

The second life of salinomycin: Chemo- and regioselective modifications of salinomycin and their influence on the anti-cancer and anti-microbial activity

Neoplastic diseases are characterized by uncontrollable and unstoppable growth and cell division which also have the ability to metastasize to other tissues and organs. According to the World Health Organization, more than eight million people die every year because of neoplastic diseases and it is estimated that within the next decades the number of people with diagnosed cancer will rise systematically. Although oncology has had several milestones in the fight against cancers, the patients are still waiting for development of effective ways to combat them. Chemotherapy, whose action is based on the inhibition of cell division, is effective towards many types of neoplastic diseases but in many others it is completely unsuccessful. On the other hand, cancer patients usually have impaired immune system and for this reason are particularly vulnerable to all types of infections, such as bacterial infections. It has been proved that half of the bacteria responsible for post-operative infections are resistant to antibiotics.

Therefore, the extremely current and important task is to search for new biologically active substances. Up to now natural compounds both in chemically unmodified form and various derivatives obtained by chemical modification of their functional groups have been used in cancer and anti-microbial treatment. Simultaneously, history of discoveries of new chemotherapeutics clearly shows that one of the easiest ways to discover new anti-cancer effective agents is chemical modification of naturally-occurring compounds with proved high biological activity, and in this group particularly interesting are ionophore antibiotics (ionophores) among which the most interesting seems to be salinomycin.

Salinomycin is currently used in veterinary medicine because of its activity against Gram-positive bacteria. In 2009 there was a breakthrough in the perception of this ionophore as a novel chemotherapeutic drug candidate. The tests conducted on over 16.000 chemical compounds proved that salinomycin shows amazing ability to kill breast cancer stem cells (CSCs), which are the subpopulation of extremely difficult to control auto-renew cells responsible for disease recurrence and metastasis. Salinomycin activity could not match any cytostatic drug tested, and the best of them was nearly 100 times weaker. Just after three years salinomycin was approved for testing on humans, and in recent years, more than 100 scientific papers describing the remarkable anti-cancer properties of this compound have been published, which proved high activity of salinomycin not only against CSCs and drug-resistant cancer cells, but also sensitizing effects of its use in conjunction with various anti-cancer drugs and radiation against the most diverse types of tumors.

In the light of these reports, a very interesting direction of research is chemical modification of skeleton of salinomycin molecule, which should significantly affect the complexing properties of derivatives obtained, and thus to improve their biological activity compared with the parent compound. Therefore, the primary aim of this interdisciplinary research project is to conduct comprehensive chemo- and regioselective chemical modification of salinomycin and to check the influence of these modifications on the structure, properties and biological activity of the completely new derivatives.

Novel salinomycin derivatives will be studied in *in vitro* tests within the interdisciplinary collaboration with experts in the field of oncology and biology both at domestic and foreign research centers. Firstly, the resulting compounds will be tested for their cytotoxic activity on human cancer cells of varying degrees of malignancy and drug-resistance, and also against normal cells in order to find derivatives of the high therapeutic index. Then, the selected compounds will undergo extended testing of their anti-bacterial and anti-parasitic activity, including activity against antibiotic-resistant hospital strains of *Staphylococcus aureus*, whose presence is a very serious problem in hospitals worldwide.

Operation of all planned studies should establish a correlation between the structure of the newly synthesized compounds and their biological activity. Dynamically growing interest in the search for highly active derivatives of salinomycin, which is currently observed in many research groups around the world, makes this project of top current interest and original as its results may help in the near future to rationally design new effective anti-cancer and anti-microbial compounds.