Cancer and Hormone Literatures

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death.Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researched on the cancer and the.
[Smith MH. **Cancer and Hormone Literatures.** *Cancer Biology* 2012;2(3):133-209]. (ISSN: 2150-1041). http://www.cancerbio.net. 8

Keywords: cancer; biology; life; disease; research; literature; hormone

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Akimoto, T., Y. Kitamoto, et al. (2004). "External beam radiotherapy for clinically node-negative, localized hormone-refractory prostate cancer: impact of pretreatment PSA value on radiotherapeutic outcomes." Int J Radiat Oncol Biol Phys **59**(2): 372-9.

PURPOSE: To analyze the results of clinically node-negative, localized hormone-refractory prostate cancer treated with external beam radiotherapy (EBRT) and to investigate the potential prognostic factors that influenced the therapeutic outcome. METHODS AND MATERIALS: Fifty-three patients who had developed localized hormone-refractory prostate cancer were treated with EBRT between 1994 and 2001. According to the 1992 American Joint Committee on Cancer clinical stage, 4 patients had T2 and 49 had T3 at the start of RT, and 14 patients had a Gleason score <7, 14 had a Gleason score of 7, and 23 had a Gleason score of 8-10. All patients were treated with EBRT using the unblocked oblique four-field technique, with a total dose of 69 Gy. The fraction dose was 3 Gy three times weekly. The median follow-up after RT was 35 months (range, 8-96 months) and after androgen ablation was 73 months (range, 42-156 months). RESULTS: Of 53 patients, 15 patients subsequently developed clinical relapse, including locoregional and/or distant metastases. The site of first relapse was bone metastasis in 10, lymph nodes in 3, and local failure in 2 patients; 3 patients died of prostate cancer during the analysis period. The 3-year and 5-year cause-specific survival rate was 94% and 87%, respectively, and the 3-year and 5-year clinical relapse-free survival rate was 78% and 56%, respectively. The univariate analysis revealed that a short prostate-specific antigen (PSA) doubling time and high PSA value at the start of RT and a high Gleason score were statistically significant factors for the risk of clinical relapse. Multivariate analysis demonstrated that the PSA value (PSA <or=15 vs. >or=15 ng/mL) at the start of RT was an independent prognostic factor. CONCLUSION: EBRT could be a treatment of choice for clinically node-negative, localized, hormone-refractory prostate cancer.

Albergaria, A., J. Paredes, et al. (2009). "Expression of FOXA1 and GATA-3 in breast cancer: the prognostic significance in hormone receptor-negative tumours." Breast Cancer Res **11**(3): R40.

INTRODUCTION: The expression of additional genes, other than oestrogen receptor (ER), may be important to the hormone-responsive phenotype of breast cancer. Microarray analyses have revealed that forkhead box A1 (FOXA1) and GATA binding protein 3 (GATA-3) are expressed in close association with ERalpha, both encoding for transcription factors with a potential involvement in the ERalpha-mediated action in breast cancer. The purpose of this study was to explore if the expression of FOXA1 and GATA-3 may provide an opportunity to stratify subsets of patients that could have better outcome, among the ERalpha-negative/poor prognosis breast cancer group. METHODS: We evaluate FOXA1 and GATA-3 expression in 249 breast carcinomas by immunohistochemistry, associating it with breast cancer molecular markers, clinicopathological features and patient's survival. The

clinicopathological features and immunohistochemical markers of the tumours were compared using the chi-square test and ANOVA. Disease-free survival was analysed through Kaplan-Meier survival curves and Cox regression. RESULTS: FOXA1 expression was demonstrated in 42% of invasive carcinomas, while GATA-3 was detected in 48% of the cases. FOXA1 expression was inversely associated with tumour size, Nottingham Prognostic Index, histological grade, lymph vascular invasion, lymph node stage and human epidermal growth factor receptor-2 (HER-2) overexpression, while GATA-3 expression showed inverse association with histological grade and HER-2. Both FOXA1 and GATA-3 were directly associated with ERalpha and progesterone receptor. Among FOXA1-positive tumours, 83.1% are comprised in the luminal A subtype, similar to GATA-3 where 87.7% of positive tumours were classified within this molecular subtype. In the subset of ERalpha-negative patients, those who were FOXA1-negative had a 3.61-fold increased risk of breast cancer recurrence when compared with the FOXA1-positive. CONCLUSIONS: FOXA1 was a significant predictor of good outcome in breast cancer, whereas GATA-3 was an important luminal marker. The expression of FOXA1 may be used for risk stratification among ERalpha-negative patients.

Alfano, C. M., B. A. McGregor, et al. (2006). "Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors." Psychooncology **15**(11): 985-1000.

Hormone-related symptoms are common in breast cancer survivors and many aspects of these symptoms are currently under study. Reliable and valid assessment tools are needed to successfully study hormone-related symptoms in breast cancer survivors; however, no gold standard currently exists for measuring these symptoms. This study evaluated the psychometric properties of a shortened version of the Breast Cancer Prevention Trial (BCPT) symptom checklist in a sample of 803 breast cancer survivors. Principal factor analysis with Promax oblique rotation revealed a five-factor structure, identifying five separate hormone-related symptoms scales: vasomotor symptoms, urinary incontinence, cognitive/mood changes, vaginal symptoms, and weight gain/appearance concern. Hormone-related symptom scale scores differed by demographic and clinical characteristics according to expectations, suggesting that these five scales from the shortened BCPT checklist are reasonably reliable and valid. Symptom scale scores were only weakly correlated with health-related quality of life scores; however, the pattern of results generally supported the validity of the symptom scales. This study adds to the evidence that breast cancer survivors experience a significant number of hormone-related symptoms. Future clinical trials and quality of life and symptom management intervention studies would benefit from accurate assessment of hormone-related symptoms with the five scales from the shortened BCPT checklist.

Andrzejewski, T., D. Deeb, et al. (2008). "Therapeutic efficacy of curcumin/TRAIL combination regimen for hormone-refractory prostate cancer." Oncol Res **17**(6): 257-67.

Because of lack of effective treatment options for hormone-refractory prostate cancer at the present time, the need for developing novel therapeutic strategies and targets to treat and prevent the progression of hormone-sensitive prostate cancer to the hormone-refractory stage is paramount. Our previous in vitro studies have shown that curcumin sensitizes both hormone-sensitive and hormone-resistant prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and that combined curcumin/TRAIL treatment induces apoptosis in cancer cells by inhibiting antiapoptotic p-Akt and nuclear factor-kappaB (NF-kappaB). In the present study, we demonstrate that curcumin and TRAIL combination regimen is also the most effective treatment for inhibiting the growth of PC3 xenografts compared to curcumin or TRAIL monotherpy. The inhibition of PC3 tumors by combined treatment correlated with significant reduction in expression of p-Akt and NF-kappaB in tumor tissue. Furthermore, tumor growth inhibition by curcumin/TRAIL combination regimen was associated with significant decrease in cell proliferation and an increase in terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells in the tumors without significant change in microvessel density. Based on the significant efficacy in this preclinical model, combined curcumin/TRAIL regimen may be an effective adjuvant therapy for hormone-refractory prostate cancer.

Aziz, M. H., N. E. Dreckschmidt, et al. (2008). "Plumbagin, a medicinal plant-derived naphthoquinone, is a novel inhibitor of the growth and invasion of hormone-refractory prostate cancer." Cancer Res **68**(21): 9024-32.

Prostate cancer (PCa) is the second leading cause of cancer-related deaths in men. Hormone-refractory invasive PCa is the end stage and accounts for the majority of PCa patient deaths. We present here that plumbagin (PL), a quinoid constituent isolated from the root of the medicinal plant Plumbago zeylanica L., may be a potential novel agent in the control of hormone-refractory PCa. Specific observations are the findings that PL inhibited PCa

cell invasion and selectively induced apoptosis in PCa cells but not in immortalized nontumorigenic prostate epithelial RWPE-1 cells. In addition, i.p. administration of PL (2 mg/kg body weight), beginning 3 days after ectopic implantation of hormone-refractory DU145 PCa cells, delayed tumor growth by 3 weeks and reduced both tumor weight and volume by 90%. Discontinuation of PL treatment in PL-treated mice for as long as 4 weeks did not result in progression of tumor growth. PL, at concentrations as low as 5 micromol/L, inhibited in both cultured PCa cells and DU145 xenografts (a) the expression of protein kinase Cepsilon (PKCepsilon), phosphatidylinositol 3-kinase, phosphorylated AKT, phosphorylated Janus-activated kinase-2, and phosphorylated signal transducer and activator of transcription 3 (Stat3); (b) the DNA-binding activity of transcription factors activator protein-1, nuclear factor-kappaB, and Stat3; and (c) Bcl-xL, cdc25A, and cyclooxygenase-2 expression. The results indicate for the first time, using both in vitro and in vivo preclinical models, that PL inhibits the growth and invasion of PCa. PL inhibits multiple molecular targets including PKCepsilon, a predictive biomarker of PCa aggressiveness. PL may be a novel agent for therapy of hormone-refractory PCa.

Bachelot, T., I. Ray-Coquard, et al. (2003). "Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients." Br J Cancer **88**(11): 1721-6.

Prediction of survival for patients with metastatic breast cancer is often inaccurate and may be helped by new biological parameters. Tumour growth being angiogenesis-dependent, it has been hypothesised that the assessment of angiogenic factor production might reflect the clinical behaviour of cancer progression. This study was designed to investigate the clinical significance of vascular endothelial growth factor (VEGF) and interleukin 6 (IL-6) in hormone-refractory metastatic breast cancer. Serum and plasma concentrations of VEGF and serum concentration of IL-6 were measured in 87 patients with a fully documented history of metastatic breast cancer using an enzyme-linked immunoassay. All patients had detectable levels of VEGF, whereas 39% patients had detectable serum levels of IL-6. There was a positive correlation between IL-6 levels and the theoretical VEGF load of platelets (P<0.001). The presence of high levels of serum IL-6, but not VEGF, was significantly correlated to a shorter survival. In a multivariate analysis along with clinical prognostic parameters, serum IL-6 was identified as an independent adverse prognostic variable for overall survival (P&<0.001). These results indicate that serum IL-6 levels correlate to poor survival in patients with hormone-refractory metastatic breast cancer. Vascular endothelial growth factor serum and plasma levels are not useful indicators of prognosis for these patients.

Bakin, R. E., D. Gioeli, et al. (2003). "Attenuation of Ras signaling restores androgen sensitivity to hormone-refractory C4-2 prostate cancer cells." Cancer Res **63**(8): 1975-80.

Progression of prostate cancer to androgen-refractory disease is correlated with increased expression of growth factors and receptors capable of establishing autocrine and/or paracrine growth-stimulatory loops. Many of these growth factor receptors engage Ras as part of their normal signaling activities, raising the possibility that activation of endogenous c-Ras could be a common mechanism for prostate cancer progression. Here we demonstrate that inducible expression of a dominant negative form of Ras restores androgen sensitivity to a hormone-refractory prostate cancer cell line. We show that expression of RasN17 in the hormone-refractory C4-2 cell line enhances in vitro sensitivity to the growth-inhibitory action of the antiandrogen Casodex and inhibits anchorage-independent cell growth. Moreover, although induction of RasN17 by itself has no observable effect on the growth of C4-2 xenografts in intact male mice, it restores androgen dependence to the C4-2 xenografts so that they dramatically regress after surgical androgen ablation.

Barabutis, N. and A. V. Schally (2008). "Antioxidant activity of growth hormone-releasing hormone antagonists in LNCaP human prostate cancer line." Proc Natl Acad Sci U S A **105**(51): 20470-5.

Hypothalamic growth hormone-releasing hormone (GHRH) controls the release of growth hormone and acts as a growth factor in various tumors. Potent antagonistic analogues of GHRH have been synthesized that strongly suppress the growth of diverse cancers through several mechanisms. However, the influence of GHRH antagonists on the redox (reduction/oxidation) status of cancers has not been investigated. Cellular generation of reactive oxygen species (ROS) is central to redox signaling and is implicated in the initiation, development, and progression of cancer. In this study, we evaluated by Western blot the effects in vitro of GHRH and its antagonist JMR-132 on proliferating cell nuclear antigen, tumor suppressor protein p53, transcription factor NF-kappaB p50 and its phosphorylated form, caspase 3, and cleaved caspase 3 in the LNCaP human prostate cancer cell line. GHRH stimulated and GHRH antagonist inhibited the expression of the major antioxidant enzymes, as well as the expression of COX 2 and cytochrome c oxidase IV, which are

enzymes involved in the generation of ROS. GHRH augmented and GHRH antagonist suppressed lipid and protein oxidative stress markers, as well as the intracellular generation of ROS. In all these tests, GHRH antagonists exerted strong antioxidant activity. Because the metabolism of ROS and oxidative stress have been associated with initiation and progression of not only prostate tumors but also other malignancies, our findings reinforce previous experimental evidence that GHRH antagonists could be useful for cancer therapy.

Barabutis, N. and A. V. Schally (2008). "Knocking down gene expression for growth hormone-releasing hormone inhibits proliferation of human cancer cell lines." Br J Cancer **98**(11): 1790-6.

Splice Variant 1 (SV-1) of growth hormone-releasing hormone (GHRH) receptor, found in a wide range of human cancers and established human cancer cell lines, is a functional receptor with ligand-dependent and independent activity. In the present study, we demonstrated by western blots the presence of the SV1 of GHRH receptor and the production of GHRH in MDA-MB-468, MDA-MB-435S and T47D human breast cancer cell lines, LNCaP prostate cancer cell line as well as in NCI H838 non-small cell lung carcinoma. We have also shown that GHRH produced in the conditioned media of these cell lines is biologically active. We then inhibited the intrinsic production of GHRH in these cancer cell lines using si-RNA, specially designed for human GHRH. The knocking down of the GHRH gene expression suppressed the proliferation of T47D, MDA-MB-435S, MDA-MB-468 breast cancer, LNCaP prostate cancer and NCI H838 non-SCLC cell lines in vitro. However, the replacement of the knocked down GHRH expression by exogenous GHRH (1-29)NH(2) re-established the proliferation of the silenced cancer cell lines. Furthermore, the proliferation rate of untransfected cancer cell lines could be stimulated by GHRH (1-29)NH(2) and inhibited by GHRH antagonists MZ-5-156, MZ-4-71 and JMR-132. These results extend previous findings on the critical function of GHRH in tumorigenesis and support the role of GHRH as a tumour growth factor.

Belochitski, O., S. Ariad, et al. (2007). "Efficient dual treatment of the hormone-refractory prostate cancer cell line DU145 with cetuximab and 1,25-dihydroxyvitamin D3." In Vivo **21**(2): 371-6.

BACKGROUND: Targeting of the epidermal growth factor receptor (EGFR) pathway is a promising treatment strategy for aggressive androgen-refractory prostate cancer (PCa). The effect of treating the androgen-resistant PCa cell line DU145 with a combination of the anti-EGFR drug cetuximab and 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) was evaluated. MATERIALS AND METHODS: DU145 cells were treated with 5 nM cetuximab, 100 nM 1,25(OH)2D3 or a combination of both. The effect of the treatments on cell growth, cell-cycle and apoptosis was evaluated. RESULTS: Single-drug treatments decreased DU145 cell growth by up to 25% and caused a 1.5-to 1.7-fold increase of apoptosis, but did not affect the cell-cycle distribution. However, dual treatment with a combination of cetuximab and 1,25(OH)2D3 inhibited DU145 cell proliferation by 40%, caused considerable cell-cycle arrest in the Go/Gl-phase, and enhanced apoptosis by 2.5-fold (compared to the control, $p < 0.0001$, $p < 0.006$ and $p < 0.0001$, respectively). CONCLUSION: A combination of cetuximab and 1,25(OH)2D3 efficiently suppresses hormone-resistant PCa cell growth and could provide a basis for its clinical application.

Bhatia, V., M. K. Saini, et al. (2009). "EB1089 inhibits the parathyroid hormone-related protein-enhanced bone metastasis and xenograft growth of human prostate cancer cells." Mol Cancer Ther **8**(7): 1787-98.

Parathyroid hormone-related protein (PTHrP) plays a major role in prostate carcinoma progression and bone metastasis. Once prostate cancers become androgen-independent, treatment options become limited. Vitamin D analogues represent a potentially valuable class of agents in this clinical context. Using the prostate cancer cell line C4-2 as a model, we studied the effects of PTHrP and the noncalcemic vitamin D analogue EB1089 on markers of prostate cancer cell progression in vitro and in vivo. C4-2 is a second-generation androgen-independent LNCaP subline that metastasizes to the lymph nodes and bone when injected into nude mice and produces mixed lytic/blastic lesions, mimicking the in vivo situation. We report that PTHrP increases cell migration and invasion, and that a pathway via which EB1089 inhibits these processes is through down-regulation of PTHrP expression. PTHrP also increases anchorage-independent cell growth in vitro and xenograft growth in vivo; EB1089 reverses these effects. The in vivo PTHrP effects are accompanied by increased tumor cell proliferation and survival. Treatment with EB1089 reverses the proliferative but not the antiapoptotic effects of PTHrP. PTHrP also increases intratumor vessel density and vascular endothelial growth factor expression; EB1089 reverses these effects. Intracardially injected C4-2 cells produce predominantly osteoblastic lesions; PTHrP overexpression decreases the latency, increases the severity and alters the bone lesion profile to predominantly osteolytic. EB1089 largely reverses

these PTHrP effects. A direct correlation between PTHrP immunoreactivity and increasing tumor grade is observed in human prostate cancer specimens. Thus, decreasing PTHrP production by treatment with vitamin D analogues may prove therapeutically beneficial for prostate cancer.

Bhuiyan, M. M., Y. Li, et al. (2006). "Down-regulation of androgen receptor by 3,3'-diindolylmethane contributes to inhibition of cell proliferation and induction of apoptosis in both hormone-sensitive LNCaP and insensitive C4-2B prostate cancer cells." Cancer Res **66**(20): 10064-72.

Despite the initial efficacy of androgen deprivation therapy, most patients with advanced prostate cancer eventually progress to hormone-refractory prostate cancer, for which there is no curative therapy. Previous studies from our laboratory and others have shown the antiproliferative and proapoptotic effects of 3,3'-diindolylmethane (DIM) in prostate cancer cells. However, the molecular mechanism of action of DIM has not been investigated in androgen receptor (AR)-positive hormone-responsive and -nonresponsive prostate cancer cells. Therefore, we investigated the effects of B-DIM, a formulated DIM with greater bioavailability, on AR, Akt, and nuclear factor kappaB (NF-kappaB) signaling in hormone-sensitive LNCaP (AR+) and hormone-insensitive C4-2B (AR+) prostate cancer cells. We found that B-DIM significantly inhibited cell proliferation and induced apoptosis in both cell lines. By Akt gene transfection, reverse transcription-PCR, Western blot analysis, and electrophoretic mobility shift assay, we found a potential crosstalk between Akt, NF-kappaB, and AR. Importantly, B-DIM significantly inhibited Akt activation, NF-kappaB DNA binding activity, AR phosphorylation, and the expressions of AR and prostate-specific antigen, suggesting that B-DIM could interrupt the crosstalk. Confocal studies revealed that B-DIM inhibited AR nuclear translocation, leading to the down-regulation of AR target genes. Moreover, B-DIM significantly inhibited C4-2B cell growth in a severe combined immunodeficiency-human model of experimental prostate cancer bone metastasis. These results suggest that B-DIM-induced cell proliferation inhibition and apoptosis induction are partly mediated through the down-regulation of AR, Akt, and NF-kappaB signaling. These observations provide a rationale for devising novel therapeutic approaches for the treatment of hormone-sensitive, but more importantly, hormone-refractory prostate cancer by using B-DIM alone or in combination with other therapeutics.

Bianco, R., R. Caputo, et al. (2004). "Combined targeting of epidermal growth factor receptor and MDM2 by gefitinib and antisense MDM2 cooperatively inhibit hormone-independent prostate cancer." Clin Cancer Res **10**(14): 4858-64.

PURPOSE: The epidermal growth factor receptor (EGFR) may play a relevant role in the progression, hormone therapy resistance, and prognosis of prostate cancer patients. Also MDM2, a negative p53 regulator that interacts with retinoblastoma (Rb), E2F, p19(arf) and the ras-mitogen-activated protein kinase(MAPK) cascade plays an important role in prostate cancer progression and prognosis. On the basis of the EGFR and MDM2 role in integrating signaling pathways critical for prostate cancer progression, we investigated whether their selective combined blockade may have a cooperative antitumor effect in prostate cancer. For this purpose, we have used the EGFR tyrosine kinase inhibitor gefitinib (ZD1839, Iressa) and a second generation hybrid oligonucleotide antisense MDM2 (AS-MDM2), respectively. EXPERIMENTAL DESIGN: Gefitinib and AS-MDM2 were administered to hormone-refractory and hormone-dependent human prostate cancer cells in vitro and to mice bearing tumor xenografts, evaluating the effects on growth, apoptosis, and protein expression, in vitro and in vivo. RESULTS: We demonstrated that the combination of gefitinib and AS-MDM2 synergistically inhibits the growth of hormone-independent prostate cancer cells in vitro. This effect is accompanied by the inhibition of MDM2, phosphorylated Akt (pAkt), phosphorylated MAPK (pMAPK), and vascular endothelial growth factor (VEGF) expression and by Rb hypophosphorylation. The combination of the two agents in nude mice bearing the same hormone-independent tumors caused a potent cooperative antitumor effect. Tumor samples analysis confirmed the inhibition of MDM2, pAkt, pMAPK, VEGF, and basic fibroblast growth factor expression. CONCLUSIONS: This study shows that EGFR and MDM2 play a critical role in the growth of prostate cancer, especially hormone-dependent, and that their combined blockade by gefitinib and AS-MDM2 causes a cooperative antitumor effect, supporting the clinical development of this therapeutic strategy.

Boccardo, F., A. Rubagotti, et al. (2008). "Prednisone plus gefitinib versus prednisone plus placebo in the treatment of hormone-refractory prostate cancer: a randomized phase II trial." Oncology **74**(3-4): 223-8.

BACKGROUND: Abnormal epidermal growth factor receptor expression and pre-clinical data prompted us to investigate the activity of gefitinib, a selective epidermal growth factor receptor tyrosine

kinase inhibitor, in hormone-refractory prostate cancer. METHODS: Eighty-two patients were randomly assigned to receive prednisone plus gefitinib (pG; n = 44) or prednisone plus placebo (ppl; n = 38). On progression, patients initially assigned to placebo were offered the possibility to receive gefitinib. Best prostate-specific antigen response was the primary endpoint. RESULTS: At a median follow-up time of 29.0 months (26.0-32.0), 77 patients progressed and 51 died. Prostate-specific antigen response was recorded in 6/38 (15.8%; 95% CI 4.2-27.4) and in 5/44 (11.4%; 95% CI 2.0-20.8) patients in pG and ppl groups, respectively. There was no difference between groups in time to progression (median pG 4.0 months, range 3.5-4.5; median ppl 4.5 months, range 3.5-5.0) and survival (median pG 26.5 months, range 16.0-37.0; median ppl 20.5 months, range 14.0-27.0). Adverse events occurred in 19 patients in each arm and were generally mild. CONCLUSIONS: pG showed a good tolerability profile but only a limited therapeutic activity in hormone-refractory prostate cancer.

Bogazzi, F., F. Ultimieri, et al. (2004). "Growth hormone inhibits apoptosis in human colonic cancer cell lines: antagonistic effects of peroxisome proliferator activated receptor-gamma ligands." Endocrinology **145**(7): 3353-62.

GH has antiapoptotic effects on several cells. However, the antiapoptotic mechanisms of GH on colonic mucosa cells are not completely understood. Peroxisome proliferator activated receptor-gamma (PPARgamma) activation enhances apoptosis, and a link between GH and PPARgamma in the colonic epithelium of acromegalic patients has been suggested. We investigated the effects of GH and of PPARgamma ligands on apoptosis in colonic cancer cell lines. Colonic cells showed specific binding sites for GH, and after exposure to 0.05-50 nm GH, their apoptosis reduced by 45%. The antiapoptotic effect was due to either GH directly or GH-dependent local production of IGF-1. A 55-85% reduction of PPARgamma expression was observed in GH-treated cells, compared with controls ($P < 0.05$). However, treatment of the cells with 1-50 microm ciglitazone (cig), induced apoptosis and reverted the antiapoptotic effects of GH by increasing the programmed cell death up to 3.5-fold at 30 min and up to 1.7-fold at 24 h. Expression of Bcl-2 and TNF-related apoptosis-induced ligand was not affected by either GH or cig treatment, whereas GH reduced the expression of Bax, which was increased by cig treatment. In addition, GH increased the expression of signal transducer and activator of transcription 5b, which might be involved in the down-regulation of PPARgamma expression. In conclusion, GH may exert a direct antiapoptotic effect on colonic cells, through an increased expression of signal transducer and activator of transcription 5b and a reduction of Bax and PPARgamma. The reduced GH-dependent apoptosis can be overcome by PPARgamma ligands, which might be useful chemopreventive agents in acromegalic patients, who have an increased colonic polyps prevalence.

Bok, R. A., S. Halabi, et al. (2001). "Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: a cancer and leukemia group B study." Cancer Res **61**(6): 2533-6.

Better prognostic markers are needed for hormone-refractory prostate cancer (HRPC) patients. No single biochemical or clinical parameter can reliably predict patient response to therapy or rapidity of disease progression. Peptide factors involved in major cancer growth pathways, such as tumor angiogenesis, are attractive candidates as markers of low- and high-risk HRPC patients. We analyzed prospectively collected urine specimens from 100 of 390 HRPC patients undergoing therapy with the growth factor antagonist suramin as part of CALGB 9480. Levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were assessed from day 1 of therapy (D1) and day 29 (D29) urine samples from this subset of 100 randomly selected patients. Growth factor levels were determined by standardized ELISA microtiter plate assays from a commercial (bFGF) or proprietary (VEGF) source. Pretreatment urine VEGF levels were predictive of survival. In univariate analysis, patients whose baseline urine VEGF level was < or =28 pg/ml (the median level) had an average survival of 17 months; those with baseline VEGF >28 pg/ml had a significantly shorter survival of 10 months ($P = 0.024$). This difference corresponded to a 60% increased risk of dying for the higher urine VEGF patients (hazard ratio, 1.62; $P = 0.03$) and remained significant in multivariate analysis (hazard ratio, 1.72, $P = 0.02$). No significant correlations between urine bFGF level or change in bFGF levels and survival were found. These results support the notion that certain peptide growth factor-mediated, mitogenic pathways are important in HRPC and that their levels can predict outcome.

Boyd, N. F., L. J. Martin, et al. (2006). "Mammographic density as a surrogate marker for the effects of hormone therapy on risk of breast cancer." Cancer Epidemiol Biomarkers Prev **15**(5): 961-6.

BACKGROUND: Some types of hormone therapy increase both risk of breast cancer and mammographic density, a risk factor for the disease,

suggesting that mammographic density may be a surrogate marker for the effects of hormones on risk of breast cancer. This research was undertaken to determine whether the effect of hormone therapy on breast cancer risk is mediated by its effect on mammographic density. METHODS: Individually matched cases and controls from three nested case-control studies in breast screening populations were studied. Cases had developed invasive breast cancer at least 12 months after the initial screen. Information was collected on hormone use and other risk factors at the time of the baseline mammogram, and percent density was measured by a computer-assisted method. RESULTS: There were 1,748 postmenopausal women, of whom 426 (24.4%) were using hormones at the time of their initial screening mammogram. Current use of hormone therapy was associated with an increased risk of breast cancer (odds ratio, 1.26; 95% confidence interval, 1.0-1.6) that was little changed by adjustment for percent density in the baseline mammogram (odds ratio, 1.19; 95% confidence interval, 0.9-1.5). Percent density in the baseline mammogram was among cases greater in current users of hormones that in never-users (difference = 5.0%, $P < 0.001$), but the difference was smaller and nonsignificant in controls (difference = 1.6%, $P = 0.3$). CONCLUSION: Although the effects of hormone therapy on mammographic density were greater in cases than controls, we did not find evidence that these effects were causally related to risk of breast cancer.

Bruckheimer, E. M. and N. Kyprianou (2001). "Dihydrotestosterone enhances transforming growth factor-beta-induced apoptosis in hormone-sensitive prostate cancer cells." Endocrinology **142**(6): 2419-26.

In this study, the potential interactions between dihydrotestosterone (DHT), a survival factor, and transforming growth factor-beta (TGF-beta), an apoptotic inducer, were examined in a derivative of the hormone-sensitive prostate cancer cell line LNCAP: The LNCaP TGF-beta receptor II cells, engineered to express TGF-beta receptor II, are sensitive to both DHT and TGF-beta. Surprisingly, when the LNCaP TGF-beta receptor II cells were treated with TGF-beta in the presence of physiological levels of DHT, both cell cycle arrest and apoptosis induction were significantly enhanced over TGF-beta alone. This effect temporally correlated with an increased expression of the cell cycle regulator p21 as well as the apoptotic executioner, procaspase-1, and a parallel down-regulation of the antiapoptotic protein, bcl-2. Expression of bax and caspase-3 proteins remained unchanged following treatment. Furthermore, apoptosis induction was suppressed by the caspase-1 inhibitor, z-YVAD, but not the caspase-3 inhibitor, z-DQMD, thus demonstrating the functional significance of increased procaspase-1 expression in TGF-beta-mediated apoptosis in prostate cancer cells. These results indicate that TGF-beta-mediated apoptosis can actually be enhanced by androgens through specific mechanisms involving cell cycle and apoptosis regulators and provide initial evidence on the ability of physiological levels of androgens to stimulate the intrinsic apoptotic potential of prostate cancer cells. Therefore, this study provides a molecular basis for the priming of prostate cancer cells for maximal apoptosis induction, during hormone- ablation therapy.

Buzdar, A. U. (2009). "Role of biologic therapy and chemotherapy in hormone receptor- and HER2-positive breast cancer." Ann Oncol **20**(6): 993-9.

BACKGROUND: To review the efficacy of chemotherapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy when used in addition to hormonal therapy for the optimal management of estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-positive (HER2+) breast cancer. Design: Literature published from January 2003 to March 2008 was reviewed to assess the use of chemotherapy and biologic therapy in addition to hormonal agents. RESULTS: Aromatase inhibitors (AIs) demonstrated greater effectiveness in the adjuvant setting than tamoxifen for the management of ER+ and HER2+ breast cancer. Evidence of cross talk between HER2- and ER-signaling pathways suggests that combined treatment with HER2 blockade and hormonal therapy may offer clinical advantages beyond those provided by hormonal therapy alone in ER+/HER2+ disease. Combined therapy with trastuzumab plus an aromatase AI significantly improves progression-free survival, response rates, and clinical benefits when compared with AI monotherapy in postmenopausal women. Several large studies demonstrated that trastuzumab significantly improves disease-free and overall survival when given in combination with, or following, chemotherapy, regardless of hormone receptor status. CONCLUSIONS: HER2-targeted therapy maybe combined with AIs for the treatment of ER+/HER2+ metastatic breast cancer in postmenopausal women. HER2-targeted therapy in combination with AIs for treatment of ER+/HER2+ early breast cancer needs to be prospectively evaluated.

Campagnoli, C., C. Abba, et al. (2001). "Breast cancer and hormone replacement therapy: putting the risk into perspective." Gynecol Endocrinol **15 Suppl 6**: 53-60.

Data on hormone replacement therapy and breast cancer risk come from a number of observational studies (mostly American studies). Those published up to 1995 were reanalyzed by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC). They involved populations where exceedingly high estrogen doses were used as first-line therapy, and a progestin was added in a minority of women. Overall, the CGHFBC reanalysis found that the relative risk increased by 0.023 for each year of use (with an absolute excess risk of two or six cases out of 1000 women treated for 5 or 10 years, respectively). Further American studies, published in 2000 and involving populations where lower doses were used, showed a risk increase of 0.01 per year of estrogen-only use. Both the CGHFBC reanalysis and the further studies did not find an increase of risk in treated overweight women. Possibly, overweight women already have a maximal estrogenic stimulus on the breast due to extraglandular estrogen production. An additional explanation could be that oral estrogens, through their hepatocellular effects, reverse some biological features of obesity (e.g. decreased sex hormone binding globulin level and increased insulin-like growth factor-I bioactivity) that potentially increase breast cancer risk, so balancing the estrogen stimulation. The CGHFBC reanalysis did not show a substantial difference in breast cancer risk between the majority using estrogen alone and the small minority using estrogen plus progestin. Conversely, Swedish studies and the recent American studies suggest that the risk increase could be higher with the addition of a progestin, compared with estrogen-only use. The biological effect of progesterone/progestins on the breast tissue is controversial. Even if the observed increase in risk could be partially ascribed to non-progesterone-like effects of some progestins (e.g. opposing the hepatocellular effects of oral estrogens) and also (in the American studies) to use-bias, a detrimental action due to progesterone-like effects cannot be excluded. However, the theoretical possibility exists that low doses of oral estrogens, plus a progestin providing progesterone-like effects only, will be shown to be associated with a limited breast cancer risk increase.

Canil, C. M., M. J. Moore, et al. (2005). "Randomized phase II study of two doses of gefitinib in hormone-refractory prostate cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group." J Clin Oncol **23**(3): 455-60.

PURPOSE: Overexpression of the epidermal growth factor receptor has been demonstrated in advanced prostate cancer and is associated with a poor outcome. A multi-institutional, randomized, phase II study was undertaken by the National Cancer Institute of Canada-Clinical Trials Group to evaluate the efficacy and toxicity of two doses of oral gefitinib in patients with minimally symptomatic, hormone-refractory prostate cancer (HRPC). PATIENTS AND METHODS: Between July and November 2001, 40 patients with HRPC and increasing prostate-specific antigen (PSA) or progression in measurable disease who had not received prior chemotherapy were randomly assigned to 250 mg (n = 19) or 500 mg (n = 21) oral gefitinib daily continuously. The primary end points were PSA response rate and objective measurable response. Functional Assessment of Cancer Therapy Prostate Cancer Subscale (FACT-P) quality-of-life questionnaires were completed at baseline and during treatment. RESULTS: None of the patients demonstrated a PSA or objective measurable response. Five (14.3%) of 35 assessable patients had stable PSA (one patient at 250 mg and four patients at 500 mg), and five patients (14.3%) had a best response of stable disease (duration, 2.5 to 16.8 months). No significant effect on the rate of increase in PSA was seen. The most common drug-related nonhematologic toxicities observed were grade 1 to 2 diarrhea (250 mg, 65%; 500 mg, 56%), fatigue (250 mg, 29%; 500 mg, 33%), and grade 1 to 2 skin rash (250 mg, 24%; 500 mg, 39%). FACT-P scores decreased during treatment, indicating worsening of symptoms compared with baseline. CONCLUSION: Gefitinib did not result in any responses in PSA or objective measurable disease at either dose level. Gefitinib has minimal single-agent activity in HRPC.

Cassinelli, G., C. Lanzi, et al. (2002). "Cellular bases of the antitumor activity of the novel taxane IDN 5109 (BAY59-8862) on hormone-refractory prostate cancer." Clin Cancer Res **8**(8): 2647-54.

Taxane-based therapies appear to have a significant efficacy in clinical trials on hormone-refractory prostate carcinoma. In the present study, we investigated the cellular response of androgen-independent prostate carcinoma cell lines to the novel taxane IDN 5109 (BAY 59-8862) and evaluated its antitumor activity. In previous preclinical studies, this new paclitaxel (PTX) analogue was characterized by high tolerability and antitumor efficacy, ability to overcome multidrug resistance, and activity by oral administration. Upon treatment, DU145 and PC3 prostate carcinoma cell lines underwent a transient mitotic arrest. This was followed by G1 arrest and rapid occurrence of apoptosis in DU145 cells, whereas in PC3 cells, which are defective for the postmitotic checkpoint, a slow cell death was preceded by DNA endoreduplication. At the biochemical level, such events were associated with tubulin polymerization, activation of the mitosis-promoting factor, and phosphorylation of Bcl-X(L)/Bcl-2/Raf-1. In addition,

IDN 5109 shared with PTX the ability to down-regulate the expression of the two potent angiogenic factors vascular endothelial growth factor and basic fibroblast growth factor. These findings indicated that IDN 5109 affected the same pathways involved in the cellular response to PTX and suggested that an antiangiogenic effect mediated by inhibition of paracrine stimulation of endothelial cells might contribute to the antitumor effect of both drugs. In in vivo experiments, the new taxane displayed a superior and more persistent effect compared with PTX against DU145 tumor xenografts. Such an effect was associated with pronounced reduction of the tumor microvessel density, superior to that achieved by PTX. These results support a potential therapeutic advantage of IDN 5109 over PTX against hormone-refractory prostate carcinoma.

Chang, K. L., H. L. Cheng, et al. (2009). "Combined effects of terazosin and genistein on a metastatic, hormone-independent human prostate cancer cell line." Cancer Lett **276**(1): 14-20.

Metastatic prostate cancer progresses from androgen-dependent to androgen-independent. Terazosin, a long-acting selective alpha1-adrenoreceptor antagonist, induces apoptosis of prostate cancer cells in an alpha1-adrenoreceptor-independent manner, while genistein, a major soy isoflavone, inhibits the growth of several types of cancer cells. The present study was designed to test the therapeutic potential of a combination of terazosin and genistein using a metastatic, hormone-independent prostatic cancer cell line, DU-145. Terazosin or genistein treatment inhibited the growth of DU-145 cells in a dose-dependent manner, whereas had no effect on normal prostate epithelial cells. Addition of 1 microg/ml of terazosin, which was inactive alone, augmented the growth inhibitory effect of 5 microg/ml of genistein. Co-treatment with terazosin resulted in the genistein-induced arrest of DU-145 cells in G2/M phase being overridden and an increase in apoptotic cells, as evidenced by procaspase-3 activation and PARP cleavage. The combination also caused a greater decrease in the levels of the apoptosis-regulating protein, Bcl-XL, and of VEGF165 and VEGF121 than genistein alone. In conclusion, the terazosin/genistein combination was more effective in inhibiting cell growth and VEGF expression as well as inducing apoptosis of the metastatic, androgen-independent prostate cancer cell line, DU-145, than either alone. The doses used in this study are in lower and nontoxic anticancer dosage range, suggesting this combination has potential for therapeutic use.

Chargari, C., R. A. Toillon, et al. (2009). "Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale?" Lancet Oncol **10**(1): 53-60.

Endocrine therapy is often given together with postoperative radiotherapy in patients with breast cancer and positive hormone-receptor status. However, few experimental or clinical studies address the combined effects of hormone and radiation therapy. Preclinical models have shown changes in tumour cell kinetics with the addition of tamoxifen, and some show reduced tumour cell death with concurrent anti-oestrogen treatment and radiotherapy. Although data from in-vitro studies support the notion of antagonistic effects of concurrent tamoxifen and radiotherapy on tumour cells, in-vivo research suggests a synergistic effect that could be attributable to micro-environmental changes in tumour responsiveness to ionising radiation and hormone therapy. Retrospective studies suggest that in practical application, concurrent administration of tamoxifen with radiotherapy does not compromise local control but might increase toxicity. Preliminary results from simultaneous treatment with aromatase inhibitors and radiation indicate that this combination of endocrine and radiation therapy could enhance cytotoxicity and improve tumour response. Further studies are needed to clarify the physiological mechanisms activated by oestrogens, which will allow a more thorough understanding of the complex interactions between 17beta-oestradiol and P53/P21(WAF1/CIP1)/Rb pathways and of the interaction between endocrine therapy and radiotherapy.

Chatzistamou, I., A. V. Schally, et al. (2001). "Inhibition of growth and reduction in tumorigenicity of UCI-107 ovarian cancer by antagonists of growth hormone-releasing hormone and vasoactive intestinal peptide." J Cancer Res Clin Oncol **127**(11): 645-52.

PURPOSE: To evaluate the tumor inhibitory activities of antagonists of growth hormone-releasing hormone (GH-RH) and vasoactive intestinal peptide (VIP) in UCI-107 human ovarian cancer model, and to investigate the role of the insulin-like growth factor (IGF) system in the response. METHODS: In the present study we investigated the effects of GH-RH antagonist JV-1-36 and VIP antagonist JV-1-52, on the growth and tumorigenicity of UCI-107 ovarian cell carcinoma xenografted into nude mice. Studies on the effects of hGH-RH(1-29)NH2, IGF-I, IGF-II, JV-1-36, and JV-1-52 on the proliferation of UCI-107 cells cultured in vitro were also performed. RESULTS: After 22 days of therapy with JV-1-36 or JV-1-52 at the dose of 20 microg/day, the final volume of UCI-107 tumors was significantly ($P<0.05$) decreased by 50.5% and 56%, respectively, compared

to controls. The concentration of IGF-II in tumors was reduced by 66% in the JV-1-36-treated group and by 62% in the group given JV-1-52 (both $P < 0.05$). Exposure in vitro to 1 microM concentrations of JV-1-36 or JV-1-52 for 24 h decreased the tumorigenicity of UCI-107 cells in nude mice. All ten mice injected with cells treated with medium alone developed tumors within 23 days after cell inoculation, while only eight of ten and four of ten mice injected with cells exposed to JV-1-36 or JV-1-52, respectively, had tumors. In vitro exposure of UCI-107 cells to 5-35 ng/ml IGF-II produced a significant suppression in the rate of cell proliferation ($P < 0.01$). CONCLUSION: Our results suggest that GH-RH and VIP antagonists inhibit the growth of UCI-107 ovarian cell carcinoma by mechanisms that appear to involve direct effects on the cancer cells.

Chatzistamou, I., A. V. Schally, et al. (2001). "Antagonists of growth hormone-releasing hormone and somatostatin analog RC-160 inhibit the growth of the OV-1063 human epithelial ovarian cancer cell line xenografted into nude mice." J Clin Endocrinol Metab **86**(5): 2144-52.

The effects of antagonists of GHRH and the somatostatin analog RC-160 on the growth of OV-1063 human epithelial ovarian cancer cells xenografted into nude mice were investigated. Treatment with 20 microg/day of the GHRH antagonist JV-1-36 or MZ-5-156 and 60 microg/day of the somatostatin analog RC-160 for 25 days decreased tumor volume by 70.9% ($P < 0.01$), 58.3% ($P < 0.05$), and 60.6% ($P < 0.01$), respectively, vs. the control value. The levels of GH in serum were decreased in all of the treated groups, but only RC-160 significantly reduced serum insulin-like growth factor I (IGF-I). The levels of messenger ribonucleic acid (mRNA) for IGF-I and -II and for their receptors in OV-1063 tumors were investigated by multiplex RT-PCR. No expression of mRNA for IGF-I was detected, but treatment with JV-1-136 caused a 51.8% decrease ($P < 0.05$) in the level of mRNA for IGF-II in tumors. Exposure of OV-1063 cells cultured in vitro to GHRH, IGF-I, or IGF-II significantly ($P < 0.05$) stimulated cell growth, but 10(-5) mol/L JV-1-36 nearly completely inhibited ($P < 0.001$) OV-1063 cell proliferation. OV-1063 tumors expressed mRNA for GHRH receptors and showed the presence of binding sites for GHRH. Our results indicate that antagonistic analogs of GHRH and the somatostatin analog RC-160 inhibit the growth of epithelial ovarian cancers. The effects of RC-160 seem to be exerted more on the pituitary GH-hepatic IGF-I axis, whereas GHRH antagonists appear to reduce IGF-II production and interfere with the autocrine regulatory pathway. The antitumorigenic action of GHRH antagonists appears to be mediated by GHRH receptors found in OV-1063 tumors.

Chaudhry, P. and E. Asselin (2009). "Resistance to chemotherapy and hormone therapy in endometrial cancer." Endocr Relat Cancer **16**(2): 363-80.

Endometrial cancer is the most common gynecological malignancy in developed countries and represents the eighth leading cause of cancer related death in women. The growing incidence of endometrial cancer leads scientists and oncologists to identify effective preventive measures and also molecular markers for diagnosis and prognosis. Chemotherapy and hormone therapy is the mainstay treatment option for advanced and recurrent endometrial cancer and response to therapy is one of the most important factor which favors prognosis and overall survival. In recent years, there have been major advances in the treatment of patients with endometrial cancer. Despite advances made in the treatment of this cancer, the overall survival of patients has not significantly improved because considerable number of patients harbor tumor refractory to these therapies and the majority of the initially responsive tumors become refractory to treatments. Therefore, determination of sensitivity/resistance is becoming increasingly important for individualization of endometrial cancer therapy. The aim of this review is to present the existing knowledge about the molecular markers that could play a crucial role in determining resistance to chemo- and hormone therapy. Extensive literature search for the cell signaling pathways and factors responsible for chemoresistance have been performed and reviewed. Several recent studies suggest that deregulations in the apoptotic pathways (such as p53, Fas/FasL, Bcl-2 family proteins, inhibitor of apoptosis proteins), survival pathways (PI3K/AKT, MAPK), hormone receptor signaling pathways (progesterone receptor), Cyclooxygenase-2 and Her-2 are considered as key factors involved in the onset and maintenance of therapeutic resistance, suggesting that resistance is a multi-factorial phenomenon.

Cheng, C. K., B. K. Chow, et al. (2003). "An activator protein 1-like motif mediates 17beta-estradiol repression of gonadotropin-releasing hormone receptor promoter via an estrogen receptor alpha-dependent mechanism in ovarian and breast cancer cells." Mol Endocrinol **17**(12): 2613-29.

Although it is recognized that estrogen is one of the most important regulators of GnRH receptor (GnRHR) gene expression, the mechanism underlying the regulation at the transcriptional level is unknown. In the present study, we demonstrated that 17beta-estradiol (E2) repressed human GnRHR promoter via

an activator protein 1-like motif and estrogen receptor-alpha, of which the DNA-binding domain and the ligand-binding domain were indispensable for the repression. Interestingly, the same cis-acting motif was also found to be important for both the basal activity and phorbol 12-myristate 13-acetate responsiveness of the GnRHR promoter. EMSAs indicated that multiple transcription factors including c-Jun and c-Fos bound to the activator protein 1-like site and that their DNA binding activity was not significantly affected by E2 treatment. In addition, we demonstrated that the E2 repression could be antagonized by phorbol 12-myristate 13-acetate, which stimulated c-Jun phosphorylation on serine 63, a process that is a prerequisite for recruitment of the transcriptional coactivator cAMP response element binding protein (CREB)-binding protein (CBP). Concomitantly, we found that overexpression of CBP could reverse the suppression in a dose-dependent manner. Taken together, our data indicate that E2-activated estrogen receptor-alpha represses human GnRHR gene transcription via an indirect mechanism involving CBP and possibly other transcriptional regulators.

Cherbonnier, C., O. Deas, et al. (2002). "Human growth hormone gene transfer into tumor cells may improve cancer chemotherapy." Cancer Gene Ther **9**(6): 497-504.

Chemotherapy remains the main tool for the treatment of cancers, but is often hampered by tumor cell resistance. In this context, the transfer of genes able to accentuate the effect of anticancer drugs may constitute a useful approach, as exemplified by inactivation of nuclear factor (NF)-kappa B via direct transfer of a gene encoding a negative dominant of its natural inhibitor I kappa B, leading to improved response to cancer chemotherapy. Following our previous report that transfection of human growth hormone (hGH) gene into human monocytic cell lines may also inactivate NF-kappa B in another situation, we decided to test the consequences of hGH gene transfer on cancer treatments. We demonstrated that hGH-transfected human myeloid leukemia U937 cells were sensitized to an apoptotic signal mediated by the anticancer drugs. In parallel, we found that, by inhibiting degradation of I kappa B, hGH gene transfer diminished NF-kappa B entry into the nuclei of U937 cells exposed to daunorubicin. Finally, we report that hGH-transfected tumor cells engrafted in nude mice responded in vivo to chemotherapy with nontoxic doses of daunorubicin whereas, under the same conditions, control tumor cells remained insensitive. Overall, this study therefore suggests that hGH gene transfer may offer new therapeutic prospects in cancer therapy.

Chintalapati, M., R. Truax, et al. (2009). "In vitro and in vivo anti-angiogenic activities and inhibition of hormone-dependent and -independent breast cancer cells by ceramide methylaminoethylphosphonate." J Agric Food Chem **57**(12): 5201-10.

Ceramide methylaminoethylphosphonate (CMAEPn) was isolated from eastern oyster (Crassostrea virginica) and screened against in vitro and in vivo angiogenesis and against MCF-7 and MDA-MB-435s breast cancer cell lines. In vitro angiogenesis was evaluated by the vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) tube formation assay. MCF-7 and MDA-MB-435s cell viability was evaluated by the CellTiter 96 AQ(ueous) One Solution Cell Proliferation assay. Apoptosis was evaluated by the caspase-9 assay, autophagy by acridine orange staining and beclin-1 level. Our study indicates that CMAEPn at 50 microM inhibited VEGF-induced tube formation by HUVEC. The viability of MCF-7 and MDA-MB-435s breast cancer cells exposed to 125 microM CMAEPn for 48 h was reduced to 76 and 85%, respectively. The viability of MCF-7 and MDA-MB-435s cells exposed to 250 microM CMAEPn for 48 h under the same conditions was reduced to 38 and 45%, respectively. CMAEPn at 125 microM inhibited VEGF-induced MDA-MB-435s cell migration and invasion. CMAEPn at 125 microM also decreased VEGF, EGF levels in the conditioned media, PI3K, IkappaB phosphorylation and degradation in the cytoplasmic extracts, and NFkappaB nuclear translocation. Both acridine orange staining and beclin-1 indicated autophagic cell death in MCF-7 and MDA-MB-435s cells, respectively. In vivo, CMAEPn at 30 mg/kg body weight inhibited bFGF-induced angiogenesis and caused a 57% reduction in hemoglobin levels in the matrigel plug assay within 7 days. This is the first report on CMAEPn-inhibited angiogenesis both in vitro and in vivo.

Chlebowski, R. T. (2009). "Menopausal hormone therapy, hormone receptor status, and lung cancer in women." Semin Oncol **36**(6): 566-71.

Gender differences in lung cancer incidence and outcome suggest a potential role for reproductive hormones. However, observational studies regarding menopausal hormone therapy use and lung cancer have given mixed results. Some have associated hormone therapy use with increased lung cancer risk, while others have shown no effect or found lower lung cancer risk in hormone therapy users. Against this background the Women's Health Initiative (WHI) randomized controlled trial evaluating conjugated equine estrogen (CEE) and medroxyprogesterone

acetate (MPA) in postmenopausal women identified an increase in malignancies in the hormone therapy group during the post intervention period. Post hoc analyses identified a statistically significant increase in deaths from lung cancer for women in the hormone group largely related to effects on non-small cell lung cancer (NSCLC). The NSCLCs were more commonly poorly differentiated and were diagnosed at a metastatic stage, suggesting a hormone effect on already established lung cancer growth. Ongoing preclinical and clinical analyses have identified estrogen receptors in the nucleus and cytoplasm of lung tissue and lung cancers. More recently, intriguing associations among estrogen receptor expression, lung cancer histology, clinical prognosis, and epidermal growth factor receptor (EGFR) mutations have been reported. The WHI clinical findings should be integrated into risk-benefit discussion with women considering combined hormone therapy use. In addition, the findings, together with ongoing studies evaluating estrogen receptor status and function, support further efforts to develop lung cancer intervention strategies targeting estrogen receptor expression.

Cho, K. S., J. S. Lee, et al. (2008). "Gene amplification and mutation analysis of epidermal growth factor receptor in hormone refractory prostate cancer." Prostate **68**(8): 803-8.

BACKGROUND: Amplification and mutation of the epidermal growth factor receptor (EGFR) and Her-2 genes were analyzed in both hormone sensitive and hormone refractory prostate cancer (HRPC). METHODS: Gene amplifications of EGFR and Her-2 were analyzed by fluorescence in situ hybridization (FISH) with direct sequencing. Studies were performed on a total of 10 patients; tissues were sampled at the time of initial diagnosis and after the conversion to HRPC (a total of 20 tissue samples). Direct sequencing was performed on exons 18-24 of EGFR and exons 19 and 20 of Her-2. Amplification and mutation were compared with clinicopathologic features. RESULTS: Gene amplification of EGFR was observed in 6 (30%) out of 20 samples. A total of six EGFR mutations in exons 18 and 19 were detected in three pairs of tissues (three patients). One patient, with hormone refractory status, had a novel deletion mutation in EGFR exon 19. EGFR mutations were associated with the acinar type of prostate cancer but were not associated with the ductal type. No significant correlation was found between mutation change and hormone sensitive or refractory status. However, the time to convert to HRPC was significantly shorter in the patients with a mutation in the EGFR gene ($P = 0.017$). There were no Her-2 gene amplifications or mutations found in any of the samples. CONCLUSIONS: EGFR gene mutation and amplification occurred frequently in advanced prostate cancer cases. EGFR mutations do not appear to play a significant role in the hormone refractory pathway but are associated with prognosis.

Corcoran, N. M. and A. J. Costello (2005). "Combined low-dose imatinib mesylate and paclitaxel lack synergy in an experimental model of extra-osseous hormone-refractory prostate cancer." BJU Int **96**(4): 640-6.

OBJECTIVE: To determine the efficacy of low-dose imatinib mesylate (STI571) alone or combined with a taxane (paclitaxel) in inhibiting the growth of experimental extra-osseous hormone-refractory prostate cancer. MATERIALS AND METHODS: Orthotopic PC3 prostate tumours were established in male severe combined-immunodeficient mice; on day 3 the mice were randomly assigned to one of four groups: paclitaxel 10 mg/kg intraperitoneally once a week; STI571 50 mg/kg once a day for 6/7 weekdays; combined paclitaxel and STI571; and vehicle-treated controls. On day 40, the primary prostate tumour and metastatic lymphadenopathy were removed and measured. Effects were correlated with tumour cell proliferation and microvessel density. RESULTS: Paclitaxel reduced the mean tumour weight and volume by 21.3% (not significant) and 73.7% ($P < 0.05$), respectively, compared to controls, and reduced the number of lymph node metastases by 49.1% ($P < 0.05$) and mean lymph node size by 13.5% (not significant). Adding low-dose STI571 had a small additive effect on tumour weight and the incidence of lymph node metastases, but this was not significant compared to paclitaxel alone. STI571 alone did not inhibit tumour progression. Antitumour effects were associated with parallel changes in tumour cell proliferation with no significant changes in neo-angiogenesis. CONCLUSION: Combined low-dose STI571 and paclitaxel had little synergy in this experimental model. Low-dose STI571 monotherapy was not effective in extra-osseous disease, apparently due to a site-specific failure to up-regulate beta-platelet-derived growth factor receptor expression in prostate cancer cells and associated tumour stroma.

Cronauer, M. V., W. A. Schulz, et al. (2003). "The androgen receptor in hormone-refractory prostate cancer: relevance of different mechanisms of androgen receptor signaling (Review)." Int J Oncol **23**(4): 1095-102.

The last decade has brought increased awareness to prostate cancer as a significant health problem. Prostate cancer is very heterogeneous in its etiology and progression, but androgen signaling

appears to be a common key element in its development and progression. Blocking of androgen signaling results in a decrease in tumor volume as well as a decline in serum PSA in the majority of patients with prostate cancer. Today, endocrine therapy involves androgen depletion by orchiectomy or by treatment with LHRH-analoga as well as blockade of the androgen receptor (AR) with anti-androgens. However, during these treatments almost all tumors relapse to a hormone-insensitive state. The mechanisms that lead from initially androgen-sensitive to androgen-unresponsive tumor cell growth have been partly elucidated by new insights into the molecular mechanisms of androgen receptor signaling over the past several years. In addition to androgen receptor mutations that broaden the ligand-specificity of the AR, androgen-independent transactivation of the AR by peptide growth factors such as epidermal growth factor and insulin-like growth factor-I has been discovered. Furthermore, analysis of proteins that interact with the AR led to the isolation of coactivator proteins that mediate transcriptional activation by the AR. The following review will discuss the elements involved in androgen receptor signaling and summarize the present knowledge of their biological and clinical relevance in advanced prostate cancer.

Curigliano, G., G. Spitaleri, et al. (2009). "Health-related quality of life in patients with hormone refractory prostate cancer receiving gefitinib." Urol Int **82**(2): 196-202.

OBJECTIVES: Improvements in quality of life (QoL) and disease-related symptoms are key goals in the treatment of hormone refractory prostate cancer (HRPC). Our aim was to evaluate the impact of gefitinib on QoL of patients with HRPC. METHODS: Patients with HRPC received gefitinib 250 mg daily in addition to antiandrogen plus luteinizing hormone-releasing hormone (LHRH) analogue for at least 2 months or until disease progression. QoL was evaluated monthly by the European Organisation for Research on the Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Pain was assessed daily by patients and scored by visual analogue scale and analgesic consumption in a diary. Monthly pain intensity was estimated using the McGill-Melzack questionnaire. RESULTS: Analysis of global health status according to EORTC QLQ-C30 showed an improvement of the status in only 6 patients (26%). The greatest benefit in the patients was in the subscale representing prostate-specific concerns (including appetite, pain, physical comfort, and genitourinary function). Improvement of symptoms was correlated with antiandrogen withdrawal. Global health status and QoL decreased during treatment according to tumor progression. CONCLUSIONS: Among HRPC patients treated with gefitinib, improvement of symptoms preceded evidence of biochemical response of prostate-specific antigen following antiandrogen withdrawal. These findings suggest no beneficial effect of gefitinib in QoL improvement.

D'Amico, A. V., J. Moul, et al. (2005). "Surrogate end point for prostate cancer specific mortality in patients with nonmetastatic hormone refractory prostate cancer." J Urol **173**(5): 1572-6.

PURPOSE: We determined whether prostate specific antigen (PSA) velocity can serve as surrogate end point for prostate cancer specific mortality (PCSM) in patients with nonmetastatic, hormone refractory prostate cancer. MATERIALS AND METHODS: The study cohort comprised 919 men treated from 1988 to 2002 at 1 of 44 institutions with surgery (560) or radiation therapy (359) for clinical stages T1c-4NxMo prostate cancer, followed by salvage hormonal therapy for PSA failure. All patients experienced PSA defined recurrence while on hormonal therapy. Prentice criteria require that the surrogate should be a prognostic factor and the treatment used did not alter time to PCSM following achievement of the surrogate end point. These criteria were tested using Cox regression. All statistical tests were 2-sided. RESULTS: PSA velocity greater than 1.5 ng/ml yearly was statistically significantly associated with time to PCSM and all cause mortality following PSA defined recurrence while undergoing hormonal therapy (Cox p <0.0001). While initial treatment was statistically associated with time to PCSM and all cause mortality (Cox p = 0.001 and 0.01), this association became insignificant when PSA velocity and potential confounding variables were included in the Cox model (p = 0.22 and 0.93, respectively). The adjusted HR for PCSM in patients who experienced a greater than 1.5 ng/ml increase in PSA within 1 year while on hormonal therapy was 239 (95% CI 10 to 5,549). CONCLUSIONS: These data provide evidence to support PSA velocity greater than 1.5 ng/ml yearly as a surrogate end point for PCSM in patients with nonmetastatic, hormone refractory prostate cancer. Enrolling these men onto clinical trials evaluating the impact of chemotherapy on time to bone metastases and PCSM is warranted.

Darb-Esfahani, S., S. Loibl, et al. (2009). "Identification of biology-based breast cancer types with distinct predictive and prognostic features: role of steroid hormone and HER2 receptor expression in patients treated with neoadjuvant anthracycline/taxane-based chemotherapy." Breast Cancer Res **11**(5): R69.

Reliable predictive and prognostic markers for routine diagnostic purposes are needed for breast cancer patients treated with neoadjuvant chemotherapy. We evaluated protein biomarkers in a cohort of 116 participants of the GeparDuo study on anthracycline/taxane-based neoadjuvant chemotherapy for operable breast cancer to test for associations with pathological complete response (pCR) and disease-free survival (DFS). Our data demonstrate that a biology-based breast cancer classification using estrogen receptor (ER), progesterone receptor (PgR), and HER2 bears independent predictive and prognostic potential. The HR+/HER2+ co-expressing carcinomas emerged as a group of tumors with a good response rate to neoadjuvant chemotherapy and a favorable prognosis. HR+/HER2- tumors had a good prognosis irrespective of a pCR, whereas patients with HR-/HER- and HR-/HER+ tumors, especially if they had not achieved a pCR, had an unfavorable prognosis and are in need of additional treatment options.

Darzy, K. H., S. S. Pezzoli, et al. (2005). "The dynamics of growth hormone (GH) secretion in adult cancer survivors with severe GH deficiency acquired after brain irradiation in childhood for nonpituitary brain tumors: evidence for preserved pulsatility and diurnal variation with increased secretory disorderliness." J Clin Endocrinol Metab **90**(5): 2794-803.

Dynamics of GH secretion in patients with GH deficiency due to radiation damage of the hypothalamic-pituitary (h-p) axis acquired in childhood has rarely been studied. Thus, we used a sensitive chemiluminescence GH assay to analyze 24-h GH profiles (20-min sampling) from 10 adult cancer survivors with severe GH deficiency acquired after brain irradiation in childhood for nonpituitary brain tumors. An age- and sex-matched control group of 30 normal healthy volunteers, eight of whom were matched for body mass index with the patients, were also studied. Cluster analysis with gender-specific comparisons revealed a significant reduction ($P < 0.05$) in all amplitude-related measurements [profile mean GH levels or area under curve for GH, absolute (maximum) GH peak height, mean peak height, and mean pulse area] in patients. No differences were observed in frequency-related measurements (pulse frequency, pulse duration, and interpulse interval). Pulsatile secretion was relatively more attenuated than basal secretion in patients, and approximate entropy (ApEn) scores were significantly ($P < 0.05$) elevated, suggesting more disordered GH secretion. Radiation inflicts quantitative damage to the h-p axis, leading to amplitude-dependent dampening of GH secretion with relative preservation of nonpulsatile secretion. Qualitative perturbation in hypothalamic control of GH release is evident by the increase in ApEn values reflecting more disordered GH secretion. The integrity of the h-p axis and GH neuroregulation is fundamentally preserved in irradiated GH-deficient patients with a GH secretory pattern similar to that observed in normal subjects and those with GH deficiency due to other etiologies.

DaSilva, J., D. Gioeli, et al. (2009). "The neuroendocrine-derived peptide parathyroid hormone-related protein promotes prostate cancer cell growth by stabilizing the androgen receptor." Cancer Res **69**(18): 7402-11.

During progression to an androgen-independent state following androgen ablation therapy, prostate cancer cells continue to express the androgen receptor (AR) and androgen-regulated genes, indicating that AR is critical for the proliferation of hormone-refractory prostate cancer cells. Multiple mechanisms have been proposed for the development of AR-dependent hormone-refractory disease, including changes in expression of AR coregulatory proteins, AR mutation, growth factor-mediated activation of AR, and AR protein up-regulation. The most prominent of these progressive changes is the up-regulation of AR that occurs in >90% of prostate cancers. A common feature of the most aggressive hormone-refractory prostate cancers is the accumulation of cells with neuroendocrine characteristics that produce paracrine factors and may provide a novel mechanism for the regulation of AR during advanced stages of the disease. In this study, we show that neuroendocrine-derived parathyroid hormone-related protein (PTHrP)-mediated signaling through the epidermal growth factor receptor (EGFR) and Src pathways contributes to the phenotype of advanced prostate cancer by reducing AR protein turnover. PTHrP-induced accumulation of AR depended on the activity of Src and EGFR and consequent phosphorylation of the AR on Tyr(534). PTHrP-induced tyrosine phosphorylation of AR resulted in reduced AR ubiquitination and interaction with the ubiquitin ligase COOH terminus of Hsp70-interacting protein. These events result in increased accumulation of AR and thus enhanced growth of prostate cancer cells at low levels of androgen.

Davis, J. N., K. J. Wojno, et al. (2006). "Elevated E2F1 inhibits transcription of the androgen receptor in metastatic hormone-resistant prostate cancer." Cancer Res **66**(24): 11897-906.

Activation of E2F transcription factors, through disruption of the retinoblastoma (Rb) tumor-suppressor gene, is a key event in the development of many human cancers. Previously, we showed that homozygous deletion of Rb in a prostate tissue

recombination model exhibits increased E2F activity, activation of E2F-target genes, and increased susceptibility to hormonal carcinogenesis. In this study, we examined the expression of E2F1 in 667 prostate tissue cores and compared it with the expression of the androgen receptor (AR), a marker of prostate epithelial differentiation, using tissue microarray analysis. We show that E2F1 expression is low in benign and localized prostate cancer, modestly elevated in metastatic lymph nodes from hormone-naive patients, and significantly elevated in metastatic tissues from hormone-resistant prostate cancer patients (P = 0.0006). In contrast, strong AR expression was detected in benign prostate (83%), localized prostate cancer (100%), and lymph node metastasis (80%), but decreased to 40% in metastatic hormone-resistant prostate cancer (P = 0.004). Semiquantitative reverse transcription-PCR analysis showed elevated E2F1 mRNA levels and increased levels of the E2F-target genes dihyrofolate reductase and proliferating cell nuclear antigen in metastatic hormone-independent prostate cancer cases compared with benign tissues. To identify a role of E2F1 in hormone-independent prostate cancer, we examined whether E2F1 can regulate AR expression. We show that exogenous expression of E2F1 significantly inhibited AR mRNA and AR protein levels in prostate epithelial cells. E2F1 also inhibited an AR promoter-luciferase construct that was dependent on the transactivation domain of E2F1. Furthermore, using chromatin immunoprecipitation assays, we show that E2F1 and the pocket protein family members p107 and p130 bind to the AR promoter in vivo. Taken together, these results show that elevated E2F1, through its ability to repress AR transcription, may contribute to the progression of hormone-independent prostate cancer.

Davol, P. A., J. A. Smith, et al. (2004). "Anti-CD3 x anti-HER2 bispecific antibody effectively redirects armed T cells to inhibit tumor development and growth in hormone-refractory prostate cancer-bearing severe combined immunodeficient beige mice." Clin Prostate Cancer **3**(2): 112-21.

The bispecific antibody (BiAb) anti-CD3 x anti-Her2/neu (Her2Bi), combines Her2/neu targeting with nonmajor histocompatibility complex-restricted cytotoxicity mediated by activated T cells (ATCs). To evaluate this adaptive immunotherapeutic strategy for augmenting antitumor immune response toward hormone-refractory prostate cancer (HRPC), normal donor or patient T cells were activated with anti-CD3, expanded ex vivo in interleukin-2, and then armed with Her2Bi (5-500 ng per million ATCs). By flow cytometry analyses, Her2Bi-armed ATCs had a proliferative advantage over unarmed ATCs and persisted in the circulation and tumor tissues longer than unarmed ATCs. These findings suggest that Her2Bi-armed ATC therapy may be an effective, nontoxic, tumor-specific treatment for Her2-positive HRPC.

Dawson, N. A. and S. F. Slovin (2003). "Novel approaches to treat asymptomatic, hormone-naive patients with rising prostate-specific antigen after primary treatment for prostate cancer." Urology **62 Suppl 1**: 102-18.

Biochemical-only recurrent prostate cancer presents the ideal setting for assessing novel agents or approaches for prostate cancer treatment. There is no clear evidence that delay in initiation of more definitive androgen-deprivation therapy is harmful, and a simple blood test--the prostate-specific antigen (PSA) level--is readily available to screen for potential antineoplastic activity. Current novel approaches include vaccines, cyclooxygenase-2 (COX-2) inhibitors, selective apoptotic antineoplastic drugs, endothelin-A receptor antagonists, chemotherapy, vitamin D, and peroxisome proliferator-activated receptor-gamma agonists. In this screening process, certain therapies have emerged as delaying PSA progression or decelerating PSA velocity. These therapies, such as the COX-2 inhibitors, will need to proceed to phase 3 trials to answer the more important question of whether this change in PSA dynamics translates into improved survival. Patients enrolling in these trials need to be clearly informed of the limited expectations of these novel exploratory approaches.

de Jong, P. C., M. A. Blankenstein, et al. (2001). "Importance of local aromatase activity in hormone-dependent breast cancer: a review." Breast **10**(2): 91-9.

The cytochrome P-450 enzyme complex aromatase is the rate-limiting step in the production of oestrogens. It catalyses the conversion of androgens to oestrogens. In the treatment of hormone-dependent breast cancer in postmenopausal women, aromatase is the target for treatment with aromatase inhibitors. Recently registered aromatase inhibitors like anastrozole, letrozole and exemestane have proven to be effective therapy for advanced breast cancer in postmenopausal patients failing to respond to treatment with tamoxifen. Intratumoural aromatase activity has predictive value for response to treatment with aromatase inhibitors. Attempts are being made to find an immunohistochemical technique to determine aromatase in tumour tissue, which may serve as a predictive factor. In situ oestrogen synthesis through local aromatase activity in the tumour and adjacent tissue is probably a very important growth-stimulating system in hormone-dependent breast cancer. This

synthesis can be blocked with aromatase inhibitors. The regulation of aromatase activity and the cell types that contribute to this process are the subject of extensive research. There seems to be a complex interaction between malignant cells and adjacent cells in which factors such as IL-6 and its soluble receptor, TNF-alpha and prostaglandin E2 play an important role in stimulating aromatase activity.

Debled, M., G. MacGrogan, et al. (2007). "Prognostic factors of early distant recurrence in hormone receptor-positive, postmenopausal breast cancer patients receiving adjuvant tamoxifen therapy: results of a retrospective analysis." Cancer **109**(11): 2197-204.

Current adjuvant hormone therapy in postmenopausal women with breast cancer is debatable between upfront aromatase inhibitors (AIs) and sequential treatment with tamoxifen. A major concern is the higher rate of early recurrences observed with sequential treatment. Between 1986 and 2000, operable breast cancer patients who received exclusively adjuvant tamoxifen for at least 3 years were selected from the authors' institutional database. Age, histology, pathologic tumor size, modified Scarff-Bloom-Richardson (mSBR) grade, mitotic index, tumor necrosis, peritumoral vascular emboli (PVE), HR status, and the number of involved axillary lymph-node were considered as prognostic factors of recurrence. RESULTS: Among 715 patients who met the inclusion criteria, a distant recurrence occurred in 38 patients (5.3%) within the first 3 years of tamoxifen therapy. Significant prognostic factors of early recurrence were mSBR, axillary lymph node involvement, tumor necrosis, mitotic index, PVE, and pathologic tumor size. Grade 1 and/or lymph node-negative tumors were excluded from the multivariate analysis (1 recurrence in 208 patients). In this model, mSBR grade 3 was the only significant predictive factor of early recurrence (hazard ratio, 3.72; P<.001). CONCLUSIONS: In this study, a subset of patients was identified that was at low-risk of early recurrence (mSBR grade 1 and/or negative lymph node status). Women in that subset could be treated using sequential hormone therapy with tamoxifen and AIs. In women with mSBR grade 3 or lymph node-positive tumors, an upfront treatment with AIs seemed to be the current optimal strategy.

della Rovere, F., A. Granata, et al. (2007). "Mast cells in invasive ductal breast cancer: different behavior in high and minimum hormone-receptive cancers." Anticancer Res **27**(4B): 2465-71.

BACKGROUND: Studies on the role of mast cells (MC) in cancer have given contrasting results. In order to contribute to the clarification of their role, research on breast cancer was carried out, because some aspects of its carcinogenesis, such as the diversity of the hormonal component, differ greatly. MATERIALS AND METHODS: This study included 50 cases of invasive ductal breast cancer not otherwise specified (NOS): 25 of them were high hormone-receptive (HHR) cancers with estrogen and progesterone receptor values not lower than 50%, 25 were minimum hormone-receptive (MHR) cancers (< 5%). In both groups, mast cells were quantified in the peritumoral area. Twenty cases of surgical interventions for non-neoplastic esthetic prosthesis in healthy women were examined as controls. The proliferation index Ki-67 (MIB1) and the c-erb B2 receptor protein were also considered in cancer patients. Mast cells were detected using Giemsa and Alcian blue stains. RESULTS: The results obtained showed that there was a highly significant increase in the number of mast cells mainly in the peritumoral area in HHR cancer cases ($p < 0.0001$) compared to MHR cancers and controls ($p < 0.0001$). Comparison between mast cells in MHR cancer and control cases was not significant ($p = 0.114$). Hormone-receptive cancers have a less severe prognosis for their higher responsiveness to therapy. This element may suggest that the higher mast cell number present in these types of cancer is a favorable prognostic factor. Moreover, mast cells tend to accumulate around the cancer area and this can be seen as an attempt to oppose the progression of the anomalous tissue. Mast cells were reported to exhibit cytolytic activity against tumor cells.

Deng, X., S. H. Tannehill-Gregg, et al. (2007). "Parathyroid hormone-related protein and ezrin are up-regulated in human lung cancer bone metastases." Clin Exp Metastasis **24**(2): 107-19.

Lung cancer often metastasizes to bone in patients with advanced disease. Identification of the factors involved in the interactions between lung cancer cells and bone will improve the prevention and treatment of bone metastases. We identified changes in metastasis-related gene expression of human HARA lung squamous carcinoma cells co-cultured with neonatal mouse calvariae using a pathway-specific microarray analysis. Nine genes were up-regulated and two genes down-regulated in HARA cells co-cultured with mouse calvariae. Five of the nine up-regulated genes, including caveolin 1, CD44, EphB2, ezrin, and Parathyroid hormone-related protein (PTHrP), and one down-regulated gene, SLPI, were further confirmed by Reverse transcription-polymerase chain reaction (RT-PCR). A mouse model was subsequently used to study the role of PTHrP and ezrin in bone metastasis in vivo. PTHrP (all three isoforms) and ezrin were up-regulated in HARA cells

at sites of bone metastasis as detected by RT-PCR and immunohistochemistry. The PTHrP 141 mRNA isoform was increased by the greatest extent (13.9-fold) in bone metastases compared to PTHrP 139 and PTHrP 173 mRNA. We then generated a HARA cell line in which PTHrP expression was inducibly silenced by RNA interference. Silencing of PTHrP expression caused significant reduction of submembranous F-actin and decreased HARA cell invasion. Ezrin up-regulation was confirmed by Western blots on HARA cells co-cultured with adult mouse long bones. Further, Transforming growth factor beta (TGF-beta) was identified as one of the factors in the bone microenvironment that was responsible for the up-regulation of ezrin. The identification of PTHrP and ezrin as important regulators of lung cancer bone metastasis offers new mechanistic insights into the metastasis of lung cancer and provides potential targets for the prevention and treatment of lung cancer metastasis.

Derin, D., Y. Eralp, et al. (2008). "Lower level of MAPK expression is associated with anthracycline resistance and decreased survival in patients with hormone receptor negative breast cancer." Cancer Invest **26**(7): 671-9.

INTRODUCTION: Hormone receptor negative breast cancer is encountered in about 30% of all patients with breast cancer and is considered as a prognostically unfavorable subset. The aim of this study is to evaluate the prognostic impact of various molecular markers in patients with receptor negative breast cancer. METHODS: Tumor specimens from 140 patients with receptor negative (ER, PR) breast cancer were analyzed for MAPK, Her-2/neu, EGFR and PI3K expression by immunohistochemistry. The prognostic significance of these molecular factors, in addition to various prognostic variables were determined with respect to disease-free and overall survival. RESULTS: Nineteen (13.6%), 45 (32.1%), 16 (11.4%) and 47 (33.5%) patients had positive staining for EGFR, PI3K, Her-2/neu and MAPK, respectively. Twenty-three patients with positive MAPK (16.4%) had a high level of expression (score 4-7) and 24 (17.1%) had a low score (1-3). A lower percentage of MAPK expression was significantly associated with a poorer OS ($p = 0.03$) and a tendency for shorter DFS ($p = 0.08$) among those who were positive for MAPK. Anthracycline resistance remained the only independent significant variable for OS by Cox regression analysis ($p = 0.001$, HR:26.1). In patients with recurrent disease, median survival after initial relapse was 16.8 months. MAPK was determined as the only prognostic factor for this endpoint. Patients with higher level of MAPK staining showed significantly shorter survival following initial recurrence ($p = 0.04$). CONCLUSION: MAPK expression is a significant prognostic factor for non-metastatic patients with hormone receptor breast cancer. A lower level of staining is shown to be associated with with antracycline resistance and oveall survival, whereas a higher expression level is correlated with shorter survival following initial relapse, suggesting possible role of different molecular mechanisms pertaining to tumor progression once recurrence occurs. Further translational research is required to elucidate molecular mechanisms of the cross-talk between intracellular signaling and molecular pathways leading to drug resistance in patients with receptor negative breast cancer.

Dieli, F., D. Vermijlen, et al. (2007). "Targeting human {gamma}delta} T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer." Cancer Res **67**(15): 7450-7.

The increasing evidence that gammadelta T cells have potent antitumor activity suggests their value in immunotherapy, particularly in areas of unmet need such as metastatic carcinoma. To this end, we initiated a phase I clinical trial in metastatic hormone-refractory prostate cancer to examine the feasibility and consequences of using the gammadelta T-cell agonist zoledronate, either alone or in combination with low-dose interleukin 2 (IL-2), to activate peripheral blood gammadelta cells. Nine patients were enlisted to each arm. Neither treatment showed appreciable toxicity. Most patients were treated with zoledronate + IL-2, but conversely only two treated with zoledronate displayed a significant long-term shift of peripheral gammadelta cells toward an activated effector-memory-like state (T(EM)), producing IFN-gamma and perforin. These patients also maintained serum levels of tumor necrosis factor-related apoptosis inducing ligand (TRAIL), consistent with a parallel microarray analysis showing that TRAIL is produced by gammadelta cells activated via the T-cell receptor and IL-2. Moreover, the numbers of T(EM) gammadelta cells showed a statistically significant correlation with declining prostate-specific antigen levels and objective clinical outcomes that comprised three instances of partial remission and five of stable disease. By contrast, most patients treated only with zoledronate failed to sustain either gammadelta cell numbers or serum TRAIL, and showed progressive clinical deterioration. Thus, zoledronate + IL-2 represents a novel, safe, and feasible approach to induce immunologic and clinical responses in patients with metastatic carcinomas, potentially providing a substantially increased window for specific approaches to be administered. Moreover,

gammadelta cell phenotypes and possibly serum TRAIL may constitute novel biomarkers of prognosis upon therapy with zoledronate + IL-2 in metastatic carcinoma.

Divisova, J., I. Kuiatse, et al. (2006). "The growth hormone receptor antagonist pegvisomant blocks both mammary gland development and MCF-7 breast cancer xenograft growth." Breast Cancer Res Treat **98**(3): 315-27.

Mammary gland development is dependent upon the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis, this same axis has also been implicated in breast cancer progression. In this study we investigated the effect of a GH antagonist, pegvisomant (Somavert, Pfizer), on normal mammary gland development and breast cancer xenograft growth. Intraperitoneal administration of pegvisomant resulted in a 60% suppression of hepatic IGF-I mRNA levels and upto a 70-80% reduction of serum IGF-I levels. Pegvisomant administration to virgin female mice caused a significant delay of mammary ductal outgrowth that was associated with a decrease in the number of terminal end buds and reduced branching and complexity of the gland. This effect of pegvisomant was mediated by a complete inhibition of both GH and IGF-IR-mediated signaling within the gland. In breast cancer xenograft studies, pegvisomant caused shrinkage of MCF-7 xenografts, with an initial 30% reduction in tumor volume, which was associated with a 2-fold reduction in proliferation and a 2-fold induction of apoptosis. Long-term growth inhibition of MCF-7 xenografts was noted. In contrast, pegvisomant had no effect on MDA-231 or MDA-435 xenografts, consistent with primary growth of these xenografts being unresponsive to IGF-I both in vitro and in vivo. In MCF-7 xenografts that regressed, pegvisomant had only minor effects upon GHR and IGF-IR signaling. This data supports previous studies indicating a role for GH/IGF in mammary gland development, and suggests that pegvisomant maybe useful for the prevention and/or treatment of estrogen receptor positive breast cancer.

Domingo-Domenech, J., P. L. Fernandez, et al. (2008). "Serum HER2 extracellular domain predicts an aggressive clinical outcome and biological PSA response in hormone-independent prostate cancer patients treated with docetaxel." Ann Oncol **19**(2): 269-75.

BACKGROUND: Human epidermal growth factor receptor 2 (HER2) overexpression has been linked to hormone-independent prostate cancer (HIPC) progression. Its clinical value and correlation with therapy is not defined. PATIENTS AND METHODS: Patients with HIPC treated with docetaxel (Taxotere) were prospectively tested for serum HER2 extracellular domain (ECD) by immunoanalysis. HER2 was determined by immunohistochemistry and fluorescence in situ hybridization (FISH) in tumor samples. RESULTS: Sixty-nine patients were included. Twenty-four (34.8%) patients had high HER2 ECD (>15 ng/ml). Prostate-specific antigen (PSA) response was 58% for patients with low HER2 ECD and 36% for patients with high HER2 ECD (P = 0.046). HER2 ECD levels were an independent prognostic factor for time to PSA progression [hazard ratio (HR) 2.82; 95% confidence interval (CI) 1.22-6.50; P = 0.015] and overall survival (HR 3.24; 95% CI 1.38-7.59; P = 0.007). Tissue samples from 17 patients were tested for HER2. Patients with negative HER2 tissue expression had lower HER2 ECD levels (median 10.5 +/- 2.7 versus 30.5 +/- 24.8 ng/ml; P = 0.016). FISH was negative in all samples. CONCLUSIONS: High HER2 ECD levels in serum are associated with a worst clinical outcome of HIPC patients treated with docetaxel.

Domingo-Domenech, J., C. Oliva, et al. (2006). "Interleukin 6, a nuclear factor-kappaB target, predicts resistance to docetaxel in hormone-independent prostate cancer and nuclear factor-kappaB inhibition by PS-1145 enhances docetaxel antitumor activity." Clin Cancer Res **12**(18): 5578-86.

PURPOSE: To investigate whether nuclear factor kappaB (NF-kappaB)/interleukin 6 (IL-6) was linked to docetaxel response in human prostate cancer cell lines, and whether inhibition of NF-kappaB sensitized tumor cells to docetaxel. We also aimed to correlate IL-6 (as a surrogate marker of NF-kappaB) and docetaxel response in hormone-independent prostate cancer (HIPC) patients. In patients with metastatic HIPC receiving docetaxel-based chemotherapy, IL-6 serum levels were assayed before chemotherapy and every 3 to 4 weeks thereafter. RESULTS: PC-3 and DU-145 cells had higher NF-kappaB activity, secreted more IL-6, and were more resistant to docetaxel than LNCaP cells. NF-kappaB activity was induced by docetaxel. Cotreatment with docetaxel and PS-1145 prevented docetaxel-induced NF-kappaB activation, reduced IL-6 production, and increased docetaxel effects on cell viability in PC-3 and DU-145 cells but not in LNCaP. Synergism with docetaxel and PS-1145, as assayed by median-effect principle, was observed in DU-145 and PC-3. In HIPC patients, pretreatment IL-6 serum levels correlated to prostate-specific antigen (PSA) response: median IL-6 level was 10.8+/-9.5 pg/mL in PSA responders versus 36.7+/-20.8 pg/mL (P=0.006) in nonresponders. A PSA response was also linked to a decline in IL-6 levels during treatment. Median overall survival was

6.8 months in patients with high IL-6 versus 16.6 months in those with low IL-6 (P=0.0007). On multivariate analysis, pretreatment IL-6 (P=0.05) was an independent prognostic factor for time to disease progression and survival. CONCLUSIONS: Inhibition of NF-kappaB emerges as an attractive strategy to enhance docetaxel response in prostate cancer. The interest of this view is further supported by a significant association between high IL-6 in sera of HIPC patients and decreased response to docetaxel.

Draghia-Akli, R., K. A. Hahn, et al. (2002). "Effects of plasmid-mediated growth hormone-releasing hormone in severely debilitated dogs with cancer." Mol Ther **6**(6): 830-6.

Cachexia is a common manifestation of late stage malignancy and is characterized by anemia, anorexia, muscle wasting, loss of adipose tissue, and fatigue. Although cachexia is disabling and can diminish the life expectancy of cancer patients, there are still no effective therapies for this condition. We have examined the feasibility of using a myogenic plasmid to express growth hormone-releasing hormone (GHRH) in severely debilitated companion dogs with naturally occurring tumors. At a median of 16 days after intramuscular delivery of the plasmid, serum concentrations of insulin-like growth factor I (IGF-I), a measure of GHRH activity, were increased in 12 of 16 dogs ($P < 0.01$). These increases ranged from 21 to 120% (median, 49%) of the pretreatment values and were generally sustained or higher on the final evaluation. Anemia resolved posttreatment, as indicated by significant increases in mean red blood cell count, hematocrit, and hemoglobin concentrations, and there was also a significant rise in the percentage of circulating lymphocytes. Treated dogs maintained their weights over the 56-day study and did not show any adverse effects from the GHRH gene transfer. We conclude that intramuscular injection of a GHRH-expressing plasmid is both safe and capable of stimulating the release of growth hormone and IGF-I in large animals. The observed anabolic responses to a single dose of this therapy might be beneficial in patients with cancer-associated anemia and cachexia.

Ellis, M. J., F. Gao, et al. (2009). "Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study." Jama **302**(7): 774-80.

CONTEXT: Estrogen deprivation therapy with aromatase inhibitors has been hypothesized to paradoxically sensitize hormone-receptor-positive breast cancer tumor cells to low-dose estradiol therapy. OBJECTIVE: To determine whether 6 mg of estradiol (daily) is a viable therapy for postmenopausal women with advanced aromatase inhibitor-resistant hormone receptor-positive breast cancer. Randomization to receive 1 oral 2-mg generic estradiol tablet 3 times daily or five 2-mg tablets 3 times daily. MAIN OUTCOME MEASURES: Primary end point: clinical benefit rate (response plus stable disease at 24 weeks). Secondary outcomes: toxicity, progression-free survival, time to treatment failure, quality of life, and the predictive properties of the metabolic flare reaction detected by positron emission tomography/computed tomography with fluorodeoxyglucose F 18. RESULTS: The adverse event rate (> or = grade 3) in the 30-mg group (11/32 [34%]; 95% confidence interval [CI], 23%-47%) was higher than in the 6-mg group (4/34 [18%]; 95% CI, 5%-22%; P = .03). Clinical benefit rates were 9 of 32 (28%; 95% CI, 18%-41%) in the 30-mg group and 10 of 34 (29%; 95% CI, 19%-42%) in the 6-mg group. An estradiol-stimulated increase in fluorodeoxyglucose F 18 uptake (> or = 12% prospectively defined) was predictive of response (positive predictive value, 80%; 95% CI, 61%-92%). Seven patients with estradiol-sensitive disease were re-treated with aromatase inhibitors at estradiol progression, among which 2 had partial response and 1 had stable disease, suggesting resensitization to estrogen deprivation. CONCLUSIONS: In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate as 30 mg, with fewer serious adverse events. The efficacy of treatment with the lower dose should be further examined in phase 3 clinical trials. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00324259.

Engel, J. B., G. Keller, et al. (2005). "Inhibition of growth of experimental human endometrial cancer by an antagonist of growth hormone-releasing hormone." J Clin Endocrinol Metab **90**(6): 3614-21.

Antagonists of GHRH are being developed for the treatment of various cancers. In this study we investigated in vivo and in vitro the effects of the GHRH antagonist MZ-J-7-118 and its mechanism of action in HEC-1A human endometrial cancer. Treatment of nude mice bearing HEC-1A xenografts with 10 mug/d MZ-J-7-118 for 6 wk significantly inhibited the volume of HEC-1A tumors by 43%, tumor weight by 40% compared with controls and prolonged the tumor doubling time from 18.7 +/- 1.4 to 25.4 +/- 3.8 d. Administration of 20 mug MZ-J-7-118, sc, twice a day significantly ($P < 0.05$) decreased HEC-1A growth, as evidenced by a 57.9% decrease in tumor volume, a 50.7% reduction in tumor weight, and the extension of tumor doubling time from 17.5

+/- 2.8 to 36.4 +/- 6.5 d. Therapy with GHRH antagonists significantly decreased serum IGF-I levels in experiment 1, and significantly increased tumoral IGF-I levels in experiment 2 in treated mice. Levels of IGF-II and vascular endothelial growth factor-A in tumors were not changed. Specific high affinity binding sites for GHRH were found on HEC-1A tumor membranes using ligand competition assays with (125)I-labeled GHRH antagonist JV-1-42. MZ-J-7-118 displaced radiolabeled JV-1-42 with an IC(50) of 0.13 +/- 0.04 nm. The expression of mRNA for GHRH and splice variants of the GHRH receptor in HEC-1A tumors was demonstrated by real-time RT-PCR analysis. HEC-1A cells cultured in vitro secreted GHRH into the medium. The GHRH antagonist MZ-J-7-118 inhibited the growth of HEC-1A cells in vitro. Our results indicate that GHRH antagonists can reduce the growth of human endometrial cancer and could be used as an alternative adjuvant therapy for the management of endometrial cancer.

Eskelinen, M., T. Norden, et al. (2004). "Preoperative serum levels of follicle stimulating hormone (FSH) and prognosis in invasive breast cancer." Eur J Surg Oncol **30**(5): 495-500.

AIMS: We investigated the association between preoperative serum levels of follicle stimulating hormone (FSH) and the prognosis in women with invasive breast cancer. METHODS: Serum levels of FSH were measured in 182 premenopausal and 581 peri- or postmenopausal women with invasive breast cancer. They were followed for a mean time of 84 months. The study endpoint was death from breast cancer (182 events). Analyses were stratified on menopausal status. RESULTS: None of the estimates showed a statistically significant result. In both pre- and postmenopausal women there was a nominally higher probability of survival with a higher FSH level. Point estimates in multivariate analysis incorporating age, tumour diameter, axillary lymph status, estrogen and progesterone receptor content and year of treatment indicated a stronger association with FSH levels in premenopausal than postmenopausal women (relative hazard 0.63 or 0.85, respectively in the highest compared with the lowest quartile). CONCLUSION: We did not find any statistically significant association between preoperative serum level of FSH and prognosis. Today, FSH is not a clinical target for intervention or a clinically useful prognostic factor and the results of clinical studies up to date can only be used for motivation of further experimental laboratory research.

Fan, J., R. McKean-Cowdin, et al. (2006). "An association between a common variant (G972R) in the IRS-1 gene and sex hormone levels in post-menopausal breast cancer survivors." Breast Cancer Res Treat **99**(3): 323-31.

Insulin receptor substrate-1 (IRS-1) is a key downstream signaling molecule common to both the insulin and IGF signaling pathways that can interact with the estrogen pathway to regulate breast cell growth. Serum estrone, estradiol, testosterone, SHBG, IGF-1 and C-peptide were measured in 468 patients at 30+ months post diagnosis. Non-protein bound hormone levels (free estradiol, free testosterone) were calculated. In African-American patients, the IRS-1 variant was associated with increased serum levels of estrone ($p = 0.02$), free estradiol ($p = 0.04$), total testosterone ($p = 0.04$), free testosterone ($p = 0.006$) and decreased levels of sex hormone-binding globulin ($p = 0.02$). No association was present for white patients. Our findings provide suggestive evidence that IRS-1 G972R variant may be associated with circulating levels of sex hormones and SHBG in African American breast cancer survivors.

Fang, S. H., Y. Chen, et al. (2009). "GATA-3 as a marker of hormone response in breast cancer." J Surg Res **157**(2): 290-5.

GATA-3 is a transcription factor that orchestrates gene expression profiles during embryogenesis of a variety of human tissues, including hematopoietic cells, skin, kidney, mammary gland, and the central nervous system. Among several other roles, GATA-3 has recently been identified as a key player of luminal cell differentiation in the mammary gland. The majority of breast cancers arise from luminal epithelial cells and hence GATA-3 appears to control a set of genes involved in the differentiation and proliferation of breast cancer. The expression of GATA-3 has a strong association with the expression of estrogen receptor-alpha (ER) in breast cancer, and there is mounting evidence that GATA-3 can be used as a clinical marker to determine response to hormonal therapy and to refine the prognosis of breast cancer patients. Here, we review the literature from the past 10 y on GATA-3 in normal and pathological states of the mammary gland. Conclusions from the literature are confirmed using meta-analyses performed by the Oncomine Research Platform.

Fister, S., A. R. Gunthert, et al. (2007). "Gonadotropin-releasing hormone type II antagonists induce apoptotic cell death in human endometrial and ovarian cancer cells in vitro and in vivo." Cancer Res **67**(4): 1750-6.

In human endometrial and ovarian cancers, gonadotropin-releasing hormone type I (GnRH-I), GnRH-II, and their receptors are parts of a negative

autocrine regulatory system of cell proliferation. Based on a tumor-specific signal transduction, GnRH-I and GnRH-II agonists inhibit the mitogenic signal transduction of growth factor receptors and related oncogene products associated with tyrosine kinase activity via activation of a phosphotyrosine phosphatase resulting in down-regulation of cancer cell proliferation. Induction of apoptosis is not involved. In this study, we show that treatment of human endometrial and ovarian cancer cells with GnRH-II antagonists results in apoptotic cell death via dose-dependent activation of caspase-3. The antitumor effects of the GnRH-II antagonists could be confirmed in nude mice. GnRH-II antagonists inhibited the growth of xenotransplants of human endometrial and ovarian cancers in nude mice significantly, without any apparent side effects. Thus, GnRH-II antagonists seem to be suitable drugs for an efficacious and less toxic endocrine therapy for endometrial and ovarian cancers.

Fister, S., L. Schlotawa, et al. (2008). "Increase of doxorubicin-induced apoptosis after knock-down of gonadotropin-releasing hormone receptor expression in human endometrial, ovarian and breast cancer cells." Gynecol Endocrinol **24**(1): 24-9.

The majority of human endometrial, ovarian and breast cancers express receptors for gonadotropin-releasing hormone (GnRH). Their proliferation is time- and dose-dependently reduced by GnRH and its agonistic analogs. GnRH agonists inhibit the mitogenic signal transduction of growth factor receptors via activation of a phosphotyrosine phosphatase, resulting in downregulation of cancer cell proliferation. Induction of apoptosis is not involved. Recently we showed that the GnRH agonist triptorelin induces activation of nuclear factor-kappaB (NFkappaB) and thus reduces the apoptosis induced by the cytotoxic agent doxorubicin in human endometrial and ovarian cancer cells. The triptorelin-induced reduction of doxorubicin-induced apoptosis was blocked by inhibition of NFkappaB translocation into the nucleus. The present study was conducted to investigate whether knock-down of GnRH receptor expression reduces GnRH agonist-induced anti-apoptotic action. We show that knock-down of GnRH receptor expression results in an increase of doxorubicin-induced apoptosis in human endometrial and ovarian cancers and in the human breast cancer cell line MCF-7. These data further demonstrate that GnRH agonists suppress chemotherapeutic drug-induced apoptosis via activation of the GnRH receptor in these cancers. The situation is different with T-47-D breast cancer cells. After knock-down of GnRH receptor expression doxorubicin-induced apoptosis was decreased, indicating that GnRH agonists do not suppress chemotherapeutic drug-induced apoptosis in T-47-D breast cancer cells.

Fontana, A., L. Galli, et al. (2009). "Clinical and pharmacodynamic evaluation of metronomic cyclophosphamide, celecoxib, and dexamethasone in advanced hormone-refractory prostate cancer." Clin Cancer Res **15**(15): 4954-62.

PURPOSE: The aims of the present study were to evaluate the clinical activity and the pharmacodynamic profile of the novel schedule of a single i.v. standard dose of cyclophosphamide (CTX) immediately followed by an oral metronomic CTX regimen with celecoxib (CXB) and dexamethasone (DEX) in advanced hormone-refractory prostate cancer patients. EXPERIMENTAL DESIGN: Twenty-eight patients (68% docetaxel-resistant) received 500 mg/m2 CTX i.v. bolus on day 1 and, from day 2, 50 mg/day CTX p.o. plus 200 mg/twice a day CXB p.o. and 1 mg/day DEX p.o. until disease progression. Plasma vascular endothelial growth factor (VEGF) and thrombospondin-1 were detected by ELISA, and real-time reverse transcription-PCR of VEGF and thrombospondin-1 gene expression on peripheral blood mononuclear cell and of VE-cadherin (VE-C) in blood samples was done. RESULTS: A confirmed prostate-specific antigen decrease of > or =50% from baseline was observed in 9 of 28 patients (32%). Median progression-free survival and overall survival were 3 months (95% confidence interval, 2.2-4.2 months) and 21 months (95% confidence interval, 12.4-29.4 months), respectively. Toxicity was mild and no grade 3 to 4 toxicities occurred. A significant relationship was found between plasma VEGF and prostate-specific antigen values ($r = 0.4223$; $P < 0.001$). VEGF levels significantly increased in nonresponders, whereas the responder patients maintained significantly lower levels of VE-C gene expression after the beginning of the treatment if compared with nonresponder ones. CONCLUSION: Metronomic CTX plus CXB and DEX showed favorable toxicity and activity profile in patients. VE-C gene expression and VEGF levels represent potentially useful pharmacodynamic markers for the clinical response.

Frogne, T., A. V. Laenkholm, et al. (2009). "Determination of HER2 phosphorylation at tyrosine 1221/1222 improves prediction of poor survival for breast cancer patients with hormone receptor-positive tumors." Breast Cancer Res **11**(1): R11.

INTRODUCTION: High expression of total HER2 protein confers poor prognosis for breast cancer patients. HER2 is a member of the HER family consisting of four receptors, HER1 to HER4. HER receptor activity is regulated by a variety of

mechanisms, and phosphorylation of the C-terminal part of the HER receptors is a marker for active signaling. The importance of phosphorylation and thereby activation of the HER1 to HER4 receptors, however, has not been investigated concomitantly in breast tumors. In the present study we examined the importance of active HER signaling in breast tumor biopsies and paired metastases, by evaluating the expression of phosphorylated HER1, HER2, HER3, Erk, Akt and the total level of HER4 and HER2. METHODS: Immunohistochemical analysis was performed on 268 primary breast tumors and 30 paired metastatic lesions from postmenopausal women with hormone receptor-positive breast tumors, who had received adjuvant tamoxifen therapy. The observed protein expression levels were analyzed for co-expression, for correlation to clinicopathological parameters and for prognostic value in relation to disease-free survival and overall survival. Lastly, the difference between protein levels in primary tumors versus metastasis was evaluated. RESULTS: In the primary tumors, 8%, 18%, 14% and 15% of cases were scored positive for total HER2, pHER1, pHER2 and pHER3 expression, respectively. HER4 was expressed with strong intensity in 68% and at moderate intensity in 29% of cases. The activated forms of Akt and Erk were quite uniformly expressed in the categories; negative, moderate or strong. In univariate analysis, expression of total HER2, pHER1, pHER2 and pHER3 was significantly associated with poor disease-free survival. Strong HER4 expression was associated with prolonged disease-free as well as with overall survival. Expression of pAkt and pErk was not correlated with survival. In multivariate analysis, pHER2 expression was clearly an independent marker for poor disease-free survival and overall survival when tested against tumor size, tumor grade, nodal status and HER2. Lastly, comparison of HER receptor expression in metastatic versus primary tumors showed a significant increase in expression of pHER1 and pHER3 in the metastases. CONCLUSIONS: In hormone receptor-positive breast cancer, determination of pHER2 yields additional prognostic information about poor prognosis compared with the current clinical standard for measuring HER2.

Fujimoto, N., H. Miyamoto, et al. (2007). "Prostate cancer cells increase androgen sensitivity by increase in nuclear androgen receptor and androgen receptor coactivators; a possible mechanism of hormone-resistance of prostate cancer cells." Cancer Invest **25**(1): 32-7.

Although androgen-hypersensitivity is one of the possible pathways of hormone-resistance in prostate cancer, the mechanisms of androgen-hypersensitivity are still largely unknown. Using androgen-hypersensitive prostate cancer cells LN-TR2, established from androgen-sensitive LNCaP cells by the long term treatment with tumor necrosis factor alpha, we explored the mechanisms of androgen-hypersensitivity in prostate cancer cells which may thus play a role in hormone-resistance. We examined the androgen receptor (AR) DNA sequence and the expression levels of AR and 8 AR cofactors in LNCaP and LN-TR2 cells. As a result, no novel mutation was developed in AR DNA in LN-TR2 cells. We observed higher expressions of nuclear AR upon androgen-treatment and 2 AR coactivators, ARA55 and TIF2, in LN-TR2 compared to LNCaP cells. An overexpression of ARA55 or TIF2 enhanced androgen-induced AR transcriptional activity in LNCaP cell. In the presence of those AR coactivators, AR activity was observed even at low concentrations of androgen. In 2 of 6 patients, the expression level of ARA55 was higher in cancer cells in hormone-resistant tumor than those in hormone-sensitive tumor. Taken together, our results suggest that prostate cancer cells change androgen-sensitivity by an overexpression of nuclear AR and AR coactivators, thus, resulting in transition from androgen-dependent to androgen-independent prostate cancer cells. An increase in nuclear AR and AR coactivators may cause androgen-hypersensitivity of prostate cancer cells and thus play a role in hormone-resistance, at least in some patients with prostate cancer.

Gasparini, G., M. Toi, et al. (2001). "Thrombospondin-1 and -2 in node-negative breast cancer: correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis." Oncology **60**(1): 72-80.

OBJECTIVE: Thrombospondins (TSP(s)) are a multigene family of five secreted glycoproteins involved in the regulation of cell proliferation, adhesion and migration. Two members of the TSP family, namely TSP-1 and TSP-2, are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to determine the prognostic significance of the determination of TSP-1 and -2 and their correlation with the angiogenic peptides vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biological and clinicopathological features investigated. METHODS: We evaluated a series of 168 women with node-negative breast cancer with a median follow-up period of 66 months, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were determined in the primary tumour by a commercially available immunometric assay. RESULTS: We found that 166 tested tumours had measurable levels of TSP-1 and -2 protein (median

value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coefficient, a weak inverse association of TSP-1 and -2 with tumour size and cathepsin D was found. Moreover, principal component analysis on ranks evidenced a poor association between TSP-1 and -2, VEGF and TP. The results of the clinical outcome were analysed by both univariate and multivariate [for relapse-free survival (RFS) only]) Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate analysis for either RFS ($p = 0.427$) or overall survival ($p = 0.069$). To investigate the 'angiogenic balance hypothesis', bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate analysis for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant ($p = 0.002$, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible ($p = 0.731$, Harrell c statistic value of 0.705). CONCLUSIONS: The results of this study suggest that TSP-1 and -2 do not provide additional prognostic contribution to the joint effects of VEGF and TP. In the series of node-negative breast cancer patients investigated, determination of the angiogenic peptides VEGF and TP gave significant prognostic information. On the contrary, TSP-1 and -2, potential naturally occurring negative regulators of angiogenesis, lacked prognostic value.

Gee, J. M., J. J. Eloranta, et al. (2009). "Overexpression of TFAP2C in invasive breast cancer correlates with a poorer response to anti-hormone therapy and reduced patient survival." J Pathol **217**(1): 32-41.

The AP-2gamma transcription factor encoded by the TFAP2C gene is a member of a family of homologous DNA binding proteins that play essential roles during vertebrate embryogenesis but show a restricted pattern of expression in the adult. Elevated expression of the AP-2alpha and AP-2gamma family members has been associated with a number of neoplasms, particularly breast cancer. Here we present an exploratory immunohistochemical study of an archival primary breast tumour series ($n = 75$) with parallel clinicopathological data using a new, well-characterized antibody to AP-2gamma. Heterogeneous, exclusively nuclear expression of AP-2gamma was found in the epithelial and myoepithelial compartments of normal breast and within tumour epithelial cells. In the breast cancer series, the most notable association was a correlation between elevated levels of AP-2gamma and shortened patient survival ($p = 0.0009$*). This relationship was also conserved in ER-positive and ErbB2-negative patients; sub-groups generally considered to have a relatively good prognosis. When patient data for survival and duration of treatment response on anti-hormone therapy were examined by multivariate analysis, AP-2gamma was revealed in this study to be an independent predictor of outcome for both survival ($p = 0.005$) and response to anti-hormone therapy ($p = 0.046$). Studies using in vitro models confirmed that while tamoxifen response is associated with lower levels of AP-2gamma, acquisition of resistance to this and other anti-hormone measures (eg faslodex or oestrogen deprivation) is associated with high levels of nuclear AP-2gamma. Together these data suggest that elevated tumour AP-2gamma expression can contribute to the failure of cells to growth arrest following anti-hormone treatment and lead to sustained growth and poorer patient outcome.

Genazzani, A. R., A. Gadducci, et al. (2001). "Controversial issues in climacteric medicine II. Hormone replacement therapy and cancer. International Menopause Society Expert Workshop. 9-12 June 2001, Opera del Duomo, Pisa, Italy." Climacteric **4**(3): 181-93.

Sex steroids are not known to damage DNA directly. They can stimulate or inhibit cell proliferation, and thus can modulate tumor developmental progression. Sex steroid-related tumors in women are represented by breast cancer and endometrial cancer, and a possible relationship exists between sex steroids and both ovarian and colon cancer. Among current ERT users or those who stopped use 1-4 years previously, the relative risk of having breast cancer diagnosed increases by a factor of 1.023 for each year of hormone use. This increase is comparable with the effect on breast cancer of delaying menopause, and seems to be largely limited to lean women. The breast cancers diagnosed during ERT are more likely to contain ER and are less aggressive. Some reports indicate no increase in breast cancer mortality in HRT users. Recent data suggest that an estrogen-progestin regimen may increase breast cancer risk beyond that associated with estrogen alone. However, the effect of progestogens on the breast awaits further clarification. ERT/HRT is generally considered to be contraindicated in breast cancer patients, as no firm data are yet available from randomized clinical trials. Despite the potential risks, ERT/HRT could be considered for breast cancer patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given, particularly in women with ER--(hormone-resistant) cancers. Unopposed estrogen therapy is known to increase endometrial cancer risk, and is appropriate only for hysterectomized women.

To negate the excess risk of endometrial hyperstimulation, an adequate progestin dose must be given in a continuous combined regimen or for an appropriate number of days in sequential regimens (10 days or more for some progestogens or 12 days or more for other progestogens). An appropriate combination of estrogen and progestin does not appear to increase, and may even decrease, the risk of endometrial cancer. HRT is generally considered to be contraindicated in endometrial cancer patients. Despite the potential risks, HRT could be considered for patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given. Available data suggest a reduced risk of colorectal adenoma and colon cancer in current users of HRT, but definitive studies are still needed. There is no contraindication to HRT prescription in colon cancer survivors. Consistent epidemiological data describe a decreased incidence of ovarian cancer with oral contraceptive use during the reproductive years. Studies on HRT and risk of epithelial ovarian cancer have produced conflicting results but most data seem to exclude a strong association. While no data contraindicate HRT use in epithelial ovarian cancer survivors, current studies do not allow us to exclude the possibility that estrogens alone could stimulate ovarian cancer growth in a small fraction of patients. Additional studies are required. It is important to consider that not all estrogens and progestins are used with the same dosage, route of administration (oral, transdermal and for estradiol intranasal) and, mostly, different estrogens do not show the same bioavailability and tissue effects. The available data do not allow to discriminate for all these variables and therefore it is inappropriate to consider jointly all forms of hormonal therapy. This issue is considered as an important area for future evaluation and research. The International Menopause Society is in the process of drawing up specific recommendations for further research in the field of HRT and cancer.

George, D. J., S. Halabi, et al. (2001). "Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480." Clin Cancer Res **7**(7): 1932-6.

PURPOSE: Plasma vascular endothelial growth factor (VEGF) levels are significantly elevated in patients with hormone-refractory prostate cancer (HRPC) compared with patients with localized disease and have been associated with disease progression in other cancer patient populations. Therefore, we measured VEGF levels in plasma prospectively collected from patients enrolled in Cancer and Leukemia Group B 9480, an intergroup study of suramin in patients with HRPC, to determine whether these levels had prognostic significance. EXPERIMENTAL DESIGN: Pretreatment plasma was collected from patients with HRPC enrolled in Cancer and Leukemia Group B 9480. In a subset of samples representative of the entire cohort, plasma VEGF levels were determined in duplicate using a Quantiglo chemiluminescent ELISA kit (R&D Systems, Minneapolis, MN). Statistical analyses were performed to determine the correlation between pretreatment plasma VEGF levels and time of overall survival. The proportional hazards model was used to assess the prognostic significance of various cut points in multivariate models. RESULTS: Plasma VEGF levels in this population ranged from 4-885 pg/ml, with a median level of 83 pg/ml. As a continuous variable, plasma VEGF levels inversely correlated with survival time (P = 0.002). Using various exploratory cut points, plasma VEGF levels appeared to correlate with survival. In multivariate models in which other prognostic factors (serum prostate-specific antigen, alkaline phosphatase, evidence of measurable disease, and hemoglobin) were included, plasma VEGF levels were significant at various cut points tested. CONCLUSION: Although these data are exploratory and need to be confirmed in an independent data set, they suggest that VEGF may have clinical significance in patients with HRPC.

Giltnane, J. M., L. Ryden, et al. (2007). "Quantitative measurement of epidermal growth factor receptor is a negative predictive factor for tamoxifen response in hormone receptor positive premenopausal breast cancer." J Clin Oncol **25**(21): 3007-14.

PURPOSE: Although there is evidence for interaction between epidermal growth factor receptor (EGFR) and estrogen receptor (ER), it is still not clear how this affects response to endocrine therapies like tamoxifen. Here we assess the relationship between EGFR expression and tamoxifen response, with a new quantitative technology. PATIENTS AND METHODS: A tissue microarray was constructed from breast cancer from a cohort of 564 patients enrolled in a randomized clinical trial for adjuvant tamoxifen treatment in early breast cancer, with a median follow-up of 14 years. EGFR expression was measured using automated quantitative analysis, a fluorescence-based method for quantitative analysis of in situ protein expression. RESULTS: In ER-positive patients, tamoxifen-treated patients with low EGFR expression (n = 113) showed a significant effect by 2 years of adjuvant tamoxifen (P = .01), in contrast to no treatment effect in the EGFR-high group (n = 73, P = .69). The untreated group showed 49% v 57% 10-year recurrence-free survival for EGFR low versus high (P = .466) in the corresponding group of ER-positive

patients. A significant beneficial effect of tamoxifen treatment was seen in the EGFR-low group (hazard ratio [HR] = 0.43 (95% CI, 0.22 to 0.84; P = .013) in contrast to no effect in the EGFR-high group (HR = 1.14; 95% CI, 0.59 to 2.22; P = .7) by using a Cox model. CONCLUSION: This study provides clinical evidence that confirms the basic work that has shown high EGFR can indicate resistance to tamoxifen. It suggests that careful measurement of EGFR protein expression might define a subset of low-stage patients that could benefit from an alternative therapy.

Gnanapragasam, V. J., S. Darby, et al. (2005). "Evidence that prostate gonadotropin-releasing hormone receptors mediate an anti-tumourigenic response to analogue therapy in hormone refractory prostate cancer." J Pathol **206**(2): 205-13.

Gonadotropin-releasing hormone analogue (GnRHa) therapy is an established method of androgen withdrawal in the treatment of prostate cancer. The present study investigated if the expression of prostate GnRH receptors (GnRHRs) might influence the response to GnRHa. GnRHR protein expression was first studied in a panel of prostate cancer cell lines. In androgen-dependent cells, GnRHR expression was unchanged following acute or chronic androgen withdrawal. In these cells, GnRHa significantly inhibited androgen-induced cell proliferation (p = 0.01). In contrast, GnRHa was unable to further suppress basal levels of cell proliferation induced by androgen withdrawal. In androgen-independent prostate cancer cells, variable levels of GnRHR expression were observed. In these cells, GnRHa treatment blocked cell proliferation (p = 0.001) and invasion (up to 70%) induced by fibroblast growth factor stimulation. Crucially, this effect was only evident in cells that expressed high levels of the GnRHR. GnRHa treatment also significantly inhibited the ability of these cells to recover from a cytotoxic insult (50% inhibition). The clinical significance of prostate GnRHR was tested by immunohistochemistry in a preliminary cohort of patients treated with GnRHa or surgical castration. There was no association between GnRHR expression and pathological grade, clinical stage, time to PSA nadir (p = 0.82) (n = 35) or progression to hormone refractory disease (p = 0.22) (n = 21), irrespective of the treatment method. GnRHa therapy in the presence of high GnRHR expression however, was found to be associated with longer disease-specific survival (mean survival 85 months, p = 0.002). In contrast, high GnRHR expression was not associated with survival among surgically castrated patients (mean survival 50 months, p = 0.7). Taken together, these data support the notion of a functional interaction between GnRHa and the GnRHR, which results in an anti-tumourigenic effect on prostate cancer cells. Findings from this report have direct implications for the use of GnRHR as a novel therapeutic target in hormone refractory prostate cancer.

Green, M. D., P. A. Francis, et al. (2009). "Gefitinib treatment in hormone-resistant and hormone receptor-negative advanced breast cancer." Ann Oncol **20**(11): 1813-7.

BACKGROUND: Acquired and de novo endocrine resistance in breast cancer (BC) may be associated with overexpression of epidermal growth factor receptor (EGFR). Gefinitib is an orally active selective EGFR inhibitor which might benefit advanced breast cancer (ABC) patients either with acquired hormone resistance or with hormone receptor (HR)-negative tumors. PATIENTS AND METHODS: A two-arm multicenter phase II trial of oral gefitinib 500 mg/day was planned in two groups of 45 patients with ABC for whom chemotherapy was not currently indicated. Group 1 had hormone-resistant BC defined as HR-positive BC with progression after treatment with tamoxifen and an aromatase inhibitor. Group 2 had HR-negative BC. Tumor response was assessed every 8 weeks. The primary end point was the clinical benefit rate (CBR). RESULTS: Forty patients with hormone-resistant BC had a CBR of 0%. Two of 25 HR-negative BC patients showed stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) at 24 weeks resulting in a CBR of 7.7% (95% CI 0.9% to 25.1%). Enrollment ceased due to the low CBR. Toxicity resulted in treatment interruption (46%), dose reduction (20%) and withdrawal (11%) of patients. CONCLUSION: At a dose of 500 mg/day, gefitinib monotherapy resulted in a low CBR and no tumor response was identified.

Grundker, C. and G. Emons (2003). "Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer." Reprod Biol Endocrinol **1**: 65.

The expression of GnRH (GnRH-I, LHRH) and its receptor as a part of an autocrine regulatory system of cell proliferation has been demonstrated in a number of human malignant tumors, including cancers of the ovary. The proliferation of human ovarian cancer cell lines is time- and dose-dependently reduced by GnRH and its superagonistic analogs. The classical GnRH receptor signal-transduction mechanisms, known to operate in the pituitary, are not involved in the mediation of antiproliferative effects of GnRH analogs in these cancer cells. The GnRH receptor rather interacts with the mitogenic signal transduction of growth-factor receptors and related oncogene products associated with tyrosine kinase

activity via activation of a phosphotyrosine phosphatase resulting in downregulation of cancer cell proliferation. In addition GnRH activates nucleus factor kappaB (NFkappaB) and protects the cancer cells from apoptosis. Furthermore GnRH induces activation of the c-Jun N-terminal kinase/activator protein-1 (JNK/AP-1) pathway independent of the known AP-1 activators, protein kinase (PKC) or mitogen activated protein kinase (MAPK/ERK). Recently it was shown that human ovarian cancer cells express a putative second GnRH receptor specific for GnRH type II (GnRH-II). The proliferation of these cells is dose- and time-dependently reduced by GnRH-II in a greater extent than by GnRH-I (GnRH, LHRH) superagonists. In previous studies we have demonstrated that in ovarian cancer cell lines except for the EFO-27 cell line GnRH-I antagonist Cetrorelix has comparable antiproliferative effects as GnRH-I agonists indicating that the dichotomy of GnRH-I agonists and antagonists might not apply to the GnRH-I system in cancer cells. After GnRH-I receptor knock down the antiproliferative effects of GnRH-I agonist Triptorelin were abrogated while the effects of GnRH-I antagonist Cetrorelix and GnRH-II were still existing. In addition, in the ovarian cancer cell line EFO-27 GnRH-I receptor but not putative GnRH-II receptor expression was found. These data suggest that in ovarian cancer cells the antiproliferative effects of GnRH-I antagonist Cetrorelix and GnRH-II are not mediated through the GnRH-I receptor.

Grundker, C., A. R. Gunthert, et al. (2004). "Gonadotropin-releasing hormone (GnRH) agonist triptorelin inhibits estradiol-induced serum response element (SRE) activation and c-fos expression in human endometrial, ovarian and breast cancer cells." Eur J Endocrinol **151**(5): 619-28.

BACKGROUND AND METHODS: The majority of human endometrial (>80%), ovarian (>80%) and breast (>50%) cancers express GnRH receptors. Their spontaneous and epidermal growth-factor-induced proliferation is dose- and time-dependently reduced by treatment with GnRH and its agonists. In this study, we demonstrate that the GnRH agonist triptorelin inhibits estradiol (E2)-induced cancer cell proliferation. RESULTS: The proliferation of quiescent estrogen receptor alpha (ER alpha)-/ER beta-positive, but not of ER alpha-negative/ER beta-positive endometrial, ovarian and breast cancer cell lines, was significantly stimulated (P<0.001) (ANOVA) after treatment with E2 (10(-8) M). This effect was time- and dose-dependently antagonized by simultaneous treatment with triptorelin. The inhibitory effect was maximal at 10(-5) M concentration of triptorelin (P<0.001). In addition, we could show that, in ER alpha-/ER beta-positive cell lines, E2 induces activation of serum response element (SRE) and expression of the immediate early-response gene c-fos. These effects were blocked by triptorelin (P<0.001). E2-induced activation of estrogen-response element (ERE) was not affected by triptorelin. CONCLUSIONS: The transcriptional activation of SRE by E2 is due to ER alpha activation of the mitogen-activated protein kinase (MAPK) pathway. This pathway is impeded by GnRH, resulting in a reduction of E2-induced SRE activation and, in consequence, a reduction of E2-induced c-fos expression. This causes downregulation of E2-induced cancer cell proliferation.

Grundker, C., P. Volker, et al. (2001). "Antiproliferative signaling of luteinizing hormone-releasing hormone in human endometrial and ovarian cancer cells through G protein alpha(I)-mediated activation of phosphotyrosine phosphatase." Endocrinology **142**(6): 2369-80.

The signaling pathway through which LHRH acts in endometrial and ovarian cancers is distinct from that in the anterior pituitary. The LHRH receptor interacts with the mitogenic signal transduction of growth factor receptors, resulting in down-regulation of expression of c-fos and proliferation. Only limited data are available on the cross-talk between LHRH receptor signaling and inhibition of mitogenic signal transduction. The present experiments were performed to analyze in endometrial and ovarian cancer cells: 1) whether mutations or splice variants of the LHRH receptor are responsible for differences in LHRH signaling, 2) the coupling of G protein subtypes to LHRH receptor, 3) the phosphotyrosine phosphatase (PTP) activation counteracting growth factor receptor tyrosine kinase activity. For these studies, the well characterized human Ishikawa and Hec-1A endometrial cancer cell lines and human EFO-21 and EFO-27 ovarian cancer cell lines were used, which express LHRH and its receptor. 1) Sequencing of the complementary DNA of the LHRH receptor from position 31 to position 1204, covering the complete coding region (position 56 to position 1042) showed that there are neither mutations nor splice variants of the LHRH receptor transcript in Ishikawa and Hec-1A endometrial cancer cells or in EFO-21 and EFO-27 ovarian cancer cells. 2) All analyzed cell lines except for the ovarian cancer cell line EFO-27 expressed both G proteins, alpha(i) and alpha(q), as shown by RT-PCR and Western blotting. In the EFO-27 cell line only G protein alpha(i), not G protein alpha(q), expression was found. Cross-linking experiments using disuccinimidyl suberate revealed that in the cell lines expressing G protein alpha(i) and G protein alpha(q), both G proteins coupled to the LHRH receptor. Inhibition of epidermal growth factor (EGF)-

induced c-fos expression by LHRH, however, was mediated through pertussis toxin (PTX)-sensitive G protein alpha(i). Moreover, LHRH substantially antagonized the PTX-catalyzed ADP-ribosylation of G protein alpha(i). 3) Using a phosphotyrosine phosphatase assay based on molybdate-malachite green, treatment of quiescent EFO-21 and EFO-27 ovarian cancer cells and quiescent Ishikawa and Hec-1A endometrial cancer cells with 100 nM of the LHRH agonist triptorelin resulted in a 4-fold increase in PTP activity ($P < 0.001$). This effect was completely blocked by simultaneous treatment with PTX, supporting the concept of mediation through G protein alpha(i). As shown by quantitative Western blotting, EGF-induced tyrosine autophosphorylation of EGF receptors was reduced 45-63% after LHRH (100 nM) treatment ($P < 0.001$). This effect was completely blocked using the PTP inhibitor vanadate ($P < 0.001$). These results demonstrate that mutations or splice variants of the LHRH receptor in human endometrial and ovarian cancer cells are not responsible for the different signal transduction compared with that in pituitary gonadotrophs. We provide evidence that the tumor LHRH receptor couples to multiple G proteins, but the antiproliferative signal transduction is mediated through the PTX-sensitive G protein alpha(i). The tumor LHRH receptor activates a PTP counteracting EGF-induced tyrosine autophosphorylation of EGF receptor, resulting in down-regulation of mitogenic signal transduction and cell proliferation.

Guerin, O., P. Formento, et al. (2008). "Supra-additive antitumor effect of sunitinib malate (SU11248, Sutent) combined with docetaxel. A new therapeutic perspective in hormone refractory prostate cancer." J Cancer Res Clin Oncol **134**(1): 51-7.

PURPOSE: Physiological and molecular findings indicate over-expression of HER proteins and dysregulation of neo-angiogenesis during progression of advanced prostate cancer. The aim of this study was to test a novel rational therapeutic approach by combining docetaxel with an EGFR-targeting agent (cetuximab) and with an anti-angiogenic agent (sunitinib, SUTENT). METHODS: Mice bearing well-established PC3 prostate tumors (mean tumor volume/treatment group approximately 250 mm(3)) were treated every week with vehicle alone (controls), sunitinib (40 mg/kg/day, 5 days/week for 3 weeks, 0.2 ml p.o.), cetuximab (0.2 mg/kg/day, 5 days/week for 3 weeks, 0.2 ml i.p.) and docetaxel (10 mg/kg, 1 day/week for 3 weeks, 0.2 ml i.p.). RESULTS: Each drug, administered as a single-agent, demonstrated comparable and moderate effects on tumor growth with approximately 50 % inhibition at the end of the 3-week dosing schedule. Computed combination ratio (CR) values for tumor growth determined on days 61, 68 and 75 after cell implantation indicated supra-additive effects for the sunitinib-docetaxel (1.53, 1.15 and 1.47, respectively) and sunitinib-cetuximab combinations (1.2, 1.32 and 1.14, respectively), and suggested additive effects only for the sunitinib-cetuximab-docetaxel combination (CR = 1). The effects on tumor growth were accompanied by a parallel diminution in tumor cell proliferation (Ki 67) and tumor vascularization (von Willebrandt factor). There were significantly higher pro-apoptotic effects (caspase-3 cleavage) observed for the sunitinib-docetaxel and sunitinib-docetaxel-cetuximab as compared to the other conditions. CONCLUSION: The supra-additive anti-tumor effect observed with the sunitinib-docetaxel combination might support innovative strategies in the management of advanced prostate cancer.

Gujral, A., D. W. Burton, et al. (2001). "Parathyroid hormone-related protein induces interleukin 8 production by prostate cancer cells via a novel intracrine mechanism not mediated by its classical nuclear localization sequence." Cancer Res **61**(5): 2282-8.

PTHrP (parathyroid hormone-related protein) overexpression by prostate carcinoma cells has been implicated in tumor progression. Although the biological effects of PTHrP can be mediated by the G-protein-coupled PTH/PTHrP receptor, PTHrP also has intracrine actions mediated by a nuclear localization sequence at residues 87-107. We investigated the effect of PTHrP transfection and treatment on production by prostate carcinoma cells of IL (interleukin)-8, which can regulate prostate cancer growth by angiogenic activity and growth-promoting effects. Six prostate cancer cell lines exhibited constitutive expression of PTHrP and IL-8 that were significantly correlated ($r = 0.93$; $P < 0.01$). We transfected wild-type and mutant PTHrP into these cells. Wild-type PTHrP1-173 and PTHrP33-173 lacking the PTH/PTHrP receptor-binding domain induced a 3-fold stimulation of IL-8 production but not production of another angiogenic factor, vascular endothelial growth factor. Transfection of the COOH-terminal truncation mutant PTHrP1-87 induced a 5-fold simulation of IL-8 and a 3-fold increase in IL-8 mRNA. Cells transfected with PTHrP1-87 and 1-173 also showed increased cell proliferation. In contrast, exogenous PTHrP1-34 and 1-86 peptides did not significantly affect IL-8 production; moreover, PTHrP-neutralizing antibodies did not inhibit the production of IL-8 by transfected PTHrP. Additional transfection studies with progressively COOH-terminally truncated PTHrP1-87 defined a 23-amino acid sequence, PTHrP65-87, required for PTHrP1-87

to robustly stimulate IL-8 in prostate cancer cells. Confocal microscopy and immunoassay demonstrated PTHrP1-87 nuclear localization. Our results demonstrate that PTHrP acts to induce IL-8 production in prostate cancer cells via an intracrine pathway independent of its classical nuclear localization sequence. This novel pathway could mediate the effects of PTHrP on the progression of prostate cancer.

Gunthert, A. R., C. Grundker, et al. (2004). "Luteinizing hormone-releasing hormone (LHRH) inhibits apoptosis induced by cytotoxic agent and UV-light but not apoptosis mediated through CD95 in human ovarian and endometrial cancer cells." Anticancer Res **24**(3a): 1727-32.

Luteinizing hormone-releasing hormone (LHRH) and its receptor are frequently expressed in human ovarian and endometrial cancers and are part of an autocrine mechanism of growth control. We have previously shown that the LHRH analog Triptorelin induces activation of nucleus factor kappa B (NFkappaB) and reduces apoptosis induced by doxorubicin in human ovarian cancer cells EFO-21 and EFO-27. The present study was performed to investigate the anti-apoptotic effects of LHRH analogs on apoptosis induced by doxorubicin, UV-light and ligation of CD95 in human endometrial and ovarian cancer cells. We further investigated the interaction of the LHRH system with the apoptotic pathway focusing on the effector-protease caspase 3. Doxorubicin (100 nM) induced apoptosis in the LHRH-receptor-positive human endometrial cancer cell line Ishikawa and in the human ovarian cancer cell lines EFO-21 and NIH:OVCAR-3. Pretreatment for 24 h with native LHRH, the LHRH agonist Triptorelin or the LHRH antagonist Cetrorelix (100 nM) significantly reduced apoptosis induced by doxorubicin in these cells. In EFO-21 cells pretreatment with 100 nM Triptorelin also reduced UV-light-induced apoptosis from 76% to 62.7% ($p<0.01$). EFO-21 cells express CD95. Cross-linking of CD95 with monoclonal antibody anti-APO-1 (500 ng/ml) increased apoptosis from spontaneous rate to 10.3% to 38.3% in EFO-21 cells ($p<0.001$). Pre-treatment with Triptorelin did not reduce CD95-mediated apoptosis in these cells. LHRH analogs protect human endometrial and ovarian cancer cells from DNA-replication-dependent cytotoxic agent and UV-light-induced apoptosis, but not from CD95-mediated apoptosis.

Gunthert, A. R., C. Grundker, et al. (2002). "Luteinizing hormone-releasing hormone induces JunD-DNA binding and extends cell cycle in human ovarian cancer cells." Biochem Biophys Res Commun **294**(1): 11-5.

Expression of luteinizing hormone-releasing hormone (LHRH) and its receptor as part of an autocrine regulatory system of cell proliferation has been demonstrated in a number of human malignant tumors, including cancers of the ovary. This study was conducted to investigate whether LHRH induces activation of JunD and affects cell cycle regulation and DNA synthesis. Treatment of primary human ovarian cancer cells and human ovarian cancer cell lines EFO-21 and EFO-27 with LHRH agonist triptorelin (100 nM) resulted in an increase in G(0/1) phase and a decrease in G(2/S) phase of cell cycle. Treatment of quiescent EFO-21 or EFO-27 cells with triptorelin (100 nM) resulted in a 46.7 or 44.2-fold increase of AP-1 activation, respectively ($p<0.001$). Maximal binding of JunD on DNA consensus sequence was found after 4 h of treatment of quiescent EFO-21 or EFO-27 cells with triptorelin (100 nM). DNA synthesis was significantly decreased to 45.5+/-11.4% (day 0=control=100%; $p<0.001$) after 3 days of triptorelin (1 nM) treatment. These results suggest that LHRH agonist triptorelin induces JunD-DNA binding, resulting in reduced proliferation as indicated by increased G(0/1) phase of cell cycle and decreased DNA synthesis. Since LHRH activates nucleus factor kappa B (NF kappa B) and protects ovarian cancer cells from doxorubicin-induced apoptosis and JunD is shown to decrease cell cycle and cell proliferation, we propose that JunD activated by LHRH acts as a modulator of cell proliferation and cooperates with the anti-apoptotic and anti-mitogenic functions of LHRH.

Hall, C. L., R. Tsan, et al. (2004). "Enhanced invasion of hormone refractory prostate cancer cells through hepatocyte growth factor (HGF) induction of urokinase-type plasminogen activator (u-PA)." Prostate **59**(2): 167-76.

BACKGROUND: Increased expression of the hepatocyte growth factor (HGF) receptor (MET) is associated with high-grade prostatic adenocarcinoma and metastasis. However, the mechanism through which MET signaling contributes to prostate cancer (CaP) metastasis remains unclear. METHODS: Human PC-3 CaP cells and in vivo selected, isogeneic variant cells of increasing metastatic potential (PC-3M, PC-3M-Pro4, and PC-3M-LN4) were used to investigate the effect of HGF on CaP cell growth, protease production, and invasion. Cell-free urokinase-type plasminogen activator (u-PA) expression and function following HGF treatment were analyzed by Western blot, ELISA, and casein/plasminogen zymography. In vitro invasion stimulated by HGF was measured using Matrigel-coated invasion chambers. RESULTS: Both mRNA

and functional protein for MET were detected in each of the CaP cell lines. HGF treatment (0-40 ng/ml) weakly increase proliferation, however, HGF induced soluble u-PA protein and activity 3-fold in the metastatic variant cells. HGF significantly stimulated the invasion of highly metastatic PC-3M-LN4 cells through Matrigel and treatment with specific urokinase receptor inhibitors diminished the HGF-stimulated invasion in a dose-dependent manner. CONCLUSIONS: These results demonstrate the biological significance of u-PA up-regulation in response to HGF in highly metastatic hormone refractory CaP cells.

Han, S. H., J. M. de Klerk, et al. (2002). "The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with (186)Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study." J Nucl Med **43**(9): 1150-6.

(186)Re-1,1-hydroxyethylidene diphosphonate (etidronate) can be used for the palliative treatment of metastatic bone pain. A randomized, placebo-controlled study using (186)Re-etidronate was conducted on end-stage prostate cancer patients with metastatic bone pain. METHODS: Pain relief was assessed using an electronic diary containing questions reflecting the multidimensional character of chronic pain. The diary was marked twice daily for a maximum of 14 wk (2 wk before and 12 wk after the injection). Pain response was determined using a specific decision rule in which pain intensity, medication index, and daily activities were the core determinants. A positive response day was defined as a day on which pain intensity was reduced > or = 25% compared with baseline values, while medication index and daily activities were at least constant, or on which pain intensity was reduced < 25% and medication index or daily activities improved > or = 25%, without worsening of the remaining factor. The total response (%) was defined as the number of positive response days divided by the number of days of follow-up. RESULTS: Of the 111 included patients, 79 were evaluable (43 (186)Re-etidronate, 36 placebo). Thirty-two patients were excluded from the analysis because of incomplete datasets. The total response of the patients treated with (186)Re-etidronate varied from 0% to 96% (mean, 27%, or 23/84 d). In the placebo group, the total response varied from 0% to 80% (mean, 13%, or 11/84 d; Mann-Whitney U test, P < 0.05). The number of patients who requested radiotherapy was higher in the placebo group (67%) than in the (186)Re-etidronate group (44%) (relative risk, 1.51; Fisher's exact test, P = 0.069). CONCLUSION: This randomized controlled trial confirmed that, compared with placebo, (186)Re-etidronate resulted in a significantly longer pain response in the treatment of bone pain from metastasized prostate cancer.

Harper, M. E., L. Goddard, et al. (2004). "Characterization of a transplantable hormone-responsive human prostatic cancer xenograft TEN12 and its androgen-resistant sublines." Prostate **58**(1): 13-22.

BACKGROUND: Models for human prostate cancer can facilitate the study of resistance to endocrine therapy, aid drug discovery, and pre-clinical assessment. METHODS: Characteristics thought relevant to the growth in athymic nude mice of TEN12, an androgen-dependent transplantable prostatic cell line derived from a primary prostate carcinoma, and its two androgen-independent sublines, TEN12F and TEN12C, have been assessed immunocytochemically. RESULTS: The xenografts of the parental TEN12 line are moderately differentiated with both papillary and glandular regions, pleomorphic nuclei and abundant mitotic figures and are extremely vascular. The cells express androgen receptor (AR), PSA, VEGF, EGFR, c-erbB2, and TGFalpha. Both TEN12F and TEN12C xenografts possessed a more anaplastic morphology and displayed significantly lower growth rates, reduced blood vessel density (BVD), decreased MIB-1 antigen and E-cadherin expression and increased cytoplasmic AR and HSP90 staining. Elevated EGFR (membrane) but not c-erbB2 expression was demonstrated in the TEN12F line only. Castration of mice bearing TEN12 xenografts rapidly induced the appearance of cytoplasmic AR in the cells, PSA levels decreased initially but recovered to below pre-castration levels whilst reduced TGFalpha and loss of VEGF expression was seen in the long-term castrates. CONCLUSIONS: TEN12 and its sublines offer additional in vivo models to study the factors involved in the progression of prostatic cancer to androgen-independence.

Hassett, M. J., M. E. Hughes, et al. (2008). "Chemotherapy use for hormone receptor-positive, lymph node-negative breast cancer." J Clin Oncol **26**(34): 5553-60.

PURPOSE: To describe the frequency of chemotherapy use for hormone receptor (HR)-positive, lymph node (LN)-negative breast cancer from 1997 to 2004 at eight National Comprehensive Cancer Network institutions, to explore whether chemotherapy use varied over time and between institutions, and to identify factors associated with the decision to forego chemotherapy. PATIENTS AND METHODS: Among women younger than age 70

years with HR-positive, LN-negative breast cancer measuring more than 1 cm, we analyzed the frequency of chemotherapy use on a yearly basis. A multivariable logistic regression model assessed the relationship between receipt of chemotherapy and year of diagnosis, institution, tumor features, and patient characteristics. Interaction terms were added to the model, and stratified analyses were conducted to further explore the determinants of chemotherapy use. RESULTS: Fifty-five percent of 3,190 women received chemotherapy. Chemotherapy use was less common for patients with 1.1- to 2-cm tumors than for patients tumors greater 2 cm (47% v 87%, respectively; P < .01) and for women age 60 to 69 years versus women younger than age 50 years (24% v 76%, respectively; P < .01). On multivariable analysis, predictors independently associated with receiving chemotherapy included larger tumor size, higher grade, human epidermal growth factor receptor 2 overexpression, younger age, and institution (P < .01 for all). Institutions exhibited dramatically different rates of chemotherapy use (from 46% to 65%) and patterns of change in chemotherapy use over time (from a 79% relative increase to a 22% relative decrease). CONCLUSION: Although institutions seemed to agree that not all women with HR-positive, LN-negative breast cancer need chemotherapy, there did not seem to be consensus regarding which women should get chemotherapy. Only prospective randomized controlled trials will conclusively establish which subtypes of HR-positive, LN-negative breast cancer benefit from chemotherapy.

Helley, D., E. Banu, et al. (2009). "Platelet microparticles: a potential predictive factor of survival in hormone-refractory prostate cancer patients treated with docetaxel-based chemotherapy." Eur Urol **56**(3): 479-84.

BACKGROUND: Several studies suggest a causal relationship between platelet activation and cancer metastasis. Activated platelet microparticles (PMPs) release vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which play a major role in angiogenesis. OBJECTIVE: We conducted a prospective, nonrandomised, single-centre study in hormone-refractory prostate cancer (HRPC) patients to determine the impact of PMPs on the outcome. DESIGN, SETTING, AND PARTICIPANTS: Eligible chemonaive and metastatic HRPC patients received docetaxel-based chemotherapy and a low dose of prednisone. INTERVENTION: PMPs in whole blood were quantified before the start of chemotherapy through flow cytometry using an anti-CD41a monoclonal antibody, and plasma VEGF and bFGF were determined with an enzyme-linked immunosorbent assay. MEASUREMENTS: The primary end point was to evaluate the impact of the PMPs on overall survival (OS). We also studied the statistical interaction between PMPs and platelets and their relationship with OS. The median PMP value was used to sort patients into two groups. RESULTS AND LIMITATIONS: Data of 43 consecutive HRPC patients treated in a single French centre were analysed. Significant correlations were observed between Eastern Cooperative Oncology Group performance status (ECOG PS), platelets, and PMP level. The median OS was significantly shorter for patients with >6867 PMPs per microl of whole blood than for those with lower values (16.7 vs 26.4 mo, p=0.013). A significant relationship was found between OS and PMPs, whereas a statistical interaction term between PMPs and platelets was significantly associated with OS (p=0.019). No association was found between OS and plasma VEGF and bFGF. In the multivariate analysis, only baseline prostate-specific antigen (PSA) and ECOG PS remained significantly predictive of risk of death. CONCLUSIONS: In HRPC patients, PMPs and their interaction with platelets were predictive of outcome. A biologic association between PMPs and the OS of HRPC patients, independent of chemotherapy regimen, should be demonstrated by confirmatory prospective studies.

Hellsten, R., M. Johansson, et al. (2008). "Galiellalactone is a novel therapeutic candidate against hormone-refractory prostate cancer expressing activated Stat3." Prostate **68**(3): 269-80.

BACKGROUND: Signal transducer and activator of transcription 3 (Stat3) is constitutively active (phosphorylated) in several forms of cancer, including prostate cancer (PCa). Stat3 signaling may be an interesting target for cancer therapy since inhibition of this pathway mediates growth inhibition and apoptosis of these cells. In this study we investigated the in vitro and in vivo effects of the fungal metabolite galiellalactone, a direct inhibitor of Stat3, on PCa cells. METHODS: The human PCa cell lines DU145, PC-3, and LNCaP were used. Nude mice with subcutaneous PCa cell xenografts were subjected to daily intraperitoneal injections of galiellalactone for 3 weeks. The effect of galiellalactone on the induction of apoptosis of cultured PCa cells was investigated by Western blot analysis, immunocytochemistry, and annexin V staining. Effects of galiellalactone on Stat3 signaling were investigated by a luciferase reporter gene assay. Expression of Stat3 associated proteins and mRNA was investigated by Western blot and real-time quantitative PCR analysis. RESULTS: Galiellalactone induced apoptosis of p-Stat3 positive PCa cells

(androgen-insensitive DU145 and PC-3) but not in cells lacking p-Stat3 (androgen-sensitive LNCaP). Galiellalactone inhibited Stat3-mediated luciferase activity (IC(50) approximately 5 microM) and reduced the expression of Bcl-2, Bcl-x(L), c-myc, and cyclin D1. Furthermore, galiellalactone significantly suppressed DU145 xenograft growth in vivo (42% growth reduction; P<0.002) and reduced the relative mRNA expression of Bcl-x(L) and Mcl-1. CONCLUSIONS: Galiellalactone induced growth inhibition and apoptosis in androgen-insensitive PCa cells expressing p-Stat3. We suggest that galiellalactone is a potential anti-tumor lead against hormone-refractory PCa with constitutively active Stat3.

Henry, N. L., R. Dunn, et al. (2006). "Phase II trial of copper depletion with tetrathiomolybdate as an antiangiogenesis strategy in patients with hormone-refractory prostate cancer." Oncology **71**(3-4): 168-75.

OBJECTIVE: Preclinical studies suggest antiangiogenesis strategies may be effective in the treatment of prostate cancer. In tumor models, the copper-chelating agent tetrathiomolybdate (TM) has been shown to be antiangiogenic. We evaluated the antitumor activity of TM in patients with hormone-refractory prostate cancer (HRPC). METHODS: Nineteen patients with asymptomatic HRPC enrolled. Copper depletion was monitored using serum ceruloplasmin levels. Once the target ceruloplasmin level of 5-15 mg/dl was attained, patients underwent staging evaluation. Patients were reassessed every 12 weeks, and TM was continued until they developed evidence of disease progression or intolerable toxicity. Prostate-specific antigen and levels of vascular endothelial growth factor, basic fibroblast growth factor, interleukin (IL)-6 and IL-8 were measured at study entry, at the time of copper depletion, and monthly while on therapy. Results: Seventeen of 19 patients achieved copper deficiency on TM therapy. Of the 16 evaluable patients, 14 developed progressive disease, 1 discontinued therapy because of toxicity and 1 patient opted to discontinue therapy because of rising prostate-specific antigen level without objective evidence of progressive disease. Levels of vascular endothelial growth factor, IL-6 and IL-8, but not basic fibroblast growth factor, were elevated when compared to normal controls prior to TM therapy, but there was no significant change during therapy. There was no correlation between prostate-specific antigen and levels of angiogenesis factors. CONCLUSIONS: Copper depletion with TM did not delay disease progression in patients with asymptomatic metastatic HRPC.

Higano, C. S., J. M. Corman, et al. (2008). "Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer." Cancer **113**(5): 975-84.

BACKGROUND: This open-label, multicenter, dose-escalation study evaluated multiple dose levels of immunotherapy in patients with metastatic hormone-refractory prostate cancer (HRPC). The immunotherapy, based on the GVAX platform, consisted of 2 allogeneic prostate-carcinoma cell lines modified to secrete granulocyte-macrophage-colony-stimulating factor (GM-CSF). METHODS: Dose levels ranged from 100 x 10(6) cells q28d x 6 to 500 x 10(6) cells prime/300 x 10(6) cells boost q14d x 11. Endpoints included safety, immunogenicity, overall survival, radiologic response, prostate-specific antigen (PSA) kinetics, and serum GM-CSF pharmacokinetics. RESULTS: Eighty men, median age 69 years (range, 49-90 years), were treated. The most common adverse effect was injection-site erythema. Overall, the immunotherapy was well tolerated. A maximal tolerated dose was not established. The median survival time was 35.0 months in the high-dose group, 20.0 months in the mid-dose, group, and 23.1 months in the low-dose group. PSA stabilization occurred in 15 (19%) patients, and a >50% decline in PSA was seen in 1 patient. The proportion of patients who generated an antibody response to 1 or both cell lines increased with dose and included 10 of 23 (43%) in the low-dose group, 13 of 18 (72%) in the mid-dose group, and 16 of 18 (89%) in the high-dose group (P = .002; Cochran-Armitage trend test). CONCLUSIONS: This immunotherapy was well tolerated. Immunogenicity and overall survival varied by dose. Two phase 3 trials in patients with metastatic HRPC are underway.

Hirata, T., C. Shimizu, et al. (2009). "Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer." Br J Cancer **101**(9): 1529-36.

BACKGROUND: To evaluate the impact of change in the hormone receptor (HR) status (HR status conversion) on the long-term outcomes of breast cancer patients treated with neoadjuvant chemotherapy (NAC). METHODS: We investigated 368 patients for the HR status of their lesions before and after NAC. On the basis of the HR status and the use/non-use of endocrine therapy (ET), the patients were categorised into four groups: Group A, 184 ET-administered patients with HR-positive both before and after NAC; Group B, 47 ET-administered patients with HR status conversion; Group C, 12 ET-naive patients with HR status conversion; Group D, 125

patients with HR-negative both before and after NAC. RESULTS: Disease-free survival in Group B was similar to that in Group A (hazard ratio, 1.16; P=0.652), but that in Group C was significantly lesser than that in Group A (hazard ratio, 6.88; P<0.001). A similar pattern of results was obtained for overall survival. CONCLUSION: Our results indicate that the HR status of tumours is a predictive factor for disease-free and overall survival and that ET appears to be suitable for patients with HR status conversion. Therefore, both the CNB and surgical specimens should be monitored for HR status.

Hiscox, S., L. Morgan, et al. (2006). "Src as a therapeutic target in anti-hormone/anti-growth factor-resistant breast cancer." Endocr Relat Cancer **13 Suppl 1**: S53-9.

Endocrine therapy is the treatment of choice in hormone receptor-positive breast cancer. However, the effectiveness of anti-hormone drugs, such as tamoxifen, is limited because of the development of resistance, ultimately leading to disease progression and patient mortality. Using in vitro cell models of anti-hormone resistance, we have previously demonstrated that altered growth factor signalling contributes to an endocrine insensitive phenotype. Significantly, our recent studies have revealed that the acquisition of endocrine resistance in breast cancer is accompanied by a greatly enhanced migratory and invasive phenotype. Furthermore, therapeutic intervention using anti-growth factor monotherapies, despite an initial growth suppressive phase, again results in the development of a resistant state and a further augmentation of their invasive phenotype. Using the dual specific Src/Abl kinase inhibitor, AZD0530, we have highlighted a central role for Src kinase in promoting the invasive phenotype that accompanies both anti-hormone and anti-growth factor resistance. Importantly, the use of Src inhibitors in combination with anti-growth factor therapies appears to be additive, producing a marked inhibitory effect on cell growth, migration and invasion and ultimately prevents the emergence of a resistant phenotype. These observations suggest that the inhibition of Src activity may present a novel therapeutic intervention strategy, particularly when used as an adjuvant in endocrine-resistant breast disease, with the potential to delay or prevent the acquisition of subsequent resistance to anti-growth factor therapies.

Hoffmann, J. and A. Sommer (2005). "Steroid hormone receptors as targets for the therapy of breast and prostate cancer--recent advances, mechanisms of resistance, and new approaches." J Steroid Biochem Mol Biol **93**(2-5): 191-200.

Surgical ovariectomy and orchiectomy, first proposed over a century ago, are effective in breast and prostate cancer therapy, respectively. Later, the discovery of steroid hormones and their nuclear receptors led to the concept that inhibition of steroid receptor function by an antagonist prevents tumour growth. While the first anti-hormones, cyproteroneacetate (CPA) and tamoxifen were found accidentally, deeper understanding of nuclear receptors as transcription factors enabled more rational, structure-activity based drug discovery. Results from a drug-finding program on pure anti-estrogens will be reported. These new steroidal anti-estrogens are highly active, pure ER-antagonists that lead to an efficient degradation of the estrogen receptor alpha (ERalpha) protein without any agonistic activity. Data obtained in preclinical tumour models in mice and rats showed a high potency in growth inhibition of ERalpha-positive breast cancer. In parallel, by comparing three independently generated anti-estrogen-resistant breast cancer cell lines, it was our intention to gain insight into the mechanisms of endocrine resistance which will allow to define new approaches for the treatment of endocrine-resistant breast cancer. Candidate proteins potentially involved in mechanisms of anti-estrogen-resistant growth of breast cancer cell lines were analyzed. ERalpha and progesterone receptor (PR) expressions were lost on the protein level in all three anti-estrogen-resistant cell lines, whereas binding of epidermal growth factor (EGF) and protein expression of epidermal growth factor receptor (EGFR) were increased. Loss of ERalpha expression may be linked to the acquisition of anti-estrogen resistance and enhanced expression of the EGFR and of members of the S100 family of Ca2+-binding proteins may contribute to the outgrowth of resistant cells. Furthermore, we describe the pharmacological development of a novel, highly potent progesterone receptor antagonist. In rat mammary tumour models, treatment with the PR antagonist completely suppressed the growth of established tumours and prevented the development of breast tumours. Advanced prostate cancer is effectively treated by androgen ablation. However, this therapy becomes inefficient although the androgen receptor (AR) is still functionally expressed. One novel strategy for the treatment of advanced prostate cancer could be the selective inhibition of AR protein expression by anti-sense oligonucleotides or small interfering RNA (siRNA) molecules. Down-regulation of the human AR caused significant inhibition of LNCaP prostate cancer growth in vivo. Taken together, many promising alternatives for endocrine therapy of breast and prostate cancer are arising.

Horti, J., A. Widmark, et al. (2009). "A randomized, double-blind, placebo-controlled phase II study of vandetanib plus docetaxel/prednisolone in patients with hormone-refractory prostate cancer." Cancer Biother Radiopharm **24**(2): 175-80.

Vandetanib (ZACTIMA) is a once-daily oral anticancer drug that selectively inhibits vascular endothelial growth factor receptor, epidermal growth factor receptor, and rearranged during transfection signaling. This randomized (1:1), double-blind study evaluated vandetanib (100 mg/day) or placebo in combination with docetaxel (D; 75 mg/m(2) every 3 weeks) and prednisolone (P; 2 x 5 mg/day) in 86 patients with metastatic hormone-refractory prostate cancer (mHRPC). The primary assessment was prostate-specific antigen (PSA) response (confirmed reduction of >or=50% from baseline) and a greater number of patients showed a PSA response with placebo + DP (67%) versus vandetanib + DP (40%); hazard ratio = 2.23 (one-sided 80% confidence limit = 2.90; one-sided p = 0.99). More patients experienced progression events (disease progression or death from any cause) with vandetanib + DP (65%) versus placebo + DP (60%); hazard ratio = 1.13 (one-sided 80% confidence limit = 1.44; one-sided p = 0.67). The overall incidence of adverse events was similar in both groups, although more patients experienced adverse events, leading to permanent discontinuation with vandetanib + DP (28%) versus placebo + DP (12%). However, the safety and tolerability profile for vandetanib was similar to that previously reported; adverse events that occurred more frequently in the vandetanib + DP arm were hypertension (14% vs. 2%), erythematous rash (14% vs. 2%), and exfoliative rash (12% vs. 2%). In this study of patients with mHRPC, vandetanib + DP did not demonstrate any efficacy benefit, compared with placebo + DP.

Humphrey, P. A., S. Halabi, et al. (2006). "Prognostic significance of plasma scatter factor/hepatocyte growth factor levels in patients with metastatic hormone- refractory prostate cancer: results from cancer and leukemia group B 150005/9480." Clin Genitourin Cancer **4**(4): 269-74.

BACKGROUND: Scatter factor, also known as hepatocyte growth factor (SF/HGF), is a polypeptide growth factor thought to be important in the growth and spread of prostatic carcinoma. PATIENTS AND METHODS: Scatter factor/HGF levels in pretreatment plasma samples from 171 men with metastatic hormone-refractory prostate cancer enrolled in CALGB 9480 were quantified by solid-phase, enzyme-linked immunosorbent assay. RESULTS: The Cox proportional hazards model was used to assess the prognostic importance of SF/HGF with adjustment for established prognostic factors. Median SF/HGF was 991 pg/mL (range, 212-2733 pg/mL). In a univariate analysis, although plasma SF/HGF levels above versus below the median value did not reach statistical significance (P = 0.0862), the cutoff point of > 935 pg/mL was associated with a significant reduction in overall survival (P = 0.0334). Patients with SF/HGF levels > 935 pg/mL experienced a median survival of 15 months compared with 19 months for men with SF/HGF levels < or = 935 pg/mL. In a multivariate analysis, adjusting for SF/HGF, prostate-specific antigen, lactate dehydrogenase, and performance status, only plasma alkaline phosphatase was significantly associated with overall survival (hazard ratio, 1.7; 95% confidence interval, 1.2-2.5; P = 0.0017). CONCLUSION: Higher plasma levels of SF/HGF in men with hormone-refractory prostate cancer are associated with a decreased patient survival. Currently, SF/HGF levels do not appear to be of value as a contributor to multivariate models for prediction of outcome, but the association with decreased survival suggests that SF/HGF might be a potential target for therapy.

Iguchi, H., E. Onuma, et al. (2001). "Involvement of parathyroid hormone-related protein in experimental cachexia induced by a human lung cancer-derived cell line established from a bone metastasis specimen." Int J Cancer **94**(1): 24-7.

Cachexia often causes deterioration in the quality of life in cancer patients; however, its mechanism remains poorly understood. Cachexia has often been observed in experimental animals with bone metastases, and parathyroid hormone-related protein (PTHrP) plays an important role in the formation of such metastases. We therefore investigated the possible involvement of PTHrP in an experimental cachexia model using human lung-cancer cells (HARA-B). HARA-B cells produce a high amount of PTHrP but no TNF-alpha, IL-6 or leukemia inhibitory factor. The s.c. inoculation of HARA-B cells into nude mice caused reductions in body weight, adipose tissue weight, muscle weight and serum glucose levels. Serum levels of calcium and PTHrP increased. Neutralization of PTHrP with antibody caused rapid weight gain along with a rapid decrease in serum calcium levels. Our findings suggest that PTHrP plays an important role in the development of cancer cachexia. PTHrP therefore is a possible target molecule for the treatment of cancer cachexia.

Izumi, K., A. Mizokami, et al. (2009). "Tranilast inhibits hormone refractory prostate cancer cell proliferation and suppresses transforming growth factor beta1-associated osteoblastic changes." Prostate **69**(11): 1222-34.

BACKGROUND: Tranilast is a therapeutic agent used in treatment of allergic diseases, although it has been reported to show anti-tumor effects on some cancer cells. To elucidate the effects of tranilast on prostate cancer, we investigated the mechanisms of its anti-tumor effect on prostate cancer. METHODS: The anti-tumor effects and related mechanisms of tranilast were investigated both in vitro on prostate cancer cell lines and bone-derived stromal cells, and in vivo on severe combined immunodeficient (SCID) mice. We verified its clinical effect in patients with advanced hormone refractory prostate cancer (HRPC). RESULTS: Tranilast inhibited the proliferation of LNCaP, LNCaP-SF, and PC-3 cells in a dose-dependent manner and growth of the tumor formed by inoculation of LNCaP-SF in the dorsal subcutis and in the tibia of castrated SCID mice. Flow cytometry and TUNEL assay revealed induction of cell cycle arrest and apoptosis by tranilast. Tranilast increased expression of proteins involved in induction of cell cycle arrest and apoptosis. Coculture with bone-derived stromal cells induced proliferation of LNCaP-SF cells. Tranilast also suppressed secretion of transforming growth factor beta1 (TGF-beta1) from bone-derived stromal cells, which induced their differentiation. Moreover, tranilast inhibited TGF-beta1-mediated differentiation of bone-derived stromal cells and LNCaP-SF cell migration induced by osteopontin. In the clinical investigation, PSA progression was inhibited in 4 of 16 patients with advanced HRPC. CONCLUSIONS: These observations suggest that tranilast may be a useful therapeutic agent for treatment of HRPC via the direct inhibitory effect on cancer cells and suppression of TGF-beta1-associated osteoblastic changes in bone metastasis.

Johnston, S., J. Pippen, Jr., et al. (2009). "Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer." J Clin Oncol **27**(33): 5538-46.

PURPOSE: Cross-talk between human epidermal growth factor receptors and hormone receptor pathways may cause endocrine resistance in breast cancer. This trial evaluated the effect of adding lapatinib, a dual tyrosine kinase inhibitor blocking epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2), to the aromatase inhibitor letrozole as first-line treatment of hormone receptor (HR) -positive metastatic breast cancer (MBC). PATIENTS AND METHODS: Postmenopausal women with HR-positive MBC were randomly assigned to daily letrozole (2.5 mg orally) plus lapatinib (1,500 mg orally) or letrozole and placebo. The primary end point was progression-free survival (PFS) in the HER2-positive population. Results In HR-positive, HER2-positive patients (n = 219), addition of lapatinib to letrozole significantly reduced the risk of disease progression versus letrozole-placebo (hazard ratio [HR] = 0.71; 95% CI, 0.53 to 0.96; P = .019); median PFS was 8.2 v 3.0 months, respectively. Clinical benefit (responsive or stable disease >or= 6 months) was significantly greater for lapatinib-letrozole versus letrozole-placebo (48% v 29%, respectively; odds ratio [OR] = 0.4; 95% CI, 0.2 to 0.8; P = .003). Patients with centrally confirmed HR-positive, HER2-negative tumors (n = 952) had no improvement in PFS. A preplanned Cox regression analysis identified prior antiestrogen therapy as a significant factor in the HER2-negative population; a nonsignificant trend toward prolonged PFS for lapatinib-letrozole was seen in patients who experienced relapse less than 6 months since prior tamoxifen discontinuation (HR = 0.78; 95% CI, 0.57 to 1.07; P = .117). Grade 3 or 4 adverse events were more common in the lapatinib-letrozole arm versus letrozole-placebo arm (diarrhea, 10% v 1%; rash, 1% v 0%, respectively), but they were manageable. CONCLUSION: This trial demonstrated that a combined targeted strategy with letrozole and lapatinib significantly enhances PFS and clinical benefit rates in patients with MBC that coexpresses HR and HER2.

Johnston, S. R., J. Head, et al. (2003). "Integration of signal transduction inhibitors with endocrine therapy: an approach to overcoming hormone resistance in breast cancer." Clin Cancer Res **9**(1 Pt 2): 524S-32S.

Recent evidence suggests that common molecular adaptations occur during resistance to both tamoxifen and estrogen deprivation that use various signal transduction pathways, often involving cross-talk with a retained and functional estrogen receptor (ER) protein. There appear to be several different levels at which this cross-talk may occur, including peptide growth factor signaling via the type 1 tyrosine kinase growth factor receptor family [epidermal growth factor receptor (EGFR) and HER2], which may become up-regulated during endocrine treatment, ultimately being harnessed by cells to allow them hormone-independent growth. ER may remain involved in cell growth with ligand-independent phosphorylation and activation via different intracellular mitogen-activated protein kinases. ER may also become involved in non-nuclear estrogen-dependent signaling via interaction with the phosphatidylinositol 3'-kinase/Akt cell survival pathway or may interact with the stress-activated protein kinase/c-Jun-NH(2)-terminal kinase pathway. Understanding these mechanisms will permit the optimal integration of new signal transduction

inhibitors (STIs) into breast cancer therapy. Preclinical approaches that have shown promise include the use of EGFR tyrosine kinase inhibitors for hormone-resistant breast cancer cells that are dependent on either EGFR or HER2 signaling. Likewise, farnesyl transferase inhibitors, mitogen-activated protein kinase inhibitors, and cell cycle inhibitors have all shown activity in experimental breast cancer models. Emerging data suggest that STIs may be more effective when given in combination with endocrine therapy either to overcome resistance or to prevent/delay emergence of the resistance phenotype. Clinical trials are in progress to determine the safety and optimal schedule for each of the various STIs, and studies of STIs in combination with aromatase inhibitors have commenced in breast cancer to see whether the therapeutic response to endocrine therapy can be enhanced further.

Kaaks, R. (2001). "Endogenous hormone metabolism as an exposure marker in breast cancer chemoprevention studies." IARC Sci Publ **154**: 149-62.

There is overwhelming evidence that alterations in endogenous hormone metabolism--as a form of endogenous exposure-may be an important metabolic risk factor for the development of breast cancer. This chapter reviews current theories and major epidemiological findings that link endogenous hormones (sex steroids and their metabolites, but also insulin, and insulin-like growth factor-I (IGF-I)) to breast cancer risk. Knowledge about these metabolic risk factors can be used to identify women at increased risk of breast cancer, who might benefit most from chemoprevention. In addition, modification of high-risk endocrine profiles may itself become a central target of chemoprevention. Possible intervention strategies include improvement of insulin sensitivity, reducing concentrations of IGF-I in blood and breast tissue, reducing ovarian overproduction of androgens, inhibiting the activity of aromatase and other enzymes involved in estrogen formation within the breast, and modifying estrogen metabolism within the breast (e.g., decreasing 16alpha- and 4alpha-hydroxylation, and increasing O-methylation of catecholestrogens). Several of these possible strategies are illustrated with examples of chemopreventive agents currently in use or proposed for use to prevent breast cancer.

Kaczmarek, P., L. Pokoca, et al. (2008). "Effect of luteinizing hormone-releasing hormone (LHRH) analogue treatment on a cytokine profile in prostate cancer patients." Pharmacol Rep **60**(3): 399-403.

The aim of the study was to test serum concentrations of the chosen cytokines in patients with prostate cancer (PCa) treated with an luteinizing hormone-releasing hormone (LHRH) analogue. We tested interleukin (IL)-2, IL-10, tumor necrosis factor (TNF)-alpha, interferon (INF)-gamma in blood at three time points; I - before the injection, II - 10 days and III - 20 days after the injection in 14 men with PCa. Patients had one depot injection of the LHRH analogue monthly. The cytokine concentrations in serum samples were determined by ELISA method. Prostate specific antigen (PSA) level was examined before and after six months of the LHRH analogue treatment. After six months of the therapy, we observed normalization of serum PSA value from 16.48 ng/ml to 1.45 ng/ml. LHRH analogue injection resulted in a significant drop of the IL-2 concentration, and the value gradually returned to normal in the next 20 days. IL-10 concentration transiently increased and then was down-regulated. Serum TNF-alpha and INF-gamma concentrations in PCa patients were significantly lower compared to controls and were not affected by the treatment. LHRH analogue treatment in PCa patients modulates concentrations of the chosen cytokines which may result both in antitumor and a transient immunosuppressive effect.

Kakugawa, Y., Y. Minami, et al. (2007). "Relation of serum levels of estrogen and dehydroepiandrosterone sulfate to hormone receptor status among postmenopausal women with breast cancer." Breast Cancer **14**(3): 269-76.

BACKGROUND: It is hypothesized that breast cancer may consist of heterogeneous diseases with different hormonal environments classified by hormone receptor status. Epidemiologic studies evaluating risk factors for breast cancer by hormone receptor status have supported the hypothesis. However, there are inconsistencies in the risk factor profiles by estrogen receptor (ER) and progesterone receptor (PR) across the studies. To clarify the heterogeneity of the disease, it is necessary to understand not only risk factor profiles but also the biologic characteristics such as the relationships among endogenous sex hormone levels and hormone receptors. METHODS: We measured serum levels of estrone (E1), estradiol (E2), dehydroepiandrosterone sulfate (DHEAS), and sex hormone-binding globulin (SHBG) in 142 postmenopausal women aged 50 and over with primary breast cancer who had undergone surgical treatment, and investigated the heterogeneity in the relations of endogenous sex hormone levels to hormone receptor status, using the case-series study method. Subjects were categorized into 3 classes based on tertiles of each hormone level in receptor-negative subjects, and odds ratios (ORs) for receptor-positive status compared with receptor-negative status

were computed, taking the lowest category as a reference category. RESULTS: There were clear trends toward higher serum levels of E1, E2, and DHEAS in women with PR+ cancer. The case-series approach revealed that PR+ status might be strongly associated with serum sex hormone levels. In particular, the OR of PR+ was large for a high DHEAS level (OR for the highest category=4.28). No significant association between serum hormone levels and ER status was observed. CONCLUSION: The association of serum sex hormone levels with hormone receptor status may differ by PR status, but not by ER status. This finding suggests that PR status may be related to the heterogeneity in hormonal environments associated with breast cancer risk.

Kanashiro, C. A., A. V. Schally, et al. (2007). "Alterations of EGFR/HER, angiogenesis and apoptosis pathways after therapy with antagonists of growth hormone releasing hormone and bombesin in non-small cell lung cancer." Int J Oncol **30**(4): 1019-28.

New therapeutic strategies are necessary to improve the treatment of lung cancer. We investigated the effects of bombesin/gastrin-releasing peptide (GRP) antagonist, RC-3940-II, and growth hormone-releasing hormone (GHRH) antagonists, MZ-J-7-114 and MZ-J-7-118, on the expression of epidermal growth factor receptor (EGFR)/HER (-2, -3, and -4) family, angiogenic factors, VEGF-A and VEGF receptors (VEGF-R1 and VEGF-R2), and the apoptotic molecules Bax and Bcl-2, in H-460 and A-549 non-small cell lung carcinomas (NSCLC). Nude mice bearing xenografts of H-460 and A-549 NSCLC were treated daily with these peptide analogues for 4 weeks. The treatment resulted in growth inhibition of H-460 by 22-77% and A-549 NSCLCs by 64-84%. The inhibition of tumor growth was associated with a down-regulation of members of EGFR/HER family. A significant reduction of the levels of expression of EGFR/HER family on both tumors varied from 29-96%: the greatest inhibition being induced by RC-3940-II. Similarly, a significant decrease in the levels of VEGF-A in tumors by 19-60% and VEGF receptors (VEGF-R1, 24-74% and VEGF-R2, 25-50%) was detected after therapy. An up-regulation of Bax by 21-63% and a down-regulation of Bcl-2 by 23-39% was observed only for H-460 NSCLC. Our study demonstrates that human H-460 and A-549 NSCLC, express receptors for GHRH and bombesin/GRP, and respond to the respective antagonists. The antagonists of bombesin/GRP and GHRH could provide a new strategy for treatment of NSCLC through down-regulation of EGFR/HER family and an interference with the angiogenic and apoptotic pathways.

Kaseb, A. O., K. Chinnakannu, et al. (2007). "Androgen receptor and E2F-1 targeted thymoquinone therapy for hormone-refractory prostate cancer." Cancer Res **67**(16): 7782-8.

Relapse of prostate cancer after androgen ablation therapy is hormone-refractory, with continued tumor growth being dependent on the androgen receptor (AR). E2F-1, a regulator of cell proliferation and viability, reportedly plays a role in the development of hormone-refractory prostate cancer. Thymoquinone is a component of Nigella sativa, an herb used for thousands of years for culinary and medicinal purposes in Asian and Middle Eastern countries and has been reported to have an antineoplastic effect both in vitro and in vivo. We observed that thymoquinone inhibited DNA synthesis, proliferation, and viability of cancerous (LNCaP, C4-B, DU145, and PC-3) but not noncancerous (BPH-1) prostate epithelial cells by down-regulating AR and E2F-1. In LNCaP cells, this was associated with a dramatic increase in p21(Cip1), p27(Kip1), and Bax. Thymoquinone blunted progression of synchronized LNCaP cells from G1 to S phase, with a concomitant decrease in AR and E2F-1 as well as the E2F-1-regulated proteins necessary for cell cycle progression. In a xenograft prostate tumor model, thymoquinone inhibited growth of C4-2B-derived tumors in nude mice. This in vivo suppression of tumor growth, as with C4-2B cell growth in culture, was associated with a dramatic decrease in AR, E2F-1, and cyclin A as determined by Western blot of tissue extracts. Tissue immunohistochemical staining confirmed a marked reduction in E2F-1 and showed induction of apoptosis on terminal deoxyribonucleotidyl transferase-mediated dUTP nick end labeling assay. These findings show that thymoquinone suppresses the expression of AR and E2F-1 necessary for proliferation and viability of androgen-sensitive as well as androgen-independent prostate cancer cells both in vitro and in vivo and, moreover, produced no noticeable side effects in mice. We conclude that thymoquinone, a naturally occurring herbal product, may prove to be effective in treating hormone-sensitive as well as hormone-refractory prostate cancer. Furthermore, because of its selective effect on cancer cells, we believe that thymoquinone can also be used safely to help prevent the development of prostate cancer.

Kaufman, B., J. R. Mackey, et al. (2009). "Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study." J Clin Oncol **27**(33): 5529-37.

PURPOSE: TAnDEM is the first randomized phase III study to combine a hormonal agent and trastuzumab without chemotherapy as treatment for human epidermal growth factor receptor 2 (HER2)/hormone receptor-copositive metastatic breast cancer (MBC). PATIENTS AND METHODS: Postmenopausal women with HER2/hormone receptor-copositive MBC were randomly assigned to anastrozole (1 mg/d orally) with or without trastuzumab (4 mg/kg intravenous infusion on day 1, then 2 mg/kg every week) until progression. The primary end point was progression-free survival (PFS) in the intent-to-treat population. Results Overall, 103 patients received trastuzumab plus anastrozole; 104 received anastrozole alone. Patients in the trastuzumab plus anastrozole arm experienced significant improvements in PFS compared with patients receiving anastrozole alone (hazard ratio = 0.63; 95% CI, 0.47 to 0.84; median PFS, 4.8 v 2.4 months; log-rank P = .0016). In patients with centrally confirmed hormone receptor positivity (n = 150), median PFS was 5.6 and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively (log-rank P = .006). Overall survival in the overall and centrally confirmed hormone receptor-positive populations showed no statistically significant treatment difference; however, 70% of patients in the anastrozole alone arm crossed over to receive trastuzumab after progression on anastrozole alone. Incidence of grade 3 and 4 adverse events was 23% and 5%, respectively, in the trastuzumab plus anastrozole arm, and 15% and 1%, respectively, in the anastrozole alone arm; one patient in the combination arm experienced New York Heart Association class II congestive heart failure. CONCLUSION: Trastuzumab plus anastrozole improves outcomes for patients with HER2/hormone receptor-copositive MBC compared with anastrozole alone, although adverse events and serious adverse events were more frequent with the combination.

Kim, K. Y., K. C. Choi, et al. (2004). "Type II gonadotropin-releasing hormone stimulates p38 mitogen-activated protein kinase and apoptosis in ovarian cancer cells." J Clin Endocrinol Metab **89**(6): 3020-6.

Recent results indicate that a novel second form of GnRH, GnRH-II, has an antiproliferative effect on ovarian and endometrial cancer cells and might be considered as a possible therapy for gynecological tumors. However, the mechanism of the GnRH-II-induced antiproliferative effect is not known. The p38 MAPK, one of the stress-activated protein kinases, is activated by diverse cellular stress and proinflammatory cytokines. In this study, the effect of GnRH-II on the activation of p38 MAPK was investigated, and its possible role in the regulation of cell proliferation and apoptosis was further examined in the human ovarian cancer cell line, OVCAR-3. Treatment with GnRH-II (100 nM) resulted in an activation of p38 MAPK in a time-dependent manner. A significant activation of p38 MAPK was observed at 2, 5, 10, and 15 min after GnRH-II treatment. The activation of p38 MAPK by GnRH-II was reversed in the presence of a specific inhibitor of p38 MAPK, SB203580 (1 microM). The transcription factor, activator protein-1, was activated (1.5-fold) by GnRH-II and attenuated in the presence of SB203580 (1 microM). Treatment with GnRH-II (1 nM, 100 nM, 10 microM) for 2, 4, and 6 d resulted in an inhibition of cell growth in OVCAR-3 cells as determined by thymidine incorporation assay. The effect of GnRH-II (100 nM) on cell proliferation was blocked by pretreatment with SB203580 (1 microM). Furthermore, a significant increase of apoptosis (1.6-fold) was observed after GnRH-II treatment, which was also reversed by pretreatment with SB203580 (1 microM). Taken together, these results indicate that p38 MAPK is involved in the GnRH-II-induced inhibition of cell growth through activator protein-1 activation, which may be related to induction of apoptosis in ovarian cancer cells.

Kimura, K., M. Markowski, et al. (2001). "Androgen blocks apoptosis of hormone-dependent prostate cancer cells." Cancer Res **61**(14): 5611-8.

Androgen plays a critical role in the promotion and growth of prostate cancer. Androgen ablation has an expanding role in prostate cancer treatment and is now used to improve the efficacy of radiation therapy in addition to its role in treatment of metastatic disease. Here we show that androgen interferes with induction of prostate cancer cell death induced by a variety of stimuli. The effect of androgen on cell death occurs predominantly by interference with caspase activation and the inhibition of caspase cleavage in both the extrinsic and intrinsic cell death pathways. Androgen inhibited apoptosis induced by both tumor necrosis factor alpha (TNF-alpha) and by Fas activation with or without concomitant irradiation. An antiapoptotic effect was seen in the presence of R1881, dihydrotestosterone, and also 17beta-estradiol within 24 h of death induction. Sustained inhibition of apoptosis at 72 h was seen only with R1881, dihydrotestosterone, cyproterone acetate, and hydroxyflutamide. Androgen treatment inhibited activation of caspases-8, -7, and -9 by TNF-alpha +/- irradiation. Androgen attenuated BAX expression and blocked appearance of the proapoptotic p18 fragment of BAX. Androgen also abrogated BID cleavage induced by TNF-alpha + irradiation that contributed to a decrease in cytochrome c egress from mitochondria

induced by TNF-alpha +/- irradiation. There was also decreased mitochondrial depolarization in response to TNF-alpha + irradiation. Production of the proapoptotic lipid metabolite ceramide was not affected by androgen, but androgen acted downstream from ceramide generation because R1881 blocked cell-death induction by bacterial sphingomyelinase. Inhibition of phosphoinositol-3-kinase activity by wortmannin induced apoptosis that was also blocked by androgen, but there was no effect on protein levels or phosphorylation of AKT, indicating that R1881 did not interact with survival signaling of phosphoinositol-3-kinase. Lastly, androgen inhibited activation of nuclear factor-kappaB during death induction, but the effect of androgen on cell death was not mediated by interference with the nuclear factor-kappaB pathway. The data suggest that androgen induced blockade of caspase activation in both intrinsic and extrinsic cell death pathways and thereby was able to protect prostate cancer cells from apoptosis induced by diverse stimuli.

Ko, Y. J., E. J. Small, et al. (2001). "A multi-institutional phase ii study of SU101, a platelet-derived growth factor receptor inhibitor, for patients with hormone-refractory prostate cancer." Clin Cancer Res **7**(4): 800-5.

In a multi-institutional Phase II trial, we evaluated the efficacy of a platelet-derived growth factor receptor (PDGF-r) inhibitor, SU101, in patients with hormonerefractory prostate cancer. The patients received a 4-day i.v. loading dose of SU101 at 400 mg/m(2) for 4 consecutive days, followed by 10 weekly infusions at 400 mg/m(2). The primary study end points were a decline in prostate-specific antigen (PSA) and a decrease in measurable tumor. Secondary end points were time to progression and an effect on pain as measured by the Brief Pain Survey. Expression of PDGF-r was examined in both metastatic and archival primary prostate tumor samples. Forty-four patients were enrolled at four centers. The median age was 72 years, the median PSA was 223 ng/ml, and 21 patients had at least one prior chemotherapy. Thirty-nine patients are evaluable for PSA, and three patients demonstrated a PSA decline >50% from baseline (55-99.9% decrease). The median time to progression was 90 days. Of 19 patients evaluable for measurable disease, 1 patient had a partial response. Nine of 35 evaluable patients had significant improvement in pain. The most frequent adverse events were asthenia (75%), nausea (55%), anorexia (50%), and anemia (41%). PDGF-r expression was detected in 80% of the metastases and 88% of primary prostate cancers. The results of this trial may warrant further clinical studies with other PDGF-r inhibitors.

Kohli, M., V. Kaushal, et al. (2003). "Prospective study of circulating angiogenic markers in prostate-specific antigen (PSA)-stable and PSA-progressive hormone-sensitive advanced prostate cancer." Urology **61**(4): 765-9.

OBJECTIVES: To prospectively describe and compare circulating vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in two groups of advanced prostate cancer patients undergoing androgen deprivation. The first patient group (n = 21) consisted of patients with stable serum prostate-specific antigen (PSA) and the second group (n = 20) consisted of patients with a rising serum PSA during androgen deprivation. METHODS: Patients with diabetes or active heart disease or those receiving anticoagulants were excluded. Circulating VEGF and bFGF were measured in platelet-poor plasma. bFGF was also measured in urine. Platelet factor 4 protein (PF4) assays were performed to evaluate platelet activity in platelet-poor plasma samples. Commercially available enzyme-linked immunosorbent assay kits were used for all assays, and all tests were performed in duplicate. RESULTS: The median age of this study population was 75 years (range 58 to 85). Median plasma VEGF measured in the PSA-stable group was 801.5 pg/mL and in the PSA-rising group was 655.5 pg/mL (P = 0.464). Circulating bFGF was undetectable in plasma, but 4 patients in the PSA-stable group had measurable urine levels. Platelet-poor plasma PF4 assays in all patients were less than 3 IU/mL (normal range 0 to 10). CONCLUSIONS: Our pilot study suggests elevated plasma VEGF levels in advanced prostate cancer do not increase during failure of androgen deprivation therapy. Most of the advanced cancer patients in this study expressed plasma VEGF. This suggests its potential role as a surrogate marker for response assessment during antiangiogenic therapy in this stage.

Koike, H., K. Ito, et al. (2005). "Insulin-like growth factor binding protein-6 inhibits prostate cancer cell proliferation: implication for anticancer effect of diethylstilbestrol in hormone refractory prostate cancer." Br J Cancer **92**(8): 1538-44.

Diethylstilbestrol (DES) is a synthetic oestrogen, and its anticancer effects are exerted in androgen-dependent prostate cancer. The administration of DES decreases serum testosterone to castration levels. However, in androgen-independent prostate cancer patients, who are already orchiectomised, the administration of DES improves symptoms and decreases prostate-specific antigen (PSA). The mechanisms responsible for these direct inhibitory effects have been explained as biological

actions not mediated by oestrogen receptors. We assessed the gene expression profiles of prostate cancer cells treated with DES, and investigated direct inhibitory effects of DES. DES inhibited the proliferation of LNCaP and PC-3 cells. cDNA microarray analysis showed that expression of many genes was downregulated by DES. However, insulin-like growth factor binding protein 6 (IGFBP-6) gene expression levels were upregulated in PC-3 cells. IGFBP-6 gene expression and protein levels significantly increased after DES treatment. Recombinant IGFBP-6 inhibited cell proliferation, and the inhibitory effect of DES was neutralised by anti-IGFBP-6 antibody. From the immunohistochemical analysis of IGFBP-6 using biopsy samples from androgen-independent prostate cancer, we found IGFBP-6 expression in androgen independent prostate cancer, and that DES treatment increased the IGFBP-6 staining intensity of the cancer cells in one sample. These findings suggested that DES induces IGFBP-6, which inhibits cell proliferation in an androgen-independent prostate cancer cell line, PC-3. IGFBP-6 therefore might be involved in the direct effects of DES in androgen-independent prostate cancer.

Kojima, S., H. Suzuki, et al. (2004). "Alternative antiandrogens to treat prostate cancer relapse after initial hormone therapy." J Urol **171**(2 Pt 1): 679-83.

PURPOSE: We studied the efficiency of second or third line hormonal therapy for prostate cancer relapse after hormone therapy. MATERIALS AND METHODS: The study included 70 patients with advanced prostate cancer treated with hormonal therapy, androgen deprivation monotherapy or maximum androgen blockade including surgical or medical castration combined with steroidal antiandrogen, 100 mg chlormadinone acetate daily or nonsteroidal antiandrogens, 375 mg flutamide (FLT) daily or 80 mg bicalutamide (BCL) daily. When the disease relapsed, we discontinued the antiandrogen and evaluated the patient for the antiandrogen withdrawal syndrome (AWS). Thereafter we administrated an alternative antiandrogen and evaluated its effect. RESULTS: The incidence of the AWS after first, second and third line hormonal therapy was 35.8%, 8.0% and 0%, respectively. The efficiency of subsequent hormonal therapy was not related to the occurrence of the AWS. Nonsteroidal antiandrogens as alternative therapies for disease relapse from primary therapy were effective in second line (FLT 38.1%, BCL 44.4%) or in third line (FLT 30.0%, BCL 28.6%) hormonal therapy. Of 5 (80%) patients who responded to second line therapy 4 (80%) had effective third line therapy, while only 1 of 12 (8.3%) second line nonresponders had effective third line therapy (p = 0.003). The survival of second line responders was significantly better than that of nonresponders (5-year survival rate 92.3% vs 23.9%, p <0.001), indicating a potential predictive value for second line responsiveness. No significant clinical factor identified second line responsiveness. CONCLUSIONS: Subsequent nonsteroidal antiandrogen therapies were effective against prostate cancer relapse after hormonal therapy. The response to third line therapy was more effective and survival was improved from the time of first line therapy relapse among second line responders than that in nonresponders. Our data support the notion that second line responders are androgen independent but still hormonally sensitive.

Koletsky, A. J., M. L. Guerra, et al. (2003). "Phase II study of vinorelbine and low-dose docetaxel in chemotherapy-naive patients with hormone-refractory prostate cancer." Cancer J **9**(4): 286-92.

PURPOSE: Vinorelbine, a semisynthetic vinca alkaloid, and docetaxel, a semisynthetic taxane, are active single agents in hormone-refractory prostate cancer and have demonstrated synergy in tumor cell lines and animal models. This study was designed to assess the efficacy and tolerability of vinorelbine and low-dose docetaxel in chemotherapy-naive, hormone-refractory prostate cancer patients whose disease had progressed after withdrawal from anti-androgens, despite castrate testosterone levels. PATIENTS AND METHODS: Patients with histologically confirmed hormone-refractory prostate cancer despite testosterone levels < or = 50 ng/mL, Karnofsky performance status > 70, and adequate bone marrow reserve were enrolled. They received vinorelbine, 20 mg/m2, followed by docetaxel, 25 mg/m2, on days 1 and 8 of a 21-day cycle. Tumor response was defined by prespecified reductions from baseline prostate-specific antigen levels or bidimensionally measurable disease. Adjustments in the dose of either agent were based on > or = grade 2 toxicity according to standard criteria. RESULTS: Twenty-one patients with a mean age of 76 years (range, 60-83 years) and a median prostate-specific antigen level of 116 ng/mL (range, 10.4-4,262 ng/mL) were enrolled and received a total of 152 courses (median, 7.5 courses) of vinorelbine and docetaxel. Of the 19 patients who were evaluable for biochemical response, prostate-specific antigen reductions from baseline of > 75%, > or = 50% to < or = 75%, and < 50% were observed in eight, three, and seven patients, respectively (median prostate-specific antigen decrease, 60% +/- 31%). Of five patients with measurable disease, three were evaluable: one patient had a complete response, and two had partial responses at the site of measurable disease. The vinorelbine/docetaxel doublet was generally well tolerated. In the first two cycles of therapy, six

patients had grade 3 and eight patients had grade 4 neutropenia as their worst-grade toxicities; all cases were manageable with granulocyte colony stimulating factor support. Acute respiratory distress syndrome was observed in one patient. There were few dose reductions or interruptions. DISCUSSION: Vinorelbine, 20 mg/m2, and low-dose docetaxel, 25 mg/m2, given on days 1 and 8 every 21 days, is a well-tolerated regimen with biochemical and objective response rates comparable to standard therapies in patients with hormone-refractory prostate cancer. A multicenter, randomized trial is under way to compare vinorelbine plus low-dose docetaxel with estramustine plus higher-dose docetaxel (60 mg/m2).

Koo, J. S., W. Jung, et al. (2009). "Impact of grade, hormone receptor, and HER-2 status in women with breast cancer on response to specific chemotherapeutic agents by in vitro adenosine triphosphate-based chemotherapy response assay." J Korean Med Sci **24**(6): 1150-7.

This study was designed to assess whether histological and biological factors of breast cancer can predict chemoresponse to specific agents. Adenosine triphosphate-based chemotherapy response assay (ATP-CRA) was employed to retrieve chemoresponse to 5-fluorouracil (5-FU), doxetaxel, doxorubicin, epirubicin, and paclitaxel in 49 patients. Tumors with high histologic and nuclear grade have higher response rate to doxorubicin (P<0.05) and palitaxel (P<0.05). Estrogen receptor (ER)-negative tumors respond well to doxorubicin (P=0.038), and progesterone receptor (PR)-negative tumors to 5-FU (P=0.039), doxetaxel (P=0.038), doxorubicin (P=0.000), epirubicin (P=0.010), and paclitaxel (P=0.003). Among the breast cancer subtypes determined by ER, PR, and HER-2 immunohistochemical stains, the HER-2+/ER- subtype has a higher response rate to doxorubicin (P=0.008). This in vitro result suggests that the combination of histologic and nuclear grade, hormone receptor, and HER-2 status can be a predictive factor of response to specific chemotherapy agents. Further in vivo study should be followed for clinical trials.

Kraus, S., G. Levy, et al. (2004). "Gonadotropin-releasing hormone induces apoptosis of prostate cancer cells: role of c-Jun NH2-terminal kinase, protein kinase B, and extracellular signal-regulated kinase pathways." Cancer Res **64**(16): 5736-44.

A standard therapy used today for prostate cancer is androgen ablation by gonadotropin-releasing hormone analogs (GnRH-a). Although most patients respond to androgen ablation as an initial systemic therapy, nearly all cases will develop androgen resistance, the management of which is still a major challenge. Here, we report that GnRH-a can directly induce apoptosis of the androgen-independent prostate cancer-derived DU145 and PC3 cell lines. Using specific inhibitors, we found that the apoptotic effect of GnRH-a is mediated by c-Jun NH2-terminal kinase (JNK) and inhibited by the phosphatidylinositol 3'-kinase (PI3K)-protein kinase B (PKB) pathway. Indeed, in DU145 cells, GnRH-a activates the JNK cascade in a c-Src- and MLK3-dependent manner but does not involve protein kinase C and epidermal growth factor receptor. Concomitantly, GnRH-a reduces the activity of the PI3K-PKB pathway, which results in the dephosphorylation of PKB mainly in the nucleus. The reduction of PKB activity releases PKB-induced inhibition of MLK3 and thus further stimulates JNK activity and accelerates the apoptotic effect of GnRH-a. Interestingly, extracellular signal-regulated kinase is also activated by GnRH-a, and this occurs via a pathway that involves matrix metalloproteinases and epidermal growth factor receptor, but its activation does not affect JNK activation and the GnRH-a-induced apoptosis. Our results support a potential use of GnRH-a for the treatment of advanced prostate cancer and suggest that the outcome of this treatment can be amplified by using PI3K-PKB inhibitors.

Krieger, N. (2008). "Hormone therapy and the rise and perhaps fall of US breast cancer incidence rates: critical reflections." Int J Epidemiol **37**(3): 627-37.

BACKGROUND: Results of the Women's Health Initiative (WHI) study-which to many unexpectedly showed that hormone therapy (HT) did not decrease and may in fact have elevated risk of cardiovascular disease, while also finding expected links between HT and breast cancer-have spurred critical reflection chiefly regarding the cardiovascular results. Suggesting similar scrutiny of cancer epidemiology is warranted are new studies linking the post-WHI drop in HT use to a substantial decline in breast cancer incidence and the implications of these findings for prior explanations of the rising rates of US breast cancer incidence during the 1980s. METHODS: Literature search for review and research articles on temporal trends in US breast cancer incidence during the past 25 years, starting in the mid-1980s, when extant epidemiologic evidence had already indicated that HT increased risk of breast cancer. RESULTS: Among the 21 articles identified, spanning from 1987 to 2007, nine included no mention of HT as a possible factor contributing to the steep rise in breast cancer incidence in the 1980s, seven included a minor mention and only five (one published in 2003, the others in 2006 and 2007) provided any substantive discussion of this issue-but only in relation to current trends and not the 1980 rise

in breast cancer incidence. CONCLUSION: A critical appraisal of the epidemiologic literature highlights important gaps in explanations for breast cancer incidence trends and also how current and changing population patterns of disease distribution are ultimately what put our aetiologic explanations to the test.

Kurebayashi, J., T. Otsuki, et al. (2001). "Hypoxia reduces hormone responsiveness of human breast cancer cells." Jpn J Cancer Res **92**(10): 1093-101.

Resistance to hormonal therapy frequently occurs following successful treatment in breast cancer. The mechanism responsible for this acquired resistance is still unknown. It has been suggested that a hypoxic tumor microenvironment promotes malignant progression of cancer, i.e., hypoxia may promote estrogen-independent growth (a more malignant phenotype) of breast cancer. To clarify this hypothesis, the effects of hypoxia on the growth responses to hormonal agents and the expression levels of estrogen receptor (ER)-alpha and progesterone receptor (PgR) were investigated in two human breast cancer cell lines, ML-20 and KPL-1. The expression level of ER-alpha was significantly decreased by hypoxia (1% O(2)) in a time-dependent manner in both cell lines. Hypoxia also significantly reduced the growth-promoting effect of estradiol (E2) and the growth-inhibitory effects of an antiestrogen, ICI 182 780, and a progestin, medroxyprogesterone acetate, in both cell lines. In addition, hypoxia markedly suppressed the induction of PgR mRNA and protein by E2 in both cell lines. To clarify further the effect of hypoxia on ER-alpha expression, the expression levels of hypoxia-inducible factor-1 alpha (HIF-1 alpha), a marker of hypoxia and ER-alpha were immunohistochemically examined in 36 breast cancer specimens. ER-alpha expression (both its proportion and intensity) was significantly lower in nuclear HIF-1 alpha-positive tumors than in negative tumors. These findings indicate that hypoxia down-regulates ER-alpha expression as well as ER-alpha function in breast cancer cells. These processes may lead to an acquired resistance to hormonal therapy in breast cancer.

Kwak, C., S. J. Jeong, et al. (2002). "Prognostic significance of the nadir prostate specific antigen level after hormone therapy for prostate cancer." J Urol **168**(3): 995-1000.

PURPOSE: We determine whether the nadir prostate specific antigen (PSA) level after hormone therapy can be used to predict the progression to hormone refractory prostate cancer. MATERIALS AND METHODS: We reviewed the progressive status and survival of 177 patients with stage C or D prostate cancer who had received hormone therapy at our institution. The overall survival rate, incidence of progression to hormone refractory prostate cancer and interval until progression were analyzed with reference to the nadir PSA level. Multiple regression analysis was used to analyze the predictive factors for progression to hormone refractory prostate cancer, and the relative efficacy of the nadir PSA level in predicting progression was evaluated by receiver operating characteristics analysis. RESULTS: Median followup was 39 months (range 3 to 89) and 85.4% of patients (151) responded to treatment, of whom 77.5% (117) had progression to hormone refractory prostate cancer. Median time until nadir PSA levels were reached after hormone therapy was 8.1 months and median time until hormone refractory prostate cancer was 24.0 months. Nadir PSA levels were less than 0.2 ng./ml. in 31% of respondents, 0.2 to 1.0 ng./ml. in 23%, 1.1 to 10 ng./ml. in 42% and greater than 10 ng./ml. in 5%. These groups had similar clinicopathological characteristics. Nadir PSA levels correlated significantly with pretreatment PSA levels, Gleason scores and progression to hormone refractory prostate cancer ($p = 0.01$, $p < 0.01$ and $p < 0.001$, respectively), and inversely correlated with the interval to the establishment of hormone refractory prostate cancer ($r = -0.465$, $p < 0.05$). By univariate analysis bone metastasis, nadir PSA, PSA at 6 months after treatment and pretreatment PSA were significantly associated with progression to hormone refractory prostate cancer. Only the nadir PSA was calculated to be an independent factor by multivariate analysis. Receiver operating characteristics analysis indicated that nadir PSA predicted progression to hormone refractory prostate cancer after 2 years with an accuracy of 86.2%. With the lower limit of the nadir PSA level set to 1.1 ng./ml., sensitivity was 80.3% and specificity was 83.8%, and these levels were deemed the most appropriate. Furthermore, nadir PSA after hormone therapy was an independent prognosticator for survival, as were initial levels of hemoglobin and alkaline phosphatase. CONCLUSIONS: The nadir PSA level after hormone therapy may be the most accurate factor predicting the progression to hormone refractory prostate cancer and is an independent prognostic factor for survival. Furthermore, a lower limit for the nadir PSA level of 1.1 ng./ml. gives optimal sensitivity and specificity.

Labrie, F., A. Belanger, et al. (2005). "Gonadotropin-releasing hormone agonists in the treatment of prostate cancer." Endocr Rev **26**(3): 361-79.

In 1979, the first prostate cancer patient was treated with a GnRH agonist at the Laval University Medical Center in Quebec City, Canada, thus rapidly leading to the worldwide replacement of surgical

castration and high doses of estrogens. The discovery of medical castration with GnRH agonists was soon followed by fundamental changes in the endocrine therapy of prostate cancer. Most importantly, the excellent tolerance accompanying the treatment with GnRH agonists has been a key factor that permitted a series of studies demonstrating a major reduction in the death rate from prostate cancer ranging from 31 to 87% at 5 yr of follow-up in patients with localized or locally advanced prostate cancer. In fact, a one third reduction in prostate cancer deaths has been calculated in the metaanalysis of all available studies. The general acceptance of this discovery by patients and physicians is illustrated by world sales above 3.0 billion U.S. dollars in 2003. Although extremely efficient in achieving complete medical castration and well tolerated, with no other side effects than the expected hypoandrogenicity, GnRH agonists should not be administered alone. In fact, shortly after discovery of the castration effects of GnRH agonists, we observed that approximately 50% of androgens remain in the prostate after castration, thus leading to the recognition of the role of adrenal dehydroepiandrosterone as an important source of the androgens synthesized locally in the prostate and in many peripheral target tissues. We therefore developed combined androgen blockade (CAB), whereby the androgens of both testicular and adrenal origins are blocked simultaneously at start of treatment with the combination of a GnRH agonist to block the testis and a pure antiandrogen to block the action of the androgens produced locally. CAB, first used in advanced metastatic disease, has been the first treatment shown to prolong life in prostate cancer. Most interestingly, in 2002, we made the observation that CAB alone given continuously for 6.5 yr or more leads to cure of the disease in at least 90% of cases, thus suggesting that androgen blockade combining a GnRH agonist and a pure antiandrogen could well be the most efficient treatment of localized prostate cancer, and thus offering the possibility of practically eliminating death from prostate cancer.

Lane, H. A. and D. Lebwohl (2006). "Future directions in the treatment of hormone-sensitive advanced breast cancer: the RAD001 (Everolimus)-letrozole clinical program." Semin Oncol **33**(2 Suppl 7): S18-25.

Therapeutics that interfere with estrogen receptor function (antiestrogens, eg, tamoxifen; aromatase inhibitors, eg, letrozole) have contributed to a dramatic reduction in breast cancer mortality; however, not all estrogen-receptor-positive breast cancers respond. The mammalian target-of-rapamycin (mTOR) is emerging as an important target molecule in the treatment of breast cancer. Furthermore, activation of growth-factor signaling pathways that involve mTOR may contribute to both the failure of endocrine therapy as well as the development of resistance. RAD001 (everolimus) is a potent, orally bioavailable inhibitor of the mTOR pathway. Preclinical data show that RAD001 effectively inhibits the proliferation and growth of a number of cancer cell lines in vitro and a range of tumor types in experimental animal models of cancer. Moreover, RAD001 exhibits an antiangiogenic activity, which may also contribute to its anticancer activity. The aromatase inhibitor letrozole is a potent endocrine therapy for breast cancer that acts to inhibit the aromatization of androgens, thereby reducing plasma and tumor estrogen levels. Combining RAD001 with letrozole is a rational approach to the treatment of advanced breast cancer, offering the potential for inhibition of tumor cell growth/proliferation and angiogenesis while at the same time potentially preventing the development of letrozole resistance. Preclinical data, derived from aromatase-expressing, estrogen-receptor-positive breast tumor models, suggest a synergistic interaction between RAD001 and letrozole that results in more profound effects on proliferation and the induction of tumor cell death. Importantly, early clinical data show no pharmacokinetic interaction or increase in toxicity with combined treatment, as compared with treatment with RAD001 alone, and there is evidence of antitumor activity. Enrollment into phase II studies is presently underway.

Lee, E. C. and M. P. Tenniswood (2004). "Emergence of metastatic hormone-refractory disease in prostate cancer after anti-androgen therapy." J Cell Biochem **91**(4): 662-70.

The anti-androgens used in prostate cancer therapy have been designed to interfere with the normal androgen receptor (AR)-mediated processes that ensure prostate cell survival, triggering tumor cells to undergo programmed cell death. While anti-androgens were originally designed to treat advanced disease, they have recently been used to debulk organ-confined prostate tumors, to improve positive margins prior to surgery, and for chemoprevention in patients at high risk for prostate cancer. However, tumors treated with anti-androgens frequently become hormone refractory and acquire a more aggressive phenotype. Progression toward metastatic hormone-refractory disease has often been regarded as the outgrowth of a small number of hormone-independent cells that emerge from a hormone-dependent tumor during anti-androgen treatment by natural selection. While a number of selective advantages have recently been identified, there is also considerable evidence suggesting that the progression toward metastatic

hormone-refractory disease is an dynamic process which involves abrogation of programmed cell death as a result of the attenuation of DNA fragmentation and maintenance of mitochondrial membrane potential in tumor cells; the upregulation of stromal-mediated growth factor signaling pathways; and the upregulation of extracellular matrix (ECM) protease expression.

Lee, L. T., A. V. Schally, et al. (2008). "Dephosphorylation of cancer protein by tyrosine phosphatases in response to analogs of luteinizing hormone-releasing hormone and somatostatin." Anticancer Res **28**(5A): 2599-605.

Protein phosphorylation/dephosphorylation of tyrosine residues is an important regulatory mechanism in cell growth and differentiation. Previously it has been reported that RC-160, an octapeptide analog of somatostatin, and [D-Trp6]LHRH, an agonist of luteinizing hormone-releasing hormone (LHRH), stimulate receptor-mediated activity of tyrosine phosphatases (PTP) and reverse growth promotion of the tyrosine kinase (PTK) class of oncogenes in tumor cells. The effect of RC-160 and [D-Trp6]LHRH on protein phosphorylation was further examined in surgical specimens of human carcinomas. Protein extracts of human ovarian, liver, breast and prostate tumor samples were preincubated with epidermal growth factor (EGF) (10(-7) M) with or without [D-Trp6]LHRH or RC-160 (10(-6) M) at 25 degrees C for 2 h, followed by incubation for 10 min with [gamma-32p]ATP. SDS-PAGE, Western blotting, autoradiography and densitometry were then used to quantify the phosphorylation level of individual protein bands. It was found that EGF enhanced, and [D-Trp6]LHRH and RC-160 reduced phosphorylation of a prominent 300-kDa band. Two proteins (65 and 60 kDa), involved in growth control in tumor cell lines, were also identified in this study. The homology of substrate phosphorylation between induced PTK and PTP in the presence of hormones provided evidence that these substrates might be identical or related in tumors. These findings, along with the previous cell culture results, suggest that many solid tumors may respond to treatment with analogues of somatostatin and LHRH. Collectively, the results further support the hypothesis that these 60-, 65- and 300-kDa protein substrates may be involved in growth-message transduction.

Lee, S. E., J. S. Chung, et al. (2008). "Preoperative serum sex hormone-binding globulin as a predictive marker for extraprostatic extension of tumor in patients with clinically localized prostate cancer." Eur Urol **54**(6): 1324-32.

OBJECTIVES: We investigated the relationships of serum sex hormone-binding globulin (SHBG) level with known prognostic factors for prostate cancer in men who received radical retropubic prostatectomy (RRP) for clinically localized prostate cancer. METHODS: Preoperative serum levels of SHBG were analyzed in 288 consecutive patients who were scheduled to undergo RRP for clinically localized prostate cancer. We investigated the potential associations of preoperative serum SHBG level with various clinical and pathological factors. Accuracy of variables in predicting adverse pathological features was assessed via receiver operator characteristics (ROC) curves. RESULTS: In univariate analysis, preoperative serum SHBG level was observed to be significantly associated with extraprostatic extension of a tumor ($p=0.019$) and with pathological Gleason score ($p=0.001$). In multivariate analysis, serum SHBG level ($p=0.039$) along with serum PSA ($p<0.001$) level, biopsy Gleason score ($p<0.001$), and clinical stage ($p=0.004$) was observed to be an independent predictor of the extraprostatic extension of prostate cancer. The area under ROC curve that demonstrated the performance of a multivariate logistic regression model (MLRM), which included serum SHBG level and other preoperative variables, in predicting extraprostatic extension of tumor was larger than that of MLRM without SHBG (0.797 vs. 0.758, $p=0.121$). Meanwhile, serum SHBG level was not observed to be significantly associated with pathological Gleason score in multivariate analysis ($p=0.303$). CONCLUSIONS: Our data showed that serum SHBG level is an independent predictive factor for extraprostatic extension of tumor in patients with clinically localized prostate cancer.

Leuschner, C., F. M. Enright, et al. (2001). "Targeted destruction of androgen-sensitive and -insensitive prostate cancer cells and xenografts through luteinizing hormone receptors." Prostate **46**(2): 116-25.

BACKGROUND: We have prepared a conjugate of a lytic peptide (hecate) and a 15-amino acid segment of the beta-chain of LH to test the concept that this conjugate will target cancer cells expressing LH receptors. METHODS: Hecate-betaLH was added in vitro to cultures of Chinese hamster ovary (CHO) cells with and without LH receptors and to prostate cancer cells in the presence or absence of steroids, follicle-stimulating hormone (FSH), epidermal growth factor (EGF), or betaLH. PC-3 xenografts were established in male athymic nude mice and treated once a week for 3 weeks with hecate-betaLH via the lateral tail vein. RESULTS: The conjugate showed concentration-dependent toxicity

for the following prostate cancer cell lines: BRF 41 T>DU145>PC-3>LNCaP, according to their LH receptor capacities. Steroid removal reduced sensitivity to the drug in a reversible manner. Hecate-betaLH reduced the tumor burden in the nude mice from 60 to 12.5 mg/g body weight. CONCLUSIONS: We conclude that the hecate-betaLH conjugate selectively kills androgen-dependent and-independent prostate cancer cells both in vivo and in vitro; its toxicity depends on the number of LH receptor sites present.

Levine, E. G., S. Halabi, et al. (2002). "Higher doses of mitoxantrone among men with hormone-refractory prostate carcinoma: a Cancer and Leukemia Group B study." Cancer **94**(3): 665-72.

BACKGROUND: Mitoxantrone in combination with a low-dose glucocorticoid has been shown to produce more favorable outcomes among men with hormone-refractory prostate carcinoma than glucocorticoid alone. Therefore, the authors sought to determine the safety and activity of higher doses of mitoxantrone in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) and a glucocorticoid in preparation for a possible Phase III trial comparing standard to dose-escalated mitoxantrone. METHODS: This Phase II trial enrolled 45 patients from October 1996 to March 1998. Twenty-one patients without pelvic irradiation (Arm I) received 21 mg/m(2) of mitoxantrone every 3 weeks, and 24 patients who had received pelvic irradiation (Arm II) were given 17 mg/m(2) on the same schedule. All patients received 40 mg of hydrocortisone in divided doses daily and GM-CSF at 500 microg/daily for a minimum of 10 days per cycle beginning on the third day of the cycle. RESULTS: In Arm I, 33% of assessable patients achieved a partial response, 50% had a > or = 50% decline in their PSA, and 35% had a > or = 75% decline in PSA values. The comparable numbers in Arm II were 24%, 48%, and 35%, respectively. The median survival times were 12 months in Arm I and 14 months in Arm II. Treatment had to be discontinued in 13% of patients because of thrombocytopenia. No other significant toxicities were encountered. CONCLUSIONS: Higher doses of mitoxantrone (17 and 21 mg/m(2)) were associated with activity comparable to many estramustine combinations and generally were well tolerated. However, because the degree and frequency of thrombocytopenia were greater than that observed with standard dose mitoxantrone (12-14 mg/m(2)), and because the median survival is apparently comparable to standard dose mitoxantrone, this approach to HRPC cannot be recommended for Phase III testing.

Lin, A. M., B. I. Rini, et al. (2007). "A phase I trial of docetaxel/estramustine/imatinib in patients with hormone-refractory prostate cancer." Clin Genitourin Cancer **5**(5): 323-8.

BACKGROUND: Docetaxel/estramustine was a commonly used regimen to treat metastatic hormone-refractory prostate cancer. Imatinib inhibits the platelet-derived growth factor receptor that is expressed in prostate cancer and is synergistic with taxanes in preclinical prostate cancer models. PATIENTS AND METHODS: A phase I trial of docetaxel/estramustine/ imatinib was undertaken to determine the safety and maximum tolerated dose of this combination. Patients with progressive, metastatic, hormone-refractory prostate cancer were treated every 21 days with fixed doses of estramustine (280 mg orally 3 times a day on days 1-5), imatinib (400 mg orally daily on days 1-21), dexamethasone (8 mg orally twice daily on days 1-3), and prophylactic warfarin (2 mg orally daily on days 1-21). Cohorts of 3-6 patients were enrolled to receive escalating doses of docetaxel on day 2 from 50 mg/m2 to 60 mg/m2 to 70 mg/m2. Thirteen patients were treated. RESULTS: On dose level 3 (docetaxel 70 mg/m2 and imatinib 400 mg daily), 2 patients experienced grade 3 elevations in prothrombin time, attributed to the interaction between imatinib and warfarin. The protocol was amended to include an intermediate dose level (docetaxel 60 mg/m2 and imatinib 300 mg daily). However, in the overall study, there were 5 unacceptable toxicities (2 cerebrovascular accidents, 1 myocardial infarction, 1 mesenteric ischemia, and 1 deep venous thrombosis) in 13 patients; 2 of those toxicities resulted in death. The study was closed early to further accrual. CONCLUSION: The high incidence of thromboembolic events observed when imatinib was combined with docetaxel/estramustine precludes further exploration of this regimen.

Lin, H. Y., H. Y. Tang, et al. (2007). "Thyroid hormone is a MAPK-dependent growth factor for thyroid cancer cells and is anti-apoptotic." Steroids **72**(2): 180-7.

Thyroid hormone (l-thyroxine, T(4), or 3,5,3'-triiodo-l-thyronine, T(3)) treatment of human papillary and follicular thyroid cancer cell lines resulted in enhanced cell proliferation, measured by proliferating cell nuclear antigen (PCNA). Thyroid hormone also induced activation of the Ras/MAPK (ERK1/2) signal transduction pathway. ERK1/2 activation and cell proliferation caused by thyroid hormone were blocked by an iodothyronine analogue, tetraiodothyroacetic acid (tetrac), that inhibits binding of iodothyronines to the cell surface receptor for thyroid hormone on integrin alphaVbeta3. A MAPK cascade inhibitor at MEK, PD 98059, also blocked

hormone-induced cell proliferation. We then assessed the possibility that thyroid hormone is anti-apoptotic. We first established that resveratrol (10 microM), a pro-apoptotic agent in other cancer cells, induced p53-dependent apoptosis and c-fos, c-jun and p21 gene expression in both papillary and follicular thyroid cancer cells. Induction of apoptosis by the stilbene required Ser-15 phosphorylation of p53. Resveratrol-induced gene expression and apoptosis were inhibited more than 50% by physiological concentrations of T(4). T(4) activated MAPK in the absence of resveratrol, caused minimal Ser-15 phosphorylation of p53 and did not affect c-fos, c-jun and p21 mRNA abundance. Thus, plasma membrane-initiated activation of the MAPK cascade by thyroid hormone promotes papillary and follicular thyroid cancer cell proliferation in vitro.

Lissoni, P., P. Vigano, et al. (2005). "A phase II study of tamoxifen in hormone-resistant metastatic prostate cancer: possible relation with prolactin secretion." Anticancer Res **25**(5): 3597-9.

Recent experimental observations, showing the potential role of prolactin (PRL) as a tumor growth factor for prostate cancer and the unfavourable prognostic significance of enhanced chromogranin-A-secreting neuroendocrine cell proliferation, could contribute to a better understanding of the mechanisms responsible for the occurrence of hormone-resistance in the prostate cancer. Moreover, it has been shown that tamoxifen, which consistently exerts estrogenic activity in males, may inhibit prostate cancer cell proliferation in experimental studies. At present, there are no clinical data in humans. This preliminary phase II study was planned in an attempt to evaluate the therapeutic efficacy of tamoxifen in hormone-refractory metastatic prostate cancer. The study included 14 consecutive metastatic prostate cancer patients, who had progressed under the classical endocrine therapy with LHRH-analogs and/or anti-androgens. Patients received the same treatment plus tamoxifen at 20 mg/day orally. A decline greater than 50% in prostate-specific antigen (PSA) levels occurred in 4/14 (29%) patients within the first 2 months of therapy, with a median duration of 5 months. Mean pre-treatment levels of PRL were significantly higher in responder patients than in those who progressed. Moreover, abnormally high pre-treatment levels of PRL were found in 5/14 (36%) patients. The percent of clinical responses observed in patients with pre-treatment hyperprolactinemia was significantly higher than that found in patients with normal pre-treatment PRL concentrations. Finally, a significant decline in mean PRL levels upon tamoxifen therapy occurred only in the responder patients. This preliminary study seems to justify further clinical research to confirm the potential efficacy of tamoxifen in the treatment of hormone-refractory prostate cancer and to identify possible parameters, which may predict the response to treatment.

Martin, L. J., S. Minkin, et al. (2009). "Hormone therapy, mammographic density, and breast cancer risk." Maturitas **64**(1): 20-6.

Percent mammographic density (PMD) is a strong independent risk factor for breast cancer. The effects of age, parity and menopause on PMD are consistent with it being a marker of susceptibility to breast cancer. In this review, we describe the association of PMD with breast cancer, the biological plausibility of this association, and discuss the extent to which PMD meets the criteria for a surrogate marker for the effects of exogenous hormones on risk of breast cancer. Combined hormone therapy is associated with a small increase in both PMD and the risk of breast cancer. However there is evidence that the associations of blood estradiol levels and HRT with breast cancer risk are independent of the association of PMD with risk, suggesting that different biological pathways may be involved. Tamoxifen, an anti-estrogenic drug, reduces both the risk of breast cancer and PMD, but the potential mediation of the effects of anti-estrogens on breast cancer risk by their effects on PMD has not yet been examined. Given the evidence that estradiol and PMD are independently associated with breast cancer risk, it seems unlikely that an effect of these agents on PMD mediates their effects on risk. We thus find that the available evidence is insufficient to conclude that PMD can be used as a surrogate marker for the effect of exogenous hormones on breast cancer. Further research to examine the potential role of PMD as a mediator of the effects of other risk factors is required.

Milewicz, T., E. L. Gregoraszczuk, et al. (2005). "Lack of synergy between estrogen and progesterone on local IGF-I, IGFBP-3 and IGFBP-2 secretion by both hormone-dependent and hormone-independent breast cancer explants in vitro. Effect of tamoxifen and mifepristone (RU 486)." Growth Horm IGF Res **15**(2): 140-7.

The aim of the present study was to investigate direct effects of estrogen (E2) or progesterone (P4) given separately vs. estrogen+progesterone on local IGF-I, IGFBP-3 and IGFBP-2 secretion. Explants obtained from estrogen receptor positive plus progesterone receptor positive (ER+/PR+) and hormone receptors negative (ER-/PR-) tumors were incubated with E2, P4 or both. Tamoxifen was added to E2-exposed cultures; mifepristone (RU 486) was added to P4, and both

were given to E2+P4-supplemented cultures. In hormone-dependent and hormone-independent tissues, treatment with estrogen+progesterone increased IGF-I and IGFBP-2 secretion with concomitant decrease in IGFBP-3, in the same manner as E2 or P4 given alone. Tamoxifen decreased the E2- and E2+P4-stimulated IGF-I secretion by hormone-dependent breast cancer explants. RU 486 decreased the P4- and E2+P4-stimulated IGF-I secretion with parallel stimulation of IGFBP-3 secretion by ER+/PR+ explants. Estradiol and progesterone had a synergistic action on IGFBP-2 secretion by hormone-dependent breast cancer explants. In conclusion, the presented data suggest that there is no synergistic action of E2 and P4 in influencing IGF/IGFBPs ratio and, additionally, suggest a protective action of antiestrogen and antiprogestagen against excessive IGF-I secretion.

Milewicz, T., J. Kolodziejczyk, et al. (2002). "Cyproterone, norethindrone, medroxyprogesterone and levonorgestrel are less potent local human growth hormone and insulin-like growth factor I secretion stimulators than progesterone in human breast cancer explants expressing the estrogen receptor." Gynecol Endocrinol **16**(4): 319-29.

The aim of the present study was to compare the ability of natural progesterone and synthetic progestins to stimulate local growth hormone (GH) and insulin-like growth factor I (IGF-I) secretion by breast cancer explants. Explants obtained during surgery were divided according to their estrogen/progesterone receptor phenotype - ER(+)PR(-); ER(+)PR(+); ER(-)PR(+) - as determined by immunocytochemistry. Natural progesterone (10(-5) mol/l) and synthetic progestins (cyproterone acetate (5 x 10(-7) mol/l), norethindrone (10(-5) mol/l), medroxyprogesterone acetate (10(-7) mol/l), and levonorgestrel (10(-7) mol/l) were tested in vitro for their ability to induce secretion of proliferation-promoting agents such as human GH (hGH) and IGF-I. All hormone-dependent breast cancer cell types responded to progesterone stimulation with increased local hGH secretion, while in the non-malignant tissue this effect was observed only in PR(+) cells. Moreover, progesterone in only PR(+) cells in vitro stimulated local IGF-I secretion by both malignant and non-malignant tissue. Medroxyprogesterone and levonorgestrel increased GH secretion by both malignant and non-malignant ER(-)PR(+) breast cancer explants, while cyproterone stimulated it only in non-malignant tissue. None of the synthetic progestins tested in this experiment exerted an effect on GH secretion by both malignant and non-malignant tissue of ER(+) breast cancer explants. The present data additionally showed that, apart from cyproterone, which increased IGF-I secretion in the same manner as progesterone by both malignant and non-malignant ER(-)PR(+) breast explants, other progestins tested had either no effect on IGF-I local secretion or decreased it. Medroxyprogesterone and levonorgestrel induced a decrease in IGF-I secretion noted in ER(+) explants of non-malignant tissue and in malignant ER(-)PR(+) breast tissue. All progestins tested decreased IGF-I secretion by malignant ER(+)PR(+) explants. Taken together, the tested synthetic progestins widely used as oral contraceptives and in hormone replacement therapy were less potent than progesterone in inducing secretion of proliferation-promoting agents such as hGH and IGF-I in ER-containing breast tissue. Despite the lack of confirmation of the link between the use of progestins and breast cancer risk, patients should be informed that the use of certain estrogen/progestin preparations is of no influence on breast cancer risk while others may increase it.

Mittal, R. D., D. Mishra, et al. (2007). "Role of an androgen receptor gene polymorphism in development of hormone refractory prostate cancer in Indian population." Asian Pac J Cancer Prev **8**(2): 275-8.

BACKGROUND: Androgen receptors play critical roles in the development of primary as well as advanced hormone-refractory prostate cancers. Since the growth of prostate cancer is androgen-sensitive, metastatic disease has been treated by hormonal therapy in the form of androgen ablation. Prostate cancer cells rely on androgen receptor (AR) for proliferation and survival. AIM: To evaluate the prognostic significance of androgen receptor polymorphism in patients under hormonal therapy in any form. METHODS: Complete follow up data were available for 87 patients out of 130 patients enrolled for study. DNA was extracted from blood samples using salting out method and then subjected to PCR Genscan for CAG and GGN genotyping. The mean follow up was 10.12+/-8.83 months. RESULTS: Out of 87 patients, 64 experienced clinical as well as biochemical recurrence. The overall hormone refractory rates were 73.4% after one year. We observed a significant shorter median CAG repeats in HRPC patients (20 vs 22). The hazard ratio for HRPCs with the < or =20 CAG repeat genotype was 0.602 (0.33-1.08, p=0.09). Kaplan-Meier analysis showed that HRPC rates were not significantly associated with CAG repeat (p=0.06) but a trend was observed with short CAG repeats. No significant association was observed with AR-GGN repeats. CONCLUSIONS: A trend for association of AR-CAG repeats with HRPC patients in north Indian population was observed, suggesting this to be a prognostic factor for determining the therapeutic regimen.

Montagnani Marelli, M., R. M. Moretti, et al. (2007). "Gonadotropin-releasing hormone agonists reduce the migratory and the invasive behavior of androgen-independent prostate cancer cells by interfering with the activity of IGF-I." Int J Oncol **30**(1): 261-71.

Androgen-independent prostate carcinoma is characterized by a high proliferation rate and by a strong metastatic behavior. We have previously shown that GnRH agonists exert a direct and specific inhibitory action on the proliferation of androgen-independent prostate cancer cells (DU 145). These compounds mainly act by interfering with the mitogenic activity of growth factors, such as the insulin-like growth factor-I (IGF-I). The present experiments were performed to clarify whether GnRH agonists might also affect the migratory and the invasive behavior of androgen-independent prostate cancer cells and to define their mechanism of action. First we showed that the GnRH agonist Leuprolide reduces the migration of DU 145 cells towards a chemoattractant and their ability to invade a reconstituted basement membrane. Experiments were then performed to clarify whether the GnRH agonist might act by interfering with the pro-metastatic activity of IGF-I. We found that, in androgen-independent prostate cancer cells, Leuprolide: a) interferes with the IGF-I system (receptor protein expression and tyrosine-phosphorylation); b) abrogates the IGF-I-induced phosphorylation of Akt (a kinase previously shown by us to mediate the pro-metastatic activity of IGF-I in prostate cancer cells); c) counteracts the migration and the invasive activity of the cells stimulated by IGF-I; d) abolishes the effects of IGF-I on cell morphology, on actin cytoskeleton organization and on alphavbeta3 integrin expression/cellular localization. These data indicate that GnRH agonists, in addition to their well known antiproliferative effect, can also exert a significant inhibitory activity on the migratory and invasive behavior of androgen-independent prostate cancer cells, expressing the GnRH receptor. GnRH agonists act by interfering with the pro-metastatic activity of the growth factor IGF-I.

Moore, C. N. and D. J. George (2005). "Update in the management of patients with hormone-refractory prostate cancer." Curr Opin Urol **15**(3): 157-62.

PURPOSE OF REVIEW: 2004 was a critical year for advances in prostate cancer treatment. The results from two pivotal multicenter phase III randomized studies are the first to demonstrate a survival benefit associated with chemotherapeutic treatment interventions in patients with hormone-refractory prostate cancer. This review will focus on an interpretation of the data from these two studies, the emerging role for chemotherapy in 2005 and beyond, and ongoing areas of clinical research. RECENT FINDINGS: Phase I and II studies have demonstrated biochemical and objective responses achieved with docetaxel-based chemotherapy in men with hormone-refractory prostate cancer. Two pivotal phase III clinical trials, TAX 327 and SWOG 9916 have demonstrated a survival advantage of docetaxel-based chemotherapy over mitoxantrone. Novel targeted therapies under investigation include calcitriol, growth factor-targeted agents, epothilones and others. SUMMARY: We now have a new standard of care for men with metastatic hormone-refractory prostate cancer. Further investigation of docetaxel-based regimens in earlier clinical states of disease is warranted and may demonstrate greater clinical benefit. Additional chemotherapy agents are being studied, and may also add to the future armamentarium available for prostate cancer. The enrolment of patients into these studies is critical to the ongoing evolution of prostate cancer management.

Muss, H. B., J. Y. Bunn, et al. (2007). "Cyclin D-1, interleukin-6, HER-2/neu, transforming growth factor receptor-II and prediction of relapse in women with early stage, hormone receptor-positive breast cancer treated with tamoxifen." Breast J **13**(4): 337-45.

We hypothesized that amplification or overexpression of HER-2 (c-erbB-2), the Ki-67 antigen (Mib1), cyclin D-1 (CD1), interleukin-6 (IL-6), or the transforming growth factor beta II receptor, (TGFbetaRII), would predict relapse in women with early stage, estrogen (ER) and/or progesterone receptor (PR) positive breast cancer treated with tamoxifen. Conditional logistic regression models and a new novel analytic method - support vector machines (SVM) were used to assess the effect of multiple variables on treatment outcome. All patients had stage I-IIIa breast cancer (AJCC version 5). We paired 63 patients who were disease-free on or after tamoxifen with 63 patients who had relapsed (total 126); both disease-free and relapsed patients were matched by duration of tamoxifen therapy and time to recurrence. These 126 patients also served as the training set for SVM analysis and 18 other patients used as a validation set for SVM. In a multivariate analysis, larger tumor size, increasing extent of lymph node involvement, and poorer tumor grade were significant predictors of relapse. When HER-2 or CD1 were added to the model both were borderline significant predictors of relapse. The SVM model, after including all of the clinical and marker variables in the 126 patients as a training set, correctly predicted relapse in 78% of the 18 patient validation samples. In this trial, HER-2 and CD1 proved of borderline significance as predictive factors for recurrence on tamoxifen. An SVM model that included all clinical

and biologic variables correctly predicted relapse in >75% of patients.

Narayanan, N. K., B. A. Narayanan, et al. (2005). "A combination of docosahexaenoic acid and celecoxib prevents prostate cancer cell growth in vitro and is associated with modulation of nuclear factor-kappaB, and steroid hormone receptors." Int J Oncol **26**(3): 785-92.

Epidemiological studies have provided evidence that high intake of saturated fat and/or animal fat increases the risk of prostate cancer, but on the other hand, diets rich in omega-3 polyunsaturated fatty acids (n-3 PUFAs), present in fish oils were found to reduce the risk. There are indications of an increased expression of immunoreactive PPARgamma in prostatic intraepithelial neoplasia (PIN) and prostate cancer, suggesting that PPARgamma ligands may exert their own potent anti-proliferative effect against prostate cancer. The experimental evidence for the role of cyclooxygenase-2 (COX-2) in prostate carcinogenesis is well established through several investigations. It clearly suggests the need for development of strategies to inhibit COX-2 mediated prostate carcinogenesis. However, administration of high doses of COX-2 inhibitors, such as celecoxib, over longer periods may not be devoid of side effects. We assessed the efficacy of DHA and celecoxib individually and in combination at low doses in three prostate cancer cell lines (LNCaP, DU145 and PC-3) measuring cell growth inhibition and apoptosis, and on the levels of expression of COX-2, nuclear factor-kappaB (NF-kappaBp65), and nuclear receptors, such as PPARgamma and retinoid X receptors (RXR), all of which presumably participate in prostate carcinogenesis. A 48-h incubation of prostate cancer cells with 5 microM each of DHA or celecoxib induced cell growth inhibition and apoptosis, and altered the expression of the above molecular parameters. Interestingly, the modulation of these cellular and molecular parameters was more pronounced in cells treated with low doses of DHA and celecoxib (2.5 microM each) in combination than in cells treated with the higher doses of individual agents. In conclusion, the present study demonstrates for the first time that a combination of lower doses of the n-3 PUFA, and DHA with the selective COX-2 inhibitor celecoxib effectively modulates the above cellular and molecular parameters that are relevant to prostate cancer. This raises the intriguing prospect that the use of low doses of a COX-2 inhibitor in combination with an n-3 PUFA could be a highly promising strategy for prostate cancer chemoprevention while minimizing undesired side effects.

Nuver, J., A. J. Smit, et al. (2005). "The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer." J Clin Oncol **23**(16): 3718-25.

PURPOSE: The metabolic syndrome may be an important risk factor for cardiovascular disease in long-term survivors of testicular cancer (TC). We investigated the associations between hormone levels and the metabolic syndrome in these men. PATIENTS AND METHODS: We included TC patients cured by orchidectomy and cisplatin-based chemotherapy, stage I TC patients after orchidectomy only, and healthy men of comparable age. Presence of the metabolic syndrome was determined using guidelines from the National Cholesterol Education Program Adult Treatment Panel III. Thyroid-stimulating hormone, follicle-stimulating hormone (FSH), inhibin B, luteinizing hormone (LH), total testosterone, sex-hormone-binding globulin, free testosterone, estradiol, dehydroepiandrosterone sulfate, and insulin-like growth factor 1 were determined in blood. Cortisol metabolite excretion was measured in urine. RESULTS: Eighty-six chemotherapy patients (median follow-up, 7 years) were compared with 44 stage I patients and 47 controls. LH and FSH were higher, and inhibin B and total and free testosterone were lower in chemotherapy patients than controls. Adrenal and thyroid hormone production were unaffected. Chemotherapy patients with the metabolic syndrome (n = 22; 26%) had a higher body mass index (BMI) pretreatment, a larger BMI increase during follow-up, lower total testosterone, and higher urinary cortisol metabolite excretion than those patients without the metabolic syndrome. BMI and insulin were associated with the metabolic syndrome, while total testosterone and urinary cortisol metabolite excretion were associated with BMI. CONCLUSION: We found gonadal dysfunction, but normal adrenal and thyroid function. Through its association with BMI, testosterone may play a role in the development of the metabolic syndrome in long-term TC survivors.

Ogawa, K., K. Nakamura, et al. (2009). "External beam radiotherapy for clinically localized hormone-refractory prostate cancer: clinical significance of Nadir prostate-specific antigen value within 12 months." Int J Radiat Oncol Biol Phys **74**(3): 759-65.

PURPOSE: To analyze retrospectively the results of external beam radiotherapy for clinically localized hormone-refractory prostate cancer and investigate the clinical significance of nadir prostate-specific antigen (PSA) value within 12 months (nPSA12) as an early estimate of clinical outcomes after radiotherapy. METHODS AND MATERIALS: Eighty-four patients with localized hormone-refractory prostate cancer treated with external beam

radiotherapy were retrospectively reviewed. The total radiation doses ranged from 30 to 76 Gy (median, 66 Gy), and the median follow-up period for all 84 patients was 26.9 months (range, 2.7-77.3 months). RESULTS: The 3-year actuarial overall survival, progression-free survival (PFS), and local control rates in all 84 patients after radiotherapy were 67%, 61%, and 93%, respectively. Although distant metastases and/or regional lymph node metastases developed in 34 patients (40%) after radiotherapy, local progression was observed in only 5 patients (6%). Of all 84 patients, the median nPSA12 in patients with clinical failure and in patients without clinical failure was 3.1 ng/mL and 0.5 ng/mL, respectively. When dividing patients according to low (<0.5 ng/mL) and high (>or=0.5 ng/mL) nPSA12 levels, the 3-year PFS rate in patients with low nPSA12 and in those with high nPSA12 was 96% and 44%, respectively ($p < 0.0001$). In univariate analysis, nPSA12 and pretreatment PSA value had a significant impact on PFS, and in multivariate analysis nPSA12 alone was an independent prognostic factor for PFS after radiotherapy. CONCLUSIONS: External beam radiotherapy had an excellent local control rate for clinically localized hormone-refractory prostate cancer, and nPSA12 was predictive of clinical outcomes after radiotherapy.

Oh, W. K., S. Halabi, et al. (2003). "A phase II study of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor support in patients with hormone-refractory prostate carcinoma: Cancer and Leukemia Group B 99813." Cancer **98**(12): 2592-8.

BACKGROUND: The authors determined the safety and efficacy of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor (G-CSF) support in patients with hormone-refractory prostate carcinoma. METHODS: In the current multicenter, cooperative group study, patients with advanced prostate carcinoma whose disease progressed despite androgen deprivation therapy were treated with a combination of oral estramustine(240 mg three times per day for 5 days), 70 mg/m2 of docetaxel, and carboplatin at a dose of (area under the curve) 5. G-CSF was used to minimize the neutropenia associated with this regimen. Each cycle was repeated every 21 days. RESULTS: Forty patients were treated with a median of 7 cycles of therapy. Of the 34 evaluable patients with elevated pretreatment prostate-specific antigen (PSA) levels, 23 (68%) had a > or = 50% decline in PSA and 20 (59%) had a > or = 75% decline. Twenty-one patients had measurable disease, with 1 complete response (5%) and 10 partial responses (47%), for an overall measurable response rate of 52% (95% confidence interval [95% CI], 30-74%). The most common Grade 3 or Grade 4 toxicities (according to the National Cancer Institute Common Toxicity Criteria) included neutropenia in 23% of patients, thrombocytopenia in 13%, and fatigue in 13%. Febrile neutropenia occurred in 1 patient (3%). The overall median time to disease progression was 8.1 months (95% CI, 6-10 months) and the overall survival period was 19 months (95% CI, 13-26 months). CONCLUSIONS: The combination of estramustine, docetaxel, and carboplatin with G-CSF support was found to have significant clinical activity with an acceptable toxicity profile in patients with progressive hormone-refractory prostate carcinoma.

Oh, W. K., K. Proctor, et al. (2007). "The risk of renal impairment in hormone-refractory prostate cancer patients with bone metastases treated with zoledronic acid." Cancer **109**(6): 1090-6.

BACKGROUND: Bisphosphonates have been used to treat bone metastases in hormone-refractory prostate cancer (HRPC), but certain agents have been associated with renal toxicity. For this observational study, the authors assessed the risk of renal impairment in patients with HRPC who received zoledronic acid from December 1999 to April 2005. METHODS: A comprehensive medical records review was performed in a major tertiary oncology center (n = 122 patients). The primary outcome of renal impairment was defined as an increase >or=0.5 mg/dL or >or=1.0 mg/dL over baseline creatinine value if the baseline value was <1.4 mg/dL or >or=1.4 mg/dL, respectively. A risk factor analysis was conducted using the Andersen-Gill extension to the Cox proportional hazards model. RESULTS: Renal impairment was observed in 23.8% of patients. The risk of renal impairment increased with an extended duration of zoledronic acid therapy (<6 months, 11.1%; >or=24 months, 26.3%) and previous pamidronate treatment (45.5% vs 19.0% for patients with no prior pamidronate). A significantly greater risk of renal impairment was associated with increasing age at zoledronic acid initiation, prior pamidronate use, and a history of renal disease, hypertension, or smoking (P <or= 0.05). CONCLUSIONS: In an outpatient clinic setting, the risk of renal impairment among patients with HRPC who received zoledronic acid was greater than the risk reported previously in clinical trials.

Orgeas, C. C., P. Hall, et al. (2009). "The influence of menopausal hormone therapy on tumour characteristics and survival in endometrial cancer patients." Eur J Cancer **45**(17): 3064-73.

INTRODUCTION: Menopausal hormone therapy (MHT) is a well-established factor in

endometrial carcinogenesis, and therefore, could have prognostic implications. We investigated the effects of ever use of MHT on tumour grade and depth of myometrial invasion and 5-year relative survival in postmenopausal endometrial cancer patients. MATERIALS AND METHODS: We used a nationwide, population-based case-case design, of 683 Swedish women aged 50-74 years diagnosed with endometrial cancer during 1994 to 1995, followed up to 5 years after diagnosis. We applied polytomous multiple logistic regression to investigate the associations between the use of MHT and tumour grade, and myometrial invasion and Poisson regression for modelling 5-year excess mortality. RESULTS: Compared to never use, ever use of any MHT entailed lower risks of having moderately and poorly differentiated tumours. The lowest odds ratios for poorly differentiated tumours were seen for ever users of cyclically combined oestrogen-progestin [OR=0.23 (95% CI=0.07-0.73)]. Ever users of any form of MHT; particularly, medium potency MHT users, had significantly lower risks for tumours with deep myometrial invasion. Adjusted estimated relative excess hazard ratios revealed significantly improved survival for ever users of any form of MHT [RER=0.40 (95% CI=0.16-0.97)]; in particular ever users of any form of oestrogens [RER=0.38 (95% CI=0.15-0.99)]. CONCLUSION: Endometrial cancer patients who were ever users of MHT had more favourable tumour characteristics and better survival compared to never users of MHT. These findings support the notion that MHT induces endometrial cancer with less aggressive characteristics.

Papatsoris, A. G., M. V. Karamouzis, et al. (2005). "Novel biological agents for the treatment of hormone-refractory prostate cancer (HRPC)." Curr Med Chem **12**(3): 277-96.

Hormone-refractory prostate cancer (HRPC) is an inevitable evolution of prostate carcinogenesis, through which the normal dependence on hormones for growth and survival is bypassed. Although advances in terms of symptoms palliation and quality of life improvement have been addressed with current treatment options, innovative approaches are needed to improve survival rates. A thorough understanding of HRPC-associated molecular pathways and mechanisms of resistance are a prerequisite for novel potential therapeutic interventions. Preclinical and early clinical studies are ongoing to evaluate new therapies that target specific molecular entities. Agents under development include growth factor receptor inhibitors, small molecules targeting signal transduction pathways, apoptosis and cell-cycle regulators, angiogenesis and metastasis inhibitors, differentiation agents, telomerase inactivators, and epigenetic therapeutics. Incorporation of these agents into existing treatment regimens will guide us in the development of a multidisciplinary treatment strategy of HRPC. This article critically reviews published data on new biological agents that are being tested in HRPC clinical trials, highlights ongoing research and considers the future perspectives of this new class of agents.

Parikh, P., J. P. Palazzo, et al. (2005). "GATA-3 expression as a predictor of hormone response in breast cancer." J Am Coll Surg **200**(5): 705-10.

BACKGROUND: Expression of estrogen receptor-alpha (ERalpha) as determined by immunohistochemistry of tumor tissue is currently the most clinically useful test to predict hormone responsiveness of breast cancer. Thirty percent of ERalpha-positive breast cancers do not respond to hormonal therapy. GATA-3 is a transcription factor that is expressed in association with ERalpha and there is evidence that GATA factors influence response to estrogen. In this pilot study, we investigated whether GATA-3 expression is associated with hormone response in breast cancer. STUDY DESIGN: Breast cancer tissue was stained for GATA-3 expression by immunohistochemistry in ERalpha-positive cancers from 28 patients, 14 of whom were defined as hormone unresponsive (cases) and 14 of whom were age-matched controls with hormone-responsive, ERalpha-positive cancers (controls). RESULTS: Comparing cases and controls, there were no differences in expression of ERalpha; progesterone receptor, ErbB2; or tumor grade. Using 20% nuclear staining to characterize tumors as GATA-3 positive or GATA-3 negative, 6 of 14 (43%) cancers in the hormone-unresponsive group and none of the controls were classified as GATA-3 negative (odds ratio, 8.2; 95% confidence interval, 1.2-infinity; p = 0.031). Using different cut points to characterize GATA-3 positivity yielded very similar results, indicating a positive association between lack of GATA-3 expression and lack of response to hormonal therapy. CONCLUSIONS: The study suggests that analyzing ERalpha-positive breast tumors for GATA-3 using immunohistochemistry might improve prediction of hormone responsiveness. The association between GATA-3 expression and hormone response suggests that GATA-3 may play a role in mechanisms controlling response to estrogen.

Park, I. H., J. Ro, et al. (2009). "Potential antitumor effects of nitrogen-containing bisphosphonate in hormone receptor negative breast cancer patients with bone metastases." BMC Cancer **9**: 154.

BACKGROUND: This retrospective study evaluated, according to hormone receptor status, the

antitumor effects of bisphosphonate especially on survival and disease progression in breast cancer patients with metastatic bone disease. METHODS: Of 317 patients with initial bone metastasis and known breast cancer subtypes, 230 patients (72.6%) had hormone receptor (HR) positive tumors, and 87 patients (27.4%) had HR negative tumors. We assessed the primary outcome of overall survival (OS), after adjusting for other factors, comparing a group that received bisphosphonates (BPs) with a group that did not receive it. RESULTS: 87.8% of HR positive and 69.0% of HR negative patients received BPs with a median number of 17.7 cycles. Although BPs treatment made no survival benefit in HR positive group, HR negative patients showed a significant prolonged survival when they received BPs treatment (hazard ratio = 0.56 [95% CI 0.34 to 0.91], P = 0.019). In multivariate analysis, disease free interval > 2 years (P = 0.036), a sum of metastatic sites < 3 (P = 0.034), and BP treatments (P = 0.007) were significant factors for survival in HR negative patients. CONCLUSION: Bisphosphonate treatment can result in a survival benefit in metastatic breast cancer patients with HR negative tumors.

Pavlenko, M., A. K. Roos, et al. (2004). "A phase I trial of DNA vaccination with a plasmid expressing prostate-specific antigen in patients with hormone-refractory prostate cancer." Br J Cancer **91**(4): 688-94.

Prostate-specific antigen (PSA) is a serine protease secreted at low levels by normal luminal epithelial cells of the prostate and in significantly higher levels by prostate cancer cells. Therefore, PSA is a potential target for various immunotherapeutical approaches against prostate cancer. DNA vaccination has been investigated as immunotherapy for infectious diseases in patients and for specific treatment of cancer in certain animal models. In animal studies, we have demonstrated that vaccination with plasmid vector pVAX/PSA results in PSA-specific cellular response and protection against tumour challenge. The purpose of the trial was to evaluate the safety, feasibility and biological efficacy of pVAX/PSA vaccine in the clinic. A phase I trial of pVAX/PSA, together with cytokine granulocyte/macrophage-colony stimulating factor (GM-CSF) (Molgramostim) and IL-2 (Aldesleukin) as vaccine adjuvants, was carried out in patients with hormone-refractory prostate cancer. To evaluate the biologically active dose, the vaccine was administered during five cycles in doses of 100, 300 and 900 microg, with three patients in each cohort. Eight patients were evaluable. A PSA-specific cellular immune response, measured by IFN-gamma production against recombinant PSA protein, and a rise in anti-PSA IgG were detected in two of three patients after vaccination in the highest dose cohort. A decrease in the slope of PSA was observed in the two patients exhibiting IFN-gamma production to PSA. No adverse effects (WHO grade >2) were observed in any dose cohort. We demonstrate that DNA vaccination with a PSA-coding plasmid vector, given with GM-CSF and IL-2 to patients with prostate cancer, is safe and in doses of 900 microg the vaccine can induce cellular and humoral immune responses against PSA protein.

Pesch, B., Y. Ko, et al. (2005). "Factors modifying the association between hormone-replacement therapy and breast cancer risk." Eur J Epidemiol **20**(8): 699-711.

OBJECTIVES: Hormone-replacement therapy (HRT) is an established risk factor for breast cancer. HRT users are different from non-users with respect to socio-economic and other characteristics. There may be women where the HRT-related risk could be modulated by other factors. METHODS: We conducted a population-based case-control study with 688 breast cancer cases and 724 controls to characterize HRT users and to estimate odds ratios (OR) and 95% confidence intervals (CI) for HRT use and potentially risk modifying factors. RESULTS: In women aged 50 years and older, 58% of controls and 61% of cases ever used HRT. Among women in natural menopause, HRT use for 10 years and more years was associated with an increased breast cancer risk (OR 1.79, 95% CI, 1.12-2.87), but not among women in surgical menopause (OR 0.61, 95% CI, 0.09-4.17). In the subgroup of women with a positive family history of breast cancer, each year of HRT use increased the risk by 1.22 (95% CI, 1.02-1.47). Another subgroup comprised women with at least 10 diagnostic mammograms (OR 4.04, 95% CI, 1.10-14.81 for using HRT 10 or more years). CONCLUSIONS: Long-term HRT use was associated with a breast cancer risk in women with natural menopause. Our findings suggest that this risk may be increased in women with a positive family history of breast cancer and in women who received frequent diagnostic mammographic screens.

Pietras, R. J. (2006). "Biologic basis of sequential and combination therapies for hormone-responsive breast cancer." Oncologist **11**(7): 704-17.

Although pharmacologic therapies that reduce or block estrogen signaling are effective treatments of estrogen receptor (ER)-positive breast cancer, acquired resistance to individual drugs can develop. Furthermore, this approach is ineffective as initial therapy for a subgroup of receptor-positive patients. The mechanisms of drug resistance are not completely understood, but the presence of alternative signaling pathways for activating ER response appears

to play a significant role. Cross-talk between signaling pathways can activate ERs when conventional ER pathways are blocked or inactivated. For example, signaling via epidermal growth factor or HER-2 receptors, mitogen-activated protein kinases, phosphatidylinositol 3' kinase/protein kinase B, and vascular endothelial growth factor receptor can lead to estrogen-independent stimulation of ERs and tumor growth. The discovery that alternative pathways are involved in estrogen signaling has prompted development of newer endocrine therapies, such as aromatase inhibitors and pure estrogen antagonists, with distinct mechanisms for interrupting signal transduction. The existence of multiple pathways may explain the effectiveness of follow-up therapy with a different class of endocrine agents after failure of prior endocrine treatment. Because they do not have the partial agonist activity of tamoxifen that is enhanced by the adaptive hypersensitivity process, these alternative endocrine agents may play an increasingly important role in the treatment of ER-positive breast cancer. Although optimal sequencing of these agents has not been determined and is continuing to evolve, current evidence allows rational recommendations to be made. The multiple pathways involved in activating ERs also provide a rationale for combining endocrine and non-endocrine therapies that block different signaling pathways, which may have synergistic and overlapping interactions.

Pizzi, H., J. Gladu, et al. (2003). "Androgen regulation of parathyroid hormone-related peptide production in human prostate cancer cells." Endocrinology **144**(3): 858-67.

PTHrP is the major pathogenetic factor for hypercalcemia in several malignancies including prostate cancer. In the current study, we have assessed the ability of androgens to regulate PTHrP production in androgen-insensitive human prostate cancer cells PC-3 and cells transfected with androgen receptor (PC-3T). Androgen responsiveness caused a marked decrease in PC-3T cell growth, and treatment of these cells with dihydrotestosterone led to inhibition of PTHrP production. These inhibitory effects were readily reversed by androgen receptor antagonist flutamide. To determine the effect of androgens on tumor growth and PTHrP production in vivo, PC-3 and PC-3T cells were injected into the right flank of male BALB/c nu/nu mice. Animals inoculated with PC-3 and PC-3T cells developed palpable tumors at wk 2 and 4, respectively. Inoculation of PC-3T cells into castrated animals resulted in rapid tumor growth in PC-3T tumors, effects that were reversed in PC-3T tumors grown in castrated hosts. Using PTHrP promoter luciferase reporter, a 30% decrease in luciferase activity was seen following treatment with dihydrotestosterone. These results indicate that PC-3 cell growth correlates inversely with androgen sensitivity and directly with PTHrP production in vitro and in vivo, androgens can regulate PTHrP production, and the androgen effect on PTHrP is mediated at least in part by transcriptional regulation via the androgen receptor.

Plonowski, A., A. V. Schally, et al. (2002). "Inhibition of proliferation of PC-3 human prostate cancer by antagonists of growth hormone-releasing hormone: lack of correlation with the levels of serum IGF-I and expression of tumoral IGF-II and vascular endothelial growth factor." Prostate **52**(3): 173-82.

BACKGROUND: Antagonists of growth hormone-releasing hormone (GHRH) such as JV-1-38 can inhibit androgen-independent prostate cancer directly by several mechanisms and/or indirectly by suppressing growth hormone/insulin-like growth factor-I (GH/IGF-I) axis. To shed more light on the mechanisms involved, the effects of JV-1-38 on PC-3 human prostate cancer were compared with those of somatostatin analog RC-160 in vivo and in vitro. METHODS: Nude mice bearing PC-3 tumors received JV-1-38 (20 microg), RC-160 (50 microg) or a combination of JV-1-38 and RC-160. The concentration of IGF-I in serum and the expression of mRNA for IGF-II and vascular endothelial growth factor (VEGF) in tumor tissue were investigated. RESULTS: In vivo, the final volume of PC-3 tumors treated with JV-1-38 was significantly lowered by 49% ($P < 0.01$), whereas RC-160 exerted only 30% inhibition (NS), compared with controls. Combined use of both compounds augmented tumor inhibition to 63% ($P < 0.001$). Serum IGF-I levels were decreased only in mice treated with RC-160. JV-1-38 suppressed mRNA for IGF-II in PC-3 tumors by 42%, whereas RC-160 alone or in combination with JV-1-38 caused a 65% reduction. JV-1-38 and RC-160 used as single drugs decreased the expression of VEGF by 50%, and their combination caused a 63% reduction. In vitro, JV-1-38 inhibited the proliferation of PC-3 cells by 39%. This effect could be partially reversed by addition of IGF-I to the serum-free medium. RC-160 alone did not affect the PC-3 cell growth in vitro, but in combination with JV-1-38 it augmented the antiproliferative effect of the GH-RH antagonist to 72%. Exposure to JV-1-38 in vitro reduced the expression of mRNA for IGF-II in PC-3 cells by 55% but did not change VEGF mRNA levels, whereas RC-160 had no effect. CONCLUSIONS: The antiproliferative effect of JV-1-38 was not associated with the suppression of serum IGF-I and was only partially correlated with the expression of IGF-II and VEGF in PC-3 tumors, suggesting that other mechanisms play a role in the antitumor action of

GHRH antagonists. Nevertheless, the stronger inhibition of tumor growth after combined treatment with JV-1-38 and RC-160 indicates that the interference with multiple local stimulatory factors leads to an enhanced inhibition of prostate cancer.

Prentice, R. L., Y. Huang, et al. (2009). "Variation in the FGFR2 gene and the effects of postmenopausal hormone therapy on invasive breast cancer." Cancer Epidemiol Biomarkers Prev **18**(11): 3079-85.

BACKGROUND: Breast cancer concern is a major reason for the recent marked reduction in use of postmenopausal hormone therapy, although equally effective means of controlling menopausal symptoms are lacking. Single nucleotide polymorphisms (SNP) in the fibroblast growth factor receptor 2 (FGFR2) gene are substantially associated with postmenopausal breast cancer risk and could influence hormone therapy effects. PARTICIPANTS AND METHODS: We interrogated eight SNPs in intron 2 of the FGFR2 gene for 2,166 invasive breast cancer cases from the Women's Health Initiative clinical trial and one-to-one matched controls to confirm an association with breast cancer risk. We used case-only analyses to examine the dependence of estrogen plus progestin and estrogen-alone odds ratios on SNP genotype. RESULTS: Seven FGFR2 SNPs, including six in a single linkage disequilibrium region, were found to associate strongly ($P < 10(-7)$) with breast cancer risk. SNP rs3750817 (minor allele T with frequency 0.39) had an estimated per-minor-allele odds ratio of 0.78, and was not in such strong linkage disequilibrium with the other SNPs. The genotype of this SNP related significantly ($P < 0.05$) to hormone therapy odds ratios. For estrogen plus progestin, the odds ratios (95% confidence intervals) at 0, 1, and 2 minor SNP alleles were 1.52 (1.14-2.02), 1.33 (1.01-1.75), and 0.69 (0.41-1.17), whereas the corresponding values for estrogen alone were 0.74 (0.51-1.09), 0.99 (0.68-1.44), and 0.34 (0.15-0.76). CONCLUSIONS: Postmenopausal women having TT genotype for SNP rs3750817 have a reduced breast cancer risk and seem to experience comparatively favorable effects of postmenopausal hormone therapy.

Qiu, Y., M. J. Langman, et al. (2004). "Targets of 17beta-oestradiol-induced apoptosis in colon cancer cells: a mechanism for the protective effects of hormone replacement therapy?" J Endocrinol **181**(2): 327-37.

Epidemiological studies show a strong link between postmenopausal hormone replacement therapy and decreased incidence of colorectal cancer. The colon cancer cell line, COLO 205, develops sensitivity to 17beta-oestradiol (E(2)) in apoptosis assays with increasing passage number (>40), and we hypothesised that genes selectively regulated in multiply passaged cells were likely to be important in E(2)-related apoptosis. Gene array analysis was used to compare the patterns of genes up- or down-regulated in E(2)-sensitive and -insensitive cells. For some genes, changes in mRNA expression were confirmed by protein expression analyses. Changes found in response to E(2) in multiply passaged cells, but not minimally passaged cells, included induction of growth arrest and DNA damage-inducible protein 153 (GADD153), and repression of Kirsten-Ras 2B (K-Ras-2B), metastasis inhibition factor NM23 and vascular endothelial growth factor. A second group of genes was regulated with E(2) exposure in both cell types, and is unlikely to be critically involved in E(2)-associated apoptosis. These included up-regulation of butyrate response factor 1 (BRF1) and down-regulation of c-jun and the breast cancer associated ring domain gene known as BARD1. By comparing control arrays from the two cell populations, cAMP-response element-binding protein (CBP), which is associated with steroid receptor-dependent target gene transcription and the oncoprotein, tyrosine kinase-T3 (TRK-T3), were up-regulated whereas retinoic acid receptor alpha (RARalpha) was down-regulated in multiply passaged cells. This study provides evidence for selective regulation of genes in colon cancer cells by E(2), indicates which of those regulated are likely to be involved in induced apoptosis, and suggests genes likely to be responsible for facilitation.

Rae, J. M., M. D. Johnson, et al. (2005). "GREB 1 is a critical regulator of hormone dependent breast cancer growth." Breast Cancer Res Treat **92**(2): 141-9.

BACKGROUND: Estrogen plays a central role in breast cancer pathogenesis and many potent risk factors for the development of the disease can be explained in terms of increased lifetime exposure to estrogen. Although estrogen regulated genes have been identified, those critically involved in growth regulation remain elusive.METHODS. To identify candidate genes involved in estrogen stimulated breast cancer growth, DNA microarray based gene expression profiles were generated from three estrogen receptor alpha (ER alpha) positive breast cancer cell lines grown under multiple stimulatory and inhibitory conditions. RESULTS: Only three genes were significantly induced by 17beta-estradiol (E2) relative to control in all three cell lines: GREB 1, stromal cell-derived factor 1 (SDF-1) and trefoil factor 1 (pS2). Quantitative real-time PCR assays confirmed that in all three cell lines, GREB 1 was induced by E2, but not by the antiestrogens tamoxifen (TAM) or ICI 182,780. GREB 1 expression level was strongly correlated with ER alpha positivity in 39 breast cancer cell lines of known ER alpha expression status. GREB

1 induction by E2 was rapid (7.3 fold by 2 h for MCF-7) and mirrored the fraction of cells entering S-phase when released from an estrogen deprivation induced cell arrest. Suppression of GREB 1 using siRNA blocked estrogen induced growth in MCF-7 cells and caused a paradoxical E2 induced growth inhibition. CONCLUSION: These data suggest that GREB 1 is critically involved in the estrogen induced growth of breast cancer cells and has the potential of being a clinical marker for response to endocrine therapy as well as a potential therapeutic target.

Rahman, K. M., S. Banerjee, et al. (2009). "3,3'-Diindolylmethane enhances taxotere-induced apoptosis in hormone-refractory prostate cancer cells through survivin down-regulation." Cancer Res **69**(10): 4468-75.

Survivin, a member of inhibitor of apoptosis family, is associated with both prostate cancer progression and drug resistance. Therefore, we hypothesized that survivin may play a potentially important role in hormone-refractory prostate cancer (HRPC) and bone metastatic disease; thus, targeting of survivin signaling could enhance therapeutic efficacy in prostate cancer. 3,3'-Diindolylmethane (DIM) has been known to have cancer chemoprevention activity. However, no information is available regarding the down-regulation of survivin by DIM, which could result in the chemosensitization of HRPC cells to Taxotere-induced killing. We investigated the effect of DIM alone or in combination with Taxotere using LNCaP and C4-2B prostate cancer cells. We observed that DIM enhanced Taxotere-induced apoptotic death in both cell lines. These enhancing effects were related to a decrease in survivin expression as well as androgen receptor and nuclear factor-kappaB (NF-kappaB) DNA-binding activity. We also found that knockdown of survivin expression by small interfering RNA transfection increased DIM-induced cell growth inhibition and apoptosis, whereas overexpression of survivin by cDNA transfection abrogated DIM-induced cell growth inhibition and apoptosis in both prostate cancer cells. Importantly, luciferase assays showed a significant reduction of survivin-Luc and NF-kappaB-Luc activity in prostate cancer cells exposed to DIM and Taxotere. Furthermore, combination treatment significantly inhibited C4-2B bone tumor growth, and the results were correlated with the down-regulation of survivin. From these results, we conclude that inactivation of survivin by DIM enhanced the therapeutic efficacy of Taxotere in prostate cancer in general, which could be useful for the treatment of HRPC and metastatic prostate cancer.

Ray, M. R., L. A. Wafa, et al. (2006). "Cyclin G-associated kinase: a novel androgen receptor-interacting transcriptional coactivator that is overexpressed in hormone refractory prostate cancer." Int J Cancer **118**(5): 1108-19.

The androgen receptor (AR), a steroid receptor family member, is a ligand-dependent transcription factor that has an integral role in normal prostate development. Alterations in AR-mediated activity can result in abnormal gene expression, dysregulated cell growth and prostate cancer. Coregulator proteins that interact with AR to influence activity and specificity of the AR-response may also have an important role in prostate cancer progression. Since the NH(2)-terminal domain (NTD) of AR encodes the ligand-independent activation function (AF)-1, this domain is incompatible with conventional yeast two-hybrid systems. Therefore, we have used the Tup1 repressed transactivator (RTA) system, which exploits the intrinsic transactivation properties of AR.NTD, for identification of novel AR-interacting proteins. Using this system, cyclin G-associated kinase (GAK) was identified as an AR interacting protein, and GST pull-down assays were used to confirm the interaction. GAK was shown to enhance the AF-1 function of AR activity in a ligand-dependent manner. Additionally, GAK enhanced the AR transcriptional response even at low concentrations of androgens, which is relevant to AR activity in androgen-independent prostate cancer. Finally, neo-adjuvant hormone therapy (NHT) tissue microarray analysis demonstrated that GAK expression increased significantly with prostate cancer progression to androgen independence, which suggests a prognostic role for GAK in advanced disease.

Rebbaa, A., F. Chu, et al. (2008). "Novel function of the thyroid hormone analog tetraiodothyroacetic acid: a cancer chemosensitizing and anti-cancer agent." Angiogenesis **11**(3): 269-76.

Previous studies from our laboratory have demonstrated that thyroid hormones play a key role in cancer progression. In addition, a deaminated form, tetraiodothyroacetic acid (tetrac), that antagonizes the proliferative action of these hormones was found to possess anti-cancer functions through its ability to inhibit cellular proliferation and angiogenesis. The present study was undertaken to investigate whether tetrac could also suppress the development of drug resistance, known as a causative factor of disease relapse. Tetrac was shown to enhance cellular response in vitro to doxorubicin, etoposide, cisplatin, and trichostatin A in resistant tumor cell lines derived from neuroblastoma, osteosarcoma, and breast cancer. The mechanism of action of tetrac did not involve expression of classical drug resistance genes. However, radiolabeled doxorubicin uptake in cells

was enhanced by tetrac, suggesting that one or more export mechanisms for chemotherapeutic agents are inhibited. Tetrac was also found to enhance cellular susceptibility to senescence and apoptosis, suggesting that the agent may target multiple drug resistance mechanisms. Tetrac has previously been shown to inhibit tumor cell proliferation in vitro. In vivo studies reported here revealed that tetrac in a pulsed-dose regimen was effective in suppressing the growth of a doxorubicin-resistant human breast tumor in the nude mouse. In this paradigm, doxorubicin-sensitivity was not restored, indicating that (1) the in vitro restoration of drug sensitivity by tetrac may not correlate with in vivo resistance phenomena and (2) tetrac is an effective chemotherapeutic agent in doxorubicin-resistant cells.

Rebbeck, T. R., A. DeMichele, et al. (2009). "Hormone-dependent effects of FGFR2 and MAP3K1 in breast cancer susceptibility in a population-based sample of post-menopausal African-American and European-American women." Carcinogenesis **30**(2): 269-74.

FGFR2 and MAP3K1 are members of the RAS/RAF/MEK/ERK-signaling pathway and have been identified from genome-wide association studies to be breast cancer susceptibility genes. Potential interactions of these genes and their role with respect to tumor markers, hormonal factors and race on breast cancer risk have not been explored. We examined FGFR2 and MAP3K1 variants, breast tumor characteristics and hormone exposures in a population-based case-control sample of 1225 European-American (EA) and 584 African-American (AA) women. FGFR2 rs1219648 and rs2981582 genotypes were significantly associated with breast cancer in EA only in estrogen receptor-positive (ER+), progesterone receptor-positive (PR+) and HER2/Neu-negative (HER2-) tumors. MAP3K1 was not associated with breast cancer in EA women, but it was associated with breast cancer in AA women, again limited to ER+, PR+ and HER2- tumors. An interaction was observed between combined hormone replacement therapy use and FGFR2 rs1219648 genotypes on breast cancer risk in EA women (P = 0.010). Finally, we observed a significant interaction between MAP3K1 rs889312 and FGFR2 rs2981582 (P = 0.022) in AA but not EA women. These results confirm that FGFR2 and MAP3K1 are involved in breast cancer susceptibility and confer their effects primarily in ER+ and PR+ tumors. We further report that these genes confer their effects in HER2- tumors, interact with one another to confer breast cancer susceptibility in AA women and interact with hormone exposures in AA and EA women.

Rebbeck, T. R., A. B. Troxel, et al. (2007). "Pharmacogenetic modulation of combined hormone replacement therapy by progesterone-metabolism genotypes in postmenopausal breast cancer risk." Am J Epidemiol **166**(12): 1392-9.

Combined hormone replacement therapy (CHRT) containing estrogens and progestins is associated with breast cancer risk. The authors evaluated interactions between CHRT use and progestin metabolism genotypes at CYP3A4 and the progesterone receptor (PGR) and their effects on breast cancer risk using the population-based Women's Insights and Shared Experiences (WISE) Study (1999-2002) of postmenopausal Caucasian women (522 breast cancer cases, 708 controls). The authors observed an elevated risk of ductal tumors in women with 3 or more years of CHRT use and PGR 331A alleles compared with those who had neither factor (odds ratio = 3.35, 95% confidence interval (CI): 1.13, 9.99; two-sided p(interaction) = 0.035). They also observed an elevated risk of progesterone receptor-positive tumors in women who had had 3 or more years of CHRT use and PGR 331A alleles compared with those who had neither factor (odds ratio = 3.82, 95% CI: 1.26, 11.55; p = 0.028). Finally, they observed an increased risk of estrogen receptor-negative tumors in women without CHRT exposure and CYP3A4*1B alleles compared with those who had neither factor (odds ratio = 6.46, 95% CI: 2.02, 20.66; p = 0.024), although the biologic interpretation of this result requires further study. When stratified by recency of use, PGR effects were observed only in current CHRT users, while CYP3A4 effects were observed only in former CHRT users. Breast cancer risk in women who have used CHRT may be influenced by genetic factors involved in progestin metabolism.

Reddy, G. P., E. R. Barrack, et al. (2006). "Regulatory processes affecting androgen receptor expression, stability, and function: potential targets to treat hormone-refractory prostate cancer." J Cell Biochem **98**(6): 1408-23.

Prostate cancer cells rely on androgen receptor (AR) for proliferation and survival. Therefore, curing prostate cancer will require elimination of AR. Although androgen is the natural ligand that activates AR, AR activity is also subject to regulation by growth factor/growth factor receptor-stimulated signaling pathways that control the cell cycle. Cell cycle regulatory proteins and protein kinases in signaling pathways affected by growth factors can lead to AR activation in the absence of androgen. While downstream signaling proteins such as cyclins, cyclin-dependent kinases (CDKs), and pRB can modulate AR activity, upstream signaling

pathways involving protein kinases such as mitogen-activated protein kinases, protein kinase A, and protein kinase B/Akt can affect post-translational modification of AR to affect not only AR function but also AR stability. Calcium and calmodulin (CaM), essential for proliferation and viability of a number of cells, including prostate cancer cells, play an important role in AR expression, stability, and function. CaM affects AR partly by interacting directly with AR and partly by activating protein kinases such as Akt and DNA-PK that can phosphorylate AR. The ubiquitin/26S proteasome pathway responsible for timely destruction of cell cycle regulatory proteins whose levels impede cell cycle progression also induces AR expression by activating NF-kappaB, and promotes AR activity by participating in the assembly of an AR transcription complex. Maspin, a serine protease inhibitor that is known mostly for its role as a tumor suppressor can also regulate AR intracellular localization and function by competing with AR for binding to the chaperone protein Hsp90 and co-repressor HDAC1, respectively. This perspective reviews the experimental evidence implicating these diverse cellular processes in AR expression, stability, and/or function, and presents a rationale for disrupting these cellular processes as a viable option for the treatment of both the hormone-sensitive and the hormone-insensitive prostate cancer.

Regan, M. M., G. Viale, et al. (2006). "Re-evaluating adjuvant breast cancer trials: assessing hormone receptor status by immunohistochemical versus extraction assays." J Natl Cancer Inst **98**(21): 1571-81.

BACKGROUND: Tumor levels of steroid hormone receptors, a factor used to select adjuvant treatment for early-stage breast cancer, are currently determined with immunohistochemical assays. These assays have a discordance of 10%-30% with previously used extraction assays. We assessed the concordance and predictive value of hormone receptor status as determined by immunohistochemical and extraction assays on specimens from International Breast Cancer Study Group Trials VIII and IX. These trials predominantly used extraction assays and compared adjuvant chemoendocrine therapy with endocrine therapy alone among pre- and postmenopausal patients with lymph node-negative breast cancer. Trial conclusions were that combination therapy provided a benefit to pre- and postmenopausal patients with estrogen receptor (ER)-negative tumors but not to ER-positive postmenopausal patients. ER-positive premenopausal patients required further study. METHODS: Tumor specimens from 571 premenopausal and 976 postmenopausal patients on which extraction assays had determined ER and progesterone receptor (PgR) levels before randomization from October 1, 1988, through October 1, 1999, were re-evaluated with an immunohistochemical assay in a central pathology laboratory. The endpoint was disease-free survival. Hazard ratios of recurrence or death for treatment comparisons were estimated with Cox proportional hazards regression models, and discriminatory ability was evaluated with the c index. All statistical tests were two-sided. RESULTS: Concordance of hormone receptor status determined by both assays ranged from 74% (kappa = 0.48) for PgR among postmenopausal patients to 88% (kappa = 0.66) for ER in postmenopausal patients. Hazard ratio estimates were similar for the association between disease-free survival and ER status (among all patients) or PgR status (among postmenopausal patients) as determined by the two methods. However, among premenopausal patients treated with endocrine therapy alone, the discriminatory ability of PgR status as determined by immunohistochemical assay was statistically significantly better (c index = 0.60 versus 0.51; P = .003) than that determined by extraction assay, and so immunohistochemically determined PgR status could predict disease-free survival. CONCLUSIONS: Trial conclusions in which ER status (for all patients) or PgR status (for postmenopausal patients) was determined by immunohistochemical assay supported those determined by extraction assays. However, among premenopausal patients, trial conclusions drawn from PgR status differed--immunohistochemically determined PgR status could predict response to endocrine therapy, unlike that determined by the extraction assay.

Rodriguez-Gonzalez, A., K. Cyrus, et al. (2008). "Targeting steroid hormone receptors for ubiquitination and degradation in breast and prostate cancer." Oncogene **27**(57): 7201-11.

Proteolysis targeting chimeric molecules (Protacs) target proteins for destruction by exploiting the ubiquitin-dependent proteolytic system of eukaryotic cells. We designed two Protacs that contain the peptide 'degron' from hypoxia-inducible factor-1alpha, which binds to the Von-Hippel-Lindau (VHL) E3 ubiquitin ligase complex, linked to either dihydroxytestosterone that targets the androgen receptor (AR; Protac-A), or linked to estradiol (E2) that targets the estrogen receptor-alpha (ERalpha; Protac-B). We hypothesized that these Protacs would recruit hormone receptors to the VHL E3 ligase complex, resulting in the degradation of receptors, and decreased proliferation of hormone-dependent cell lines. Treatment of estrogen-dependent breast cancer cells with Protac-B induced the degradation of ERalpha in a proteasome-dependent manner. Protac-B

inhibited the proliferation of ERalpha-dependent breast cancer cells by inducing G(1) arrest, inhibition of retinoblastoma phosphorylation and decreasing expression of cyclin D1, progesterone receptors A and B. Protac-B treatment did not affect the proliferation of estrogen-independent breast cancer cells that lacked ERalpha expression. Similarly, Protac-A treatment of androgen-dependent prostate cancer cells induced G(1) arrest but did not affect cells that do not express AR. Our results suggest that Protacs specifically inhibit the proliferation of hormone-dependent breast and prostate cancer cells through degradation of the ERalpha and AR, respectively.

Rubenstein, M., K. M. Anderson, et al. (2006). "Synthesis of branched antisense oligonucleotides having multiple specificities. Treatment of hormone insensitive prostate cancer." Med Hypotheses **67**(6): 1375-80.

Antisense oligonucleotides (oligos) directed against transforming growth factor-alpha (TGF-alpha) and its binding site, the epidermal growth factor receptor (EGFR), have demonstrated in vitro and in vivo efficacy against both the PC-3 and LNCaP prostate tumor models. In an attempt to increase the efficiency of these oligos a new type of antisense compound called a bispecific oligo has been evaluated in vitro both alone and in combination with traditional chemotherapeutic agents. These bispecifics, which were first proposed in this journal in 2004, include binding sites for both TGF-alpha and EGFR along the same stretch of complementary DNA. Such bispecifics are able to deliver essentially two antisense activities in an equal molar ratio and can be directed against mRNA encoding proteins of different biochemical pathways. The first bispecifics were developed against two proteins regulating a single autocrine loop. Subsequent bispecifics have been developed which target both EGFR and the apoptosis regulating protein bcl-2. Bispecific activity of a single linear sequence oligo has already been shown to have efficacy. To further develop this multispecific approach, we now propose a branched antisense compound, again, having multiple binding site activities (to complementary sequenced mRNA). Active oligos would be attached to a fat soluble backbone which might enhance targeting and also intracellular entry, release and activity. Such a structure would also permit the customization of these branched forms to include oligos targeting specific proteins related to the growth of various tumor types. Problems associated with the development of antisense oligos have included both membrane solubility and specific targeting. By designing this branched form of antisense structure, multiple activities can be retained (added), solubility improved and delivery enhanced. Such a new formulation would include several antisense oligos covalently bound to and branching off from a lipid-like backbone. An elongated hydrocarbon chain would increase fat solubility and would permit oligo incorporation into nanoparticles or liposome derived delivery vehicles. Specific delivery of oligos could also be enhanced by the tendency of these nanoparticle or liposomal microbubbles to be disrupted under the influence of ultrasonic waves beamed at the targeted tissue.

Russo, I. H. and J. Russo (2007). "Primary prevention of breast cancer by hormone-induced differentiation." Recent Results Cancer Res **174**: 111-30.

Breast cancer is a fatal disease whose incidence is gradually increasing in most industrialized countries and in all ethnic groups. Primary prevention is the ultimate goal for the control of this disease. The knowledge that breast cancer risk is reduced by early full-term pregnancy and that additional pregnancies increase the rate of protection has provided novel tools for designing cancer prevention strategies. The protective effect of pregnancy has been experimentally reproduced in virgin rats by treatment with the placental hormone human chorionic gonadotropin (hCG). HCG prevents the initiation and inhibits the progression of chemically induced mammary carcinomas by inducing differentiation of the mammary gland, inhibiting cell proliferation, and increasing apoptosis. It also induces the synthesis of inhibin, a tumor suppressor factor, downregulates the level of expression of the estrogen receptor alpha (ER-alpha) by methylation of CpG islands, imprinting a permanent genomic signature that characterizes the refractory condition of the mammary gland to undergo malignant transformation. The genomic signature induced by hCG is identical to that induced by pregnancy and is specific for this hormone. Comparison of the mammary gland's genomic profile of virgin Sprague-Dawley rats treated daily with hCG for 21 days with that of rats receiving 17beta-estradiol (E2) and progesterone (Pg) (E2 + Pg) revealed that in hCG-treated rats 194 genes were significantly up-modulated (> 2.5 log2-folds) ($p < 0.01$) and commonly expressed, whereas these genes were not expressed in the E2 + Pg group. The genomic signature induced by hCG and pregnancy included activators or repressors of transcription genes, apoptosis, growth factors, cell division control, DNA repair, tumor suppressor, and cell-surface antigen genes. Our data indicate that hCG, like pregnancy, induces permanent genomic changes that are not reproduced by steroid hormones and in addition regulates gene expression through epigenetic mechanisms that are differentiation-dependent processes, leading us to conclude that hormonally

induced differentiation offers enormous promise for the primary prevention of breast cancer.

Ryan, C. J., A. H. Harzstark, et al. (2008). "A pilot dose-escalation study of the effects of nordihydroguareacetic acid on hormone and prostate specific antigen levels in patients with relapsed prostate cancer." BJU Int **101**(4): 436-9.

OBJECTIVE: To assess the tolerability of the effects of nordihydroguareacetic acid (NDGA) and its effect on prostate-specific antigen (PSA) kinetics in patients with relapsed prostate cancer, as among the many biological effects of NDGA is the inhibition of the insulin-like growth factor 1 receptor (IGF-1R) tyrosine kinase. PATIENTS AND METHODS: Eligible patients were those with an increasing PSA level after definitive local therapy, in either the non-castrate (androgen-dependent prostate cancer, ADPC) or the castrate state (castration-resistant prostate cancer, CRPC) with no evidence of metastatic disease by bone scan or computed tomography of the abdomen or pelvis. Treatment consisted of continuous oral daily dosing according to a planned dose escalation of 750, 1250, 1750, 2250 and 2500 mg of NDGA. PSA levels were measured every 28 days. Serial levels of testosterone, dihydrotestosterone, oestradiol and sex hormone-binding globulin were measured at baseline and monthly while on study therapy. RESULTS: Fifteen patients were enrolled, including 11 with ADPC and four with CRPC. There were asymptomatic increases in transaminase in six patients, two of which were grade 3, all occurring at >or=3 months. The increases in transaminase resolved after stopping NDGA but recurred with repeated dosing. Doses of NDGA up to 2500 mg/day caused no other toxicities. A median (range) of 5.5 (1-13) cycles were delivered. Of the 11 patients with ADPC, one had a decline in PSA level of >50% of the baseline value and one a decline of <50%. Three patients with ADPC had a greater than three-fold increase in PSA doubling time while on therapy, one from 11 to 46 months (750 mg), one from 9.5 to 49.5 months (1750 mg), and one from 5.9 to 46.2 months (2500 mg). There were no reductions in PSA level in patients with CRPC. There were no significant effects on levels of testosterone, dihydrotestosterone, oestradiol or sex hormone-binding globulin. CONCLUSIONS: Continuous daily dosing with NDGA is reasonably well tolerated but is associated with transaminitis in some patients, that occurs after several months on therapy. There were apparent effects on the rate of increase in PSA. Further study is required to determine the optimum pharmacokinetics and antitumour effects of this therapy.

Ryden, L., G. Landberg, et al. (2008). "HER2 status in hormone receptor positive premenopausal primary breast cancer adds prognostic, but not tamoxifen treatment predictive, information." Breast Cancer Res Treat **109**(2): 351-7.

BACKGROUND: Overexpression of human epidermal growth factor receptor 2 (HER2) or amplification of its gene is a prognostic factor in primary breast cancer and a predictor for tamoxifen treatment efficacy in oestrogen receptor (ER) positive disease. In the present study we explored a defined cohort of breast cancer patients included in a randomised trial in order to assess prognostic and tamoxifen treatment information yielded by HER2 status. METHODS: Premenopausal breast cancer patients with stage II tumours (n = 564) were included and allocated to 2 years of adjuvant tamoxifen treatment versus no adjuvant treatment. ER, progesterone receptor (PR) status and HER2 status was determined by immunohistochemistry using a tissue microarray. HER2 amplification was analysed by fluorescent in situ hybridisation and tumours being amplified and/or HER2 3+ were considered HER2+. HER2 status was evaluable in 83% of the patients and 12.6% were HER2+. In untreated patients, HER2 was a negative prognostic factor in ER+ patients, HR 2.95; 95% CI: 1.61-5.38, $p < 0.001$, but not in ER- patients, HR 0.67; 95% CI: 0.28-1.61, $p = 0.4$, and a significant interaction between the two markers was found, $p < 0.01$. HER2 status was not related to tamoxifen treatment efficacy in ER+ patients (term of interaction $p = 0.95$). When stratifying for PR status, similar results were achieved. DISCUSSION: HER2+ and ER+ breast cancer constituted a subgroup of tumours with poor prognosis in premenopausal breast cancer, whereas no treatment interaction was found between HER2 status and tamoxifen in ER+ tumours. The poor prognosis in HER2+ and ER+ patients may interfere with the interpretation of HER2 data in non-randomised trials of adjuvant tamoxifen.

Salzberg, M., C. Rochlitz, et al. (2007). "An open-label, noncomparative phase II trial to evaluate the efficacy and safety of docetaxel in combination with gefitinib in patients with hormone-refractory metastatic prostate cancer." Onkologie **30**(7): 355-60.

BACKGROUND: Prostate cancer is the most common type of cancer in men, however, therapeutic options are limited. 50-90% of hormone-refractory prostate cancer cells show an overexpression of epidermal growth factor receptor (EGFR), which may contribute to uncontrolled proliferation and resistance to chemotherapy. In vitro, gefitinib, an orally administered tyrosine kinase inhibitor, has shown a significant increase in antitumor activity when combined with chemotherapy. PATIENTS AND

METHODS: In this phase II study, the safety and efficacy of gefitinib in combination with docetaxel, a chemotherapeutic agent commonly used for prostate cancer, was investigated in patients with hormone-refractory prostate cancer (HRPC). 37 patients with HRPC were treated continuously with gefitinib 250 mg once daily and docetaxel 35 mg/m2 i.v. for up to 6 cycles. PSA response, defined as a =50% decrease in serum PSA compared with trial entry, was the primary efficacy parameter. PSA levels were measured at prescribed intervals. RESULTS: The response rate and duration of response were consistent with those seen with docetaxel monotherapy. The combination of docetaxel and gefitinib was reasonably well tolerated in this study. CONCLUSION: Future studies should investigate whether patients with specific tumor characteristics, e.g. EGFR protein overexpression, respond better to gefitinib than patients without, leading to a more customized therapy option.

Sarvilinna, N., H. Eronen, et al. (2006). "Steroid hormone receptors and coregulators in endocrine-resistant and estrogen-independent breast cancer cells." Int J Cancer **118**(4): 832-40.

Resistance to hormonal therapy is often a problem in the treatment of breast cancer patients. It has been suggested that resistance could be explained by altered nuclear hormone receptor or coregulator levels or inappropriately increased agonist activity of selective estrogen receptor modulator (SERM). To test these hypotheses, we have established novel MCF-7 cell line-derived in vitro models of anti-estrogen- and progestin-resistant and estrogen-independent breast cancer by long-term culture in the presence of toremifene and medroxyprogesterone acetate (MPA) and in the absence of estradiol, respectively. Using cell growth and multiprobe ribonuclease protection assays, the expression of 5 nuclear hormone receptors and 9 coregulators as well as the alterations in the cell proliferation and target gene transcription in response to hormonal treatments were studied. Progesterone receptor (PR) expression was decreased and silencing mediator for retinoid acid and thyroid hormone receptors (SMRT) and amplified in breast cancer-1 (AIB1) expression increased in anti-estrogen-resistant cells. Estrogen caused PR and ERbeta upregulation in all cell lines, but we did not observe increased agonist activity of anti-estrogen measured by regulation of these estrogen target genes. Basal ERalpha levels and estrogenic growth response were decreased and p300/CBP-associated factor (pCAF) and AIB1 upregulated by estrogen in progestin-resistant cells, but coregulator levels were unchanged. Estrogen-independent cells were still estrogen-responsive and PR, nuclear receptor corepressor (N-CoR) and SMRT expression was increased whereas steroid receptor coactivator-1 (SRC-1a) and CBP-related protein p300 (p300) expression decreased. Their growth was inhibited by toremifene, but estradiol was able to abrogate this effect, which might have interesting clinical implications concerning the use of postmenopausal hormone replacement therapy.

Schabath, M. B., X. Wu, et al. (2004). "Hormone replacement therapy and lung cancer risk: a case-control analysis." Clin Cancer Res **10**(1 Pt 1): 113-23.

PURPOSE: To date, there are few published data regarding the use of hormone replacement therapy (HRT) and lung cancer risk. Therefore, we analyzed data regarding HRT use from a large case-control study designed to study genetic susceptibility to lung cancer to determine whether HRT affected risk of lung cancer. Experimental Design: In a secondary analysis, we compared self-reported HRT use among 499 women with lung cancer and 519 healthy age-matched controls. RESULTS: HRT use was associated with an overall reduced risk of 34% [odds ratio (OR), 0.66; 95% confidence interval (CI), 0.51-0.89] of lung cancer, after adjusting for age, ethnicity, smoking status, education, body mass index, and menopausal status. The use of estrogen replacement therapy alone was associated with a 35% reduction in lung cancer risk (OR, 0.65; 95% CI, 0.47-0.89) and the use of combination therapy (estrogen and progestin) was associated with a 39% reduction in lung cancer risk (OR, 0.61; 95% CI, 0.40-0.92). HRT use was also associated with a statistically significantly reduced risk of lung cancer in current smokers (OR, 0.59; 95% CI, 0.38-0.92), but the risk estimates were not statistically significant in never (OR, 0.72; 95% CI, 0.37-1.40) or former smokers (OR, 0.73; 95% CI, 0.46-1.15). In addition, as the cigarette pack-years increased among ever smokers, the protective effect diminished, so that light smokers appeared to benefit the most from HRT use. Decreased lung cancer risks were also evident when the data were stratified by age, ethnicity, and body mass index. The joint effects of HRT use and mutagen sensitivity suggest that HRT use modifies lung cancer risk for genetically susceptible women. HRT use was also associated with a lower risk of death and improved survival compared with the women not taking HRT. To provide a possible biological mechanism to explain our findings, we compared plasma levels of insulin-like growth factor I in users and nonusers, and demonstrated that HRT use was associated with statistically significantly lower insulin-like growth factor I levels for both cases and controls compared with non-HRT users. CONCLUSIONS: These data suggest an association of HRT use with a decrease in lung cancer risk. However, there are several limitations to this

secondary analysis, requiring that the data be viewed with caution, and confirmation is required in well-designed hypothesis driven studies. The biological role of HRT in lung cancer remains understudied, and only extensive research can yield new insights into the mechanisms underlying a protective effect of HRT for lung cancer.

Schiff, R. and C. K. Osborne (2005). "Endocrinology and hormone therapy in breast cancer: new insight into estrogen receptor-alpha function and its implication for endocrine therapy resistance in breast cancer." Breast Cancer Res **7**(5): 205-11.

Estrogen and its receptor (ER) are critical for development and progression of breast cancer. This pathway is targeted by endocrine therapies that either block ER functions or deplete ER's estrogen ligand. While endocrine therapies are very effective, de novo and acquired resistance are still common. Laboratory and clinical data now indicate that bidirectional molecular crosstalk between nuclear or membrane ER and growth factor receptor pathways such as HER2/neu is involved in endocrine resistance. Preclinical data suggest that blockade of selected growth factor receptor signaling can overcome this type of resistance, and this strategy is already being tested in clinical trials.

Schubert, A., H. Schulz, et al. (2008). "Expression of osteoprotegerin and receptor activator of nuclear factor-kappaB ligand (RANKL) in HCC70 breast cancer cells and effects of treatment with gonadotropin-releasing hormone on RANKL expression." Gynecol Endocrinol **24**(6): 331-8.

BACKGROUND: The majority of human breast cancers and in addition most breast-cancer cell lines express gonadotropin-releasing hormone (GnRH) receptors. Their proliferation and in addition their bone-directed invasion is time- and dose-dependently reduced by GnRH. Osteolytic metastases are characteristic for breast cancer-derived metastasis. Since the osteolytic activity depends on the receptor activator of nuclear factor-kappaB (NFkappaB) ligand (RANKL)/osteoprotegerin (OPG) ratio, we analyzed RANKL and OPG expression in different breast-cancer cell lines. METHODS: Different human breast-cancer cell lines were tested for expression of GnRH receptor, OPG and RANKL. Using a co-culture system of breast-cancer cell lines and human primary osteoblasts (hOB), we analyzed the expression of OPG and RANKL in the GnRH receptor-positive breast-cancer cell line HCC70 co-cultured with or without hOB. In addition, we assessed the effects of GnRH analog treatment on OPG and RANKL mRNA and protein levels. RESULTS: All tested breast-cancer cell lines were GnRH receptor-positive. The majority of these cell lines expressed OPG but not RANKL. The HCC70 breast-cancer cell line derived from an invasive ductal carcinoma with metastases was positive for both OPG and RANKL. The expression of RANKL by HCC70 cells was increased when co-cultured with hOB. Treatment with GnRH analogs reduced the expression of RANKL by HCC70 cells co-cultured with hOB. No effects were observed on breast cancer OPG expression. CONCLUSIONS: These data show that the majority of human breast-cancer cell lines express OPG but not RANKL. The HCC70 breast-cancer cell line is RANKL-positive. Co-culture of HCC70 breast cancer cells with hOB increases RANKL expression. Activation of tumor GnRH receptors reduces RANKL expression. These experiments demonstrate that HCC70 breast cancer cells are able to activate osteoclasts directly via RANKL. The interaction between HCC70 breast cancer cells and osteoblasts induces osteoclastogenesis through an increase of RANKL expression. GnRH seems to play an important role by modulating the RANKL expression in HCC70 breast cancer cells.

Shanmugam, R., V. Jayaprakasan, et al. (2006). "Restoring chemotherapy and hormone therapy sensitivity by parthenolide in a xenograft hormone refractory prostate cancer model." Prostate **66**(14): 1498-511.

BACKGROUND: Nuclear Factor kappa B (NFkappaB) is a eukaryotic transcription factor that is constitutively active in human cancers and can be inhibited by the naturally occurring sesquiterpene lactone, parthenolide (P). METHODS: The in vitro effects of P were assessed using the androgen independent cell line, CWR22Rv1, and human umbilical endothelial cells (HUVECs). The in vivo activity of P as a single agent and its ability to augment the efficacy of docetaxel and the anti-androgen, bicalutamide, were determined using the CWR22Rv1 xenograft model. RESULTS: Parthenolide at low micromolar concentration inhibited proliferation of CWR22Rv1 and HUVEC cells, promoted apoptosis and abrogated NFkappaB-DNA binding. Parthenolide downregulated anti-apoptotic genes under NFkappaB control, TRAF 1 and 2, and promoted sustained activation of c-jun-NH2 kinase (JNK). Parthenolide also augmented the in vivo efficacy of docetaxel and restored sensitivity to anti-androgen therapy. CONCLUSION: These studies demonstrate parthenolide's anti-tumor and anti-angiogenic activity, and its potential to augment the efficacy of chemotherapy and hormonal therapy.

Shi, Y., F. H. Brands, et al. (2001). "Her-2/neu expression in prostate cancer: high level of expression

associated with exposure to hormone therapy and androgen independent disease." J Urol **166**(4): 1514-9.

PURPOSE: HER-2/neu is a proto-oncogene that encodes a transmembrane receptor belonging to the family of epidermal growth factor receptors. Increasing evidences indicates that HER-2/neu may contribute to hormone resistance in prostate cancer. We investigated HER-2/neu expression in primary, androgen dependent and advanced androgen independent prostate cancer, and its potential value as a marker of disease progression. MATERIALS AND METHODS: Immunohistochemical testing was performed to investigate HER-2/neu expression in 81 patients with prostate cancer, including 31 with pathological stage C disease treated with radical prostatectomy without preoperative androgen ablation therapy (untreated group), 30 with pathological stage C disease treated before surgery with androgen ablation therapy (treated group) and 20 with advanced androgen independent prostate cancer (androgen independent group). Tumors were classified based on the percent of tumor cells showing HER-2/neu membrane immunoreactivity as low (50% or less) and high (50% or greater) expression. RESULTS: Of the 31 prostate tumors in the untreated group 9 (29%) showed high HER-2/neu expression versus 15 of 30 (50%) in the treated and 17 of 20 (85%) in the androgen independent groups. The difference in HER-2/neu expression was significant in the untreated and androgen independent ($p < 0.001$) and in the treated and androgen independent ($p = 0.016$) groups. There was a significant association of Gleason score with HER-2/neu expression in the untreated group ($p = 0.038$) but not in the treated group. No association was found of tumor substage with HER-2/neu expression. In the untreated group patients with tumors showing high HER-2/neu expression had a decreased survival rate ($p = 0.044$). CONCLUSIONS: High HER-2/neu expression is highly associated with exposure to hormone therapy and androgen independence. It may contribute to androgen independence in prostate cancer and identify patients with prostate cancer more likely to have disease progression, particularly those not exposed to previous hormone therapy.

Simons, J. W., M. A. Carducci, et al. (2006). "Phase I/II trial of an allogeneic cellular immunotherapy in hormone-naive prostate cancer." Clin Cancer Res **12**(11 Pt 1): 3394-401.

PURPOSE: To determine the toxicity, immunologic, and clinical activity of immunotherapy with irradiated, allogeneic, prostate cancer cells expressing granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with recurrent prostate cancer. PATIENTS AND METHODS: A single-institution phase I/II trial was done in hormone therapy-naive patients with prostate-specific antigen (PSA) relapse following radical prostatectomy and absence of radiologic metastases. Treatments were administered weekly via intradermal injections of 1.2 x 10(8) GM-CSF gene-transduced, irradiated, cancer cells (6 x 10(7) LNCaP cells and 6 x 10(7) PC-3 cells) for 8 weeks. RESULTS: Twenty-one patients were enrolled and treated. Toxicities included local injection-site reactions, pruritus, and flu-like symptoms. One patient had a partial PSA response of 7-month duration. At 20 weeks post first treatment, 16 of 21 (76%) patients showed a statistically significant decrease in PSA velocity (slope) compared with prevaccination ($P < 0.001$). Injection site biopsies showed intradermal infiltrates consisting of CD1a+ dendritic cells and CD68+ macrophages, similar to previous clinical trials using autologous GM-CSF-transduced cancer cells. Posttreatment, patients developed new oligoclonal antibodies reactive against at least five identified antigens present in LNCaP or PC-3 cells. A high-titer antibody response against a 250-kDa antigen expressed on normal prostate epithelial cells was induced in a patient with partial PSA remission; titers of this antibody decreased when treatment ended, and subsequent PSA relapse occurred. CONCLUSIONS: This non-patient-specific prostate cancer immunotherapy has a favorable safety profile and is immunologically active. Continued clinical investigation at higher doses and with longer boosting schedules is warranted.

Simpson, J. A., D. R. English, et al. (2007). "A comparison of different methods for including 'age at menopause' in analyses of the association between hormone replacement therapy use and breast cancer." J Fam Plann Reprod Health Care **33**(1): 11-6.

BACKGROUND AND METHODOLOGY: Late 'age at menopause' is a recognised risk factor for postmenopausal breast cancer and is also associated with decreased use of hormone replacement therapy (HRT). When investigating the association between HRT use and breast cancer risk it is therefore necessary to adjust for the potential confounder, 'age at menopause'. 'Age at menopause', however, cannot be determined for women with a hysterectomy and ovarian conservation. Using data on 13 357 postmenopausal women in whom 396 cases of invasive breast cancer were diagnosed during 9 years of follow-up from the Melbourne Collaborative Cohort Study, we compared the estimates of relative risk of HRT use for breast cancer for three different methods of dealing with missing data: complete-case analysis, single imputation and multiple imputation. RESULTS: 'Age at menopause' was missing for 17% of the data. Both HRT use and 'age at menopause'

were significant risk factors for breast cancer, although 'age at menopause' only marginally confounded the estimates of risk for HRT. Women with 'age at menopause' missing did not represent a random sample of the population. Complete-case analyses resulted in higher estimates of the risk associated with HRT use compared with the different methods of imputation. DISCUSSION AND CONCLUSIONS: We recommend that analyses investigating the association between HRT and breast cancer should present the results in two ways: excluding women with 'age at menopause' missing and including the women using multiple imputation. For both methods, estimates of risk, with and without the adjustment of 'age at menopause', should be given.

Singh, R. P., G. Sharma, et al. (2004). "In vivo suppression of hormone-refractory prostate cancer growth by inositol hexaphosphate: induction of insulin-like growth factor binding protein-3 and inhibition of vascular endothelial growth factor." Clin Cancer Res **10**(1 Pt 1): 244-50.

PURPOSE: Diet composition is an important etiologic factor in prostate cancer (PCA) growth and has significant impact on clinical PCA appearance. Because inositol hexaphosphate (IP6) is a dietary phytochemical present in cereals, soy, legumes, and fiber-rich foods, we evaluated efficacy of IP6 against PCA growth and associated molecular events. EXPERIMENTAL DESIGN: DU145 cells were injected into nude mice, and animals were fed normal drinking water or 1 or 2% IP6 in drinking water for 12 weeks. Body weight, diet, water consumption, and tumor sizes were monitored. Tumors were immunohistochemically analyzed for proliferating cell nuclear antigen, terminal deoxynucleotidyl transferase-mediated nick end labeling, and CD31. Tumor-secreted insulin-like growth factor binding protein (IGFBP)-3 and vascular endothelial growth factor (VEGF) were quantified in plasma by ELISA. RESULTS: IP6 feeding resulted in suppression of hormone-refractory human prostate tumor growth without any adverse effect on body weight gain, diet, and water consumption during entire study. At the end of study, tumor growth inhibition by 1 and 2% IP6 feeding was 47 and 66% ($P = 0.049$-0.012) in terms of tumor volume/mouse and 40 and 66% ($P = 0.08$-0.003) in terms of tumor weight/mouse, respectively. Tumor xenografts from IP6-fed mice showed significantly ($P < 0.001$) decreased proliferating cell nuclear antigen-positive cells but increased apoptotic cells. Tumor-secreted IGFBP-3 levels were also increased up to 1.7-fold in IP6-fed groups. Additionally, IP6 strongly decreased tumor microvessel density and inhibited tumor-secreted VEGF levels. CONCLUSIONS: IP6 suppresses hormone-refractory PCA growth accompanied by inhibition of tumor cell proliferation and angiogenesis and increased apoptosis. IP6-caused increase in IGFBP-3 and decrease in VEGF might have a role in PCA growth control.

Sivaraman, L. and D. Medina (2002). "Hormone-induced protection against breast cancer." J Mammary Gland Biol Neoplasia **7**(1): 77-92.

Reproductive history is a consistent risk factor for human breast cancer. Epidemiological studies have repeatedly demonstrated that early age of first full-term pregnancy is a strong protective factor against breast cancer and provides a physiologically operative model to achieve a practical mode of prevention. In rodents, the effects of full-term pregnancy can be mimicked by exposure to low doses of estrogen and progesterone or treatment with human chorionic gonadotropin. The cellular and molecular mechanisms that underlie hormone-induced refractoriness are largely unresolved. Several hypotheses have been proposed to explain the protective effects of hormones. These involve the induction of differentiation of the mammary gland to provide a less responsive cell population to carcinogens, a decrease in proliferative activity in the parous gland compared to the age-matched virgin, an altered hormonal environment mediated by a decrease in circulating growth hormone, and an alteration in cell fate mediated by specific molecular changes induced by estrogen and progesterone. The evidence for and against these hypotheses is discussed along with recent results on possible molecular alterations that may underlie the refractory state. One central question that is still unresolved is whether the refractoriness is intrinsic to the mammary epithelial cells and/or mediated by persistent alterations in the host environment.

Slanger, T. E., J. C. Chang-Claude, et al. (2009). "Menopausal hormone therapy and risk of clinical breast cancer subtypes." Cancer Epidemiol Biomarkers Prev **18**(4): 1188-96.

BACKGROUND: Breast cancer is a heterogeneous disease with subtypes that may vary in their etiologies. Menopausal hormone therapy has been associated more strongly with lobular and tubular than ductal histologic types and with tumors that are smaller, hormone receptor-positive, and of lower grade. At the same time, correlations have been observed between histology and clinical characteristics. To identify those tumor subtypes most strongly associated with hormone therapy use, it is necessary to disentangle these interrelationships. METHODS: Based on 3,464 postmenopausal breast cancer cases and 6,657 controls from the population-

based Mammary carcinoma Risk factor Investigation study, we used polytomous logistic regression to evaluate associations between hormone therapy use and risk of invasive breast cancer subtypes. We assessed variations in risk for selected tumor characteristics among histologic and hormone receptor subtypes, both overall and for specific hormone therapy regimens. RESULTS: Lobular and mixed types showed less variation by prognostic factors than did ductal tumors. Current hormone therapy use had the strongest associations with prognostic variables in estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive ductal tumors and in lobular tumors regardless of ER/PR status, with little effect on ER/PR-negative ductal tumors. The observed associations varied minimally by hormone therapy type or regimen. CONCLUSION: Current hormone therapy use was associated with more favorable breast cancer characteristics for ductal tumors but had less effect on prognostic characteristics in women with lobular tumors. Both histologic type and estrogen receptor/progesterone receptor status seem to be important in explaining the role of hormone therapy in the etiology of breast cancer subtypes.

Small, E. J., J. Fontana, et al. (2007). "A phase II trial of gefitinib in patients with non-metastatic hormone-refractory prostate cancer." BJU Int **100**(4): 765-9.

OBJECTIVE: To investigate, in a phase II trial, the use of the epidermal growth factor receptor (EGFR) inhibitor gefitinib as monotherapy in patients with non-metastatic hormone refractory prostate cancer (HRPC), as current treatment options for this disease are limited, and agents which target the EGFR should be assessed because EGFR is highly expressed in prostate cancer and associated with a poor prognosis. PATIENTS AND METHODS: Patients with histologically or cytologically confirmed cancer of the prostate with no evidence of metastatic disease were enrolled into this open-label, multicentre study of monotherapy with gefitinib 500 mg/day. The primary endpoint of the study was biochemical response, defined as a >/=50% decrease in serum prostate-specific antigen (PSA) level. RESULTS: Fifty-eight men were enrolled across 10 centres in the USA; none of the 40 evaluable patients had a PSA response. Gefitinib was generally well tolerated, with diarrhoea being the most common treatment- related adverse event, in 71% of patients. There was treatment-related grade 3 diarrhoea in 5% of patients, with no grade 4 adverse events or deaths during the course of the study. CONCLUSIONS: Gefitinib has no single-agent activity in non-metastatic HRPC, as assessed by decreases in serum PSA level. This phase II study also confirmed the well-established favourable tolerability profile of gefitinib monotherapy.

Small, E. J., N. Sacks, et al. (2007). "Granulocyte macrophage colony-stimulating factor--secreting allogeneic cellular immunotherapy for hormone-refractory prostate cancer." Clin Cancer Res **13**(13): 3883-91.

PURPOSE: This trial evaluated the safety, clinical activity, and immunogenicity of an allogeneic cellular immunotherapy in 55 chemotherapy-naive patients with hormone-refractory prostate cancer (HRPC). The immunotherapy, based on the GVAX platform, is a combination of two prostate carcinoma cell lines modified with the granulocyte macrophage colony-stimulating factor (GM-CSF) gene. EXPERIMENTAL DESIGN: HRPC patients with radiologic metastases (n = 34) or rising prostate-specific antigen (PSA) only (n = 21) received a prime dose of 500 million cells and 12 boost doses of either 100 million cells (low dose) or 300 million cells (high dose) biweekly for 6 months. End points were changes in PSA, time to progression, and survival. RESULTS: Median survival was 26.2 months (95% confidence interval, 17, 36) in the radiologic group: 34.9 months (8, 57) after treatment with the high dose (n = 10) of immunotherapy and 24.0 months (11, 35) with the low dose (n = 24). The median time to bone scan progression in the radiologic group was 5.0 months (2.6, 11.6) with the high dose and 2.8 months (2.8, 5.7) with the low dose. In the rising-PSA group (n = 21) receiving the low dose, the median time to bone scan progression was 5.9 months (5.6, not reached), and median survival was 37.5 months (29, 56). No dose-limiting or autoimmune toxicities were seen; the most common adverse events were injection site reaction and fatigue. CONCLUSIONS: These results suggest that this GM-CSF-secreting, allogeneic cellular immunotherapy is well tolerated and may have clinical activity in patients with metastatic HRPC. Phase 3 trials to confirm these results are under way.

So, W. K., J. C. Cheng, et al. (2008). "Gonadotropin-releasing hormone and ovarian cancer: a functional and mechanistic overview." Febs J **275**(22): 5496-511.

The hypothalamic decapeptide gonadotropin-releasing hormone (GnRH) is well known for its role in the control of pituitary gonadotropin secretion, but the hormone and receptor are also expressed in extrapituitary tissues and tumor cells, including epithelial ovarian cancers. It is hypothesized that they may function as a local autocrine regulatory system in nonpituitary contexts. Numerous studies have demonstrated a direct antiproliferative effect on ovarian cancer cell lines of GnRH and its synthetic

analogs. This effect appears to be attributable to multiple steps in the GnRH signaling cascade, such as cell cycle arrest at G(0)/G(1). In contrast to GnRH signaling in pituitary gonadotropes, the involvement of G(alpha q), protein kinase C and mitogen-activated protein kinases is less apparent in neoplastic cells. Instead, in ovarian cancer cells, GnRH receptors appear to couple to the pertussis toxin-sensitive protein G(alpha i), leading to the activation of protein phosphatase, which in turn interferes with growth factor-induced mitogenic signals. Apoptotic involvement is still controversial, although GnRH analogs have been shown to protect cancer cells from doxorubicin-induced apoptosis. Recently, data supporting a regulatory role of GnRH analogs in ovarian cancer cell migration/invasion have started to emerge. In this minireview, we summarize the current understanding of the antiproliferative actions of GnRH analogs, as well as the recent observations of GnRH effects on ovarian cancer cell apoptosis and motogenesis. The molecular mechanisms that mediate GnRH actions and the clinical applications of GnRH analogs in ovarian cancer patients are also discussed.

Son, D. J., M. H. Park, et al. (2007). "Inhibitory effect of snake venom toxin from Vipera lebetina turanica on hormone-refractory human prostate cancer cell growth: induction of apoptosis through inactivation of nuclear factor kappaB." Mol Cancer Ther **6**(2): 675-83.

We investigated whether the snake venom toxin (SVT) from Vipera lebetina turanica inhibits cell growth of human prostate cancer cells by inducing apoptosis and also studied possible signaling pathways involved in this cell death. SVT inhibited growth of PC-3 and DU145 cells, androgen-independent prostate cancer cells, but not LNCaP cells, a human androgen-dependent prostate cancer cell. Cells were arrested in the G(2)-M phase by SVT with a concomitant decrease in the expression of the G(2)-M phase regulatory protein cyclin B1 and were also arrested in the G(1)-S phase with decreasing expression of cyclin-dependent kinase 4, cyclin D1 and cyclin E. In addition to the growth-inhibitory effect, SVT increased the induction of apoptotic cell death. Untreated PC-3 cells show high DNA binding activity of nuclear factor kappaB (NF-kappaB), an antiapoptotic transcriptional factor, but this was inhibited by SVT and accompanied by a significant inhibition of p50 translocation into the nucleus, as well as phosphorylation of inhibitory kappaB. Consistent with the induction of apoptosis and inhibition of NF-kappaB, this toxin increased the expression of proapoptotic proteins such as p53, Bax, caspase-3, and caspase-9, but down-regulated antiapoptotic protein Bcl-2. However, SVT did not show an inhibitory effect on cell growth and caspase-3 activity in cells carrying mutant p50 and inhibitory kappaB kinase plasmids. Confocal microscopy analysis showed that SVT is taken up into the nucleus of the cells. These findings suggest that a nanogram concentration range of SVT from V. lebetina turanica could inhibit hormone-refractory human prostate cancer cell growth, and the effect may be related to NF-kappaB signal-mediated induction of apoptosis.

Sotomayor, S., M. J. Carmena, et al. (2007). "Transactivation of HER2 by vasoactive intestinal peptide in experimental prostate cancer: Antagonistic action of an analog of growth-hormone-releasing hormone." Int J Oncol **31**(5): 1223-30.

Receptors for vasoactive intestinal peptide (VIP) and the human epidermal growth factor family of tyrosine kinase receptors (HER) are potent promoters of cell proliferation, survival, migration, adhesion and differentiation in prostate cancer cell lines. In this study, we analyzed the cross-talk between both classes of receptors through the regulation of HER2 transactivation and expression by VIP. Three growth-hormone-releasing hormone analogs endowed with antagonistic activity for VIP receptors (JV-1-51, -52, and -53) abrogated the autocrine/paracrine stimuli of VIP on androgen-independent PC3 cells in the absence or the presence of 10% fetal bovine serum. Semiquantitative and real-time quantitative RT-PCR together with Western blotting showed increased expression levels of both mRNA and proteins for HER2 and HER3 in PC3 and androgen-dependent LNCaP prostate cancer cells as compared to non-neoplastic RWPE-1 cells. VIP (100 nM) stimulated the expression levels of both HER2 and HER3 in PC3 cells in a time-dependent manner. Whereas these effects were relatively slow, VIP rapidly (0.5 min) increased HER2 tyrosine phosphorylation. This pattern of HER transactivation was blocked by H89, a protein kinase A (PKA) inhibitor, as well as by the specific VIP antagonist JV-1-53, indicating the involvement of VIP receptors and PKA activity in phosphorylated HER2 formation. These findings support the merit of further studies on the potential usefulness of VIP receptor antagonists and both HER2 antibodies and tyrosine kinase inhibitors for prostate cancer therapy.

Stadler, W. M., D. Cao, et al. (2004). "A randomized Phase II trial of the antiangiogenic agent SU5416 in hormone-refractory prostate cancer." Clin Cancer Res **10**(10): 3365-70.

PURPOSE: To assess the activity of the antiangiogenic agent and VEGFR2 inhibitor SU5416 in hormone-refractory prostate cancer. Patients and Methods: Thirty-six chemotherapy naive patients were

randomized to treatment with SU5416 (145 mg/m(2)) and dexamethasone premedication or dexamethasone alone. Patients in the control arm could cross over to experimental therapy after progression. Prostate-specific antigen (PSA) was measured every 2 weeks, and radiological evaluation was performed every 8 weeks. In vitro assessment of SU5416 on PSA secretion was assessed in the LNCaP cell line. Baseline serum basic fibroblast growth factor and plasma vascular endothelial growth factor (VEGF) were explored as prognostic factors. RESULTS: VEGF receptor-2 expression is detectable in prostate cancer cell lines, and SU5416 inhibited in vitro PSA secretion. No effect of SU5416 on PSA secretion or time to progression is detectable in patients. VEGF and basic fibroblast growth factor were not prognostic. Headache and fatigue were the most common SU5416 toxicities, but hyperglycemia, hyponatremia, lymphopenia, infection, and adrenal suppression, all attributable to steroids and the required central line, were common. CONCLUSION: No disease modifying effects of SU5416 were detectable in this small study. Modest toxicity, an inconvenient administration schedule, and availability of other VEGFR-targeted agents support the decision to halt further evaluation of SU5416 in prostate cancer.

Sweeney, C., G. Liu, et al. (2005). "A phase II multicenter, randomized, double-blind, safety trial assessing the pharmacokinetics, pharmacodynamics, and efficacy of oral 2-methoxyestradiol capsules in hormone-refractory prostate cancer." Clin Cancer Res **11**(18): 6625-33.

PURPOSE: To determine whether the preclinical antitumor and antiangiogenic activity of 2-methoxyestradiol can be translated to the clinic. EXPERIMENTAL DESIGN: Men with hormone-refractory prostate cancer were enrolled into this phase II randomized, double-blind trial of two doses of oral 2-methoxyestradiol capsules (400 and 1,200 mg/d) given in 4-week cycles. Pharmacokinetic sampling was done on day 1 of cycles 1 and 2 and trough samples were obtained weekly. RESULTS: Thirty-three men were accrued between February and September 2001. The notable toxicity related to therapy was one grade 2 and two grade 3 episodes of liver transaminase elevation, which resolved with continued treatment in two patients. There were two cases of deep venous thromboses. The drug had nonlinear pharmacokinetic, rapid conversion to 2-methoxyestrone and approximately 85% conjugation. Trough plasma levels of unconjugated 2-methoxyestradiol and 2-methoxyestrone were approximately 4 and 40 ng/mL, respectively. Prostate-specific antigen declines between 21% and 40% were seen in seven patients in the 1,200 mg group and in one patient in the 400 mg group. The higher-dose group showed significantly decreased prostate-specific antigen velocity (P = 0.037) and compared with the 400 mg dose had a longer median time to prostate-specific antigen progression (109 versus 67 days; P = 0.094) and time on study (126 versus 61 days; P = 0.024). There was a 2.5- and 4-fold increase in sex hormone-binding globulin for the 400 and 1,200 mg dose levels, respectively, at days 28 and 56. CONCLUSION: 2-Methoxyestradiol is well tolerated and, despite suboptimal plasma levels and limited oral bioavailability with this capsule formulation, still showed some anticancer activity at 1,200 mg/d.

Swerdlow, A. J., C. D. Higgins, et al. (2002). "Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study." Lancet **360**(9329): 273-7.

BACKGROUND: Growth hormone raises serum concentrations of insulin-like growth factor IGF-I, which is mitogenic and antiapoptotic. There is evidence that raised endogenous levels of growth hormone and IGF-I might be associated with increased risk of certain solid cancers, but there have been no data on long-term risks of solid cancers after growth hormone treatment. METHODS: We did a cohort study to investigate cancer incidence and mortality in 1848 patients in the UK who were treated during childhood and early adulthood with human pituitary growth hormone during the period from 1959 to 1985. Patients were followed up for cancer incidence to December, 1995 and for mortality to December, 2000. Risk of cancer in the cohort was compared with that in the general population, controlling for age, sex, and calendar period. FINDINGS: Patients treated with human pituitary growth hormone had significantly raised risks of mortality from cancer overall (standardised mortality ratio 2.8, 95% CI 1.3-5.1; ten cases), colorectal cancer (10.8, 1.3-38.8; two cases), and Hodgkin's disease (11.4, 1.4-41.3; two cases). Incidence of colorectal cancer was also greatly raised (7.9, 1.0-28.7). After exclusion of patients whose original diagnosis rendered them at high risk of cancer, the significance and size of the risks of colorectal cancer incidence and mortality, and of Hodgkin's disease mortality were increased. INTERPRETATION: Although based on small numbers, the risk of colorectal cancer is of some concern and further investigation in other cohorts is needed. We have no evidence as to whether growth hormone in modern dosage regimens is associated with an increased risk of colorectal cancer.

Tai, P., E. Yu, et al. (2006). "Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

in patients with limited stage small cell lung cancer." Lung Cancer **53**(2): 211-5.

A few series in the literature were published before 1987 on syndrome of inappropriate antidiuretic hormone secretion (SIADH) in small cell lung cancer (SCLC). This study examines the outcome in more recent era. From 1981-1998, there were 1417 new cases of SCLC diagnosed in the provincial registry, of which 244 were of limited stage (LS). A chart review and statistical analyses were performed using Mann-Whitney test, chi-square test and Kaplan-Meier method. Fourteen LS patients (group A) had SIADH at presentation. Group B consisted of 230 LS patients without SIADH. There were more patients with poorer performance status (ECOG 2-4) in group A than B (28.6% versus 7.8%, P=0.03). Otherwise, sex, age at diagnosis, nodal spread, pleural effusion, bronchial obstruction, superior vena cava obstruction, performance status, weight loss, and lactic dehydrogenase at presentation, were comparable between the two groups. Treatments given, e.g., extent of surgical resection (if performed, whether complete/incomplete), total number of chemotherapy cycles, radiotherapy doses, were comparable (P>0.05). The response to chemo-radiation was not significantly different (P=0.7). Five-year overall survival (8% versus 19%, P=0.08), and cause-specific survival (16% versus 20%, P=0.13) showed that group A patients had a worse outcome, though of borderline significance. Symptoms related to SIADH included: weakness, 4 patients; tiredness, 3; change in level of consciousness, 1; seizure, 1. The range of lowest sodium level was 110-129. Two patients also had paraneoplastic myopathy. SIADH resolved in 12 patients at 1.6-44.7 weeks (median: 4.3). Among the 14 patients who initially presented with SIADH and recurred later, 10 had recurrence of SIADH at the time of tumor recurrence. Serum sodium was useful for post-treatment surveillance in SCLC patients who presented with SIADH, with 71% (10/14) developing SIADH again at the time of recurrence. SIADH is a poor prognostic factor for LS SCLC.

Tangjitgamol, S., S. Manusirivithaya, et al. (2008). "Hormone replacement therapy after treatment of endometrial cancer." Gynecol Obstet Invest **65**(1): 35-8.

Hormone replacement therapy (HRT) after endometrial cancer (EMC) treatment is an uncertain subject with limited exploration among gynecologic cancer research. Because estrogen is a well-recognized etiologic factor of EMC, most physicians are probably reluctant to provide a replacement therapy, or limit its use to only a selected group of patients. In order to give an overview on this subject, we searched the English-language literature to identify relevant studies or reports. We found that HRT did not appear to increase the recurrence or death rates in EMC. However, most information came from retrospective studies with selection bias, or from a small prospective non-randomized study. The only randomized controlled trial of the Gynecologic Oncology Group could also not provide a definite answer regarding its safety and recommendation. In conclusion, on the basis of the currently available studies, HRT after EMC treatment does not appear to have an adverse effect on EMC. Nevertheless, because of a limitation of data, the physician should thoroughly consider all possible benefits and theoretical risks of recurrence or mortality in each individual to provide the best of care for their patients.

Torrisi, R., A. Balduzzi, et al. (2008). "Tailored preoperative treatment of locally advanced triple negative (hormone receptor negative and HER2 negative) breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel." Cancer Chemother Pharmacol **62**(4): 667-72.

BACKGROUND: No specific treatment guidelines are available for triple-negative breast cancers, defined by a lack of expression of estrogen (ER), progesterone (PgR), and HER2 receptors. Thirty patients are evaluable. Median age was 41 years (28-64 years). Twenty-three of 25 evaluable tumors stained positively for epidermal growth factor receptor. An objective response, either complete and partial, was observed in 26 patients (86, 95% CI 69.3-96.2%). and a pCR was obtained in 12 patients (40, 95% CI 22.7-59.4%). Two patients progressed during paclitaxel. Negative axillary nodes were found in 80% (95% CI 61.4-92.3%) of patients at surgery. Twenty-six patients (86, 95% CI 61.4-92.3%) underwent breast conserving surgery. Grade >2 non-hematological toxicity was observed in three and two patients during ECF and paclitaxel, respectively. The 2-year disease free survival (DFS) was 87.5% (95% CI 74.7-100%). No significant correlation was observed between EGFR staining and either pCR or DFS. CONCLUSIONS: Preoperative cisplatin containing chemotherapy followed by paclitaxel induced an high pCR rate in a population of triple-negative breast cancer. The impact of this schedule on long-term outcome should be investigated in larger series.

Turcotte, S., M. A. Forget, et al. (2007). "Prostate-derived Ets transcription factor overexpression is associated with nodal metastasis and hormone receptor positivity in invasive breast cancer." Neoplasia **9**(10): 788-96.

Prostate-derived Ets transcription factor (PDEF) has recently been associated with invasive

breast cancer, but no expression profile has been defined in clinical specimens. We undertook a comprehensive PDEF transcriptional expression study of 86 breast cancer clinical specimens, several cell lines, and normal tissues. PDEF expression profile was analyzed according to standard clinicopathologic parameters and compared with hormonal receptor and HER-2/neu status and to the expression of the new tumor biomarker Dikkopf-1 (DKK1). Wide ranging PDEF overexpression was observed in 74% of tested tumors, at higher levels than the average expression found in normal breasts. High PDEF expression was associated with hormone receptor positivity ($P < .001$), moderate to good differentiation (less than grade III, $P = .01$), and dissemination to axillary lymph nodes ($P = .002$). PDEF was an independent risk factor for nodal involvement (multivariate analysis, odds ratio 1.250, $P = .002$). It was expressed in a different subgroup compared to DKK1-expressing tumors ($P < .001$). Our data imply that PDEF mRNA expression could be useful in breast cancer molecular staging. Further insights into PDEF functions at the protein level, and possible links with hormone receptors biology, bear great potential for new therapeutic avenues.

Uemura, H., H. Hasumi, et al. (2006). "Renin-angiotensin system is an important factor in hormone refractory prostate cancer." Prostate **66**(8): 822-30.

BACKGROUND: The aim of this study was to perform a comprehensive evaluation of the renin-angiotensin system (RAS) in prostate cancer. METHODS: We investigated the expression of RAS components in prostate cancer cells treated with hormonal agents. Real-time PCR data showed the expression of the AT1 receptor, angiotensin I converting enzyme (ACE), and angiotensin I/II (Ang-I/II) precursor in all 87 prostate tissue samples. RESULTS: Expression of these genes in hormone refractory prostate cancer (HRPC) was significantly higher than that in normal prostate tissue and untreated prostate cancer tissue. Western blot showed that protein expression of the AT1 receptor and Ang-I/II was enhanced in LNCaP cells cultivated in steroid-free medium. When LNCaP cells were stimulated with dihydrotestosterone (DHT), estradiol (E2), dexamethasone (DEX), or anti-androgen drugs, protein expression of the AT1 receptor and Ang-I/II was augmented. CONCLUSIONS: The present data suggest that prostatic RAS is overexpressed in HRPC tissue, and expression of its components is influenced by several kinds of hormonal stimulation.

Urruticoechea, A., H. Aguilar, et al. (2008). "Pre-clinical validation of early molecular markers of sensitivity to aromatase inhibitors in a mouse model of post-menopausal hormone-sensitive breast cancer." Breast Cancer Res Treat **109**(3): 463-70.

INTRODUCTION: Changes in breast cancer cell biology following hormonal treatment have been claimed as promising predictor markers of clinical benefit even outperforming clinical response. From previous work we selected 10 genes showing both a well known regulation by oestrogen and a high level of early transcriptional regulation following therapy with aromatase inhibitors. Here we use an animal breast cancer model to explore the feasibility of the determination of their expression in minimally invasive samples and to further assess the magnitude of their regulation by letrozole. ANIMAL AND METHODS: Aromatase inhibitor sensitive breast cancer tumours were grown in athymic mice under supplement with androstenedione. Following initial tumour growth animals were assigned to a control group or to receive letrozole at two different dosages. Fine needle aspirates were obtained at the moment of treatment assignation and one week later. Expression of the following genes at both time points was determined: Ki-67, Cyclin D1, pS2, Trefoil Factor 3, PDZ domain containing 1, Ubiquitin-conjugating enzyme E2C, Stanniocalcin 2, Topoisomerase 2 alfa, MAN1A1 and FAS. RESULTS: Fine needles aspirates were found to be a feasible and reproducible technique for RNA extraction. Trefoil Factor 3, pS2, Cyclin D1 and Stanniocalcin 2 were significantly downregulated by letrozole. Among them pS2 appears to be most sensitive to aromatase inhibitor treatment even differentiating sub-optimal from optimal letrozole dosage. DISCUSSION: We present pre-clinical evidence to justify the exploration in clinical trials of pS2, Trefoil factor 3, Cyclin D1 and Stanniocalcin as dynamic markers of oestrogen-driven pathway activation.

Van Themsche, C., S. Parent, et al. (2009). "VP-128, a novel oestradiol-platinum(II) hybrid with selective anti-tumour activity towards hormone-dependent breast cancer cells in vivo." Endocr Relat Cancer **16**(4): 1185-95.

We have previously reported the synthesis of VP-128, a new 17beta-oestradiol (E(2))-linked platinum(II) hybrid with high affinity for oestrogen receptor alpha (ERalpha). In the present study, we have investigated the anti-tumour activity of VP-128 towards breast cancer cells in vitro and in vivo. We used human ERalpha-positive (MCF-7) and -negative (MDA-MB-468) cells as a model for treatment with increasing doses of VP-128, cisplatin or E(2) in vitro and for xenograft experiments in nude mice in vivo. Compared with cisplatin, VP-128 showed markedly improved in vitro and in vivo anti-tumour activity towards ERalpha-positive MCF-7 breast cancer cells,

without increased systemic toxicity. In these caspase-3-deficient cells, treatment with VP-128 overcame weak cellular sensitivity to cisplatin in vitro and in vivo. In these cells, only the hybrid induced apoptosis in an ERalpha-dependent manner, inactivated both X-linked inhibitor of apoptosis protein and Akt, and induced selective nuclear accumulation of ERalpha and the expression of ER-regulated genes c-myc and tff1, which was blocked by ERalpha-specific antagonist ICI 282 780. In the case of ERalpha-negative MDA-MB-468 cells, VP-128, but not cisplatin, induced nuclear accumulation of apoptosis-inducing factor and inhibited c-myc expression. However, VP-128 did not show enhanced in vivo anti-tumour activity compared with cisplatin. These results reveal two different modes of action for VP-128 in ERalpha-positive and -negative breast cancer cells, and highlight the promising therapeutic value of this unique E(2)-platinum hybrid for selective targeting of hormone-dependent cancers.

Weiss, L. K., R. T. Burkman, et al. (2002). "Hormone replacement therapy regimens and breast cancer risk(1)." Obstet Gynecol **100**(6): 1148-58.

Hormone replacement therapy (HRT) has increased in the United States over the past 2 decades in response to reports of long-term health benefits. A relationship between HRT and breast cancer risk has been observed in a number of epidemiological studies. In 2002, the Women's Health Initiative Randomized Controlled Trial reported an association between continuous combined HRT and breast cancer risk. The objective of this study was to examine the association between breast cancer risk and HRT according to regimen and duration and recency of use.A multicenter, population-based, case-control study was conducted in five United States metropolitan areas from 1994 to 1998. Analyzed were data from 3823 postmenopausal white and black women (1870 cases and 1953 controls) aged 35-64 years. Odds ratios (ORs) were calculated as estimates of breast cancer risk using standard, unconditional, multivariable logistic regression analysis. Potential confounders were included in the final model if they altered ORs by 10% or more. Two-sided P values for trend were computed from the likelihood ratio statistic. Continuous combined HRT was associated with increased breast cancer risk among current users of 5 or more years (1.54; 95% confidence interval 1.10, 2.17). Additionally, a statistically significant trend indicating increasing breast cancer risk with longer duration of continuous combined HRT was observed among current users (P =.01). There were no positive associations between breast cancer risk and other HRT regimens. Our data suggest a positive association between continuous combined HRT and breast cancer risk among current, longer term users. Progestin administered in an uninterrupted regimen may be a contributing factor. Risk dissipates once use is discontinued.

Wells, A., J. C. Souto, et al. (2002). "Luteinizing hormone-releasing hormone agonist limits DU-145 prostate cancer growth by attenuating epidermal growth factor receptor signaling." Clin Cancer Res **8**(4): 1251-7.

PURPOSE: Advanced prostate cancer is treated initially by central suppression of androgen production by luteinizing hormone-releasing hormone (LHRH) agonists. Intriguingly, even hormone-independent cancers often show some, if only slight, growth retardation when these agonists are delivered in pharmacological doses. Previous studies have shown in cell lines and animal xenograft models that activation of peripheral LHRH receptors on prostate carcinoma cells lead to growth suppression. In parallel, there is a decrease of epidermal growth factor receptors (EGFRs) and activity. Because autocrine EGFR stimulation exists in most, if not all, prostate carcinomas and is required for cell proliferation, we asked whether LHRH signaling cross-attenuated EGFR to limit tumor growth. One possible mechanism was suggested by LHRH receptors triggering phospholipase-C (PLC) to activate protein kinase C (PKC) because PKC activation limits EGFR tyrosine kinase activity by phosphorylating EGFR at threonine 654. EXPERIMENTAL DESIGN: To determine the role of this cross-attenuation mechanism, we mutated the threonine 654 amino acid to an alanine (A654) to abrogate this inhibition. DU-145 cells stably expressing wild-type and A654 EGFR were grown as xenografts in the s.c. space of athymic mice. RESULTS: DU-145 cells, overexpressing wild-type EGFR, formed tumors in athymic mice that were inhibitable by goserelin acetate (Zoladex). Tumors expressing the A654 EGFR were resistant to this growth inhibition. These results paralleled in vitro studies in which goserelin acetate blocked proliferation of the WT DU-145 but not A654 DU-145 cells. CONCLUSIONS: These data support the model of LHRH agonists preventing EGFR-mediated tumor growth through a PKC pathway. This suggests new targets of modulatory intervention to limit the growth of androgen-independent prostate carcinomas.

Wilson, M. A. and S. A. Chrysogelos (2002). "Identification and characterization of a negative regulatory element within the epidermal growth factor receptor gene first intron in hormone-dependent breast cancer cells." J Cell Biochem **85**(3): 601-14.

The epidermal growth factor receptor (EGFR) exhibits an inverse correlation with estrogen

receptor (ER) expression in the majority of breast cancers, predicting a poor response to endocrine therapy and poor survival rate. Inappropriate overexpression of EGFR in breast cancer is associated with a more aggressive phenotype. Transcriptional regulation is the major regulatory mechanism controlling EGFR overexpression in breast cancer cells. We have identified a region within the first intron of the EGFR gene that mediates transcriptional repression of EGFR gene expression in ER +/low EGFR expressing but not in ER-/high EGFR expressing breast cancer cells. Utilizing transient transfections of homologous and heterologous promoter-reporter constructs, we localized optimal repressive activity to a 96 bp intron domain. The 96 bp fragment displayed differential DNA-protein complex formation with nuclear extracts from ER + vs. ER- breast cancer cells. Moreover, factors interacting with this intron negative regulatory element appear to be estrogen-regulated. Consequently, our results suggest that we have identified a potential mechanism by which maintenance of low levels of EGFR expression and subsequent EGFR upregulation may be attributed to the loss of transcriptional repression of EGFR gene expression in hormone-dependent breast cancer cells.

Woodfield, G. W., A. D. Horan, et al. (2007). "TFAP2C controls hormone response in breast cancer cells through multiple pathways of estrogen signaling." Cancer Res **67**(18): 8439-43.

Breast cancers expressing estrogen receptor-alpha (ERalpha) are associated with a favorable biology and are more likely to respond to hormonal therapy. In addition to ERalpha, other pathways of estrogen response have been identified including ERbeta and GPR30, a membrane receptor for estrogen, and the key mechanisms regulating expression of ERs and hormone response remain controversial. Herein, we show that TFAP2C is the key regulator of hormone responsiveness in breast carcinoma cells through the control of multiple pathways of estrogen signaling. TFAP2C regulates the expression of ERalpha directly by binding to the ERalpha promoter and indirectly via regulation of FoxM1. In so doing, TFAP2C controls the expression of ERalpha target genes, including pS2, MYB, and RERG. Furthermore, TFAP2C controlled the expression of GPR30. In distinct contrast, TFAP2A, a related factor expressed in breast cancer, was not involved in estrogen-mediated pathways but regulated expression of genes controlling cell cycle arrest and apoptosis including p21(CIP1) and IGFBP-3. Knockdown of TFAP2C abrogated the mitogenic response to estrogen exposure and decreased hormone-responsive tumor growth of breast cancer xenografts. We conclude that TFAP2C is a central control gene of hormone response and is a novel therapeutic target in the design of new drug treatments for breast cancer.

Wu, A. H., M. C. Yu, et al. (2007). "Body size, hormone therapy and risk of breast cancer in Asian-American women." Int J Cancer **120**(4): 844-52.

Historically, breast cancer rates have been low in Asia but rates have increased substantially in Asian-Americans for reasons that are not well understood. The authors conducted a population-based case-control study of breast cancer in Los Angeles County, which included 1,277 (450 Chinese, 352 Japanese, 475 Filipinos) women with incident, histologically confirmed breast cancer and 1,160 control subjects (486 Chinese, 311 Japanese, 363 Filipinos). A detailed in-person interview was conducted, which included questions on menopausal hormone therapy (HT) use, height, weight in each decade of life and reproductive factors. Breast cancer risk increased with increasing recent weight in postmenopausal women (p trend = 0.015). Use of HT was a significant risk factor; risk increased 26% per 5 years of current use of estrogen and progestin therapy (p trend = 0.017). The increased risk associated with high body weight was observed irrespective of HT use. Use of HT and high body size might have contributed to the rapid increase of breast cancer in Asian-Americans.

Yano, S., H. Matsuyama, et al. (2006). "Identification of genes linked to gefitinib treatment in prostate cancer cell lines with or without resistance to androgen: a clue to application of gefitinib to hormone-resistant prostate cancer." Oncol Rep **15**(6): 1453-60.

Understanding the molecular action of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, might allow us to perform more effective therapies for hormone-independent advanced prostate cancer. A DNA microarray study was undertaken to comprehensively analyze the alteration of levels of 1,081 genes after gefitinib treatment in androgen-independent PC3 and DU145 cells and androgen-dependent LNCaP cells. The proliferation of PC3, DU145 and LNCaP cells was significantly inhibited by 50.2%, 83.8% and 55.2%, respectively, 6 days after 10 microM gefitinib administration. Of the above 1,081 genes, we identified 23, 13 and 33 genes with significantly different expression in PC3, DU145 and LNCaP cells, respectively, 24 h after 10 microM-gefitinib exposure. Among the identified genes, only Quiescin Q6, a negative cell cycle regulator, was increased after gefitinib treatment in all three cell lines regardless of gefitinib sensitivity. Except for Quiescin

Q6, there were no overlapping genes between PC3 and DU145 cells. However, levels of several oncogenes or proliferation-related genes were changed after gefitinib treatment in the 2 androgen-independent cell lines. We also identified 7 unique genes [glycyl-tRNA synthetase, interferon, alpha-inducible protein, stratifin, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1, dual specificity phosphatase 9, guanine nucleotide binding protein (G protein) beta polypeptide 2, neural retina leucine zipper] whose levels were altered exclusively after gefitinib administration in gefitinib-resistant PC3 and LNCaP cells, but not in DU145 cells, suggesting that these 7 genes could be targets for overcoming gefitinib resistance. Collectively, our molecular profiling data will serve as a framework for understanding the molecular action of gefitinib for prostate cancer.

Yasuda, T., T. Yoshida, et al. (2008). "Anti-gout agent allopurinol exerts cytotoxicity to human hormone-refractory prostate cancer cells in combination with tumor necrosis factor-related apoptosis-inducing ligand." Mol Cancer Res **6**(12): 1852-60.

Allopurinol has been used for the treatment of gout and conditions associated with hyperuricemia for several decades. We explored the potential of allopurinol on cancer treatment. Allopurinol did not expose cytotoxicity as a single treatment in human hormone refractory prostate cancer cell lines, PC-3 and DU145. However, allopurinol drastically induced apoptosis of PC-3 and DU145 in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which is a promising candidate for anticancer agent but its efficacy is limited by the existence of resistant cancer cells. We examined the underlying mechanism by which allopurinol overcomes the resistance of prostate cancer cells to TRAIL. Allopurinol up-regulated the expression of a proapoptotic TRAIL receptor, death receptor 5 (DR5). Allopurinol increased DR5 protein, mRNA, and promoter activity. Using DR5 small interfering RNA (siRNA), we showed that allopurinol-mediated DR5 up-regulation contributed to the enhancement of TRAIL effect by allopurinol. Furthermore, we examined the mechanism of allopurinol-mediated DR5 up-regulation. DR5 promoter activity induced by allopurinol was diminished by a mutation of a CAAT/enhancer binding protein homologous protein (CHOP)-binding site. In addition, allopurinol also increased CHOP expression, suggesting that allopurinol induced DR5 expression via CHOP. Allopurinol possesses the activity of a xanthine oxidase (XO) inhibitor. We used XO siRNA instead of allopurinol. XO siRNA also up-regulated DR5 and CHOP expression and sensitized the prostate cancer cells to TRAIL-induced apoptosis. Here, we show the novel potential of allopurinol in cancer treatment and indicate that the combination of allopurinol with TRAIL is effective strategy to expand the TRAIL-mediated cancer therapy.

Yin, D., F. Vreeland, et al. (2007). "Clinical pharmacodynamic effects of the growth hormone receptor antagonist pegvisomant: implications for cancer therapy." Clin Cancer Res **13**(3): 1000-9.

PURPOSE: The present study evaluated and compared the efficacy of pegvisomant and octreotide in blocking the growth hormone (GH) axis in humans based on pharmacodynamic biomarkers associated with the GH axis. The study also evaluated the safety of pegvisomant given at high s.c. doses for 14 days. EXPERIMENTAL DESIGN: Eighty healthy subjects were enrolled in five cohorts: cohorts 1 to 3, s.c. pegvisomant at 40, 60, or 80 mg once dailyx14 days (n=18 per cohort); cohort 4, s.c. octreotide at 200 microg thrice dailyx14 days (n=18); and cohort 5, untreated control (n=8). Serial blood samples were collected to measure plasma concentrations of total insulin-like growth factor type I (IGF-I), free IGF-I, IGF-II, IGF-binding protein 3 (IGFBP-3), and GH in all subjects and serum pegvisomant concentrations in subjects of cohorts 1 to 3. All subjects receiving treatment were monitored for adverse events (AE). RESULTS: After s.c. dosing of pegvisomant once daily for 14 days, the mean maximum suppression values of total IGF-I were 57%, 60%, and 62%, at 40, 60, and 80 mg dose levels, respectively. The maximum suppression was achieved approximately 7 days after the last dose and was sustained for approximately 21 days. Pegvisomant also led to a sustained reduction in free IGF-I, IGFBP-3, and IGF-II concentrations by up to 33%, 46%, and 35%, respectively, and an increase in GH levels. In comparison, octreotide resulted in a considerably weaker inhibition of total IGF-I and IGFBP-3 for a much shorter duration, and no inhibition of IGF-II. AEs in pegvisomant-treated subjects were generally either grade 1 or 2. The most frequent treatment-related AEs included injection site reactions, headache, and fatigue. CONCLUSIONS: Pegvisomant at well-tolerated s.c. doses was considerably more efficacious than octreotide in suppressing the GH axis, resulting in substantial and sustained inhibition of circulating IGF-I, IGF-II, and IGFBP-3 concentrations. These results provide evidence in favor of further testing the hypothesis that pegvisomant, through blocking the GH receptor-mediated signal transduction pathways, could be effective in treating tumors that may be GH, IGF-I, and/or IGF-II dependent, such as breast and colorectal cancer.

Zatelli, M. C., M. Minoia, et al. (2009). "Growth hormone excess promotes breast cancer chemoresistance." J Clin Endocrinol Metab **94**(10): 3931-8.

CONTEXT: GH and IGF-I are known to promote breast carcinogenesis. Even if breast cancer (BC) incidence is not increased in female acromegalic patients, mortality is greater as compared with general population. OBJECTIVE: The objective of the study was to evaluate whether GH/IGF-I excess might influence BC response to chemotherapy. DESIGN: We evaluated GH and IGF-I effects on cell proliferation of a BC cell line, MCF7 cells, in the presence of doxorubicin (Doxo), frequently used in BC chemotherapy, and the possible mechanisms involved. RESULTS: GH and IGF-I induce MCF7 cell growth in serum-free conditions and protect the cells from the cytotoxic effects of Doxo. GH effects are direct and not mediated by IGF-I because they are apparent also in the presence of an IGF-I receptor blocking antibody and disappear in the presence of the GH antagonist pegvisomant. The expression of the MDR1 gene, involved in resistance to chemotherapeutic drugs, was not induced by GH. In addition, c-fos transduction was reduced by Doxo, which prevented GH stimulatory effects. Pegvisomant inhibited basal and GH-induced c-fos promoter transcriptional activity. Autocrine GH action is ruled out by the lack of endogenous GH expression in this MCF7 cell strain. CONCLUSIONS: These data indicate that GH can directly induce resistance to chemotherapeutic drugs with a mechanism that might involve GH-induced early gene transcription and support the hypothesis that GH excess can hamper BC treatment, possibly resulting in an increased mortality.

Zhan, P., E. C. Lee, et al. (2002). "Induction of invasive phenotype by Casodex in hormone-sensitive prostate cancer cells." J Steroid Biochem Mol Biol **83**(1-5): 101-11.

The cellular mechanisms of anti-androgen-induced tumor regression have not been investigated in great detail. We have compared the induction of cell death in the androgen-dependent, non-invasive LNCaP prostate cancer cell line by Casodex and TNF-alpha. Both agents induce a dose and time-dependent decrease in cell viability in vitro. However, Casodex does not induce classical DNA fragmentation to oligonucleosomes typically induced by TNF-alpha, but rather induces cleavage to form intermediate 60 kb DNA fragments. RT-PCR based analysis demonstrates that in LNCaP cells Casodex coordinately alters the expression of steady-state level of mRNAs of several matrix metalloproteases and their cognate inhibitors (most notably MMP2 and TIMP1). Zymography and reverse zymography confirm that the ratio of metalloprotease(s) to inhibitor(s) is altered in favor of activation of the proteases. In a small percentage of the treated LNCaP cells, the activation of the extracellular matrix (ECM)-proteases by Casodex also induces an invasive phenotype. The acquisition of an invasive phenotype is not seen when LNCaP cells are treated with TNF-alpha, and is not seen when the LNCaP cells are treated with both compounds simultaneously, suggesting that the phenomenon may be specific to particular classes of compounds. These observations have significant implications in the treatment of prostate cancer, since the appearance of a more aggressive phenotype following treatment is clearly undesirable.

Zhang, Y., B. I. Graubard, et al. (2007). "Maternal hormone levels and perinatal characteristics: implications for testicular cancer." Ann Epidemiol **17**(2): 85-92.

PURPOSE: It was hypothesized that the risk for testicular germ cell tumors (TGCTs) is associated with maternal hormone levels. To examine the hypothesis, some studies used perinatal factors as surrogates for hormone levels. To determine the validity of this assumption, hormone-perinatal factor relationships were examined in the Collaborative Perinatal Project. METHODS: Maternal estradiol, estriol, and testosterone levels in first- and third-trimester serum samples were correlated with perinatal factors in 300 mothers representative of populations at high (white Americans) or low (black Americans) risk for TGCT. RESULTS: For white participants, testosterone levels were associated negatively with maternal height ($p < 0.01$) and age ($p = 0.02$) and positively with maternal weight ($p = 0.02$) and body mass index (BMI; $p < 0.01$), whereas estradiol levels were associated negatively with height ($p = 0.03$) and positively with son's birth weight ($p = 0.04$). For black participants, estriol levels were associated negatively with maternal weight ($p = 0.01$), BMI ($p = 0.02$), and gestational age $p < 0.01$) and positively with son's birth weight ($p < 0.01$), length ($p = 0.04$), and head circumference ($p = 0.03$). CONCLUSIONS: These findings indicate that use of perinatal characteristics as surrogates for hormone levels should be limited to a specific ethnic group. For white men, previously reported associations of TGCT with maternal weight and age may be caused by lower maternal testosterone levels.

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