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 regulate homeostasis in 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.

“Our findings demonstrate that RANK overexpression induces senescence in luminal mammary epithelial cells through p16/p19, and that Rank-induced senescence enhances stemness.”
Our previous results indicate that Rank signalling enhances stemness in mouse and human mammary epithelial cells (MECs) and mediates mammary tumour initiation. Mammary tumours induced by oncogenes or carcinogen exposure display high levels of Rank, and Rank pathway inhibitors have emerged as a new strategy for breast cancer prevention and treatment. Here we show that ectopic Rank expression in the mammary epithelia unexpectedly delays tumour onset and reduces tumour incidence in the oncogene-driven Neu and PyMT models. Mechanically, we have found that ectopic expression of Rank or exposure to Rank induces senescence, even in the absence of other oncogenic mutations. Rank leads to DNA damage and senescence through p16/p19. Moreover, RANK absence of other oncogenic mutations. Rank leads to DNA damage and senescence through p16/p19. Indeed, Rank-induced senescence is essential for Rank-driven stemness and, although it initially translates into delayed tumour growth, it could also prevent and/or treat BC and regulate the tumour immune crosstalk: The D-Biomark clinical trial aims to identify denosumab-driven changes in breast cancer cells and to identify the population of breast cancer patients who may benefit from denosumab.

Patients with early-stage HER2-negative BC, candidates to tumour excision as first therapeutic approach are included. Patients are randomised 2:1 to denosumab : control (no treatment). Experimental arm received 2 doses of 120 mg subcutaneous denosumab (once per week) before surgery (2-4 weeks later). Putative changes in tumour cell proliferation by Ki67 immunohistochemistry (IHC), cell survival by cleaved caspase 3 IHC (primary endpoints), and stromal tumour infiltrating lymphocytes (TILs) quantified by haematoxylin and eosin staining between baseline (biopsy sample) and surgery are evaluated.

We present the results of the first 36 patients enrolled out of 60. Clinical and tumour characteristics were well balanced between the groups. No relevant toxicities were reported. No statistically significant differences in Ki67 and cleaved caspase 3 IHC were observed after denosumab treatment. Interestingly, a statistically significant increase in TILs was observed in the denosumab-treated group (p < 0.05). A ≥10% increase in TILs vs 0% in the control group (p = 0.80). 33% of patients treated denosumab showed a ≥10% increase in TILs vs 0% in the control group (p < 0.05).