Drugs in the Pipeline for HBV

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INTRODUCTION

Global Burden

Despite the introduction of an effective vaccine almost 40 years ago, hepatitis B virus (HBV) remains a major cause of chronic liver disease. Globally, an estimated 257 million people have chronic hepatitis B (CHB), and 600,000 to 1 million deaths occur annually because of the end-stage complications of cirrhosis and hepatocellular carcinoma. The global burden of disease attributable to chronic viral hepatitis (B and C combined) has increased over the last 2 decades. Viral hepatitis was the seventh leading cause of death worldwide in 2013, compared with tenth in 1990.

Hepatitis B Virus Life Cycle

The complex HBV life cycle has recently been extensively reviewed and presents multiple potential antiviral targets. Replication begins when circulating HBV binds to a...
hepatocyte through interactions between hepatitis B surface antigen (HBsAg) and sodium taurocholate cotransporting polypeptide (NTCP) as a receptor. Subsequently, the viral capsid is released into the cell and traffics to the nuclear pore, where the HBV relaxed circular DNA (rcDNA) can be delivered to the nucleus. In the nucleus, the rcDNA is converted by host polymerases to covalently closed circular DNA (cccDNA), which is a nuclear mini-chromosome-like moiety that exists in low copy numbers in infected hepatocyte nuclei. cccDNA is thought to be relatively stable in quiescent hepatocytes but may be lost during cell division.

cccDNA molecules function as templates for transcription of full-length pregenomic RNA (pgRNA) and subgenomic messenger RNAs (mRNAs) that encode viral proteins. These proteins include HBV polymerase/reverse transcriptase (pol/RT), hepatitis B x-protein, core protein, hepatitis B e-antigen (HBeAg), and HBsAg. HBV pol/RT binds to pgRNA and is encapsidated within 120 core protein dimers to form a nascent viral capsid, where the pgRNA is reverse transcribed to produce viral rcDNA. The capsid can then either acquire an HBsAg-containing envelope and be secreted as infectious virus or traffic back to the nucleus and replenish the cccDNA pool. The lifespan of individual cccDNA molecules is not well understood and in the setting of an antiviral immune response may be shorter than the life of a hepatocyte.

In cell culture systems, cccDNA has been estimated to have a half-life of approximately 40 days, whereas human studies evaluating cccDNA turnover have suggested that populations of cccDNA can convert from mutant to wild type (or versa) in as little as 12 weeks. However, cccDNA may persist longer in a residual pool of quiescent nondividing hepatocytes. cccDNA is not known to tether to the nuclear spindle, and most cccDNA is thought to be lost during hepatocyte expansion, as occurs, for example, following an immune response and clearance of infected cells. Importantly, HBV is not a cytopathic virus; thus, in the absence of an adequate antiviral immune response, there is not thought to be a virus-derived trigger to drive hepatocyte loss or proliferation.

Possible targets for therapeutic intervention include HBV binding and absorption, capsid dissociation, cccDNA formation, gene expression, protein synthesis, capsid assembly, viral DNA synthesis, capsid envelopment, and virion release. Most of these targets are being addressed by ongoing therapeutic research programs. In addition, because attenuation of the HBV-specific immune response is a key feature of chronic HBV infection, multiple approaches are being explored to restore immune responsiveness to allow immune-mediated clearance of HBV-infected hepatocytes.

**Goal of New Therapies**

The ultimate goal of ongoing research for novel HBV therapeutics is eradication of the cccDNA viral reservoir. Because measurement of cccDNA itself is challenging, requiring a biopsy and sophisticated assays that have not yet been standardized, surrogates for cccDNA loss or inactivation are required. These surrogates must include a sustained viral response (SVR), lack of viral rebound with persistent normal liver function and lack of inflammation, after a finite course of therapy. In addition to loss of detectable serum HBV DNA, additional biomarker changes expected to coincide with such improved off-treatment responses include a loss of serum HBeAg and either loss or a decline to a stable low level of detectable serum HBsAg. Loss of HBsAg in particular, although uncommon with current therapies, has been associated with sustained posttreatment virologic responses and is generally considered a clinical marker of a functional cure, indicating that treatment is no longer required. Although HBsAg clearance is accepted as a desirable
endpoint, its achievement has been somewhat confounded by the discovery that, at least in chimpanzees, circulating HBsAg may arise from HBV integrants, which, although unable to produce complete virus, may produce a significant fraction of the total circulating HBsAg.\textsuperscript{15} Unfortunately, even in the rare instances in which HBsAg loss has been achieved, reactivation in the setting of immunosuppression is possible. The exact mechanisms by which immune control and escape occur are only partially understood, suggesting that the understanding of even such “functional cures” is still evolving.\textsuperscript{16}

Given the challenges of defining what constitutes a “cure” for CHB (functional or otherwise) with today’s technology, the author proposes that a more appropriate definition of the clinical goals for current studies may be similar to those used as hepatitis C therapeutics were being developed. An initial objective should be “sustained viral response” as measured by lack of viral DNA or antigen rebound for a fixed period off treatment. Subsequently, “cure” could be declared in individuals in whom SVR is maintained over a more extended time frame.

**Current Options**

Current options for CHB therapy include nucleos(t)ide analogues and interferons. In brief, nearly all patients respond during treatment with nucleos(t)ide analogues, but beneficial responses are rarely sustained after treatment. Interferons, in contrast, may provide sustained responses more frequently, but only in a limited subset of patients defined primarily by HBV genotype and disease characteristics.\textsuperscript{17–19} Although neither of these therapies, alone or in combination, has dramatically increased cure rates in patients with CHB, it is highly likely that a successful curative regimen will entail combinations with either or both of these modalities.
Interferons

In 1991, interferon alfa-2b became the first treatment approved for CHB therapy; pegylated interferon alfa-2a was approved in 2005. Interferons are typically administered by subcutaneous injection for up to 12 months and can elicit durable posttreatment suppression of HBV replication and antigenemia. Tolerability can be poor, however, and clinically significant response rates are generally achievable by only a small subset of patients.

Nucleos(t)ide Analogues

The most commonly used therapies for CHB at present, nucleos(t)ide HBV pol/RT inhibitors, profoundly inhibit HBV DNA synthesis, frequently reducing serum HBV DNA to levels at the limit of quantification. This response is associated with improvement of hepatic fibrosis and reduced risk of hepatocellular carcinoma. All agents in this class have similar modes of action. Lamivudine, approved in the United States in 1998, was the first antiviral nucleos(t)ide analogue available for treatment of CHB. Subsequently, adefovir (2002), entecavir (2005), telbivudine (2006), tenofovir disoproxil fumarate (2008), and tenofovir alafenamide (2016) were approved. Clevudine and besifovir dipivoxil maleate are approved in South Korea but not in the United States. Agents in this class exhibit some differences with respect to potency, safety, and resistance profiles. The most important difference is the superior barrier to resistance exhibited by tenofovir and entecavir, as demonstrated by negligible rates of virologic failure even after years of therapy. Tenofovir alafenamide elicits virologic responses similar to those associated with tenofovir disoproxil fumarate, but with reduced risk of bone and renal toxicities.

Despite their success in persistently inhibiting HBV pol/RT, because cccDNA formation from rcDNA is catalyzed primarily by cellular polymerases, nucleos(t)ide analogues have minimal effects on cccDNA establishment and affect HBV gene expression only indirectly. Over the last several years, several lines of evidence have also suggested that nucleos(t)ide analogues alone are unable to fully inhibit all HBV replication. For example, analysis of liver biopsies has shown that HBV replication often persists at low levels even after years of nucleos(t)ide analogue therapy. As long as low-level replication persists, new hepatocytes can be reinfected continuously, and it is unlikely that nucleos(t)ide analogues alone will cure most individuals; clinically, this is apparent from the slow HBsAg declines and low cure rates seen on current standards of care. As a result, for most patients, lengthy if not lifelong treatment is likely to be needed. In those few patients in whom both serum antigens and HBV DNA do become undetectable, a sustained posttreatment virologic response is often achieved if therapy is stopped, supporting HBsAg clearance as a possible biomarker of functional cure.

Combination therapy with a nucleos(t)ide analogue and pegylated interferon has been explored with generally disappointing results. Although a few studies have reported higher rates of sustained posttreatment responses with peginterferon combined with entecavir or tenofovir versus interferon alone, response rates are typically low and the population likely to benefit appears similar to that with interferon alone. Several Asian studies have reported no incremental benefit from combination therapies.

Novel Therapies

Novel therapies in clinical development include both direct-acting antivirals (DAAs), which target viral proteins or viral RNAs, and host-directed antivirals, such as entry
inhibitors and immunomodulators (Table 1). Additional approaches, such as direct cccDNA targeting, epigenetic modifiers, and RNAse H inhibition, remain preclinical but are anticipated to initiate clinical evaluation over the next few years.

THERAPIES IN CLINICAL DEVELOPMENT

As discussed, inhibition of the HBV pol/RT by nucleos(t)ide analogues is of limited efficacy owing to their primary mode of action, which has little impact on either cccDNA establishment or viral gene expression. They have repeatedly been shown to incompletely suppress intrahepatic viral replication, resulting in rapid recurrence of viral replication if treatment is stopped. Over the past 5 to 10 years, other aspects of the HBV replication cycle have been explored with the aim of identifying agents that could address these limitations and achieve antiviral effects that persist after treatment.

Direct-Acting Antivirals

Novel DAAs are being developed with the rationale that hepatocytes have a finite lifespan; thus, if new (uninfected) hepatocytes can be protected from infection by a potent antiviral regimen, then the duration of the infection cannot exceed the lifespan of the hepatocytes and may be shorter if cccDNA loss is more rapid than hepatocyte loss. If current standard-of-care nucleos(t)ide therapies are, in fact, achieving low cure rates as a result of ongoing intrahepatic HBV replication (ie, primary antiviral failure), then combining a nucleos(t)ide analogue with a DAA for a sufficient length of time may be all that is required to achieve a cure for CHB. DAAs in development include entry inhibitors, RNA inhibitors, and core protein inhibitors.

Entry Inhibitors

Blockade of HBV entry into hepatocytes, thus preventing the earliest step of infection, has been explored concurrent with identification of NTCP as the HBV receptor. Bulevirtide (myrcludex B; Hepatera Ltd), a specific NTCP inhibitor, blocks attachment of viral pre-S1 via high-affinity binding to NTCP. Current clinical studies of bulevirtide are focused on patients with hepatitis delta virus (HDV) coinfection. Because infectivity of both HBV and HDV depends on the presence of HBsAg in the viral envelope, these studies will assess virologic responses of both HDV and HBV. Phase 2 data showed a marked reduction of HDV RNA after 24 weeks of bulevirtide combined with tenofovir, and after 48 weeks of bulevirtide with or without peginterferon-alfa. In the latter study, the HBsAg decline was greater with bulevirtide in combination with peginterferon-alfa. Planned phase 3 studies will explore extended therapy with bulevirtide as monotherapy or in combination with peginterferon-alfa in patients with HBV/HDV coinfection, focusing on HDV clearance as the primary objective. Although entry blockers would not be expected to directly interfere with HBV cccDNA formation, entry inhibition with bulevirtide would be anticipated to protect still uninfected cells and thus may contribute to HBV therapy either alone or in combination with other modalities.

RNA Interference

RNA interference (RNAi) is a natural process by which a small interfering RNA (siRNA) duplex directs sequence-specific posttranscriptional silencing by binding to complementary mRNA, triggering its elimination. Because the HBV genome is compact with multiple overlapping reading frames, targeting viral transcripts with siRNA has emerged as an attractive approach anticipated to reduce expression of multiple viral
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**Abbreviations:** NOD2, nucleotide-binding oligomerization domain-containing protein 2; RIG-I, retinoic acid-inducible gene-I.
antigens. Of particular interest has been the implication of reducing HBsAg, which has been proposed to contribute to specific impairment of an effective anti-HBV immune response.

Various approaches have been taken to safely enhance delivery of the siRNA moiety and to target the HBV genome within hepatocytes. Although most of these programs remain preclinical, several have entered human studies with mixed results. An early siRNA against HBV, ARC-520 (Arrowhead Pharmaceuticals), was composed of 2 siRNAs conjugated to cholesterol and administered with a polymer-based system containing N-acetyl galactosamine; together these conjugates enhance delivery to the hepatocyte cytoplasm.51,52 Monthly injections of ARC-520 in combination with standard oral entecavir achieved multilog reductions of serum HBsAg concentrations in HBeAg-positive patients that persisted for months after discontinuing ARC-520; lesser (<1 log) reductions of HBsAg were reported in HBeAg-negative patients.53 These results helped demonstrate the significant percentage of circulating HBsAg that could be derived from integrated HBV sequences in HBeAg-negative patients. Subsequently, 3 monthly subcutaneous injections of a follow-on product, JNJ-3989 (formerly ARO-HBV; Johnson & Johnson/Arrowhead), which targets a different region of the HBV genome, also elicited dose-related reductions of serum HBsAg of 1.3 to 3.8 log10 IU/mL, as well as reductions of HBV DNA, HBV RNA, HBeAg, and hepatitis B core-related antigen.54,55 Viral antigen responses were similar with or without concomitant nucleos(t)ide analogue therapy and in both HBeAg-positive and HBeAg-negative patients, in contrast to previous results with ARC-520.53,56

AB-729 (Arbutus) is a subcutaneously delivered N-acetylgalactosamine-conjugated siRNA moiety that demonstrated significant suppression of HBsAg in mouse models of HBV infection.57 Initial clinical evaluation is planned for 2019. Clinical development of ARB-1467, Arbutus’ initial product in this category, has been discontinued.

Core Protein Inhibitors

The HBV core protein plays several essential roles in the HBV life cycle, including capsid formation.58–67 The kinetics of core protein assembly are critical for functional capsid formation, encapsidation of pgRNA, and formation of infectious virions. The HBV capsid is also essential for nuclear importation of HBV rcDNA through a regulated interaction with nuclear pore proteins, allowing replenishment of nuclear cccDNA pools from either newly formed capsids or incoming virus.68 Nuclear forms of the HBV core protein have been implicated in modulating the expression of viral and host genes and contributing to regulated splicing and nuclear export of HBV RNAs, and to cccDNA function.69,70

These findings suggest that allosteric modulation of the core protein would allow targeting of multiple aspects of the viral life cycle and predict that HBV core protein inhibitors (also known as core inhibitors, or core protein allosteric modulators) may be potent antivirals. Several classes of core inhibitors have been described across multiple chemotypes71; all are thought to bind to the same pocket in the dimer-dimer interface, nucleating inappropriate oligomerization and rendering nascent capsids unable to encapsidate viral RNA. Subtle differences in core oligomer morphologies following addition of core inhibitors in vitro have been described, ranging from empty capsids to “cracked” capsids with potential changes in cellular localization following core protein aggregation.72 How these may relate to clinical outcomes remains to be demonstrated. Importantly, all core inhibitors in clinical development exhibit a common property: in addition to potent inhibition of new rcDNA formation, all inhibit viral RNA packaging, and at higher doses, may inhibit the establishment of cccDNA. In contrast, nucleos(t)ide analogues inhibit neither of these processes to a significant degree.
Preclinically, several core inhibitors have shown attractive profiles as once-daily oral therapeutics, with potential for additive to synergistic activity in combination with nucleos(t)ide analogues. Several core inhibitors are currently in clinical evaluation. Early data from phase 1b monotherapy studies suggest that this novel class has the potential to be at least as potent as nucleos(t)ide analogue monotherapy, with single-agent HBV DNA declines of up to 4 log10 IU/mL, as well as 2 to 3 log10 declines in viral RNA over ≤28 days. Early data from phase 2 evaluations of core inhibitors are anticipated in 2019, including combinations with other therapeutic modalities. If preclinical data with these combinations, suggesting additive to synergistic interactions, are reflected by anticipated enhanced declines in viral load, it will be extremely interesting to assess whether these effects are followed by viral antigen reductions or loss, which would be predicted if an enhanced antiviral effect reduces cccDNA persistence.

Novel Viral Polymerase Inhibitors

Besifovir dipivoxil maleate has recently been approved in Korea, based on phase 3 data indicating noninferior HBV DNA suppression versus tenofovir disoproxil fumarate, with significantly reduced bone and renal toxicities at 48 weeks. However, further clinical evaluation appears to be limited to studies in Korea, suggesting that broader registration efforts may not be forthcoming. A lipid-conjugated, liver-targeted prodrug of tenofovir (tenofovir exalidex; ContraVir) is in early clinical development, with the primary objective of improving safety over current tenofovir disoproxil fumarate formulations.

Immunotherapeutic Strategies

From an immunologic perspective, it has been shown that a persistent, HBV-specific immunologic dysfunction exists in CHB, with both a paucity and a functional impairment of HBV-specific T cells. Although the nature of this dysfunction is only partially understood, multiple potential immunotherapeutic approaches have been suggested as a means to achieve a cure by restoring immune competence against HBV and HBV-infected hepatocytes. A thesis underlying immunotherapeutic approaches is that HBV is a disease that can be fully suppressed and functionally cured in the context of most (adult) acute infections. If the deficit that allows CHB persistence could be resolved, then immune restoration may allow a similar clinical cure for CHB. Immunotherapeutics in clinical development include toll-like receptor (TLR)7 AND TLR8 agonists, checkpoint inhibitors (eg, anti-PD-1), an RIG-I agonist, and therapeutic vaccines.

Toll-like Receptor Agonists

TLRs are intracellular pathogen-sensing receptors that, when triggered, can arm the immune response to produce antiviral cytokines, such as interferons alfa and gamma, and induce activation of both natural killer and T cells. In animal models, both TLR7 and TLR8 have shown an impressive ability to cure woodchucks of woodchuck hepatitis virus infection, although tolerability has arisen as a potential concern. The ability to deliver TLR agonists such as Gilead TLR7 agonist vesatolimod (GS-9620) and TLR8 agonist (GS-9688) orally has led to the hope that a “presystemic” antiviral immune response that was limited to the portal circulation might be generated, potentially providing the benefits seen with injected interferons without systemic side effects. Although early clinical results with vesatolimod in patients with CHB were disappointing, GS-9688 as well as TLR7 agonists from Roche (RO7020531) and Johnson & Johnson (JNJ-4964) are still advancing in clinical trials.
and have been shown to successfully stimulate immune responses in both healthy volunteers and patients with CHB.102–105

**Checkpoint Blockers**

The presence of an “exhausted” CD8+ T-cell phenotype in patients with CHB has spurred exploration of PD1-PDL1 interactions as a possible strategy for restoration of an anti-HBV immune response.106 Several checkpoint modulators are approved for use in oncology and are thus already available for exploratory studies in CHB patients. One immunologic study concluded that maturation of HBV-specific B cells is adversely affected by the presence of serum HBsAg regardless of disease stage, and that B-cell maturation could be partially restored by addition of anti-PD1 antibodies.93 However, in a small study of patients with HBeAg-negative CHB, the addition of nivolumab (Bristol-Myers Squibb), an anti-PD1 monoclonal antibody, to GS-4774 (Gilead Sciences), an experimental therapeutic T-cell vaccine, did not significantly impact HBsAg levels except in a single patient, although changes in T-cell and natural killer cell composition were reported.107,108 The combination of an anti-PD-L1 antibody with siRNA in a woodchuck model led to sustained reductions of HBsAg in some animals.106 Whether combinations of checkpoint inhibitors with alternative regimens will significantly improve efficacy in the clinic remains to be seen.

**Therapeutic Vaccines**

There is an extensive and largely unsuccessful history of therapeutic vaccine development for patients with CHB.109 Previous failures have prompted more sophisticated approaches designed to broaden HBV-specific immune responses110 and explore combinations with both immunomodulators (anti-PD-1/anti-PDL1) and DAAs (such as siRNA).111 Although preclinical work has demonstrated exciting results in nonclinical models, these have yet to be validated in human studies.111,112

**OTHER CLINICAL STAGE THERAPEUTICS OF INTEREST**

**Nucleic Acid Polymers**

In addition to the development programs mentioned above, several other therapeutic classes are currently being evaluated in the clinic. These therapeutic classes include the nucleic acid polymers being developed by Replicor (REP 2139).113 In patients coinfected with HDV and HBV, REP 2139 in combination with peginterferon alfa-2a provided marked suppression of plasma HDV RNA and HBsAg concentrations; HDV RNA remained undetectable at 1 year after treatment in 7 of the 12 patients, and, after 1.5 to 2 years, HBsAg remained undetectable in 4 patients.114,115 In a subsequent study, patients with HBeAg-negative CHB were treated for 48 weeks with combinations of REP 2139 or REP 2165 and both tenofovir and peginterferon alfa-2a.116,117 At 24 to 48 weeks of posttreatment follow-up, 14 of 34 patients had undetectable HBsAg and HBV DNA; significant alanine aminotransferase flares were common and were correlated with antiviral responses. Positive results have also been reported in an uncontrolled study conducted in Bangladesh.118

A different approach is being taken by Spring Bank, which is developing inarigivir (SB9200), an orally administered linear dinucleotide, as an RIG-I agonist with the objective of activating cellular innate immune responses in HBV-infected cells.119 Inarigivir is also a relatively weak inhibitor of the HBV polymerase.120 After 12 weeks of dosing in patients with CHB, inarigivir elicited modest declines in both HBV DNA and HBV RNA, with somewhat greater efficacy reported in HBeAg-negative versus HBeAg-positive patients at doses up to 100 mg.121–123 Data at higher doses are
anticipated in 2019. A collaborative study with Gilead Sciences is evaluating inarigivir in combination with tenofovir alafenamide in adults with CHB; other phase 2 and phase 3 combination studies are planned.

**Farnesoid X Receptor Agonists**

The gene encoding the NTCP receptor, which mediates HBV entry into hepatocytes, contains 2 farnesoid X receptor (FXR) \( \alpha \) response elements.\(^{124}\) FXR agonists reportedly inhibit HBV replication, and at least 1 FXR agonist (EYP001, Enyo Pharma) is entering phase 2 evaluation in patients with CHB, based on preclinical data, suggesting potential to suppress both HBsAg and HBeAg production.\(^{125}\)

**FUTURE THERAPIES (NOT YET IN CLINICAL DEVELOPMENT)**

In addition to the studies in clinical development, a growing number of targets are being explored preclinically.

**PAPD5/7 Inhibition**

Dihydroquinolizinones have been identified as small molecules that can reduce production of both viral DNA and viral antigens.\(^{126}\) Elucidation of the target for these agents determined that they inhibit the catalytic domain of 2 enzymes, PAPD5 and PAPD7, leading to destabilization of HBV mRNA without impacting production of transcripts. Although this target has accrued significant interest, no compounds of this type have yet progressed to studies in patients with CHB.

**RNAse H**

RNAse H activity is required for production of new infectious virus and replenishment of nuclear cccDNA through conversion of rcDNA into cccDNA. Ablating HBV RNase H activity causes accumulation of long RNA:DNA heteroduplexes, truncates minus-polarity DNA strands, and blocks production of the plus-polarity DNA strand.\(^{127}\) Several chemical leads have been identified, but they also have not yet entered clinical evaluation.\(^{128}-^{130}\)

**Epigenetic Modifiers**

Epigenetic regulation of HBV has recently been extensively reviewed.\(^{131}\) “Epigenetics” refers to (heritable) alterations in gene expression that occur to a chromosome without changes in DNA sequence. Because HBV cccDNA exists as a nucleosome-decorated minichromosome, replete with histones and other host proteins, it can presumably be regulated by small-molecule epigenetic-modifying agents, such as those that target histone deacetylases (HDAC), histone acetyltransferases, methyltransferases, and demethylases (KDMs). Indeed, HDAC inhibitors have been shown to suppress cccDNA transcription in tissue culture under nontoxic conditions.\(^{132}\) Interestingly, transcription from HBV DNA integrated into the host genome was enhanced, suggesting that cccDNA is regulated differently than transcription from an integrated genome.\(^{133}\) As HDAC inhibitors have been approved for other indications, it may be anticipated that these could be used in patients with CHB as well, perhaps in combination with an immunotherapeutic, should they be useable at a dose that is free of toxicity. Other epigenetic approaches have also been contemplated, and at least 1 company (Gilead Sciences) has explored targeting KDM5, demonstrating potent reductions of viral antigens as well as RNA associated with histone demethylation (H3K4me3:H3)\(^{134}\); however, future development for this target indication is uncertain.
Direct cccDNA Targeting
The ability to directly eliminate or silence HBV cccDNA has been considered the “holy grail” of HBV therapies. However, until recently, such direct targeting of the viral reservoir has not been feasible. The emergence of CRISPR-Cas9 and other technologies that can directly edit DNA (zinc finger nucleases and such) has the potential to target cccDNA directly. Several companies have emerged around this exciting platform, and in nonclinical studies, several academic groups have shown that this approach can successfully reduce functional cccDNA.135–138 Although the data are exciting, several important caveats remain: (1) elimination of off-target effects need to be addressed; (2) the vector for delivery would need to access all infected hepatocytes to remove the potential for reactivation; and (3) although studies have shown that integrated genomes may be targeted, cleavage of such integrants runs the theoretical risk of inducing genomic instability, with the concomitant risk of carcinogenesis. It remains to be seen whether these questions can be addressed before entry into the clinic.

SUMMARY
The last several years have seen a dramatic resurgence of interest in HBV therapeutic research, with multiple novel targets beyond the HBV pol/RT being explored for the first time in almost 20 years. Although it is early, it is anticipated that the next several years will yield important new insights into the underlying biology of HBV in parallel with new treatments that may have the potential to cure substantially more patients than can be achieved today.

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