FGFR2→JunB axis in progression of ER+ breast cancer - molecular analyses and prognostication

Breast cancer (BCa) is the most common cancer in women, with approximately 1.7 million new cases diagnosed every year. The most frequent are hormone-dependent i.e. **ER+** (**estrogen receptor-positive**/luminal) subtypes, representing up to 70% of all BCa cases. ER is the main regulator of the disease progression. ER, when activated by ligand (i.e., estradiol), binds to the specific sequences within DNA (ERE, estrogen response elements), leading to the regulation of ER-dependent genes expression. ER can also indirectly regulate the expression of genes without ERE sequences by binding to DNA via other proteins. One of them is the **AP-1 complex**, composed of Jun and Fos proteins. AP-1 by tethering of ER leads to a rearrangement in the genes expression profile.

The standard of care for ER+ BCa patients involves drugs inhibiting ER activity (e.g. tamoxifen), that significantly improve patients' outcomes. However, *de novo* or acquired resistance to such agents afflicts most of the patients. **Fibroblast growth factors** (FGFs), which originate from tumour microenvironment, bind to specific receptors (FGFR1-4) on the BCa cells and promote progression of the disease and resistance to anti-ER drugs. In our previous studies, **FGFR2** was shown to activate ER in a ligand-independent manner, induce progression of ER+ BCa and counteract the effect of tamoxifen for cell growth. However, our clinical analyses showed that the presence of FGFR2 in BCa patients is associated with a good prognosis of ER+ BCa patients suggesting that the role of FGFR2 is complex and might be regulated by other factors. On the other hand, we have recently found that FGFR2 upregulates expression of **JunB** (a component of AP-1 complex) *in vitro* and strongly correlates with *JunB* gene in BCa samples. Taking into account these findings, there is a possibility that FGFR2 by promoting ER activity and expression of JunB can regulate interplay between ER and AP-1 complex, which influence patients' response to anti-ER drugs. Therefore, the main goal of this study is to investigate FGFR2→JunB axis in ER+ BCa growth, response to anti-ER treatment and patients` outcomes.

Specifically, we will: a) analyse the mechanism of FGFR2-promoted JunB expression and how this affects AP-1 complex formation and AP-1/ER interaction; b) verify the role of FGFR2→JunB axis in regulation of ER and AP-1 binding to DNA and transcriptional activity; c) study an engagement of FGFR2→JunB pathway in BCa cell response to tamoxifen; and d) determine a prognostic value of FGFR2/JunB interdependence in ER+ BCa. The project will involve two complementary levels of investigation i.e. *in vitro* studies and clinical analyses to determine the prognostic value of FGFR2/JunB interdependence in samples from ER+ BCa patients. It is foreseen that such a broad and detailed approach will provide valuable information on the role of FGFR2 in ER+ BCa and potentially identify a subgroup of patients who might benefit from FGFR2-targeting therapy.