Computational drug design strategy targeting herpesviral kinases

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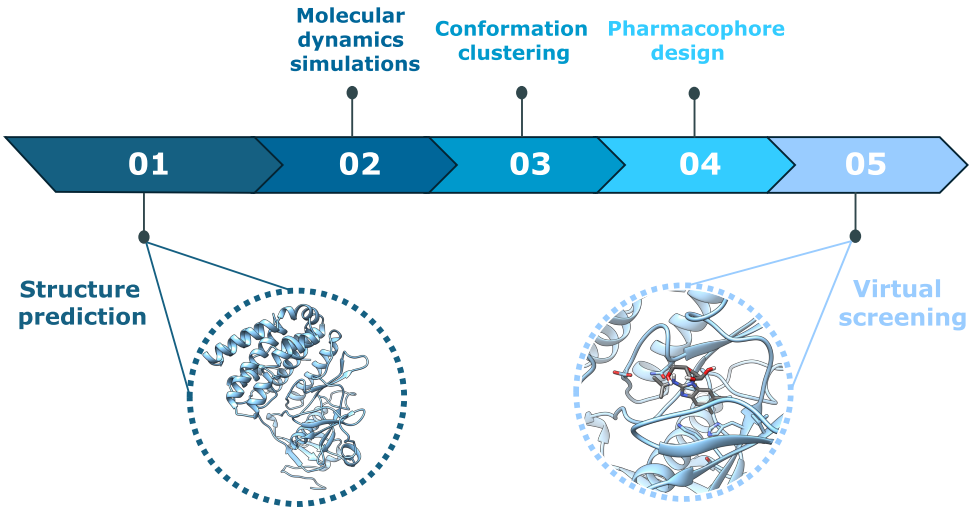
Herpesviruses are a large family of DNA viruses that establish lifelong persistence in humans. A key feature of these viruses is their ability to remain latent after primary infection and reactivate under certain conditions, such as immunosuppression. [1] Among them, human cytomegalovirus (HCMV) and the Epstein–Barr virus (EBV) are of particular clinical importance. HCMV can cause severe disease in immunocompromised individuals and newborns, while EBV is best known as the cause of infectious mononucleosis and is associated with several malignancies. Despite their clinical relevance, treatment options during active infection remain limited, especially for HCMV due to drug toxicity and the emergence of antiviral resistance. [2,3]

HCMV and EBV encode viral kinases, pUL97 and BGLF4, respectively, which are critical for viral replication, nuclear egress, and the modulation of specific host processes, including cell cycle progression and DNA damage signaling. [1] While these kinases share functional similarities with human cyclin-dependent kinases (CDKs), they diverge significantly in sequence and domain architecture, especially within their N-terminal regions and key kinase motifs. Although pUL97 has been established as a therapeutic target, and BGLF4 is increasingly recognized as a promising candidate, detailed structural and pharmacological characterization, particularly of BGLF4, remains limited.



To address this gap, we employ a structure-guided strategy to characterize and target the ATP-binding sites of pUL97 and BGLF4. High-confidence structural models of both kinase domains, generated by AI-based protein structure prediction tools, serve as the basis. The most representative protein structures of clustered all-atom molecular dynamics simulations were compared with experimentally resolved human CDK structures to identify key residues and structural differences within the ATP-binding pockets. Based on this analysis, we aim to develop pharmacophore models to identify novel small-molecule inhibitors targeting the viral kinases, thereby enabling the identification of antiviral inhibitors and advancing the treatment options for HCMV and EBV.

[1] T. Jacob, C. van den Broeke, H.W. Favoreel, Viral serine/threonine protein kinases. *J Virol.*, **2011**, *85*, 1158–1173.
[2] N. S. Lurain, S. Chou, Antiviral drug resistance of human cytomegalovirus. *Clin Microbiol Rev,* **2010**, *23*, 689–712.
[3] Y. Zhang, H. Lyu, R. Guo, X. Cao, J. Feng, X. Jin, W. Lu, M. Zhao, Epstein–Barr virus-associated cellular immunotherapy. *Cytotherapy*, **2023**, *25*, 903–912.