NOVEL AUTOPHAGY INDUCER INHIBITS HEPATITIS B VIRUS S ANTIGEN SECRETION

ZUZANA SMAHELOVA[a], MARKETA PIMKOVA POLIDAROVA[a,b], JINDRICH SEDLACEK[a,b], OLENA BEREHOVSKA[a,b], VACLAV JANOVEC[a,b] , MICHAEL ADAMEK[a], IVAN HIRSCH[a,b], ALES MACHARA[b] KLARA GRANTZ SASKOVA[*a]

[a] Department of Genetics and Microbiology, Charles University and Research Center BIOCEV, Prumyslova 595, 25250 Vestec, Czech Republic
[b] Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo n. 2, 16610 Prague, Czech Republic
zuzana.smahelova@natur.cuni.cz

Chronic hepatitis B (CHB), a liver infection caused by the hepatitis B virus (HBV), affects more than 300 million people worldwide. If left untreated, CHB can progress to liver cirrhosis and hepatocellular carcinoma, resulting in over 800,000 deaths annually. While current therapies based on nucleot(s)ide analogues effectively slow disease progression and reduce viral load, they require lifelong adinistration. Pegylated interferon alpha therapy can achieve clearance in a small fraction of patients but is associated with significant side effects.[1]

The primary goal of CHB treatment is to eliminate HBV DNA from liver cells, though this remains a considerable challenge. Recent therapeutic research is focused on targeting different stages of the viral life cycle, with a particular emphasis on reducing the secretion of the HBV surface antigen (HBsAg). HBsAg is a key factor in the disruption of immune system function in CHB. Lowering HBsAg levels could improve the efficacy of combination therapies.[2]

HBsAg is a transmembrane protein produced in the endoplasmic reticulum (ER) and may be secreted via ER-phagy, a process involving the degradation of part of the ER by vacuoles or lysosomes. It is then transported to multivesicular bodies, where infectious virions assemble. These virions, along with empty HBsAg subviral particles, are subsequently released from the cell through exocytosis.[3] Disrupting the HBsAg trafficking pathway could potentially reduce the amount of secreted HBsAg.

In this study, we introduced a small-molecule compound that enhances proteasome activity and autophagy by triggering downstream events dependent on Nuclear Factor Erythroid 2-related factor 1 (NRF1), without inducing ER stress. Notably, this compound significantly reduced HBsAg secretion in both *in vitro* HBV infection models (Figure 1) and HBV-producing cell lines.

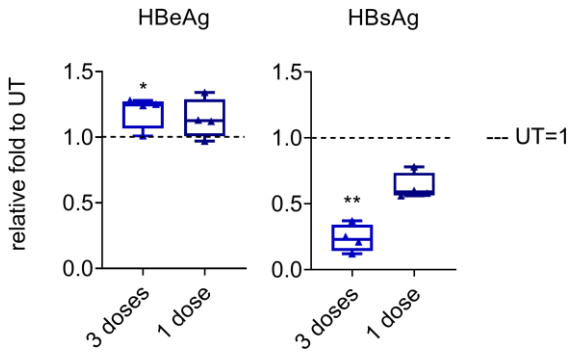

Figure 1. Effect of tested compound on secretec HBV antigens E (HBeAg) and S (HBsAg) by HBV-infected HepG2-NTCP cells. Results represent relative fold change to untreated infected HepG2-NTCP (UT). N=4, Friedmann test with uncorrected Dunn|s post/hoc test for multiple comparissons: *=p≤0.05, **=p≤0.01

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