Inhibition of HBsAg secretion by a novel autophagy inducer

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Chronic hepatitis B (CHB) is a viral liver infection caused by hepatitis B virus (HBV), affecting over 300 million people world-wide. Untreated CHB can lead to liver cirrhosis and hepatocellular carcinoma, causing over 800,000 deaths annually. Current nucleot(s)ide analogue-based therapies effectively slow disease progression and reduce viral load, but require life-long application. Pegylated interferon alpha therapy clears the virus in a small percentage of patients, but has serious side effects. Therefore, a universally effective and definitive cure of CHB is still elusive.

The primary objective of CHB therapy is to clear HBV DNA from hepatocytes, yet this goal is difficult to achieve. Recent therapeutic investigation targets multiple steps of the virus life cycle, including the reduction of HBV S antigen (HBsAg) secretion. HBsAg plays a significant role in immune system dysregulation in CHB. Reducing HBsAg levels may enhance the effectiveness of combined therapies.

HBsAg is a transmembrane protein synthesized on the endoplasmic reticulum, secreted possibly through ER-phagy (autophagy of endoplasmic reticulum), and transported to multivesicular bodies. Here, infectious virions assemble and are released, along with empty HBsAg subviral particles, through exocytosis.

Our goal is to inhibit HBsAg secretion by targeting its trafficking pathway. Here, we present a small-molecule compound that increase proteasome activity and autophagy through activation of Nuclear Factor Erythroid 2-related factor 1 (NRF1)-dependent downstream events. This compound effectively decreases HBsAg secretion in both *in vitro* HBV infection and HBV-producing cell lines.