Developing of histone deacetylase-inhibiting hybrid analogs of pleurocidin and their potential in the treatment of HPV-induced cervical cancer

Cervical cancer ranks second among the leading causes of cancer-related deaths among women aged 15 to 44 years in Europe. Of the several risk factors for cervical cancer, human papillomavirus (HPV) infection is considered the most clinically relevant, as it can be detected in 99.7% of patients with cervical cancer. In recent years, epigenetic modifications, affecting how genes are expressed, have gained increasing interest in terms of the development of new anticancer drugs. Thus, inhibitors of histone deacetylases (HDACi), enzymes that modulate chromatin structure, have been presented as new anticancer molecules approved by the U.S. Food and Drug Administration (FDA). A steadily increasing number of studies show that HDACi have great potential in the fight against cervical cancer due to their ability to induce intracellular anticancer mechanisms and reduce HPV expression in cancer cells.

Pleurocidins, antimicrobial peptides of marine origin, isolated from the tissues of winter flounder, are proposed as a new group of anticancer molecules due to their ability to interact with the biological membrane of cells and, at the same time, their intracellular activity. In the project, we hypothesize that, at the molecular level, pleurocidin and its derivatives, by inhibiting HDAC activity, will promote anticancer events in cervical cancer cells and regulate signaling pathways disrupted by HPV infection. Furthermore, we hypothesize that by modulating the physicochemical properties of pleurocidins, as well as adjusting the structure of the peptides by altering their amino acid composition or including non-peptide groupings (e.g. lipids), it is possible to control their intracellular localization and final delivery after cellular uptake, thereby tailoring the molecular action of these agents in cervical cancer cells, including their effect on HDAC activity. Using these properties, we propose to optimize pleurocidins and produce novel dual-compound formulations by combining pleurocidin variants with HPV-targeting molecules, i.e. binding to peptides targeting the HPV E6 and/or E7 oncoprotein.

The implementation of the project will extend the topic of rational design of peptides with high affinity for HPV oncoproteins in the context of combating HPV-induced cervical cancer. It is assumed that, in combination with HPV-targeting agents, the selectivity of the developed anti-cancer formulation to cervical cancer cells can be achieved, paving the way for an innovative and highly effective therapeutic approach to HPV-related cancers.