Research in the Transformation and Metastasis Group aims to identify novel therapeutic targets for epithelial cancer treatment and to elucidate resistance mechanisms to drugs currently available. Tumours exploit and manipulate for their benefit the same mechanisms that work correctly in the healthy tissue. Thus, we first aim to understand normal development, and then to identify the key events that lead to tumour initiation, progression and metastasis in order to avoid and combat them. Complementary tools including primary cell cultures and organoids, mouse models and clinical samples are used with the final goal of translating basic knowledge into clinically relevant findings.

One of our research lines aims to characterise the role of the TNF family member RANK in mammary gland development and breast cancer and to elucidate its therapeutic potential. “Clinical and preclinical findings support that activation of RANK signalling in breast cancer cells induces immunosuppression and that its blockage leads to a T cell dependent anti-tumour response.”
Most breast cancers exhibit low immune infiltration and are unresponsive to immunotherapy. We hypothesised that inhibition of the RANK signalling pathway may enhance anti-tumour immune response. Using preclinical mouse models, we found that loss of RANK signalling in tumour cells increases infiltration by leukocytes, lymphocytes, and CD8+ T cells, and reduces macrophage and neutrophil infiltration. CD8+ T cells mediate the attenuated tumour phenotype observed upon RANK loss, whereas neutrophils, supported by RANK-expressing tumour cells, induce immunosuppression. Moreover, RANK inhibition increases the anti-tumour effect of immunotherapies in mouse mammary tumours through a tumour cell-mediated effect. Comparably, preoperative single-agent denosumab in premenopausal early-stage breast cancer patients from the Phase-II D-BEYOND clinical trial (NCT01864798) was well tolerated, inhibited RANK pathway, and increased tumour infiltrating lymphocytes and CD8+ T cells. Higher RANK signalling activation in tumours and serum RANK levels at baseline predict the immune-modulatory effects driven by denosumab.

Altogether, our preclinical and clinical findings reveal that tumour cells exploit the RANK pathway as a mechanism to evade immune surveillance and support the use of RANK inhibitors to prime luminal breast cancer for immune response orchestrated by CD8+ T cells. For each measured parameter, the corresponding boxplot is displayed on the right-hand side. (a) RANK expression in breast cancer cells overexpressing RANK (c) and downstream pathways (d).

RANK signalling increases after anti-HER2 therapy contributing to the emergence of resistance in HER2-positive breast cancer Around 15-20% of primary breast cancers are characterised by HER2 protein overexpression and/or HER2 gene amplification. Despite the successful development of anti-HER2 drugs, intrinsic or acquired resistance represents a major hurdle. RANK and RANKL proteins are more frequently detected in HER2-positive tumours that have acquired resistance to anti-HER2 therapies than in treatment-naïve ones. RANK (but not RANKL) gene expression increased after dual anti-HER2 neoadjuvant therapy in the cohort from the SOL-1104 PAMELA trial. Results in HER2-positive breast cancer cell lines recapitulate the clinical observations, with increased RANK expression after short-term treatment with anti-HER2 therapies and enhanced NF-κB activation in lapatinib-resistant HER2+ breast cancer cells. Moreover, we found that overactivation of the RANK signalling pathway enhances ERK and NF-κB signalling and increases lapatinib resistance in different HER2-positive breast cancer cell lines. Our results indicate that ErkB signalling is required for RANK/RANKL-driven activation of ERK in several HER2-positive cell lines. In contrast, lapatinib is not able to counteract the NF-κB activation elicited after RANKL treatment in HER2-overexpressing cells. Finally, we showed that enhanced RANK pathway activation alters HER2 phosphorylation status and RANK binding to HER2 in breast cancer cells. Altogether, our data support a physical and functional link between RANK and HER2 signalling in breast cancer and demonstrate that increased RANK signalling may contribute to the development of lapatinib resistance through NF-κB activation (Sanz-Moreno et al., Breast Cancer Research, 2020).