Development of cIAP1-targeting CDK4/6 degraders (PROTACs) containing a phosphoroorganic warhead (POWERTAP)

The alteration of the cell cycle is often found in malignant tumors, including breast cancer thus proteins such as cyclin-dependent kinases (CDK) 4/6 responsible for its regulation are considered as effective targets for cancer treatment. Due to similar properties of CDK4 and 6 their simultaneous inhibition is essential for an effective antiproliferative effect. So far, a multitude of ongoing clinical trials involving CDK4/6 inhibitors have indicated promising therapeutic effects (both when used alone or in combination with other agents). One example, the CDK4/6 inhibitor palbociclib, blocks binding of ATP in CDK4/6 (ATP-competitive inhibitor), therefore prevents retinoblastoma protein phosphorylation what finally leads to the G1 phase arrest and tumor growth suppression. Although some tumors are initially susceptible to CDK4/6 inhibitors, they might become insensitive to these therapies over time. One significant challenge in breast cancer therapy is the development of cell resistance to small-molecule inhibitors that occurs after prolonged exposure. Such insensitivity could be triggered by upregulation of CDK6 driving the necessity of developing more potent/more specific inhibitors as well as alternative strategies. Additionally, considering the kinase-independent activity of CDK6, the silencing the protein, rather than its inhibition, is more valuable. The development of a novel strategy against CDK6-centered malignancies is of great interest and importance. One of such strategies is the application of proteolysis targeting chimeras (PROTACs).

PROTACs are heterobifunctional molecules that are designed to precisely degrade the protein of interest (POI). The concept of PROTACs is based on the idea that one part of the molecule is responsible for initiation of POI degradation by proteasome. The other part of the molecule interacts with the POI and brings it in the optimal proximity to ligase so it can be ubiquitinated and consequently degraded.

The goal of the POWERTAP project (phosphoroorganic warhead for enhanced targeting of proteolysis) is to design, synthesis, and evaluation of new phosphoroorganic heterobifunctional molecules with the potential to act as a cIAP1-targeting CDK4/6 degraders. The idea of using the cIAP1 protein as a ubiquitin ligase that conducts ubiquitination of POI may be beneficial due to its autoubiquitination ability, what is especially valuable in the light that elevated level of cIAP1 has been observed for many types of malignant cells correlating with poor prognosis. The expected effect of using the designed compounds is ubiquitination of POI and cIAP1 leading to the proteasomal degradation of both proteins. Palbociclib, a well-studied and characterized CDK4/6 inhibitor of known selectivity against certain kinases will be used. If successful, the application of phosphoroorganic compounds as pro-apoptotic agents and cIAP1 selective ligands for PROTAC technology could represent an important step in the development of novel anticancer therapies.