The aim of the proposed research is to discover small-molecule antagonists which would effectively antagonize the PD-1/PD-L1 interaction, mimicking the effect of the known mAbs and having significantly improved drug-like properties. The undertaken work would be aimed at design, synthesis and determination of the biological activity of novel class of human PD-1/PD-L1 inhibitors.

Binding of the programmed death-ligand 1 (PD-L1) to its target receptor, programmed cell death-1 (PD-1), suppresses the immune responses and thus results in the inhibition of T cell proliferation, cytokine release and cytotoxicity, which causes apoptosis of specific T lymphocytes. Blocking PD-1 or PD-L1 restores T-cell function and allows T cells to kill cancer cells. PD-1 and PD-L1 are the most important members of the so-called immune checkpoint regulators. Inhibition of these immune checkpoint regulators is now used in clinics around the world and was recognized with the 2018 Nobel Prize in Physiology or Medicine. Traditionally, the inhibition of PD-1/PD-L1 interactions is achieved with monoclonal antibodies (mAbs) that target PD-1 (e.g. pembrolizumab, nivolumab, cemiplimab, etc.) or PD-L1 (e.g. atezolizumab, avelumab, durvalumab). Despite medical and commercial success, mAb-based immunotherapies possess several drawbacks, including the high production cost, potential immunogenicity, immune-related adverse events (irAEs), and poor penetration of solid tumors. Small-molecule inhibitors are expected to overcome the problems associated with antibody-based therapeutics, with benefits such as oral bioavailability, better tumor penetration, longer shelf-life, and lower production costs. The search for low-molecular-weight inhibitors of the PD-1/PD-L1 is thus intensively pursued, and has also become the subject of my interest.

The main aim of my research is the construction of a novel group of the "elongated" C_2-symmetric small-molecule antagonists of the PD-1/PD-L1 immune checkpoint. The undertaken work will involve the design, synthesis, structural studies, and analysis of the biological activity of such extended PD-1/PD-L1 inhibitors. The activity of the synthesized compounds will be determined on the basis of the homogeneous time-resolved fluorescence (HTRF) bioassay. The C_2-symmetric 'dimeric type' of the PD-L1 small molecules should enhance the binding potency of the inhibitor to PD-L1 by increasing the interface interaction with the PD-L1 protein. The proposed project should lead to the development of novel small-molecule inhibitors and the discovery of new structural motifs involved in the formation of a complex with the PD-L1 protein. This should broaden our understanding of the immune checkpoint regulation.