Small-molecule immune system modulators: A step forward in cancer immunotherapy

Rita C. Guedes¹, R. Acúrcio¹, A. Scomparin², R. Satchi-Fainaro², H. F. Florindo¹

¹Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal.
²Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

rguedes@ff.ulisboa.pt

Immunotherapy is nowadays a powerful strategy in cancer therapy with very exciting outcomes. In particular, modulation of immune checkpoint receptors have gained special attention. These immune regulators limit activation and proliferation of T cells and other immune cells enrolled in these signaling pathways. Under normal conditions, they are essential in modulating immune responses; however, they are also one of the major mechanisms used by tumors to evade immune system recognition and destruction. To date, several immune checkpoint receptors have been identified and used as therapeutics in oncology, as programmed cell death protein 1 (PD-1). When engaged by one of its ligands (PD ligand 1 (PD-L1) and PD ligand 2) PD-1 limits autoimmunity. PD-1 ligands are upregulated in many human cancers and their blockade could lead to activation of T cells and therefore enforce tumor recognition. In fact, PD-1/PD-L1 pathway is one of the most successful pathways in the context of clinical cancer immunotherapy with several approved drugs. The most successful therapies rely on the use of antibodies. However, despite their outstanding success, they still have numerous disadvantages as severe immune-related adverse [1, 2].

Recently, the hypothesis of small-molecule modulators as safer therapeutic alternatives has been raised. However, limited efforts have been directed toward immune checkpoint receptors. Our study is focused on the discovery of small molecules targeting PD-L1 that can block PD-1/PD-L1 interaction in order to overcome antibody therapy disadvantages. The limited structural information concerning PD-L1 led us to a detailed structural characterization based on in silico studies in order to assess structural flexibility, gating or binding pockets. Following a computer assisted drug discovery approach to achieve PD-L1 inhibitors, we accomplished a de novo design campaign based on the (2-methyl-3-biphenylyl)methanol derivatives generating several scaffolds. Potential PD-L1 inhibitors were selected using several parameters. The binding affinity and functionality of selected PD-L1 inhibitors were assessed on different human and mice cancer cell lines by ELISA and Flow Cytometry.

References

Figures

Figure 1. The crystallographic inhibitor docked and superimposed on the 5J89 structure.