

POSTER 46**HIF-1 α -ACTIVE NATURAL PRODUCT EXTRACTS WITH THERAPEUTIC POTENTIAL FOR KSHV RELATED DISEASE**

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We recently proposed an “Oncoweed Hypothesis” to partly explain the geographical variation in KSHV prevalence and disease. We developed a KSHV reactivation screen and used it to identify natural products from KSHV endemic regions that reactivate KSHV from latency. It has been reported that KSHV can also be reactivated during hypoxia. The transcription factor hypoxia inducible factor alpha (HIF1 α) is a key regulator of cellular responses to hypoxic stress. We sought to test natural products extracts identified as having activity in a HIF1 α assay in our KSHV reactivation screen. Viral reactivation has been proposed as a novel therapeutic strategy for herpesvirus related cancers in which the virus is maintained in latency and therefore inaccessible to current anti-herpesvirus agents. Since KSHV latently infects malignant cells in Kaposi’s sarcoma (KS) and primary effusion lymphoma (PEL), novel therapeutics that cause viral reactivation could play a role in future treatment strategies.

Crude natural products extracts from the DTP repository were solubilized at concentrations ranging from 25 to 200 μ g/ml and incubated with a KSHV latently-infected cell line, BCBL-1, at 50,000 cells per well for 4 days. KSHV viral loads were determined using qPCR and compared to unstimulated and phorbol ester stimulated (sodium butyrate) controls. Selected time points were assayed using a KSHV whole genome array to profile changes in viral gene expression. Four extracts induced potent reactivation of KSHV from latency, resulting in viral loads more than 1 log higher than sodium butyrate positive controls. Extracts from Rubiaceae species having a geographical distribution similar to that of KS were found to be reactivators of latent KSHV, while a sampling of Rubiaceae from other regions failed to demonstrate activity. The activity of the extracts was confirmed in a 96 hour time course study. Viral gene expression analysis showed an upregulation of viral genes in an ordered manner confirming viral reactivation.

Our results show that screening natural products for targets such as HIF-1 α can be informative for other targets such as KSHV based on the intersection of the hypoxia pathways and viral biology.