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# ABSTRACTS OF THE SEVENTH INTERNATIONAL CONFERENCE OF ANTICANCER RESEARCH

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found that the effects of InsP6 on UVB-induced signal transduction strongly blocked UVB-induced activator protein-1 (AP-1) and nuclear factor KB (NF-KB) transcriptional activities in a dose-dependent manner. InsP6 also suppressed UVB-induced AP-1 NF-KB DNA binding activities and inhibited UVB-induced phosphorylation of extracellular signal-regulated protein kinases (Erks) and c-Jun NH2terminal kinases (JNKs). Phosphorylation of p38 kinases was not affected. InsP6 blocked UVB-induced phosphorylation of IKB- $\alpha$ , which is known to result in the inhibition of NF-KB transcriptional activity. InsP6 also blocked TPA-or EGFinduced phosphatidylinositol-3' (PI-3) kinase activity. Because AP-1 and NF-KB are important nuclear transcription factors that are related to tumor promotion, our work suggests that InsP6 prevents skin carcinogenesis by inhibiting AP-1 and NFκB transcription activities.

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#### THE ROLE OF CYSTATIN C AND THE ANGIOGENIC CYTOKINES VEGF AND bFGF IN PATIENTS WITH ESOPHAGEAL CARCINOMA

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Angiogenesis is the formation of new blood vessels out of the existing vascular bed. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are potent circulating angiogenic factors while cystatin C is one of the most important extracellular inhibitors of several cysteine proteinases. Malignant transformations of human cells are associated with increased expression of growth factors. Since proteases degrade interstitial connective tissue and basement membranes during tumor growth and metastasis, an association between cystatin C and the angiogenic factors seems plausible. The primary aim of the present study was to investigate if such a correlation exists between these serum markers. The secondary aim was to determine the prognostic value of these circulating cvtokines and cystatin C, collected prior to therapy, in patients with esophageal carcinoma.

A total of 42 patients with esophageal carcinoma donated serum samples prior to therapy. VEGF and bFGF were correlated to platelet and leukocyte counts and VEGF was correlated to tumour volume (p=0.04), whereas bFGF was not (p=0.08). VEGF was significantly correlated with cystatin C (p=0.027). Survival analysis showed that VEGF, regarded as a continous variable, was associated with a significantly poorer survival in the univariate analysis (p=0.023), this was, however, not found for bFGF (p=0.46). Neither of the angiogenic factors was associated with survival in the multivariate analysis. Cystatin C was in the univariate analysis correlated with survival (p=0.01); this was however not found in the multivariate analysis (p=0.28).

In conclusion, VEGF was correlated with cystatin C but the use of the angiogenic factors as prognostic factors, according to the results from the present study, seems limited.

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#### IP6 + INOSITOL AS ADJUVANT TO CHEMOTHERAPY OF COLON CANCER: OUR CLINICAL EXPERIENCE

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Purpose: To evaluate: a) the possible positive effects of IP6 + Inositol in the therapy of advanced colorectal carcinoma and b) diminishing side-effects of chemotherapy applied according to the Mayo protocol. Materials and Methods: From 2000 to 2004, 22 patients with colorectal carcinoma [Dukes as B2, C and D] were surgically operated and submitted to adjuvant polychemotherapy - Mayo protocol, and radiotherapy. During chemotherapy, they were given 3 capsules [1530 mg] of IP6 + Inositol 4 times daily, 30 minutes before meals. Following chemotherapy they continued with IP6 + Inositol, 3 capsules twice daily for one year. Preoperatively, the patients underwent the following routine tests: CBC with differentials, urine, glucose, urea, creatinine, AST, ALT, y-GT, electrolytes, proteins, albumin, lung X-ray, abdominal CT, abdominal ultrasound, CEA, CA19-9. Surgical procedures were: right hemicolectomy in 3 patients, subtotal colectomy in 3 patients, low anterior resection according to Dixon in 12 patients, and amputation of rectum in 4 patients. During chemo- and radiotherapy, the patients were monitored with CBC with differentials, creatinine, electrolytes, AST, ALT, y-GT, glucose, CEA, CA19-9. Results: Of the 22 patients with colorectal carcinoma treated with IP6 + Inositol, 16 were males, 41 to 71 years old (mean: 64) and 6 females 54 to 70 years old (mean: 66). Four patients were classified as Duke D, 10 as Dukes C, and 8 as Dukes B2. Three patients from Duke D died during the observation period. All patients treated with adjuvant polychemotherapy according to the Mayo protocol and IP6 + Inositol had significantly reduced chemotherapyrelated side-effects (drop in leukocyte and platelet counts, nausea, vomiting, fever, diarrhea and alopecia). All of the laboratory parameters during therapy were within normal range. Thus, in contrast to standard chemotherapy-alone regimen wherein we are often forced to stop the chemo owing to severe side-effects, it was never necessary to

interrupt the chemotherapy for patients on adjuvant Inositol + IP6. During this period, one patient was found to have liver metastases, and 2 patients had lung metastases. Conclusion: Based on clinical observations in this nonrandomized and non-controlled clinical trial, it can be concluded that patients operated for colorectal carcinoma chemoradiotherapy, needing adjuvant manifested diminished side-effects of chemotherapy with improved quality of life in the presence of IP6 + Inositol. However, further prospective and randomized clinical trials, to determine the effect of IP6 + Inositol as supportive therapy in the treatment of colorectal carcinoma and in tumor regression, are needed.

#### 126 = 1P6 + INOSITOL IN TREATMENT OF DUCTAL INVASIVE BREAST CARCINOMA: OUR CLINICAL EXPERIENCE

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Purpose: To evaluate the efficacy of IP6 + Inositol in the treatment of ductal invasive breast carcinoma. Materials and Methods: Between 2001 and 2003, four patients of 36, 54, 55 and 60 years of age, surgically operated for ductal invasive carcinoma, were postoperatively submitted to adjuvant chemotherapy, radiotherapy and, depending on the hormonal status, to tamoxifen, and most recently to anastrozole (Arimidex). During chemotherapy they were given 4 capsules of IP6 + Inositol (2040 mg) thrice daily, 30 minutes before meals. Following chemotherapy they continued with 1 capsule of IP6 + Inositol 3 times daily. Preoperatively, patients underwent the following routine testing: CBC with differentials, urine, glucose, urea, creatinine, AST, ALT, y-GT, electrolytes, proteins, albumin, lung X-ray, abdominal ultrasound, sceletal scintigraphy, and CA 15-3. All patients underwent either radical or modified mastectomy with axillar lymphnode dissection. During chemo- and radiotherapy, the patients were monitored with CBC with differentials, creatinine, electrolytes, AST, ALT, y-GT, glucose, and CA15-3. Mammography and ultrasound of the breast were performed 6 and 12 months postoperatively and, after that period, once yearly. Results: Two of the 4 patients with ductal invasive carcinoma were found to be in stage II, and the other 2 in stage IIIa. All were treated with radiotherapy. One patient was given tamoxifen, one anastrozole. Chemotherapy given to 3 patients was the combination of 5 fluorouracil (5-FU), epirubicin, and cyclophosphamide, while one was receiving a combination of 5-FU, cyclophosphamide, and doxorubicine. IP6 + Inositol was given during chemotherapy (4 capsules of IP6 + Inositol thrice daily continued with 1 capsule thrice daily afterwards). During chemotherapy, all of the laboratory test results were within normal range; thus, it was never necessary to interrupt the treatment owing to severe toxicity of chemotherapy alone. Although alopecia, moderate to total, was present, other chemotherapy-related side-effects, such as nausea, vomiting, diarrhea, fever, and neurological symptoms, were so minimal that quality of life was not impaired. All patients are alive, with no recurrence detected to date. *Conclusion:* From this clinical experience, we can conclude that patients on IP6 + Inositol during chemotherapy have diminished chemotherapy-related sideeffects, that the oncological therapy was never interrupted, and that their quality of life was not impaired. However, a further controlled clinical study is needed to evaluate the effect of IP6 + Inositol in the treatment of invasive ductal carcinoma of breast.

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#### INTESTINAL ALKALINE SPHINGOMYELINASE – A POTENTIAL GENE PRODUCT INHIBITING COLON CANCER

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Sphingomyelin (SM) is a type of sphingolipid and is present in the eukaryotic cell membranes and also in dietary products such as egg, milk and meat. SM is hydrolysed by sphingomyelinase (SMase) to ceramide, which has been found to inhibit cell proliferation and induce cell differentiation and apoptosis. Previous studies have shown that administration of SM in the diet inhibits the formation of colon cancer in animals.

In the intestinal tract there is a type of SMase called alkaline SMase, which is located in the intestinal brush border as an ecto-enzyme. This enzyme is responsible for hydrolysis of both dietary SM and SM in the mucosa. We purified and characterised the enzyme and cloned the cDNA. The gene of the enzyme is located in chromosome 17q25 with 6 exons, of which exon 1 to 5 are translated.

Intestinal alkaline SMase may have inhibitory effects on colonic tumorigenesis based on the following findings from our laboratory:

1. The activity of alkaline SMase is decreased by 50% in human colonic adenomas, by 75% in human cancer tissues and by about 90% in the mucosa of familial adenomatous polyposis. We also found a reduction of alkaline SMase activity in the inflammatory tissues of long-standing ulcerative colitis, which has high risk of colon cancer.

2. The expression of alkaline SMase in colon cancer is abnormal. In human colon cancer HT29 cells the transcription of exon 4 is skipped, resulting in a truncated enzyme that has no SMase activity. Skip of exon 4 is also The dog, driven by its sexual appetite and consequently contracting transmissible venereal disease (TVT), is an example of how an individual can be tricked into hosting cancer. As for most tumors, in TVT the - in evolution - genetically transformed tumor cells, steer the stroma (ECM, fibroblasts, immune cells) into a program that permits or supports tumor growth and sometimes, metastasis. This should not be seen as predetermined misleading behavior, but rather as the accidental activation by tumor cells of programs in stromal cells, that are devised for other purposes: formation and renewal of tissues (construction, repair, involution, defense). Also tumor growth/spread may be promoted by the inappropriate use of physical components of the ECM designed for normal states of tissue development.

Many classes of molecules take part in the crosstalk between tumor cells and stroma: e.g., growth factors (GF), proteinases and cytokines. These factors are either secreted by the tumor cells, or by fibroblasts or immune cells in a response to tumor cell-derived stimuli. GF activity may be also released by any such cell from ECM-stores. A wide array of examples will be given during the session "Adverse crosstalk: interaction between tumor and stroma". Angiogenic (and other) factors released upon tissue trauma and helpful in tissue repair, will inadvertently accommodate outgrowth of tumors. Procoagulant factors functioning to guard the integrity of vessels, if produced by tumor cells or tumor endothelium, may catalyze the formation of microthrombi helping tumor cell arrest in capillaries at distant sites. The (change of) composition of the matrix, and the balance of presence and level of activity of proteases and their inhibitors - derived from tumor cells or stromal cells or both - all determine the efficacy of tumor cells to infiltrate. The migration of tumor cells further depends on the production of motility factors (such as hepatocyte growth factor, also called scatter factor) by tumor cells or the environment.

In dogs and less so in cats, mast cell tumors are frequent. These mast cells often attract many eosinophils and trigger inflammation, which may favor tumor growth and spreading. Relatively few dog/cat cancers invade bone (apart from myeloma), but squamous cell cancers often do. Mammary cancers rarely invade bone in these animals, in contrast to a high incidence in the human. Similarities and differences between tumors in human and those in companion animals may help to elucidate tumorstroma interactions promoting tumor growth and metastasis. Increased crosstalk between investigators from human and veterinary science may lead to increased knowledge about tumor behavior and the design of new methods to interfere.

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#### HYPERTENSION AND RISK OF BRAIN METASTASIS FROM SMALL CELL LUNG CANCER: A RETROSPECTIVE FOLLOW-UP STUDY

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Although metastatic brain cancer is one of the most common forms of cancer, little is known about the factors associated with its development. We examined the hypothesis that hypertension may increase the risk for brain metastasis (BM) in patients with primary small cell lung cancer (SCLC). Materials and Methods: A retrospective review of medical charts of patients diagnosed with SCLC, between June, 1986 and June, 2003 at MeritCare in Fargo, ND, was done to determine which of these patients subsequently developed brain metastases. The effects of hypertension, age, gender, body mass index, and the site of SCLC on the risk of developing BM were examined using both univariate and multivariable Cox proportional-hazards regression models. Two-way interactions between hypertension and other covariates were also included in the analyses. Results: Two-hundred and thirty-two patients were identified with SCLC and 185 patients were eligible for this study. Eighty-five (45.9%) patients developed BM. Over 54% of SCLC occurred in the right lobe and more than 70% of the patients with BM had them in multiple locations. The risk of BM is significantly higher in younger patients (pvalue < 0.03). Univariate analysis showed a hazard ratio (HR) for hypertension of 1.01 (95%Confidence Interval (CI) 0.6-1.6) for BM from SCLC. The multivariable Cox model showed an adjusted HR for hypertension of 1.06 (95%CI 0.7-1.6) for BM from SCLC. Conclusion: As has been consistently observed for other lung cancers, SCLC is more common in the right lung. The higher incidence of BM in younger patients suggests the possibility that more aggressive therapy is needed in these patients. Hypertension does not appear to increase the risk of BM from SCLC.

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#### IP6 PLUS INOSITOL TREATMENT AFTER SURGERY AND POST-OPERATIVE RADIOTHERAPY, REPORT OF A CASE: BREAST CANCER

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Inositol hexaphosphate (IP6) affects intra-cellular signal transduction pathways, resulting in mitotic cell cycle arrest. Thus, it reduces cell proliferation of various cancers. It increases differentiation of malignant cells and induces phenotypic normalization with decreased production of tumor markers. IP6 also enhances host immunity, induces apoptosis of malignant cells and controls metastases of cancer. Accumulated evidence supports that IP6 + Inositol can be used as a potent therapeutic agent for advanced cancer. Herein, we report our clinical experience with a breast cancer patient who developed metastasis and has been successfully treated by IP6 + Inositol. The patient continues to enjoy a good quality of life despite metastatic cancer and old age. Case Report: A 79-year-old female underwent typical right mastectomy plus lymph nodes dissection (Halsted) and post-operative radiation therapy for her breast cancer (T2N2M0, stage IIIA) at the age of 70 (Oct. 1995). Periodic follow-up thereafter revealed metastases (pleural effusion) in the left lung 6 years post-operatively (Jan. 2002), and more recently in the liver. Tumor markers (NCC-ST-439, CA15-3) increased significantly. She began to take the IP6 + Inositol product twice daily in April 2002. Four months later, the tumor markers had dropped to a normal level. An additional 2 months later, the pleural effusion had decreased in volume. However, it began to increase in volume again in May 2003. The tumor markers also continuously increased thereafter, reaching 35- to 40-fold higher than normal level in July 2004. While the signs of the metastatic disease show progression, her general condition is not impaired and quality of life status remains favorable. Discussion and Conclusion: The reason for the patient's favorable condition, in spite of a large burden of the relapsed tumor mass, may be partly attributed to the fact that she has taken IP6 + Inositol every day for more than two years. In combination with an oral intake of chemotherapeutic agents (anti-estrogen agent and tegafururacil mixture), IP6 + Inositol may contribute to improved quality of life and prolonged survival of patients with metastatic recurrence of breast cancer.

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#### LONG-TERM SURVIVAL OF A PATIENT WITH ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH INOSITOL HEXAPHOSPHATE (IP6) PLUS INOSITOL TREATMENT COMBINED WITH CHEMO-RADIOTHERAPY. REPORT OF CASE

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The antineoplastic potential of inositol hexaphosphate (IP6) combined with inositol has been widely recognized. Lung cancer is the first leading cause of deaths in Japan. The prognosis of the advanced stage of this disease is very poor, the 5-year survival rate being less than 5% for stages IIIB or IV. In the present work, clinical experience with a patient treated with Inositol + IP6 following termination of incomplete chemo-radiotherapy and still surviving long after the diagnosis, in spite of very dismal prognosis, is reported. Case Report: The case was 53-year-old female with smoking history for 30 years. She had had diagnosis of left lung cancer (adenocarcinoma of S6 origin, c-T2N3M0, stage IIIB) at age 49. Evidence-based medicine indicated chemo-radiotherapy (CRT) instead of surgery for this patient. However, CRT was terminated in mid-course because of its adverse effects (leukopenia, alopecia, nausea, vomiting, diarrhea). The overall effect of CRT, at termination, was Partial Response (PR); the original tumor had regressed 60%, while metastatic lymph nodes in the mediastinum showed 95% regression. Eight months later, following the CRT termination, she began to take IP6 + Inositol twice daily. Four years and 4 months have passed since termination of CRT. She now enjoys a completely healthy life without any signs of relapse. Periodic check-up of her chest and abdomen by computed tomography (CT) and, recently, by multi-detector CT, revealed no evidence of tumor regression; only the fibrotic change and cicatrization of part of the mediastinum and the middle part of the left lung where the original tumor existed are the findings confirmed by radiologists. Serum CEA level drastically decreased to normal when the CRT was terminated and continues to be normal. This might be partly attributed to the fact that she has taken IP6 + Inositol every day for more than three years, without any other treatments. She has not shown any adverse effect during this observation period. Discussion and Conclusion: Neither IP6 nor Inositol have any adverse effect on humans, which is most important for a candidate therapeutic agent, and more importantly for long-term use as a preventive agent against cancer. IP6 + Inositol has a potential value in cancer therapy and initiation of large scale clinical studies should be justified.

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## ROLE OF HGF/C-MET RECEPTOR TYROSINE KINASE IN LUNG CANCER

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Receptor tyrosine kinases (RTKs) have been shown to be important in a variety of malignancies, such as HER2/NEU in