DOI: 10.46991/JISEES.2025.SI1.088

Small-Molecule PD-L1 Modulators as Alternatives to Checkpoint Antibodies: Implications for Infection-Associated Immune Toxicities

Siranuysh Grabska[1,2*], Hovakim Grabski[1], Ruben Abagyan[3]

[1] L.A. Orbeli Institute of Physiology, National Academy of Sciences, Yerevan, Armenia

[2] Department of Biochemistry, Microbiology & Biotechnology, Yerevan State University, Yerevan, Armenia

[3] Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA, USA

ABSTRACT

Immune checkpoint inhibitors (ICIs), including anti-PD-1, PD-L1, and CTLA-4 antibodies, have advanced cancer therapy but are often associated with serious immune-related adverse events (irAEs). Analysis of over 80,000 monotherapy reports from the FDA Adverse Event Reporting System revealed that co-occurring infections significantly increase irAE risk - including events such as sarcoidosis, pneumonitis, colitis, hepatitis, myocarditis, and nephritis. The presented work and our initial findings [1] highlights the critical need for improved therapeutic strategies. To overcome the limitations of antibody-based ICIs - such as therapeutic efficacy, high cost, limited tissue penetration, and immunogenicity and engage new mechanism of PD-L1 internalization - we performed an *in silico* screening to identify small-molecule PD-L1 "glue" like modulators. We used ICM-Pro software with GPU acceleration to screen 1.5 million compounds from the ChemBridge library. After that, we filtered the results based on their chemical properties. Next, we selected 20,000 compounds and performed redocking. Finally, we refined the top 200 compounds for further analysis. Final candidates were selected for *in vitro* testing. Two lead compounds are currently under experimental evaluation and being compared with BMS-202, a known PD-L1 small molecule inhibitor. This combined clinical and computational approach supports the development of next-generation, low-toxicity immunotherapies.

Keywords: immune checkpoint inhibitors, PD-L1, co-occurring infections, irAEs, *in silico* screening, GPU-accelerated docking

References:

1. Grabska, S.; Grabski, H.; Makunts, T.; Abagyan, R. Co-Occurring Infections in Cancer Patients Treated with Checkpoint Inhibitors Significantly Increase the Risk of Immune-Related Adverse Events. *Cancers* **2024,** *16*, 2820. DOI:10.3390/cancers16162820

*Corresponding Author:

Siranuysh Grabska, L.A. Orbeli Institute of Physiology, National Academy of Sciences, Yerevan 0028, Armenia; Researcher at Department of Biochemistry, Microbiology & Biotechnology, Yerevan State University, 1 Alex Manoogian Str., 0025 Yerevan, Armenia.
Email: siranuysh.grabska@gmail.com