Application of bioconjugation strategy to the synthesis of anticancer Trojan horses

Although many difficulties in the fight against cancer have been overcome in recent years, patients are still awaiting effective methods to combat this group of diseases. Chemotherapy, which works by inhibiting the division and growth of cancer cells, is effective in the treatment of many types of cancer, unfortunately, when applied to a wide spectrum of diseases it still fails. One of the most challenging problems faced by modern oncology is the effective fight against cancer stem cells (CSCs), which are the precursors of other cancer cells and play a crucial role in the process of oncogenesis. Given the unsatisfactory effectiveness of currently used chemotherapy drugs and the troublesome side effects that can result from their use, the search for new anticancer agents has become a major challenge for contemporary science.

So far, various natural compounds have been used as anticancer drugs – both in their chemically unmodified form and as derivatives obtained by modifying their native structures. The history of the discovery of new chemotherapeutics clearly shows that one of the most followed rational ways to invent effective anticancer agents is the chemical modification of natural compounds with proven high biological activity. One such natural compound is salinomycin, a well-known polyether ionophore. Tests conducted in 2009 on around 16,000 chemical compounds unequivocally demonstrated that salinomycin has an extraordinary potential to selectively kill breast cancer stem cells. No tested cytostatic drug could match the activity of salinomycin, and the best among them was nearly 100 times less effective. Another promising candidate from the group of natural ionophores with broad anticancer activity is monensin, which in our tests was more effective at destroying cancer cells compared to salinomycin and commonly used oncology drugs.

In the framework of this interdisciplinary project, we plan to create – as stated in the title – "anticancer Trojan horses", i.e., original and innovative bioconjugates of salinomycin and monensin, which should be essentially non-toxic but, after selectively entering cancer cells, would release highly bioactive components, thereby eliminating the cancer cells. Particularly interesting in this context are rationally designed prodrugs, which are hybrids (chimeras) of natural ionophores with other highly active anticancer compounds from the group of nucleoside analogs and nitrogen mustards, designed to recognize and exploit morphological and physiological differences between normal and cancer cells. The project also includes the design and synthesis of a series of innovative hybrids that exploit the characteristic features of cancer cells in the fight against themselves, such as the overexpression of vitamin receptors.

The newly synthesized hybrids will undergo *in vitro* testing as part of an interdisciplinary collaboration with oncology and biology experts from a leading national research center. Initially, the obtained bioconjugates will be tested for their antiproliferative activity against human cancer cells of varying malignancy and drug resistance levels, as well as against normal cells, to identify derivatives with a high therapeutic index. Selected hybrids will then undergo expanded testing to determine their detailed anticancer mechanism of action. The completion of all planned experiments will ultimately lead to the identification of the relationship between the structure of the derivatives and their biological activity (structure-activity relationship, SAR).

The growing interest in the search for highly active anticancer compounds, observed currently in many research groups around the world, makes this project highly relevant and, due to its direction and scope, highly original. The results obtained in this project could have practical applications in the fight against cancer (leading to the development of a new type of anticancer agents) and could also become, shortly, a contribution or even a turning point in the rational design of new and effective "anticancer Trojan horses".