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Meeting abstract

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Growth factor signaling – cell biology turned into medicine

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A series of novel drugs targeting growth factor signaling – including antibodies targeting growth factors or their receptors, low-molecular weight tyrosine kinase (TK) inhibitors and mTOR inhibitors – are approved as cancer drugs. These drugs differ with regard to target cells and target molecules. Best effects of drugs targeting TKs on malignant cells are, in general, observed in tumors where target TK is activated by amplification, translocation or point-mutations. Mutational activation of down stream signaling proteins, such as PI3 kinase or RAS, is associated with reduced sensitivity to TK-targeting drugs. Determinants of resistance and sensitivity to anti-angiogenic drugs remain mostly unknown. Results from breast cancer suggest that many of these drugs will display highest efficacy when used in adjuvant settings.

Our studies on the role of PDGF receptor signaling in cancer have revealed important roles of autocrine PDGF receptor signaling in dermatofibrosarcoma protuberans and glioblostoma. However, in common solid tumors, PDGF receptor signaling is predominantly involved in the regulation of tumor stroma through effects on pericytes and cancer-associated fibroblasts (CAFs). Studies in animal models have demonstrated that inhibition of stromal PDGF-receptors improves tumor drug uptake, and thus suggest a novel rational for combination treatments with PDGF inhibitors and other cancer drugs. Recent analyses of large series of human breast cancer have also identified high stromal PDGF receptor expression as a marker for worse prognosis.

Ongoing studies in our group also aim at identification of novel stroma-derived cancer drug targets. By gene expression profiling of prostate CAFs we have identified CXCL14 as a novel CAF-derived multi-modal stimulator of tumor growth. Ongoing studies also explore how paracrine crosstalk between CAFs and malignant cells, will affect the proliferation, migration and drug response of malignant cells.