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Hot News

Hepatitis B Gene Therapy Coming to Age

The major pandemics caused by chronic viral infections is produced by HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV), with estimates of 38, 70, and 250 million people worldwide, respectively (Fig. 1). During the last couple of years, the advent of direct oral antivirals has allowed pursuing global HCV eradication. In an unprecedented manner, these drugs cure more than 95% of hepatitis C patients when given for only 2-3 months. The enthusiasm on HCV has renewed the interest for curative strategies for both HIV and HBV. However, important biological differences between all three viruses may preclude envisioning a similar rapid success for either HIV or HBV than for HCV infection.

As shown in figure 1, once infection of targeted cells has occurred, the viral genetic material only replicates in the cytosol for HCV whereas it enters the nucleus and integrates into the chromosomes as provirus for HIV or is converted in a circular covalently closed form (cccDNA) for HBV (Fig. 1). Blocking viral nucleic acid replication for a minimum lag of time allows definitive clearance of HCV infection, with degradation of residual cytoplasmic HCV-RNA strands. In contrast, blocking viral replication has only a transient effect on HIV or HBV, as mRNA expression resumes following treatment discontinuation, given the stability of the HIV provirus or the HBV cccDNA, respectively.

The European Liver meeting took held in Paris on April 2018. A relatively large number of presentations addressed distinct new hepatitis B therapeutic strategies. Table 1 summarizes some of the molecules that have been investigated so far with more promising results, grouping them into distinct drug classes (*Soriano et al. Exp Op Inv Drugs 2017;26:843-51*), based on their distinct mechanism of action and targeted steps in the HBV life cycle (Fig. 2).

Considering the pros and cons of novel HBV therapeutic candidates, it has become apparent new HBV

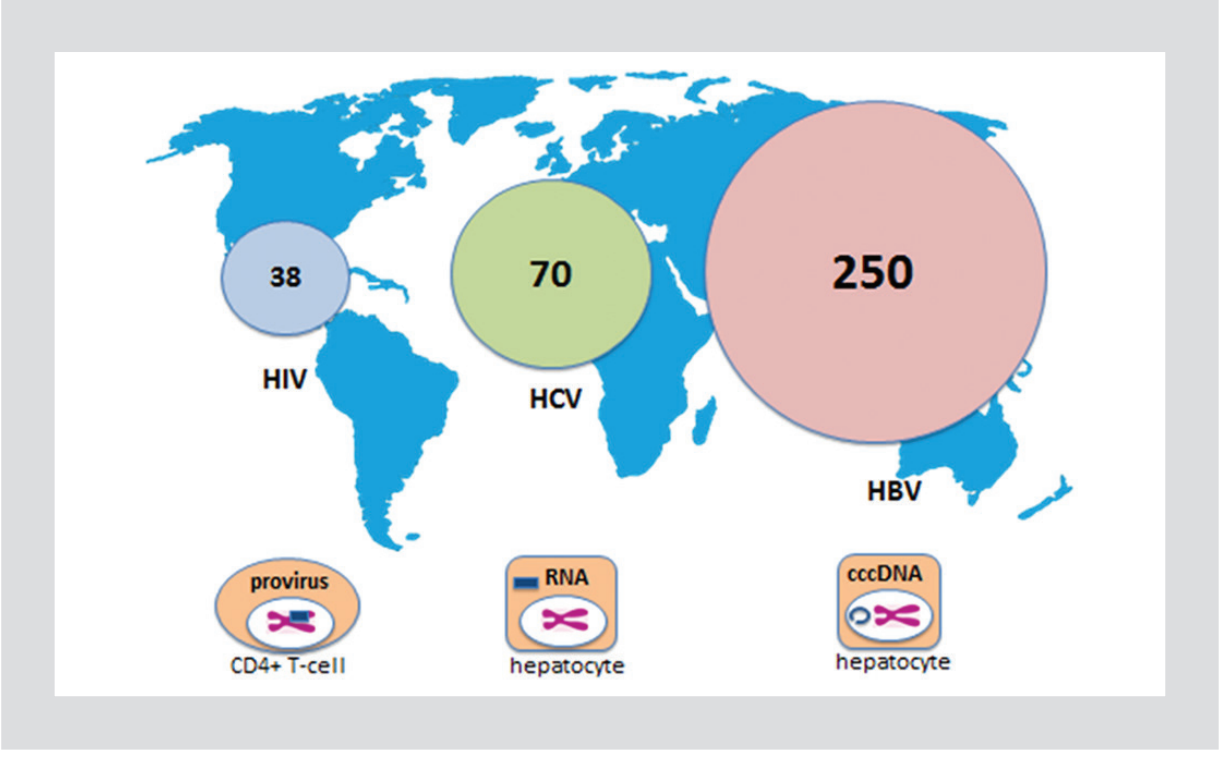

Figure 1. *Major chronic viral pandemics.*

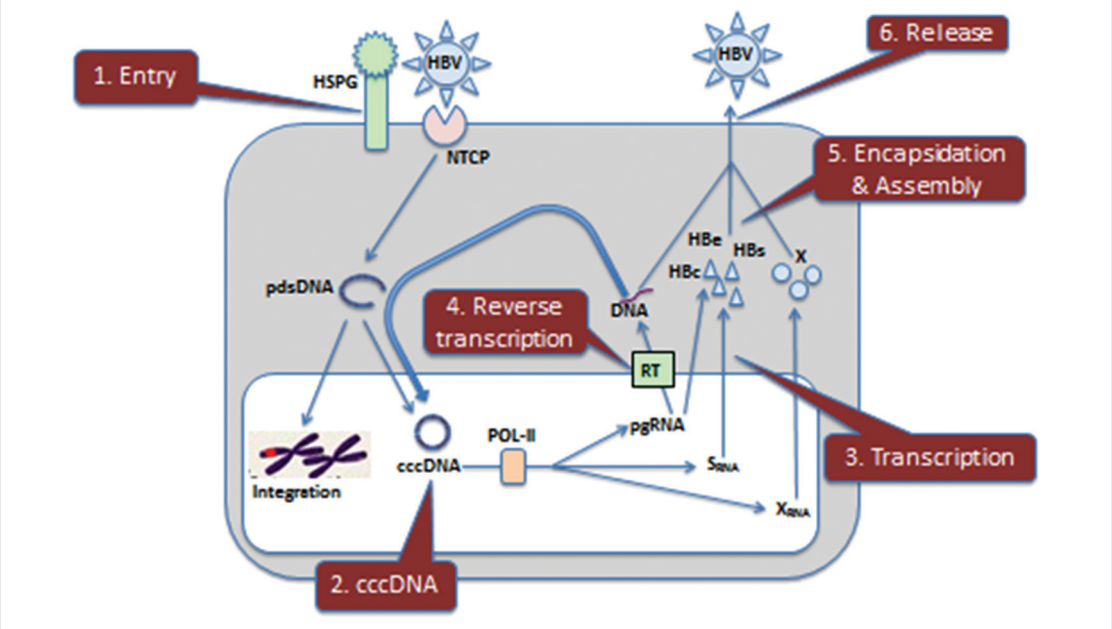

Figure 2. *Major hepatitis B virus therapeutic targets.*

Table 1. New HBV armamentarium

Drug class	Mechanism	Drugs
Antivirals (life cycle)	Entry inhibitors	Myrcludex*
	cccDNA cleavage (gene editing)	CRISPR/cas9, TALENS, ZFNs
	Transcription inhibitors (RNA interference)	ARC-520, ARO-HBV, ARB-1740, AB-729, ALN-HBV, TKM-HBV, RG-7334
	Polymerase inhibitors	TAF, CMX-157, AGX-1009, besifovir, lagociclovir
	Capsid blockers	GLS-4, NVR 3-778, JNJ-379, AT-130
	Release inhibitors	Rep-2139, Rep-2165
Immune-modulators (immunity)	Innate immunity	TLR-agonists (GS-9620) Anti-PD1 (Nivolumab)
	Adaptive immunity	Therapeutic vaccines (GS-4774, TG-1050) Engineered T cells

Soriano et al. Exp Op Inv Drugs 2017;26:843-51. HBV: hepatitis B virus, cccDNA: covalently closed circular DNA

gene therapies among the most attractive. Several advances have contributed to position gene therapy in front within the experimental HBV armamentarium. First, progresses in delivery systems, including the use of polymers and nanoformulations have allowed developing easier forms of administration that now are becoming subcutaneous and monthly. Second, the synthetic production of oligonucleotide formulations has reduced costs. Third, the specificity against HBV is higher than for other experimental agents, as immune modulators that enhance innate immunity, such as TLR agonists (i.e., GS-9620) or checkpoint inhibitors

(i.e., nivolumab). Fourth, significant declines in serum hepatitis B surface antigen (HBsAg) are demonstrated during gene therapy, which have never been seen using the most potent polymerase inhibitors (i.e., tenofovir or entecavir). Finally, unanticipated significant reductions in cccDNA are seen with HBV gene therapy, most likely as prove of an indirect benefit of waning the immunosuppressive effect of large over amounts of HBsAg released by infected hepatocytes that contributes to T-cell exhaustion.

In a pioneering study, Roche was the first to publish the potent effect of an oral small molecule that blocked HBV gene expression (*Mueller et al. J Hepatol 2018;68:412-20*). The drug belonged to the dihydroquinolizinone class, and directly or indirectly modified viral RNAs, promoting their degradation. This post-transcriptional silencing was accompanied by rapid drops in HBV-DNA and more importantly in serum HBsAg in the humanized mice. However, Roche decided to discontinue any further clinical development of the drug.

Nowadays, two major groups of agents are being developed as HBV gene therapies. At this time, interference RNA (iRNA) molecules and nucleic acid polymers (NAPs) are the most promising. Overall, iRNA is double-stranded RNA molecules, 20 nucleotides long. One strand matches a segment of specific HBV mRNA and induces its degradation. Several iRNA molecules have entered into Phase II clinical trials (*Flisiak et al. Exp Op Biol Ther, in press*), including ARB-1467 and AB-729 (Arbutus), ARO-HBV (Arrowhead), ALN-HBV (Alnylam), and IONIS-HBVRx (Ionis). In most cases, they are tested as part of combination therapy with nucleos(t)ide analogs and/or peginterferon.

NAPs are phosphorothioate 40 length oligonucleotides that no map any HBV sequence. However, they interact with a liver host target protein (apolipoprotein-like) and result in specific inhibition of HBV mRNAs. This is followed by rapid suppression of HBsAg release (*Roehl et al. Mol Ther Nuc Acids 2017;8:1-12*). In a pilot study with intravenous REP-2139, investigators from Replicor demonstrated strong reductions in HBV-DNA along with significant drops in HBsAg and seroconversion in some patients. More interestingly was the recognition of significant reductions in hepatic cccDNA, most likely a result of an indirect effect following the removal of large amounts of HBsAg from the bloodstream that contributes to impaired T-cell responses in chronic hepatitis B patients (*Bazinet et al. EASL, Paris 2018; abstract FRI-343*). An improved NAP, named REP-2165 and subcutaneous administration are currently being tested.

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Dr. Robert Redfield Appointed as New CDC Director

Well-known AIDS researcher Robert Redfield picked to lead the CDC on March 2018. He is one of the HIV/AIDS pioneers in the United States. During two decades at the Walter Reed Army Institute of Research, in Bethesda, MD, he made pivotal contributions, highlighting the importance of heterosexual HIV transmission, developing the Walter Reed staging system for HIV infection, and demonstrating that active HIV replication takes place during all stages of HIV disease.

In 1996, he was one of the cofounders of the Institute of Human Virology in Baltimore, MD. Nowadays, he was running a treatment network for HIV and hepatitis C patients. With this background, he would be well prepared to combat one of the DHHS and CDC's top priorities, the opioid epidemic (*Kolodny et al. JAMA 2017;318:1537-8*).

In an interview, Robert Gallo, director of the Institute of Human Virology, said "Redfield is a dedicated and compassionate physician who truly cares about his patients and is deeply committed to ensuring patients receive the highest quality of care possible. Dr. Redfield has served his country well, and consistently demonstrates strong public health instincts that are grounded in science and clinical medicine. In my view, despite the loss to our institute, I believe this makes him the ideal candidate to direct the CDC".

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