High grade serous ovarian cancer (HGSOC) and triple negative breast cancer (TNBC) have limited treatment options, as only few targeted therapies effectively kill cancerous cells and patients frequently develop resistance to standard therapies. The tumour microenvironment actively supports cancer pathology and is populated by a variety of cell types that also offer alternative routes for therapy. Our research focuses on cancer-associated fibroblasts (CAFs), as we and other have shown that they play a major role in modulating cancer pathology. CAFs strongly influence the function of cancer and other stromal cells by secreting extracellular matrix (ECM) components, ECM modifiers, soluble factors and extracellular vesicles (EVs). We aim to understand the molecular mechanisms through which CAFs support cancer, and envisage targeting CAFs in combination with cancer cells as a promising strategy to hamper cancer growth and metastasis.

Our research primarily focuses on the role of CAFs in HGSOC and TNBC. These tumours contain vast regions of stroma, which are densely populated by CAFs, while CAFs were shown to play active roles in the progression of both diseases. Importantly, HGSOC cells and TNBC cells have few recurrent mutations, therefore limiting the availability of targeted therapies against cancer cells. As such, CAFs offer a valid alternative therapeutic opportunity in these tumour types (Santi et al., 2018, Proteomics; Domen et al., 2021, Cancer). We aim to decipher how CAFs create a pro-tumorigenic microenvironment and how we can block this process to make the tumour microenvironment unfavourable to cancer growth and tumours more vulnerable to therapeutic interventions; our overarching goal is to determine strategies that target CAFs for therapy.

CAFs can originate from normal fibroblasts resident at the site where the primary tumour develops. When a tumour starts developing, normal fibroblasts become activated. This activation induces extensive reprogramming of gene expression and protein levels, such that CAFs become able to secrete a plethora of soluble factors and ECM components (Figure 1) that actively support cancer progression. CAFs were also shown to secrete EVs whose cargos could aid tumour progression by supporting cancer cell growth and invasion (Santi et al., 2018, Proteomics). While CAFs are the results of the reprogramming of normal cells, we aim to find ways to revert CAFs to normal cell-like phenotype that does not support cancer and that improves response to therapies.

To understand how to target CAFs in tumours, it is essential that we understand how CAFs make the tumour microenvironment pro-tumorigenic and pro-metastatic, and what the molecular mechanisms are that sustain CAF functions. Our major interest is the role of cell metabolism (Kay et al., 2021, Front Oncol; Kay & Zanivan, 2021, Curr Opin Syst Biol) and extracellular vesicles (EVs) secreted by CAFs. For our research model, we mostly use CAFs that we isolate from tumour tissues that were kindly donated by patients for research purposes (Hernandez-Fernaud, Ruengeler et al., 2017, Nat Commun; Kugeratski et al., 2019, Sci Signal). We have also shown that the ECM secreted by CAFs play an active role in the metastatic dissemination through facilitating the binding of the cancer cells to the blood vessels (Ried et al., 2017, EMBO J). We have now found that CAFs also influenced EC function by transferring functional proteins through EVs. In particular, CAFs can transfer plasma membrane and membrane-bound proteins to the surface of the endothelial cells. This process confers the ability to the endothelium to interact with other cell types, such as monocytes, which influence aspects of tumour progression, including antitumor immunity and metastasis. We therefore discovered another way through which CAFs