in *in situ* carcinoma and normal epithelium. Reduced expression of TIMP-3 protein within cancer cells was correlated with carcinomas of high nuclear and histological grade \( (p = 0.032 \text{ and } p = 0.015, \text{ respectively}) \), and low ER expression \( (p = 0.053) \). Moreover, TIMP-3 immuno-positivity was inversely correlated with the expression of Bcl-2 proteins \( (p = 0.002) \), whereas it was positively associated with p53 expression \( (p = 0.020) \). Reduced expression of TIMP-3 protein within cancer cells was found to have an unfavorable impact on disease-free survival \( (p = 0.052) \) in the entirety of the patient population, as well as in subgroups of lymph-node-positive patients \( (p = 0.007) \). The patients with TIMP-3 positive treated with tamoxifen differed greatly in prognosis compare to TIMP-3 negative \( (p = 0.0003) \).

**Conclusion:** This is the first immunohistochemical study to show that TIMP-3 protein within cancer cells is associated with tumor phenotype. Reduced expression of TIMP-3 protein within cancer cells was found to correlate with an aggressive tumor phenotype, negatively affecting the disease-free survival in subgroups of lymph node-positive patients. More ever, TIMP-3 is associated with successful tamoxifen treatment of patients with breast cancer.

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**Early Stage Breast Cancer Invasion Signalling: A Network of Novel Clinical Biomarkers and Therapeutic Targets**

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Breast cancer remains a prevalent disease worldwide. Despite a significant progress in early detection, many cancer patients at primary diagnosis experience recurrence of the cancer. Of these scenarios, development of metastases is the most life threatening and ultimately incurable with the best therapies available to date. A crucial early event by which cancer cells switch from localized to invasive states is initiated by the acquisition of autonomous motile and invasive properties. This process is tightly regulated by multiple focal adhesion (FA) and cytoskeleton molecules, including integrins, Src kinases, Fak, Pyk2, paxillin, Cas, talin, vinculin, and myosins. Most of these proteins are regulated through posttranslational modifications and dynamic intermolecular collisions with partners. Together, they initiate and drive cancer cell invasion by regulating the formation of cancer cell protrusions and migration in response to chemotactic stimuli that cancer cells receive from the surrounding microenvironment.

Using genomic and proteomic approaches, we identified key molecules of the focal adhesion (FA) protein network that are differentially regulated between non-invasive and invasive forms of breast cancer. The expression level of a subset of FA proteins, including FAK, Pyk2, and fascin were upregulated in invasive breast carcinomas and lymph node metastases compared to benign and DCIS from over 160 cases treated at the Jewish General Hospital. A systematic inhibition of FA signaling network using genetic approaches led to the identification of the critical rate limiting molecules whose inhibition can prevent early cancer progression to metastases in 3-dimensional invasion assays and preclinical animal cancer models. In collaboration with the Chemical Biology group at Harvard University, Ontario Institute for Cancer Research, and the Institute of Marine Biology in Qingdao (China) we identified small molecule inhibitors that effectively inhibit selective FA protein signalling and prevented cell invasion in preclinical models. This presentation will interface our basic and preclinical finding with clinical implications of FA as biomarkers and as novel therapeutic targets for invasive cancers.

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**NP regimen as adjuvant chemotherapy for breast cancer: final result of a phase II trial**

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**Background:** Postoperative chemotherapy for patients with breast cancer has been conducted for more than 30 years in China. However, few clinical trials showed superiority among commonly used regimens regarding to their survival in mainland China. To develop a potentially effective adjuvant chemotherapy regimen, we conducted a pilot study on vinorelbine, and cisplatin (NP). The primary objective was to determine the feasibility of the regimen; the secondary objective was to estimate the disease-free and overall survival.

**Methods:** Chinese breast cancer patients, who were pathologically confirmed with adenocarcinoma in Jiangsu Cancer Hospital & Research Institute received postoperative NP chemotherapy. Vinorelbine was administered 25mg/m² on day1 and day8, cisplatin 25mg/m² on day 1 to day3, or cisplatin 20mg on day1 to day5, repeated every 3 weeks.

**Results:** Between Sep 1994 and April 2005, 89 patients were enrolled. Median age was 49 years (range, 25–69 years). According to TNM stage system, stage I, II, III and IV patients accounted for 7%, 61%, 29% and 3% respectively. Median number of cycle of chemotherapy was 4 (range, 1–8), and 56 patients received 4 to 6 cycles of NP. All patients can be evaluated with regard to toxicities. Twenty patients (22%) developed grade 4/grade 3 leucocytopenia during treatment; they recovered after G-CSF injection. Other grade 3 toxicities included 1 thrombocytopenia (1%), 5 nausea/vomiting (5.6%) and 3 diarrhea (3.4%). There were no treatment related deaths. After a median follow-up of 47 months, 6 dead and 22 relapse were documented. Median disease-free survival was 44 months.

**Conclusions:** NP is effective and feasible at the doses tested. However, randomized clinical trial is needed to compare NP with other conventional regimens.

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**Drug Mediated S-glutathionylation of PDI leads to alterations in secondary structure, inhibition of isomerase activity, and triggers ER-stress induced apoptosis**

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Proliferation of cancer cells mandates a high protein turnover. The endoplasmic reticulum (ER) is an organelle that is intimately involved in protein processing. An accumulation of unfolded or mis-folded proteins in the ER leads to a cascade of transcriptional