Profiling of the stroma by spatial transcriptomics in aid of prognostication in FGFR2-mediated luminal breast cancer

Breast cancer (BC) affects 1 in 8 women during their lifetime and is the second leading cause of cancer-related death in women. However, death rates from breast cancer have been declining since the late 80s, which is believed to be the result of early detection, increased awareness and, above all, an improved treatment, owed mainly to the considerable advances in basic science. The standard of care for luminal BC (hormone-dependent) involves anti-ER therapy (e.g. tamoxifen, fulvestrant) with/without chemotherapy. Despite significant improvements in the management of patients, *de novo* or acquired resistance to endocrine treatment still remains a major clinical problem. One of the possible explanations is insufficient characterization of the factors that promote the progression of the tumour, in particular those secreted by the cells of the surrounding microenvironment (stroma). In luminal BC, interactions between tumour and its stroma are mediated by Fibroblast Growth Factors (FGFs), that through their receptor FGFR2 on cancer cells activate various processes vital for BC survival and development of resistance to endocrine therapy. **The project aims, therefore, to establish a molecular profile of the stroma that will allow more accurate assessment of the prognostic and predictive value of FGFR2 in the context of other clinicopathological features of the tumour.** To this end, the project will consist of the characterization of the stroma at both mRNA and protein levels. Genetic analyses will be conducted in tissue isolated by tissue microarray technology (TMA) using the Xenium in situ (10x Genomics) spatial transcriptomics, a highly specialized technology that enables analysis with subcellular resolution by profiling up to 1,000s of targets, each in the context of their spatial localization patterns. The analysis will include an evaluation of the expression of 328 genes selected by Applicant, named here the “FGFR2-related functional profile”. The results will be verified by immunohistochemistry, to enable identification of a clinically significant stroma-derived factor/s potentially to be introduced to the routine diagnostics.

Analyses of the molecular and clinical data are expected to reveal an association between the molecular profile of the stroma and the prognostic/predictive value of FGFR2 in luminal BC. It is foreseen that **the project might provide new and more reliable criteria for further classification of breast cancer** and, consequently, assist in the identification of a subgroup of patients who might benefit from the FGFR-targeted therapy.