Synthesis and evaluation of PD-L1 inhibitors based on mixed-mode scaffolds containing amino acid derivatives, short peptides, and peptidomimetics

The main goal of this research is to design, synthesize, and optimize amino acid, short peptides, and peptidomimetics linked to the anchoring scaffold of small-molecule antagonists of the cancer-related protein-protein interaction between the programmed cell death protein 1 (PD-1) and its ligand (PD-L1). The binding of these small molecules to PD-L1 and their potency and selectivity will be assessed using nuclear magnetic resonance spectroscopy (NMR), homogeneous time-resolved fluorescence (HTRF), and cell-line assays.

PD-1 and its ligand PD-L1 are involved in suppression of the immune system to prevent autoimmune diseases, to prevent killing health cells during infection, and others. When this system is dysregulated by aberrant overexpression of the PD-L1, it can be exploited by the cancer cells to avoid the organism's defense against it. Therefore the inhibition of either PD-1 or PD-L1 should lead to the reactivation of the organism's defense system. Indeed this approach has led to revolutionary results in cancer treatments and it is now known as the immune checkpoint blockade (ICB) PD-1/PD-L1-based cancer immunotherapy. Recognition of the importance of cancer immunotherapy was provided by the 2018 Nobel Prize in physiology or medicine given to James P. Allison and Tasuko Honjo ”for their discovery of cancer therapy by inhibition of negative immune regulation.” Up to now, the PD-1/PD-L1 ICB therapy has been based on monoclonal antibodies. Although the antibody-based therapies for PD-1/PD-L1 provided extraordinary results, they have some significant drawbacks therefore the development of small-molecule inhibitors capable of disrupting the PD-1/PD-L1 complex is needed.

Besides antibodies, promising results have been reported for low-molecular-weight inhibitors (peptides, small molecules, peptidomimetic, macrocycles). Worth mentioning is the fact, that although there are a variety of compounds, only very few of them conclude in clinical trials, and up to now, non was approved for the treatment. The main effort in designing new small-molecule inhibitors of PD-L1 has been put on the evaluation of central hydrophobic cores of inhibitors and there are limited examples of research on the structure-activity relationship based on the position of the solubilizer tag, mainly utilized in medicinal chemistry to improve water solubility and other physical properties. Despite, this approach may be used in commonly targeted protein with deep, small, and define pockets it shouldn’t be used for PD-L1 with its undruggable, flat, and challenging binding structure characteristic.

In the course of this project, I would like to synthesize a library of compounds that addresses the position of a solubilizing tag of the current anchoring hydrophobic core of the small-molecule PD-L1 inhibitors. This area is often overlooked, but in the challenging PD-1/PD-L1 complex this spot needs to be addressed more carefully and can be beneficial not only for the compound physical properties (solubility) but also should have an impact on the inhibitor affinities. The herein presented research utilizes the entire area of the binging surface of PD-L1 by prolonging the inhibitor structure by longer, amino acid-based, or peptidomimetic tags. In the search for the more extended PD-L1 inhibitors, amino acid derivatives and short peptides are suitable candidates. They create a perfect starting point for the new pharmacophores important for binding to the PD-1 binding site in PD-L1.