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First experience with gosereline and ibandronate as medical prevention in premenopausal patients with increased familiary breast cancer risk: The GISS study

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Surgical ovarectomy can decrease the risk for the development of breast cancer in premenopausal BRCA mutation carriers to approx. 50% (Rebbeck, 1999). Does temporary medical suppression of ovarian function provide an alternative with a higher acceptance by the affected women? In this randomised phase II study 100 premenopausal participants (P) with a life time risk for breast cancer of > 25% are planned to receive either a medical prevention with Goserelin 3.6 mg/4 weeks and Ibandronate 2 mg/12 weeks for 2 years or only intensified breast cancer surveillance according to standard recommendations. Primary aims of the GISS study are acceptance and compliance of this kind of medical prevention. Approximately 10% of the invited women have agreed to the participation in the trial. Up to now 30 P (13 with treatment and 17 as a control) have been included in this trial in 8 active centres. One patients has withdrawn consent directly after randomisation. A known BRCA mutation is present in 4 P. In the other P the familiarly risk can be described as: 1st degree relative with known BRCA mutation (1), 1st degree relative with breast cancer < 35 years (4), 1st degree relative with bilateral breast cancer < 50 years (2), More than 2 relatives with breast cancer, one < 50 years (11), 1st degree relative with ovarian cancer < 40 years (3), 1st degree relative with breast cancer < 35 and > 2 relatives with breast cancer (2),1st degree relative with bilateral breast cancer and > 2 relatives with breast cancer (3). Two or 3 affected 1st degree relatives are present in 7 and 5 P, respectively. The median duration on treatment by now is 12.3 months. Reported side effects (grade 2-4) are headache (11), orthostatic dysfunction (5), hot flashes (4), pain (4), menstrual spotting (4), vaginal dryness (2), nausea (1), myalgia (1), insomnia (1), fatigue (1). Up to now only one P has discontinued treatment due to pain in relation to the application of Ibandronate. Acceptance to a medical prevention with Gosereline and Ibandronate is low, however compliance and side effects of this intervention appears to be favourable. Medical prevention may present an alternative to surgical ovarectomy, if efficacy can be proven to be equivalent.

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Pineal hormone melatonin as a modificator of a sensitivity of cancer cells to cisplatin

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Background: Cisplatin-based combination chemotherapy displays significant antitumor activity against cancers of the testis, ovary, head and neck, and also lung. Despite its success against testicular cancer, its effectiveness in the treatment of other cancers is more limited because of acquired or intrinsic resistance. We considered of interesting to study whether melatonin may or may not play a role an sensitivity of cancer cells to cisplatin.

Methods and materials: The oncostatic effects of melatonin have been studied both in vitro and in vivo. In vitro by using MCF-7 human breast cancer cell line (cis-DDP-sensitive and cis-DDP- resistant (4-fold) cells) as a model, and in vivo by using metastatic Lewis lung carcinoma (3LL) in mice C57Bl/6. Cell proliferation rates were detected after melatonin (Sigma, USA) and cisplatin (Ebewe, Austria) treatment upon short-term and long-term incubation. Quantification of hormone status of MCF-7/S or MCF-7/DDP4 cells was performed using EnVision system (Dako, Denmark).

Results: It was shown that upon long incubation (5th day) with melatonin in a concentration range 0,01-1nM, an inhibition of the growth of the resistant human cell line was registered. The growth of parental MCF-7/S cells was inhibited only at the highest dose of hormone (1nM). Moreover, the incubation MCF-7/S and MCF-7/DDP4 with melatonin simultaneously with cisplatin significantly increased the cytotoxical index, compared to cisplatin applied alone. The cytotoxic effect was more cleally indicated in MCF-7/DDP4 cells upon long-termed incubation. Moreover, melatonin administration changed the expression of progesteron and estrogen receptors, p53 or bcl-2 proteins and E-cadherin on MCF-7/S and MCF-7/DDP4. In in vivo condition melatonin enhanced the sensitivity of resistant 3LL cells to cisplatin.

Conclusion: The data suggests that melatonin could exerts its oncostatic action toward cisplatin-resistant tumor cells as well in vivo as in vitro. The results lends supports for a possible role of melatonin as a modificator of cancer cells sensitivity.

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The chemopreventive effect of garlic on tumorigenesis

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The cancer inhibitory effects of garlic has been claimed for years. In our labaoratory, we demonstrated that garlic possessed chemopreventive ability both in vivo and in vitro investigations, such as, garlic inhibited DMBA induced cheek pouch carcinoma in hamsters; and; garlic protected NIH3T3 cells from carcinogen transformation, etc. Therefore, in this study, we

further detected the mechanisms of garlic's inhibitory effects on cell transformation. Both NIH3T3 cells and garlic treated human oral carcinoma cells were cultured in the 5% CO2 incubator at 37°C. NIH3T3 cells were treated first with various concentrations of garlic extracts and followed by the chemical carcinogen DMBA. All of the cells were then extracted for purified DNA, and, thin-layer chromatography was performed for DNA-adduct analysis. The alterations of DNA-adduct in NIH3T3 cells, carcinoma cells, and garlic treated cells were clearly recognized. It indicates that the mechanism of chemopreventive efficacy of garlic on cell transformation might be related to DNA stereochemistry.

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Cancer prevention by selenium

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In 1993 the results of the nutrition intervention trial performed in Linxian were published (J Natl Cancer Inst 85: 141-149). The observation of 29,584 randomly assigned participants who were supported with micronutrients over 5 years resulted in a significant reduction of cancers in the selenium, β-carotin, and a-tocopherol group. In the Clark study (JAMA 1996;276:1957-63) a total of 1312 patients with skin tumors were randomized on 200 ug of yeast selenium or placebo for 4.5 yr of treatment and 6.5 yr of observation. Total cancer mortality was 50% less in the selenium vs placebo group (p 0.002). Relative to the placebo group the selenium group had 37% less total cancers, 63% less prostate cancer, 64% less colorectal cancer, and 46% less lung cancer. As far as the mechanism of tumor prevention by selenium is concerned there are several mechanisms under discussion. Selenium as part of the selenium-dependent enzymes like GSHPx protects cells against the DNA damage caused by reactive oxigen species. Further effects of selenium are the activation of DNA repair, modulation of cell division, therby inhibiting rapid cell growth, and the development of mutations and mistakes of DNA replication. A recently published paper by Seo et al. (PANAS 2002;99:14548-53) indicates that maintenance of genomic stability by p53 can be separated from ist growth suppressor or pro-apoptotic functions and may involve direct activation of DNA repair machinery. This is achieved by p53 interaction with a selenium containing compound. Seo et al. found that incubation with slenomethionine (SeMet) results in an unusual activation of p53 in cultured cells:a reduction of two specific cysteine residues within p53 leads to a conformational shift and induction of p53 DNA binding activity. This procedure requires a cellular protein Ref 1, a known redox factor that interacts with p53. Thus p53 becomes capable of activating DNA repair without affecting cell growth. Hence, p53 can contribute to genomic stability not only by elimina- ting damaged cells, but also through directly activating a DNA repair system,converting from a killer to a healer (Gudkov Nature Med 2002;8:1196-98).

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Progesterone receptor antagonists an alternative for breast cancer prevention

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The biological activity of progesterone is mediated by the progesterone receptor (PR), which induces a cascade of transcriptional events, critical for maintenance and development of female reproductive organs. Blocking PR function by using a PR-antagonist allows the modulation of various endocrine processes which also might be responsible for gynecological or oncological diseases. It is well known that progesterone, in physiological concentrations participate in the proliferation of mammary carcinomas. Therefore it is obvious that antiprogestins can block the growth of breast tumors functionally expressing the PR. We describe the pharmacological characterization of a novel, highly potent PR-antagonist, that has a considerable potential for therapeutic intervention in breast cancer. The PR-antagonist showed high antiprogestagenic activity in vitro on both PR isoforms PR-A and PR-B. This high antiprogestagenic activity could also be demonstrated in several in vivo models. Subsequent experiments with breast cancer models showed a strong antiproliferative activity. In the nitroso-methylurea (NMU) and dimethyl-benzanthracene (DMBA)-induced mammary tumor models in the rat, treatment with the PR-antagonist completely suppressed the growth of established tumors and prevented the development of breast tumors when given prophylactic. Induction of tumor cell apoptosis was also found in our studies. The ability of these compounds to induce tumor cell differentiation that leads to apoptosis is unique among all other endocrine therapeutics. Our results revealed that the biological response to a progesterone antagonist does not seem to be only the result of competition of progesterone but rather may be accompanied by additional mechanisms. With these pharmacological properties a PR-antagonist may be a promising new option for clinical breast cancer therapy.

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Novel marine compounds - antitumor or genotoxic: Role of endpoint biomarkers

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In the past two decades, thousands of novel marine compounds and their derivatives have been reported with diverse biological activities ranging from antiviral to antitumor. However, till date not a single anticancer drug was commercially developed. Based on the preliminary anticancer activities, many