Mechanisms of breast tumor heterogeneity, metastasis and resistance

Breast cancer is diagnosed in ~1.5 million women worldwide and ~500,000 lives are lost to the disease annually, the vast majority due to metastasis. Curing metastatic breast cancer represents an unmet medical need. Patients may do well after surgery and adjuvant treatment but drug-resistant, fatal metastases often develop. Critical to the phenomenon of resistance is tumor heterogeneity and this is the thread connecting the research in our lab. At the molecular, cellular, and whole-organism levels, we assess mechanisms that influence normal and neoplastic breast stem cells, metastasis, and resistance to therapy. We explore both cell autonomous (genetics, epigenetic, and proteomic) and non-cell autonomous mechanisms (immune cells, adipocytes, etc). We use systems medicine quantitative methods, unbiased pooled shRNA, CRISPR, transposon-based screens, and hypothesis-driven approaches. Computational biology is a very important part of our research. Moreover, we use multiphoton intravital imaging to assess the interactions between cancer cells and immune cells. These interdisciplinary projects seek to elucidate the integrated effects of signaling pathways and epigenetics on breast cancer fate and tumor heterogeneity, and to leverage this mechanistic understanding into therapy. With clinicians from the University Hospital of Basel, we are building a breast cancer personalized medicine program wish should ultimately improve treatment for patients (Fig 1). M. Bentires-Alj is the founder and president of the European Network for Breast Development and Cancer (www.enbdc.org) that fosters global interactions between labs in these areas, and co-founder with Profs. Walter Paul Weber, Gerhard Christofori and Christoph Rochlitz of the Basel Breast Consortium (www.BaselBC.org), which is committed to promoting local basic, clinical, and translational interdisciplinary research projects within Switzerland.

Molecular mechanisms controlling normal and neoplastic breast stem cells: PIK3CAH1047R induces multipotency and multi-lineage mammary tumors.

We have discovered a paradoxical effect of the CC chemokine ligand 2 (CCL2) in metastatic breast cancer. Secretion of CCL2 by mammary tumors recruits CCR2-expressing inflammatory monocytes to primary tumors and metastatic sites, and CCL2 neutralization in mice inhibits metastasis by retaining monocytes in the bone marrow. Surprisingly, interruption of CCL2 inhibition leads to an overshoot of metastases and accelerates death. This is the result of monocytic release from the bone marrow, enhancement of cancer cell mobilization from the primary tumor, as well as blood vessel formation and increased proliferation of metastatic cells in the lungs in an IL-6/VEGF-A-dependent manner. Our results call for caution when considering anti-CCL2 agents as monotherapy in metastatic disease and highlight the tumor microenvironment as a critical determinant of successful anti-metastatic therapy (Bonapace et al., Nature 2014).

Discontinuation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. We have discovered a paradoxical effect of the CC chemokine ligand 2 (CCL2) in metastatic breast cancer. Secretion of CCL2 by mammary tumors recruits CCR2-expressing inflammatory monocytes to primary tumors and metastatic sites, and CCL2 neutralization in mice inhibits metastasis by retaining monocytes in the bone marrow. Surprisingly, interruption of CCL2 inhibition leads to an overshoot of metastases and accelerates death. This is the result of monocytic release from the bone marrow, enhancement of cancer cell mobilization from the primary tumor, as well as blood vessel formation and increased proliferation of metastatic cells in the lungs in an IL-6/VEGF-A-dependent manner. Our results call for caution when considering anti-CCL2 agents as monotherapy in metastatic disease and highlight the tumor microenvironment as a critical determinant of successful anti-metastatic therapy (Bonapace et al., Nature 2014).