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Review Article

Tumor Vaccines in Hepatocellular Carcinoma: Advances, Challenges, and the Path Toward Precision Immunotherapy

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Abstract

Primary hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide, with curative options still limited for patients with advanced disease. As an emerging modality of cancer immunotherapy, tumor vaccines represent a promising approach that activates the host immune system to recognize and eliminate malignant cells. Multiple vaccine platforms, including peptide vaccines, dendritic-cell vaccines, nucleic-acid vaccines, and viral-vector vaccines, have been explored for HCC. Among these, peptide- and dendritic-cell-based vaccines are supported by the most extensive clinical data, demonstrating favorable safety and immunogenicity profiles. The advent of personalized therapeutic cancer vaccines based on tumor-specific antigens has further refined the precision of vaccine design. Nevertheless, several major challenges persist, including immune suppression within the tumor immune microenvironment, marked tumor heterogeneity, immune-escape mechanisms, and limited vaccine immunogenicity, all of which hinder clinical efficacy. In addition, issues related to standardization, large-scale production, and regulatory oversight remain unresolved. Recent advances in sequencing technology, nanotechnology, and artificial intelligence have opened new avenues for optimizing vaccine platforms and delivery strategies. Combination therapies that integrate cancer vaccines with immune checkpoint inhibitors, chemotherapy, or locoregional treatments are also being actively investigated to improve patient outcomes. In summary, although vaccine-based immunotherapy for HCC is still at an early stage, its integration with personalized medicine and multimodal therapeutic strategies holds great potential for improving the long-term prognosis of patients with HCC. Therefore, this review aims to systematically summarize current advances in tumor vaccine–based immunotherapy for hepatocellular carcinoma, with a particular focus on vaccine platforms, target antigens, clinical trial outcomes, and future challenges for clinical translation.

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Introduction

Primary liver cancer is the sixth most common malignancy worldwide and the third leading cause of cancer-related mortality, with approximately 906,000 new cases and 830,000 deaths reported annually.[1] Notably, China accounts for nearly 45% of the global disease burden, and this proportion is expected to increase in the coming years.[2] Hepatocellular carcinoma (HCC), the predominant histological subtype of liver cancer, is primarily associated with chronic liver diseases such as viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis.[3]

At present, only about 40% of patients with HCC in China are eligible for potentially curative therapy, as the majority have already missed the surgical window by the time of diagnosis.[4] The advent of locoregional interventions and targeted immunotherapies has provided additional treatment options for patients who are not surgical candidates. However, high recurrence rates, distant metastasis, and drug resistance continue to result in poor long-term outcomes.[5] The five-year survival rate for HCC in China remains only 14.8%.[6] These data underscore the urgent need for novel therapeutic strategies for HCC.

Immunotherapy has become a first-line treatment for advanced HCC and is often combined with surgery, chemotherapy, or radiotherapy.[7] Tumor vaccines, as a key component of immunotherapy, have opened new therapeutic avenues for HCC patients.[8] The favorable safety and efficacy observed in tumor vaccine trials for other solid tumors have gradually made them a focus of research in HCC. This review summarizes recent advances in the development and clinical application of therapeutic tumor vaccines for HCC.

To ensure a comprehensive and balanced overview, relevant studies on tumor vaccines for HCC were identified through a systematic search of PubMed and ClinicalTrials.gov. The search terms included "hepatocellular carcinoma," "liver cancer," "vaccine," "immunotherapy," "peptide," "dendritic cell," "viral vector," "DNA," and "mRNA." Both preclinical and clinical studies published in English were reviewed. Studies were included if they reported on vaccine mechanisms of action, antigen targets, vaccine platforms, or clini-

cal outcomes. Conference abstracts and publications without accessible data were excluded. Reference lists of all selected articles were also cross-checked to identify additional relevant studies. This systematic approach ensured methodological transparency and minimized selection bias in the body of evidence reviewed.

Tumor vaccines are a therapeutic modality designed to activate the body's immune system to recognize and eliminate malignant cells. Broadly, they can be categorized into prophylactic and therapeutic vaccines. Prophylactic tumor vaccines aim to protect individuals who are at risk of developing cancer, often due to identifiable etiologic factors. For instance, the widely used hepatitis B virus vaccine has effectively reduced the incidence of HCC.[9] This review focuses on therapeutic tumor vaccines, which introduce tumor antigens to enhance the antigen-specific cytotoxic response of $CD8^+$ T cells (CTLs), enabling targeted killing of tumor cells. In contrast to conventional chemotherapy and radiotherapy, tumor vaccines offer distinct advantages, including high specificity, favorable safety profiles, and the capacity to induce durable immune memory.[10]

Historically, William Coley, regarded as the "father of immunotherapy," developed *Coley's toxins* in the 1890s from filtrates of *Streptococcus* and *Serratia marcescens* cultures.[11] Although these toxins exhibited low tumor specificity, they were pioneering in demonstrating that immune stimulation could elicit antitumor effects. Subsequently, Álvaro Morales advanced the field by introducing the Bacillus Calmette–Guérin vaccine for the treatment of superficial bladder cancer.[12] This approach gained Food and Drug Administration (FDA) approval in 1990, representing the first widely approved cancer vaccine and a milestone in the history of cancer immunotherapy. In the mid-1990s, Marcelo Harari further extended this progress by developing a DNA vaccine for melanoma, which successfully induced tumor-specific immune responses and laid the foundation for subsequent applications of DNA vaccines in oncology.

Different types of tumor vaccines share similar mechanisms of action, all involving multiple steps of the cancer–immunity cycle. The adjuvant and antigen components of tumor vaccines independently activate the patient's innate and adaptive immune responses, respectively. Innate immune activation is mediated by pattern recognition receptors, which detect pathogen-associated molecular patterns or damage-associated molecular patterns. This recognition triggers immune activation, stimulates the secretion of cytokines and chemokines, and promotes the recruitment and activation of diverse immune cell subsets.[13]

Adaptive immunity represents the primary therapeutic mechanism of tumor vaccines. After tumor antigens are released from the vaccine, they are captured and processed by antigen-presenting cells (APCs), primarily dendritic cells (DCs). DCs present the processed antigens on their surface via major histocompatibility complex (MHC) molecules and migrate to secondary lymphoid organs such as lymph nodes and the spleen. There, MHC–antigen peptide complexes interact with T cell receptors, transmitting antigenic information to T cells and inducing co-stimulatory signaling.[14] Activated CTLs then localize to the tumor site, releasing perforin and granzymes that mediate the lysis and apoptosis of tumor cells.[15] In parallel, activated $CD4^+$ T cells secrete cytokines such as interferon-γ and tumor necrosis factor, which further promote CTL activation and amplify the antitumor immune response.[16] B cells also contribute to tumor immunity by producing antibodies against tumor antigens, leading to direct or indirect tumor-cell killing through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In addition, B cells can function as APCs to further enhance T cell activation. Importantly, tumor vaccines can induce the formation of memory T and B cells, generating long-lasting immune memory that helps prevent tumor recurrence (Fig. 1).[17]

Antigen selection and vaccine design for HCC

Targeting antigens in HCC

In the design of HCC-targeted vaccines, the selection of liver cancer–specific antigens is critical to achieving clinical efficacy. Tumor antigens are molecules that are either aberrantly overexpressed or newly generated during tumor progression and are generally categorized as tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs).[18]

TAAs are expressed at very low levels in normal tissues but are markedly upregulated in tumor cells, often as a result of gene amplification or epigenetic dysregulation. Representative TAAs in HCC include alpha-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), and glypican-3 (GPC3), which are frequently overexpressed in malignant hepatocytes. However, their limited tumor specificity and potential to induce autoimmune toxicity have constrained their success as therapeutic targets.[19,20]

AFP remains the most widely used serum biomarker, typically employed in combination with ultrasound for HCC surveillance. Its widespread adoption largely reflects its low cost, accessibility, and integration into major clinical guidelines. The American Association for the Study of Liver Diseases recommends surveillance with ultrasound plus AFP, using a threshold of 20 ng/mL to trigger diagnostic evaluation.[21] Similarly, the Asian Pacific Association for the Study of the Liver endorses ultrasound + AFP–based surveillance, emphasizing its practicality and cost-effectiveness.[22] DCP has demonstrated higher specificity than AFP, particularly in Asian cohorts. Combining DCP—or AFP-L3–based composite indices such as GALAD or GAAD—with imaging can enhance detection compared with AFP alone. Recent studies from Vietnam and other regional analyses have reported superior diagnostic performance of DCP and GALAD/GAAD, even at earlier disease stages, supporting their selective incorporation into surveillance algorithms where resources allow.[23] GPC3 occupies a unique dual niche: it serves as both a validated vaccine or therapeutic target and a tissue or serum biomarker with growing—though still context-dependent—clinical utility. Serum GPC3 can complement AFP in diagnosis in specific clinical settings, while tissue overexpression correlates with more aggressive tumor biology and has driven the development of GPC3-directed therapies.[24,25]

Overall, viewing AFP, DCP, and GPC3 as both vaccine antigens and clinically actionable biomarkers provides a coherent translational framework. AFP supports broad, low-cost population surveillance; DCP refines diagnostic specificity; and GPC3 bridges diagnostic pathology with antigen-directed immunotherapy. Together, these markers can guide patient selection, disease monitoring, and endpoint integration in future HCC vaccine trials.

In contrast, TSAs are neoantigens that are completely absent from normal tissues and arise exclusively in tumor cells as a result of oncogenic viral proteins, nonsynonymous somatic mutations, or post-translational modifications. Compared with TAAs, TSAs exhibit markedly higher specificity and immunogenicity. Personalized therapeutic cancer vaccines (PTCVs) based on TSAs have therefore emerged as a highly promising immunotherapeutic approach. By integrating high-throughput sequencing with advanced bioinformat-

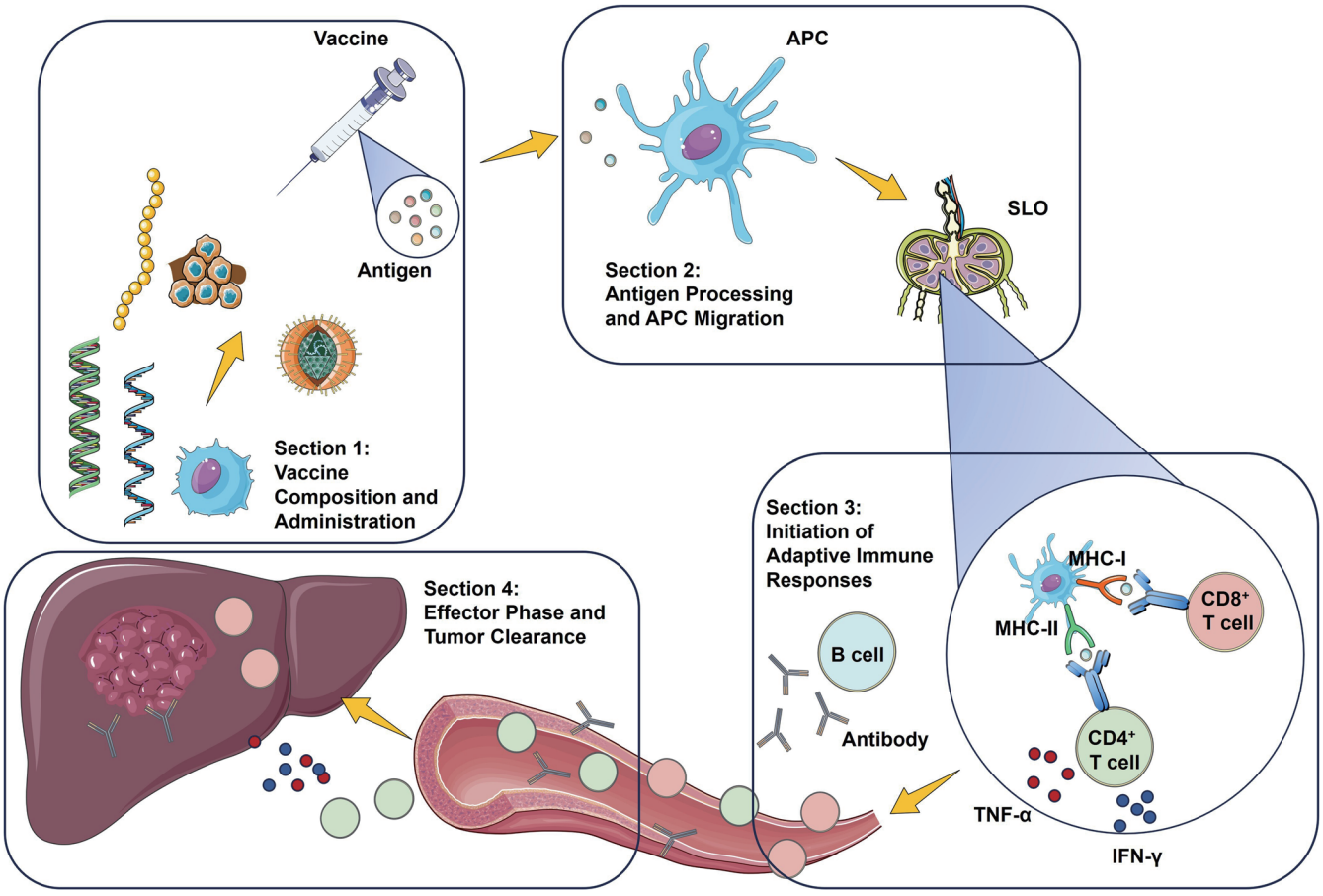

Fig. 1. Immune mechanisms triggered by tumor vaccines in hepatocellular carcinoma. The diagram contains multiple elements representing vaccine sources, antigen-processing steps, and immune effector cells. In the upper left block, various vaccine platforms - including peptide antigens, dendritic-cell vaccines, nucleic-acid constructs, viral vectors, and tumor-derived materials - are illustrated as distinct molecular or cellular icons. A syringe indicates the mode of vaccine administration. Arrows denote the directional movement of vaccine components toward antigen-presenting cells. The central region shows an antigen-presenting cell that has taken up vaccine-derived material. A magnified circular inset depicts processed antigens displayed on MHC-I and MHC-II complexes. Separate icons illustrate the recognition of MHC-I by $CD8^+$ T cells and the recognition of MHC-II by $CD4^+$ T cells. Additional symbols represent B cells and antibody molecules shown in the diagram. The lower portion of the figure depicts the liver and vascular system, showing circulating immune cells, antibodies, and lymphocytes distributed within the hepatic environment. Arrows indicate the movement of activated immune cells from the site of antigen presentation into the bloodstream and liver tissue. All icons, arrows, and color-coded elements represent individual steps or cell populations included in the schematic. APC, antigen-presenting cell; SLO, secondary lymphoid organ; MHC, major histocompatibility complex; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha.

ics pipelines, these vaccines exploit each patient's unique tumor mutational landscape to design precise immunogens targeting their individualized TSAs, thereby eliciting robust immune responses and promoting effective tumor elimination.[26]

Platforms for HCC vaccines

Vaccine platforms for HCC, which serve as delivery systems, play a critical role in vaccine development by enhancing antigen stability, facilitating antigen uptake by APCs, and improving immune activation and antitumor efficacy.

Water-in-oil emulsions represent a traditional yet effective vaccine platform that has been widely applied in various vaccine formulations. Their mechanism is believed to rely on the sustained and gradual release of antigens, which prolongs antigen exposure, enhances stability, and strengthens immune responses.[27] Lipid nanoparticles (LNPs) provide an additional advantage by protecting antigens from enzymatic degradation and maintaining their biological activity.[28]

Moreover, viral vector–based vaccines exhibit strong intrinsic immunogenicity and efficiently infect APCs, thereby promoting antigen processing and presentation to effectively activate T cell–mediated immune responses. Despite their promising clinical potential, the broad application of viral vectors is limited by pre-existing antiviral immunity, and their long-term safety still requires further validation.

Immunoenhancement strategies

Insufficient activation of antitumor immune responses remains a major cause of the limited clinical efficacy observed with cancer vaccines. Accordingly, adjuvants and immunomodulators play critical roles in enhancing vaccine performance.

Adjuvants increase the immunogenicity of antigens and prolong their persistence within the host. However, conventional adjuvants such as incomplete Freund's adjuvant and alum primarily stimulate humoral immunity and may even impair antigen-specific T cell function by inducing sequestration, thereby limiting their effectiveness in cancer immunotherapy.[29] In contrast, water-in-oil emulsions (e.g.,

Table 1. Classification and characteristics of tumor vaccines in hepatocellular carcinoma

Vaccine	Mechanism	Advantages	Limitations
Cellular vaccine	Uses autologous or allogeneic tumor cell lysates as antigen source	Broad antigen coverage; minimizes antigen omission; strong immune activation	Low stability; complex and costly production; difficult standardization; strict storage requirements; high technical barriers
Peptide vaccine	Induces targeted immune response against tumor-surface antigens	High specificity; low risk of off-target or autoimmune reactions; simple, low-cost production	Weak immunogenicity; limited target range; dependent on known epitopes; efficacy varies according to genetic background
Nucleic acid vaccine	Delivers exogenous DNA or mRNA encoding tumor antigens for *in vivo* antigen expression	Flexible design; encodes full-length tumor antigens; potential for multi-cancer application	Easily degraded nucleic acids; low delivery efficiency; risk of genomic integration; limited safety data
Viral vaccine	Delivers tumor antigens via viral vectors to activate host immune responses	Efficient cellular entry; robust antigen presentation; strong immunogenicity	Risk of hepatotoxicity and systemic inflammation; pre-existing anti-vector immunity; limited safety data
DC vaccine	Captures and processes tumor antigens for presentation to T cells	Provides antigens and co-stimulatory signals; enhances T-cell activation; complements existing therapies	Complex manufacturing; high production cost

DC, dendritic cell.

Montanide ISA 720, Montanide ISA-51) and Toll-like receptor agonists (e.g., monophosphoryl lipid A, CpG oligonucleotides) have been shown to enhance vaccine efficacy and are widely incorporated into cancer vaccine formulations.[30] Furthermore, novel adjuvants such as CD40 agonists and stimulator of interferon gene agonists have demonstrated substantial enhancement of T cell responses, making them strong candidates for next-generation tumor vaccine development.

Immunomodulators regulate and amplify immune responses through various mechanisms. Traditional agents such as transfer factor, thymosin, interferons, levamisole, and immunoribonucleic acids have long been used to strengthen antitumor immunity.[31] More recently, the addition of small-molecule immunomodulators has been shown to synergistically potentiate adjuvant activity by modulating intracellular signaling pathways such as NF-κB and interferon regulatory factors, thereby improving the magnitude and durability of vaccine-induced immune responses.[32]

Clinical and preclinical evidence

Tumor vaccines for HCC encompass a range of technological platforms that differ in composition, delivery mechanism, and immunologic focus. According to their source and preparation method, these vaccines can be broadly categorized into cellular, peptide, nucleic acid, viral vector, and DC vaccines.[33]

Each platform exhibits distinct strengths, such as broad antigen coverage, targeted immune activation, or ease of standardization, while also presenting challenges including limited immunogenicity, production complexity, and cost constraints. To provide an overview of these modalities, Table 1 summarizes the major advantages and limitations of the five principal vaccine types currently under investigation for HCC.

Cellular vaccines

HCC cellular vaccines utilize autologous or allogeneic tumor cell lysates as immunogens. Their major advantage lies in encompassing the full repertoire of potential TAAs, thereby providing broad antigenic coverage and reducing the likelihood of omitting relevant targets, an issue more common with single-antigen vaccine formulations. This broad-spectrum antigen exposure confers a distinct advantage in cancer immunotherapy.

In clinical studies, cell-based vaccines have demonstrated safety and therapeutic efficacy in several solid tumors, including colorectal and pancreatic cancers.[34,35] However, in HCC, most cell-based vaccine strategies have thus far relied on DC–based approaches, and there remains a lack of clinical data for conventional whole-cell vaccines. Consequently, their clinical application in HCC still requires extensive investigation. An ongoing Phase II/III clinical trial (NCT04206254) is currently evaluating the efficacy of a peptide complex derived from autologous tumor cells in patients with HCC, with results pending.

Recent studies have reported that HCC cell lysates can prevent tumor-induced exhaustion of T cells and natural killer cells, suppress tumor growth in murine HCC models, and improve long-term survival.[36] Further research has confirmed that whole-cell HCC lysates exhibit superior antitumor efficacy compared with glutaraldehyde-fixed tumor cells, underscoring their translational relevance in vaccine development.[37]

Nonetheless, several challenges remain for cell-based vaccines, including antigen stability, insufficient immune activation, and potential adverse effects. Moreover, compared with other cancer vaccine types, cell-based vaccines entail greater production complexity and cost, difficulties in standardization, and stringent storage and transport requirements. These high technical and manufacturing barriers continue to limit their broader clinical implementation.

Peptide vaccines

Peptide-based vaccines for HCC are antigen-specific formulations designed to elicit therapeutic effects by stimulating the activation of antigen-specific T cells and antibody production. Their high specificity reduces the risk of off-target effects and autoimmune reactions. In addition, they are easy to manufacture, cost-effective, and broadly applicable, making them highly promising candidates for HCC immunotherapy.[38]

AFP and GPC3 are the most well-established TAAs in HCC and are frequently targeted by peptide-based vaccine strate-

gies. Butterfield *et al*. demonstrated that HCC patients can mount T cell responses to exogenous AFP epitopes, providing a strong rationale for AFP-derived vaccine development.[39] In a phase I clinical trial, Nakagawa *et al*. administered AFP-derived peptides to 15 HCC patients, among whom one achieved complete remission and eight exhibited delayed tumor progression, with no treatment-related adverse events.[40]

Similarly, in a phase I study conducted by Sawada *et al*., GPC3-derived peptides induced antigen-specific immune responses in HCC patients, producing measurable antitumor activity without severe toxicity.[41] However, in a phase II trial of GV1001, a telomerase-targeting peptide vaccine, although reductions in $CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs) were observed, no antigen-specific immune responses were detected. Moreover, GV1001 failed to demonstrate objective antitumor efficacy based on clinical endpoints.[42] Likewise, Ikeda *et al*. developed two multi-epitope peptide vaccines targeting GPC3, WD repeat containing protein, and nei endonuclease VIII–like protein 3; however, no objective tumor responses were achieved in HCC patients enrolled in the trial.[43]

Recently, Cai *et al*. applied multi-omics sequencing and epitope-prediction analyses to design and administer PTCVs based on peptide antigens among patients with HCC. The results demonstrated a significant improvement in recurrence-free survival without major adverse events, supporting personalized peptide vaccination as an effective strategy for preventing HCC recurrence.[44]

No dose-limiting toxicity or dose-specific adverse events have been reported in published clinical trials. Transient immune-related reactions, such as drug fever, rash, or flushing, have occasionally occurred but were generally mild and self-limiting, indicating that peptide-based vaccination is well tolerated. Despite these advantages of specificity and safety, peptide vaccines still face challenges related to immunogenicity, durability, target diversity, and inter-patient variability. Their weak immunogenicity often necessitates the use of adjuvants or repeated dosing to maintain immune responses. Furthermore, peptide vaccines are restricted to known antigenic epitopes, thereby limiting their target range. Clinical efficacy may also vary substantially among individuals due to human leukocyte antigen genotype differences, resulting in heterogeneous therapeutic outcomes.[29]

Nucleic acid vaccines

Nucleic acid vaccines for HCC involve the delivery of exogenous DNA or mRNA sequences encoding tumor antigens into the host, leading to endogenous antigen expression and subsequent activation of the immune system to elicit antitumor immune responses. Key advantages of this approach include design flexibility, the capacity to encode full-length tumor antigens, and the elimination of large-scale, cell-based antigen production. As a result, nucleic acid vaccines have become a major focus of current HCC vaccine research.[45]

DNA vaccines: DNA vaccines operate by delivering plasmids carrying antigen-encoding genes into host cells, where the expressed proteins are processed and presented to stimulate immune activation. Although research on DNA-based cancer vaccines has been conducted for several decades, only a limited number of clinical trials have demonstrated clear therapeutic efficacy.

Butterfield *et al*. demonstrated the safety and good tolerability of an AFP-encoding plasmid DNA vaccine administered to patients with HCC, supporting its further evaluation in larger-scale clinical trials.[46] More recently, Yarchoan *et al*. confirmed the therapeutic potential of a personalized neoantigen-based DNA vaccine in combination with a programmed cell death protein-1 (PD-1) inhibitor. This vaccine, GNOS-PV02, encodes up to 40 neoantigens and is co-formulated with a DNA plasmid encoding interleukin (IL)-12. Clinical outcomes showed that 30.6% of patients achieved objective responses, including complete remission in 8.3%.[47] Single-cell sequencing analyses further verified that most patients developed robust antigen-specific T cell responses.

Numerous preclinical studies on HCC DNA vaccines are currently underway.[48–50] Building upon these findings, additional investigations are optimizing antigen design, delivery methods, and adjuvant formulations. Hi *et al*. developed a dual-targeting DNA vaccine encoding high mobility group box protein 1 and GPC3 using polyethylenimine technology, which elicited strong CTL responses and significantly suppressed tumor growth in murine models.[51] Wu *et al*. proposed an erythrocyte-driven, spleen-targeting strategy, in which nanoparticle-encapsulated DNA vaccines preferentially accumulate in the spleen, enhancing APC-mediated antigen expression and presentation. This approach promoted marked tumor regression and induced potent systemic immune responses in mice.[52]

Completed clinical studies on DNA vaccines for HCC remain limited. Nevertheless, available trials have reported favorable safety profiles, with no dose-limiting or severe adverse events observed. These results provide valuable guidance for optimizing vaccine design, offering a foundation for improved clinical translation. Despite this safety advantage, the progress of DNA vaccine development has been relatively slow. Major obstacles include the rapid degradation of naked nucleic acids, inefficient *in vivo* delivery to hepatocytes, and insufficient antigen expression. Additionally, excessive innate immune activation, high production costs, and stringent regulatory requirements have restricted large-scale clinical evaluation. Overcoming these barriers will be essential to fully realize the therapeutic potential of DNA-based vaccination for HCC.

mRNA vaccines: Since the FDA approval of the first mRNA-based coronavirus disease 2019 vaccine in 2021, the therapeutic potential of mRNA vaccines in oncology has gained growing attention and recognition. Compared with DNA vaccines, mRNA vaccines bypass nuclear membrane penetration and are directly translated into target proteins, thereby avoiding transcriptional errors and insertional mutagenesis associated with DNA delivery.[53]

Several clinical trials (e.g., NCT05192460, NCT05761717, NCT05738447, NCT05981066) are currently evaluating the therapeutic efficacy of mRNA vaccines in HCC; however, large-scale clinical data confirming their effectiveness are not yet available. Recent bioinformatic analyses have identified FXYD6, JAM2, GALNT16, C7, and CCDC146 as promising candidate antigens for the development of HCC-targeted mRNA vaccines.[54]

At the preclinical level, numerous studies have investigated the feasibility of mRNA-based immunotherapy for HCC.[55,56] These vaccines exert antitumor effects by encoding tumor suppressor genes, immunostimulatory molecules, or tumor antigens. Their efficacy has been demonstrated in multiple murine tumor models, including melanoma, lymphoma, and prostate cancer. Deng *et al*. synthesized an mRNA vaccine encoding the co-stimulatory molecule OX40 ligand and delivered it via LNPs in HCC-bearing mice, resulting in marked T cell activation and significant tumor growth inhibition.[57]

Despite these encouraging findings, the direct clinical application of mRNA delivery for HCC remains limited. From a mechanistic standpoint, mRNA vaccines share several drawbacks with DNA platforms, including suboptimal delivery to hepatocytes, transient innate immune activation that can reduce antigen expression, and a dependence on repeated

dosing or optimized delivery systems to achieve durable responses. In addition, mRNA vaccines face unique challenges stemming from the intrinsic instability of RNA molecules, their susceptibility to hydrolysis, and the strict cold-chain requirements necessary for preservation. The short cytoplasmic half-life of mRNA leads to brief antigen expression, whereas DNA vaccines, once delivered to the nucleus, can sustain expression for longer periods but exhibit lower transfection efficiency and a theoretical risk of genomic integration. Collectively, these contrasts underscore the complementary strengths and inherent limitations of each nucleic-acid platform in HCC vaccine development.

In summary, DNA- and mRNA-based vaccines represent promising and innovative strategies for HCC therapy. Despite strong preclinical momentum, their clinical translation has progressed slowly due to platform-specific and extrinsic constraints. Beyond biological and immunologic barriers, major obstacles include manufacturing and regulatory challenges. Large-scale good manufacturing practice production of plasmid DNA or *in vitro*-transcribed mRNA remains expensive and technically demanding, particularly for personalized designs that limit scalability. Moreover, mRNA platforms require precise LNP formulation and rigorous cold-chain logistics—conditions originally optimized for infectious-disease vaccines. Regulatory frameworks for individualized nucleic-acid therapeutics also remain underdeveloped, creating uncertainty in approval and quality-control processes. Together, these manufacturing and regulatory bottlenecks, rather than immunologic limitations alone, largely account for the slow clinical transition of DNA and mRNA vaccines in HCC.

Viral vaccines

Viral vector–based immunization has emerged as a cutting-edge strategy in cancer immunotherapy. These vaccines efficiently deliver antigens to the immune system to elicit tumor-specific immune responses. Compared with other vaccine platforms, viral vectors can enter host cells and express encoded antigens, thereby ensuring efficient antigen presentation and robust immune activation.[58]

A wide range of viral backbones, including adenoviral, lentiviral, retroviral, and adeno-associated viral systems, have been utilized as gene-delivery vehicles in cancer vaccine development.[58] The virological and structural characteristics of each platform, such as cellular tropism, genome capacity, and intrinsic immunogenicity, largely determine their performance and applicability across different oncologic contexts. Among these, adenoviral vectors have received particular attention because they combine efficient gene transfer with low pathogenicity and can accommodate relatively large genetic inserts.[59]

Recent preclinical and clinical studies of viral vector–based cancer vaccines have produced encouraging results. Rodriguez-Madoz *et al*. demonstrated in murine models that a Semliki Forest virus–based vaccine expressing high levels of IL-12 induced dose-dependent tumor regression.[60] In addition, a phase II dose-escalation trial involving 30 patients with HCC reported that a modified poxvirus–based vaccine conferred dose-related survival benefits, generating substantial clinical interest.[61]

Although multiple clinical trials are currently evaluating viral vector–based vaccines for HCC, their clinical application remains relatively underexplored. Notably, viral vectors can induce acute hepatotoxicity through the activation of intrahepatic immune cells. This hepatotoxic potential has been primarily documented in gene-therapy and vaccine platforms utilizing adenoviral or adeno-associated viral backbones. Clinical and preclinical evidence indicates that high-dose vector administration can provoke dose-dependent elevations of serum transaminases and, in rare cases, acute hepatic injury mediated by intrahepatic immune activation. *Roy et al.* reported that transient increases in alanine and aspartate aminotransferase levels occurred in up to 10–20% of patients following gene therapy, typically resolving without lasting hepatic damage.[62] Similarly, *Jagadisan et al.* highlighted that vector-derived capsid proteins and unmethylated CpG motifs may stimulate Kupffer cells and infiltrating T cells, triggering short-term inflammatory hepatotoxicity.[63] Although these immune-mediated effects are generally mild and reversible, they underscore the need for careful vector-dose optimization and immune-monitoring strategies in future viral vaccine trials for HCC.

Because most patients with HCC have underlying chronic liver disease, hepatotoxicity represents a particularly critical concern when evaluating viral vector–based immunotherapies. While reports from gene-therapy and vaccine studies have described transient, immune-mediated liver injury in certain contexts, HCC-specific safety data remain limited. In a phase Ib trial evaluating intrahepatic administration of a viral vector combined with pembrolizumab, no significant deterioration in liver function was observed, and no dose-limiting hepatotoxicity occurred within the HCC cohort.[64] However, given the small sample size, these findings should be interpreted cautiously.

Fever was the most common treatment-related event, occurring in approximately 80% of patients, higher than the rates typically observed with other vaccine platforms. The mechanism underlying this frequent febrile response remains uncertain, though prior studies of viral-vector and virus-like particle vaccines suggest that systemic exposure to viral antigens or structural components may activate innate immune pathways beyond the liver, potentially triggering transient, cytokine-mediated febrile reactions.[65] Although these events are usually mild, they emphasize the importance of both hepatic and systemic safety monitoring in future HCC vaccine studies. Overall, early combination trials of viral vectors with immune checkpoint inhibitors (ICIs) have shown acceptable tolerability, though long-term safety data are still lacking.

DC vaccines

DCs are the most potent APCs in the human immune system. When used as vaccines, DCs deliver tumor antigens together with essential co-stimulatory signals required for T-cell activation, thereby representing a promising strategy to elicit individualized anti-tumor immunity.[66]

Clinical studies have demonstrated that DC-based vaccines are safe and feasible for HCC. In a phase I trial, Wang *et al*. evaluated autologous DCs in patients with HCC and reported favorable tolerability.[67] Another phase I study confirmed the safety of allogeneic DCs—used either as monotherapy or combined with sorafenib—and showed induction of tumor-specific immune responses in advanced HCC, providing a potential universal platform for personalized immunotherapy.[68]

At present, three principal strategies are employed to generate DC-based HCC vaccines: (1) co-culturing DCs with tumor-cell lysates from HCC cell lines; (2) pulsing DCs with defined tumor-associated peptides or recombinant proteins such as AFP; and (3) transfecting DCs with nucleic acids encoding known tumor antigens.[69–73] Across reported trials, no significant adverse events have been observed, confirming that DC vaccines for HCC are safe and well-tolerated. Most recipients develop antigen-specific immune responses, although the overall clinical efficacy of DC vaccination still

requires further optimization and large-scale validation.

Numerous preclinical studies are underway to improve DC vaccine efficacy for HCC, with advances seen in adjuvant formulations, nanotechnology, and exosome-based delivery platforms.[74–76] Jin *et al*. evaluated a novel sulfated polysaccharide adjuvant and found that DC vaccines incorporating this adjuvant significantly extended survival, reduced tumor burden, and suppressed tumor growth in tumor-bearing mice, outperforming conventional LPS maturation agents.[77] Wang *et al*. tested a nanoparticle-based DC vaccine coated with membranes from mature DCs pulsed with H22-specific neoantigens; the formulation induced strong CTL responses, effectively inhibited tumor growth, and prolonged survival in murine models.[78] In another study, Zuo *et al*. developed dendritic-cell–derived exosome (DEX) vaccines by conjugating DEX with the HCC-targeting peptide P47-P, AFP, and the functional domain of high-mobility group nucleosome-binding protein 1 (N1ND-N). The resulting formulation, DEXP&A2&N, achieved complete tumor eradication in an orthotopic HCC mouse model.[79]

Among all HCC vaccine modalities, DC-based vaccines are the most clinically advanced. However, their complex manufacturing processes and high production costs remain major obstacles to widespread clinical implementation. Continued research aimed at optimizing antigen loading, adjuvant selection, and delivery systems underscores their potential as a promising personalized immunotherapeutic approach for HCC.

To date, a growing number of clinical studies have been initiated to evaluate the safety, feasibility, and immunogenicity of tumor vaccine strategies in HCC. Table 2 summarizes the main characteristics of these representative trials, while Supplementary Table 1 provides detailed information regarding study design, patient populations, and preliminary outcomes.

Most HCC vaccine studies remain in phase I or I/II, typically employing single-center, open-label designs aimed primarily at establishing safety and early immune responses. Geographically, early investigations of peptide- and DC–based vaccines were predominantly conducted in Europe and North America, whereas more recent DNA and mRNA vaccine trials have been concentrated in East Asia, reflecting the region's high burden of hepatitis B virus-related HCC. Overall sample sizes remain small, and inclusion criteria vary considerably. Although studies encompass a wide range of clinical contexts, including treatment-naïve localized disease, post-resection surveillance, and bridge-to-transplant settings, only a minority explicitly apply standardized staging systems such as the Barcelona Clinic Liver Cancer or Hong Kong Liver Cancer classifications. Few trials stratify participants by etiology, viral status, or ethnicity, leading to marked heterogeneity that limits cross-study comparability.

Technological advances have also shaped the current landscape of HCC vaccine development. The field has gradually shifted from traditional peptide and DC vaccines toward next-generation nucleic-acid platforms. Earlier trials primarily targeted classical antigens such as AFP, GPC3, and telomerase, whereas recent efforts have focused on multi-epitope neoantigen vaccines and DNA/mRNA approaches. Nucleic-acid platforms offer advantages including flexible design and rapid manufacturability; however, most available studies remain exploratory, with limited validation of mechanistic endpoints or durability of immune responses.

Recent trends further indicate a growing emphasis on combinatorial strategies rather than vaccine monotherapy. Multiple trials have explored the integration of tumor vaccines with ICIs, particularly PD-1/programmed cell death ligand-1 (PD-L1) blockade, or with locoregional treatments such as transarterial chemoembolization, radiofrequency/microwave ablation, and stereotactic radiotherapy, with the goal of enhancing antigen exposure and immune priming within the immunosuppressive hepatic microenvironment. While early data suggest acceptable tolerability, most of these trials are still single-arm and non-randomized, underscoring the need for stronger methodological rigor. In terms of endpoints, immune response rates, cytokine profiling, and safety remain the predominant outcomes, whereas clinical measures such as overall survival or recurrence-free survival are seldom incorporated. Dynamic biomarker monitoring, for example, AFP, DCP, or circulating tumor DNA, has been limited to isolated studies, and integration of such biomarkers into efficacy evaluation is still uncommon.

Collectively, current clinical trials have established an important foundation for vaccine-based immunotherapy in HCC, but they remain characterized by notable heterogeneity and methodological immaturity. Future studies should aim to standardize trial design through consistent application of staging systems (Barcelona Clinic Liver Cancer, Hong Kong Liver Cancer), clearer inclusion criteria, and incorporation of molecular or immune stratification. The integration of mechanistic biomarkers as efficacy endpoints and the use of adaptive, basket, or multicenter collaborative frameworks will be crucial for improving interpretability and reproducibility. Through methodological consolidation and harmonized evaluation criteria, the immunologic potential of cancer vaccines in HCC may eventually be translated into reliable clinical benefit and improved patient outcomes.

Overall, the collective evidence on tumor vaccines for HCC highlights both encouraging progress and persisting limitations. Across published studies, nearly all vaccine platforms, peptide, DC, viral, and nucleic acid, have demonstrated favorable safety and tolerability profiles, even in cirrhotic or post-surgical populations. Consistent induction of tumor-specific immune responses, including cytotoxic T-cell activation and interferon-γ secretion, confirms the immunogenic potential of vaccination within the immunosuppressive hepatic milieu. Technological advances, particularly the transition toward DNA and mRNA platforms and the development of personalized neoantigen vaccines, further underscore the field's rapid evolution toward precision immunotherapy.

Despite these advances, significant methodological and translational barriers remain. Most studies are exploratory and underpowered, limiting the ability to correlate immune activation with clinical benefit. The lack of standardized staging criteria, heterogeneous inclusion strategies, and minimal biomarker integration impede cross-trial comparability and weaken evidence synthesis. Moreover, survival outcomes and recurrence endpoints are rarely incorporated, leaving the true clinical value of vaccination uncertain. These limitations highlight the need for larger, multicenter phase II/III trials with predefined immunologic and clinical endpoints, supported by consistent molecular stratification and real-time biomarker monitoring.

From a clinical perspective, the cumulative data suggest that cancer vaccines are unlikely to function as stand-alone therapies in the near term. Their most promising application may lie in perioperative or adjuvant settings, where immune competence is preserved and tumor burden is minimal. Integration with ICIs, locoregional therapies, and biomarker-guided surveillance could amplify antitumor efficacy while maintaining acceptable safety. Ultimately, translating vaccine-induced immune responses into durable clinical outcomes will depend on rigorous trial design, standardized assessment frameworks, and continued innovation at the

Table 2. Representative clinical trials of tumor vaccines for hepatocellular carcinoma

Year	Trial ID	Phase	Vaccine platform	Target antigen	Combined therapy	Tumor stage/Clinical classification	Primary endpoint(s)
2016	NCT02432963	I	Viral vaccine	p53	Pembrolizumab	Advanced/unresectable	Safety
2018	NCT03674073	I	DC vaccine	NR	Microwave ablation	HKLC Stage IIa	Safety
2018	NCT03552718	I	Peptide vaccine	NR	-	Localized/resectable	SafetyRecommended Dose
2019	NCT04147078	I	DC vaccine	NR	-	Localized/resectable	DFS at 5 years
2019	NCT03942328	I/II	DC vaccine	NR	EBRT + atezolizumab + bevacizumab	Advanced/unresectable	PFS at 2 years
2019	NCT04206254	II/III	Cellular vaccine	NR	-	AJCC TNM II, III, IV	RFS at 2 years
2019	NCT04317248		DC vaccine	NR	Cyclophosphamide + Radical surgery therapy or TACE or targeted agents therapy	Localized/resectable	PFS at 20 years
2020	NCT04248569	I	Peptide vaccine	DNAJB1-PRKACA	Poly-ICLC+ Nivolumab+ Ipilimumab	Advanced/Unresectable (FLC)	PFS at 0.5 year; Immunogenicity; Safety
2021	NCT05059821	I	Peptide vaccine	NR	Cyclophosphamide	Recurrent	Safety; Immunogenicity
2021	NCT04912765	II	DC vaccine	NR	Nivolumab	Localized/resectable	RFS at 2 years; Immunogenicity
2022	NCT05528952	II	Peptide vaccine	CD4 Th1-inducer form Telomerase	Atezolizumab + Bevacizumab	Advanced/unresectable (BCLC A-B)	ORR at 0.5 year
2022	NCT05269381	I/II	Peptide vaccine	Personalized Neoantigen	Cyclophosphamide + Sargramostim + Pembrolizumab	Advanced/unresectable	Safety
2022	NCT05192460	N/A	Nucleic acid vaccine (mRNA)	Personalized Neoantigen	With or without PD-1/L1	Advanced/unresectable	Safety; ORR at 2 years
2022	NCT06218511	I	Peptide vaccine	NR	Montanide + Durvalumab	BCLC 0–B	Safety
2023	NCT05761717	N/A	Nucleic acid vaccine (mRNA)	Personalized Neoantigen	Stintilimab	Localized/resectable	ORS and OS at 1 year
2023	NCT05937295	I	Peptide vaccine	DNAJB1-PRKACA	Atecolizumab	Advanced/Unresectable (FLC)	Immunogenicity; Safety
2023	NCT05738447	I	Nucleic acid vaccine (mRNA)	HBV	-	Advanced/unresectable	Safety; OR, PFS and OS at 1 year
2023	NCT05964361	I/II	DC vaccine	WT1	-	Advanced/unresectable	Feasibility (leukapheresis, vaccine manufacture & administration); Safety
2023	NCT05981066	N/A	Nucleic acid vaccine (mRNA)	NR	-	Advanced/unresectable	Safety
2023	NCT06088459	I	Nucleic acid vaccine (DNA)	GPC3	-	Localized/resectable (BCLC A/B)	DLT; Safety
2025	NCT06789198	I	Peptide vaccine	DNAJB1-PRKACA	-	Localized/resectable (FLC)	Immunogenicity; Safety
2025	NCT07053072	I/II	Nucleic acid vaccine (mRNA)	PD-1	Routine regimen	Advanced/unresectable	ORR at 2 years
2025	NCT07077356	I	Nucleic acid vaccine (mRNA)	HBV	-	Localized/transplant-eligible	DLT; Safety
2025	NCT07077369	I	Nucleic acid vaccine (mRNA)	HBV	Tislelizumab	Localized/resectable	DLT

AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; DC, dendritic cell; DFS, disease-free survival; DLT, dose-limiting toxicity; EBRT, external beam radiation therapy; FLC, fibrolamellar carcinoma; GPC3, glypican-3; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer classification; mRNA, messenger RNA; NR, not reported; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization.

intersection of immunology, bioengineering, and computational modeling.

Barriers to clinical translation

Tumor immune microenvironment in HCC

The tumor immune microenvironment (TIME) refers to the complex milieu within and surrounding tumors, comprising diverse immune cells, vascular and stromal components, as well as cytokines and chemokines.[80] Within this intricate network of signaling molecules, immune cells interact dynamically, profoundly influencing HCC progression and serving as key targets for therapeutic intervention.

Cancer vaccines, as a form of immunotherapy, primarily aim to activate the immune system, particularly CTLs, to recognize and eliminate tumor cells. However, the TIME in HCC is typically immunosuppressive. Tregs and myeloid-derived suppressor cells, which are highly enriched in the HCC microenvironment, suppress the activity of CTLs and natural killer cells.[47] In addition, tumor-associated neutrophils, tumor-associated macrophages, and regulatory DCs secrete a variety of cytokines that promote tumor proliferation and progression, ultimately compromising the efficacy of cancer vaccines.[81–83]

Heterogeneity of HCC

Heterogeneity in HCC encompasses the genetic, phenotypic, and behavioral diversity observed both among different patients and across distinct tumor regions within the same individual. This complexity arises from the combined effects of genetic mutations, epigenetic alterations, transcriptional variability, and microenvironmental influences.[84] Such heterogeneity poses major challenges for the development and evaluation of cancer vaccines, as it often results in inconsistent or unpredictable responses to immunotherapy.

Molecular heterogeneity in HCC is particularly evident in inter-patient variability in mutational profiles, signaling-pathway activation, and immune-microenvironment composition. For instance, cancer-related genes such as TTN, CTNNB1, RB1, ZFHX4, and TP53, along with their associated pathways, display distinct expression patterns across patients.[85] These molecular differences not only shape tumor biology but also strongly influence the degree of immunogenicity elicited by cancer vaccines.

Furthermore, intra-patient (intratumoral) heterogeneity is well documented in HCC, with substantial differences in gene-expression signatures and immune-cell infiltration observed among different tumor regions within the same liver.[86] This intratumoral diversity may prevent vaccines targeting a single antigen from achieving comprehensive tumor coverage, thereby reducing overall therapeutic efficacy.

Drug resistance and immune evasion in HCC

Drug resistance represents another major obstacle to the clinical success of cancer vaccines in HCC. Resistance develops through multiple mechanisms, often driven by the TIME and the underlying molecular heterogeneity of the disease.[87,88] Epigenetic alterations, including chromatin remodeling, DNA methylation, histone modifications, and regulation by non-coding RNAs, also contribute to therapeutic resistance.[89] These adaptive processes enable HCC cells to survive and proliferate despite immune activation induced by cancer vaccines, ultimately leading to treatment failure.

Immune evasion refers to the ability of tumor cells to avoid recognition and elimination by the host immune system. Key mechanisms include downregulation or loss of tumor-antigen expression, upregulation of immunosuppressive molecules such as PD-L1, and secretion of immunosuppressive cytokines including transforming growth factor-βand IL-10.[90] Notably, immune evasion and drug resistance are often interlinked, acting synergistically to allow HCC cells to circumvent vaccine-induced immune responses and sustain tumor progression.

Quality control and regulatory guidelines for cancer vaccines

Cancer vaccine technologies remain in the early stages of development, underscoring the need for comprehensive quality-control standards encompassing raw-material selection, adjuvant and platform specification, and final-product testing to ensure manufacturing consistency and clinical feasibility. To date, only one therapeutic cancer vaccine has received FDA approval, while most others remain under clinical investigation. Robust trial design, rigorous implementation, and standardized data analysis are essential to ensure reproducibility and regulatory credibility.

Outcome selection also plays a pivotal role in evaluating vaccine efficacy. Although overall survival is the most clinically meaningful endpoint, most current studies primarily assess immunogenicity, safety, and preliminary efficacy. Standardized evaluation criteria, objective immunologic correlates, and long-term follow-up data remain insufficient.

Furthermore, there are currently no formal guidelines or expert consensus governing the clinical use of cancer vaccines. Most existing trials are small-scale and exploratory, and standardized recommendations on optimal administration timing, dosage, adjuvant combinations, and delivery routes are still lacking. Establishing unified regulatory frameworks and consensus-driven best practices will be critical to accelerate the clinical translation and real-world integration of cancer vaccines.

Future directions for cancer vaccines

Combination strategies for cancer vaccines

With growing insights into the molecular features and heterogeneity of HCC, both experimental and computational advances have increasingly focused on overcoming the TIME that constrains vaccine efficacy. Among these efforts, combination therapy strategies involving cancer vaccines have emerged as a major research focus to enhance therapeutic outcomes.

The combination of cancer vaccines with ICIs has demonstrated encouraging preliminary results. Several clinical trials are currently underway to evaluate vaccine–ICI combinations in HCC (e.g., NCT04248569, NCT04912765, NCT05269381). Tregs and myeloid-derived suppressor cells accumulate in cirrhotic livers and suppress cytotoxic T-cell activity. By blocking inhibitory pathways such as PD-1/PD-L1, ICIs help dismantle tumor immune-evasion mechanisms, thereby creating a more permissive environment for vaccine-induced immune responses and enhancing their therapeutic efficacy.[91] Although the small sample sizes and single-arm designs of current trials limit the ability to attribute efficacy solely to vaccines, response rates in these combination regimens have exceeded those observed with PD-1 inhibitor monotherapy in historical HCC cohorts.[47]

Beyond ICIs, cancer vaccines are being investigated in combination with chemotherapy, radiotherapy, and targeted therapies because of their potential synergistic effects. Radiation and cytotoxic agents can induce tumor apoptosis

and necrosis, releasing TAAs that stimulate antitumor immune responses. Therefore, post-chemotherapy or post-radiotherapy settings may offer an ideal therapeutic window for vaccine administration.[92] Cyclophosphamide, which modulates the TIME and depletes Tregs, is being evaluated in combination with cancer vaccines in ongoing HCC trials (e.g., NCT04317248, NCT05269381). Likewise, colony-stimulating factor 1 receptor/C-C chemokine receptor type 2 inhibitors have been shown to transiently deplete immunosuppressive myeloid populations and restore antitumor immunity.[93]

In parallel, mesenchymal stem cell–derived exosomes have demonstrated the capacity to reprogram macrophages toward an M1-like phenotype and attenuate transforming growth factor-β–driven fibrosis, thereby alleviating stromal barriers that restrict T-cell infiltration.[94,95] These microenvironment-modulating strategies underscore the importance of coupling immunotherapy with stromal remodeling to achieve durable vaccine responses. Moving forward, optimizing combinatorial regimens and identifying the most effective therapeutic sequences may substantially improve clinical outcomes for patients with HCC.

Design of personalized cancer vaccines

Compared to ICIs, clinical development of cancer vaccines for HCC remains limited, partly due to the unsatisfactory outcomes of early studies, largely attributed to challenges in identifying truly effective TAAs and TSAs.[96] Early vaccine targets such as GPC3 and AFP lack complete tumor specificity, frequently leading to immune tolerance and suboptimal antitumor responses. Consequently, identifying and designing tumor-specific neoantigens has become a critical prerequisite for the success of HCC vaccines.

Recent advances in high-throughput sequencing and bioinformatics have facilitated the identification of patient-specific neoantigens in HCC. Nucleic acid–based vaccine platforms now enable precise antigen engineering, and the development of PTCVs has become a central focus of research. For example, GNOS-PV02, a neoantigen-based PTCV, has demonstrated robust immunogenicity and preliminary clinical efficacy in HCC patients.[47] In China, a personalized neoantigen vaccine designed for high-risk recurrent HCC significantly prolonged disease-free survival among vaccinated individuals.[44]

In parallel, computational algorithms are increasingly being employed to identify patient-specific neoantigens and optimize vaccine formulation. Machine-learning frameworks that integrate multi-omics datasets can predict immunogenic mutations, MHC binding affinity, and potential immune-escape pathways, thereby supporting the rational selection of vaccine targets and real-time monitoring of immunologic responses.[97] Together, these computational and biological innovations mark a new phase of precision immunotherapy in HCC.

Currently, several clinical trials evaluating PTCVs in HCC are ongoing (e.g., NCT03674073, NCT03552718, NCT04147078, NCT05059821). However, high production costs, lengthy manufacturing timelines, and the requirement for highly individualized clinical trial designs remain substantial obstacles. In the future, streamlining personalized vaccine design workflows and incorporating individual tumor-genetic and immune signatures may enable more precise and effective therapeutic strategies, ultimately improving outcomes for patients with HCC.

Design optimization and emerging technologies

Optimization of cancer vaccine design and the integration of emerging technologies are key to improving vaccine efficacy.

Recent advances in nanotechnology, synthetic biology, gene editing, and artificial intelligence have opened new directions for vaccine development. Nanoparticles, as delivery systems, enhance antigen stability and delivery efficiency, thereby amplifying immune responses. For instance, LNPs have markedly improved the delivery and immunogenicity of mRNA vaccines.[98] Synthetic biology enables the rational design of novel antigens and adjuvants to enhance vaccine immunogenicity, while CRISPR/Cas9 genome editing allows precise modification of tumor-related genes, increasing vaccine specificity and potency.[99] Artificial intelligence-based technologies have also provided powerful tools for cancer-vaccine research, including neoantigen prediction, antibody engineering, and immune-response modeling.[100]

At the same time, advances in preclinical modeling are essential to facilitate clinical translation. Most HCC vaccine studies still rely on subcutaneous xenografts, which fail to reproduce the chronic inflammation and fibrosis typical of human disease. Recent reviews of HCC modeling emphasize that chemically induced or diet-driven fibrotic HCC models and fully humanized mouse models more accurately recapitulate the myeloid-cell infiltration and T-cell exclusion observed in patients.[101] Meanwhile, patient-derived tumor organoids co-cultured with autologous immune cells are emerging as *ex vivo* platforms for evaluating vaccine–immune combinations and stromal penetration in a patient-specific context.[102] These systems provide critical testbeds for early-phase vaccine development, enabling the integration of microenvironment-modulating agents, immune-monitoring assays, and antigen-vaccine interventions within models that closely mimic the human HCC ecosystem.

Taken together, the clinical translation of cancer vaccines for HCC is constrained by multiple interconnected barriers, including an immunosuppressive tumor microenvironment, pronounced tumor heterogeneity, immune evasion mechanisms, and unresolved regulatory challenges. Addressing these limitations will require coordinated advances in therapeutic strategies, vaccine design, and enabling technologies (Fig. 2).

Conclusions

Cancer vaccines hold broad therapeutic promise for the treatment of HCC. Among the various platforms, peptide-based and DC vaccines have demonstrated clinical feasibility supported by substantial trial data. However, despite modest efficacy in early-phase studies, their overall therapeutic impact remains limited. With the rapid advancement of high-throughput sequencing technologies, liver-cancer vaccine research is shifting toward next-generation platforms, particularly DNA- and mRNA-based vaccines.

Nevertheless, cancer-vaccine research in HCC remains in its infancy, with most clinical trials still at phase I/II. More extensive datasets and long-term follow-up are needed to comprehensively assess both efficacy and safety. Future development will likely focus on combinatorial treatment strategies, optimization of PTCVs, and the integration of emerging technologies such as artificial intelligence.

In conclusion, although multiple biological and methodological challenges persist, diversified vaccine-based and multimodal therapeutic strategies offer tremendous potential. These innovations may ultimately deliver more precise and effective treatments for patients with HCC and improve their long-term clinical outcomes.

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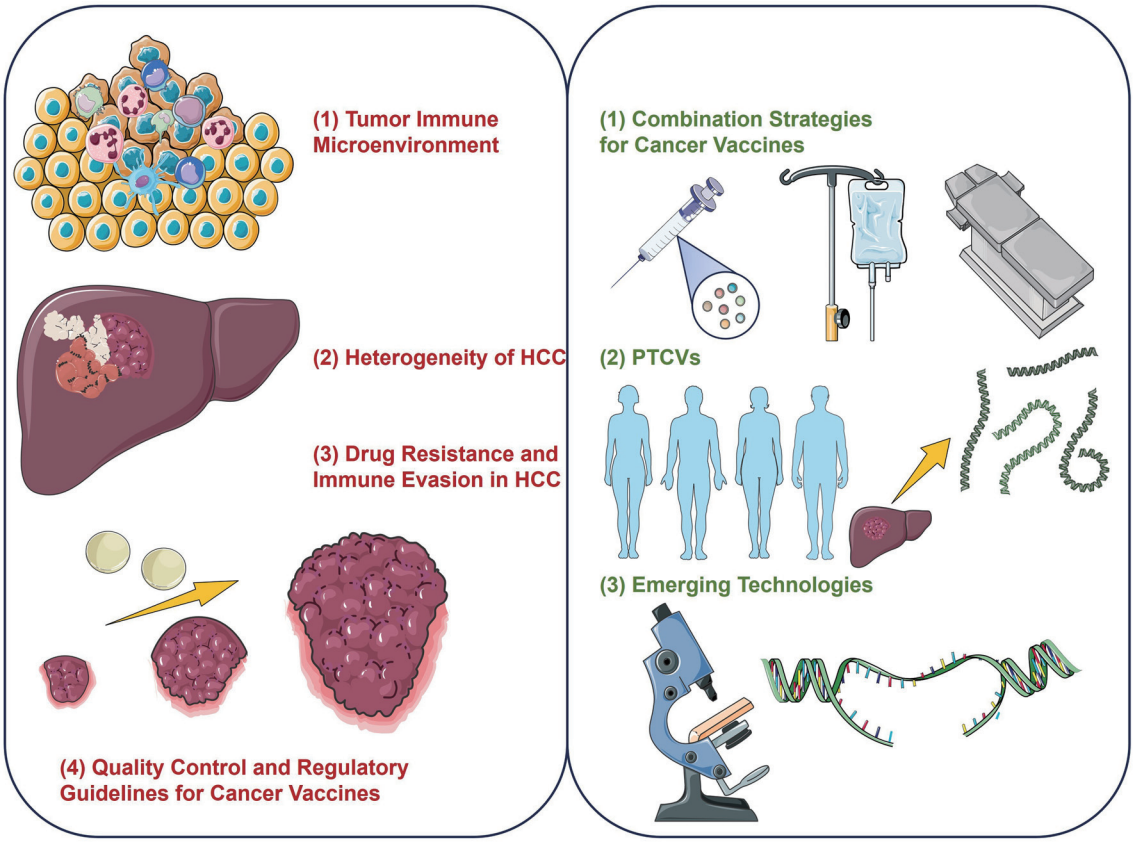

Fig. 2. Challenges and future directions for HCC vaccines. The diagram illustrates several conceptual modules associated with limitations and emerging directions in hepatocellular carcinom vaccine development. The left portion highlights four challenge categories. A cluster of tumor and immune cells represents the tumor immune microenvironment. A liver illustration containing multiple nodules represents HCC heterogeneity. A sequence of progressively enlarging tumor masses accompanied by an arrow indicates a category related to tumor growth patterns. The fourth label, quality control and regulatory guidelines for cancer vaccines, is shown as text only and is not associated with a specific graphic element. The right portion of the figure depicts three groups of strategies or emerging areas. Icons of syringe-based delivery, infusion equipment, and laboratory devices represent combination strategies for cancer vaccines. Silhouettes of human figures correspond to personalized therapeutic cancer vaccines. Illustrations of sequencing patterns, microscopy equipment, and nucleic acid structures indicate emerging biotechnologies relevant to vaccine development. All visual elements denote conceptual categories rather than specific biological mechanisms. HCC, hepatocellular carcinoma; PTCV, personalized tumor specific cancer vaccine.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

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