FGF/FGFR-SIGNALLING IN MEDIATION OF RESISTANCE TO THERAPY IN TRIPLE-POSITIVE BREAST CANCER: CLINICAL IMPLICATIONS OF PAM50 INTRINSIC SUBTYPES

The aim of the project it to investigate a **new molecular mechanism** likely to be responsible for development of resistance to therapy in patients with a specific type of breast cancer (triple-positive/TPBC).

Breast cancer (BC) affects 1 in 8 women during their lifetime and is the second leading cause of cancer-related death in women (exceeded only by lung cancer). 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. For the therapy to be efficient, it is of paramount importance that it is adjusted to the type of the tumour, so it arrests its progression by targeting the relevant molecular factors. As molecular mechanisms governing function of cancer cells are specific for the type of the tumour, their understanding is prerequisite for development of new efficient therapies.

It is now well documented that breast cancer is not a single disease but represents a spectrum of tumour types. The **triple-positive** (ER+/PR+/HER2+) **breast carcinoma** (**TPBC**) is a relatively rare subtype (approx. 10% of all BC cases), commonly perceived as HER2-positive breast cancer. Accordingly, chemotherapy with anti-HER2 agents is the backbone of the treatment. However, emerging clinical data suggest, that TPBCs represent a distinct subtype with a better prognosis than the HER2-positive BC. This implicates that current therapeutic strategies in the management of patients with TPBC should be revised. It is suggested that response of TPBCs to the treatment relies on interactions between ER and HER2, likely to be influenced by stimuli derived from the tumour stroma, mediated by a family of **FGFR** receptors. Response to the treatment may also be specific to the 'intrinsic subtype' (this can be identified by a **PAM50** test) of the tumour, only recently recognised as a very important predictive indicator in breast cancer. As molecular mechanisms underlying these interactions are not fully understood, the proposed project aims to reveal their nature and clarify their possible impact on the course of disease and response to treatment. This will be done at three complementary levels in: *in vitro* and *in vivo* TPBC as well as clinical material. *In vitro* studies, using TPBC cell lines, we aim to: i) identify specific factors (FGFs) that mediate stimuli from the stroma and, via FGFR affect a crosstalk between ER and HER2 (in a culture dish we will create an environment that mimics a situation *in vivo*); ii) investigate molecular mechanisms of FGFR-driven mediation of the ER-HER2 interaction, iii) evaluate cellular effects of FGFR on TPBC cell growth and, finally, iv) clarify a role of FGFR in response/resistance to established therapies. In the animal model, the mechanisms identified *in vitro* will be verified *in vivo*. Clinical analyses will determine whether the results of experimental studies are applicable to human pathology. The tissue of breast cancer surgically removed from patients with TPBC will be thoroughly examined by experienced pathologists with regards to specific features reflecting the described molecular phenomena. Clinical studies will also include in-depth analyses aimed to reveal a genetic/phenotypic profile associated with resistance to routinely applied therapies in this type of breast cancer. In all analyses, results will be related to the TPBC intrinsic subtype defined by the PAM50 test.

If our hypothesis is correct, these results may provide foundations for revised treatment regimens, which will enable, in some cases, **to avoid an overtreatment**, in others, **to identify true therapeutic targets** and thus improve an outcome of patients with TPBC.