Anti-CDK4/6 PROTACs and their efficiency in degradation on different cancer cell lines

P-27-111

A. Slota[I,II], J. Plewka[III], L. Skalniak[IV], K. Magiera-Mularz[IV]

[I]Jagiellonian University, Doctoral School of Exact and Natural Sciences, Lojasiewicza Street 11, Krakow, Poland, [II]Jagiellonian University, Faculty of Chemistry, Gronostajowa Street 2, Krakow, Poland, [III]Jagiellonian University, Department of Chemistry, Gronostajowa Street 2, Krako, Poland, [IV]Jagiellonian University, Department of Chemistry, Gronostajowa Street 2, Krakow, Poland

Proteolysis targeting chimeras (PROTACs) are bifunctional compounds that consist of 3 components: a ligand binding to the targeted protein, a ligand binding to E3 ubiquitin ligase, and linker between them. PROTACs binding lead to the proteasomal degradation of targeted protein by bringing it to the proximity of the E3 ligase [1]. Due to ability of PROTACs to selectively decrease the level of targeted proteins, their use can be extended to the anticancer treatment. Cyclin dependent kinases 4 and 6 (CDK 4 and 6) are well-known targets in anticancer therapies. Several CDK4/6 inhibitors have been approved by US Food and Drug Administration (FDA) and are being administrated to breast cancer patients [2]. By combining the effectiveness of anti-CDK4 and CDK6 compounds with the properties of PROTACs, it has been demonstrated that they can work more efficiently than FDA-approved therapies [3]. In this study, commercially available CDK4 and CDK6 PROTACs, are tested thoroughly for their activity, using among all Western blot technique to assess how PROTACs affect the phosphorylation of the retinoblastoma (Rb) protein - a tumor suppressor protein that is highly dysfunctional in many cancers, and the levels of CDK4 and CDK6 in various human and mouse cancer cell lines. The conducted research reveals variations in the activity of these compounds across different cell lines and dose-dependency in both the degradation of targeted CDK4/6 and the phosphorylation levels of Rb protein.

Funding sources from the National Science Centre, Poland, grant UMO-2021/43/B/NZ7/03170

[1] Goel S et al. Targeting CDK4 and CDK6 in cancer. Nat Rev Cancer. 2022;22(6):356-372.
[2] Spring LM et al. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. Lancet. 2020;395(10226):817-827.
[3] Wu X et al. Distinct CDK6 complexes determine tumor cell response to CDK4/6 inhibitors and degraders. Nat Cancer. 2021;2(4):429-443.