How to achieve HBV cure?

Fabien Zoulim

Head of Hepatology Department and Head of the Viral Hepatitis Research Laboratory

Current therapies of chronic hepatitis B remains limited to either pegylated-interferon-alpha (Peg-IFN), or one of the five approved nucleoside analogues (NAs) treatment. While viral suppression can be achieved in the majority of patients with high-barrier-to-resistance new-generation NAs, i.e. entecavir and tenofovir, HBsAg loss is achieved in only 10% of patients with both classes of drugs after a follow-up of 5 years. Attempts to improve the response by administering two different NAs or a combination of NA and Peg-IFN have been unsuccessful. Therefore, there is a renewed interest to investigate a number of steps in the HBV replication cycle and specific virus-host cell interactions as potential targets for new antivirals. These includes a direct inhibition of viral replication: entry inhibitors, targeting cccDNA formation and structure, silencing cccDNA, targeting viral transcripts with siRNA, capsid assembly modulators, targeting viral envelope proteins. Restoration of immune responses is a complementary approach which includes the restoration of innate immunity against HBV for instance with TLR agonists or delivery of specific antiviral cytokines, and restoration of adaptive immunity with inhibitors of negative check point regulators, therapeutic vaccine, or engineering of specific T cells. Novel targets and compounds could readily be evaluated using both relevant in vitro and newly developed in vivo models of HBV infection. The addition of one or several new drugs to current regimens should offer the prospect of markedly improving the response to therapy, thus reducing the burden of drug resistance, as well as the incidence of cirrhosis and hepatocellular carcinoma.