Blocking the TNF-TNFR2 interactions as novel approach to the ovarian carcinoma treatment

Every second in the human body there is a fight between good and evil. Good is the immune system and its armies of cells, whose task is to defend the body from diseases. Evil are pathogens, viruses, bacteria and mutant cells that are programmed to inflict damage to the body. As it often happens, good guys fight the evil ones. In the case of cancer, cells of the immune system (good guys) do not always win, because cancer cells (bad guys) have learned to cheat the immune system and escape from its supervision. For this purpose, they use molecules referred to as checkpoints of the immune system. Immune checkpoints are proteins that are found on the surface of T lymphocytes (receptors) and on the surface of tumor cells (ligands) and as a result of receptor-ligand complex formation, they inhibit the immune system (good guys do not fight the bad ones). However, the immune system can be mobilized to fight cancer cells by using immunotherapy based on blocking the binding of proteins belonging to the checkpoints.

Ovarian cancer is an important problem in women's medicine. Annually, about 23,000 new cases are diagnosed around the world and about 13,000 women die. Currently, monoclonal antibodies such as *Ipilimumab* (which blocks binding of the CTLA-4 receptor to CD80 / CD86 ligands) and *Nivolumab* and *Pembrolizumab* (which inhibit the interaction of PD1 proteins with PD-L1 / PD-L2) are used to treat ovarian cancer. Unfortunately, many patients do not respond to currently used immunotherapeutics, directed at the aforementioned proteins. The use of novel approaches in immunotherapy seems therefore necessary and can significantly affect the development of oncology.

One of the potential targets used in immunotherapy may be a tumour necrosis factor receptor (TNFR2), which is elevated on the surface of ovarian cancer cells. By blocking the binding of the TNFR2 receptor to its ligand, tumour necrosis factor (TNF) can stimulate the immune system to fight the tumour cells. In this project, we intend to block the interaction between TNF and TNFR2 proteins using small molecules, i.e. (i) peptides - fragments of TNF or LTα protein and (ii) peptidomimetics - designed to "mimic" peptides. The ability of the designed and obtained compounds to interact with the TNFR2 protein will be tested using various physicochemical and biological tests.

The identification of novel therapeutic compounds, such as those proposed in this project, could potentially revolutionize the current approach to the treatment of ovarian cancer and have a significant impact on medicine, patient well-being and survival.