doi: 10.53388/ghr2020-12-026

# Research Progress and Reflection on New Drugs for the Treatment of Chronic Hepatitis B

**Zhen-Zhou Long [1], Qing-He Nie [1]***

[1]Department of Infectious Diseases (National Key Discipline)/Military Diagnosis and Treatment Center of Infectious Disease, Tangdu Hospital of the Air Force Military Medical University (Fourth Military Medical University), Xi'an, Shaanxi, 710038.

***Corresponding to**: Qing-He Nie, Department of Infectious Diseases (National Key Discipline)/Military Diagnosis and Treatment Center of Infectious Disease, Tangdu Hospital of the Air Force Military Medical University (Fourth Military Medical University), Xi'an, Shaanxi, 710038. E-mail: nieqinghe@163.com.

**Abstract:** Chronic hepatitis B (CHB) affects more than 257 million individuals with high liver-related morbidity and mortality worldwide. This review summarizes research progress and reflection on new drugs for the treatment of CHB. Some available HBV therapeutic strategies and their corresponding stages of development from preclinical to various clinical phases are indicated in this article. Through this review, the author aims to give us a comprehensive understanding of the global research trends and the latest progress of new drugs for treating chronic hepatitis B, so as to gain useful enlightenment.
**Key words:** hepatitis B, chronic; new drug's research & development; covalently closed circular DNA (cccDNA); cure, reflection

***Acknowledgments*:** Thanks the editage for polishing the language of the manuscript.

***Abbreviations*:** CHB, Chronic hepatitis B; cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; HCC, hepatocarcinoma; CHB, chronic hepatitis B; PEG-IFN, pegylated interferon; NAs, nucleoside/tide analogs; NTCP, sodium taurocholate co-transporting polypeptide; NIH, National Institutes of Health; BSV, besifovirdipivoxil maleate; SiRNA, small interfering RNA; DAAs, direct-acting antivirals; IAAs, indirect-acting antivirals; RNAi, RNA interference; EASL, European Association for the Study of Liver; HDV, hepatitis D virus; EC, European Commission; CMA, conditional marketing authorization; MHC, major histocompatibility complex; TCRs, T cell receptors.

***Authors' Contributions*:** All authors made substantial contribution before submission, and all authors have read and approved the final manuscript.

***Competing interests*:** The authors have no conflicts of interest relevant to this article.

***Citation*:** Long ZZ, Nie QH. Research Progress and Reflection on New Drugs for the Treatment of Chronic Hepatitis B. *Gastroenterol Hepatol Res*. 2020;2(4):125-131. doi: 10.12032/ghr2020-12-026.

***Executive Editor*:** Ming-Zhong Xiao.

***Submitted*:** 27 October 2020, ***Accepted*:** 07 December 2020, ***Published*:** 12 December 2020

© 2020 By Authors. Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license (http://creativecommons.org/licenses/BY/4.0/).

## Background

Worldwide, there are approximately 257 million people infected with chronic hepatitis B virus (HBV). As there is currently no complete cure for HBV infection, these infected individuals face the threat of severe liver disease complications and liver cancer, and more than 887,000 deaths due to HBV-related diseases are recorded each year. Approximately 40% of hepatocarcinoma (HCC) cases are related to chronic hepatitis B (CHB), and HCC ranks second among cancer-related mortalities worldwide. With regards to the treatment of HBV, the existing hepatitis B vaccine for preventing HBV infection has no effect on existing HBV infection. The antiviral drugs approved by various countries for the treatment of CHB are divided into two categories, namely, pegylated (long-acting) interferon (PEG-IFN) and oral nucleoside/tide analogs (NAs). Medication strategies include single or combined medication, the latter of which also includes sequential medication.

From the perspective of CHB treatment, there are multiple objectives. Existing NAs can generally be used to completely inhibit HBV replication, and with respect to achieving clinical cure, the administration of PEG-IFN combined with NAs has led to satisfactory outcomes in certain populations, despite inconsistent cure rates in different countries. Currently, however, it is not possible to achieve a complete cure, that is, to completely eliminate the covalently closed circular DNA (cccDNA) of HBV in hepatocytes. Consequently, even though HBV replication can be successfully inhibited, patients would still be at risk of developing HCC, particularly those suffering from liver cirrhosis.

## 1. Progress in research on the life cycle of HBV

The complete life cycle of the virus causing hepatitis B includes the steps of attachment, entry, uncoating, trafficking, cccDNA production, transcription, translation, encapsidation, replication, assembly, and secretion. A lack of insight into the HBV life cycle, particularly with respect to the processes associated with viral biogenesis, homeostasis, and cccDNA reservoir update, is a major obstacle in research on a cure for CHB.

Nevertheless, in recent years, advances in science and technology have led to certain theoretical breakthroughs relating to HBV. For example, the sodium taurocholate co-transporting polypeptide (NTCP), discovered in 2012, has been identified as a receptor that is necessary for the entry of HBV into hepatocytes, which has led to optimism that a cure for CHB may soon be achieved [1]. Available systems such as NTCP and primary human hepatocytes, human hepatocarcinoma cell lines (HepaRG cells), transient transfection systems, stable transformed cell lines, induced pluripotent stem cell-derived hepatocyte-like cells, and humanized mice have collectively contributed to the development of diverse cell culture models, thereby making it possible to reproduce the entire HBV replication cycle [2]. Systematic research on the mechanisms that underly the control HBV biogenesis, homeostasis, and decay of the cccDNA transcriptional template will enable us to identify vulnerabilities in the cccDNA machinery, and such vulnerabilities may conceivably be exploited to eliminate HBV from infected cells.

A further consideration is age at the time of HBV infection, which is closely related to the chronicity of infection. In this regard, in more than 90% of individuals infected with HBV in infancy, acute hepatitis will subsequently develop to a chronic lifelong viral infection. In contrast, more than 90% of those individuals infected with HBV in adulthood will mount a strong immune response to clear the infected cells, or will develop neutralizing antibodies to provide long-term protection.

Once HBV infection is confirmed, affected patients are at risk of developing chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. The natural history of the CHB virus infection typically consists of five phases: immune tolerance [HBeAg-positive, high levels of serum HBV DNA, normal alanine transferase (ALT), and minimal histopathological changes], immune clearance(HBeAg-positive, gradual decline in the level of serum HBV DNA, elevated ALT, and enhanced histopathological changes), immune control (anti-HBe-positive, low levels of serum HBV DNA, normal ALT, and minimal histopathological changes), immune clearanceof variant HBV (HBeAg-negative, elevated ALT, increased hepatitis activity, and high levels of serum HBV DNA), and recovery [HBsAg-negative, with or without hepatitis B surface antigen (anti-HBs)]. These five stages differ with respect to HBV replication level, virus antigen expression, and liver inflammation, and accordingly necessitate different treatment strategies.

Each year, spontaneous negative conversion of HBsAg occurs in approximately 1% of individuals with CHB virus infection, thereby presenting the possibility of pharmacological and immunological control of HBV infection. However, recovery from chronic and acute HBV infection is not indicative of the complete clearance of HBV. As a small number of cccDNA-positive hepatocytesremain in these individuals for a prolonged period of time, HBV reactivation and replication is likely to occur in some immunosuppressed individuals [3].

Thus, future CHB cure strategies that seek to eliminate HBV cccDNA from infected cells, or control its expression, will require a better understanding of the mechanisms that underlie cccDNA biogenesis and homeostasis.

TMR
doi: 10.53388/ghr2020-12-026

## 2. Strategies for CHB cure

Establishing a complete cure for CHB will be far from straightforward, as it will necessitate the control of HBV infection, the clearance of HBV and its associated genes, and the treatment of HBV-related liver disease. Those who have sought to develop a cure for CHB have previously focused on the cure of HBV infection, including the clearance of HBV, control of viral replication, and the induction of a host immune response to eliminate HBV-infected cells, thereby preventing the spread of HBV infection to other healthy cells. Such multiple prerequisites for the treatment of CHB virus infection have given rise to the concept of multiple treatment modalities.

### 2.1 Treatment modalities

#### 2.1.1 Complete cure

Complete cure refers to complete recovery from CHB, with no detectable levels of serum HBsAg and the elimination of all HBV DNA from the body (including cccDNA and HBV DNA that is genetically integrated into that of hepatocytes). Complete cure is difficult to determine using the existing test methods.

#### 2.1.2 Clinical cure

Clinical cure is characterized by consistently negative test results for HBsAg and HBV DNA in the serum with or without the production of hepatitis B surface antibodies, although low levels of cccDNA and HBV DNA integrated into host genes are still present in the hepatocytes.

#### 2.1.3 Partial cure

The third type of cure is partial cure, which is defined as that subsequent to a limited course of treatment. Although HBsAg is detectable in the body, serum HBV DNA continues to be undetectable, and biochemical and histological changes are restored to the original states.

As it is currently not possible to eliminate the HBV cccDNA reservoir and integrated HBV DNA from all HBV-infected hepatocytes, clinical cure has become a more practical therapeutic goal compared with the other two types of cure.

### 2.2 HBV cure research

In 2019, the National Institutes of Health (NIH) of the USA formulated a new strategic plan to cure CHB, emphasizing the need to focus on research in three key areas.

#### 2.2.1 Basic research on HBV

This part includes, but is not limited to, research on the biology, pathogenesis, immunity, and reactivation of HBV, the viral and host factors that are related to HBV transmission, and the impact of HBV co-infection with other hepatitis viruses.

#### 2.2.2 Development of shared research tools and resources

This part includes experimental design, method development and standardization, establishment of animal models, disease progression research, mother-to-child transmission, and biomarker detection.

#### 2.2.3 Improvement in CHB prevention and cure strategies

Among other factors, this part focuses on measures that can be used to block HBV replication, induce an anti-HBV immune response, and eliminate HBV-infected cells.

## 3. Progress in the development of new drugs for CHB treatment

### 3.1 Clinical trials of new drugs for hepatitis B treatment

Current antiviral treatments do not provide a cure for CHB, which can be attributed primarily to the persistence of a reservoir of HBV cccDNA, the transcriptional template of which forms in the nucleus of hepatocytes during viral infection.

Existing antiviral drugs approved for the treatment of CHB include pegylated interferon-α [PEG-IFN α-2b(1991) and PEG-IFN α-2a(2005)] and six NAs, namely lamivudine (1998), adefovir dipivoxil (2002), entecavir (2005), telbivudine (2006), tenofovir (2008), tenofovir alafenamide (TAF, 2016) [4].

The aforementioned antivirals are anti-HBV drugs that have been approved by the US FDA, whereas outside of the U.S., a new hepatitis B drug, besifovirdipivoxil maleate (BSV) [5], also an inhibitor of HBV DNA polymerase, has been marketed in South Korea since 2017. Studies have shown that the 48-week efficacy of BSV is comparable to that of tenofovir and that its use appears to be safer with respect to the kidneys and bones.

To date, however, none of the other drugs under development have entered Phase III clinical trials. The HBVentry inhibitor MyrcludexB and capsid inhibitors Morphothiadin, JNJ 56136379, and ABI-H0731 are still in Phase II clinical trials. Similarly, small interfering RNA (SiRNA) drugs (such as VIR-2218) that interfere with and destroy viral RNA, antisensedrugs (such as IONIS-HBVRx) that can bind viral mRNA to prevent it from being translated into viral proteins, HBsAg secretion inhibitors such as REP 2139 and REP 2165, the monoclonal anti-HBsAg antibody GC1102, and the agonist RIG-1/NOD-2 are all currently in Phase II clinical trials. Immunomodulators, such as toll-like receptor agonists, cellular inhibitors of apoptosis-1, and certain therapeutic vaccines, are also being used to enhance innate and adaptive immunity to control HBV infection,

and are currently in Phase I clinical trials. Furthermore, some clinical trials are also presently evaluating the synergistic or additional effects of combined treatments [6].

In August 2020, the website of the International Hepatitis B Foundation updated the progress being made on new anti-hepatitis B drugs, and although at present there have been nonmajor breakthroughs, there is some good news regarding research on new anti-hepatitis B drugs. For example, three new anti-hepatitis B drugs have emerged, namely the therapeutic vaccine VTP-300, entering Phase I clinical trials, and the novel peptide GV1001 and oral microbiome drug CP101, which are currently at the stage of preclinical testing. Moreover, some studies on new drugs have made certain progress. For example, the capsid inhibitor ABI-H2158 has entered Phase II clinical trials, the therapeutic vaccine VBI-2601 has entered Phase Ib/IIa clinical trials from preclinical testing, and the second-generation capsid inhibitor ABI-H2158 and RNAi drug JNJ3989(ARO-HBV) have entered Phase II clinical trials. Thus, although no new hepatitis B drugs have recently entered Phase III clinical trials, the future looks promising. In addition, research on the therapeutic potential of combining new drugs with existing NAs and PEG-IFN α is ongoing, and in this regard, some reports of high clinical cure rates indicate the potential efficacy of the combined administration of new and existing drugs. There is accordingly optimism that the era of complete clinical cure will arrive in the not too distant future [7].

### 3.2 Classification of new anti-hepatitis B drugs

According to the current target design principlesfor new anti-hepatitis B drugs, these drugs can be divided into two categories, namely direct-acting antivirals (DAAs) and indirect-acting antivirals (IAAs).

#### 3.2.1 DAAs

DAAs work by targeting HBV and interfering with the HBV replication process. These drugs include siRNAs as silencers of gene expression that interfere with and destroy viral RNA, entry inhibitors that interfere with HBV entry into hepatocytes, capsid inhibitors that destabilize the nucleocapsid, HBsAg inhibitors that interfere with HBsAg production, and antisense RNA drugs that bind with viral mRNA, thereby preventing viral protein synthesis.

#### 3.2.2 IAAs

The design principle of IAAs is mainly related to targeting the human immune system, thereby inducing immune cells and cytokines to attack HBV. Therapeutic vaccines, once the most popular and invariably highly anticipated, belong to this class of drugs and reflect a therapeutic philosophy fusing vaccine technology to activate the body's immune system. Compounds that activate the innate immune system, such as toll-like receptor agonists, are involved inan innate immune defense pathway, whereas compounds that induce programmed cell death (apoptosis) are involved in a host-acting pathway [8]. In addition, IAAs include gene-editing agents, HBsAg monoclonal antibodies, PD-L1 and its inhibitors, T-cell immunotherapy, microRNAs, FXR agonists, antisense locked nucleic acids, novel peptides, direct killing of HBV-infected cells by nucleic acids, and oral microbiome drugs(Table1).

### 3.3 Selected new drugs

#### 3.3.1 ALN-HBV02 (Vir-2218)

VIR-2218 is a subcutaneously administered RNA interference (RNAi) drug that targets novel sites on the HBV RNA during development and is currently in Phase II clinical trials. The European Association for the Study of Liver (EASL) recently reported two research advances on VIR-2218, in which preclinical testing has shown that this drug targets a highly conserved region of the HBV genome, and in vitro experiments have confirmed that it has pan-genotypic anti-HBV activity. Similarly, VIR-2218 has shown effective and sustained antiviral activity in an AAV-HBV mouse model. These data provide convincing evidence that VIR-2218 can be used to treat HBV-infected patients. The latest report has also presented the results of a Phase I clinical trial of VIR-2218 in healthy subjects, which indicate that VIR-2218 is suitable for subcutaneous administration and has good pharmacokinetic properties in healthy subjects. Research is currently underway to evaluate the efficacy of VIR-2218 in HBV-infected patients.

#### 3.3.2 Hepcludex (bulevirtide)

Hepcludex is a virus entry inhibitor (formerly named Myrcludex B), developed to treat chronic HBV and hepatitis D virus (HDV) infections. The drug can inhibit the HBV/HDV receptor NTCP on the surface of hepatocytes and prevent the infection of regenerative cells and the spread of viruses in the liver. On August 4, 2020, the German biotechnology company MYR Pharmaceuticals announced that the European Commission (EC) had granted conditional marketing authorization (CMA) for its lead compound Hepcludex (with bulevirtide as the active substance) in the EU, which is to be used in the treatment of adult chronic HDV infection and compensated liver disease. The CMA approval is based on the results of two Phase II trials (MYR202 and MYR203) the data from which indicate that Hepcludex significantly reduces viremia and improves liver function during the treatment of hepatitis D, with good tolerance and safety. A Phase III clinical trial of long-term treatment of HDV with Hepcludex and a Phase II clinical trial of treatment of HDV with Hepcludex in combination with pegylated interferon are ongoing, whereas treatment of CHB with Hepcludex is in Phase II clinical trials.

TMR
doi: 10.53388/ghr2020-12-026

Table 1 Anti-hepatitis B drugs in development for clinical trials (up to August 2020).

| Category | Drugs | Mechanism | R&D company | Approval status |
|---|---|---|---|---|
| 1. Silencing RNAs (siRNAs): interfere with and destroy viral RNA | VIR-2218 | RNA interference (RNAi) | Alnylam and Vir Biotech, USA | Phase II |
| | RG6346 (DCRHBVS) | RNA interference (RNAi) | Roche, Switzerland | Phase I/II |
| | ARO-HBV | RNA interference (RNAi) | Arrowhead Pharma with Janssen, USA | Phase I/II |
| | AB-729 | RNA interference (RNAi) | Arbutus Biopharma, USA | Phase I |
| | BB-103 | RNA interference (RNAi) | Benitec, Australia | Preclinical |
| | Lunar-HBV | RNA interference (RNAi) | Arcturus with Janssen, USA | Preclinical |
| 2. Entry inhibitors: interfere with HBV entry into hepatocytes | Hepcludex (Bulevirtide formerly Myrcludex B) | Entry inhibitor | Hepatera, Russia with MYR GmbH, Germany | Phase II |
| 3. Capsid or core inhibitors: interfere with the viral DNA protein coat | Morphothiadin | Capsid inhibitor | HEC Pharma, PR China | Phase II |
| | JNJ 56136379 | Capsid inhibitor | Janssen, Ireland | Phase II |
| | ABI-H0731 | Capsid inhibitor | Assembly Biosciences, USA | Phase II |
| | ABI-H2158 | Capsid inhibitor | Assembly Biosciences, USA | Phase II |
| | RG7907 | Capsid inhibitor | Roche, Switzerland | Phase I |
| | QL-007 | Capsid inhibitor | Qilu, PR China | Phase I |
| | EDP-514 | Capsid inhibitor | Enanta Pharma, USA | Phase I |
| | ABI-H3733 | Capsid inhibitor | Assembly Biosciences, USA | Phase I |
| | ZM-H1505R | Capsid inhibitor | ZhiMeng Biopharma, PR China | Phase I |
| | GLP-26 | Capsid inhibitor | Emory University, USA | Preclinical |
| | ALG-000184 | Capsid inhibitor | Aligos Therapeutics, USA | Preclinical |
| 4.HBsAg inhibitors :interfere with theproduction ofHBsAg | REP 2139 | HBsAg inhibitor | Replicor, Canada | Phase II |
| | REP 2165 | HBsAg inhibitor | Replicor, Canada | Phase II |
| | ALG-10133 | STOPs (HBsAg transport-inhibiting oligonucleotide polymers) | Aligos Therapeutics, USA | Phase I |
| 5. Antisense molecules: bind to the viral mRNA preventing viral protein synthesis | GSK 3228836 (IONIS-HBVRx) | Prevents viral protein production | Ionis with GSK, USA | Phase II |
| | ALG-020572/020576 | Prevents viral protein production | Aligos Therapeutics, USA | Preclinical |
| 6. Therapeutic vaccines: vaccine technology used to stimulate the immune system as a treatment | HepTcell | Therapeutic vaccine | Altimmune, USA | Phase II |
| | AIC 649 | Therapeutic vaccine | AiCuris, Germany | Phase I |
| | INO-1800 | Therapeutic vaccine | Inovio, USA | Phase I |
| | HB-110 | Therapeutic vaccine | Ichor Medical Genexine, USA | Phase I |
| | TG1050 | Therapeutic vaccine | Transgene, France | Phase I |
| | VTP-300 | Therapeutic vaccine | Vaccitech, USA | Phase I |
| | JNJ 64300535 | Therapeutic vaccine | Janssen, Ireland | Preclinical |
| | HBV | Therapeutic vaccine | GeoVax, USA | Preclinical |
| | VBI-2601 | Therapeutic vaccine | VBI Vaccines, USA | Preclinical |
| | Chimigen HBV | Therapeutic vaccine | Akshaya, Canada | Preclinical |
| | CARG-201 | Therapeutic vaccine | CaroGen, USA | Preclinical |
| | HBV | Therapeutic vaccine | HOOKIPA Pharma, Austria, with Gilead | Preclinical |
| | TherVacB | Therapeutic vaccine | Helmholtz ZentrumMuenchen, Germany | Preclinical |
| 7. Innate immune defense pathway: compounds that activate the innate immune system | GS9688 | TLR-8 agonist | Gilead Sciences, USA | Phase I |
| | RG7854 | TLR-7 agonist | Roche, Switzerland | Phase I |
| 8. Host-acting pathway: compounds that target cell functions needed by the HBV | APG-1387 | Apoptosis inducer | Ascentage Pharma, PR China | Phase II |
| | CRV 431 | Ciclofillininhibitor | Hepion , USA (formerly ContraVir) | Phase I |
| 9. Gene editing | EBT106 | CRISPR/Cas 9 | Excision Bio, USA | Preclinical |
| | HBV | ARCUS platform | Precision Bio, USA | Preclinical |
| 10. Other drugs | GC1102 | Monoclonal anti-HBsAg antibody | Green Cross, South Korea | Phase II |
| | IMC-1109V | ImmTAVmolecule | Immunocore, USA | Phase I/II |
| | EYP001 | FXRagonist | Enyo Pharma, France | Phase I |
| | RG6084 | Host-targeting antisense (LNA) | Roche, Switzerland | Phase I |
| | ASC22 (KN035) | PD-L1 | Ascletis Pharma, PR China | Phase I |
| | LTCR-H2-1 | T cell immunotherapy | Lion TCR, Singapore | Preclinical |
| | HBV | MicroRNA | Regulus, USA | Preclinical |
| | ENOB-HB-01 | Nucleic acid-directed HBV cell killing | Enochian BioSciences, USA | Preclinical |
| | GV1001 | "Novel peptide" | GenVax& KAEL, South Korea | Preclinical |
| | CP101 | Oral microbiome drug | Finch Therapeutics, USA | Preclinical |

**Note**: **1-5**: DIRECT-ACTING ANTIVIRALS: target the virus and interfere with the HBV replication process; **6-10**: INDIRECT-ACTING ANTIVIRALS: target the human immune system to attack the HBV.

### 3.3.3 VTP-300

VTP-300 utilizes the heterologous prime-boost viral vector platform ChAdOx-MVA to deliver three full-length HBV antigens, which induce the body to generate an effective specific immune response, thereby actively disrupting immune tolerance and eliminating HBV. As a novel anti-HBV vaccine, VTP-300 has been shown to induce powerful, broad anti-HBV CD8+ and CD4+ T cell and antibody responses in mice. The first subject in a Phase I clinical trial of this vaccine has completed a course of medication.

### 3.3.4 VBI-2601

VBI-2601 is a recombinant, protein-based, immunotherapeutic drug candidate, and is currently being investigated for its efficacy in treating CHB. Its use is based on the induction and maintenance of broadly effective immunity against HBV by targeting both B-cell and T-cell immunity through multiple key mechanisms of action, including neutralizing the circulation of HBV, blocking the infection of hepatocytesvia Pre-S1 immunity, and facilitating immune-mediated clearance of HBV-infected hepatocytes.

### 3.3.5 ABI-H2158

The second-generation capsid inhibitor ABI-H2158 has entered Phase II clinical trials and was registered on May 21, 2020. The results of Phase I clinical trials of this ABI-H2158indicated a rapid decline in the levels of HBV DNA and HBV RNA in subjects treated with this drug. ABI-H2158 has high anti-HBV activity, and treated subjects show good drug tolerance.

### 3.3.6 GV1001

GV1001 is a new type of peptide. Dendritic cells, a type of antigen-presenting cell, introduce foreign peptides (GV1001) into cells via phagocytosis, wherein they are broken down by lysosomal enzymes. A proportion of the peptides degraded by the major histocompatibility complex (MHC) receptors on dendritic cells are presented on T cells via an interaction between the MHC receptors and T cell receptors (TCRs). The antigen (GV1001) presented by dendritic cells can induce the activation and proliferation of T cells, which in turn recognize the telomerase that is highly expressed in cancer cells in the blood circulation and selectively eliminate these cells. In addition to being an anticancer agent, GV1001also has anti-inflammatory, antioxidant, and hormone-modulating effects when used to treat other disorders such as prostatic hyperplasia and Alzheimer's disease.

### 3.3.7 CP101

CP101 is an investigational oral microbiome therapeutic, originally designed to prevent recurrent *Clostridium difficile* infection, and is currently being evaluated for its efficacy in treating chronic HBV infection. CP101 issued with the objective of restoring the composition and function of the microbiome. Studies have shown that microbiome dysfunction may mediate CHB, and the findings of a number of independent clinical trials have indicated that microbiota transplantation can eliminate the active HBV virus in CHB patients, in whom HBeAg remains positive following long-term antiviral treatment.

### 3.3.7 IMC-I109V

The ImmTAC (immune mobilizing monoclonal TCRs against cancer) platform based on TCR is a new class of bispecific biological macromolecules comprising an engineered TCR and anti-CD3scFv. In addition to cancer, the biotechnology company Immunocore has applied its TCR technology platform in the treatment of viral and bacterial (ImmTAV and ImmTAB) infectious diseases, and the company's product IMC-I109Vis a new drug for the treatment of CHB. The latest abstract of EASL2020has presented a progress update on preclinical testing of the drug, which indicates that the ImmTAV molecule can effectively and specifically eliminate HBV-infected cells. The main ImmTAV molecule IMC-I109V has now passed the preclinical testing phase, and the data provide support for the first human trial. These data provide evidence for a novel immunotherapy strategy that aims to achieve rapid functional cure for patients with chronic HBV infection.

## 4. Reflections on a cure for CHB

A study on chimpanzees has indicated that during the self-healing process of acute HBV infection, almost all infected hepatocytes are cleared by CD8+ T cells, although there are also non-cellular pathways involved in the clearance of HBV [9]. Typically, only a small fraction of HBV-infected cells will eventually survive, but the anti-HBs produced in response to infection can prevent new cells from further infection. Each year, a similar mechanism occurs almost naturally among tens of thousands of individuals with acute HBV infection. However, using the existing treatment methods, it is currently not possible to achieve such clearance in patients with chronic HBV infection. Nevertheless, the result indicates that treatment of HBV infection does not necessarily require complete viral clearance in order to achieve long-term viral control.

Administration of curative HBV drugs may be a better approach for achieving the desired outcomes for individuals with chronic HBV infection. If such drugs can be used to generate a response in these patients similar to that stimulated in patients with acute HBV infection, or to treat some patients with chronic HBV infection who self-cure, administration of such drugs maybe a safer treatment strategy.

From the perspective of curing CHB, elimination of cccDNA is the most direct and effective strategy. The use of current antiviral drugs does not entirely eliminatecccDNA, even if taken for a prolonged period of time, as has also been founding in vitro studies and animal models. Dynamic observation of cytokine levels has revealed that interferon-α can induce the APOBEC-dependent deamination of HBV DNA, which raises concerns regarding whether a sustained decrease in cccDNA would be possible [10]. Although the use of CRISPR/Cas9 or other gene editing methods to directly target cccDNA has shown promising results in experimental studies, issues regarding the precise localization of hepatocytes and the consequences of targeting failure (and how to avoid these)continue to raise concerns as to the likelihood of certain unforeseen consequences [11]. Such risks and difficulties necessitate further examination of the effects of virus-targeting or host protein-targeting methods on the synthesis, stability, and expression of cccDNA. In this regard, current advances in basic research have made it possible to gain an understanding of the complete replication process of HBV. In our opinion, these advances will contribute to the eventual development of an effective cure for CHB, and we believe that the elimination of cccDNA may be

TMR
doi: 10.53388/ghr2020-12-026

the only viable strategy with the potential to achieve a safe and long-lasting cure for HBV infection. In short, there remains considerable progress to be made in the treatment of CHB, and accordingly more research is needed.

## References

1. Revill PA, Chisari FV, Block JM, et al. A global scientific strategy to cure hepatitis B. *Lancet Gastroenterol Hepatol*. 2019;4(7):545-558.
2. Thomas H. Viral hepatitis: A new model for HBV infection of primary human hepatocytes. *Nat Rev Gastroenterol Hepatol*. 2018,15(4):190.
3. Wu D, Ning Q. Toward a Cure for Hepatitis B Virus Infection: Combination Therapy Involving Viral Suppression and Immune Modulation and Long-term Outcome. *J Infect Dis*. 2017;216(suppl 8):S771-771S777.
4. Königer C, Wingert I, Marsmann M, et al. Involvement of the host DNA-repair enzyme TDP2 in formation of the covalently closed circular DNA persistence reservoir of hepatitis B viruses. *Proc Natl Acad Sci USA*. 2014;111(40): E4244-4253.
5. YimHJ, Kim W, Ahn SH, et al. BesifovirDipivoxil Maleate 144-Week Treatment of Chronic Hepatitis B: An Open-Label Extensional Study of a Phase 3 Trial. *Am J Gastroenterol*. 2020;115(8): 1217-1225.
6. Locarnini S, Littlejohn M, Aziz MN, et al. Possible origins and evolution of the hepatitis B virus (HBV). *Semin Cancer Biol*. 2013;23(6Pt B):561-575.
7. Boni C, Janssen H, Rossi M, et al. Combined GS-4774 and Tenofovir Therapy Can Improve HBV-Specific T-Cell Responses in Patients with Chronic Hepatitis. *Gastroenterology*. 2019;157(1): 227-241.e7.
8. Liem KS, van Campenhout M, Xie Q, et al. Low hepatitis B surface antigen and HBV DNA levels predict response to the addition of peginterferon to entecavir in hepatitis B e antigen positive chronic hepatitis B. *Aliment Pharmacol Ther*. 2019;49(4):448-456.
9. Yuen MF, GaneEJ, Kim DJ, et al. Antiviral Activity, Safety, and Pharmacokinetics of Capsid Assembly Modulator NVR 3-778 in Patients with Chronic HBV Infection. *Gastroenterology*. 2019; 156(5):1392-1403.e7.
10. Schuch A, Salimi Alizei E, Heim K, et al. Phenotypic and functional differences of HBV core-specific versus HBV polymerase-specific CD8+ T cells in chronically HBV-infected patients with low viral load. *Gut*. 2019;68(5): 905-915.
11. Seeger C, Sohn JA. Complete Spectrum of CRISPR/Cas9-induced Mutations on HBV cccDNA. *Mol Ther*. 2016;24(7):1258-1266.