Summary

Cancer is an abnormal growth in a part of the body, caused by uncontrolled division of cells forming a tumor. In principle, tumors can be surgically removed so that they would not pose a health risk to the patients anymore. However, there are cases where the tumors are inoperable due to their location or the fitness of the patient. Such tumors, and non-solid tumors of the blood and lymphatic system, have to be fought against by drugs. Moreover, surgical operations still have the risk of having reminiscent cancer cells that can regrow as tumors. Therefore, even when surgery is possible, patients still receive therapy as an extra measure. Most cancer patients undergo systemic chemotherapy, which causes several side effects. As an alternative, several less invasive targeted therapies have been developed where a specific molecule or pathway is targeted via inhibitors or antibodies. Unfortunately, such drug treatments also do not ensure a definitive cure owing to therapy resistance caused by factors like tumor heterogeneity, secondary mutations, parallel pathway activation, and feedback mechanisms. In fact, drug resistance is a major factor in relapse of many malignancies. A minority of cells that are unresponsive to the treatment(s) due to either intrinsic or acquired resistance eventually grow out. Nowadays, this phenomenon is so common that most therapies are designed as combinatorial treatments with two or more drugs. Although important, drug resistance is not the sole reason of recurrence. Metastasis is another major cause of relapse and one of the hallmarks of cancer. Many tumors resurface at a distant site, formed by the cells that escaped from the primary location and any localized treatment such as surgery or radiation therapy. Metastasis is a very complex process and is still poorly understood despite extensive research. In this thesis, we focused on these two distinct aspects that lead to fatal cancer progression.

In Chapter 1 we give a brief introduction to targeted therapies and approaches to circumvent the obstacle of drug resistance. We also describe the dynamic process of metastasis and why it is important to understand metastatic capability of cancer in more detail.

Chapter 2 of this thesis focuses on finding an effective targeted combination treatment for triple-negative breast cancer (TNBC), a breast cancer subtype that is currently being treated only with surgery, chemotherapy, radiotherapy or combinations of these. We aimed to discover novel targeted therapies for TNBC and found that combination of
EGFR and ROCK inhibitors leads to cell cycle arrest and the eventual death of TNBC cells.

Understanding the underlying mechanism of drug response is crucial to develop more effective approaches. Therefore, in Chapter 3 we tried to shed light on why combined inhibition of EGFR and ROCK leads to cell death in TNBC cells. We found that, this combination of inhibitors simultaneously leads to induction of autophagy and inhibition of rpS6, a molecule crucial for various cellular processes.

Chapter 4 and Chapter 5 focus on the role of the transcription factor Fra-1 in metastasis. We established the in vivo significance of Fra-1 in colon and bladder cancer cell lines by experimental metastasis models. Moreover, our analyses show that Fra-1 on its own is a predictive marker in bladder cancer while in colon cancer the group Fra-1-regulated genes have prognostic power to stratify patients based on their gene expression profiles.

In conclusion, this thesis proposes a novel targeted therapy approach for TNBC and signifies the essential role of Fra-1 in the regulation of metastasis as well as in disease prognosis.