FGFR2-triggered signalling in regulation of ER/PR interdependence - molecular mechanism and predictive value for patients with luminal A breast cancer

Breast cancer is the most common cancer among women worldwide. The most frequent is luminal A subtype (approx. 50-60% of all cases) positive for both **estrogen (ER)** and **progesterone (PR) receptor**. Routine treatment for these cases involves drugs targeting function of ER (e.g. tamoxifen, fulvestrant). Unfortunately during the therapy almost all patients develop resistance to applied therapeutics, that poses a serious clinical problem. A variety of molecular mechanisms driving the resistance have been proposed. Recently, it was demonstrated that at the presence of progesterone and estrogen there is a direct interaction between ER and PR, which results in better response to tamoxifen treatment and improved patients' clinical outcome. However, there is still a lack of detailed research focused on the mechanism of this interaction.

Tumor microenvironment has been proved to play a crucial role in modulation of response to various anti-cancer therapies. Cancer-associated fibroblasts by secretion of FGFs (fibroblasts growth factors) were shown to activate steroid hormone receptors independently of hormones action. **Fibroblast growth factor receptor 2 (FGFR2)** was described as an important tumorigenic factor contributing to the development and progression of breast cancer. In our recent studies we have shown FGFR2-driven activation of independently ER or PR (in steroid-free conditions), that was connected with worse response to tamoxifen treatment and disease progression. Therefore, the project aim is to study in details FGFR2 involvement in regulation of steroid hormones-triggered ER/PR interdependence.

The project involves three complementary levels of analyses: i) extensive *in vitro* studies of FGFR2 action towards regulation of ER/PR interdependence, ii) *in vivo* experiments aiming at revealing the role of FGFR2 in steroid hormones-dependent growth of BCa in mice, and iii) clinical analysis on a group of ER/PR-positive BCa patients to evaluate a potential prognostic significance of FGFR2-driven expression of ER/PR-related genes.

We believe that this kind of a broad and detailed approach will provide a set of valuable data describing the role of FGFR2 in mediation of tumour microenvironment-originating signal which affects steroid hormones receptors` function in luminal A breast cancer. By assessing the interaction between FGFR2 signalling and ER/PR transcriptional signature (not the level of ER or PR expression, as routinely carried out in histopathological evaluation), the study might identify a subgroup of patients who might benefit from FGFR2-targeted therapy.