Chronic Myeloid Leukemia (CML) is a blood cancer characterized by expression of BCR-ABL oncogene and protein with tyrosine kinase activity. Although current, very specific therapies with tyrosine kinase inhibitors are effective in CML patients in chronic phase, the resistance often develops in progressive blast crisis phase. That is why looking for novel therapeutic targets and novel therapeutic strategies is necessary. Recent research has led to discovery of novel signaling pathways, which correlate with development and progression of leukemias, including chronic myeloid leukemia (CML). As a consequence, novel therapeutic strategies have been proposed to treat leukemia, especially in patients resistant to tyrosine kinase inhibitors of 1 and 2 generation.

Many of the novel strategies rely on the idea of personalized therapy that separates patients into different groups depending on the previous diagnosis and detection of biomarkers specific for the treatment. One of the proposed is a treatment with PARP inhibitors, which is based on the synthetic lethality principles. This therapy is proposed for BRCA1-deficient cancers – mainly breast and ovarian cancer associated with *BRCA1* gene mutations.

The presented project is based on our previous research, which has revealed that expression of BCR-ABL oncogene, responsible for CML development, leads to decrease of BRCA1 protein level. Previously, CML was not classified as a BRCA1-deficient type of cancer, due to lack of mutations and other genetic changes in the *BRCA1* gene. Next, we have shown that despite the high level of *BRCA1* mRNA expression, the synthesis/translation of BRCA1 protein is inhibited in CML cells. This is a result of binding of *BRCA1* mRNA with RNA binding protein - TIAR and storage of newly formed complexes in stress granules - the structures involved in the protection of mRNA from translation. The storage of mRNA in stress granules containing RNA-protein complexes results in sequestration of mRNA from translation and as a consequence lower protein level. That is why understanding of mechanisms responsible for regulation of BRCA1 synthesis/translation is crucial for indicating new targets for cancer therapy, therapeutic strategies and novel biomarkers for selection of cohort of patients sensitive to PARP inhibitors.

Our preliminary data has indicated that another RNA binding protein - FMRP (Fragile-X Mental Retardation Protein) can be also involved in the regulation of BRCA1 translation. Interestingly, FMRP is investigated in the context of regulation of neuronal functions and synaptic plasticity and has not been described in leukemia. However, involvement of FMRP in cancerogenesis has been recently proposed.

The aim of the proposed project is verification of the novel function of FMRP as a regulator of BRCA1 translation in chronic myeloid leukemia cells.