

PMA-induced, K-ras- and Src-induced gene expression. New data will be presented in this lecture showing that the newly characterized tumor suppressor Pdc4 suppresses u-PAR gene expression, this again in part being mediated by Sp3 bound to the -152/-135 motif.

Furthermore, the lecture will focus on the differential binding of transcription factors to both u-PAR promoter elements in vivo, having been investigated in a large series of resected tumor and normal tissue of colorectal and gastric cancer patients. We will demonstrate that, depending on the transcription factor and cis-element, patient subgroups of different size can be selected in which transactivation via these promoter elements might be tumor-tissue-specific, suggesting subgroups for tumor-selective targeting. Also, the lecture will outline that different u-PAR-promoter motifs may be of different tumor-specificity in vivo. We will also suggest patient subgroups in which a synergistic regulation of u-PAR gene expression in resected tissues via both promoter elements can be postulated. Finally, first data on a clinical-prognostic relevance of differential transcription factor binding to specific u-PAR-promoter motifs will be shown, suggesting the binding of, for example, Sp1, and transcription factor combinations out of Sp1/AP-2 and AP-1-binding as new and independent predictors of disease-specific survival. A first molecularly extended staging model will be presented from these data. Potential conclusions for a more target-oriented patient selection and therapy out of transcriptional and oncogenic regulators of the uPA-R gene will be discussed.

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#### **S11. uPA AND PAI-1: CLINICALLY AND TECHNICALLY VALIDATED PROGNOSTIC MARKERS IN BREAST CANCER**

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For optimum management of patients with cancer, accurate prognostic factors are required. The primary determinant of outcome in patients with malignancy is cancer progression, especially the formation of distant metastases. Based on data from model systems, urokinase plasminogen activator (uPA) is one of the critical mediators of cancer progression. uPA appears to mediate progression via multiple mechanisms including remodelling of the extracellular matrix, enhancing cell proliferation and migration and modulating cell adhesion. PAI-1, although originally identified as an inhibitor of uPA, is also causally involved in cancer progression. Consistent with their roles in cancer progression, multiple independent studies have shown that elevated levels of uPA and PAI-1 predict poor prognosis in patients in breast cancer. The prognostic impact of uPA and PAI-1 is potent (e.g., RR > 2.0), independent of standard prognostic factors and found in both lymph node-negative and lymph node-positive disease. Importantly, the prognostic impact of uPA/PAI-1 has been validated in both a randomized prospective trial and a pooled analysis, i.e., in 2 level I evidence studies. In addition to clinical validation, specific ELISA for uPA and PAI-1 have undergone technical validation including validation in an external quality assurance program. uPA and PAI-1 are thus now ready for clinical application, especially in the identification of newly

diagnosed breast cancer patients that may be able to avoid having to receive adjuvant chemotherapy.

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#### **S12. EXPRESSION OF MARKERS OF INVASION AND PROGRESSION - COMPARING MOLECULAR DETERMINANTS WITH PHENOTYPES**

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Cancer cells usually have a distinct morphological and genetic profile that allows to determine between reactive, premalignant and malignant lesions. In some tumor entities, however, morphological and expression profiles do not necessarily reflect the true nature of the putative lesion. Molecular biological advances could further clarify the biological potential in some tumor entities, in others however, morphological and topographical criteria are still crucial, since no evident typical molecular profiles could be determined so far.

Prostate cancer is a prominent example of cancer where exocrine and neuroendocrine (NE) tumor cells can occur within the same tumor. The role of these NE cells is still under debate, even the question of its neoplastic nature and its biological significance. Since in these NE cells no proliferation could be demonstrated so far, NE tumor cells in prostate cancer are regarded as post-mitotic and their significance has been regarded as 'low'. The interesting question is, therefore, whether a post-mitotic cancer cell still deserves the attribute "cancer cell" and what are its biological functions in the cancerous orchestration. Although molecular and clinical data seem to give evidence that NE tumor cells are the result of a transdifferentiation process and possess a prognostic significance, their final role in vivo is not yet completely understood.

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#### **S13. MOLECULAR MECHANISMS OF MATRIX METALLOPROTEINASE (MT-MMP) INDUCTION OF CANCER CELL MIGRATION AND METASTASIS**

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Matrix metalloproteinases (MMPs) are important in cancer dissemination by virtue of degradation of extracellular matrix, as well as diverse effects on cell growth, apoptosis, migration, and angiogenesis. Negative results from clinical drug trials of MMP inhibitors in advanced cancers has refocused attention on the role of MMPs in early cancer development. Experimental and clinical evidence suggests that membrane type 1-matrix metalloproteinase (MT1-MMP) may serve as a master regulator of cancer progression. The mechanism underlying this process