Journal of Clinical and Translational Hepatology **2026** | Epub
DOI: 10.14218/JCTH.2026.00549

Review Article

Adoptive Immune Transfer in the Functional Cure of Chronic Hepatitis B: Insights from Hematopoietic Stem Cell Transplantation

He Ma, Jia-Rui Zheng, Xin-Kun Liu, Lin-Xiang Huang, Yan-Di Xie and Bo Feng*

Peking University People's Hospital, Peking University Hepatology Institute, Infectious Disease and Hepatology Center of Peking University People's Hospital, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis, Beijing, China.

Received: July 20, 2026 | **Revised:** October 05, 2026 | **Accepted:** October 23, 2026 | **Published online:** November 17, 2026

Abstract

Achieving a functional cure for chronic hepatitis B remains challenging, primarily due to the inability to reconstitute effective host immune responses against the virus. The unexpected functional cure of chronic hepatitis B following allogeneic hematopoietic stem cell transplantation provides a unique proof-of-principle model for immune-mediated HBsAg clearance. This review aims to elucidate that the core mechanism underlying hematopoietic stem cell transplantation-mediated HBsAg clearance lies in "adoptive immune transfer", and to explore design principles and future directions for modern cell-based immunotherapies based on this mechanism. We reviewed available case reports and meta-analytic evidence, acknowledging their limitations, and dissected the immunological mechanisms by which donor-derived hepatitis B virus-specific T and B cells may jointly reconstitute adaptive immunity and break host immune tolerance. We then comparatively evaluated the technical characteristics and limitations of chimeric antigen receptor T cell therapy and T-cell receptor-engineered T-cell therapy. Current engineered T-cell therapies, while translating the core principle of adoptive transfer, exhibit fundamental limitations including monoclonal specificity, inability to remodel the host microenvironment, and absence of durable humoral reconstitution. A broader functional-cure strategy may require adopting the paradigm of synergy and systemic immune reshaping exemplified by hematopoietic stem cell transplantation. Future strategies should develop temporally optimized, multilayered combination therapies, offering a possible pathway for next-generation therapeutics capable of systemically rebuilding antiviral immunity.

Introduction

Chronic hepatitis B (CHB) remains a major global public health challenge. Although current standard therapies—nucleos(t)ide analogues (NAs) and pegylated interferon-alpha (Peg-IFN-α)—effectively suppress viral replication and delay disease progression, the rate of functional cure in CHB (i.e., hepatitis B surface antigen (HBsAg) loss with or without anti-HBs seroconversion) is exceedingly low. Long-term data show that the annual HBsAg clearance rate after NA therapy is less than 1%, and Peg-IFN-α has limited efficacy as well.[1] The root of this dilemma lies in the persistent reservoir of hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) within the nuclei of infected hepatocytes, coupled with the integration of viral DNA fragments into the host genome.[2,3] This forms a viral reservoir that is extremely difficult to eradicate or silence. In recent years, while clinical trials of direct-acting antiviral agents (such as capsid assembly modulators and entry inhibitors) have continued to advance, no fundamental breakthrough has been achieved in attaining sustained HBsAg clearance.[4,5] There is a growing consensus that CHB is characterized by a dysfunctional antiviral immune response, where the functional exhaustion and paucity of virus-specific T cells constitute the central barrier preventing the host from clearing the virus autonomously. As a result, breaking

Keywords: Hematopoietic stem cell transplantation; Chronic hepatitis B; Functional cure; Adoptive immune transfer; Chimeric antigen receptor T cells; T-cell receptor-engineered T cells.

***Correspondence to:** Bo Feng, Peking University People's Hospital, Peking University Hepatology Institute, Infectious Disease and Hepatology Center of Peking University People's Hospital, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis, Beijing, China. ORCID: https://orcid.org/0000-0001-5084-6715. Tel: +86-13810254109, E-mail: fengbo@pkuph.edu.cn.

How to cite this article: Ma H, Zheng JR, Liu XK, Huang LX, Xie YD, Feng B. Adoptive Immune Transfer in the Functional Cure of Chronic Hepatitis B: Insights from Hematopoietic Stem Cell Transplantation. *J Clin Transl Hepatol.* Published online: Nov 17, 2026. DOI: 10.14218/JCTH.2026.00549.

© 2026 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Journal of Clinical and Translational Hepatology* at https://doi.org/10.14218/JCTH.2026.00549 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/jcth".

immune tolerance and reconstituting effective antiviral immune responses have become promising strategies for achieving functional cure for CHB.[6]

Hematopoietic stem cell transplantation (HSCT), a well-established treatment for hematological malignancies, has unexpectedly provided a unique "natural experiment" and historical insight for immune-mediated functional cure in CHB. Since the 1990s, clinical observations have consistently documented that hematologic patients with CHB who undergo allogeneic HSCT (allo-HSCT) from HBV-immune donors (HBsAg-negative, often accompanied by anti-HBc positivity) achieved durable clearance of their own HBsAg and developed protective anti-HBs.[7,8] This phenomenon is unlikely to be attributed solely to chemotherapy or immunosuppression. A central mechanism is thought to be "adoptive immune transfer", namely, the pre-existing, fully functional HBV-specific B and T cells from the donor are transferred to the recipient along with the stem cell graft. This may reconstitute a potent antiviral adaptive immunity, thereby overcoming a challenge that the recipient's own immune system had failed to resolve for years.[9] Given the significant risks, complexity, and high costs inherent to the HSCT procedure itself, it is not a feasible routine therapy for CHB. However, its irreplaceable scientific value is that it directly validates the core immunological principle in an unprecedented manner at the human level: adoptively transferring pre-formed antiviral immunity can achieve HBsAg clearance. This provides foundational proof-of-concept for all research aimed at achieving functional cure for CHB through immune intervention.

This review is guided by a central question: How can the high-risk, high-intensity, systemic 'macro' immune-mediated functional cure model of HSCT be decoded and reconfigured into safe, precise, and controllable 'micro' immunotherapeutic strategies? To answer this, we critically re-evaluate the clinical evidence and underlying immunological mechanisms of HSCT-mediated CHB functional cure, building a conceptual framework that connects historical discovery to modern translation. Allo-HSCT acts as a "proof-of-principle" model that demonstrates that wholesale transfer of a complete immune system can reconstitute immunity potent enough to support HBsAg clearance. However, its nonspecific nature and substantial risks prevent broader clinical use. Nevertheless, an ideal clinical cure strategy should maintain equivalent potency while exhibiting high target specificity and controllability. This is the goal of modern adoptive cell therapies like chimeric antigen receptor T cells (CAR-T) and T-cell receptor-engineered T cells (TCR-T), which represent potential engineered, safety-focused refinements of the principles first revealed by HSCT. Thus, clarifying this translational gap is essential for designing next-generation combination immunotherapies and advancing functional cure toward widespread clinical reality.

Clinical evidence for HSCT-mediated functional cure of CHB

Pooled analysis of cases: identifying HBsAg clearance from key cases

A review of cases reporting HBsAg clearance following HSCT over the past three decades (Table 1) provides clinical observations consistent with a role for adoptive immune transfer in HBsAg clearance.[10-16] Notably, as shown in Table 1, among the 11 patients in the reported cases of HBsAg clearance following HSCT, all donors (11/11, 100%) were anti-HBs-positive, and 4 donors (4/11, 36.4%) exhibited dual positivity for anti-HBc and anti-HBs.[10,11,13,14] Ilan *et al.*[11] reported a case in which a child with chronic HBV infection achieved rapid HBsAg seroclearance within 14 days after receiving bone marrow transplantation (BMT) and donor lymphocyte infusion from a double-positive sibling. Additionally, HBeAg-negative recipients accounted for 81.8% (9/11) of the cases,[10-13,15] and transient ALT elevation coinciding with HBsAg clearance was reported in 60% (6/10) of instances with available data.[10-15] In subsequent reports, the use of prophylactic NAs to control baseline viral load gained attention, with at least 3 reports in Table 1 explicitly adopting this strategy.[13,14,16] The subsequent development of high-titer, sustained anti-HBs after HBsAg clearance (e.g., > 1,000 mIU/mL in the Chiang 2011 case) is consistent with the successful establishment of donor-derived humoral immunity.[16] However, these studies differ in conditioning intensity, antiviral prophylaxis regimens, use of donor lymphocyte infusion, graft-versus-host disease and possible graft-versus-liver effects, immune reconstitution kinetics, baseline HBeAg and HBV DNA levels, quantitative HBsAg, hematological disease status, and overall survivorship. The contribution of concurrent nucleos(t)ide analogue therapy cannot be easily disentangled from the immunological effect of HSCT. Furthermore, the available patient-level data are heterogeneous and incomplete across reports, and the absence of a non-clearance comparator group means that the reported proportions describe only the successful cases and should be interpreted as descriptive rather than as evidence of causal determinants.

Effects of HSCT on HBV serological markers: evidence from quantitative meta-analysis

The individual cases summarized above suggested that HSCT may induce HBsAg clearance in a subset of CHB patients, but the absence of a non-clearance comparator and the small number of cases precluded a reliable quantitative estimate of the clearance rate. To address this gap, we conducted a systematic review and single-arm meta-analysis of published studies reporting HBsAg seroclearance after HSCT.[17] Nine studies comprising 308 patients met the inclusion criteria. Because substantial heterogeneity was anticipated, a random-effects model was used.

The pooled HBsAg clearance rate after HSCT was 26% (95% CI 14%–39%). Heterogeneity was high (I^2 = 87.1%, τ^2 = 0.0279, P < 0.0001), indicating that the effect varied considerably across studies. Sensitivity analysis using the leave-one-out method showed that the pooled proportion remained between 17% and 30% after omitting any single study, suggesting that the overall estimate was not driven by a single study. Small-study effects were assessed using Egger's test (P = 0.271), which did not suggest significant asymmetry, although the small number of studies limits the power of this assessment.

To explore the sources of heterogeneity, subgroup analyses were performed. Donor anti-HBs positivity was associated with a higher HBsAg clearance rate: 55% (95% CI 28%–82%) in recipients of anti-HBs-positive donors, compared with 8% (95% CI 0%–21%) in those receiving anti-HBs-negative grafts (P < 0.01). However, this association is based on retrospective,

Table 1. Table 1. Characteristics of patients with chronic hepatitis B achieving HBsAg seroclearance after allogeneic hematopoietic stem cell transplantation

Case (Author, Year)	Patient (Age, Sex, Disease)	Donor HBV Status (Relation)	Transplant (Source, Prophylaxis)	Pre-HSCT HBsAg/HBeAg/HBV DNA[a]	Time to HBsAg Loss/Anti-HBs (days)[b]	ALT Peak (U/L)[c]	Immune Evidence	Follow-up (months)[d] & Outcome
Lok 1992[10]	26, M, NR	Anti-HBc+/anti-HBs+ (Sister)	BMT, No prophylaxis	+ / − / NR	~270 / ~390	Present (symptomatic at 10 mo)	Histology: lobular necroinflammation; anti-HBs seroconversion	>13, sustained
Ilan 1993[11]	12, M, ALL	Anti-HBc+/anti-HBs+ (Brother, boosted)	BMT + DLI, No prophylaxis	+ / − / High (not quantified)	14 / 28	Mild (63, day 40)	Anti-HBs seroconversion post-DLI	>8, sustained
Brugger 1997[12]	29, M, AML (CR2)	Anti-HBs+ (Vaccinated sister)	BMT, NR	+ / − / Serum: Undetectable; Liver: Positive (PCR)	20 / 10	Present (coincident with seroconversion)	Anti-HBs with memory response (booster)	>12, sustained
Chiba 2003[13]	38, M, ALL	Anti-HBc+/anti-HBs+ (Brother)	PBSCT, Lamivudine (pre and post)	+ / − / Undetectable	64 / 64	Mild (197, day 25)	Anti-HBs seroconversion; possible GVHD association	24, sustained
Groll 2003[14]	12, F, ALL (CR2)	Anti-HBc+/anti-HBs+ (Brother)	PBSCT, Lamivudine (pre and post)	+ / + / 2×10^7 IU/mL (1×10^8 copies/mL)	~180 / ~180	Present during IS taper and seroconversion	Anti-HBs and Anti-HBe seroconversion	22, sustained
Pang 2009 (n = 5)[15]	Avg 36, 4M/1F, AML/CML/MDS	Anti-HBs+ (5 donors, HLA-matched)	Allo-PBSCT, NR	+ / − / NR	Avg 60 (30–90) / Avg 99 (90–108)	Minimal (1 patient)	Anti-HBs seroconversion and persistence	Avg 40 (12–75), sustained in all 5
Chiang 2011[16]	46, F, AML(M1)	Anti-HBs+ (Donor)	PBSCT + DLI, Lamivudine + Adefovir (pre and post)	+ / + / 8.10×10^3 IU/mL	278 / 58 (anti-HBs same)	NR (ALT normal on therapy)	Anti-HBs seroconversion post-DLI	25, sustained

This table summarizes key demographic, clinical, and virological data from published case reports and series (1992–2011) describing patients who cleared HBsAg following HSCT. [a] HBV DNA values are expressed in IU/mL where available, with original copies/mL in parentheses (1×10^8 copies/mL ≈ 2×10^7 IU/mL). "Undetectable" indicates below the detection limit of the assay used in the original study; assay detection limits were not uniformly reported across the 7 studies and therefore could not be standardized. "NR" denotes not reported. [b] Time to HBsAg loss and anti-HBs appearance converted to days where original data were in months (1 month ≈ 30 days). [c] ALT peak values were reported in U/L. [d] Follow-up converted to months (1 month ≈ 30 days). ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; BMT, bone marrow transplantation; CML, chronic myeloid leukemia; CR2, second complete remission; DLI, donor lymphocyte infusion; F, female; GVHD, graft-versus-host disease; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; IS, immunosuppression; M, male; MDS, myelodysplastic syndrome; NR, not reported; PBSCT, peripheral blood stem cell transplantation; PCR, polymerase chain reaction.

heterogeneous data and cannot establish causality. Recipient HBeAg status also differed: HBeAg-negative recipients had a clearance rate of approximately 29%, whereas HBeAg-positive recipients had a rate of only 2%. Notably, residual heterogeneity remained high even within the anti-HBs-positive subgroup (I^2 = 85.5%), suggesting that additional unmeasured factors may contribute to the outcome. Furthermore, the apparent association between donor anti-HBs positivity and recipient HBeAg negativity (10 of 11 cases with detailed serology) was derived from fragmented case-level data and should be considered hypothesis-generating.

In summary, this meta-analysis provides a quantitative estimate of HBsAg seroclearance

after HSCT and suggests that donor anti-HBs positivity and recipient HBeAg negativity may be associated with clearance. However, the high heterogeneity, retrospective nature of the included studies, and lack of individual patient data underscore that these findings are exploratory and require validation in prospective, controlled cohorts with standardized donor-recipient immunological profiling.

Integration of evidence and research gaps

The clinical evidence from HSCT, although limited by the absence of controlled comparisons and by substantial heterogeneity, provides a rational starting point for exploring the immunological mechanisms by which adoptive transfer may contribute to viral control. In this section, we integrate these observations into a conceptual framework that links donor-derived cellular and humoral immunity to HBsAg clearance, while explicitly acknowledging the gaps that require prospective validation.

The adoptive transfer of potent, polyclonal cytotoxic capacity

HBV-specific $CD8^+$ T cells from donors—particularly those from anti-HBc^+/anti-HBs^+ donors—have not been depleted by the host's chronic infection environment and retain proliferative capacity and the ability to reconstitute functional cellular immunity after adoptive transfer. In a prospective study of HLA-identical BMT recipients, donor PBMCs showed significant proliferation to HBcAg (stimulation index 4.6), and recipient-derived, donor-origin $CD4^+$ and $CD8^+$ T cells maintained HBcAg-specific proliferation for at least 52 weeks post-transplant.[18] The frequency of core-specific T cells was several-fold higher than that of surface antigen-specific T cells. A separate HCT study demonstrated that donor-derived cellular HBV immunity was detectable in 67% of recipients two weeks post-transplant and spontaneously reappeared in 83% of recipients without revaccination, indicating durable immune memory transfer.[19] These cells may recognize multiple viral epitopes and directly clear infected hepatocytes. This process is clinically marked by transient ALT elevation coinciding with HBsAg clearance.[20,21] This model suggests that a successful adoptive immunotherapy should infuse not a single-specificity cell group, but rather a product similar to the combination of polyclonal T-cell receptors (TCRs) generated during natural immune responses.

The deep reset of the host immune regulation environment

The myeloablative preconditioning and immunosuppression before transplantation may reduce the network of exhausted T cells, regulatory T cells (Tregs), and other inhibitory elements formed by the host, creating a favorable space for donor immune cell engraftment and function.[22] This suggests that effective adoptive immunotherapy is not just a "cell replacement" but a process of "systemic reset." For modern therapies like CAR-T and TCR-T, this requires the implementation of strategies to reshape the host's immune microenvironment before or at the same time as infusion of engineered cells. This suggests that combined therapies may be necessary.[21]

The reconstitution of active, long-lasting humoral immune surveillance

Donor-derived HBsAg-specific B cells and memory B cells may migrate to the recipient's bone marrow and differentiate into long-lived plasma cells, so that they can continue to produce anti-HBs endogenously.[12,23] This may support viral neutralization and sustained reductions in antigen load while helping preserve immune function, thus consolidating the therapeutic effect.

Despite these mechanistic insights, several critical gaps remain. A prospective controlled study directly comparing HSCT recipients with matched CHB patients receiving standard therapy is lacking, so the observed associations cannot be considered causal. Equally important, individual patient-level data are lacking, preventing multivariable adjustment for confounders such as conditioning intensity, antiviral prophylaxis, donor lymphocyte infusion, and graft-versus-host disease. The immunological basis for the apparent advantage of anti-HBs-positive donors and HBeAg-negative recipients also remains undefined; whether this reflects pre-formed antibody transfer, memory T-cell reconstitution, or a permissive host microenvironment is unknown. Furthermore, the durability of HBsAg loss and the status of intrahepatic cccDNA after HSCT have not been systematically assessed. Finally, it remains unclear how the immunological principles of HSCT can be translated into safe, targeted therapies for the general CHB population. These gaps define the research agenda for translating HSCT observations into clinical benefit.

Immunological mechanisms of HBsAg seroclearance promoted by adoptive transfer in HSCT

Immunological barriers to HBV infection

The core challenge in achieving functional cure of chronic HBV infection is persistent immune dysfunction arising from interactions between the virus and the host immune system, characterized by three interconnected immunological barriers (shown in Fig. 1A). In the early stage of infection, the virus produces HBsAg and HBeAg at higher levels than physiological norms, thereby establishing "antigen overload" tolerance.[24] A cross-sectional study of 233 HBV-infected patients quantified HBsAg across disease phases and demonstrated a stepwise decline from immune tolerance to inactive disease: immune tolerance (4.50 ± 0.43 $\log_{10}$ IU/mL), HBeAg-positive CHB (4.17 ± 0.66 $\log_{10}$ IU/mL), inactive HBV carrier (3.32 ± 0.44 $\log_{10}$ IU/mL), and HBeAg-negative CHB (3.23 ± 0.40 $\log_{10}$ IU/mL). This stage-dependent gradient suggests that antigen burden is highest precisely when immune control is least effective.[25] In addition, the structural polymorphisms in the key antigenic loop (AGL) of HBsAg also make it difficult to identify neutralizing antibodies.[26] The next barrier involves profound dysfunction in the host adaptive immune system, particularly among virus-specific $CD8^+$ T cells. A phenotypic study of HBV-specific $CD8^+$ T cells from 17 patients (16 HBeAg-negative, 1 HBeAg-positive) with significant HBV-specific T-cell frequencies found that inhibitory receptor expression followed a hierarchy dominated by PD-1 and 2B4, with lower expression of CD160, KLRG1, and Tim-3.[27] Building on this, a subsequent *ex vivo* functional study demonstrated that HBV-specific $CD8^+$ T cells with a functionally exhausted phenotype ($LAG3^+TIM3^+PD\text{-}1^+$) lacked *ex vivo* functionality, and that PD-L1 blockade enhanced responses only in patients with low exhaustion levels ($LAG3^-TIM3^-PD\text{-}1^+$), while responses were abrogated in patients with high frequencies of

 DOI: 10.14218/JCTH.2026.00549 | 2026

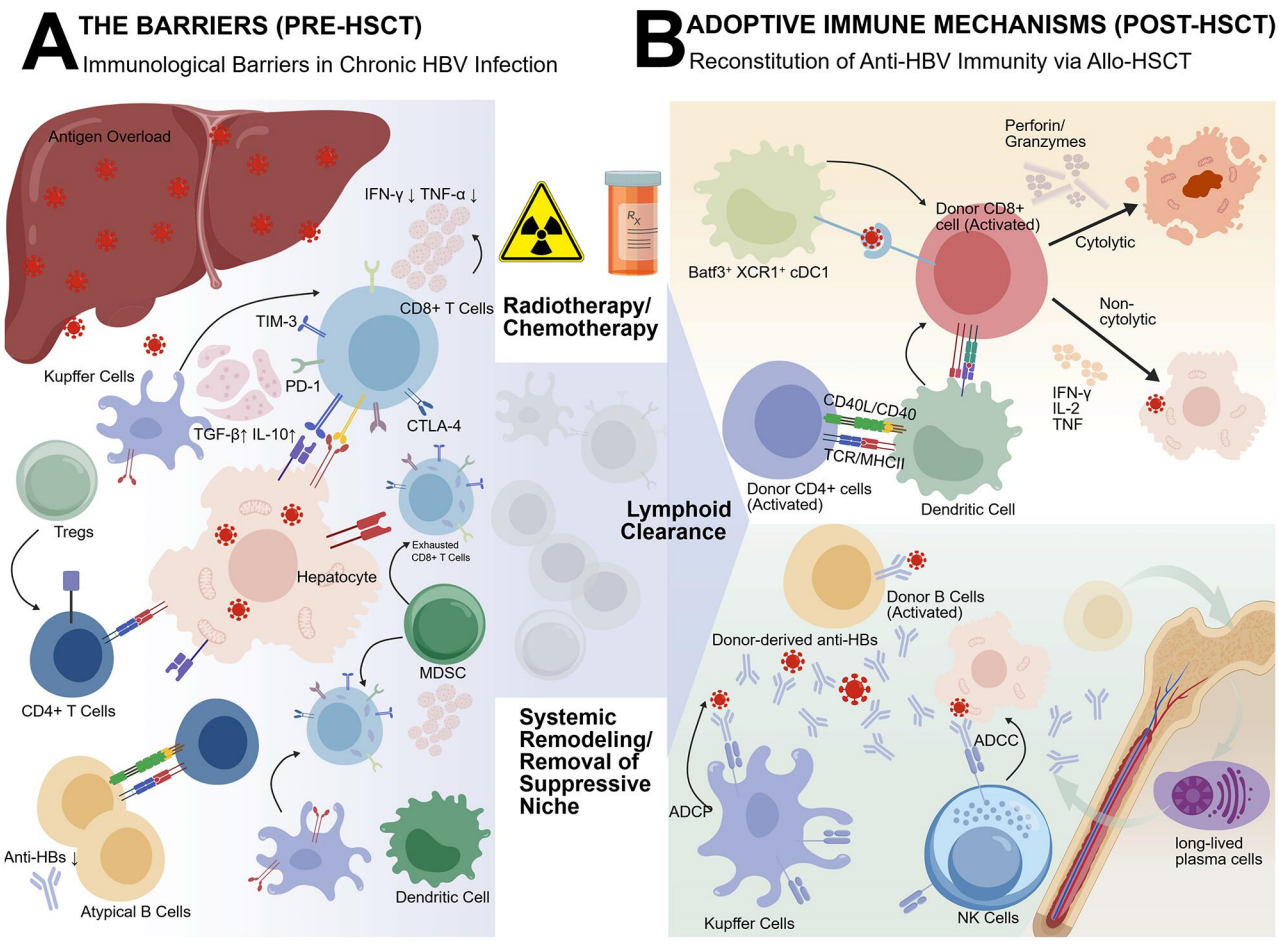


Fig. 1. Sequential immunological events leading to HBsAg seroclearance following allo-HSCT. This schematic delineates the transition from chronic HBV-induced immune tolerance to adoptive immune-mediated viral clearance through two critical phases. (A) Barriers before HSCT: immunosuppressive milieu in chronic HBV infection. Prior to transplantation, the hepatic microenvironment is characterized by profound immune dysfunction. Infected hepatocytes contribute to antigen overload and harbor persistent viral reservoirs. HBV-specific $CD8^+$ T cells exhibit functional exhaustion, as evidenced by upregulated inhibitory receptors including PD-1, TIM-3, and CTLA-4. This exhausted state is reinforced by immunosuppressive cellular components, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and Kupffer cells secreting TGF-β and IL-10. Concurrently, effector cytokine production (IFN-γ and TNF-α) is markedly diminished. Atypical B cells exhibit impaired antibody generation (anti-HBs↓), collectively precluding effective viral clearance. (B) Adoptive immune mechanisms after HSCT: Myeloablative conditioning reduces host suppressive cells, enabling donor engraftment. Donor $CD8^+$ T cells are activated by $Batf3^+XCR1^+$ cDC1s via cross-presentation, with $CD4^+$ T-cell help (CD40L-CD40, TCR-MHCII). They clear infected hepatocytes through cytolytic (perforin/granzyme) and non-cytolytic (IFN-γ, IL-2, TNF) pathways. Donor B cells produce anti-HBs, neutralizing virus and mediating ADCC/ADCP via Fc receptors; some B cells become long-lived plasma cells in bone marrow, ensuring sustained immunity. Created with BioGDP.com.[102] ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ALT, alanine aminotransferase; anti-HBs, antibodies to hepatitis B surface antigen; Batf3, basic leucine zipper ATF-like transcription factor 3; cccDNA, covalently closed circular DNA; CD40L, CD40 ligand; cDC1, type 1 conventional dendritic cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HSCT, hematopoietic stem cell transplantation; IFN-γ, interferon gamma; IL, interleukin; MDSC, myeloid-derived suppressor cell; MHCII, major histocompatibility complex class II; NK, natural killer; PD-1, programmed cell death protein 1; TCR, T-cell receptor; TGF-β, transforming growth factor beta; TIM-3, T-cell immunoglobulin and mucin-domain-containing protein 3; TNF, tumor necrosis factor; Treg, regulatory T cell; XCR1, chemokine (C motif) receptor 1.

$LAG3^+TIM3^+PD\text{-}1^+$ cells.[28] This indicates that PD-1/PD-L1 monotherapy is insufficient for deeply exhausted T cells. The helper function of $CD4^+$ T cells is also impaired: in HBV-ACLF, BTLA levels were significantly increased on circulating and intrahepatic $CD4^+$ T cells, and BTLA crosslinking suppressed activation (CD25, CD38, CD69), proliferation, and production of IFN-γ, IL-2, and TNF-α, while promoting apoptosis; BTLA knockdown reversed these effects.[29] The reaction of B cells is also affected. A direct *ex vivo* characterization of B cells from blood and liver of CHB patients found that purified, differentiated HBsAg-specific B cells had defective antibody production, consistent with undetectable anti-HBs *in vivo*. HBsAg-specific and

global B cells showed accumulation of $CD21^{-}CD27^{-}$ atypical memory B cells (atMBCs) with high expression of inhibitory receptors including PD-1, and these atMBCs demonstrated altered signaling, homing, differentiation, survival, and cytokine production that could be partially rescued by PD-1 blockade.[30] This identifies B-cell exhaustion as a reversible barrier. The last barrier is the uniquely immunosuppressive microenvironment of the liver.[31] The liver is enriched with Kupffer cells, Tregs, myeloid-derived suppressor cells (MDSCs), and others. These cells secrete cytokines such as TGF-β and IL-10 and interact with highly expressed receptors like PD-1 and TIM-3, collectively weaving a dense inhibitory network.[32,33] Together, these three factors form a vicious cycle: persistent viral antigen causes immune exhaustion, while exhausted immune cells and the suppressive microenvironment mutually reinforce each other, making it difficult for the body's own immune response to break this equilibrium.

Prerequisites for HSCT-mediated HBsAg clearance: systemic remodeling of the immune microenvironment by preconditioning

To overcome the deep immune tolerance formed by chronic HBV infection (as described above), it may be necessary not only to introduce new antiviral immunity but also to reshape the host's pre-existing, dysfunctional immune system. The myeloablative conditioning (chemotherapy/radiotherapy) in allo-HSCT is a critical step to achieve this goal. Its core function is to substantially remove the host's exhausted HBV-specific T cells, Tregs, and other suppressive immune cell populations through deep lymphoid clearance. A comparative study of conditioning regimens demonstrated that lymphodepleting regimens achieve profound and selective depletion of T and B lymphocytes: $CD3^{+}$ T cells declined by approximately 50% and $CD19^{+}$ B cells by over 90% by the time of transplantation.[34] This process transcends mere immunosuppression, constituting a systemic remodeling of the host's immune microenvironment. It transforms the originally inhibitory state, unfavorable for immune responses, into a necessary environment that permits the successful engraftment, activation, and functional execution of donor-derived immune cells. It is worth noting that CHB patients undergoing auto-HSCT can also achieve HBsAg seroclearance.[35] In this process, although there is no exogenous immune cell infusion, the same conditioning regimen can still induce endogenous immune reconstitution.[36] By clearing preexisting ineffective immune memory, allo-HSCT permits the reconstruction of a novel, non-depleted T-cell repertoire from the transplanted stem cells. The reconstitution of this new repertoire may follow a defined kinetic: thymic output can be detected by approximately 100 days post-transplant, and increased thymic output correlates with broader T-cell-receptor repertoires.[37] A large study of 62 allo-HSCT recipients demonstrated that $CD3^{+}CD8^{+}$ cell recovery was observed in 91.9% of patients by 6 months, whereas $CD3^{+}CD4^{+}$ recovery was achieved in only 22.6% of patients at 6 months, increasing to 61.3% by 12 months.[38] This enables the body to produce a fresh, effective immune response against HBV antigens, finally achieving viral control.[39] Therefore, the curative contribution of preconditioning is indispensable for both allogeneic and autologous HSCT. This strongly shows that breaking the host's inherent immunosuppressive state is an indispensable prerequisite for the realization of any form of immune-mediated functional cure.

In-depth analysis of adoptive immune mechanisms in HSCT

Adoptive cellular immunity

Donor-derived HBV-specific $CD8^{+}$ T cells: Compared with the deeply exhausted $CD8^{+}$ T cells within the recipient, these cells derived from healthy, immune-competent donors have not experienced long-term antigen exposure and retain effector function and proliferative potential. When these cells enter the recipient's body with the graft, they can be reactivated by viral antigens present in the liver. A key study clarifies their activation pathway[40]: liver-resident $Batf3^{+}XCR1^{+}$cDC1 (type 1 conventional dendritic cells) efficiently activate these donor-derived $CD8^{+}$ T cells by directly obtaining processed and presented HBsAg peptides from the surface of infected hepatocytes through a mechanism termed "cross-dressing". Key co-stimulatory signals such as ALCAM, LFA-1, and CD80 are also crucial for an optimal T-cell response (Fig. 1B). The activated $CD8^{+}$ T cells directly kill HBV-infected hepatocytes by secreting perforin, granzymes, and other mediators, thereby reducing the cccDNA reservoir by eliminating infected hepatocytes.[41] Clinically, this process is manifested as a transient elevation in ALT levels coinciding with HBsAg clearance post-HSCT, providing observable direct evidence of immune attack. This non-cytolytic control operates primarily through APOBEC3A/3B-mediated cccDNA deamination and subsequent decay, rather than through epigenetic silencing; knockdown of APOBEC3A/3B restores cccDNA levels under cytokine treatment.[42] However, this APOBEC-mediated degradation pathway has been characterized predominantly in acute infection models and *in vitro* systems, and its extent and durability in the chronic infection setting—particularly following HSCT-mediated adoptive transfer—remain incompletely defined. In contrast, epigenetic silencing of cccDNA—characterized by reduced acetylation of cccDNA-bound histones H3K9 and H3K27—is mediated by IFN-α, not by IFN-γ/TNF-α.[43] Notably, the HBV regulatory protein HBx counteracts this silencing by recruiting acetyltransferases onto the cccDNA minichromosome.[44] Recent work has further revealed that HBx-induced heat shock protein B1 (HSPB1) enhances cccDNA stability by reducing the recruitment and binding of APOBEC3A/APOBEC3B to cccDNA.[45] Importantly, neither mechanism achieves complete cccDNA eradication; both reduce or silence the cccDNA reservoir without eliminating it entirely.

Donor-derived HBV-specific $CD4^{+}$ T cells: However, the robust and durable $CD8^{+}$ T-cell response relies on indispensable co-stimulatory signals provided by donor-derived HBV-specific $CD4^{+}$ T cells. The traditional view is that such help primarily occurs in secondary lymphoid organs, but new evidence indicates that $CD4^{+}$ T cells can exert a more direct, on-site rescue function in the liver.[46] Studies reveal that effector $CD4^{+}$ T cells can migrate to the liver and activate hepatic macrophages (Kupffer cells) through CD40-CD40L interactions, prompting them to produce IL-27. IL-27 plays a critical role in this process. It can directly reverse the exhausted state in $CD8^{+}$ T cells induced by persistent antigen exposure from hepatocytes, thereby restoring their effector functions. Furthermore, $CD4^{+}$ T cells, particularly follicular helper T cells (Tfh), migrate to the germinal centers of secondary lymphoid organs, providing the necessary signals for the selection,

proliferation, and differentiation of donor-derived B cells into plasma cells. This process is crucial for the production of high-affinity antibodies and the formation of germinal centers.[40]

Adoptive humoral immunity

Donor-derived HBsAg-specific antibodies (anti-HBs): The primary function of the transferred anti-HBs is to directly neutralize circulating HBV virions and excessive HBsAg subviral particles, thereby potentially blocking their binding to the sodium taurocholate cotransporting polypeptide (NTCP) receptor on hepatocyte membranes.[47] This prevents new infections at their source. More importantly, these antibodies can recruit innate immune cells such as natural killer (NK) cells and macrophages via Fc-mediated antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). This constitutes an active immune clearance mechanism that eliminates infected hepatocytes or viral particles expressing HBsAg on their surface (Fig. 1B).[48]

Donor-derived HBsAg-specific B cells: Early studies reported that transplanting bone marrow from HBV-vaccinated donors to recipients can lead to donor-derived anti-HBs seroconversion within weeks post-transplantation. More importantly, long-term follow-up has shown that protective anti-HBs levels (> 10 mIU/mL) can be maintained for nearly four years in over 50% of such recipients.[49] This clearly demonstrates that the transplant conveys not only preformed antibodies but also, crucially, the B-cell clones themselves capable of producing anti-HBs. These B cells, as memory B cells or precursor plasma cells, home to the recipient's bone marrow, establish new survival niches, and differentiate into long-lived plasma cells. A mathematical modeling study of antibody persistence estimated that a subset of plasma cells can survive for decades, providing antigen-specific long-term protection without replenishment from B-cell precursors.[51] This endows the recipient with the ability to endogenously and continuously produce high-titer anti-HBs—an active immunity that can be sustained for years or even decades. Critically, this active immunity can continuously and effectively reduce the high circulating load of HBsAg. The persistent presence of HBsAg is precisely the core driver of T-cell exhaustion and immune tolerance. Thus, through this "antigen cleansing" effect, adoptive humoral immunity fundamentally reshapes the recipient's immune microenvironment. It transforms the immunosuppressive "high-antigen-load" state into a permissive "low-antigen-load" state, clearing the fundamental obstacles for the functional expression of adoptive cellular immunity and subsequent innate immune responses. Recent research on a "virus-hunter vaccine" corroborates this point from a different angle: engineered antibodies that actively clear HBsAg can effectively reverse immune tolerance and restore HBV-specific T-cell and B-cell responses.[52]

Synergistic integration

The effects of adoptive immune transfer may extend beyond the additive contributions of cellular and humoral immunity; instead, they may involve a highly coordinated and mutually enhanced dynamic network. Their synergy is reflected in multiple spatio-temporal dimensions. In the early post-transplant phase, the rapidly produced donor-derived anti-HBs can quickly reduce the viral load, alleviating the inhibitory antigen pressure on the adoptively transferred T cells and creating an opportunity for their activation and expansion. Research by Zhou *et al.* provides a theoretical basis for adoptive immunity,[53] suggesting that functional $CD8^+$ T cells can clear the virus more efficiently within a favorable immune microenvironment. Subsequently, activated $CD8^+$ T cells attack infected hepatocytes, thereby reducing the production of HBsAg at its source. This reduces the burden on humoral immunity, allowing sustained long-term therapeutic efficacy. In addition, donor-derived HBV-specific $CD4^+$ T cells serve as the physical and signaling hub for this synergy. They both enhance $CD8^+$ T cell function by secreting cytokines (e.g., IL-2, IL-27) and support B cells in producing high-quality antibodies.[46,54] This synergistic effect has been validated in clinical practice. Following allo-HSCT, patients often experience near-simultaneous or sequential HBsAg clearance and anti-HBs seroconversion, accompanied by long-term virological remission. This suggests the successful co-construction of a robust defense by both immune mechanisms.[55] This complex, spatiotemporally coordinated synergy is schematically summarized in Figure 1, which illustrates critical phases from the pre-transplant immunosuppressive barrier to post-transplant durable immune surveillance.

Importantly, HBsAg seroclearance—the current definition of functional cure—does not equate to elimination of intrahepatic cccDNA. HBsAg can originate from both cccDNA and integrated HBV DNA, and serum HBsAg measurements cannot distinguish these sources. Thus, a decline in HBsAg may reflect altered transcription or clearance of cells expressing integration-derived antigen, rather than direct evidence that cccDNA-containing hepatocytes have been eliminated. Indeed, serum HBsAg cannot distinguish between cccDNA-derived and integration-derived HBsAg, and integrated HBV DNA can maintain HBsAg production even when cccDNA transcription is suppressed or cccDNA is eliminated.[56-58] Notably, among patients achieving functional cure following pegylated interferon–based therapy, 68.1% remain cccDNA-positive on liver biopsy, and 25.5% harbour intrahepatic HBsAg-positive hepatocytes, with residual intrahepatic HBsAg mainly derived from transcriptionally active integrated HBV DNA.[59] Although these data derive from Peg-IFN–treated patients rather than HSCT recipients, they illustrate that functional cure is generally not associated with complete cccDNA eradication. Given that complete cytolytic elimination of all cccDNA-positive hepatocytes across the entire liver would be incompatible with survival, the durable HBsAg loss observed post-HSCT is most plausibly maintained through long-term immune surveillance—memory Tscm and sustained plasma cell–derived anti-HBs titers—that continuously suppress viral replication and prevent transcriptional reactivation of silenced intrahepatic cccDNA reservoirs, rather than through absolute eradication of cccDNA.[60,61]

Limitations of HSCT in treating CHB

Although allo-HSCT provides proof-of-principle for the immune-mediated HBsAg clearance, its adoption as a routine therapeutic strategy faces fundamental limitations. Its unfavorable risk–benefit profile makes it suitable only for patients primarily seeking treatment for life-threatening hematologic malignancies.[62] For the vast majority of CHB patients without concurrent hematological disease, this therapy is associated with unacceptable severe risks.

The 26% HBsAg clearance rate observed in our meta-analysis must be weighed against substantial transplant-related risks. Without antiviral prophylaxis, HBV reactivation occurs in 33%–81% of HBsAg-positive recipients, and even with prophylaxis, the 3-year cumulative incidence remains 9%–30%.[63,64] HBV-related hepatitis occurs in 10%–19.5% of HBsAg-positive recipients, and liver cirrhosis develops in 9.8% versus 0% in HBsAg-negative recipients ($P < 0.001$).[8] In a large cohort of 12,653 AML patients receiving HLA-matched SCT with standard calcineurin-based GVHD prophylaxis, the rates of acute GVHD grade II–IV, chronic GVHD, and extensive chronic GVHD were 23.8%, 37.0%, and 16.3%, respectively.[65] In a retrospective study of CHB patients undergoing allo-HSCT, 26.7% died from non-liver-related causes, primarily severe pneumonia or underlying hematologic disease.[66] Thus, the risk-benefit ratio is unacceptable for routine CHB management. The HSCT data are further limited by their retrospective nature, small sample sizes, and substantial heterogeneity ($I^2 = 87.1\%$). The contributions of conditioning chemotherapy, immunosuppression, and concurrent NA therapy cannot be fully disentangled from adoptive immune transfer. The patient population (hematological malignancy requiring HSCT) differs fundamentally from the general CHB population. These limitations underscore that HSCT should be regarded as a proof-of-principle model rather than a directly translatable therapeutic protocol.

Therefore, the core objective of this review is not to advocate HSCT as a routine CHB therapy. Instead, it aims to conduct an in-depth analysis of the successful immunological logic unveiled by HSCT as a "natural experiment" model—namely, adoptive transfer or systemic reconstitution of effective antiviral immunity is the key to achieving functional cure. This paradigm provides a solid historical legacy and theoretical foundation for developing safer and more controllable novel targeted immunotherapies, such as CAR-T and TCR-T.

Modern translational applications of adoptive immunotherapy

As mentioned above, current research focuses on translating its core immunological principles to develop safer, more precise, and clinically accessible therapeutic strategies. This section aims to outline the technological foundations and current clinical status of CAR-T and TCR-T therapies. Through a systematic comparison with the HSCT paradigm, it seeks to reveal their inherent limitations and future directions for optimization.[67]

Technical pathways of modern adoptive cell therapies

Adoptive cell therapy represents a precision immune engineering strategy. Both CAR-T and TCR-T therapies are fundamentally based on the genetic modification of the patient's own T cells to specifically recognize and eliminate target cells. However, they differ radically in their recognition mechanisms and, consequently, in the antigens they can target. CAR-T therapy uses a synthetically constructed chimeric antigen receptor to recognize antigens on the cell surface directly. This process does not rely on Major Histocompatibility Complex (MHC) presentation, granting it broader potential applicability and stronger signal activation. In the context of HBV, CAR-T cells are therefore structurally restricted to envelope antigens such as HBsAg and preS1, and remain vulnerable to the circulating HBsAg, which can sequester and exhaust engineered T cells before they reach infected hepatocytes (Fig. 2, left panel). In contrast, TCR-T therapy introduces optimized genes encoding natural T-cell receptors, enabling them to identify intracellular antigen peptides presented by MHC molecules. This mechanism is closer to physiological T-cell immune surveillance, allowing it to target intracellularly abundant antigens, including HBV core antigen (HBcAg), which is shielded from soluble serum decoys (Fig. 2, right panel). However, TCR-T is limited by the patient's specific HLA haplotypes. As shown in Figure 2, these two technological pathways provide distinct engineered approaches to emulate the adoptive cellular immunity observed in HSCT, and their differences directly determine which HBV antigens can be targeted by each modality. HBcAg, for example, is an intracellular antigen and is therefore not accessible to conventional CAR-T, whereas it can be recognized by TCR-T in the context of an appropriate HLA molecule.

Advances and challenges of CAR-T and TCR-T therapies for CHB

CAR-T therapy

CAR-T therapy has shown substantial clinical benefit in hematological malignancies; however, its application in chronic HBV infection remains largely in the preclinical or early exploratory stages.[68-70] Its theoretical advantage lies in its potent, MHC-independent activation, offering potential to overcome immune tolerance. Preclinical studies have provided quantitative evidence of both efficacy and toxicity. In AAV-HBV-infected mice, a fully human S-CAR reduced HBsAg to < 1% of pretreatment levels by day 140, with transient ALT elevation (2 to 4 fold) and persistent effector T cells in liver and spleen.[71] In HBV transgenic mice, S-CAR T cells controlled viral replication with only transient liver damage, and circulating antigen did not impair T cell function.[72]

Despite these encouraging signals, clinical translation faces three major challenges. First, hepatotoxicity is a primary concern. Systematic reviews indicate that approximately 38% of CAR-T-treated patients develop some degree of liver dysfunction, with any-grade ALT elevation occurring in 7%–54% and AST elevation in 14%–69% of recipients.[73] In a meta-analysis of adverse effects, the pooled incidence of ALT increase was 30% (95% CI 26%–34%).[74] Patients with chronic HBV frequently present with fibrosis or subclinical impairment of hepatic functional reserve, significantly lowering their tolerance to inflammatory insults and predisposing them to CAR-T-induced liver injury. Second, the high circulating HBsAg load and the immunosuppressive liver microenvironment jointly promote CAR-T exhaustion through distinct but convergent mechanisms. Persistent exposure to high antigen burden—particularly HBsAg—is a key determinant limiting T-cell efficacy, driving progressive upregulation of PD-1 and co-expression of TOX, a transcription factor that induces epigenetic changes to maintain the exhausted state.[75] As noted in a recent review, the hepatic high-antigen environment rapidly drives infused CAR-T cells into the same exhaustion state they were designed to circumvent, necessitating pre-engineering strategies such as TOX deletion.[76] In parallel, the immunosuppressive hepatic milieu—characterized by inflammation, fibrosis, hypoxia, and checkpoint molecule

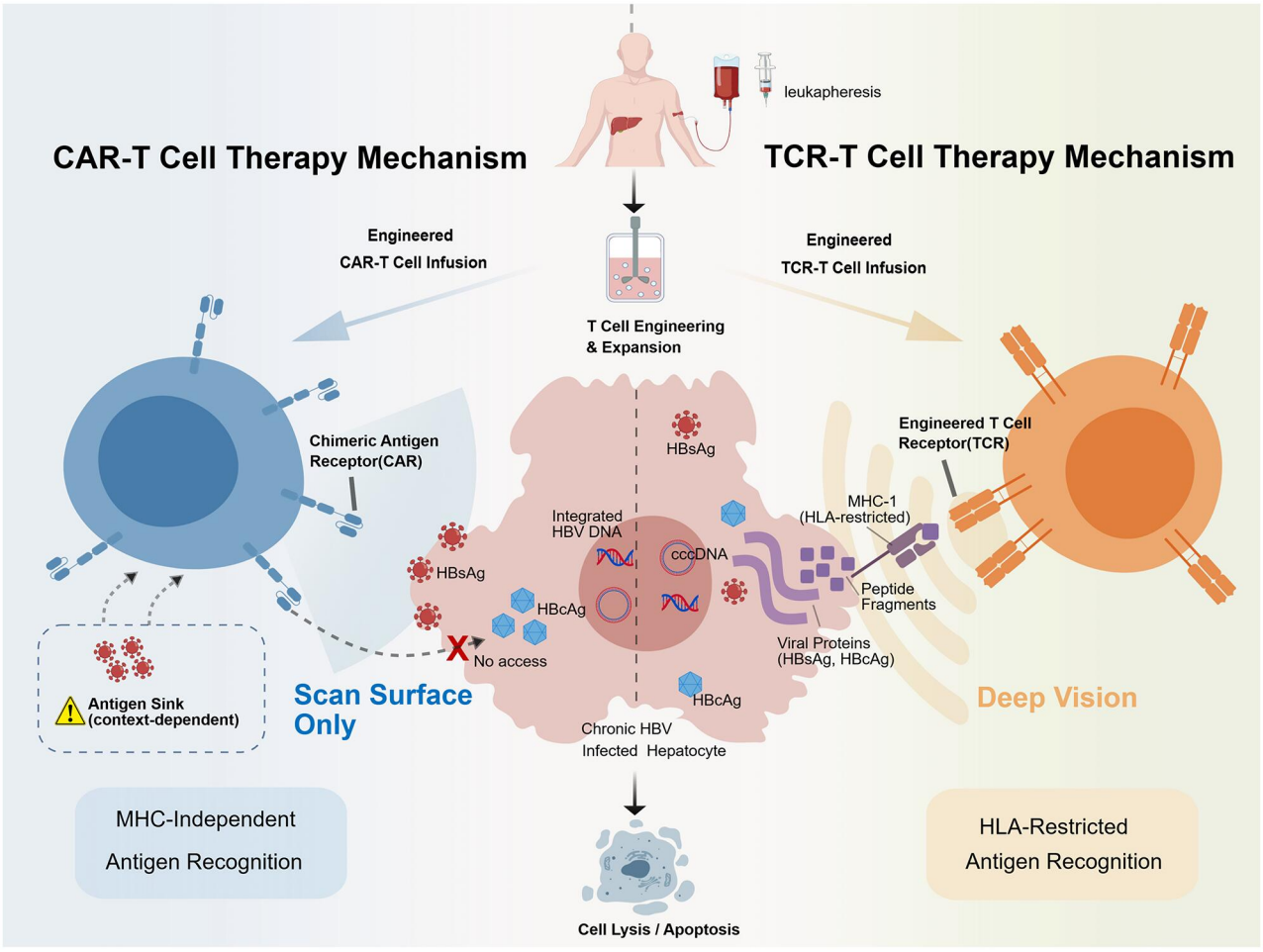


Fig. 2. Mechanistic distinctions between CAR-T and TCR-T recognition in chronic hepatitis B. CAR-T cells recognize cell-surface HBsAg in an MHC-independent manner (left). Their activity may be influenced by a circulating HBsAg-mediated antigen sink, the magnitude and biological importance of which are context-dependent (dashed box) and vary with construct design, epitope accessibility, antigen concentration, and tissue context. Conventional CAR-T cells cannot access intracellular HBcAg (cross symbol). TCR-T cells recognize intracellular peptide–HLA complexes in an MHC-dependent, HLA-restricted manner (right), enabling targeting of peptides derived from intracellular viral proteins including HBcAg, but restricting patient coverage to specific HLA haplotypes. HBsAg can originate from both cccDNA and integrated HBV DNA (icons in nucleus), and serum HBsAg measurements cannot distinguish these sources. Thus, CAR-T and TCR-T are not parallel strategies; they differ fundamentally in antigen recognition, MHC dependence, target range, and susceptibility to circulating antigen. Created with BioGDP.com[102] CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell; cccDNA, covalently closed circular DNA; DNA, deoxyribonucleic acid; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HLA, human leukocyte antigen; MHC, major histocompatibility complex; TCR, T-cell receptor; TCR-T, T-cell receptor-engineered T cell.

upregulation—further impairs CAR-T fitness. These two mechanisms—chronic antigenic stimulation and microenvironmental suppression—converge to limit CAR-T persistence and long-term antiviral activity. Third, HBV reactivation has been reported in 4.04% of CAR-T recipients, with 6.98% in resolved infection and 14.29% in chronic infection; severe hepatitis occurred in 50% of reactivation cases.[77] These limitations collectively indicate that CAR-T monotherapy is unlikely to achieve the systemic viral control demonstrated by HSCT.

TCR-T therapy

TCR-T therapy leverages the natural recognition mechanism of T cells, offering a theoretical advantage in targeting intracellular pathogens. In 2011, Gehring *et al.* demonstrated that an HLA-A2-restricted, HBV-specific TCR could recognize HBV-infected cells and HCC tumor cells expressing viral antigens from integrated HBV DNA.[78] Subsequent preclinical studies established the safety and efficacy of TCR-T in physiologically relevant animal models. In a humanized mouse model of HBV infection, T cells grafted with high-affinity HBcAg-specific TCRs eliminated HBV from infected HepG2-NTCP cultures, and a single transfer controlled infection with virological markers declining 4–5 $\log_{10}$ or below the detection limit[79]; importantly, when only a minority of hepatocytes were infected—as in a typical clinical setting—engineered T cells specifically cleared infected hepatocytes

without damaging non-infected cells, with ALT peaking at day 5–7 and normalizing thereafter.

Clinical translation has recently advanced, but the available data derive from a specific patient population with important limitations. In a first-in-human phase 1 trial, six HLA-A*02:01-positive patients with advanced HBV-related HCC received SCG101, an autologous TCR-T product targeting HBsAg. Serum HBsAg declined by 1.96 (range 0.16–3.84) $\log_{10}$ within 2 weeks in 4 of 6 patients (66.7%). Tumor shrinkage occurred in 3 of 6 patients, with target lesion reductions of -19.5%, -74.6%, and -100%; one patient achieved complete remission of the target lesion and remained progression-free for 27 months. All patients experienced transient ALT elevation (one case reaching 1,404 U/L on day 3) and grade ≤3 CRS, which were non-dose-limiting and manageable with corticosteroids, anti-IL-6, and/or vasopressors. No neurotoxicity was observed.[80,81]

These findings suggest on-target activity, but several limitations must be acknowledged. First, the study population comprised patients with advanced HBV-HCC who had failed prior systemic therapies; in this setting, a decline in circulating HBsAg may be influenced by tumor burden and by antigen expressed from integrated HBV sequences within tumor cells. Indeed, integrated HBV DNA is present in at least 80% of HBV-related HCCs and can produce and secrete HBsAg,[82,83] meaning that HBsAg decline cannot be attributed solely to clearance of infected hepatocytes. Second, the therapeutic objective in HCC—tumor control—and the acceptable balance between immune-mediated liver injury and clinical benefit differ fundamentally from those in non-malignant CHB. The observed ALT elevation (up to 1,404 U/L) would be poorly tolerated in patients with compensated CHB, and the risk of immune-mediated hepatotoxicity remains a platform-level concern that is not resolved by targeting a specific antigen. Third, TCR-T recognition is restricted by HLA class I molecules, typically HLA-A*02:01 in current HBV TCR-T products. Data compiled from global allele frequency databases indicate that HLA-A*02:01 is most prevalent in populations of European ancestry (approximately 25%–39%) but considerably less frequent in African (approximately 12%) and Asian (approximately 7%–11%) populations, meaning that an HLA-A*02:01-restricted product would be applicable to only a fraction of CHB patients worldwide, a limitation with direct implications for patient selection and the global deployment of TCR-T therapies. In contrast, allo-HSCT requires HLA matching for donor selection, but the resulting polyclonal immune reconstitution is not restricted to a single HLA allele. Fourth, the autologous manufacturing process—requiring leukapheresis, *ex vivo* expansion, and lymphodepletion—poses substantial logistical and cost barriers. These constraints are particularly relevant for CHB, a disease with a global prevalence exceeding 250 million and a disproportionately high burden in low- and middle-income countries.

Encouragingly, the field is now moving beyond HCC. SCG101V, a derivative therapy, has received China NMPA approval for a phase 1/2 trial in non-HCC chronic hepatitis B, and LioCyx-M004, an mRNA-electroporated TCR-T therapy, has received FDA IND clearance for a phase 1b/2 trial in CHB (NCT06885710). These trials will evaluate safety and antiviral efficacy in non-malignant populations, with endpoints focused on HBsAg and HBeAg changes rather than tumor response. Until these data are available, however, the HCC observations provide evidence of target engagement in a cancer setting but do not establish antiviral efficacy in the broader CHB population. Dedicated trials with longer follow-up and standardized safety monitoring are urgently needed.

Safety and toxicity management of engineered T-cell therapies in CHB

A critical safety consideration for adoptive T-cell therapies targeting HBV is the dual risk of cytokine release syndrome (CRS) and acute hepatic flare, the latter resulting from synchronous killing of infected hepatocytes and compounded by potential HBV reactivation. In HBV-related settings, this risk is further compounded by the possibility of HBV reactivation, which has been documented in patients with resolved HBV infection receiving CAR-T therapy at a rate of approximately 6.7% without antiviral prophylaxis, with one case presenting with severe hepatitis (ALT 592.1 U/L) and HBsAg seroconversion 14 months post-infusion. Prophylactic nucleos(t)ide analogue therapy with regular HBV DNA monitoring effectively controls reactivation, as demonstrated in patients with resolved HBV infection receiving CAR-T therapy.[84] Transient-expression platforms, such as mRNA-electroporated HBV-TCR-T cells, limit the duration of effector activity and have shown acceptable safety with no CRS or neurotoxicity in a phase I trial.[85] For longer-acting products, small-molecule-regulated switchable CAR platforms allow reversible control of T-cell activity,[86] and dose fractionation has been used in early-phase CAR-T trials to limit hepatotoxicity. Preclinical models of chronic HBV infection have further demonstrated that HBsAg-targeted CAR-T cells induce only moderate and self-limiting liver damage, with ALT peaking at approximately day 14 and normalizing thereafter without evidence of persistent tissue injury.[87] In the SCG101 TCR-T trial, grade 3 CRS occurred but was non-dose-limiting and manageable with corticosteroids, anti-IL-6 agents, and vasopressors, with only transient ALT elevation.[81] Should CRS or hepatic injury occur, management follows established toxicity grading frameworks, with tocilizumab and corticosteroids for CRS and prompt antiviral escalation for suspected HBV reactivation.[88]

Comparison and integration: gaps and implications between modern therapies and the HSCT paradigm

While CAR-T/TCR-T therapies share the underlying principle of adoptive immune transfer with HSCT, both are grounded in the "adoptive immune transfer" paradigm and aim to reconstitute antiviral immunity from an external source,[89] they differ fundamentally in the quality and scope of their immunological output, which dictates the limitations of their application as monotherapies. First, regarding the breadth and specificity of the immune response, HSCT provides a polyclonal repertoire of HBV-specific T cells and B cells from an immune-competent donor, capable of launching a coordinated attack against multiple viral antigen epitopes. In contrast, current CAR-T/TCR-T therapies are inherently monoclonal or oligoclonal, targeting a single or a limited number of epitopes, rendering them more vulnerable to viral antigen variation or immune escape. Second, concerning the persistence and systemic nature of immune memory, HSCT can reconstruct the entire adaptive immune

system. It not only transfers donor memory T cells but, more crucially, allows donor-derived HBsAg-specific B cells to home to the recipient's bone marrow, where they differentiate into long-lived plasma cells. This achieves endogenous, sustained production of anti-HBs for years or even decades.[90] This active, continuous humoral immune surveillance is key to consolidating the functional cure and preventing relapse. In stark contrast, current engineered T-cell therapies primarily generate effector T cells and lack the capacity to reconstitute this endogenous, long-lasting humoral immunity. Finally, in terms of the systemic remodeling of the host immune microenvironment, the myeloablative preconditioning prior to HSCT clears the host's original network of exhausted immunity, creating a completely new permissive space. CAR-T/TCR-T therapies, however, merely infuse effector cells into the pre-existing, suppressive immune microenvironment, where their function may be rapidly exhausted.[91]

These fundamental differences indicate that single-modality engineered cell therapies are unlikely to fully recapitulate the systemic immune reconstruction and durable immune surveillance that maintains functional cure achieved by HSCT. Neither HSCT nor engineered T-cell therapies eradicate intrahepatic cccDNA; the distinction lies in the capacity of HSCT to establish long-term humoral and cellular surveillance that continuously suppresses cccDNA transcription. The immunological disparities are illustrated conceptually in Figure 3 (left panel). Bridging these gaps will require multi-layered combination strategies, which are discussed in detail in Section 5.

Implications and outlook: the pathway to transforming HSCT into a functional-cure strategy

Key implications of HSCT for the design of immunotherapies

Insights gleaned from HSCT cases provide design principles for next-generation therapies that may extend beyond single-target approaches. In target selection, priority should be given to antigens that are indispensable in the viral life cycle. Compared to HBsAg, which serves as a major tolerogen and is subject to the circulating antigen sink effect, HBcAg represents a potentially attractive target—but its applicability is strictly modality-dependent. For CAR-T, conventional constructs recognize cell-surface proteins and cannot access intracellular HBcAg; therefore, HBcAg is not a feasible CAR-T target. For TCR-T, HBcAg-derived peptides can be presented on HLA molecules and recognized by engineered TCRs, enabling targeting of intracellular core epitopes shielded from soluble serum decoys. However, HBcAg-directed TCR-T remains subject to HLA coverage limitations, and the risk of hepatotoxicity cannot be excluded. The clinical association between HBcAg-specific T-cell responses and reduced relapse after nucleos(t)ide analogue withdrawal (hazard ratio 0.21; 95% CI 0.05–0.88) supports the immunological relevance of HBcAg-specific T cells,[92] but it does not establish HBcAg as the optimal engineered-cell target, nor does it resolve HLA coverage, antigen presentation, or hepatotoxicity concerns. Thus, HBcAg represents a potential target for TCR-T, but its clinical validation remains to be established through dedicated trials. In addition, targeting HBcAg alone does not resolve the intrinsic limitations of the TCR-T platform, including HLA restriction, MHC class I downregulation, and the risk of immune-mediated hepatotoxicity. Addressing these challenges will likely require modality-level innovations—such as non-polymorphic HLA-E-restricted TCRs, soluble bispecific TCR platforms,[93] combination with anti-PD-L1-IFN-α-adjuvanted HBsAg vaccine agonists to restore antigen presentation,[94] and inducible safety switches like iC9,[95] but each of these approaches remains at an early stage of development and faces substantial hurdles in efficacy, safety, and clinical translation.

Combination therapy: establishing a multi-tiered collaborative strategy

Given the difficulty of replicating the multifaceted immune effects of HSCT through monotherapy, combination therapies based on sequential timing and complementary mechanisms may offer a useful pathway toward achieving functional cure (Fig. 3, right panel). The core concept is to reproduce selected features of the immunological conditions that sustain functional cure after HSCT, constructing a multi-layered, synergistic viral control system. The foundation of this strategy (Layer 1) is the sustained use of NAs and other viral-targeting agents to maximally suppress viral replication and reduce antigen burden. Importantly, Peg-IFN-α should be incorporated as a critical immunomodulatory component within this layer, rather than viewed merely as an antiviral agent. Recent randomized trials suggest that adding Peg-IFN to other modalities significantly increases functional cure rates. In the Piranga trial, xalnesiran plus Peg-IFN was associated with HBsAg loss at 24 weeks after treatment in 23% of patients (95% CI 10%–40%), compared with 3%–12% in groups receiving xalnesiran alone or with a TLR7 agonist.[96] Similarly, in the B-Together trial, sequential bepirovirsen followed by Peg-IFN reduced post-treatment relapse, with 9%–15% of participants achieving sustained HBsAg < 0.05 IU/mL and HBV DNA <LLOQ, and all responders had baseline HBsAg ≤3,000 IU/mL.[97] The 2026 APASL guideline now recommends that for patients with undetectable HBV DNA and HBsAg < 1,500 IU/mL on NUC therapy, a finite course of Peg-IFN-α (up to 96 weeks) should be considered to pursue functional cure.[98] These data underscore that immunomodulation—rather than antiviral suppression alone—is essential for durable HBsAg loss. However, the absolute efficacy of these combinations remains modest (23% at best), and patient selection based on baseline HBsAg levels is critical, which limits broad applicability.

Building upon this foundation (Layer 2), targeted adoptive cell therapies (e.g., CAR-T/TCR-T) could be introduced as candidate approaches to reducing HBV-infected hepatocytes and the cccDNA reservoir. Preclinical and early clinical data suggest that engineered T cells can achieve rapid HBsAg decline (e.g., 1.96 $\log_{10}$ within 2 weeks in the SCG101 trial), but their durability and safety in non-malignant CHB remain to be established. The combination with Peg-IFN or other immunomodulators may enhance their function by improving antigen presentation and reducing exhaustion.

Finally (Layer 3), immunomodulators are combined to ameliorate the liver's immunosuppressive microenvironment and sustain the response. For instance, TLR8 agonists may activate myeloid dendritic cells and monocytes to promote a pro-antiviral cytokine environment[99]; short-term, judicious use of PD-1/PD-L1 pathway inhibitors may help reverse T-cell functional exhaustion;

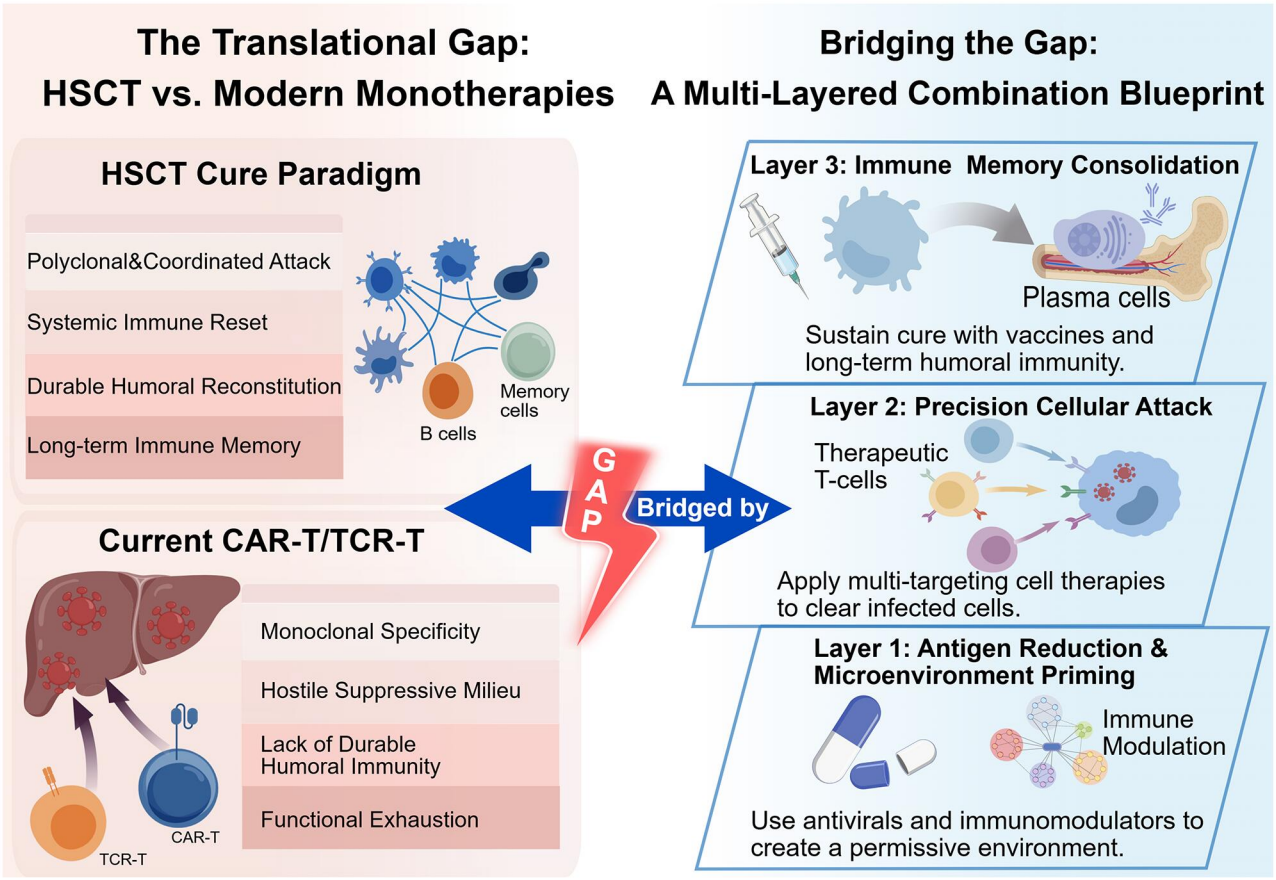


Fig. 3. The translational gap and the multi-layered combination blueprint: a translational pathway from the HSCT paradigm to next-generation adoptive immunotherapies. This schematic contrasts the fundamental immunological disparities between allogeneic hematopoietic stem cell transplantation (HSCT) and current engineered T-cell therapies (CAR-T/TCR-T), and subsequently presents a multi-layered combination strategy framework derived from the manuscript's discussion. The left panel juxtaposes the immunological characteristics of two therapeutic modalities. Upper box (HSCT cure paradigm) depicts a "wholesale" immune reconstitution. A polyclonal repertoire of donor-derived T cells ($CD8^+$, $CD4^+$) and B cells cooperatively infiltrate the liver to target and reduce infected hepatocytes. Lower box (CAR-T/TCR-T monotherapy) illustrates a "precision but constrained" monoclonal approach. A single engineered T cell (bearing a CAR or TCR) attempts to target an infected hepatocyte. The right panel proposes a three-tiered, vertically integrated combination strategy designed to systematically address the gap delineated on the left. Layer 1 (foundation) employs potent antiviral agents and immunomodulators to remodel the immunosuppressive liver milieu, creating a permissive "therapeutic window" for subsequent interventions. Layer 2 (core) introduces multi-targeting engineered T cells (e.g., combinations of CAR-T or TCR-T cells directed against distinct viral epitopes) to achieve precise elimination of HBV-infected hepatocytes and reduction of the intrahepatic cccDNA reservoir. Layer 3 (apex) utilizes therapeutic vaccination to expand endogenous HBV-specific T-cell responses, coupled with strategies to induce long-lived humoral immunity (e.g., sustained anti-HBs production by bone marrow plasma cells), thereby establishing durable immune surveillance to prevent viral relapse. These therapeutic layers are intended to be implemented in a timed sequence and function synergistically. Created with BioGDP.com.[102] CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell; cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem cell transplantation; TCR, T-cell receptor; TCR-T, T-cell receptor-engineered T cell.

and therapeutic vaccination may expand endogenous HBV-specific T-cell responses.[100] These approaches aim to establish durable immune surveillance. However, each layer faces challenges: Peg-IFN has significant side effects; engineered T cells are costly and complex to manufacture; and immunomodulators may risk immune-related adverse events. Therefore, the optimal sequence, dosing, and patient selection for this multi-tiered strategy require prospective validation.

In summary, a multi-layered combination strategy that integrates antiviral suppression, immune modulation, and engineered cell therapy may provide a rational direction for research toward functional cure. Yet, the current evidence base is limited by small trials, heterogeneous patient populations, and short follow-up. Future studies must provide quantitative endpoints, standardized protocols, and rigorous safety monitoring to translate this blueprint into clinical reality.

Future research directions

Building on the gaps identified in the preceding sections, several research directions warrant exploration. At the level of immune-

cell source identification and characterization, a potentially informative strategy is the direct reverse-engineering analysis of individuals who achieved functional cure following HSCT. By integrating scRNA-seq, scTCR-seq, and scBCR-seq, it is possible to precisely identify the donor-derived, reconstituted HBV-specific T-cell and B-cell clones within these individuals that possess potent antiviral activity and durable memory potential. This approach could identify candidate TCR sequences and antibody genes, potentially providing a basis for designing highly effective engineered cell or antibody therapies. This direction directly addresses the core limitation of "lack of polyclonality" in current therapies, aiming to define what constitutes the "optimal" immune response from this successful HSCT model. Secondly, at the level of engineering optimization, it is crucial to improve safety and accessibility. This includes developing remote-controllable "switchable" CAR-T cells, whose activity can be regulated by small-molecule drugs. This scheme seeks to resolve the safety conflict between the uncontrollability of HSCT and the on-target toxicity of engineered cell therapies, achieving a dynamic balance between therapeutic potency and safety. Concurrently, the use of gene-editing technologies like CRISPR to manufacture universal (off-the-shelf) cell products aims to overcome the bottlenecks of high cost and complex manufacturing associated with autologous cell therapies.[101] However, it must be noted that although this path enhances accessibility, it also faces new challenges such as addressing allogeneic rejection and potentially sacrificing individualized immune synergy. Finally, at the level of clinical translation, there is an urgent need to establish a patient stratification system based on biomarkers.[6,21] For example, by comprehensively analyzing baseline HBsAg levels, precursor frequency of HBV-specific T cells, and characteristics of the liver immune microenvironment, it may be possible to predict the sensitivity of different patients to cell therapies. The goal is to prospectively identify patients with a more permissive immune microenvironment, thereby maximizing clinical benefit and optimizing the allocation of therapeutic resources.

Limitations

This review constructs a translational framework from the principles of HSCT to modern adoptive immunotherapies, yet its perspective is subject to certain limitations. Its core arguments rely heavily on historical case reports or small-series studies of HSCT-mediated HBsAg clearance, which provide a limited level of evidence. The lack of prospective controlled data may affect the universal applicability of the conclusions. Furthermore, theoretical simplifications exist when generalizing the systemic immune reset model demonstrated by HSCT to single-component therapies like CAR-T/TCR-T. In fact, it remains challenging for engineered cells to fully recapitulate the polyclonal immune synergy and long-term reconstitution effects achieved by HSCT with respect to persistence *in vivo*, overcoming local immunosuppression, and avoiding functional exhaustion. In addition, many novel cell therapies discussed are still in preclinical or early-stage trials. Their long-term safety, durability of efficacy, and optimal combination strategies ultimately need validation through future larger-scale, longer-term clinical studies.

Conclusions

This review suggests that allo-HSCT serves as a natural experiment model, supporting the concept that CHB can be functionally cured through adoptive immune transfer. By analyzing the immunological mechanisms of donor-derived HBV-specific T cells and antibodies that clear the virus synergistically, we propose that the central mechanism involves reconstitution of effective adaptive immunity. Based on this fundamental immunological principle, modern engineered adoptive cell therapies, represented by CAR-T and TCR-T, aim to translate this macro-mechanism into safe, controllable, and precise therapeutic strategies. The current research frontier and challenge lie in how to systemically build a multi-layered, temporally optimized synergistic treatment system through combinations with potent antiviral agents and novel immunomodulators. The ultimate goal is to translate this functional cure paradigm, derived from a unique clinical observation, into a widely applicable clinical reality

Acknowledgments

We thank the researchers whose published data contributed to this review. We also acknowledge Peking University People's Hospital for providing a research platform. We apologize to colleagues whose work could not be cited due to space constraints.

Funding

This study was funded in full by the Capital's Funds for Health Improvement and Research (CFH), grant number [2024-24084].

Conflict of interest

BF has been an Editorial Board Member of Journal of Clinical and Translational Hepatology since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (BF, HM), acquisition of data (HM, JRZ, XKL, LXH), analysis and interpretation of data (HM), drafting of the manuscript (HM), critical revision of the manuscript for important intellectual content (BF), administrative, technical, or material support (BF, YDX), and study supervision (BF). All authors have contributed to this study and have approved the final manuscript.

References

[1] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–398. DOI: 10.1016/j.jhep.2017.03.021, PMID: 28427875.

[2] Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol 2022;22(1):19–32. DOI: 10.1038/s41577-021-00549-4, PMID: 34002067.

[3] Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut 2015;64(12):1972–1984. DOI: 10.1136/gutjnl-2015-309809, PMID: 26048673.

[4] Yu YY, Li J, Wang WX, Fan PY, Wang FS. [Research progress on new drugs for the treatment of chronic hepatitis B virus infection].

Zhonghua Gan Zang Bing Za Zhi 2025;33(5):493–499. DOI: 10.3760/cma.j.cn501113-20240521-00258, PMID: 40528594.

[5] Fanning GC, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov 2019;18(11):827–844. DOI: 10.1038/s41573-019-0037-0, PMID: 31455905.

[6] Thimme R, Hofmann M, Bertoletti A, Le Bert N. Decoding HBV-specific adaptive immunity: from natural clearance to cure. Gut 2026;75(9):1857–1866. DOI: 10.1136/gutjnl-2025-337129, PMID: 41314788.

[7] Lau GK, Lok AS, Liang RH, Lai CL, Chiu EK, Lau YL, *et al*. Clearance of hepatitis B surface antigen after bone marrow transplantation: role of adoptive immunity transfer. Hepatology 1997;25(6):1497–1501. DOI: 10.1002/hep.510250631, PMID: 9185774.

[8] Hui CK, Lie A, Au WY, Leung YH, Ma SY, Cheung WW, *et al*. A long-term follow-up study on hepatitis B surface antigen-positive patients undergoing allogeneic hematopoietic stem cell transplantation. Blood 2005;106(2):464–469. DOI: 10.1182/blood-2005-02-0698, PMID: 15797991.

[9] Ilan Y, Nagler A, Adler R, Naparstek E, Or R, Slavin S, *et al*. Adoptive transfer of immunity to hepatitis B virus after T cell-depleted allogeneic bone marrow transplantation. Hepatology 1993;18(2): 246–252. DOI: 10.1002/hep.1840180204, PMID: 8340054.

[10] Lok AS, Liang RH, Chung HT. Recovery from chronic hepatitis B. Ann Intern Med 1992;116(11):957–958. DOI: 10.7326/0003-4819-116-11-957_2, PMID: 1580459.

[11] Ilan Y, Nagler A, Adler R, Tur-Kaspa R, Slavin S, Shouval D. Ablation of persistent hepatitis B by bone marrow transplantation from a hepatitis B-immune donor. Gastroenterology 1993;104(6): 1818–1821. DOI: 10.1016/0016-5085(93)90664-x, PMID: 8500741.

[12] Brugger SA, Oesterreicher C, Holfmann H, Kalhs P, Greinix HT, Müller C. Hepatitis B virus clearance by transplantation of bone marrow from hepatitis B immunised donor. Lancet 1997; 349(9057):996–997. DOI: 10.1016/S0140-6736(05)62893-0, PMID: 9100630.

[13] Chiba T, Yokosuka O, Goto S, Fukai K, Imazeki F, Shishido H, *et al*. Successful clearance of hepatitis B virus after allogeneic stem cell transplantation: beneficial combination of adoptive immunity transfer and lamivudine. Eur J Haematol 2003;71(3):220–223. DOI: 10.1034/j.1600-0609.2003.00114.x, PMID: 12930325.

[14] Groll AH, Baumann-Köhler M, Storkebaum B, Kühn J, Jürgens H, Vormoor J. Durable clearance of hepatitis B virus after allogeneic blood stem cell transplantation by adoptive immunity transfer and antiviral chemotherapy. Pediatr Infect Dis J 2003;22(8):753–755. DOI: 10.1097/01.inf.0000078161.13315.cc, PMID: 12938680.

[15] Pang Y, Feng Y, Chen R, Hua J. HBsAg seroconversion after allogeneic hematopoietic stem cell transplantation: 5 cases[in Chinese]. J Pract Med. 2009; 25(6):846

[16] Chiang LT, Yao M, Ko BS, Chen CH. Development of immunity against hepatitis B virus after donor lymphocyte infusion in a peripheral blood stem cell transplantation recipient with chronic hepatitis B. Infection 2011;39(4):363–365. DOI: 10.1007/s15010-011-0120-x, PMID: 21544586.

[17] Ma H, Zheng J, Huang L, Qiu Z, Wang Z, Xie Y, *et al*. Single-Arm Meta-Analysis and Systematic Review on Clinical Cure of Chronic Hepatitis B After Haematopoietic Stem Cell Transplantation: Immunoregulatory Mechanisms and Clinical Translational Insights. J Viral Hepat 2026;33(1):e70114. DOI: 10.1111/jvh.70114, PMID: 41363012.

[18] Lau GK, Suri D, Liang R, Rigopoulou EI, Thomas MG, Mullerova I, *et al*. Resolution of chronic hepatitis B and anti-HBs seroconversion in humans by adoptive transfer of immunity to hepatitis B core antigen. Gastroenterology 2002;122(3):614–624. DOI: 10.1053/gast.2002.31887, PMID: 11874993.

[19] Lindemann M, Barsegian V, Runde V, Fiedler M, Heermann KH, Schaefer UW, *et al*. Transfer of humoral and cellular hepatitis B immunity by allogeneic hematopoietic cell transplantation. Transplantation 2003;75(6):833–838. DOI: 10.1097/01.TP.0000054841.42796.68, PMID: 12660511.

[20] Lau GK, Liang R, Lee CK, Yuen ST, Hou J, Lim WL, *et al*. Clearance of persistent hepatitis B virus infection in Chinese bone marrow transplant recipients whose donors were anti-hepatitis B core- and anti-hepatitis B surface antibody-positive. J Infect Dis 1998;178(6): 1585–1591. DOI: 10.1086/314497, PMID: 9815208.

[21] Maini MK, Burton AR. Restoring, releasing or replacing adaptive immunity in chronic hepatitis B. Nat Rev Gastroenterol Hepatol 2019;16(11):662–675. DOI: 10.1038/s41575-019-0196-9, PMID: 31548710.

[22] Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 2015;15(8):486–499. DOI: 10.1038/nri3862, PMID: 26205583.

[23] Radbruch A, Muehlinghaus G, Luger EO, Inamine A, Smith KG, Dörner T, *et al*. Competence and competition: the challenge of becoming a long-lived plasma cell. Nat Rev Immunol 2006;6(10): 741–750. DOI: 10.1038/nri1886, PMID: 16977339.

[24] Bertoletti A. The immune response in chronic HBV infection. J Viral Hepat 2024;31 Suppl 2:43–55. DOI: 10.1111/jvh.13962, PMID: 38845402.

[25] Tan Z, Li M, Kuang X, Tang Y, Fan Y, Deng G, *et al*. Clinical implications of hepatitis B surface antigen quantitation in the natural history of chronic hepatitis B virus infection. J Clin Virol 2014;59(4):228–234. DOI: 10.1016/j.jcv.2014.01.013, PMID: 24529415.

[26] He X, Tao W, Kang Y, Xu J, Liu X, Chen L. Structural polymorphism of the antigenic loop in HBV surface antigen dictates binding of diverse neutralizing antibodies. Cell Discov 2025;11(1):57. DOI: 10.1038/s41421-025-00803-2, PMID: 40523894.

[27] Bengsch B, Martin B, Thimme R. Restoration of HBV-specific CD8+ T cell function by PD-1 blockade in inactive carrier patients is linked to T cell differentiation. J Hepatol 2014;61(6):1212–1219. DOI: 10.1016/j.jhep.2014.07.005, PMID: 25016223.

[28] Ferrando-Martinez S, Snell Bennett A, Lino E, Gehring AJ, Feld J, Janssen HLA, *et al*. Functional Exhaustion of HBV-Specific CD8 T Cells Impedes PD-L1 Blockade Efficacy in Chronic HBV Infection. Front Immunol 2021;12:648420. DOI: 10.3389/fimmu.2021.648420, PMID: 34589081.

[29] Yu X, Yang F, Shen Z, Zhang Y, Sun J, Qiu C, *et al*. BTLA contributes to acute-on-chronic liver failure infection and mortality through CD4(+) T-cell exhaustion. Nat Commun 2024;15(1):1835. DOI: 10.1038/s41467-024-46047-8, PMID: 38418488.

[30] Burton AR, Pallett LJ, McCoy LE, Suveizdyte K, Amin OE, Swadling L, *et al*. Circulating and intrahepatic antiviral B cells are defective in hepatitis B. J Clin Invest 2018;128(10):4588–4603. DOI: 10.1172/jci121960, PMID: 30091725.

[31] van Buuren N, Ramirez R, Turner S, Chen D, Suri V, Aggarwal A, *et al*. Characterization of the liver immune microenvironment in liver biopsies from patients with chronic HBV infection. JHEP Rep 2022; 4(1):100388. DOI: 10.1016/j.jhepr.2021.100388, PMID: 34950863.

[32] Bosch M, Kallin N, Donakonda S, Zhang JD, Wintersteller H,

Hegenbarth S, *et al*. A liver immune rheostat regulates CD8 T cell immunity in chronic HBV infection. Nature 2024;631(8022): 867–875. DOI: 10.1038/s41586-024-07630-7, PMID: 38987588.

[33] Baudi I, Kawashima K, Isogawa M. HBV-Specific CD8+ T-Cell Tolerance in the Liver. Front Immunol 2021;12:721975. DOI: 10.3389/fimmu.2021.721975, PMID: 34421926.

[34] Pavletic SZ, Bociek RG, Foran JM, Rubocki RJ, Kuszynski CA, Wisecarver JL, *et al*. Lymphodepleting effects and safety of pentostatin for nonmyeloablative allogeneic stem-cell transplantation. Transplantation 2003;76(5):877–881. DOI: 10.1097/01.TP.0000084869.08639.A0, PMID: 14501873.

[35] Lau GK, Liang R, Chiu EK, Lee CK, Lam SK. Loss of HBsAg in chronic hepatitis B carrier following high-dose chemotherapy and autologous peripheral blood stem cell rescue for lymphoma. Am J Hematol 1995;50(4):317–318. DOI: 10.1002/ajh.2830500424, PMID: 7485117.

[36] Junt T, Calzascia T, Traggiai E, da Costa AN, Gergely P, Schett G, *et al*. Defining immune reset: achieving sustained remission in autoimmune diseases. Nat Rev Immunol 2025;25(7):528–541. DOI: 10.1038/s41577-025-01141-w, PMID: 40044810.

[37] Douek DC, Vescio RA, Betts MR, Brenchley JM, Hill BJ, Zhang L, *et al.* Assessment of thymic output in adults after haematopoietic stem-cell transplantation and prediction of T-cell reconstitution. Lancet 2000;355(9218):1875–1881. DOI: 10.1016/S0140-6736(00)02293-5, PMID: 10866444.

[38] Naseeb S, Ahmed P, Nasir S, Zahur U, Mahmood K, Ali H. Immune Reconstitution Following Allogeneic Hematopoietic Stem Cell Transplantation. J Haematol Stem Cell Res. 2025 Apr 18; 5(1):5–11

[39] Santana-Gonçalves M, Malmegrim K, Farge D, Oliveira MC. Immune reconstitution in rheumatic disease patients after autologous hematopoietic stem cell transplantation. Handb Clin Neurol 2024;202:75–91. DOI: 10.1016/B978-0-323-90242-7.00015-8, PMID: 39111920.

[40] Li X, Sun W, Xu X, Jiang Q, Shi Y, Zhang H, *et al*. Hepatitis B virus surface antigen drives T cell immunity through non-canonical antigen presentation in mice. Nat Commun 2025;16(1):4591. DOI: 10.1038/s41467-025-59985-8, PMID: 40382385.

[41] Verdon DJ, Mulazzani M, Jenkins MR. Cellular and Molecular Mechanisms of CD8(+) T Cell Differentiation, Dysfunction and Exhaustion. Int J Mol Sci 2020;21(19):7357. DOI: 10.3390/ijms21197357, PMID: 33027962.

[42] Xia Y, Stadler D, Lucifora J, Reisinger F, Webb D, Hösel M, *et al*. Interferon-γ and Tumor Necrosis Factor-α Produced by T Cells Reduce the HBV Persistence Form, cccDNA, Without Cytolysis. Gastroenterology 2016;150(1):194–205. DOI: 10.1053/j.gastro.2015.09.026, PMID: 26416327.

[43] Liu F, Campagna M, Qi Y, Zhao X, Guo F, Xu C, *et al*. Alpha-interferon suppresses hepadnavirus transcription by altering epigenetic modification of cccDNA minichromosomes. PLoS Pathog 2013;9(9):e1003613. DOI: 10.1371/journal.ppat.1003613, PMID: 24068929.

[44] Belloni L, Pollicino T, De Nicola F, Guerrieri F, Raffa G, Fanciulli M, *et al*. Nuclear HBx binds the HBV minichromosome and modifies the epigenetic regulation of cccDNA function. Proc Natl Acad Sci U S A 2009;106(47):19975–19979. DOI: 10.1073/pnas.0908365106, PMID: 19906987.

[45] Yuan H, Zhao L, Yang G, Zhang S, Lv P, Zhang S, *et al*. HBx-induced HSPB1 is a potential therapeutic target owing to its modulation of HBV cccDNA and hepatic immune responses. J Hepatol 2026;84(3): 517–530. DOI: 10.1016/j.jhep.2025.09.033, PMID: 41109416.

[46] Venzin V, Beccaria CG, Perucchini C, Delfino P, Bono EB, Giustini L, *et al*. CD4(+) T cells license Kupffer cells to reverse CD8(+) T cell dysfunction induced by hepatocellular priming. Nat Immunol 2025;26(8):1352–1366. DOI: 10.1038/s41590-025-02199-3, PMID: 40588520.

[47] Li S, Hao L, Deng J, Zhang J, Yu F, Ye F, *et al*. The Culprit Behind HBV-Infected Hepatocytes: NTCP. Drug Des Devel Ther 2024;18:4839–4858. DOI: 10.2147/DDDT.S480151, PMID: 39494152.

[48] Li D, He W, Liu X, Zheng S, Qi Y, Li H, *et al*. A potent human neutralizing antibody Fc-dependently reduces established HBV infections. Elife 2017;6:e26738. DOI: 10.7554/eLife.26738, PMID: 28949917.

[49] Ilan Y, Nagler A, Zeira E, Adler R, Slavin S, Shouval D. Maintenance of immune memory to the hepatitis B envelope protein following adoptive transfer of immunity in bone marrow transplant recipients. Bone Marrow Transplant 2000;26(6):633–638. DOI: 10.1038/sj.bmt.1702571, PMID: 11035369.

[50] Fooksman DR, Jing Z, Park R. New insights into the ontogeny, diversity, maturation and survival of long-lived plasma cells. Nat Rev Immunol 2024;24(7):461–470. DOI: 10.1038/s41577-024-00991-0, PMID: 38332373.

[51] Simons BD, Karin O. Tuning of plasma cell lifespan by competition explains the longevity and heterogeneity of antibody persistence. Immunity 2024;57(3):600–611.e6. DOI: 10.1016/j.immuni.2024.02.005, PMID: 38447570.

[52] Chen X, Liu X, Xu T, Wang Y, Wang P, Liu H, *et al*. Engineered virus-hunter vaccine overcomes HBV immune tolerance. Gut 2026;75(6):1211–1225. DOI: 10.1136/gutjnl-2025-335806, PMID: 41198172.

[53] Zhou D, Liu J, Jia J, Li H, Qin L, Zhang Z, *et al*. Interferon therapy-induced reduction in PD-1 + CD8 + and CD160 + CD8 + T cells is associated with functional cure in hepatitis B. BMC Infect Dis 2025;25(1):1728. DOI: 10.1186/s12879-025-12042-7, PMID: 41419829.

[54] Jobin K, Seetharama D, Rüttger L, Fenton C, Kharybina E, Wirsching A, *et al*. A distinct priming phase regulates CD8 T cell immunity by orchestrating paracrine IL-2 signals. Science 2025;388(6743):eadq1405. DOI: 10.1126/science.adq1405, PMID: 40208984.

[55] Woo SY, Cho SH, Lee SM, Koh MB, Noh CH, Kim CW, *et al*. [Change in the serologic markers of hepatitis B after allogenic hematopoietic stem-cell transplantation]. Korean J Hepatol 2009;15(2):131–139. DOI: 10.3350/kjhep.2009.15.2.131, PMID: 19581765.

[56] Grudda T, Hwang HS, Taddese M, Quinn J, Sulkowski MS, Sterling RK, *et al*. Integrated hepatitis B virus DNA maintains surface antigen production during antiviral treatment. J Clin Invest 2022;132(18):e161818. DOI: 10.1172/JCI161818, PMID: 35797115.

[57] Suslov A, Matter MS, Calabrese D, El Taher A, Wieland S, Heim MH. Serum HBsAg cannot distinguish cccDNA activity from integrated HBV DNA expression in chronic hepatitis B virus infection. J Hepatol 2026: S0168-8278(26)02861-8. DOI: 10.1016/j.jhep.2026.08.018, PMID: 42668120.

[58] Taddese M, Grudda T, Belluccini G, Anderson M, Cloherty G, Hwang HS, *et al*. Transcription of hepatitis B surface antigen shifts from cccDNA to integrated HBV DNA during treatment. J Clin Invest 2025;135(6):e184243. DOI: 10.1172/JCI184243, PMID: 39898797.

[59] Gao N, Guan G, Xu G, Wu H, Xie C, Mo Z, *et al*. Integrated HBV DNA and cccDNA maintain transcriptional activity in intrahepatic HBsAg-positive patients with functional cure following PEG-IFN-based therapy. Aliment Pharmacol Ther 2023;58(10):1086–1098. DOI: 10.

1111/apt.17670, PMID: 37644711.

[60] Ionescu L, Urschel S. Memory B Cells and Long-lived Plasma Cells. Transplantation 2019;103(5):890–898. DOI: 10.1097/TP.0000000000002594, PMID: 30747835.

[61] Abe-Chayama H, Kawase T, Ichinohe T, Ishida Y, Tateno C, Hijikata M, *et al*. Hepatitis B virus-specific human stem cell memory T cells differentiate into cytotoxic T cells and eradicate HBV-infected hepatocytes in mice. FEBS Lett 2024;598(11):1354–1365. DOI: 10.1002/1873-3468.14842, PMID: 38594179.

[62] Umeda K. Unresolved issues in allogeneic hematopoietic cell transplantation for non-malignant diseases. Int J Hematol 2022;116(1):41–47. DOI: 10.1007/s12185-022-03361-5, PMID: 35568772.

[63] Wu Y, Huang H, Luo Y. Management of Hepatitis B Virus in Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol 2020;11:610500. DOI: 10.3389/fimmu.2020.610500, PMID: 33613534.

[64] Murt A, Elverdi T, Eskazan AE, Salihoglu A, Ar MC, Ongoren S, *et al*. Hepatitis B reactivation in hematopoietic stem cell transplanted patients: 20 years of experience of a single center from a middle endemic country. Ann Hematol 2020;99(11):2671–2677. DOI: 10.1007/s00277-020-04206-z, PMID: 32737632.

[65] Shimoni A, Peczynski C, Labopin M, Kulagin A, Meijer E, Cornelissen J, *et al*. Post-transplant cyclophosphamide separates graft-versus host disease and graft versus leukemia effects after HLA-matched stem-cell transplantation for acute myeloid leukemia. Leukemia 2025;39(1):222–228. DOI: 10.1038/s41375-024-02445-x, PMID: 39482353.

[66] Wang Q, Huang P, Zhang Q, Liu Y, Zang Q, Zhu C, *et al*. HBsAg loss in recipients with chronic hepatitis B after allogeneic hematopoietic stem-cell transplantation: a retrospective cohort study exploring kinetic dynamics. BMC Infect Dis 2026;26(1):688. DOI: 10.1186/s12879-026-12863-0, PMID: 41742102.

[67] Bertoletti A, Tan AT. HBV as a target for CAR or TCR-T cell therapy. Curr Opin Immunol 2020;66:35–41. DOI: 10.1016/j.coi.2020.04.003, PMID: 32361634.

[68] Bohne F, Chmielewski M, Ebert G, Wiegmann K, Kürschner T, Schulze A, *et al*. T cells redirected against hepatitis B virus surface proteins eliminate infected hepatocytes. Gastroenterology 2008;134(1):239–247. DOI: 10.1053/j.gastro.2007.11.002, PMID: 18166356.

[69] Zou F, Tan J, Liu T, Liu B, Tang Y, Zhang H, *et al*. The CD39(+) HBV surface protein-targeted CAR-T and personalized tumor-reactive CD8(+) T cells exhibit potent anti-HCC activity. Mol Ther 2021;29(5):1794–1807. DOI: 10.1016/j.ymthe.2021.01.021, PMID: 33484968.

[70] Guo G, He W, Zhou Z, Diao Y, Sui J, Li W. PreS1- targeting chimeric antigen receptor T cells diminish HBV infection in liver humanized FRG mice. Virology 2023;586:23–34. DOI: 10.1016/j.virol.2023.06.015, PMID: 37478771.

[71] Festag MM, Festag J, Fräßle SP, Asen T, Sacherl J, Schreiber S, *et al*. Evaluation of a Fully Human, Hepatitis B Virus-Specific Chimeric Antigen Receptor in an Immunocompetent Mouse Model. Mol Ther 2019;27(5):947–959. DOI: 10.1016/j.ymthe.2019.02.001, PMID: 30852138.

[72] Krebs K, Böttinger N, Huang LR, Chmielewski M, Arzberger S, Gasteiger G, *et al*. T cells expressing a chimeric antigen receptor that binds hepatitis B virus envelope proteins control virus replication in mice. Gastroenterology 2013;145(2):456–465. DOI: 10.1053/j.gastro.2013.04.047, PMID: 23639914.

[73] Fettiplace A, Regev A, Kiazand A, Heinzel-Pleines U, Bahjat M, Garg A, *et al*. Hepatic Effects, Potential Drug-Induced Liver Injury, and Other Liver Safety Considerations of Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in the New Era of Expanding Non-oncology Indications: Literature Review and Expert Consensus. Drug Saf 2026;49(6):631–654. DOI: 10.1007/s40264-025-01635-5, PMID: 41345813.

[74] Luo W, Li C, Zhang Y, Du M, Kou H, Lu C, *et al*. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis. BMC Cancer 2022;22(1):98. DOI: 10.1186/s12885-021-09102-x, PMID: 35073859.

[75] Öz EA, Su J, Gültan M, Tulessin M, Müller N, Kerth HA, *et al*. High HBV antigen levels drive loss of vaccine-induced CD8(+) T-cell function in carrier mice over time. JHEP Rep 2026:102033. DOI: 10.1016/j.jhepr.2026.102033, PMID: 42722105.

[76] Liang L, Xie X, He S, Zhou L, Yue Y. From exhaustion to functional cure: frontiers in reversing HBV-specific T-cell immunity. Front Immunol 2026;17:1877059. DOI: 10.3389/fimmu.2026.1877059, PMID: 42519330.

[77] Fu S, Zhang Q, Jing R, Zu C, Ni F, Lv Y, *et al*. HBV reactivation in patients with chronic or resolved HBV infection following BCMA-targeted CAR-T cell therapy. Bone Marrow Transplant 2023;58(6):701–709. DOI: 10.1038/s41409-023-01960-2, PMID: 37002410.

[78] Gehring AJ, Xue SA, Ho ZZ, Teoh D, Ruedl C, Chia A, *et al*. Engineering virus-specific T cells that target HBV infected hepatocytes and hepatocellular carcinoma cell lines. J Hepatol 2011;55(1):103–110. DOI: 10.1016/j.jhep.2010.10.025, PMID: 21145860.

[79] Wisskirchen K, Kah J, Malo A, Asen T, Volz T, Allweiss L, *et al*. T cell receptor grafting allows virological control of Hepatitis B virus infection. J Clin Invest 2019;129(7):2932–2945. DOI: 10.1172/JCI120228, PMID: 31039136.

[80] Wan X, Wisskirchen K, Jin T, Yang L, Wang X, Wu X, *et al*. Genetically-modified, redirected T cells target hepatitis B surface antigen-positive hepatocytes and hepatocellular carcinoma lesions in a clinical setting. Clin Mol Hepatol 2024;30(4):735–755. DOI: 10.3350/cmh.2024.0058, PMID: 38808361.

[81] Wu X, Quan D, Li W, Wisskirchen K, Wu W, Zhou Y, *et al*. Clinical results of an HBV-specific T-cell receptor-T-cell therapy (SCG101) in patients with HBV-related hepatocellular carcinoma treated in an investigator-initiated, interventional trial. Gut 2025;75(1):147–160. DOI: 10.1136/gutjnl-2025-335456, PMID: 40803751.

[82] Podlaha O, Wu G, Downie B, Ramamurthy R, Gaggar A, Subramanian M, *et al*. Genomic modeling of hepatitis B virus integration frequency in the human genome. PLoS One 2019;14(7):e0220376. DOI: 10.1371/journal.pone.0220376, PMID: 31356634.

[83] Ren H, Chen X, Wang J, Chen Y, Hafiz A, Xiao Q, *et al*. Temporal and structural patterns of hepatitis B virus integrations in hepatocellular carcinoma. J Med Virol 2023;95(10):e29187. DOI: 10.1002/jmv.29187, PMID: 37877809.

[84] Li P, Zhou L, Ye S, Zhang W, Wang J, Tang X, *et al*. Risk of HBV Reactivation in Patients With Resolved HBV Infection Receiving Anti-CD19 Chimeric Antigen Receptor T Cell Therapy Without Antiviral Prophylaxis. Front Immunol 2021;12:638678. DOI: 10.3389/fimmu.2021.638678, PMID: 34335561.

[85] Yang F, Zheng X, Koh S, Lu J, Cheng J, Li P, *et al*. Messenger RNA electroporated hepatitis B virus (HBV) antigen-specific T cell receptor (TCR) redirected T cell therapy is well-tolerated in patients with recurrent HBV-related hepatocellular carcinoma

post-liver transplantation: results from a phase I trial. Hepatol Int 2023;17(4):850–859. DOI: 10.1007/s12072-023-10524-x, PMID: 37067675.

[86] Zhang ZA, Herring L, Shwe TH, Hu Y, Song X, Cao W, *et al*. Precise Control of Switchable Chimeric Antigen Receptor T Cells Allows Enhanced Safety and Less T Cell Exhaustion. bioRxiv 2025: 2025. DOI: 10.64898/2025.12.07.692875, PMID: 41427399.

[87] Schreiber S, Dressler LS, Loffredo-Verde E, Asen T, Färber S, Wang W, *et al*. CARs derived from broadly neutralizing, human monoclonal antibodies identified by single B cell sorting target hepatitis B virus-positive cells. Front Immunol 2024;15:1340619. DOI: 10.3389/fimmu.2024.1340619, PMID: 38711498.

[88] Brudno JN, Kochenderfer JN. Current understanding and management of CAR T cell-associated toxicities. Nat Rev Clin Oncol 2024;21(7):501–521. DOI: 10.1038/s41571-024-00903-0, PMID: 38769449.

[89] Anderson GSF, Chapman MA. T cell-redirecting therapies in hematological malignancies: Current developments and novel strategies for improved targeting. Mol Ther 2024;32(9):2856–2891. DOI: 10.1016/j.ymthe.2024.07.028, PMID: 39095991.

[90] Shouval D, Ilan Y. Immunization against hepatitis B through adoptive transfer of immunity. Intervirology 1995;38(1-2):41–46. DOI: 10.1159/000150413, PMID: 8666523.

[91] Gumber D, Wang LD. Improving CAR-T immunotherapy: Overcoming the challenges of T cell exhaustion. EBioMedicine 2022;77:103941. DOI: 10.1016/j.ebiom.2022.103941, PMID: 35301179.

[92] Tseng TC, Cheng HR, Su TH, Lin PH, Wang CC, Yang HC, *et al*. Higher hepatitis B core-specific T cell response is associated with a lower risk of clinical relapse after discontinuation of oral antiviral treatment. J Microbiol Immunol Infect 2024;57(5):700–708. DOI: 10.1016/j.jmii.2024.07.012, PMID: 39153879.

[93] Murugesan G, Paterson RL, Kulkarni R, Ilkow V, Suckling RJ, Connolly MM, *et al*. Viral sequence determines HLA-E-restricted T cell recognition of hepatitis B surface antigen. Nat Commun 2024; 15(1):10126. DOI: 10.1038/s41467-024-54378-9, PMID: 39578466.

[94] Meng CY, Liang Y, Xu L, Li H, Guo J, Xu H, *et al*. Anti-PD-L1-IFN-α-adjuvanted HBsAg vaccine overcomes HBV immune tolerance through targeting both DCs and macrophages. JCI Insight 2025; 10(23):e198097. DOI: 10.1172/jci.insight.198097, PMID: 41355797.

[95] Klopp A, Schreiber S, Kosinska AD, Pulé M, Protzer U, Wisskirchen K. Depletion of T cells via Inducible Caspase 9 Increases Safety of Adoptive T-Cell Therapy Against Chronic Hepatitis B. Front Immunol 2021;12:734246. DOI: 10.3389/fimmu.2021.734246, PMID: 34691041.

[96] Hou J, Zhang W, Xie Q, Hua R, Tang H, Morano Amado LE, *et al*; Piranga Study Group. Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B. N Engl J Med 2024; 391(22):2098–2109. DOI: 10.1056/NEJMoa2405485, PMID: 39774313.

[97] Buti M, Heo J, Tanaka Y, Andreone P, Atsukawa M, Cabezas J, *et al*. Sequential Peg-IFN after bepirovirsen may reduce post-treatment relapse in chronic hepatitis B. J Hepatol 2025;82(2):222–234. DOI: 10.1016/j.jhep.2024.08.010, PMID: 39214467.

[98] You H, Maiwall R, Chen J, Ahn SH, Dokmeci K, Dou X, *et al*. APASL clinical practice guidelines on the management of chronic hepatitis B infection: 2026 version. Zhonghua Gan Zang Bing Za Zhi 2026; 34(7):640–667. DOI: 10.3760/cma.j.cn501113-20260416-00155, PMID: 42503908.

[99] Roca Suarez AA, Plissonnier ML, Grand X, Michelet M, Giraud G, Saez-Palma M, *et al*. TLR8 agonist selgantolimod regulates Kupffer cell differentiation status and impairs HBV entry into hepatocytes via an IL-6-dependent mechanism. Gut 2024;73(12):2012–2022. DOI: 10.1136/gutjnl-2023-331396, PMID: 38697771.

[100] Fisicaro P, Valdatta C, Massari M, Loggi E, Biasini E, Sacchelli L, *et al.* Antiviral intrahepatic T-cell responses can be restored by blocking programmed death-1 pathway in chronic hepatitis B. Gastroenterology 2010;138(2):682–693, 693.e1. DOI: 10.1053/j.gastro.2009.09.052, PMID: 19800335.

[101] Stadtmauer EA, Fraietta JA, Davis MM, Cohen AD, Weber KL, Lancaster E, *et al*. CRISPR-engineered T cells in patients with refractory cancer. Science 2020;367(6481):eaba7365. DOI: 10.1126/science.aba7365, PMID: 32029687.

[102] Jiang S, Li H, Zhang L, Mu W, Zhang Y, Chen T, *et al*. Generic Diagramming Platform (GDP): a comprehensive database of high-quality biomedical graphics. Nucleic Acids Res 2025;53(D1): D1670–D1676. DOI: 10.1093/nar/gkae973, PMID: 39470721.