-kDa DNA-binding ER, and despite a markedly reduced ER content in the ICI 182,780-treated tumors, the expressed ER in these antiestrogen-resistant tumors exhibited full ability to form ER-ERE complexes. These findings indicate that breast tumors with acquired antiestrogen resistance continue to express ER of normal size and DNA-binding ability and suggest that the failure of antiestrogens to arrest tumor growth during emergence of clin. resistance results from an altered gene-regulatory mechanism(s) other than ER-ERE complex formation.

Answer 42:

### Bibliographic Information

**Tamoxifen-mediated growth inhibition of human cholangiocarcinoma.** Sampson, Lorenzo K.; Vickers, Selwyn M.; Ying, Weizhong; Phillips, John O. Department of Surgery, Division of Gastroenterology and Hepatology, The University of Alabama at Birmingham, Birmingham, AL, USA. Cancer Research (1997), 57(9), 1743-1749. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 127:13079 AN 1997:313639 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Cholangiocarcinoma represents a challenging primary malignancy of the liver with no effective medical therapy and a poor prognosis. We have investigated the role of tamoxifen and estrogen receptors (ERs) in the regulation of growth of human cholangiocarcinoma. Two human cholangiocarcinoma cell lines, OZ and SK-ChA-1, were grown in the presence of graded concns. of tamoxifen; the effects on cell growth were detd. by cell counting or 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium proliferation assay. The presence of ER protein was tested by indirect immunofluorescence and immunopptn. In addn., cells were grown in estrogen-depleted media supplemented with exogenous 17 $\beta$ -estradiol. ER mRNA was evaluated by reverse transcription-PCR and Northern blotting. Finally, one cholangiocarcinoma cell line was grown as a xenograft in athymic nude mice; tamoxifen effects on in vivo tumor growth were detd. with biweekly caliper measurements. Tamoxifen (5-10  $\mu$ M) caused dose-dependent in vitro growth inhibition of two human cholangiocarcinoma cell lines. In addn., growth inhibition of one cell line (SK-ChA-1) grown as a xenograft in nude mice by tamoxifen was obsd. The presence of ER protein was suggested by 17 $\beta$ -estradiol stimulation of tumor cell growth in vitro and confirmed by immunopptn. Immunofluorescence microscopy was ineffective at detection of ER protein. Reverse transcription-PCR demonstrated the presence of ER mRNA in both cell lines. Northern blot anal. confirmed the presence of full-length 6.5-kb ER mRNA. No ER deletion mutants were detected. Tamoxifen inhibited the growth of human cholangiocarcinoma in vitro and in vivo. ER protein and mRNA were detected in both cell lines. The mechanism(s) of tamoxifen-mediated growth inhibition is unclear but may occur via ER protein or addnl. pathways. The ability of tamoxifen to inhibit tumor growth may offer an alternative adjunctive treatment for cholangiocarcinoma.

Answer 43:

**Bibliographic Information**

**Synthesis, Biodistribution, and Estrogen Receptor Scintigraphy of Indium-111-Diethylenetriaminepentaacetic Acid-Tamoxifen Analog.** Delpassand, Ebrahim S.; Yang, David J.; Wallace, Sidney; Cherif, Abdallah; Quadri, Syed M.; Price, Janet; Joubert, Angela; Inoue, Tomio; Podoloff, Donald A. M. D. Anderson Cancer Center, University of Texas, Houston, TX, USA. *Journal of Pharmaceutical Sciences* (1996), 85(6), 553-559. Publisher: American Chemical Society, CODEN: JPMSAE ISSN: 0022-3549. Journal written in English. CAN 124:311345 AN 1996:284717 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

This study was aimed at developing a hydrophilic diethylenetriaminepentaacetic acid-tamoxifen (DTPA-Tam) analog for use in imaging estrogen receptor pos. (ER+) lesions. In rat uterine cytosol, the IC<sub>50</sub> of DTPA-Tam conjugate was 1  $\mu$ M and of tamoxifen, 2  $\mu$ M. Biodistribution, autoradiog., and radionuclide imaging of <sup>111</sup>In-DTPA-Tam in breast-tumor-bearing rats showed that tumor-to-tissue ratios increased steadily between 30 min and 48 h. The in vivo response of MCF-7 breast cancer xenografts to tamoxifen and DTPA-Tam in nude mice demonstrated that DTPA-Tam could reduce tumor growth rate. These results indicate that DTPA-Tam, a new hydrophilic ER+ ligand, might be useful in diagnosing ER+ lesions.

Answer 44:

**Bibliographic Information**

**Estrogen stimulation and tamoxifen inhibition of leiomyoma cell growth in vitro and in vivo.** Howe, Susan R.; Gottardis, Marco M.; Everitt, Jeffrey I.; Walker, Cheryl. Dep. Carcinogenesis, Univ. Texas, Smithville, TX, USA. *Endocrinology* (1995), 136(11), 4996-5003. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 123:306819 AN 1995:897650 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Uterine leiomyomas (fibroids) are the most common gynecol. neoplasms and may be assocd. with significant morbidity. Recently, we described a rat model (Eker rat) of fibroid development in which reproductive tract leiomyomas develop spontaneously with high frequency. The present studies describe the estrogen and antiestrogen responsiveness of an Eker rat leiomyoma-derived cell line in

vitro and a nude mouse xenograft system in vivo. In this cell line, estradiol stimulated growth in estrogen-depleted medium, whereas the nonsteroidal antiestrogen tamoxifen maximally inhibited cell proliferation in medium contg. 10% charcoal-stripped serum. Proliferation was also decreased by the biol. active tamoxifen metabolite 4-hydroxytamoxifen; the metabolite was more effective than the parent compd. in exerting this growth inhibition. Compared to placebo-treated controls, estradiol increased the size of tumors that developed in a nude mouse xenograft system, whereas tamoxifen increased tumor latency and decreased tumor size. This study of leiomyoma cells in a well defined system suggests that antiestrogens may prove efficacious in the treatment of this clin. important neoplasm.

Answer 45:

#### **Bibliographic Information**

**Tamoxifen inhibits growth, migration, and invasion of human follicular and papillary thyroid cancer cells in vitro and in vivo.** Hoelting, Thomas; Siperstein, Allan E.; Duh, Quan-Yang; Clark, Orlo H. Dep. of Surgery, Univ. of Heidelberg, Heidelberg, Germany. *Journal of Clinical Endocrinology and Metabolism* (1995), 80(1), 308-13. Publisher: Endocrine Society, CODEN: JCEMAZ ISSN: 0021-972X. Journal written in English. CAN 122:96005 AN 1995:327810 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

It has been proposed that sex steroids protect premenopausal women from aggressive thyroid malignancies. Some thyroid tissues have estrogen receptors, and estrogen stimulates human thyroid cells. Tamoxifen is thought to exert its antiproliferative effects mainly by blocking estrogen stimulation. However, recently, mechanisms independent of estrogen interactions were found to be important for the favorable effect. The effect of tamoxifen on growth, migration, and invasion were investigated in 3 follicular thyroid cancer cell lines (FTC133, primary; FTC236, lymph node; and FTC238, lung metastasis) and 2 papillary lines (PTC-UC1 and PTC-UC3). In vivo expts. used xenografts of FTC133 in nude mice. Tamoxifen (1.5  $\mu$ M) inhibited the growth of all the thyroid cancer cell lines (FTC133, 59%; FTC236, 42%; FTC238, 46%). This effect was less pronounced in PTC-UC1 (25%) and PTC-UC3 (19%) cell lines. Tamoxifen also inhibited migration and invasion of FTC cells more than PTC cells. Invasion of FTC133 was inhibited by 36%, FTC236 by 30%, and FTC238 by 32%. Immunohistochem. showed no estrogen receptors in any cell line used. Also, estradiol had no effect on the growth, migration, or invasion of FTC or PTC. Tamoxifen treatment inhibited the growth of FTC133 xenografts in nude mice by 52% compared to that in placebo-treated controls. In conclusion, tamoxifen inhibited the growth, migration, and invasion of differentiated thyroid cancer cells in vitro and in vivo. This was not reversed by estrogen. Tamoxifen acts independently of estrogen interactions and may be useful as an adjuvant treatment for some differentiated human thyroid malignancies.

Answer 46:

#### **Bibliographic Information**

**Growth inhibition of estrogen receptor-positive human ovarian carcinoma by antiestrogens in vitro and in a xenograft model.** Langdon, S.P.; Crew, A.J.; Ritchie, A.A.; Muir, M.; Wakeling, A.; Smyth, J.F.; Miller, W.R. ICRF Med. Oncol. Unit, West. General Hospital, Edinburgh, UK. *Eur. J. Cancer, Part A* (1994), 30A(5), 682-6. CODEN: EJCTEA Journal written in English. CAN 121:195173 AN 1994:595173 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

This paper presents results of the in vitro and in vivo effects of antiestrogens on the growth of human ovarian cancer cells. Tamoxifen and the "pure" antiestrogens ICI 164,384 and ICI 182,780 inhibited the estrogen-stimulated growth of the estrogen receptor (ER)-pos. PE04 and PE01 cell lines grown in culture, the latter 2 compds. being more potent than tamoxifen. In the absence of 17 $\beta$ -estradiol (E2), tamoxifen (10<sup>-7</sup>-10<sup>-9</sup>M), but not the pure antiestrogens, produced a small degree of growth stimulation in the PE01 and PE04 lines. In contrast, growth of the ER-neg. PE014 line was unaffected by E2 and all 3 antiestrogens. The effects of tamoxifen and ICI 182,780 on PE04 cells grown as xenografts in nude mice were also studied. Both antiestrogens produced significant growth-inhibitory effects. These results indicate that ovarian carcinoma cells may be sensitive to antiestrogens in vitro and in vivo, and support the view that antiestrogens merit further clin. studies in patients with ER-pos. tumors.

Answer 47:

### Bibliographic Information

**cDNA transfection followed by the isolation of a MCF-7 breast cell line resistant to tamoxifen in vitro and in vivo.** Toi, M.; Harris, A.L.; Bicknell, R. Mol. Oncol. Lab., Imp. Cancer Res. Fund, Oxford, UK. British Journal of Cancer (1993), 68(6), 1088-96. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 120:289541 AN 1994:289541 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

A tamoxifen-resistant cell line (clone 9) has been isolated from the tamoxifen-sensitive, hormone-responsive MCF-7 breast carcinoma cell line after transfection with mixed cDNA libraries, followed by tamoxifen selection in the presence of estrogens. Transfection was confirmed by Southern anal. with vector probes. Clone 9 is several-fold more resistant to tamoxifen and other anti-estrogens than wild type cells when cultured either as a monolayer or as colonies in soft agar but retains estrogen receptors. Clone 9 was less responsive to 17- $\beta$ -estradiol than were wild type MCF-7. In addn. to showing in vitro tamoxifen resistance, clone 9 was also tamoxifen resistant in vivo when xenografted into the nude mouse. Culture medium conditioned by clone 9 cells stimulated quiescent cells of the same clone as well as wild type cells, whereas medium conditioned by wild type MCF-7 was inhibitory to both, suggesting that clone 9 may be secreting an autocrine growth factor. Clone 9 provides a novel model for further investigation of the mechanism of anti-estrogen resistance that occurs without loss of estrogen receptors. Preliminary results suggest that an autocrine growth stimulatory mechanism may be one pathway of such resistance.

Answer 48:

### Bibliographic Information

**Human recombinant interferon- $\beta$ SER and tamoxifen: growth suppressive effects for the human breast carcinoma MCF-7 grown in the athymic mouse.** Gibson, David F. C.; Johnson, Delinda A.; Goldstein, David; Langan-Fahey, Susan M.; Borden, Ernest C.; Jordan, V. Craig. Compr. Cancer Cent., Univ. Wisconsin, Madison, WI, USA. Breast Cancer Research and Treatment (1993), 25(2), 141-50. CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 119:108502 AN 1993:508502 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Human recombinant interferon- $\beta$ SER (rIFN- $\beta$ SER) inhibited the growth in vitro of the estrogen receptor (ER) pos. breast cancer cell line MCF-7 and the ER neg. breast cancer cell line MDA-MB-231. This inhibitory effect was achieved at doses of 50 U/mL and above. The growth of MCF-7 tumors in estradiol-stimulated athymic mice was greatly inhibited by high dose rIFN- $\beta$ SER treatment (106 U/day). In spite of the impressive antitumor effects upon MCF-7 tumors, rIFN- $\beta$ SER had no effect upon ER levels within the tumors at either the RNA or protein level. High dose rIFN- $\beta$ SER (106 U/day) did result in some inhibition in the growth in vivo of the tamoxifen-stimulated MCF-7 variant MCF-7 TAM, although not to the same extent as was obsd. with the estradiol-stimulated MCF-7 tumors. RIFN- $\beta$ SER was also administered to animals bearing MCF-7 tumors and treated with estradiol and tamoxifen. In the animals undergoing high dose therapy (106 U/day), tumor growth was completely suppressed. Furthermore, tumor growth continued to be suppressed in those animals in which the rIFN- $\beta$ SER therapy was halted and the tamoxifen capsule removed. No tumors were obsd. in spite of the environment of estradiol stimulation. Thus, the combination of interferon and tamoxifen was totally growth suppressive for MCF-7 xenografts in nude mice.

Answer 49:

### Bibliographic Information

**Recombinant human interferon- $\alpha$ 2a increases hormone receptor level of a human breast carcinoma xenograft in nude mice and enhances the anti-proliferative activity of tamoxifen.** Josui, Kazuya; Kubota, Tetsuro; Kitajima, Masaki. Sch. Med., Keio

Univ., Tokyo, Japan. Japanese Journal of Cancer Research (1992), 83(12), 1347-53. CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 118:145698 AN 1993:145698 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The effect of recombinant human interferon- $\alpha$ 2a (rhIFN- $\alpha$ 2a) on the hormone receptor level and antitumor activity of tamoxifen (TAM) was investigated in nude mice using ZR-75-1, an estrogen receptor (ER)-pos., and progesterone receptor (PgR)-neg. human breast carcinoma xenograft. ER levels (max. binding sites) of tumors treated with rhIFN- $\alpha$ 2a at a dose of  $6 \times 10^5$  U/mouse/day for 1 or 3 wk were not different from the control, whereas those with rhIFN- $\alpha$ 2a at a dose of  $6 \times 10^4$  U/mouse/day for 1 or 3 wk were higher than the control (3.9-4.4-fold) with a significant difference. The increase of ER by the rhIFN- $\alpha$ 2a was investigated using a sucrose d. gradient method. The peak was only seen at 8 S in both rhIFN- $\alpha$ 2a-treated tumor and control ER, and the sedimentation patterns were almost the same, suggesting that both ERs were essentially equiv. On the other hand, PgR of all the treated groups could be detected, while that of the control group was undetectable. The antitumor effect of the combination treatment of rhIFN- $\alpha$ 2a and TAM was compared with those of single treatments. While rhIFN- $\alpha$ 2a at a dose of  $6 \times 10^5$  U/mouse/day and TAM did not show a combination effect, rhIFN- $\alpha$ 2a at a dose of  $6 \times 10^4$  U/mouse/day and TAM showed a synergistic combination effect, and ER was decreased to the threshold of detection by the combination treatment. Thus, a low dose of rhIFN- $\alpha$ 2a increased the ER levels of ER-pos. human breast cancer in vivo as well as in vitro and enhanced the anti-proliferative effect of TAM, and the newly synthesized ER was essentially the same as the original ER.

Answer 50:

### Bibliographic Information

**Antitumor effect of a triphenylethylene derivative (TAT-59) against human breast carcinoma xenografts in nude mice.** Koh, Junichi; Kubota, Tetsuro; Asanuma, Fumiki; Yamada, Yoshinori; Kawamura, Eiji; Hosoda, Yoichiro; Hashimoto, Mitsumasa; Yamamoto, Osami; Sakai, Shoji; et al. Dep. Surg., Soc. Insurance Saitama Chuo Hosp., Urawa, Japan. Journal of Surgical Oncology (1992), 51(4), 254-8. CODEN: JSONAU ISSN: 0022-4790. Journal written in English. CAN 118:139350 AN 1993:139350 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

TAT-59 had higher activity than tamoxifen citrate against xenografts of estrogen receptor-pos. human breast carcinomas in female nude mice. The redn. of estrogen receptors and the prodn. of progesterone receptors after treatment with TAT-59 were greater than after tamoxifen, suggesting that TAT-59 exerts its antitumor effect through binding to estrogen receptors. TAT-59 might merit human clin. trials in breast cancer patients.

Answer 51:

### Bibliographic Information

**ICI 182,780, a new antiestrogen with clinical potential.** Wakeling, Alan E.; Bowler, Jean. Mereside Lab., ICI Pharm., Macclesfield/Cheshire, UK. Journal of Steroid Biochemistry and Molecular Biology (1992), 43(1-3), 173-7. CODEN: JSBBEZ ISSN: 0960-0760. Journal written in English. CAN 117:185126 AN 1992:585126 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Previous studies identified a series of 7 $\alpha$ -alkylamide analogs of 17 $\beta$ -estradiol which are pure antiestrogens. Among this initial series of compds., exemplified by ICI 164,384, none was of sufficient in vivo potency to merit serious consideration as a candidate for clin. evaluation. Further structure-activity studies identified a compd., ICI 182,780, 7 $\alpha$ -[9-(4,4,5,5,5-pentafluoro-pentylsulphonyl)nonyl]estra-1,3,5(10)-triene-3,17 $\beta$ -diol, with increased antiestrogenic potency. The

antiuterotrophic potency of ICI 182,780 is > 10-fold greater than that of ICI 164,384. ICI 182,780 has no estrogen-like trophic activity and, like ICI 164,384 is peripherally selective in its antiestrogenic effects. The increased in vivo potency of ICI 182,780 was also reflected, in part, by intrinsic activity at the estrogen receptor and in the growth inhibitory potency of ICI 182,780 in MCF-7 human breast cancer cells. ICI 182,780 was a more effective inhibitor of MCF-7 growth than 4'-hydroxytamoxifen, producing an 80% redn. of cell no. under conditions where 4'-hydroxytamoxifen achieved a max. of 50% inhibition. Sustained antiestrogenic effects of ICI 182,780, following a single parenteral dose of ICI 182,780 in oil suspension, were apparent in both rats and pigtail monkeys. In vivo, the antitumor activity of ICI 182,780 was demonstrated with xenografts of MCF-7 and Br10 human breast cancers in athymic mice where, over a 1 mo period, a single injection of ICI 182,780 in oil suspension achieved effects comparable with those of daily tamoxifen treatment. Thus, ICI 182,780 provides the opportunity to evaluate clin. the potential therapeutic benefits of complete blockade of estrogen effects in endocrine-responsive human breast cancer.

Answer 52:

### Bibliographic Information

**Specific binding of cholecystokinin, estradiol and somatostatin to human pancreatic cancer xenografts.** Singh, Pomila; Townsend, Courtney M., Jr.; Poston, Graeme J.; Reubi, Jean Claude. Dep. Surg., Univ. Texas Med. Branch, Galveston, TX, USA. *Journal of Steroid Biochemistry and Molecular Biology* (1991), 39(5A), 759-67. CODEN: JSBBEZ ISSN: 0960-0760. Journal written in English. CAN 116:51820 AN 1992:51820 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

It was recently reported that human pancreatic cancers differentially respond to the growth inhibitory effects of an estradiol (E2) receptor antagonist, tamoxifen, and a long-acting analog of somatostatin, Sandostatin. In the present study two human pancreatic cancers, established as xenografts in nude mice, were examd. as representative of cancers that respond to either tamoxifen (PGER) or Sandostatin (SKI), for the presence of binding sites for various hormones. Male nude mice were inoculated with either SKI or PGER, by passage of tumor chunks (3 mm<sup>2</sup>) to the interscapular region. Tumors, obtained from mice after .apprx.30 days of in vivo growth, were analyzed for binding to cholecystokinin-octapeptide (CCK), somatostatin and E2, by published procedures, using either crude tumor membranes (CCK), cytosol and nuclear fractions (E2), or cryostat sections of whole tumors (somatostatin). SKI was highly pos. for high-affinity (K<sub>d</sub> = .apprx.1 nM) CCK binding sites at the time of resection with a binding capacity of .apprx.1000 fmol/mg protein. With increasing passages, the total no. of high-affinity binding sites for CCK, was reduced to non-detectable levels in SKI tumors, while non-saturable binding (K<sub>d</sub> = >10 nM) became increasingly evident. Early passages of PGER tumors were similarly pos. for high-affinity binding sites for CCK, that steeply declined with increasing passages. Specific binding sites for E2 were obsd. only in the cytosolic fractions of PGER, with a high binding affinity (K<sub>d</sub> .apprx.0.05 nM) and a low binding capacity (15 fmol/mg cytosolic proteins), at all passages examd.; E2 binding sites were not detected in cytosolic and nuclear fractions of SKI and in the nuclei of PGER at all passages. SKI and PGER at different passages were examd. for somatostatin binding, and both the early and late passages of PGER were devoid of somatostatin binding sites, while SKI tumors were pos. for them.

Based on the above results, it appears likely that Sandostatin directly inhibited the growth of SKI tumors, since SKI was pos. for somatostatin binding sites; it appears less likely that Sandostatin indirectly mediated its inhibition by attenuating possible stimulatory effects of CCK. Growth inhibitory effects of tamoxifen on PGER were apparently via E2 binding sites, since only the tumors pos. for E2 binding sites (PGER) reponded to tamoxifen; it remains to be detd. if tamoxifen can exert addnl. effects independent of E2 binding sites on pancreatic cancers. Screening of pancreatic cancers for specific binding sites for putative growth regulatory hormones/factors, such as E2, somatostatin, and CCK, may thus help in the future to det. a more appropriate treatment for patients, in a fashion analogous to treatment of breast cancer.

Answer 53:

### Bibliographic Information

**Experimental combined chemo- and endocrino- therapy of UFT and tamoxifen on human breast carcinoma xenografts serially transplanted into nude mice.** Kubota, Tetsuro; Josui, Kazuya; Ishibiki, Kyuya; Abe, Osahiko; Yamada, Yoshinori; Asanuma, Fumiki; Kawamura, Eiji; Koh, Junichi; Shiina, Eiichi. Sch. Med., Keio Univ., Tokyo, Japan. *Nippon Gan Chiryo Gakkaishi* (1990), 25(12), 2767-73. CODEN: NGCJAK ISSN: 0021-4671. Journal written in Japanese. CAN 115:336 AN

1991:400336 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The exptl. combined chemo- and endocrino-therapy with UFT and tamoxifen (TAM) on two human breast carcinoma xenografts, R-27 and Br-10 with estrogen receptors (ER) serially transplanted into nude mice was investigated. When s.c. inoculated tumor started the exponential growth, the treatments were initiated in four groups which were control UFT 20 mg/kg (as tegafur) po daily for 18 times, TAM 5 mg/kg i.m. twice a week for 6 times and UFT + TAM groups. The antitumor activity of the agents were assessed by the growth curves, the lowest T/C ratios of the relative mean tumor wt. and the actual tumor wts. at the end of the expts. TAM alone was effective on both R-27 and ineffective on Br-10, while UFT alone was ineffective on R-27 and Br-10. The combination antitumor activity was obsd. in R-27 but not in Br-10. When 5 mg of TAM per kg and 20 mg of UFT per kg as tegafur was administered daily po for 2 wk, there were no statistically significant differences between the concn. of 5-FU in UFT alone and UFT + TAM groups for the two strains. By the assay of ER and progesterone receptors using the same specimen, it was obsd. that ER was stable by the treatment of UFT, while ER was suppressed by the treatment of TAM in both tumor strains. In addn., this suppression of ER by TAM alone was enhanced by the combined treatment with UFT in both the strains. Although these changes of hormone receptors by UFT and TAM could not explain the different sensitivity of R-27 and Br-10 to the combination therapy of UFT and TAM, this enhancement of hormone receptors by UFT and TAM might be one of the mechanisms for the combined antitumor activity of UFT and TAM.

Answer 54:

### Bibliographic Information

**Implications of tamoxifen metabolism in the athymic mouse for the study of antitumor effects upon human breast cancer xenografts.** Robinson, Simon P.; Langan-Fahey, Susan M.; Jordan, V. Craig. Dep. Hum. Oncol., Univ. Wisconsin, Madison, WI, USA. *European Journal of Cancer & Clinical Oncology* (1989), 25(12), 1769-76. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 112:229366 AN 1990:229366 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The metab. of tamoxifen in the human has been well established and may be important in the antiestrogenic activity of this agent. This study exams. whether tamoxifen metab. in the athymic mouse xenograft model is similar to tamoxifen metab. in the breast cancer patient. Serum taken from athymic mice 24 h after a single large oral dose (200 mg/kg) of tamoxifen contained compds. corresponding to stds. of tamoxifen, 4-hydroxytamoxifen, N-demethyltamoxifen, 4-hydroxy-N-demethyltamoxifen and tamoxifen N-oxide when analyzed by HPLC. The administration of large single doses (200 mg/kg) of 4-hydroxytamoxifen and N-demethyltamoxifen either alone or in combination produced the expected peaks for the administered agents and a peak confirming the identity of 4-hydroxy-N-demethyltamoxifen. 4-Hydroxy-N-demethyltamoxifen was detected in serum from six of 10 breast cancer patients receiving 10 mg tamoxifen twice daily. These patients had tamoxifen, 4-hydroxytamoxifen and N-demethyltamoxifen levels of 108, 2.6, and 238 ng/mL, resp. Repeated large oral doses (200 mg/kg/day for 6 days) of tamoxifen to athymic mice produced a similar array of serum metabolites as seen after the single dose and in the breast cancer patient. However, levels of 4-hydroxytamoxifen (628 ng/mL) were similar to those of tamoxifen (441 ng/mL), whereas N-demethyltamoxifen (1343 ng/mL) levels were 2-3 times greater. A similar pattern of metabolites was produced with a 50-mg/kg dose of tamoxifen although levels were considerably reduced. S.c. administration of tamoxifen (200 mg/kg/day for 6 days) produced serum levels of the parent compd. (120 ng/mL) in the same range as tamoxifen levels in the breast cancer patient. However, although N-demethyltamoxifen was the major metabolite, levels (115 ng/mL) were equiv. only to those of tamoxifen itself, and 4-hydroxytamoxifen levels (26 ng/mL) were appreciably higher than those in the breast cancer patient. Lowering the dose of tamoxifen (50 mg/kg) administered s.c. produced not only lower circulating tamoxifen levels (41 ng/mL) but also changed the metabolite profile. Rather than N-demethyltamoxifen levels equiv. to those of tamoxifen, as seen with the higher dose, they were reduced to those of 4-hydroxytamoxifen (7 ng/mL). Low levels of both N-demethyltamoxifen and 4-hydroxytamoxifen compared to the parent compd. were characteristic of metabolite profiles produced by 0.25-, 1.25- or 2.5-cm silastic capsules releasing an av. of 53, 84 and 192 µg tamoxifen per day, resp. These capsules demonstrated their ability to inhibit 17β-estradiol-stimulated MCF-7 tumor growth in a dose-related manner. The largest capsule (2.5 cm) produced serum levels of tamoxifen (51.8 ng/mL), 4-hydroxytamoxifen (3.5 ng/mL) and N-demethyltamoxifen (3.8 ng/mL) which were sufficient to produce complete inhibition of tumor growth. The athymic mouse hydroxylates oral tamoxifen more readily than the human and therefore produces a different metabolite profile.

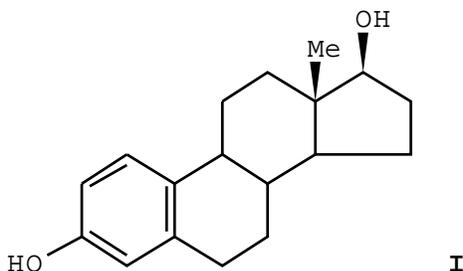
Answer 55:

### Bibliographic Information

**Experimental hormonal treatment of human ovarian carcinomas xenotransplanted in nude mice.** Kleine, W.; Fuchs, A.; Niederstadt, T.; Teufel, G.; Pfeleiderer, A. Universitaetsfrauenklin., Freiburg, Fed. Rep. Ger. Editor(s): Bastert, Gunther B.; Fortmeyer, Hans Peter; Schmidt-Matthiesen, Heinrich. Thymusaplastic Nude Mice Rats Clincial Oncol., Proc. Symp. (1981), Meeting Date 1979, 137-43. Publisher: Fischer, Stuttgart, Fed. Rep. Ger CODEN: 46XEAJ Conference written in English. CAN 96:97885 AN 1982:97885 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The effects of medrogestone [977-79-7], gestonorone [2137-18-0], tamoxifen [10540-29-1], and estradiol (I) [50-28-2] were studied on xenotransplanted human ovarian carcinomas in nude mice and the effect correlated with the presence or absence of steroid receptors. Growth of transplanted tumor was independent of the sex of the recipient. Medrogestone increased the growth rate of transplanted tumor independently of the presence of steroid receptor. Tamoxifen and gestonorone produced variable results and had no effect, resp. I affected tumor growth in an estrogen receptor-dependent manner. In receptor pos. tumors, I decreased growth whereas in estrogen receptor neg. tumors it increased growth. Evidently, hormonal treatment is less effective than cytotoxic chemotherapy for ovarian carcinoma xenotransplanted to nude mice.



Answer 56:

### Bibliographic Information

**Dietary flaxseed interaction with tamoxifen induced tumor regression in athymic mice with MCF-7 xenografts by downregulating the expression of estrogen related gene products and signal transduction pathways.** Chen Jianmin; Power Krista A; Mann Jaskaren; Cheng Astor; Thompson Lilian U Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada Nutrition and cancer (2007), 58(2), 162-70. Journal code: 7905040. ISSN:0163-5581. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 17640162 AN 2007422586 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

Our previous short-term study has shown that 10% flaxseed (FS) inhibits the growth of human estrogen dependent estrogen receptor positive breast tumors (MCF-7) xenografts in ovariectomized (OVX) athymic mice and enhances the tumor inhibitory effect of tamoxifen (TAM). This study determined the long-term effect of 5% and 10% FS, with or without TAM, on the growth of MCF-7 xenografts in athymic mice and the potential mechanisms of actions. OVX mice with established MCF-7 tumors were treated with basal diet (control), 5% FS (5FS), 10% FS (10FS), and TAM (5 mg/pellet, 60-day release), alone or in combination, for 16 wk without estrogen supplementation. Tumor growth was monitored weekly. At sacrifice, the tumors were analyzed by immunohistochemistry for cell proliferation, apoptosis, and expression of estrogen-related genes and signal transduction pathways. Both 5FS and 10FS regressed the pretreatment tumor size

by over 90% similar to control. TAM initially regressed the tumors but then induced a regrowth; thus, only a final 6% reduction from pretreatment tumor size was achieved, which was attenuated by combining TAM with 10FS but not with 5FS. TAM combined with 10FS regressed tumors to 55% of pretreatment tumor size due to decreased cell proliferation and increased apoptosis. The expressions of cyclin D1, estrogen receptor alpha, human epidermal growth factor receptor 2, and insulin-like growth factor I receptor in the TAM group were significantly reduced when TAM was combined with 5FS or 10FS. In conclusion, after long-term treatment, FS did not stimulate tumor growth and combined with TAM, regressed tumor size in part due to downregulation of the expression of estrogen-related gene products and signal transduction pathways.

Answer 57:

#### **Bibliographic Information**

##### **Efficacy of selective estrogen receptor modulators in nude mice bearing human transitional cell carcinoma.**

Sonpavde Guru; Okuno Norihiko; Weiss Heidi; Yu Jiang; Shen Steven S; Younes Mamoun; Jian Weiguo; Lerner Seth P; Smith Carolyn L U.S. Oncology Research, Webster, Texas, USA Urology (2007), 69(6), 1221-6. Journal code: 0366151. E-ISSN:1527-9995. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17572228 AN 2007359074 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

**OBJECTIVES:** To evaluate estrogen receptors as a therapeutic target for human bladder cancer. **METHODS:** The ability of the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene to inhibit 5637 human transitional cell carcinoma cell proliferation was determined in vitro and in xenograft studies using 5637 cells in female athymic BALB/c nu/nu mice. **RESULTS:** Treatment with tamoxifen, raloxifene, or the pure antiestrogen ICI 182,780 inhibited proliferation of 5637 cells in vitro. In the first xenograft study, raloxifene (10, 100, or 1000 microg/day) administered by oral gavage inhibited the growth of tumors compared with placebo or untreated controls ( $P < 0.05$ ). In a second experiment, tamoxifen (8.3, 125, or 1250 microg/day) delivered by time-release pellet inhibited tumor growth compared with placebo-treated controls ( $P < 0.01$ ). A comparison study in which tamoxifen (8.3 or 125 microg/day) or raloxifene (100 microg/day) was administered by slow-release pellet demonstrated that both SERMs reduced growth compared to placebo-treated controls ( $P < 0.05$ ), with comparable effectiveness. There was no detectable tumor in 17 of 30 treated mice. In all studies, average tumor volumes in SERM-treated animals declined over the course of treatment. **CONCLUSIONS:** Selective estrogen receptor modulators inhibit the growth of 5637 transitional cell carcinoma cell xenografts, supporting the rationale to evaluate these agents as targeted therapeutics for patients with urothelial carcinoma.

Answer 58:

#### **Bibliographic Information**

##### **Tamoxifen increases apoptosis but does not influence markers of proliferation in an MCF-7 xenograft model of breast cancer.**

Hawkin R A; Arends M J; Ritchie A A; Langdon S; Miller W R Edinburgh Breast Unit Research Group, The Medical School, Teviot Place, Edinburgh EH8 9AG, UK Breast (Edinburgh, Scotland) (2000), 9(2), 96-106. Journal code: 9213011. ISSN:0960-9776. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 14731708 AN 2004031576 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

#### **Abstract**

Twenty-four nude mice bearing MCF-7 breast cancer cells grown as xenografts and treated with tamoxifen (2.5 mg slow-release pellet) were studied for up to 35 days. Tumour size was measured in 2 dimensions at regular time-intervals and tumours were harvested on each of days 2, 4, 7, 14, 28 and 35 after the start of treatment. Control animals (8) received no treatment and the tumours were harvested after 0 or 35 days. Tumour sections were assessed for

prevalence of apoptosis and mitosis and examined immunocytochemically for Ki(67)(MIB-1) and bcl-2 expression. Tumours increased in size during tamoxifen-treatment, but at a significantly slower rate (max. 2.6-fold) than in the untreated control animals; thus tumours not actually regressing may, nevertheless, be responding significantly to tamoxifen. MIB-1 and bcl-2 immunostaining and mitosis failed to show any consistent change over the period of study. Apoptosis, however, increased progressively and significantly to day-28 in tamoxifen-treated tumours, reaching approximately a 5-fold increase over day-0 values, then decreasing again to nearly 3-fold by day-35 ( $P = 0.0002$ ). The apoptosis: mitosis ratio in treated tumours also increased to approximately 10-fold on day-28 over day-0 values, decreasing to nearly 4-fold by day-35 ( $P = 0.037$ ). Within the treated group, apoptosis was significantly inversely correlated with both mitosis ( $R = -0.38$ ,  $P = 0.03$ ) and expression of bcl-2 ( $R = -0.48$ ,  $P = 0.0056$ ) and strongly positively correlated with both time on tamoxifen ( $R = +0.63$ ,  $P = 0.0003$ ) and the % inhibition of growth by tamoxifen ( $R = +0.58$ ,  $P = 0.0012$ ) in the 28 individual, treated tumours (estimated relative to the mean growth rate in the controls). The apoptosis: mitosis ratio was also inversely correlated with bcl-2 expression ( $R = -0.56$ ,  $P = 0.0021$ ) and positively correlated with both time on tamoxifen ( $R = +0.50$ ,  $P = 0.0068$ ) and % inhibition of growth ( $R = +0.56$ ,  $P = 0.0019$ ).

In this hormone-sensitive tumour model for breast cancer, in which tamoxifen caused inhibition rather than regression, it was not possible to detect significant changes in the marker proteins Ki(67) and bcl-2, or in the prevalence of mitosis in relation to treatment; these factors may therefore not be accurate indices of response to tamoxifen in all situations. By contrast, however, tamoxifen induced a significant, early increase in the prevalence of apoptosis associated with inhibition of tumour growth and an inverse relationship in both mitosis and bcl-2 expression, suggesting that apoptosis may be an accurate and sensitive early marker of even a moderate response to tamoxifen.

Answer 59:

### Bibliographic Information

**Statistical analysis of array expression data as applied to the problem of tamoxifen resistance.** Comment in: J Natl Cancer Inst. 1999 Mar 3;91(5):400-1. PubMed ID: 10070933 Hilsenbeck S G; Friedrichs W E; Schiff R; O'Connell P; Hansen R K; Osborne C K; Fuqua S A Department of Medicine, The University of Texas Health Science Center, San Antonio 78248-7884, USA Journal of the National Cancer Institute (1999), 91(5), 453-9. Journal code: 7503089. ISSN:0027-8874. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 10070945 AN 1999168493 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

**BACKGROUND:** Although the emerging complementary DNA (cDNA) array technology holds great promise to discern complex patterns of gene expression, its novelty means that there are no well-established standards to guide analysis and interpretation of the data that it produces. We have used preliminary data generated with the CLONTECH Atlas human cDNA array to develop a practical approach to the statistical analysis of these data by studying changes in gene expression during the development of acquired tamoxifen resistance in breast cancer. **METHODS:** For hybridization to the array, we prepared RNA from MCF-7 human breast cell tumors, isolated from our athymic nude mouse xenograft model of acquired tamoxifen resistance during estrogen-stimulated, tamoxifen-sensitive, and tamoxifen-resistant growth. Principal components analysis was used to identify genes with altered expression. **RESULTS AND CONCLUSIONS:** Principal components analysis yielded three principal components that are interpreted as 1) the average level of gene expression, 2) the difference between estrogen-stimulated gene expression and the average of tamoxifen-sensitive and tamoxifen-resistant gene expression, and 3) the difference between tamoxifen-sensitive and tamoxifen-resistant gene expression. A bivariate (second and third principal components) 99% prediction region was used to identify outlier genes that exhibit altered expression. Two representative outlier genes, erk-2 and HSF-1 (heat shock transcription factor-1), were chosen for confirmatory study, and their predicted relative expression levels were confirmed in western blot analysis, suggesting that semiquantitative estimates are possible with array technology. **IMPLICATIONS:** Principal components analysis provides a useful and practical method to analyze gene expression data from a cDNA array.

The method can identify broad patterns of expression alteration and, based on a small simulation study, will likely provide reasonable power to detect moderate-sized alterations in clinically relevant genes.

Answer 60:

**Bibliographic Information**

**Hormonal regulation of proliferation and transforming growth factors gene expression in human endometrial adenocarcinoma xenografts.** Gong Y; Murphy L C; Murphy L J Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada The Journal of steroid biochemistry and molecular biology (1994), 50(1-2), 13-9. Journal code: 9015483. ISSN:0960-0760. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8049128 AN 94325185 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

We have previously shown that estrogen and progestins regulate both cellular proliferation and transforming growth factor (TGF) expression in human endometrial adenocarcinoma cells in vitro. In the current study we examined the regulation of TGF- $\alpha$  and - $\beta$  1 expression in endometrial adenocarcinoma xenografts. Four human endometrial adenocarcinoma cell lines were inoculated into female BALB/c nude mice. Administration of 17  $\beta$ -estradiol (E2) increased tumor size in intact mice inoculated with Ishikawa, HEC-50 and HEC-1B cells but inhibited growth of HEC-1A xenografts. 4-Hydroxy tamoxifen (OH-Tam) had similar effects to E2 in animals carrying Ishikawa and HEC-1A cell xenografts but had no significant effect on growth of HEC-50 or HEC-1B xenografts. In intact mice inoculated with OH-Tam pellets and Ishikawa cells, the tumors were larger and had lower levels of TGF- $\alpha$  mRNA than in untreated or E2 treated mice. In mice carrying Ishikawa, HEC-50 and HEC-1B cell xenografts none of the hormones or agents tested altered TGF- $\beta$  1 mRNA levels. In contrast, both E2 and OH-Tam significantly increased xenografts TGF- $\beta$  1 mRNA levels in HEC-1A xenografts as well as significantly reduced tumor size. Medroxyprogesterone acetate (MPA) had no effect on tumor size of Ishikawa, HEC-1A and HEC-1B cell xenografts but significantly increased the size of HEC-50 xenografts. MPA significantly reduced TGF- $\alpha$  expression in Ishikawa cell xenografts but had no effect in the other cell xenografts. MPA had no effect on TGF- $\beta$  1 expression in any of the xenografts. These observations demonstrate a discordance between the hormonal effects on TGF expression and cellular proliferation and argue against a major role for the TGFs in regulation of human endometrial adenocarcinoma cell proliferation in vivo.

Answer 61:

**Bibliographic Information**

**Experimental chemoendocrine therapy of human breast carcinoma xenograft serially transplanted into nude mice.** Watanabe O Department of Surgery, Tokyo Women's Medical College Daini Hospital Nippon Geka Gakkai zasshi (1994), 95(4), 263-70. Journal code: 0405405. ISSN:0301-4894. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7910941 AN 94254805 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

The antitumor effect of combined chemoendocrine therapy with tamoxifen (TAM) and 5-fluorouracil (5-FU) on breast carcinoma xenograft (R-27), serially transplanted into the nude mice, was examined from the aspect of estrogen receptors (ER) and cytological features. The mice were given 6 intramuscular injections of TAM (5mg/kg) at 3-day intervals (TAM group), 3 intraperitoneal injections of 5-FU (60 mg/kg) at 4-day intervals ((5-FU group), or a combination of the two drugs (combined group). When the tumor was resected on 21 days after the initial treatment, the ER were assayed and %S was determined by flowcytometry. Furthermore, proliferative cell nuclear antigen (PCNA) was stained, and the stained cells were counted. A synergistic antitumor effect of TAM and 5-FU was found in mice given combined therapy. Reduction in the ER level was more marked in this group than in the others, but there were no significant differences in the %S value or the ratio of PCNA positive cells among the three treated groups. These results suggest that the combined effect of TAM and 5-FU has no relation to the inhibition of DNA synthesis.

Answer 62:

**Bibliographic Information**

**Immuno-biochemical assay for determination of nuclear steroid receptors during tamoxifen therapy.** Vering A; Vockel A; Stegmuller M; Bender H G Department of Gynecology, University Medical Center, Frankfurt am Main, Germany Journal of cancer research and clinical oncology (1993), 119(7), 415-20. Journal code: 7902060. ISSN:0171-5216. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8491762 AN 93260000 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

The exact knowledge of hormone receptor status is critical for therapeutic strategies in hormone-dependent tumors. The influence of tamoxifen on estrogen receptor concentration has to be taken into account when evaluating results in tamoxifen-treated patients. We studied the receptor modulation of tumors xenotransplanted into nude mice (one breast and one endometrial carcinoma) after injection of 50 micrograms tamoxifen/mouse. To differentiate between unoccupied and occupied receptors, determinations were done by an enzyme immunoassay for the estrogen receptor under low- and high-salt extraction. With low-salt extraction we found a temporary decrease of the estrogen receptor concentration within the first hours after tamoxifen treatment. This decrease lasted for several days before recovery to pretreatment levels occurred. The hormone-receptor complexes, tightly bound to acceptor sites of the DNA, increased more than 15 times within 24 h. These values remained at increased levels for 2-7 days, after which a decrease to initial level was observed.

Answer 63:

**Bibliographic Information**

**Transforming growth factor beta 1 is implicated in the failure of tamoxifen therapy in human breast cancer.** Thompson A M; Kerr D J; Steel C M Department of Surgery, Royal Infirmary, Edinburgh, UK British journal of cancer (1991), 63(4), 609-14. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2021547 AN 91214827 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

Transforming growth factor-beta 1 (TGF-beta 1) is inhibitory for breast epithelial cells in vitro and treatment of breast cancer cell lines with tamoxifen results in a rise in TGF-beta 1 mRNA expression with associated inhibition of cell growth. To study whether these findings apply in vivo we examined TGF-beta 1 mRNA expression in an oestrogen-dependent mouse xenograft system following systemic treatment of the mice with tamoxifen. In agreement with in vitro studies. TGF-beta 1 mRNA expression was sustained at high levels and associated with a reduction in tumour size. A subsequent study of breast tumour tissue from 56 patients demonstrated high levels of TGF-beta 1 mRNA in 45 of the tumours. High expression was found to correlate with premenopausal status, but not with tumour oestrogen receptor content or other parameters. In a subgroup of 11 patients who had received tamoxifen therapy for 3 to 6 months prior to surgery, unexpectedly high levels of TGF-beta 1 mRNA were demonstrated in tumours increasing in size and unresponsive to tamoxifen. Data from this study indicate that in patients with breast cancer, TGF-beta 1 in the tumour may not behave as in vitro and xenograft studies have suggested. We speculate that failure of tamoxifen therapy may be due to failure of the autocrine inhibitory functions of TGF-beta 1 either alone or in combination with paracrine stimulation of stromal cells or angiogenesis and localised immunosuppression. Further studies of active TGF-beta 1, TGF-beta receptors and the interactions with other growth factors will be required to elucidate the precise role of TGF-beta 1 in human breast cancer and in the failure of tamoxifen therapy.

Answer 64:

**Bibliographic Information**

**Effects of tamoxifen and somatostatin analogue on growth of human medullary, follicular, and papillary thyroid carcinoma cell lines: tissue culture and nude mouse xenograft studies.** Weber C J; Marvin M; Krekun S; Koschitzky T; Karp F; Benson M; Feind C R Department of Surgery, College of Physicians and Surgeons, Columbia University, New York, NY 10032 Surgery (1990), 108(6), 1065-71. Journal code: 0417347. ISSN:0039-6060. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1978945 AN 91062840 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### Abstract

The knowledge that (1) the normal thyroid contains somatostatin, (2) polypeptide growth factors influence thyroid cell function, and (3) thyroid cells contain steroid hormone receptors prompted us to add somatostatin analogue No. 201-995 (SMS) (5 ng/ml) and/or tamoxifen citrate (TAM) (5  $\mu$ mol/L) to 7-day monolayer cultures (50,000 cells/well) of three separate human thyroid carcinoma cell lines: DR081 (medullary), WR082 (follicular), and NPA'87 (papillary). Results, tabulated as cell numbers/well ( $\times 10^5$ ) on day 7, revealed that TAM inhibited growth of medullary and follicular cells and that TAM plus SMS inhibited growth of papillary cells. In vivo studies of subcutaneous tumor cell xenografts in nude mice have documented that TAM (5 mg subcutaneous pellet) significantly inhibits the growth of medullary implants. Flow cytometric DNA studies of medullary cell cultures demonstrated a reduced G2 + M phase with TAM treatment. For papillary cell implants, TAM plus SMS (5 micrograms subcutaneously, twice daily) did not suppress tumor growth. All three cell lines were negative for estrogen receptor; addition of estradiol (5 ng/ml) to medullary cell cultures neither stimulated replication nor reversed the inhibitory effects of TAM in vitro. We conclude that (1) TAM slowed the growth of a cell line of human medullary carcinoma, both in vitro and in vivo; (2) this effect was not reversed by estradiol; (3) TAM plus SMS inhibited replication of a papillary carcinoma cell line in vitro, but not in vivo; and (4) TAM alone and TAM plus SMS inhibited replication of cultures of a human follicular thyroid carcinoma cell line. TAM and SMS may be useful in treatment of some human thyroid carcinomas.