Strategies for cancer therapy and prevention involve many different groups of drugs. Studies of recent years show important role of nonsteroidal anti-inflammatory drugs (NSAIDs) in this process. Numerous analysis proved that in patients who regularly used NSAIDs the risk of cancer is decreased even up to 70% depending on type of cancer and used NSAIDs. Potential mechanism of anticancer action for NSAID is explained on the basis of their inhibitory effect on cyclooxygenase (COX) which is frequently overexpressed in many types of cancer. It is related to regulation on processes as: proliferation, migration, neoangiogenesis, apoptosis resistance, metastasis and invasion in which COX plays an important role. Nonetheless it was also demonstrated that NSAIDs evoked similar proapoptic effect in cancer cells which do not express COX enzyme or in model of cancer cells with knocked-down COX. We suggest that this group of drugs may evoke antineoplastic activity through PPARγ receptor. PPAR receptors belongs to the nuclear receptor family and have transcriptional activity. Involved in gene expression regulation play important role in energetic metabolism, apoptosis and inflammation processes. It is known that NSAIDs are ligands for PPARγ receptor which induces PRODH/POX expression and it leads to activation of apoptosis pathway.

PRODH/POX is a mitochondrial enzyme catalyzing the conversion of proline to pyrrolidine-5-carboxylic acid (P5C). During the conversion of proline to P5C, electrons are transported to the respiratory chain, producing ATP or reactive oxygen species (ROS). In the first case, activation of PRODH/POX leads to the production of ATP for survival, in the second one, ROS induces apoptosis. The mechanism of switching the PRODH/POX function from inhibitory to stimulatory for tumor cell growth is not known. Probably the availability of proline in this process may play an important role in the mechanism of regulation of apoptosis/autophagy.

The aim of this project is to identify molecular mechanism of anticancer action of selected NSAIDs as a PPARγ receptor agonists in experimental models of breast cancer cells by analysis of expression of transcription factors, selected receptors, signaling proteins and apoptosis markers in breast cancer cells MCF-7 with modified PRODH/POX expression.

In order to carry out the project, clones of MCF-7 breast cancer cells with modified PRODH / POX expressions will be used. The effect of different NSAIDs (for example: Ibuprofen, Indomethacin, Celecoxib and others) on some metabolic processes in these cells will be studied. It is planned to evaluate the effect of selected NSAIDs on cell proliferation, DNA biosynthesis, collagen biosynthesis, prolidase activity, expression of some apoptosis markers, PRODH/POX, some growth factor receptors, transcription factors, as well as proteins of signaling pathways by RT-qPCR technique, and Western immunoblot, immunocytochemistry using confocal microscopy and flow cytometry. Analysis of amino acids by high performance liquid chromatography or gas chromatography coupled with mass spectrometry (LC-MS / GC-MS) will be performed at the final stage of the study, evaluating the effect of selected NSAIDs on the amino acid profile (mainly proline and its metabolites) MCF-7 cells with modified PRODH/POX expression. The impact of NSAIDs on the cell cycle will also be assessed.

This project aims to investigate molecular mechanism of anticancer action of selected NSAIDs as a PPARγ receptor agonists in experimental models of breast cancer cells. The biological effects of NSAIDs on breast cancer cells will be assessed with respect to the potential use in development of a new targeted experimental cancer pharmacotherapy. Understanding the role of NSAIDs on PRODH/POX-dependent apoptosis will be useful for improvement of pharmacotherapy of cancer. The scientific results of the research project will be documented in journals with a high impact factor and reports presented at national and international scientific conferences.