Mutations in the *SMARCA4* that encodes BRG1, an enzymatic subunit of the SWI/SNF complex, occur in various types of cancer with a frequency of up to 16%. SWI/SNF plays an important role in structural chromatin rearrangements, hence also in and gene transcription. It is responsible for the mobility of nucleosomes, their density within chromatin and availability of DNA for the transcriptional machinery. The meaning of BRG1 loss for tumor transformation and subsequent disease progression remains unknown. The results of our recent studies showed that low expression of the *SMARCA4* correlates with high expression of genes encoding proteins crucial for lysosomal activity such as *LAMP1*, *LAMP2*, *LAMP3*, *LIMP2* in cancer patients. Anticancer drug accumulation in these organelles lose their cytotoxicity and genotoxicity. According to the results I have published, the mechanism of inactivation of anticancer drugs in lysosomes is crucial for the acquisition of multidrug resistance in cancers during paclitaxel therapy, and a reduction in the activity of these organelles sensitizes resistant cells to chemotherapeutics. Importantly, from the point of view of lysosome function and cancer resistance, the expression levels of proteins that are key components of lysosomes correlate with the levels of estrogen receptor ERa and BRM protein - the second enzymatic subunit of the SWI/SNF complex in patients with mutated and dysfunctional BRG1 protein. Such a relationship is not observed in patients with normal BRG1.

The aim of the project is to understand the role of BRM and ERα in conditioning multidrug resistance in *SMARCA4* mutant cancers. The research hypothesis is that BRM forms a functional complex with ERα that increases the expression of lysosomal genes that determine chemotherapy resistance in the absence of BRG1 activity. At the molecular and cellular level, the project aims to identify the effect of BRG1 on BRM-ER complex formation and activity, but also to test and validate the BRG1/BRM inhibitor, estrogen receptor down-regulating compound (SERD), and selective estrogen receptor modulators (SERMS), which are currently used in ER+ cancer therapies, as potential agents to prevent lysosome biogenesis. Moreover, we aim to identify the cofactor that allows for BRM-ER-dependent transcription control of lysosomal genes in the absence of BRG1.

As a model for our study we will use paclitaxel-resistant phenotypes of non-small lung cancer cells since these tumor types are often treated with paclitaxel, which drives their resistance by enhancing lysosomal drug sequestration. Therefore, we chose A549 cell line with a spontaneous mutation in the *SMARCA4* gene, and NCI H441 with wild-type *SMARCA2* (BRM) and *SMARCA4*. Methodology includes ChIP- and RNA-Seq techniques, bioinformatics analysis, study of drug accumulation in lysosomes using flow cytometry and confocal microscopy, as well as cytotoxicity analyses.

From the scientific point of view and for the development of the scientific discipline, the project will contribute to the understanding of the unknown basis BRM-ERα interaction in cells with acquired multidrug resistance, in particular, the emergence of BRM-ERα-dependent genes and regions in the genome where such a functional and physical interaction can occur. The role of the BRG1 protein in the complex formation or synergistic action of the aforementioned proteins will be determined. In addition, the project aims to identify chromatin-bound cofactors of the BRM-ER complex, which likely contribute to increased transcription of lysosomal genes, but also other genes, in paclitaxel-resistant phenotypes. These cofactors may represent potential targets for anti-lysosomal therapies, in which these organelles play an important role in resistance to specific chemotherapeutics. The SERD and SERMS compounds tested are also potential candidates for anticancer therapies in combination with other drugs that are passively (by diffusion) or actively (via ABC transporters) transported to lysosomes in non-small lung cancer patients with an identified inactivating mutation in *SMARCA4*.