International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Hydrogel-Based Immunomodulation of Tumor Immune Microenvironment in Hepatocellular Carcinoma: Current Strategies and Future Directions

Shanyong Zhang[1], Lei Ding[2], Tingting Hou[1], Dengjian Lin[1], Yuan Qu[1]

[1]Department of Spine Surgery, The Second Hospital of Jilin University, Changchun, People's Republic of China; [2]Department of Orthopedics, The Second Hospital of Jilin University, Changchun, People's Republic of China

Correspondence: Yuan Qu, Department of Spine Surgery, The Second Hospital of Jilin University, 4026 Yatai Street, Changchun, Jilin, 130000, People's Republic of China, Email quyuan0127@jlu.edu.cn

Abstract: Hepatocellular carcinoma (HCC) remains one of the most aggressive malignancies, with poor prognosis and limited treatment options, particularly due to the immunosuppressive tumor immune microenvironment (TIME). Hydrogels have emerged as a promising biomaterial platform for local and controlled delivery of immunomodulatory agents, offering a novel strategy to remodel the TIME and enhance the efficacy of existing therapies. This review explores hydrogel-based strategies for immunomodulation in HCC, focusing on their potential to localize immune regulation, improve immune cell infiltration, and overcome immune evasion. Hydrogels can be engineered to encapsulate a range of therapeutic agents, including immune checkpoint inhibitors, cytokines, tumor antigens, and adjuvants, allowing for sustained release and targeted action within the tumor. The integration of hydrogels with therapies such as ablation, CAR-T cell therapy, and tumor vaccines has demonstrated synergistic effects, significantly enhancing antitumor immunity and reducing tumor recurrence. However, challenges remain in optimizing hydrogel composition, biocompatibility, degradation rates, and the efficiency of agent delivery. Personalized hydrogel-based therapies, tailored to individual patient's TIME, hold great potential for precision immunotherapy in HCC. This review highlights the current advances, challenges, and future directions for hydrogel-based immunomodulation strategies in HCC treatment, underscoring their transformative potential in cancer therapy.

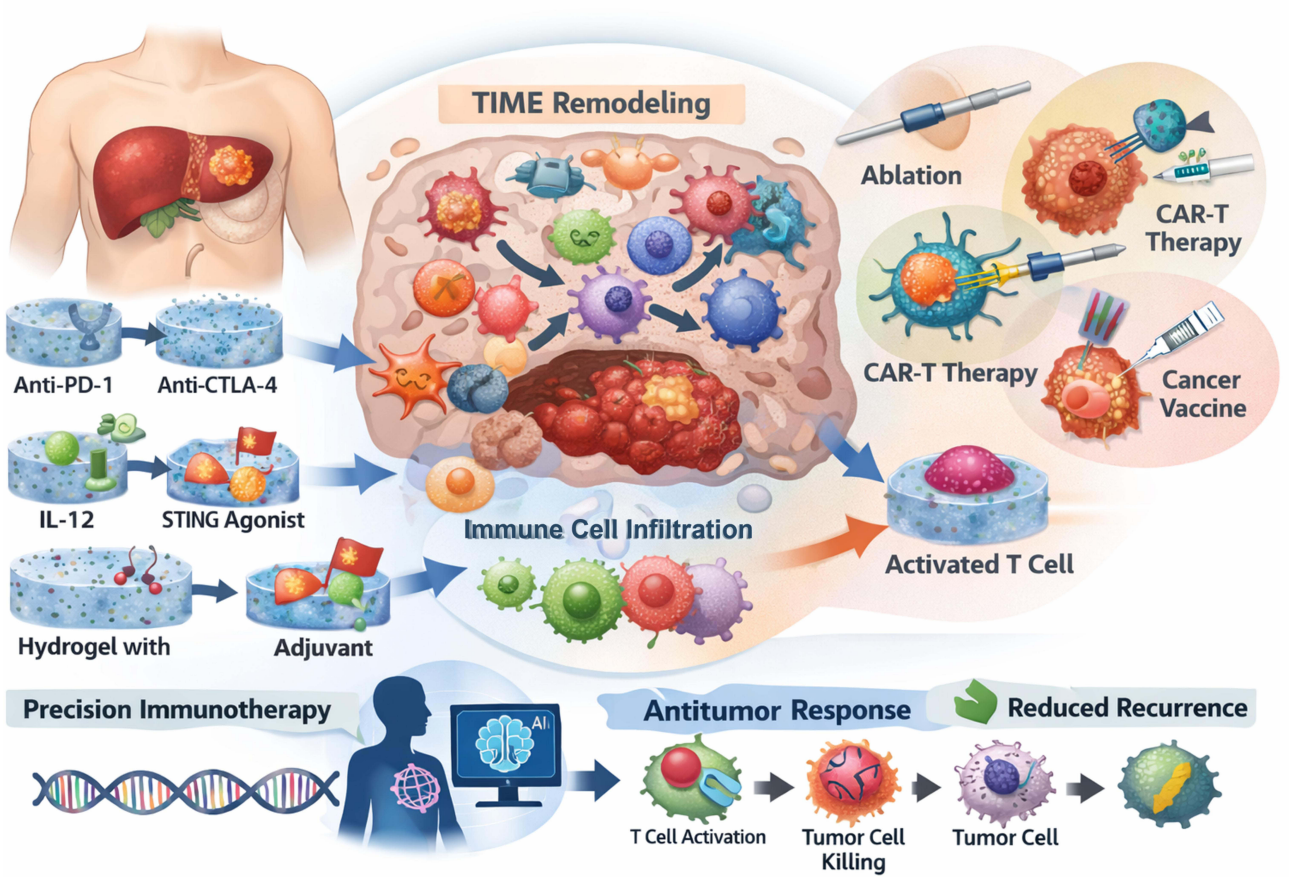
Keywords: hepatocellular carcinoma, tumor immune microenvironment, hydrogels, immunotherapy, precision medicine, ablation, CAR-T

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, representing the third leading cause of cancer-related mortality globally.[1,2] Its incidence continues to rise, particularly in regions with a high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, as well as in populations suffering from non-alcoholic steatohepatitis (NASH) and alcoholic liver disease.[3,4] Despite significant advances in diagnostic methodologies and therapeutic interventions, HCC remains notoriously difficult to treat, with prognosis largely dependent on the stage of diagnosis. Late-stage detection, coupled with limited curative treatment options and high rates of recurrence and metastasis, contributes to the overall poor survival rates for HCC patients.[5] Unique to HCC is its development within a chronically inflamed and fibrotic liver environment, which inherently fosters a tolerogenic immune landscape that hampers effective immune responses. This immunosuppressive tumor immune microenvironment (TIME) plays a pivotal role in the progression, therapeutic resistance, and immune evasion of HCC.[6–8] Key immunosuppressive cell populations within the TIME, including tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and exhausted T cells, are central players in this immune dysfunction, acting to suppress

https://doi.org/10.2147/IJN.S576091
Received: 22 October 2025
Accepted: 22 February 2026
Published: 4 March 2026

Graphical Abstract



antitumor immune responses and facilitate tumor progression.[9] Furthermore, the overexpression of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), alongside the activation of immune checkpoint pathways like PD-1/PD-L1 and CTLA-4, exacerbates immune dysfunction and promotes tumor immune escape.

Traditional systemic delivery of immune modulators, including cytokines and immune checkpoint inhibitors, often results in insufficient accumulation at the tumor site, limiting therapeutic efficacy and increasing the risk of immune-related adverse events.[10,11] These challenges underscore the need for more targeted, localized therapies that can provide precise spatial and temporal control over immune regulation within the tumor microenvironment (TME).[12,13] In recent years, hydrogels have emerged as a promising class of biomaterials, offering unique advantages in the field of biomedical applications. Hydrogels form through cross-linking, and advanced designs include stimuli-responsive cross-linking that reacts to pH, enzyme levels, or redox conditions typical of TME.[14,15] These include high biocompatibility, tunable mechanical properties, controlled degradation rates, and the ability to encapsulate a wide range of therapeutic agents.[16,17] Hydrogels, in the context of HCC, have shown tremendous potential as local delivery platforms for a variety of immune modulators, such as cytokines, immune checkpoint inhibitors, and tumor antigens.[18,19] Their capacity for controlled and sustained release allows for prolonged therapeutic effects, while minimizing systemic toxicity.[20–22] Additionally, hydrogels can be engineered to respond to specific tumor-associated stimuli, such as alterations in pH, the presence of specific enzymes, or reactive oxygen species (ROS), thereby enhancing their specificity and effectiveness in remodeling the TIME.[23–27] By leveraging these characteristics, hydrogels can locally modulate the immune microenvironment to

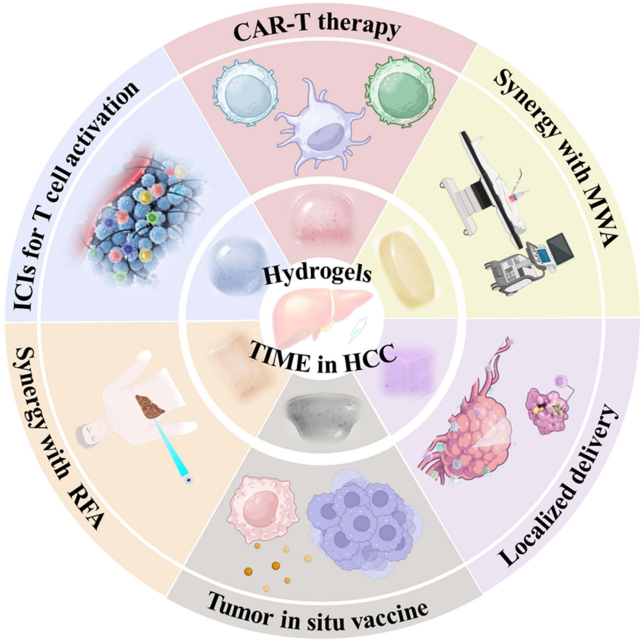


Figure 1 Hydrogel-based strategies for remodeling the TIME in HCC.

enhance antitumor immunity, synergize with existing therapies, and overcome the immunosuppressive barriers of the TIME in HCC. While existing reviews tend to organize hydrogel platforms by therapeutic modality, this review establishes a mechanism-guided design framework that systematically links tumor biology of HCC with rational hydrogel design parameters.[18,28–30] This framework provides predictive guidance for selecting or engineering hydrogel properties tailored to specific HCC pathophysiology. In this review, we provide an in-depth exploration of hydrogel-based strategies for remodeling the TIME in HCC, examining their potential to localize immune modulation, enhance therapeutic outcomes, and contribute to the evolving landscape of precision immunotherapy (Figure 1). We also discuss the challenges and future directions of these systems, particularly in terms of clinical translation and their integration into combination therapies for HCC treatment.

Mechanisms of the Tumor Immune Microenvironment (TIME) in HCC for Therapy

TIME in HCC is a highly dynamic and immunosuppressive niche that plays a central role in tumor development and progression.[31] The tolerogenic hepatic environment dampens immune surveillance and promotes tumor immune escape.[32] Understanding the cellular composition and molecular characteristics of the TIME in HCC is crucial for designing effective immunomodulatory strategies, including hydrogel-based delivery platforms.[33] HCC frequently arises in the setting of chronic inflammation, liver fibrosis, and cirrhosis. This microenvironment is dominated by pro-inflammatory cytokines, chemokines, and immune cells that influence tumor progression. While acute inflammation typically elicits immune activation, chronic inflammation in HCC leads to immune tolerance. This shift from inflammation to tolerance is a key characteristic of the HCC TIME and contributes to immune suppression. The liver's immunologic tolerance to self-antigens and its role in maintaining homeostasis play a significant role in the immune suppression in HCC. The TIME of HCC is composed of a diverse array of cellular and non-cellular components, including tumor cells, stromal cells (eg, hepatic stellate cells, fibroblasts), endothelial cells, immune cells, extracellular matrix (ECM), and soluble mediators such as cytokines, chemokines, growth factors, and metabolic byproducts.[34] These elements engage in complex crosstalk that regulates immune cell recruitment, polarization, and function.[35] Several key features define the HCC immune microenvironment, including chronic inflammation, immune cell exhaustion, immunosuppressive dominance, and dense ECM and poor immune infiltration.[36–38] Sustained inflammatory signaling

promotes an immunosuppressive milieu that supports tumor growth and neoangiogenesis. A stiff and fibrotic stroma impairs immune cell trafficking into tumor cores, limiting immunotherapy efficacy.

The TIME of HCC is characterized by complex immune dysfunction, which plays a critical role in tumor progression and immune escape. T cells in the HCC microenvironment often exhibit upregulation of exhaustion markers such as PD-1, TIM-3, and LAG-3, leading to functional anergy. Cells like Tregs, TAMs, and MDSCs are abundant and actively suppress antitumor immunity. The key immune cells in TIME of HCC and their function are listed in Table 1. Key immune regulatory mechanisms, such as the Tregs and the increased recruitment of MDSCs, further exacerbate immune dysfunction. These cells and factors contribute to the persistence of tumors and facilitate their escape from immune surveillance. TAMs are among the most abundant immune cells in the TIME of HCC and are typically skewed toward an M2-like, immunosuppressive phenotype, by secreting IL-10, TGF-β, and VEGF, suppressing CTLs.[39] Reprogramming TAMs toward a pro-inflammatory M1 phenotype is a promising therapeutic strategy.[40] $CD8^+$ CTLs often become exhausted in HCC due to chronic antigen exposure and inhibitory signaling. $CD4^+$ helper T cells may also contribute to immune suppression depending on their differentiation into Th2 or Treg lineages.

Table 1 Key Immune Cells in the Tumor Immune Microenvironment of Hepatocellular Carcinoma: Functions, Immunosuppressive Mechanisms, and Therapeutic Implications

Cell Type	Full Name	Function	Immunosuppressive Mechanisms	Implications for Therapy
TAMs	Tumor-Associated Macrophages	Promote tumor progression through the secretion of pro-inflammatory cytokines (eg, IL-1β, TNF-α); contribute to immune suppression by secreting IL-10 and TGF-β.	TAMs, especially in the M2 polarization, promote immunosuppressive functions by secreting IL-10, TGF-β, and other factors that inhibit T cell activation.	Targeting TAM polarization and reducing immunosuppressive cytokines such as TGF-β can enhance antitumor immunity.
$CD8^+$ CTLs	$CD8^+$ Cytotoxic T Lymphocytes	Primary effectors of antitumor immunity. Exhaustion of $CD8^+$ CTLs within the TME leads to ineffective immune surveillance.	Exhaustion occurs through continuous antigen stimulation within the TME, upregulating inhibitory receptors like PD-1, CTLA-4, and TIM-3.	Immunotherapy strategies targeting PD-1/PD-L1 or CTLA-4 can reinvigorate exhausted CTLs.
$CD4^+$ Th	$CD4^+$ Helper T Cells	Coordinate and regulate immune responses by secreting cytokines that promote the activation and differentiation of other immune cells (eg, Th1, Th2, and Th17).	Th2-polarized $CD4^+$ T cells contribute to tumor progression by secreting cytokines such as IL-4 and IL-13, which enhance the accumulation of Tregs and suppress antitumor immunity.	Redirecting Th cell polarization from Th2 to Th1 can enhance antitumor immunity.
Tregs	Regulatory T Cells	Suppress effector T cell activity and inhibit immune responses through the secretion of immunosuppressive cytokines (eg, IL-10, TGF-β).	The secretion of cytokines like IL-10 and TGF-β, leading to a local immunosuppressive environment.	Depleting or inhibiting Tregs can enhance immune responses.
DCs	Dendritic Cells	Initiate and regulate T cell responses by presenting tumor antigens and activating $CD4^+$ and $CD8^+$ T cells.	DCs in HCC adopt a tolerogenic phenotype, which promotes the expansion of Tregs and reduces the activation of effector T cells.	Improving DC function and antigen presentation can boost T cell responses.
MDSCs	Myeloid-Derived Suppressor Cells	Suppress both innate and adaptive immune responses, inhibiting T cell activation and NK cell activity.	MDSCs suppress T cell responses by depleting essential amino acids like arginine and secreting ROS that damage immune cells.	Targeting MDSCs and their immunosuppressive mechanisms can boost immune responses.
NK	Natural Killer Cells	Contribute to early antitumor immunity by directly killing tumor cells and secreting cytokines (eg, IFN-γ) that enhance immune responses.	The TME in HCC induces NK cell dysfunction through the upregulation of inhibitory receptors and the secretion of suppressive cytokines.	Enhancing NK cell function through immune checkpoint inhibitors or cytokine therapy (eg, IL-15) can improve early antitumor immunity.

Enriched Tregs are involved in cytokine secretion (IL-10, TGF-β) and cell-cell contact mechanisms.[41] DCs are professional antigen-presenting cells (APCs). However, DCs often display a dysfunctional or immature phenotype in HCC, leading to impaired antigen presentation and reduced T cell priming. MDSCs are immature myeloid cells that accumulate in the HCC microenvironment and promote immune escape. NK cells recognize and eliminate transformed cells. In HCC, NK cell frequency and cytotoxicity are diminished, partly due to the immunosuppressive cytokine milieu and the presence of ligands for inhibitory NK receptors.

In addition to immune cells, the TIME in HCC is heavily influenced by the cytokine milieu and extracellular matrix (ECM) components, which further facilitate immune evasion and tumor progression. The immunosuppressive behavior of the HCC TIME is reinforced by a cytokine and chemokine network that regulates immune cell differentiation, migration, and function.[42] Specifically, CCL2, CCL5, and CXCL12 recruit TAMs and MDSCs to the tumor site. VEGF and GM-CSF support angiogenesis and suppress DC maturation. In parallel, the expression of immune checkpoint molecules such as PD-L1 on tumor cells and TAMs leads to T cell exhaustion.[43] Other inhibitory pathways including CTLA-4, LAG-3, and TIM-3 are also frequently upregulated and contribute to impaired immune surveillance.[44] IL-10 and TGF-β promote Treg expansion, inhibit CTLs and NK cells, and contribute to ECM remodeling. The ECM in HCC is often remodelled by tumor cells and stromal cells, creating a dense, fibrotic barrier that physically impedes immune cell infiltration into the tumor. Collagen deposition, fibrosis, and the upregulation of ECM remodeling enzymes such as matrix metalloproteinases (MMPs) contribute to the suppression of immune cell function and the promotion of tumor cell invasion and metastasis.

Hydrogel-Based Localized Delivery of Immunomodulatory Agents

Hydrogels, as innovative drug delivery platforms, show significant advantages in precisely delivering therapeutic agents. Hydrogels can not only provide sustained, controlled release of drugs but also locally deliver immunomodulatory agents, tumor antigens, or immune checkpoint inhibitors, reshaping the TIME and activating anti-tumor immune responses.[45] Three key parameters, pore size, mechanical stiffness, and degradation rate play crucial roles in modulating immune cell behavior and enhancing therapeutic efficacy of hydrogel.[46] The effectiveness of immunotherapy in HCC is often limited by the challenges of achieving localized, sustained, and controlled release of therapeutic agents within the TME. The motivation for localized immunotherapy, particularly in the context of HCC, stems from the unique challenges posed by the TIME. HCC is characterized by an immunosuppressive TIME, which includes an abundance of immune-suppressive cells. Thus, local administration of immunomodulatory agents offers several advantages, including enhanced concentration at the tumor site, sustained and controlled release, and synergy with other therapeutic modalities. The research progresses are listed in Table 2. Beyond simple drug delivery, hydrogels can act as scaffolds for immune cells, providing a physical framework that enhances immune cell infiltration and spatial organization within the tumor. This ability to modulate immune cell positioning is crucial for the effective activation and recruitment of specific immune cells to the TME. By physically supporting immune cells at the site of the tumor, hydrogels can ensure localized immune activation and counteract the immune suppression within the TME, which is often seen in HCC. Hydrogels can be functionalized with bioactive molecules that enhance the local immune response. These functionalized hydrogels can directly activate immune cells or redirect immune responses towards the tumor site, improving immune cell recruitment and activation. Hydrogels can create a favorable niche for immune cell interactions by providing a biocompatible, non-inflammatory microenvironment that supports immune cell survival and function. Hydrogels can also modulate immune cell signaling pathways by delivering small molecules or biomolecules that activate immune pathways.

Traditional systemic administration of cytokines and immunostimulants is often limited by short half-lives, off-target effects, and severe immune-related adverse events. To address these challenges, hydrogel-based delivery systems have emerged as a promising solution for the localized delivery of immunomodulatory agents, offering controlled release, enhanced biocompatibility, and the ability to target specific tumor-associated stimuli.[54] Localized delivery of immunomodulatory agents via hydrogels aims to enhance immune activation within the TME while minimizing systemic toxicity.[55] Injectable or implantable hydrogels have been engineered to deliver pro-inflammatory cytokines to activate cytotoxic T cells and NK cells within the HCC TIME.[56] In addition to cytokines, hydrogel matrices can incorporate immune-stimulating adjuvants, which mimic pathogen-associated molecular patterns (PAMPs) and activate innate immune pathways. When delivered locally via hydrogel depots, these adjuvants potentiate DC activation and promote

Table 2 Hydrogel-Based Therapeutic Approaches for Modulating the Tumor Immune Microenvironment (TIME) in Hepatocellular Carcinoma (HCC)

Hydrogel-Based Immunomodulation Strategies	Study	Hydrogel Composition	Immunomodulatory Agents	Therapeutic Strategy	Key Findings	Target Disease	Unique Aspect	Advantages	Limitations	Reference
Localized Delivery of Immunomodulatory Agents	**Cao et al (2023)**	RADA16-I peptide hydrogel	Lysed OK-432 (immunoadjuvant), Doxorubicin	Post-surgery treatment for residual liver cancer	Induced local immune response and enhanced antitumor activity post-RFA	Residual liver cancer after incomplete RFA	Combination of immunotherapy and chemotherapy using a hydrogel system	Localized therapy reduces systemic exposure; enhances antitumor effects at surgical margins	May still require optimization of release kinetics; potential inflammation at site	[47]
	Li et al (2022)	Polypeptide hydrogel/ nanogel composite	TGF-β inhibitor (LY3200882), Regorafenib	Targeted inhibition and immunoactivation in TME	Enhanced drug delivery and immune activation within the TME	Solid tumors	Adapted hydrogel delivery system responsive to TME conditions	Stimuli responsive release; improved penetration and retention	Complexity of design may challenge scalability and reproducibility	[48]
Immune Checkpoint Inhibition for T Cell Activation	**Tang et al (2024)**	Personalized neoantigen hydrogel	Anti-PD-1 and anti-CTLA-4 antibodies	Tumor vaccination combined with immune checkpoint blockade	Activated intratumoral CD8+CD69+ T cells and improved antitumor response	Liver metastases	Personalized neoantigen vaccine combined with immune checkpoint blockade	Personalized immune activation; synergistic T cell response	Personalized production is costly and time consuming	[49]
Synergy with Ablation Therapy	**Shen et al (2025)**	Cholesterol-targeted catalytic hydrogel	Anti-PD-L1 antibody	Combination with microwave ablation	Enhanced immune response and tumor ablation synergy	Hepatocellular carcinoma	Utilization of tumor debris in hydrogel to synergize with ablation therapy	Converts ablation debris into immune stimulation; enhanced efficacy	Relies on effective ablation; risk of variable response	[50]
	Ao et al (2024)	STING agonist-loaded hydrogel	Interleukin-15 (IL-15) nanoparticles	STING agonist immunotherapy combined with RFA	Boosted immune activation and synergized with RFA	Hepatocellular carcinoma	STING agonist-loaded hydrogel to enhance immune activation in combination with RFA	Strong innate immune activation; synergistic with RFA	Complex agent combination may increase risk of toxicity	[51]

https://doi.org/10.2147/IJN.S576091

CAR-T Therapy and Tumor in Situ Vaccines	**Hu et al (2021)**	Hyaluronic acid-based hydrogel	CAR-T cells, Anti-PD-L1-conjugated platelets	Post-surgery recurrence prevention	Inhibited local and distant tumor recurrence via abscopal effect	Solid tumors (eg, melanoma)	Combination of CAR-T therapy and immune checkpoint blockade to prevent recurrence after surgery	Supports cell therapy persistence; abscopal immune effects	CAR T encapsulation may affect viability; translation to HCC needs validation	[52]
	Li et al (2024)	Hydrogel encapsulating G-Rh2	PD-1 antibody	Tumor microenvironment remodeling and immune modulation	Enhanced T cell activation and synergy with systemic immunotherapy	Solid tumors	Hydrogel encapsulated G-Rh2 as an in situ vaccine and its synergy with systemic immunotherapy	Synergistic immune activation; adaptable formulation	Systemic synergy may complicate mechanism interpretation	[53]

https://doi.org/10.2147/IJN.S576091

adaptive antitumor immunity. A promising example of hydrogel-based immunomodulation was developed by loading lysed OK-432 (lyOK-432) and doxorubicin (DOX) for the treatment of residual liver cancer following incomplete radiofrequency ablation (iRFA) of HCC.[47] This hydrogel was shown to effectively activate DCs and stimulate the STING pathway, leading to enhanced antitumor immune responses. The hydrogel resulted in the highest tumor necrosis rate and extended survival times, significantly increasing the percentages of CD4+ and CD8+ T cells while reducing Treg cells. Furthermore, the hydrogel induced higher levels of pro-inflammatory cytokines such as IFN-γ and TNF-α, demonstrating its potential as a powerful localized delivery platform to modulate immune responses in HCC. Monoclonal antibodies targeting immunosuppressive molecules have also been integrated into hydrogel delivery systems. These biomaterials prolong antibody residence time in the tumor and enhance localized immune modulation without the need for repeated systemic administration.

Hydrogels can be designed to respond to specific tumor-associated cues, such as acidic pH, overexpression of specific enzymes such as MMPs, or ROS, which are characteristic of the TME in HCC.[57] These stimuli-responsive hydrogels ensure that immunomodulatory agents are released only within the tumor microenvironment, thereby enhancing the specificity and effectiveness of the therapy while avoiding unnecessary systemic exposure.[58] Hydrogels offer versatility in terms of the types of agents they can encapsulate. This includes small molecules, biologics, RNA-based therapeutics, or even nanoparticles that can be used in combination with immunomodulatory therapies. This ability to co-deliver multiple agents within a single hydrogel system enables a more synergistic therapeutic approach, targeting different aspects of immune modulation within the TME simultaneously.[59] For example, Li et al developed an innovative tumor microenvironment-adapted composite, which provides precisely sequential drug release, enabling the combination of molecularly targeted therapies with immune activation (Figure 2).[48] In this system, regorafenib (REG) is first released from the hydrogel to inhibit tumor growth and promote ROS generation, which then triggers the on-demand release of LY3200882 (LY), a selective TGF-β inhibitor, from the nanogel. LY prevents the epithelial-mesenchymal transition and immune escape of tumor cells induced by elevated TGF-β, therefore inhibiting liver metastases. Overall, hydrogel-based localized immunotherapy presents a promising strategy to reshape the immunosuppressive landscape of HCC into a more immunogenic and therapeutically responsive environment.

Hydrogel-Based Immune Checkpoint Inhibition for T Cell Activation

The advent of immune checkpoint inhibitors (ICIs) has significantly transformed cancer therapy, especially in cancers like HCC.[60] ICIs, which target immune checkpoints such as PD-1/PD-L1 and CTLA-4, aim to restore immune surveillance and enhance the body's natural ability to recognize and destroy tumor cells. Immune checkpoint inhibitors (ICIs) have revolutionized cancer immunotherapy by blocking inhibitory pathways that dampen the immune response against tumors.[61,62] However, while ICIs have shown promising results in various cancers, their clinical efficacy in HCC is often hampered by the immunosuppressive TIME.[31,63,64] In particular, chronic immune suppression and the presence of inhibitory immune cells such as Tregs, MDSCs, and TAMs limit the effectiveness of ICIs in HCC patients. A promising approach to overcome these limitations is the use of hydrogel-based delivery systems in combination with ICIs.[65] Hydrogels can address these challenges by providing a controlled and localized release of ICIs within the tumor site. By encapsulating ICIs, such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies, within hydrogel matrices, these agents can be released in a sustained manner, ensuring prolonged exposure at the tumor site. This hydrogel-based synergy not only improves the pharmacokinetics of ICIs but also reduces systemic toxicity, enhancing the therapeutic index of ICIs in HCC. For example, a recent study developed a neoantigen hydrogel vaccine (NPT-gels) for liver metastasis, a condition characterized by immune tolerance and poor response to conventional therapies (Figure 3).[49] The NPT-gels, prepared with hyaluronic acid, neoantigen peptides, and clinical adjuvants, were designed to induce a sustained, high-intensity immune response. When combined with immune checkpoint blockade (ICB) targeting PD-1 and CTLA-4 (PCDB), the NPT-gels significantly improved the infiltration of neoantigen-specific CD8+ T cells and overcame the immune suppression inherent in liver metastases. This combination therapy enhanced the antitumor immune response, not only by boosting T-cell activation but also by inhibiting Tregs, which are known to dampen immune responses in the TME. Additionally, the NPT-gels effectively unlocked the immunosuppressive microenvironment, inducing long-term immune memory and improving survival rates in preclinical liver metastasis models. The

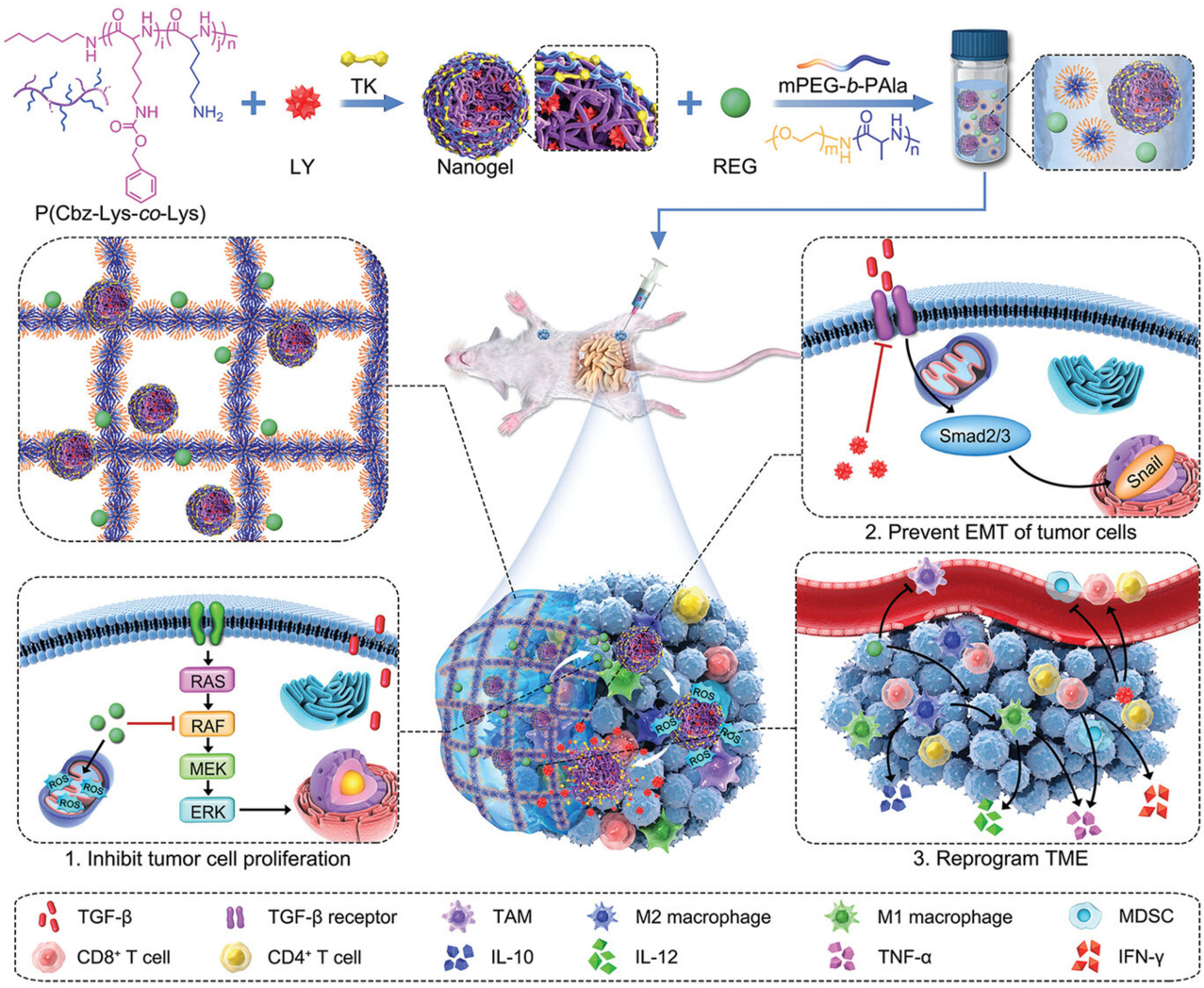


Figure 2 Localized delivery of immunomodulatory agents (adapted from *Advanced materials 2022; 34(21):e2200449*).[48] After in situ administration, REG and LY were sequentially released from the hydrogel/nanogel composite, which synergistically inhibited tumor growth, prevented distant metastases, and reversed the immunosuppressive TMEs to trigger T-cell-dependent immune responses.

success of this study highlights the potential of combining hydrogel-based delivery systems with ICIs to enhance immune responses in liver cancers. By using hydrogels to deliver ICIs and neoantigens in a controlled manner, it is possible to modulate the TME and promote the recruitment and activation of effector T cells, particularly CD8+CD69+ T cells, which are key to effective tumor elimination. This strategy could offer a powerful approach to improve the efficacy of immunotherapies in HCC and liver metastasis, providing a framework for future clinical translation.

T cell exhaustion represents a significant barrier to the success of immunotherapy in HCC.[66–68] Consequently, T cell exhaustion in HCC contributes to therapeutic resistance and poor clinical outcomes.[69] Hydrogels offer more than just a drug delivery function; their unique material properties allow them to program the immune microenvironment in ways that can reverse T cell exhaustion. T cell exhaustion in the TME is a critical barrier to effective immunotherapy, as it results from chronic exposure to tumor antigens, leading to upregulation of inhibitory receptors such as PD-1, TIM-3, and LAG-3, which impair T cell function. Hydrogels can program the immune microenvironment through their material properties, mechanistically reversing T cell exhaustion. In addition to blocking inhibitory signals, hydrogels can be engineered to deliver costimulatory molecules, such as anti-OX40 or anti-4-1BB antibodies, which provide a "second signal" necessary for optimal T cell activation.[70] These costimulatory molecules work synergistically with ICIs by promoting T cell proliferation, survival, and effector function, further enhancing the therapeutic efficacy of immune

https://doi.org/10.2147/IJN.S576091

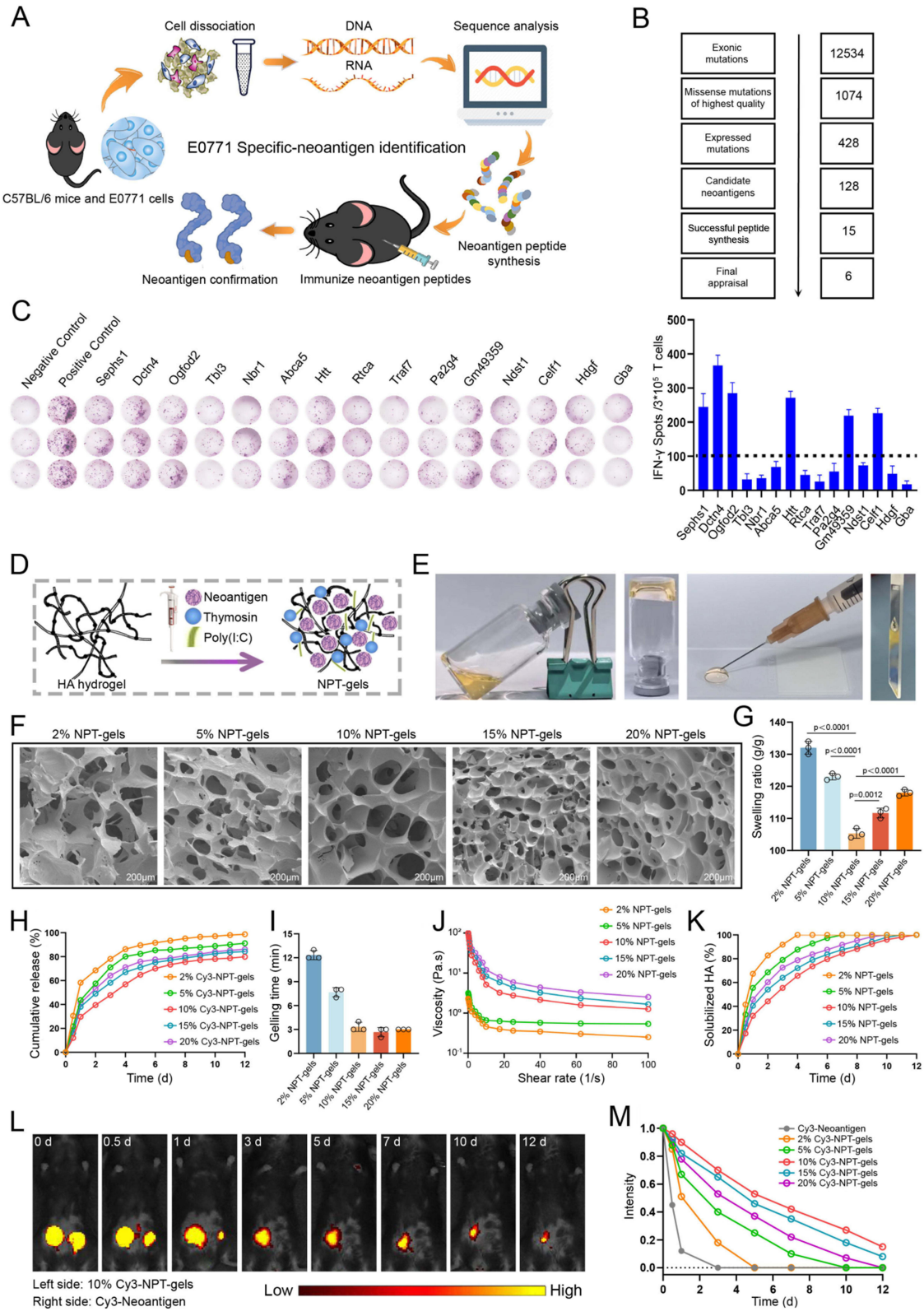


Figure 3 Combination with immune checkpoint inhibitors (adapted from *J Immunother Cancer 2024; 12(12):e009543*).[49] (**A**) Identifying tumor neoantigen mutation sites. (**B**) Workflow of tumor neoantigen mutation site screening. (**C**) Potential neoantigen immunogenicity validation. (**D** and **E**) Process and appearance of neoantigen hydrogel vaccine preparation. (**F** and **G**) Three-dimensional structure and swelling rate of neoantigen hydrogel vaccines. (**H**) In vitro release curves. (**I**) The gelling time. (**J**) Viscosity. (**K**) Degradation curves. (**L** and **M**) In vivo release.

checkpoint blockade.[71] By simultaneously blocking inhibitory signals and providing costimulatory signals, hydrogel-based systems help restore the balance between immune activation and suppression, overcoming T cell exhaustion and revitalizing antitumor immunity in HCC. This strategy holds great promise for improving the efficacy of immunotherapies in HCC by not only enhancing T cell activation and reinvigorating exhausted T cells but also by reprogramming the immune environment to support sustained immune responses.

Hydrogel-Based Synergy with Ablation Therapy

Ablation therapies, including microwave ablation (MWA) and radiofrequency ablation (RFA) have become mainstays in the treatment of HCC, particularly for patients who are not candidates for surgical resection or liver transplantation.[72] These therapies work by inducing localized tumor cell death through thermal or freezing mechanisms, leading to necrosis and the release of tumor antigens. However, while ablation therapies are effective at reducing tumor burden, they often fail to induce a robust, durable immune response against residual tumor cells, primarily due to the immunosuppressive nature of the TIME.[73] The combination of ablation therapies with hydrogel-based immunomodulation presents an innovative strategy to enhance the antitumor immune response and promote long-term tumor control.[74] Hydrogel-based delivery systems can enhance the efficacy of ablation therapies by providing controlled, localized release of immunomodulatory agents. By encapsulating these agents in hydrogels, their release can be sustained over time, allowing for prolonged immune activation within the TME.

Hydrogel-Based Synergy with MWA

A promising strategy to enhance the effectiveness of MWA in HCC treatment involves the use of hydrogel-based systems that modulate the immunosuppressive tumor microenvironment and boost the antitumor immune response. A complementary approach was explored in the context of MWA, where the immunosuppressive residual tumor microenvironment (IRTM) remains a significant barrier to effective treatment.[75] Cholesterol-rich tumor fragments contribute to the deterioration of IRTM, exacerbating immune suppression and hindering the antitumor immune response. To address this, a study developed a cholesterol-targeted catalytic hydrogel, DA-COD-OD-HCS, which enhanced the synergy between MWA and ICIs for HCC treatment.[50] This hydrogel contained cholesterol oxidase (COD), modified to release in the acidic IRTM, to degrade cholesterol. The hydrogel network, formed by oxydextran (OD) and hemin-chitosan (HCS), ensured the long-term retention of COD and hemin in the IRTM following MWA. In both in vitro and in vivo models, the DA-COD-OD-HCS hydrogel effectively degraded cholesterol, induced tumor cell ferroptosis, and enhanced the antitumor immune response. When combined with anti-PD-L1 immunotherapy, this approach inhibited primary tumor growth and distant metastasis, without causing damage to adjacent tissues. This strategy demonstrated the power of combining hydrogel-based catalytic therapies with ICIs to enhance immune responses in liver cancer treatment, suggesting a novel therapeutic avenue to improve the efficacy of MWA and ICIs in HCC. These studies demonstrate how hydrogel-based delivery systems, when combined with immune checkpoint inhibitors, can enhance the antitumor immune response, overcome immune suppression in the TME, and offer promising approaches for the treatment of HCC and liver metastasis. The ability of hydrogels to modulate the TME, control the release of therapeutic agents, and boost immune activation positions them as a valuable tool in improving the clinical outcomes of immunotherapies.

Hydrogel-Based Synergy with RFA

Hydrogels have demonstrated significant potential in enhancing the effectiveness of RFA for HCC, particularly in overcoming the immunosuppressive effects associated with incomplete RFA (iRFA). The residual TME after iRFA is often characterized by immune suppression, which hinders the long-term success of the treatment, contributing to local recurrence and distant metastasis of HCC.[76] To address this issue, a promising strategy involves the use of hydrogel-based systems in combination with RFA. For instance, a recent study explored the mechanisms behind the formation of an immunosuppressive TME in residual tumors following iRFA and developed a TAK-981-loaded nanocomposite hydrogel to target this environment.[77] The research found that upregulation of small ubiquitin-like modifier 2 (Sumo2) and the activation of SUMOylation pathways played a crucial role in fostering the immunosuppressive conditions in the residual tumor. By knocking down Sumo2 or inhibiting SUMOylation with the use of TAK-981, a small molecule

inhibitor, the study showed that it was possible to activate interferon-1 (IFN-1) signaling, which promoted DC maturation and subsequently enhanced the immune response. Additionally, the hydrogel treatment led to an increase in PD-L1 expression, making the residual tumors more responsive to immune checkpoint blockade therapies. When combined with PD-L1 blockade, this treatment strategy synergistically eradicated the residual tumors and suppressed distant metastases, significantly improving the overall therapeutic outcomes. A study investigated the changes in the TIME induced by iRFA in HCC and demonstrated that iRFA promotes a suppressive TIME, characterized by M2 macrophage polarization, reduced DC antigen presentation, and decreased CTL infiltration. To address this issue, the study employed a calcium ion (Ca2+)-responsive sodium alginate (ALG) hydrogel as a carrier for the STING agonist MSA-2, which was designed to reverse the immune suppression caused by iRFA (Figure 4).[51] The injectable ALG@MSA-2 hydrogel exhibited sustained drug release in situ and successfully activated anti-tumor immunity. It promoted M1 macrophage polarization, enhanced antigen presentation by DCs, and increased CTL infiltration, ultimately inhibiting residual tumor growth and inducing

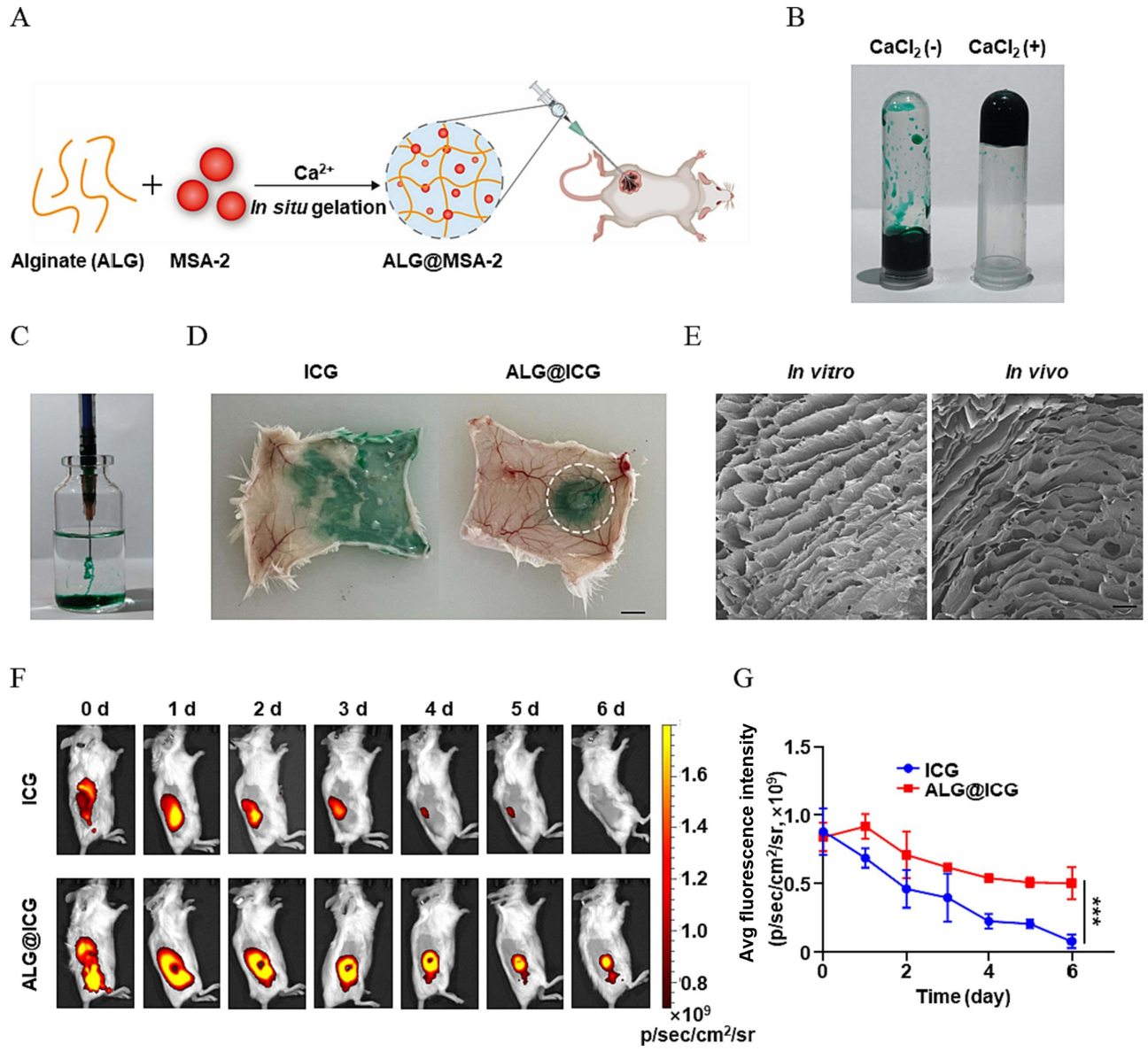


Figure 4 STING agonist-based hydrogel enhances immune activation in synergy with radiofrequency ablation for hepatocellular carcinoma treatment (adapted from *J Control Release 2024; 369: 296–308*).[51] (**A**) Scheme illustrating gelation of the ALG/MSA-2 hybrid fluid locally injected into tumors after iRFA. (**B**) The solution state (left) and the hydrogel state (right). (**C**) Gelation of the ALG@ICG hybrid fluid in the Ca2+ solution. (**D**) The ability of the ALG system to form a hydrogel (white dashed circle) in vivo. (**E**) The morphology by SEM. (**F**) Representative IVIS images and (**G**) statistical plots. ***, $p < 0.001$.

complete regression of contralateral tumors and liver metastases. Additionally, ALG@MSA-2 demonstrated excellent biosafety, with no significant adverse effects on body weight or blood biochemical parameters in mice. This study provides promising insights into enhancing the therapeutic efficacy of RFA for HCC through immunomodulation and suggests that STING pathway activation can play a crucial role in reshaping the TIME for improved outcomes.

Hydrogel-Based CAR-T Therapy and Tumor in situ Vaccines

A major advantage of hydrogel-based strategies is their potential to personalize treatment approaches based on the unique characteristics of each patient's TIME. As the field of precision medicine continues to evolve, profiling the TIME of individual patients will become increasingly important for tailoring hydrogel formulations and delivery systems.[78] Personalized therapies that account for the distinct composition and immune cell dynamics of a patient's TIME could significantly enhance treatment efficacy. In particular, understanding the heterogeneity of the TIME is crucial for optimizing hydrogel-based delivery systems. Personalized approach in HCC involves several emerging immunotherapies, each targeting different aspects of the immune response to improve patient outcomes (Figure 5).[79] These therapies include adoptive cell therapies, such as lymphokine-activated killer (LAK) cells, cytokine-induced killer (CIK) cells,

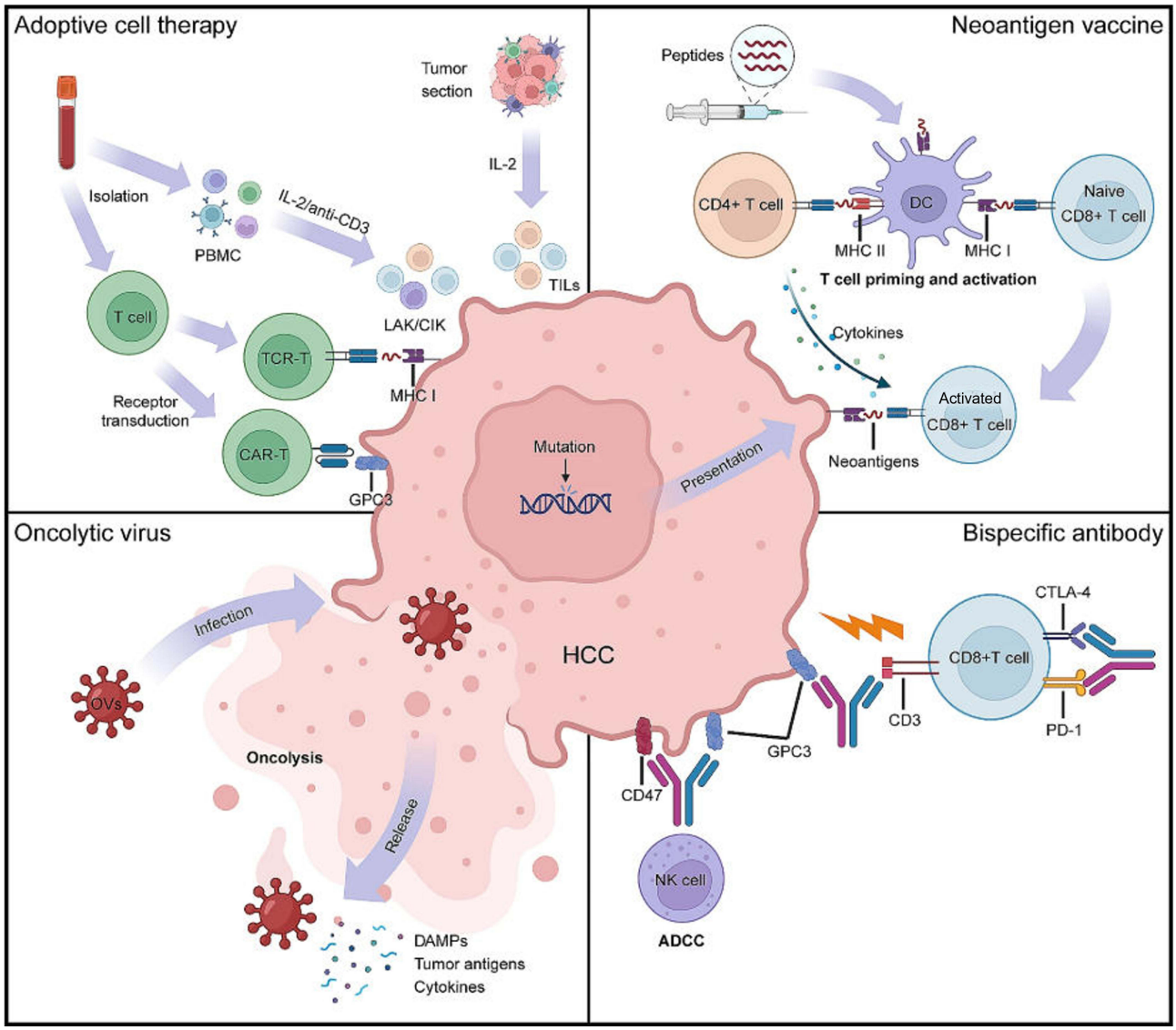


Figure 5 Overview of the emerging immunotherapies in hepatocellular carcinoma (adapted from *J Hematol Oncol 2024; 17(1):25*).[79]

https://doi.org/10.2147/IJN.S576091

tumor-infiltrating lymphocytes (TILs), and chimeric antigen receptor T (CAR-T) cells. These therapies involve the ex vivo expansion and reinfusion of immune cells, which are designed to target and eliminate tumor cells more effectively. Additionally, neoantigen vaccines can be utilized, which are taken up by DCs and presented to CD4+ or CD8+ T cells via MHC molecules, leading to the activation of tumor-specific T cells. This activation contributes to anti-tumor immunity. By profiling the TIME and tailoring hydrogel-based treatments to the specific needs of individual patients, we can improve therapeutic outcomes and potentially reduce the recurrence of HCC.

Hydrogel-Based CAR-T Therapy

CAR-T cell therapy has emerged as a groundbreaking approach in cancer immunotherapy, offering the potential for durable and highly specific tumor elimination.[80] CAR-T cells are engineered to express receptors that recognize specific tumor antigens, enabling them to selectively target and kill tumor cells.[81] However, despite their clinical success in hematologic malignancies, the application of CAR-T therapy in solid tumors, including HCC, is limited by the immunosuppressive TME, inadequate T cell infiltration, and poor persistence of CAR-T cells in the TME.[82] Hydrogel-based delivery systems provide an innovative solution to enhance the efficacy of CAR-T cell therapy by creating a localized, controlled environment that supports immune activation, improves CAR-T cell infiltration, and enhances the presentation of tumor antigens.[83] Hu et al explores the use of a hyaluronic acid (HA) hydrogel to release CAR-T cells targeting the human chondroitin sulfate proteoglycan 4 (CSPG4), cytokine encapsulated polymer nanoparticles, and platelets conjugated with the immune checkpoint inhibitor PD-L1 (Figure 6).[52] The hydrogel served as a reservoir for CAR-T cells, ensuring their sustained release and enhanced distribution within the surgical bed following tumor resection. This local delivery system mitigated the challenges of inadequate CAR-T cell infiltration and reduced the systemic toxicity often associated with traditional CAR-T cell infusion. The combination of CAR-T cells within a hydrogel matrix represents a highly translational strategy for preventing the recurrence of resectable tumors. This localized delivery method could be applicable not only for melanoma but also for other solid tumors like HCC, where surgical resection and adjuvant immunotherapy could be combined to improve patient outcomes.

Hydrogel-Based Tumor in situ Vaccines

Similarly, tumor in situ vaccines, which aim to generate a localized immune response by delivering tumor-associated antigens (TAAs) and immune stimulatory agents directly to the tumor site, also face challenges in overcoming the immunosuppressive barriers of the TME.[84,85] Hydrogel-based delivery systems have emerged as an innovative platform for the targeted and sustained release of tumor antigens and vaccines, which are critical for enhancing immune responses against HCC.[86] These systems are designed to address the limitations of traditional vaccine delivery methods, such as rapid degradation and poor tissue penetration, by providing controlled release and localized antigen presentation within the TME. An example of such an approach is the development of a hydrogel-based in situ vaccine for delivering ginsenoside Rh2 (G-Rh2) to enhance its therapeutic efficacy in liver cancer (Figure 7).[53] G-Rh2, despite its strong pharmacological properties, suffers from poor solubility and bioavailability. To address this, researchers created an indocyanine green carboxylic acid-hydroxypropyl cellulose-abietic acid-bovine serum albumin (ICG-HPC-AA/BSA) hydrogel, which encapsulated G-Rh2 and acted as a tumor in situ vaccine. The hydrogel enhanced the permeability and retention of G-Rh2 within the tumor site, as well as its tumor-targeted therapeutic efficacy. In preclinical studies using murine models of H22 liver cancer and CT26 colon cancer, the combination of G-Rh2-loaded hydrogel and PD-1 blockade resulted in significantly improved tumor growth inhibition compared to the use of either treatment alone. Importantly, the hydrogel-mediated delivery of G-Rh2 induced significant changes in the immune microenvironment of the tumors, increasing the infiltration of cytotoxic T cells and promoting a more favorable immune landscape that was conducive to antitumor immunity.

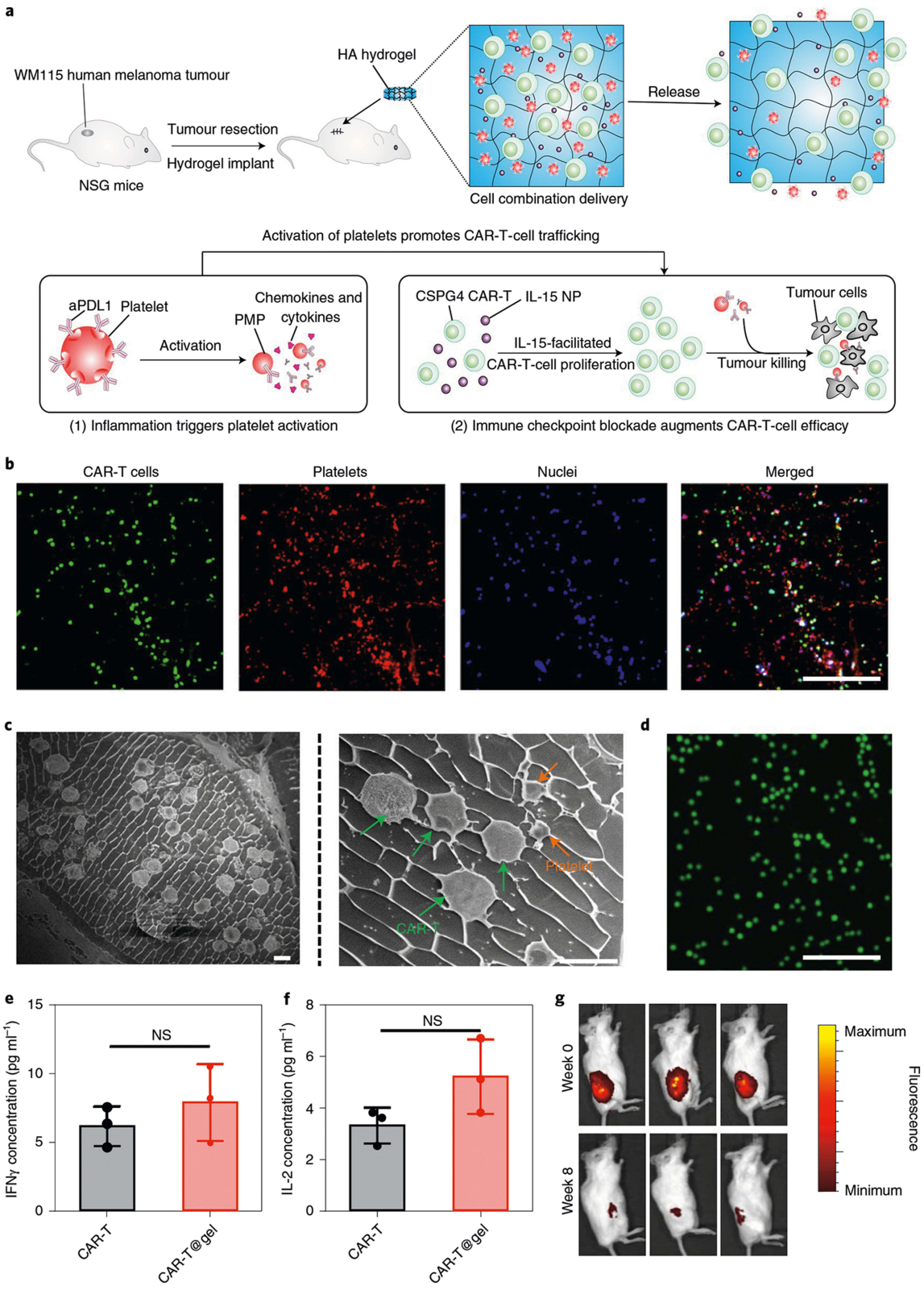


Figure 6 Inhibition of Post-Surgery Tumor Recurrence via Hydrogel-Based CAR-T Cell Therapy (adapted from *Nat Biomed Eng 2021; 5(9):1038–1047*).[51] (**a**) Schematic of the tumour resection model and implantation of the engineered HA hydrogel. (**b**) Confocal imaging of CAR-T cells and P–aPDL1 encapsulated in the hydrogel. Scale bar, 100 μm. (**c**), Cryo-scanning electron microscopy imaging. Scale bars, 10 μm. (**d**), Confocal imaging of the live/dead assay of CAR-T cells released from the hydrogel. Scale bar, 100 μm. Human IFNγ (**e**) and IL-2 (**f**) released by CAR-T cells encapsulated in the hydrogel. NS, no significance. (**g**) In vivo degradation.

https://doi.org/10.2147/IJN.S576091

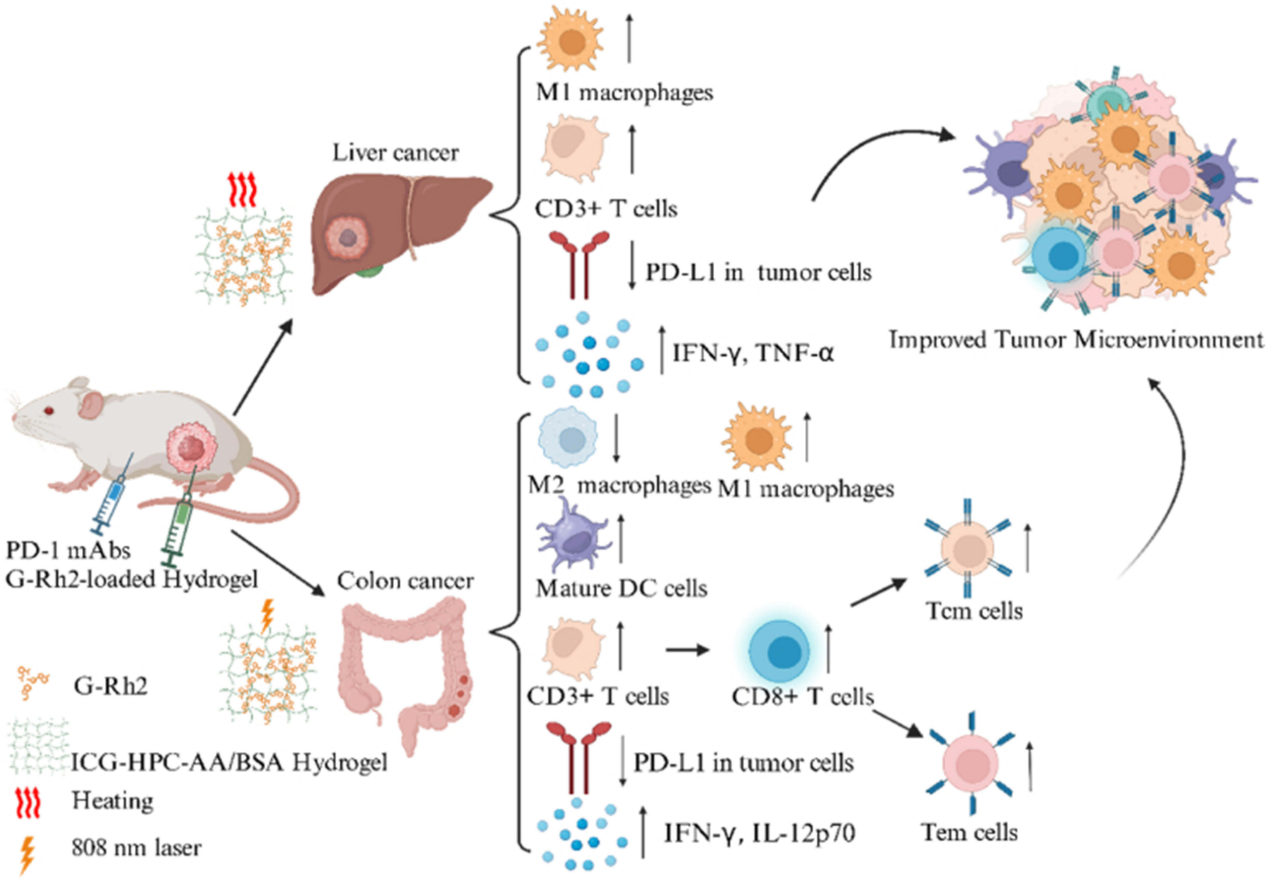


Figure 7 Remodeling the TIME through hydrogel encapsulated G-Rh2 in situ vaccine and systemic immunotherapy (adapted from *Mater Today Bio 2024; 29: 101,281*).[53] Upward and downward arrow represents up-regulation and down-regulation, respectively.

Challenges in Clinical Application: Biocompatibility, Degradation, and Delivery Efficiency

Hydrogels offer unique advantages in localized immune modulation for HCC immunotherapy by providing sustained, controlled release of therapeutic agents and supporting immune cell infiltration, whereas nanoparticles and microspheres excel in targeted or systemic delivery but lack the dynamic properties and scaffold support of hydrogels.[87] Hydrogels have distinct advantages in embolization due to their injectability, shear-thinning behavior, tunable gelation, and ability to occlude tumor-feeding arteries while enabling localized therapy delivery. For example, hydrogel-based tumor embolization and synergistic therapeutic strategies emphasizes innovative design strategies for embolic hydrogels that combine mechanical occlusion with drug delivery and multimodal therapeutic functions, providing controlled, localized release and enhanced antitumor effects during transarterial embolization procedures.[88] Hydrogels can be injected directly into the tumor site, offering localized delivery of immunotherapy agents. This approach not only increases the local concentration of therapeutic agents but also minimizes systemic toxicity. This localized administration is particularly beneficial in HCC, where direct tumor modulation is essential to overcome the immunosuppressive TIME. For non-invasive approaches, hydrogels can be used in intravesical administration or transarterial routes, such as through catheter-based delivery in embolization procedures. This personalized approach allows clinicians to select the most appropriate drug delivery route based on the patient's disease characteristics, optimizing therapeutic efficacy and minimizing unnecessary systemic exposure.

The integration of hydrogel-based strategies in cancer immunotherapy holds immense promise, but there are several hurdles to overcome before these approaches can be widely adopted in clinical settings. For instance, specific antigen

targets, immune checkpoint profiles, and tumor-associated macrophage polarization could be identified to customize hydrogel-based therapies for optimized immune activation and targeted drug release.[89] Advances in high-throughput sequencing, spatial transcriptomics, and multiplex immunohistochemistry are enabling deeper insights into the TME, facilitating patient-specific profiling and more precise therapeutic designs.[90] Moreover, understanding the variability in immune responses among patients will allow for the development of hydrogel-based systems that can modulate specific immune pathways, ensuring a more effective response.[91] The combination of personalized hydrogels with ICIs could allow for more effective activation of the immune system and better tumor targeting, ultimately leading to improved clinical outcomes. Despite the significant promise shown by hydrogel-based systems, several challenges remain in their clinical application. Key concerns include biocompatibility, degradation, and delivery efficiency, all of which need to be carefully addressed for these therapies to succeed in real-world clinical settings. Hydrogel-based delivery systems must be non-toxic and non-immunogenic to avoid adverse reactions in patients. While most hydrogels are designed to be biocompatible, the incorporation of biologically active molecules, such as immunotherapeutic agents or chemotherapeutics, can sometimes lead to unintended immune responses or toxicity.[92] The long-term safety of hydrogels, especially those intended for repeated or sustained release, will require rigorous testing to ensure that they do not cause chronic inflammation, fibrosis, or other systemic complications.[93] The rate at which hydrogels degrade in vivo is a critical factor in determining their effectiveness. In many cases, hydrogels need to release their therapeutic payload over an extended period, which requires precise control over their degradation kinetics.[94] If hydrogels degrade too quickly, the therapeutic agents may be released prematurely, reducing their effectiveness. Conversely, if degradation is too slow, it may lead to unwanted accumulation of the materials in the body, potentially causing complications. The development of hydrogels with tunable degradation profiles that match the therapeutic needs of specific cancers is essential for their clinical success. For hydrogels to be effective, they must deliver their payload to the tumor site in a manner that maximizes therapeutic benefit while minimizing off-target effects.[95] This requires careful design of the hydrogel to ensure that it can both target the tumor tissue selectively and release its contents in a controlled and predictable manner.[96] Additionally, the ability of hydrogels to cross physiological barriers, such as the blood-brain barrier in the case of brain tumors or other specific tissues, remains a significant challenge that needs to be addressed for broader clinical applicability.

The primary challenge in translational research lies in the heterogeneity of the TME, which complicates the design of universal hydrogel formulations. Personalized hydrogel approaches, guided by patient-specific profiling using technologies like single-cell RNA sequencing, can improve treatment efficacy by tailoring hydrogel properties to the unique TME. Single-cell RNA-seq (scRNA-seq) is now discussed as a powerful tool that can help identify heterogeneous immune cell populations in the TME and evaluate how these populations interact with hydrogel-delivered immunomodulatory agents.[97] scRNA-seq has been employed to assess how hydrogel-based immunotherapies modulate immune cell subsets such as cytotoxic T cells, dendritic cells, and macrophages in response to checkpoint inhibitors or adjuvants encapsulated within hydrogels.[49] In clinical studies, challenges include regulatory approval due to novel materials and limited patient cohorts in early trials. To address these, adaptive clinical trial designs and quality-by-design principles can facilitate faster regulatory approval and more targeted studies. Hydrogel manufacturing faces challenges in scalability and cost, as the complexity of formulations requires expensive materials and advanced techniques. Solutions include the standardization of production methods, such as microfluidic technologies and automated platforms, to reduce costs and improve scalability. Quality control is another hurdle, as maintaining consistency in properties like degradation rates and release profiles is critical for therapeutic success. The use of advanced characterization tools and real-time monitoring during production can address these concerns. Finally, to overcome these challenges, collaborations between academia and industry can help bridge the gap between preclinical research and clinical application, while 3D printing technologies offer opportunities for customizing hydrogel formulations to create patient-specific treatments. These efforts will not only enhance the clinical translation of hydrogel-based therapies but also improve the personalization of treatments, making them more effective and accessible to a broader range of patients.

Conclusion

Hydrogel-based immunomodulation strategies offer a promising approach to overcoming the challenges posed by the TIME in HCC. These strategies enable the localized, sustained, and controlled delivery of immune modulators,

cytokines, tumor antigens, and immune checkpoint inhibitors, effectively reshaping the immunosuppressive TIME. By enhancing immune cell infiltration, overcoming T cell exhaustion, and promoting long-term immune memory, hydrogel-based systems can significantly improve the efficacy of existing therapies, including ablation therapies, CAR-T cell therapy, and tumor in situ vaccines. However, several challenges remain, including the need to optimize hydrogel biocompatibility, degradation kinetics, and delivery efficiency to ensure clinical safety and effectiveness. Personalized hydrogel-based treatments, tailored to the unique characteristics of individual patients' TIMES, offer a promising path forward for precision cancer therapy. A key direction is the AI-assisted design of hydrogels, where machine learning algorithms could be used to optimize hydrogel material properties based on individual TME profiles. In conclusion, while hydrogel-based immunomodulation holds great potential for enhancing cancer immunotherapy in HCC, future research must focus on optimizing these systems for clinical translation, evaluating their safety, and integrating them with other therapies to further improve treatment outcomes.

Funding

This study is funded by Department of Science and Technology of Jilin Province (YDZJ202201ZYTS066), and Special Project for Medical and Health Talents in Jilin Province (2024WSZX-B20).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Koshy A. Evolving global etiology of Hepatocellular Carcinoma (HCC): insights and trends for 2024. *J Clin and Exp Hepatol*. 2025;15(1):102406. doi:10.1016/j.jceh.2024.102406
2. Toh MR, Wong EYT, Wong SH, et al. Global epidemiology and genetics of hepatocellular carcinoma. *Gastroenterology*. 2023;164(5):766–782. doi:10.1053/j.gastro.2023.01.033
3. Wang Y, Deng B. Hepatocellular carcinoma: molecular mechanism, targeted therapy, and biomarkers. *Cancer and Metastasis Rev*. 2023;42 (3):629–652. doi:10.1007/s10555-023-10084-4
4. C-MS FJ, Desdouets C. NAFLD-related hcc: focus on the latest relevant preclinical models. *Cancers*. 2023;15(14):3723. doi:10.3390/cancers15143723
5. Lee YT, Fujiwara N. Risk stratification and early detection biomarkers for precision HCC screening. *Hepatology*. 2023;78(1):319–362. doi:10.1002/hep.32779
6. Bicer F, Kure C, Ozluk AA, El-Rayes BF, Akce M. Advances in Immunotherapy for Hepatocellular Carcinoma (HCC). *Nat Rev Gastroenterol Hepatol*. 2023. 30(11):9789–9812. doi:10.3390/curroncol30110711
7. Chen Y, Deng X, Li Y, et al. Comprehensive molecular classification predicted microenvironment profiles and therapy response for HCC. *Hepatology*. 80(3):536–551. doi:10.1097/hep.0000000000000869
8. Seyhan D, Allaire M, Fu Y, et al. Immune microenvironment in hepatocellular carcinoma: from pathogenesis to immunotherapy. *Cell. Mol. Immunol*. 2025;22(10):1132–1158. doi:10.1038/s41423-025-01308-4
9. WQ HJ, Geller DA, Yan Y. Macrophage metabolism, phenotype, function, and therapy in hepatocellular carcinoma (HCC). *J Transl Med*. 2023;21 (1):815. doi:10.1186/s12967-023-04716-0
10. Mazzaferro V, Pinato DJ, Pikarsky E. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19(3):151–172.
11. Xing R, Gao J, Cui Q, Wang Q. Strategies to improve the antitumor effect of immunotherapy for hepatocellular carcinoma. *Front Immunol*. 2021;12:783236. doi:10.3389/fimmu.2021.783236
12. Foglia B, Beltrà M, Sutti S, Cannito S. Metabolic reprogramming of HCC: a new microenvironment for immune responses. *Int J Mol Sci*. 2023;24 (8). doi:10.3390/ijms24087463
13. Ho DW, Tsui YM, Chan LK, et al. Single-cell RNA sequencing shows the immunosuppressive landscape and tumor heterogeneity of HBV-associated hepatocellular carcinoma. *Nat Commun*. 12(1):3684. doi:10.1038/s41467-021-24010-1
14. Wong SHD, Yin B, Li Z, et al. Mechanical manipulation of cancer cell tumorigenicity via heat shock protein signaling. *Sci Adv*. 2021;9(27): eadg9593. doi:10.1126/sciadv.adg9593
15. Wu Y, Xiao Y, Yin B, Wong SHD. Dynamic hydrogels: adaptive biomaterials for engineering tumor microenvironment and cancer treatment. *Int J Mol Sci*. 2025;26(19). doi:10.3390/ijms26199502
16. Shan BH, Wu FG. Hydrogel-based growth factor delivery platforms: strategies and recent advances. *Adv. Mater*. 2024;36(5):e2210707. doi:10.1002/adma.202210707
17. Ho TC, Chang CC, Chan HP, et al. Hydrogels: properties and applications in biomedicine. *Molecules*. 2022;27(9). doi:10.3390/molecules27092902
18. Xu X, Liu Y, Liu Y, et al. Functional hydrogels for hepatocellular carcinoma: therapy, imaging, and in vitro model. *J Nanobiotechnol*. 22(1):381. doi:10.1186/s12951-024-02547-9
19. Chew SA, Moscato S, George S, Azimi B, Danti S. Liver cancer: current and future trends using biomaterials. *Cancers*. 11(12). doi:10.3390/cancers11122026
20. Gong Y, Cheng Y, Zeng F, et al. A self-gelling hemostatic powder boosting radiotherapy-elicited NK cell immunity to combat postoperative hepatocellular carcinoma relapse. *Biomaterials*. 2025;317:123068. doi:10.1016/j.biomaterials.2024.123068

21. Ke J, Liu Y, Liu F, et al. In-situ-formed immunotherapeutic and hemostatic dual drug-loaded nanohydrogel for preventing postoperative recurrence of hepatocellular carcinoma. *J Control Release*. 2024;372:141–154. doi:10.1016/j.jconrel.2024.06.030
22. Zheng L, Li C, Huang X, et al. Thermosensitive hydrogels for sustained-release of sorafenib and selenium nanoparticles for localized synergistic chemoradiotherapy. *Biomaterials*. 2019;216:119220. doi:10.1016/j.biomaterials.2019.05.031
23. Pu M, Cao H, Zhang H, et al. ROS-responsive hydrogels: from design and additive manufacturing to biomedical applications. *Mater Horiz*. 2024;11 (16):3721–3746. doi:10.1039/d4mh00289j
24. Liu D, Lu G, Shi B, et al. ROS-scavenging hydrogels synergize with neural stem cells to enhance spinal cord injury repair via regulating microenvironment and facilitating nerve regeneration. *Adv Healthc Mater*. 2023;12(18):e2300123. doi:10.1002/adhm.202300123
25. Zhou X, Kandalai S, Hossain F, Zhang N, Li H, Zheng Q. pH-responsive and recyclable hydrogels for gas releasing and scavenging. *Macromol Rapid Commun*. 2023;44(8):e2300008. doi:10.1002/marc.202300008
26. Chen H, Cheng J, Cai X, et al. pH-switchable antimicrobial supramolecular hydrogels for synergistically eliminating biofilm and promoting wound healing. *ACS Appl Mater Interfaces*. 2022;14(16):18120–18132. doi:10.1021/acsami.2c00580
27. Bonafé Allende JC, Ambrosioni F, Ruiz Moreno FN, et al. Pyrogallol-rich supramolecular hydrogels with enzyme-sensitive microdomains for controlled topical delivery of hydrophobic drugs. *Biomater Adv*. 2025;166:214075. doi:10.1016/j.bioadv.2024.214075
28. Tang Z, Deng L, Zhang J, et al. Intelligent hydrogel-assisted hepatocellular carcinoma therapy. *Research*. 2024;7:0477. doi:10.34133/research.0477
29. Erfani A, Diaz AE, Doyle PS. Hydrogel-enabled, local administration and combinatorial delivery of immunotherapies for cancer treatment. *Mater Today*. 2023;65:227–243. doi:10.1016/j.mattod.2023.03.006
30. Mohaghegh N, Ahari A, Zehtabi F, et al. Injectable hydrogels for personalized cancer immunotherapies. *Acta Biomater*. 2023;172:67–91. doi:10.1016/j.actbio.2023.10.002
31. Liu Y, Xun Z, Ma K, et al. Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. *J Hepatol*. 2023;78(4):770–782. doi:10.1016/j.jhep.2023.01.011
32. Oura K, Morishita A. Tumor immune microenvironment and immunosuppressive therapy in hepatocellular carcinoma: a review. *Int J Mol Sci*. 2021;22(11):5801. doi:10.3390/ijms22115801
33. Donne R, Lujambio A. The liver cancer immune microenvironment: therapeutic implications for hepatocellular carcinoma. *Hepatology*. 77 (5):1773–1796. doi:10.1002/hep.32740
34. Childs A, Aidoo-Micah G, Maini MK, Meyer T. Immunotherapy for hepatocellular carcinoma. *JHEP Rep*. 2024;6(10):101130. doi:10.1016/j.jhepr.2024.101130
35. Yang C, Geng H, Yang X, et al. Targeting the immune privilege of tumor-initiating cells to enhance cancer immunotherapy. *Cancer Cell*. 2024;42 (12):2064–2081.e19. doi:10.1016/j.ccell.2024.10.008
36. Gao Y, You M, Fu J, et al. Intratumoral stem-like CCR4+ regulatory T cells orchestrate the immunosuppressive microenvironment in HCC associated with hepatitis B. *J Hepatol*. 2022;76(1):148–159. doi:10.1016/j.jhep.2021.08.029
37. Li M, Wang L, Cong L, et al. Spatial proteomics of immune microenvironment in nonalcoholic steatohepatitis-associated hepatocellular carcinoma. *Hepatology*. 79(3):560–574. doi:10.1097/hep.0000000000000591
38. Chen S, Liao C, Hu H, et al. Hypoxia-driven tumor stromal remodeling and immunosuppressive microenvironment in scirrhous HCC. *Hepatology*. 2024;79(4):780–797. doi:10.1097/hep.0000000000000599
39. CN CK, Zhu J, Yang X, Liang H, Zhang W. Tumor-associated macrophages in liver cancer: from mechanisms to therapy. *Cancer Commun*. 2022;42(11):1112–1140. doi:10.1002/cac2.12345
40. Yu Z, Li Y, Li Y, et al. Bufalin stimulates antitumor immune response by driving tumor-infiltrating macrophage toward M1 phenotype in hepatocellular carcinoma. *Journal for Immunotherapy of Cancer*. 2022;10(5):e004297. doi:10.1136/jitc-2021-004297
41. Du G, Dou C, Sun P, Wang S, Liu J, Ma L. Regulatory T cells and immune escape in HCC: understanding the tumor microenvironment and advancing CAR-T cell therapy. *Front Immunol*. 2024;15:1431211. doi:10.3389/fimmu.2024.1431211
42. Ruf B, Heinrich B, Greten TF. Immunobiology and immunotherapy of HCC: spotlight on innate and innate-like immune cells. *Cell Mol Immunol*. 2021;18(1):112–127. doi:10.1038/s41423-020-00572-w
43. Wang Z, Wang Y, Gao P, Ding J. Immune checkpoint inhibitor resistance in hepatocellular carcinoma. *Cancer Lett*. 2023. 555:216038. doi:10.1016/j.canlet.2022.216038
44. Rimassa L, Finn RS, Sangro B. Combination immunotherapy for hepatocellular carcinoma. *J Hepatol*. 2023;79(2):506–515. doi:10.1016/j.jhep.2023.03.003
45. Chen Y, Li X, Shang H, et al. Mechanism exploration of synergistic photo-immunotherapy strategy based on a novel exosome-like nanosystem for remodeling the immune microenvironment of HCC. *Nano Converg*. 2024. 11(1):31. doi:10.1186/s40580-024-00441-6
46. Xiang G, Yin B, Shiroud Heidari B, et al. Programmable hydrogels: frontiers in dynamic closed-loop systems, biomimetic synergy, and clinical translation. *Adv Sci*. 2025;12(47):e12037. doi:10.1002/advs.202512037
47. Cao Y, Sun T, Sun B, et al. Injectable hydrogel loaded with lysed OK-432 and doxorubicin for residual liver cancer after incomplete radiofrequency ablation. *J Nanobiotechnol*. 2023;21(1):404. doi:10.1186/s12951-023-02170-0
48. Li Z, Xu W, Yang J, et al. A tumor microenvironments-adapted polypeptide hydrogel/nanogel composite boosts antitumor molecularly targeted inhibition and immunoactivation. *Adv. Mater*. 2022;34(21):e2200449. doi:10.1002/adma.202200449
49. Tang S, Tang R, Chen G, et al. Personalized neoantigen hydrogel vaccine combined with PD-1 and CTLA-4 double blockade elicits antitumor response in liver metastases by activating intratumoral CD8(+)CD69(+) T cells. *Journal for Immunotherapy of Cancer*. 12(12). doi:10.1136/jitc-2024-009543
50. Shen L, Yang Z, Zhong Y, et al. Cholesterol targeted catalytic hydrogel fueled by tumor debris can enhance microwave ablation therapy and anti-tumor immune response. *Adv Sci*. 2025;12(5):e2406975. doi:10.1002/advs.202406975
51. Ao F, Li X, Tan Y, et al. STING agonist-based hydrogel enhances immune activation in synergy with radiofrequency ablation for hepatocellular carcinoma treatment. *J Control Release*. 2024;369:296–308. doi:10.1016/j.jconrel.2024.01.048
52. Hu Q, Li H, Archibong E, et al. Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets. *Nat Biomed Eng*. 2021;5(9):1038–1047. doi:10.1038/s41551-021-00712-1
53. Li C, Lei D, Huang Y, et al. Remodeling the tumor immune microenvironment through hydrogel encapsulated G-Rh2 in situ vaccine and systemic immunotherapy. *Mater Today Bio*. 2024;29:101281. doi:10.1016/j.mtbio.2024.101281

54. Cheng H, Guo Q, Zhao H, et al. An injectable hydrogel scaffold loaded with dual-drug/sustained-release PLGA microspheres for the regulation of macrophage polarization in the treatment of intervertebral disc degeneration. *Int J Mol Sci*. 2022;24(1). doi:10.3390/ijms24010390
55. Abbaszadeh S, Nosrati-Siahmazgi V, Musaie K, et al. Emerging strategies to bypass transplant rejection via biomaterial-assisted immunoengineering: insights from islets and beyond. *Adv Drug Deliv Rev*. 2023;200:115050. doi:10.1016/j.addr.2023.115050
56. Chen Y, Bei J, Chen M, et al. Intratumoral lactate depletion based on injectable nanoparticles-hydrogel composite system synergizes with immunotherapy against postablative hepatocellular carcinoma recurrence. *Adv Healthc Mater*. 2024;13(6):e2303031. doi:10.1002/adhm.202303031
57. Cheng Y, Gong Y, Chen X, et al. Injectable adhesive hemostatic gel with tumor acidity neutralizer and neutrophil extracellular traps lyase for enhancing adoptive NK cell therapy prevents post-resection recurrence of hepatocellular carcinoma. *Biomaterials*. 2022;284:121506. doi:10.1016/j.biomaterials.2022.121506
58. Cheng Y, Gong Y, Li X, et al. A spreadable self-gelling hemostatic powder sensitizes CAR-NK cell therapy to prevent hepatocellular carcinoma recurrence postresection. *J Nanobiotechnol*. 2025;23(1):353. doi:10.1186/s12951-025-03424-9
59. Lee SY, Choi JW, Hwang C, et al. Intravascular casting radiopaque hydrogel systems for transarterial chemo/cascade catalytic/embolization therapy of hepatocellular carcinoma. *Small*. 2024;20(46):e2400287. doi:10.1002/smll.202400287
60. Harkus U, Wankell M, Palamuthusingam P, McFarlane C, Hebbard L. Immune checkpoint inhibitors in HCC: cellular, molecular and systemic data. *Semin Cancer Biol*. 2022;86(Pt 3):799–815. doi:10.1016/j.semcancer.2022.01.005
61. Naimi A, Mohammed RN, Raji A, et al. Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons. *Cell Commun Signal*. 2022;20(1):44. doi:10.1186/s12964-022-00854-y
62. Dall'Olio FG, Marabelle A, Caramella C, et al. Tumour burden and efficacy of immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2022;19(2):75–90. doi:10.1038/s41571-021-00564-3
63. Pinter M, Scheiner B, Pinato DJ. Immune checkpoint inhibitors in hepatocellular carcinoma: emerging challenges in clinical practice. *Lancet Gastroenterol Hepatol*. 2023;8(8):760–770. doi:10.1016/s2468-1253(23)00147-4
64. Akula V, Chen L, Acikgoz Y, et al. Neoadjuvant immune checkpoint inhibitors for hepatocellular carcinoma. *NPJ Precis Oncol*. 2025;9(1):60. doi:10.1038/s41698-025-00846-4
65. Ma M, Yu C, Liu H, et al. Methacrylated carrageenan/gelatin interpenetrating network microspheres loaded with targeted drugs and combined with pd-l1 inhibitors for hepatocellular carcinoma treatment. *ACS Appl Mater Interfaces*. 2025;17(30):42893–42914. doi:10.1021/acsami.5c12363
66. Chi H, Zhao S, Yang J, et al. T-cell exhaustion signatures characterize the immune landscape and predict HCC prognosis via integrating single-cell RNA-seq and bulk RNA-sequencing. *Front Immunol*. 2023;14:1137025. doi:10.3389/fimmu.2023.1137025
67. Wang S, Wang R, Xu N, et al. SULT2B1-CS-DOCK2 axis regulates effector T-cell exhaustion in HCC microenvironment. *Hepatology*. 2023;78(4):1064–1078. doi:10.1097/hep.0000000000000025
68. Meng Y, Ye F, Nie P, et al. Immunosuppressive CD10(+)ALPL(+) neutrophils promote resistance to anti-PD-1 therapy in HCC by mediating irreversible exhaustion of T cells. *J Hepatol*. 2023;79(6):1435–1449. doi:10.1016/j.jhep.2023.08.024
69. Seimiya T, Otsuka M, Fujishiro M. Overcoming T-cell exhaustion: new therapeutic targets in HCC immunotherapy. *Hepatology*. 78(4):1009–1011. doi:10.1097/hep.0000000000000039
70. Liang X, Li X, Wu R, et al. Breaking the tumor chronic inflammation balance with a programmable release and multi-stimulation engineering scaffold for potent immunotherapy. *Adv Sci*. 2024;11(28):e2401377. doi:10.1002/advs.202401377
71. Zhang B, Li M, Ji J, et al. A syringeable immunotherapeutic hydrogel enhances T cell immunity via in-situ activation of STING pathway for advanced breast cancer postoperative therapy. *Front Immunol*. 2025;16:1523436. doi:10.3389/fimmu.2025.1523436
72. Bosi C, Rimini M, Casadei-Gardini A, Giorgio E. Understanding the causes of recurrent HCC after liver resection and radiofrequency ablation. *Expert Rev Anticancer Ther*. 2023;23(5):503–515. doi:10.1080/14737140.2023.2203387
73. Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):293–313. doi:10.1038/s41575-020-00395-0
74. Liu J, Chen X, Zheng S. Immune response triggered by the ablation of hepatocellular carcinoma with nanosecond pulsed electric field. *Front Med*. 2021;15(2):170–177. doi:10.1007/s11684-020-0747-z
75. Yang L, Wei S, Liu Z, et al. Radiofrequency ablation and immunotherapy: orchestrating the immune microenvironment for improved hepatocellular carcinoma control. *Immunology*. 2025. doi:10.1111/imm.70004
76. Sharma P, Pandita A, Murthy RS. Concepts and strategies for the site specific delivery of nanocarrier based delivery systems for treating hepatocellular carcinoma. *Curr Drug Deliv*. 2013
77. Liu J, Li X, Chen J, et al. Targeting SUMOylation with an injectable nanocomposite hydrogel to optimize radiofrequency ablation therapy for hepatocellular carcinoma. *J Nanobiotechnol*. 2024;22(1):338. doi:10.1186/s12951-024-02579-1
78. Yang X, Yang C, Zhang S, et al. Precision treatment in advanced hepatocellular carcinoma. *Cancer Cell*. 2024;42(2):180–197. doi:10.1016/j.ccell.2024.01.007
79. Shen KY, Zhu Y, Xie SZ, Qin LX. Immunosuppressive tumor microenvironment and immunotherapy of hepatocellular carcinoma: current status and prospectives. *J Hematol Oncol*. 2024;17(1):25. doi:10.1186/s13045-024-01549-2
80. Dabas P, Danda A. Revolutionizing cancer treatment: a comprehensive review of CAR-T cell therapy. *Med Oncol*. 2023;40(9):275. doi:10.1007/s12032-023-02146-y
81. Chohan KL, Siegler EL, Kenderian SS. CAR-T cell therapy: the efficacy and toxicity balance. *Curr Hematol Malig Rep*. 2023;18(2):9–18. doi:10.1007/s11899-023-00687-7
82. Patel KK, Tariveranmoshabad M, Kadu S, Shobaki N, June C. From concept to cure: the evolution of CAR-T cell therapy. *Mol Ther*. 2025;33(5):2123–2140. doi:10.1016/j.ymthe.2025.03.005
83. Li X, Gong N, Tian F, et al. Suppression of cytokine release syndrome during CAR-T-cell therapy via a subcutaneously injected interleukin-6-adsorbing hydrogel. *Nat Biomed Eng*. 2023;7(9):1129–1141. doi:10.1038/s41551-023-01084-4
84. Gong N, Alameh MG, El-Mayta R, Xue L, Weissman D, Mitchell MJ. Enhancing in situ cancer vaccines using delivery technologies. *Nat Rev Drug Discov*. 2024;23(8):607–625. doi:10.1038/s41573-024-00974-9
85. Huang L, Rong Y, Tang X, et al. Engineered exosomes as an in situ DC-primed vaccine to boost antitumor immunity in breast cancer. *Mol Cancer*. 2022;21(1):45. doi:10.1186/s12943-022-01515-x

86. Shao S, Cao Z, Xiao Z, et al. Programming of in situ tumor vaccines via supramolecular nanodrug/hydrogel composite and deformable nanoadjuvant for cancer immunotherapy. *Nano Lett*. 2024;24(29):9017–9026. doi:10.1021/acs.nanolett.4c02113
87. Yin B, Wong WK, Ng YM, Yang M, Leung FK, Wong DS. Smart design of nanostructures for boosting tumor immunogenicity in cancer immunotherapy. *Pharmaceutics*. 2023;15(5). doi:10.3390/pharmaceutics15051427
88. Peng Y, Wu X, Liu H, et al. Hydrogel-based tumor embolization and synergistic therapeutic strategies. *Bioact Mater*. 2026;59:17–44. doi:10.1016/j.bioactmat.2025.12.031
89. Zhang Y, Feng Z, Liu J, et al. Polarization of tumor-associated macrophages by TLR7/8 conjugated radiosensitive peptide hydrogel for overcoming tumor radioresistance. *Bioact Mater*. 2022;16:359–371. doi:10.1016/j.bioactmat.2021.12.033
90. Yu B, Ma W. Biomarker discovery in hepatocellular carcinoma (HCC) for personalized treatment and enhanced prognosis. *Cytokine Growth Factor Rev*. 2024;79:29–38. doi:10.1016/j.cytogfr.2024.08.006
91. Foerster F, Gairing SJ, Ilyas SI, Galle PR. Emerging immunotherapy for HCC: a guide for hepatologists. *Hepatology*. 2022;75(6):1604–1626. doi:10.1002/hep.32447
92. Wen G, Xue L, Qiu M, Qiu J, Zhu X, Ren H. Biohybrid hydrogel inhibiting β-klotho/HDAC3 axis for hepatocellular carcinoma treatment. *Int J Biol Macromol*. 2024;277(Pt 3):134369. doi:10.1016/j.ijbiomac.2024.134369
93. Yan X, Sun T, Song Y, et al. In situ thermal-responsive magnetic hydrogel for multidisciplinary therapy of hepatocellular carcinoma. *Nano Lett*. 2022;22(6):2251–2260. doi:10.1021/acs.nanolett.1c04413
94. Humzah D, Molina B, Salti G, Cigni C, Bellia G, Grimolizzi F. Intradermal injection of hybrid complexes of high- and low-molecular-weight hyaluronan: where do we stand and where are we headed in regenerative medicine? *Int J Mol Sci*. 2024;25(6). doi:10.3390/ijms25063216
95. Zhao B, Zhou B, Shi K, et al. Sustained and targeted delivery of siRNA/DP7-C nanoparticles from injectable thermosensitive hydrogel for hepatocellular carcinoma therapy. *Cancer Sci*. 2021;112(6):2481–2492. doi:10.1111/cas.14903
96. Yang Q, Zhuge X, Lin W, et al. Hydrogel-based miR-192 delivery inhibits the development of hepatocellular carcinoma by suppressing the GSK3β/Wnt/β-catenin pathway. *Neoplasma*. 2023;70(4):555–565. doi:10.4149/neo_2023_230317N150
97. Zhuang Q, Zhao B, Lin Z, et al. Navoximod modulates local HSV-1 replication to reshape tumor immune microenvironment for enhanced immunotherapy via an injectable hydrogel. *Commun Biol*. 2023;6(1):621. doi:10.1038/s42003-023-04983-z