The aim of the project it to investigate a new molecular mechanism likely to be responsible for development of resistance to hormonal therapy in patients with a specific type of breast cancer (luminal B).

Breast cancer affects (BCa) 1 in 8 women during their live-time and is the second (after lymph node involvement) leading cause of cancer-related death in women (exceeded only by lung cancer). However, death rates from breast cancer have been declining since about 1989, which is believed to be the result of earlier detection, increased awareness and, above all, improved treatment.

For the therapy to be efficient, it is of paramount importance it is adjusted to the type of tumour so it arrests its progression by targeting relevant molecular regulators. As molecular mechanisms governing function of cancer cells are specific for the type of 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 most common type, representing 75% of all BCas and characterized by the presence of estrogen receptor (ER) on the surface of tumour cells, is called luminal BCa. It was revealed that this type is in fact made up of two distinct subtypes, namely luminal A and B. Cancer cells of both types have ER but differ with regard to the presence of another hormone receptor, the progesterone receptor (PR) (normal/healthy breast cells have both ER and PR). Luminal B type is deprived of PR. It is well documented that the course of its progression is much more aggressive and treatment of patients with this type of tumour poses a significant clinical challenge. Both luminal A and B types are ER-positive, but estrogen-targeted therapy is efficient only in luminal A. This implies that the mechanisms responsible for loss of PR are the main driving forces of luminal B growth. No specific therapy for patients with luminal B is currently available. However, it is highly likely that targeting the causes of PR loss might prove clinically efficient in this group of patients.

Little is known about the molecular mechanisms governing progression of luminal B tumours, however, there is some evidence to suggest that it largely depends on stimuli (in a form of specific soluble factors) generated by tumour environment (stroma). Results of our pilot study confirm this and suggest that a cascade of biological effects induced by a particular factor, not previously reported, (FGF, fibroblast growth factor), significantly contributes to the loss of PR by luminal BCa cells.
The proposed project aims to expand our initial observation and investigate in depth molecular basis of this phenomenon, i.e. interaction between FGF and PR.

This will be done at **three complementary** levels:
1) ***in vitro* BCa mode**l (cell culture), that will be based on tumour cells of appropriate characteristics isolated from human breast cancer and immortalized, so they do not change while grown in a dish. We will introduce certain genetic modifications to the cells and perform a number of experiments. The goal of this part of the project is fourfold: i) *identification of specific factors (FGFs) that induce decrease of PR* - in a culture dish we will create an environment that mimics a situation *in vivo*. Closely controlled manipulations of such an experiment will allow to determine a specific factor/s under investigation; ii) *studies of molecular mechanism of FGF-driven decrease in PR level* – having defined a specific factor (FGF) we will now investigate whether its effect on cancer cells is due to its action on gene and/or proteins. This is important in light of potential therapeutic designs; iii) *analysis of cross-talk between FGF and PR* - we will check how the collaboration between these two molecules takes place i.e., whether they interact directly or through mediators and iv) *cellular effects of FGFR/PR cooperation* – in a set of experiments we will investigate what are the functional effects, i.e. what kind of cell behaviour (increased motility and/or spread), are induced by the aforementioned phenomenon;
2 **xenotransplants** – human BCa cells (same as in *in vitro* studies) will be injected into mice so they can grow in a 'more natural environment', i.e. in a living organism, and form tumours similar to those developed in humans. When fully formed, they will be evaluated by pathologists according to the criteria used in the routine clinic. This will let us know how and to what extend results of previous (*in vitro*) studies can be extrapolated to *in vivo* situation;
3) **clinical analyses** – in the final and conclusive part of the project we will determine whether the results of experimental studies can be applied to human pathology. Tissue of breast cancer surgically removed from patients with luminal B BCa will be thoroughly examined by experienced pathologists with regards to specific features reflecting the described molecular phenomena. If our hypothesis is correct, these results may provide foundations for novel efficient therapies for patients with this currently incurable cancer.

Luminal B breast cancer is one of the most aggressive type of cancer in women. No treatment that will cure or at least slow down its progression is at present available. A pressing clinical need and the applicants' long developed interest in research focused on related topics were the incentives for the proposed study.