Poster

EBNA1 PROTAC Development

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Epstein Barr Virus (EBV), one of the most common human viral infections, is one of the few viruses known to lead to the development of cancers, such as Hodgkin lymphoma, Burkitt's lymphoma, and nasopharyngeal carcinoma (NPC) [1]. NPC has a high mortality of patients with advanced and recurrent disease but very few druggable targets [2].

EBV encoded nuclear antigen 1 (EBNA1) has been shown to be essential for the viral genome maintenance and control of viral gene expression in EBV and is found in all EBV-carrying tumours, playing a very important role in the oncogenic process in human malignancies [3]. This indicates it to be a key druggable target which could be exploited, particularly as it has no cellular homologue. Some binding compounds are already available but not developed into clinically applicable drug molecules, often not having a high enough specificity to be used without off-target toxicity [3].

Proteolysis targeting chimeras (PROTACs) are bifunctional molecules consisting of three components: a ligand recruiting an E3 ubiquitin ligase, an appropriate linker, and a ligand recruiting a target protein of interest (POI) [4]. These hijack the ubiquitin-protease system (UPS) through formation of a ternary complex of the E3 ligase, PROTAC, and POI in a favourable orientation to tag the POI with ubiquitin to undergo subsequent degradation by the proteasome [4]. The catalytic nature of PROTACs allows them to act sub stoichiometrically which significantly lowers the amount of PROTAC required compared to a small molecule [4]. This lower exposure for the same level of target degradation leads to fewer off-target toxicity effects [4], a key issue with current EBNA1 small molecule drugs. The cooperativity observed with the ternary complex increases the selectivity of the PROTAC over individual ligands, which allows for binding of ligands with relatively weak affinities [4]. This indicates a great advantage for working to convert current EBNA1 binding molecules into PROTAC drugs.

Therefore, this project aims to express, purify, and crystallise EBNA1 protein constructs to test a library of compounds developed by E. Taylor-Newmann, and use structure-based PROTAC design to develop a series of PROTAC-drug molecules against EBV. This protein awaits characterisation by structural techniques (x-ray crystallography and cryogenic electron microscopy), though will be aided by characterisation by biophysical techniques, including spectral shift, thermal shift assay, and surface plasmon resonance.

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