“Molecular mechanism of death of non-small cell lung cancer cells and pancreatic cancer cells treated with combination of sorafenib and betulinic acid”

Current treatments for advanced non-small cell lung cancer (NSCLC) and pancreatic cancer (PDAC) are limited due to the significant cytotoxicity of the chemotherapeutic agents. Tyrosine kinase inhibitors have demonstrated activity against specific signaling pathways involved in oncogenesis processes in all types of tumors. Recent research highlights the importance of combined, targeted therapy based on specific molecular targets. One of the most common mutations in NSCLC and PDAC is the KRAS mutation that activates the RAS/ RAF/ERK pathway responsible for proliferation and indicates a poor prognosis. Unfortunately, despite many studies, there is still no direct targeted therapy for Ras-active tumors. Therefore, many studies focus on the development of agents that inhibit further elements of the pathway, such as Raf kinases. One of such inhibitors is sorafenib.

The aim of the presented doctoral project is to present the molecular mechanisms of interaction of the combination of sorafenib and betulinic acid with molecules and key factors associated with proliferation and apoptosis pathways of NSCLC and PDAC cells. Studies have shown that the combination of sorafenib and betulinic acid significantly reduces the viability and proliferation of NSCLC cells, induces apoptosis and reduced the clonogenic potential. Analysis of signaling pathways by western blotting showed changes in CHOP protein expression and proteins involved in the mitochondrial apoptosis-Bcl-2 and Bax pathway. Moreover, caspase-8 and caspase-9 and cleaved PARP appearance, and Akt and mTOR kinase is inhibited. Additionally, the combination of the same compounds synergistically inhibits the proliferation and clonogenicity of PDAC cells. The mechanism of action is different from that observed in lung cancer. The combination of compounds inhibits the proliferation of PDAC cells by the G2 cell cycle arrest strongly associated with increased expression of p21 and decreased expression of c-Myc and cyclin D1 and by inhibiting ERK1/2 and Akt kinases. In addition, which is very interesting, the combination of compounds does not induce apoptosis in cancer cells. Furthermore, the combination does not have toxic effects on normal peripheral blood (PBL) cells.

The combination of sorafenib with betulinic acid is effective in the therapy for NSCLC as well as against other types of cancer, including difficult to treat pancreatic cancer.