Hepatology Snapshot:

Hepatitis B virus – recent therapeutic advances and challenges to cure

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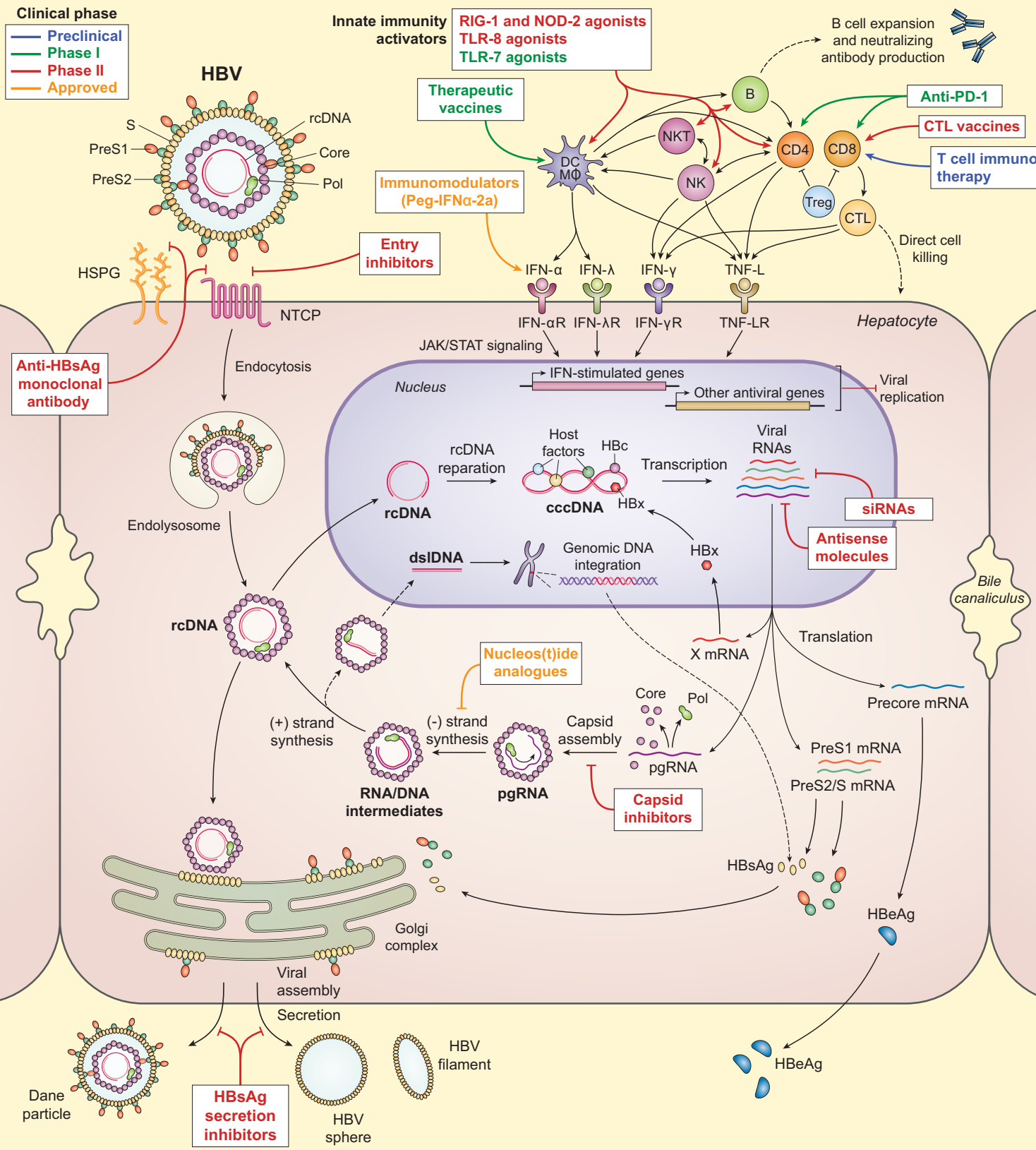
Karim Mouzannar[1], T. Jake Liang[1,*]

[1]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, 20892, USA.
*Corresponding author. Address: Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, 20892, USA; Tel.: +1-301-496-1721. E-mail address: jakel@bdg10.niddk.nih.gov (T.J. Liang)



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Chronic hepatitis B (CHB) remains a major global health problem affecting more than 240 million people with high liver-related morbidity and mortality worldwide. This snapshot summarizes available HBV therapeutic strategies and highlights their corresponding stages of development from late preclinical to various clinical phases, which are indicated by different colors. The complete HBV life cycle is depicted including attachment, entry, uncoating, trafficking to nucleus, covalently closed circular DNA (cccDNA) formation, transcription, translation, encapsidation, assembly, and secretion. Above this illustration, immune cells involved in innate and adaptive immune responses activated by HBV infection are shown with their mechanisms of antiviral action.

Current antiviral therapy does not cure CHB due to the persistence of cccDNA, the HBV transcriptional template that is formed during infection in the hepatocyte nucleus. The scientific community defines a functional cure as the equivalent of an acute resolved infection. It results in the loss of HBsAg with or without seroconversion of anti-HBs antibodies, undetectable viral DNA in serum and the persistence of the transcriptionally inactive cccDNA, therefore making it possible to consider stopping treatment. Complete cure has the same characteristics as functional cure but with the physical elimination of cccDNA[1] – this goal may be difficult to achieve.

The modes of action of direct-acting antivirals and host-targeting agents have been described previously.[2,3] Briefly, approved antiviral drugs for CHB treatment include pegylated interferon-α and 6 nucleo(s)tide analogues. The entry inhibitor Myrcludex B and capsid inhibitors (for example, Morphothiadin, JNJ 56136379, ABI-H0731) are in clinical phase II. Small interfering RNA (VIR-2218) that interferes and destroys viral RNA, antisense molecules (IONIS-HBVRx) that bind to viral mRNA to prevent it from translating into viral protein, HBsAg secretion inhibitors (REP 2139 and REP 2165), monoclonal anti-HBsAg antibody (GC1102), and RIG-1/NOD-2 agonists are in clinical phase II. Immunomodulators such as Toll-like receptor agonists, programmed death-1 inhibitors, and therapeutic vaccines are used to enhance innate and adaptive immune responses to control HBV infection and are in clinical phase I. Currently, clinical trials are assessing the additive or synergistic effects of combination therapies.[1]

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Equal contribution for both authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.015.

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