Small molecule inhibitors show treatment potential for EBV-associated cancers

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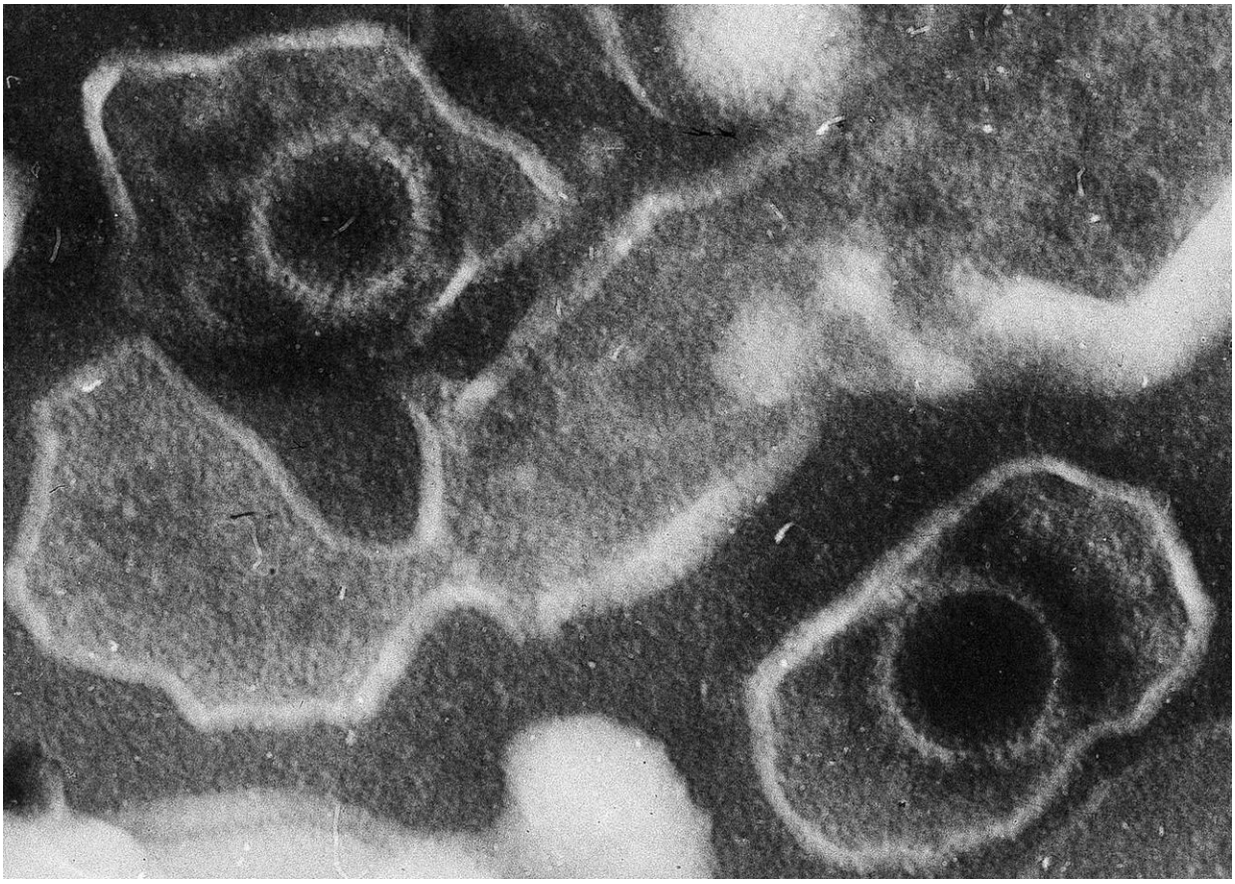

This electron microscopic image of two Epstein Barr Virus virions (viral particles) shows round capsids—protein-encased genetic material—loosely surrounded by the membrane envelope. Credit: DOI: 10.1371/journal.pbio.0030430.g001

Researchers at The Wistar Institute have created a drug candidate for cancers associated with Epstein-Barr Virus (EBV), the virus that causes infectious mononucleosis. In a study published in *Science Translational Medicine*, they described inhibitors of an EBV protein called Epstein-Barr Nuclear Antigen 1 (EBNA1), showing efficacy in preclinical models.

More than 90% of adults are infected with EBV worldwide. The virus establishes life-long, latent infection in B lymphocytes, which is, in rare cases, associated with development of different cancer types, including Burkitt's lymphoma, nasopharyngeal carcinoma (NPC) and Hodgkin's lymphoma. EBNA1 is a DNA-binding protein critical for virus replication and for continuous proliferation of infected cells.

"EBNA1 is found in all EBV-associated tumors and does not look like any other protein in the human body," said Paul M. Lieberman, Ph.D., Hilary Koprowski, M.D., Endowed Professor, leader of the Gene Expression & Regulation Program at Wistar, and corresponding author on the study. "These characteristics, along with the protein's particular structure, make EBNA1 a very attractive therapeutic target."

Based on the 3-D structure of the protein, Lieberman and colleagues created a class of small molecule inhibitors of EBNA1 that block its ability to bind to DNA, as confirmed in EBV-infected NPC cells.

The efficacy of these inhibitors was tested in vivo in relevant mouse models of EBV-associated cancers, established by transplanting tumor cells or patient-derived tumor samples into immunocompromised mice. Researchers observed a dramatic reduction in tumor growth in all conditions tested. The tumor growth inhibition was greater than that achieved with gamma irradiation or chemotherapy, which are the standard-of-care treatments for NPC patients.

"It has taken the lab nearly a decade to go from concept to identifying a clinical candidate," said Troy E. Messick, Ph.D., first and co-corresponding author on the study and senior staff scientist in the Lieberman Lab. "We are excited about the activity of these inhibitors in a number of preclinical studies and look forward to the next steps of development."

Pharmacological inhibition of EBNA1 had profound effects on gene expression of both EBV and host-cell genes, which correlated with substantial decrease in EBV DNA copy number and suppression of EBV-driven tumor promoting pathways.

Importantly, tests showed a favorable pharmacological profile and little to no evidence of drug resistance after prolonged treatment.

More information: T.E. Messick el al., "Structure-based design of small-molecule inhibitors of EBNA1 DNA binding blocks Epstein-Barr virus latent infection and tumor growth," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aau5612

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