Development of macrocyclic peptide antagonists of the PD-1/PD-L1 pathway. Characterization of simultaneous administration of two immunomodulating agents in antitumor response

Cancer immunotherapy has revolutionized cancer treatment during the last decade. This powerful strategy, of mobilizing the immune system to attack tumor cells, has shown impressive results with durable clinical antitumor responses and comprises a breakthrough in fight against cancer, even forcing formerly untreatable late stage tumors into complete remission. Current cancer immunotherapies involve the use of monoclonal antibodies that selectively block the immune checkpoint receptors. Immune checkpoint blockade has been selected a Breakthrough of the Year 2013 by the Science magazine. It is now clear that immuno-oncology has become the Fifth Pillar of cancer therapy alongside chemotherapy, surgery, radiation, and targeted treatments. Finally, in 2018 cancer immunotherapy became the basis of the highest scientific distinction, the Nobel Prize.

The aim of this proposal is to discover new macrocyclic peptides that would potently antagonize the interaction between the 'so-called' immune checkpoint receptors, the programed cell death protein-1 (PD-1) and the programed cell death protein ligand-1 (PD-L1). PD-1 is expressed on T lymphocyte cells and PD-L1 on tumor cells. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells. Blocking the binding of PD-L1 to PD-1 with an antagonist allows the T cells to kill tumor cells. I furthermore propose to investigate an antitumor effect of combining two agents: the macrocyclic peptide against PD-L1 and a targeted medicine agent, an antagonist of the ubiquitin-specific protease 7 (USP7). Overexpression of USP7 has been seen in numerous types of human cancer and correlate with poor prognosis of these cancers. This research should unravel the cellular and molecular basis of two highly important oncogenic pathways.