The development of malignant tumors is in part characterized by a tumor cell’s capability to overcome cell-cell adhesion and to invade surrounding tissue by a process referred to as epithelial-mesenchymal-transition (EMT). An EMT underlies the conversion of epithelial, differentiated cells to mesenchymal, migratory and invas ive cells. In the past years, we have learned that an EMT occurs in multiple stages and is regulated by sophisticated molecular networks regulating the expression of a large number of protein, IncRNA and mRNA-encoding genes. More recently, we have noted that an EMT also selects for cancer cells exhibiting hallmarks of cancer stem cells and increased drug resistance. Notably, we have identified a large number of transcription factors that act as master regulators not only in the initiation and execution of the morphogenic process of an EMT but also in providing survival signals to cancer cells and thus allowing cancer cells to seed and grow metastases in distant organs. We investigate the direct target genes of these transcription factors and their role in tumor metastasis. We also assess the role of miRNAs and lncRNAs and their target genes in the regulation of an EMT and of metastatic dissemination. With these experimental approaches we aim at identifying the master regulators of an EMT and cancer metastasis and we plan to scrutinize the potential of these transcription factors as therapeutic targets for preventing metastatic disease.

In a second line of research, we investigate the molecular pathways underlying the development of evasive resistance to targeted cancer therapy. We employ a number of cultured cancer cell lines and mouse models to study the pathological, physiological and molecular consequences of therapies targeting tumor angiogenesis and malignant tumor progression. In particular, we use cell biological, biochemical and bioinformatical analysis to delineate the molecular pathways allowing cancer cells to escape from targeted therapy. Recently, we have found that tumors shift their metabolism to glycolysis and acquire a status of metabolic symbiosis between individual cells of a tumor to overcome anti-angiogenic therapy. Finally, in collaboration with pharmaceutical companies we are investigating the efficacy and biological consequences of various anti-angiogenic and anti-metastatic cancer treatments.

**Selected Publications**


Selected Papers

**Fig. 1:** Tazemetostat upregulation and Yap/Taz subcellular Localization during EMT. Morphological differences between epithelial and mesenchymal counterparts of murine breast cancer cells (phase contrast, scale bar, 50 µm). Immunofluorescence staining of Taz and co-factors Yap and Taz shows their increased expression and nuclear translocation in mesenchymal cells where they activate the expression of genes involved in EMT and metastasis. E-cadherin staining shows epithelial cell junctions. DAPI was used to visualize nulei (scale bar, 25 µm). Diepenbruck, Waldmeier et al., 2014.

**Fig. 2:** IGFR-F2 production as a public goods games network. The microscopic picture shows a co-culture of cancer cells which do not produce IGFR-F2 (colorless cells) and cancer cells which express IGFR-F2 (green cells). Both cell types require IGFR-F2 for their survival and they compete against each other to reach a specific homestasis of producer cells and consumer cells. Guess who will win? (answer: Archetti et al., 2015).

**Fig. 3:** Targeting metabolic symbiosis overcomes resistance to anti-angiogenic therapy. Metabolic symbiosis as a mechanism underlying evasive resistance to anti-angiogenic therapy by the multi-kinase inhibitors sunitinib and sorafenib. Inhibition of glycolysis by 2PO or genetic ablation of the lactate exporter MCT4 in tumor cells disrupts metabolic symbiosis, overcomes therapy resistance, and suppresses tumor growth (Pisek et al., 2015).

**Group Members**

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**Connection to Clinical Practice**

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Evasive resistance to targeted therapy and tumor heterogeneity

The development of resistance to targeted cancer therapy (evasive resistance) has appeared a major obstacle in treating the disease. In two network projects connecting patient care (Markus Heim), biomedical research (Mike Hall, Biozentrum) and computational biology (Niko Beerenwinkel and Jörg Stelling, D-BiSE, ETHZ, Basel), we aim at the molecular dissection of the pathways underlying the development of drug resistance to current cancer therapy. We have generated drug-sensitive cell lines and their drug-resistant counterparts and novel transgenic and patient-derived xenografted (PDX) mouse models of hepatocellular carcinoma (HCC) which recapitulates the development of HCC in patients. These cellular and animal models are now being used for molecular, biochemical and genomic analysis of the processes underlying evasive resistance and to test first alternative therapies to overcome evasive resistance. These projects are supported by a European Research Council (ERC) Synergy Grant and by a SystemsX.ch MTD Grant.

In a second network project, in collaboration with the Department of Surgery of the University Hospital Basel (Walter Weber) and in collaboration with computational researchers of the Friedrich-Miescher-Institute in Basel (Mohammed Bentires-Alj and Michael Studer), the University of Zürich (Bernd Bodenmüller) and R&M Rüschlikon (María Rodriguez), we address basic questions regarding breast cancer cell heterogeneity in patients and in experimental models and aim at identifying the cancer-propagating, metastatic breast cancer cell population and learn about the genetic programs driving these cells. This project is funded by a SystemsX.ch MTD Grant.