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Review Article

Reversal of postoperative breast cancer metastasis by the use of embedded hydrogel

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Abstract: Surgery is the primary treatment strategy for breast cancer (BC). However, postoperative recurrence is a great challenge faced by current surgical treatment strategies for BC. Therefore, it is worth studying how to prevent the recurrence of BC after surgery effectively. This paper reviews the process of BC metastasis, the alteration of the immune microenvironment after surgery, and the published synthetic methods and composition principles of hydrogel for BC postoperative *in situ* treatment. Recent advances in the use of hydrogel in the postoperative treatment of BC to prevent recurrence are emphasized. Current shortcomings and future directions are discussed.

Keywords: Breast cancer, postoperative, recurrence, hydrogel

Introduction

Breast cancer (BC) is the most common non-skin malignancy among women worldwide and the leading cause of cancer-related death [1]. In clinical practice, surgery is the preferred method for the comprehensive treatment for primary BC [2, 3]. The goal of both mastectomy and breast-conserving surgery is to remove as much tumor tissue as possible [4]. However, residual tumor cells and circulating tumor cells (CTCs) around the resection cavity [5-7], as well as postoperative inflammation-associated immunosuppression, can lead to recurrence and ultimately death of the patient [8, 9]. Postoperative BC metastasis can be divided into three processes: (1) *in situ* invasion of residual BC cells after surgery, (2) endosmosis and survival of BC cells within the circulatory system, and (3) extravasation of BC cells and formation of metastatic foci. The immune system plays a crucial role in the process of metastasis (**Figure 1**).

To reduce the risk of recurrence, chemotherapy and radiotherapy are currently the primary interventions for treating BC after surgery. However, due to the patient's limited ability to tolerate the adverse effects of multiple treatment strategies, the combination of radiotherapy and chemotherapy with surgery usually requires at least a one-month interval and cannot be applied during the perioperative period. Additionally, chemotherapy drugs face the challenges such as low solubility, high side effects, and short blood circulation time. Rdiotherapy also has drawbacks, including adverse side effects, treatment resistance, and radiation damage [10, 11], which limit its application and reduce patients' quality of life [12, 13]. Unlike radiotherapy and chemotherapy, immunotherapy works by enabling the host's immune system to recognize and attack residual tumor cells, thereby preventing cancer recurrence [14-16]. Immunotherapeutic strategies, including cancer vaccines [17, 18], immune checkpoint blockade [19], adoptive cell therapy [20], cytokine therapy [21], chimeric antigen receptor (CAR)-T cell therapy [22], and monoclonal antibody therapy [21], have shown promising therapeutic results. However, in clinical practice, immunotherapy is influenced by various factors, such as the tumor microenvironment and immunosuppression, and its stability needs to be improved [23-25]. New therapeutic approaches need to be developed to meet the need for comprehensive postoperative BC treatment.

Local drug delivery involves implants or injecting drugs directly into the surgical cavity to elim-

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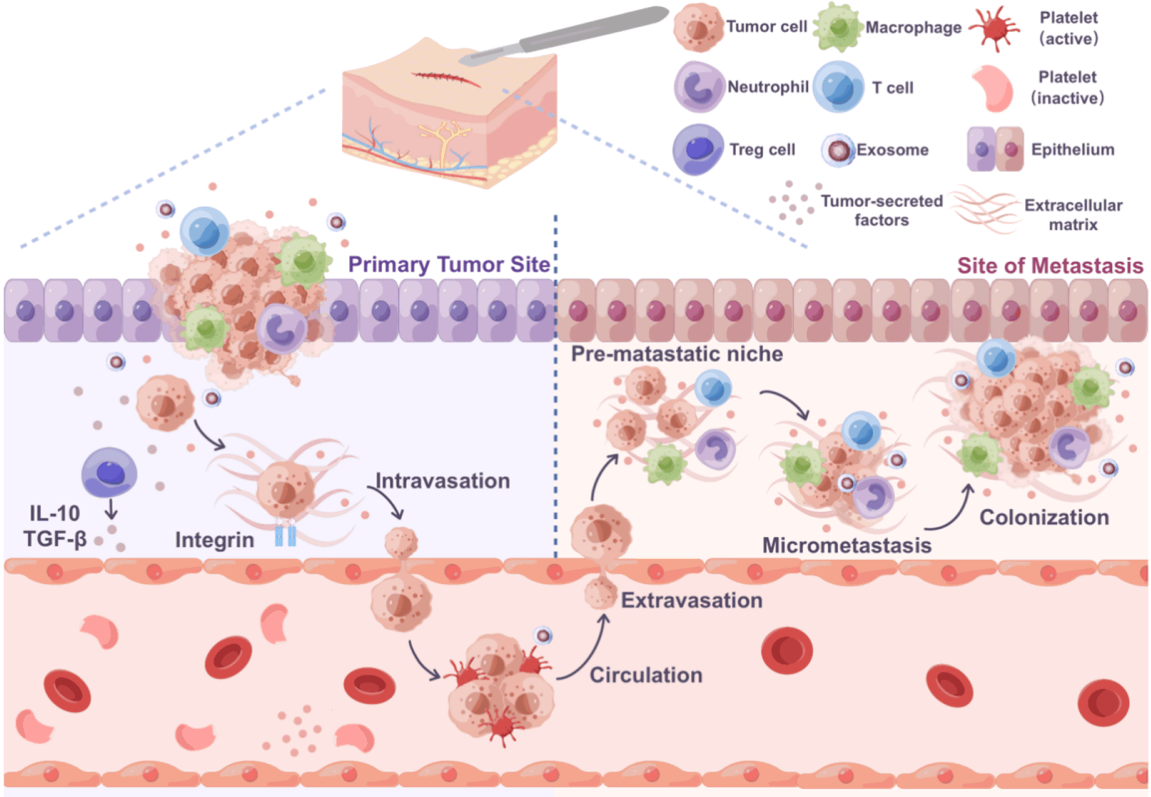

Figure 1. Three processes of postoperative BC metastasis and the essential role of immune system.

inate residual tumor cells after resection [26, 27]. Compared to systemic therapy, local administration of drugs can increase the concentration of drugs near the residual tumor tissue. This approach allows the drugs to be localized directly to the cancerous area, avoiding excessive circulation through the bloodstram. This not only improves the speed at which the drugs reach the tumor site but also reduces the high side effects associated with systemic therapy [28]. With advancements in various fields, combined treatments in various fields of molecular biology, oncology, pharmacology, materials science, and other disciplines have broadened BC treatment [29, 30]. Hydrogel-based cancer therapeutic platforms have gained significant attention due to their superior characterization. The excellent biocompatibility and degradability of hydrogels help prevent strong immune rejection and systemic organ toxicity in humans [31]. Compared to traditional drug delivery platforms, hydrogels' slow-release properties and high drug-loading capacity ensure a higher local concentration of therapeutic drugs, thereby minimizing adverse reactions associated with high blood drug concentration [32]. Hydrogels made from different materials and synthesis using various methods can be customized with different functionalities and therapeutic effects to meet the needs of diverse cancer treatment strategies due to their excellent drug co-encapsulation compatibility [33]. Specific modifications and the incorporation of different sensitizers allow hydrogels to respond to various external stimuli, including light [34], near-infrared light (NIR) [35-37], temperature [38, 39], Ph [40], magnetic fields [41], and enzymes [42]. Natural hydrogels, such as collagen, hyaluronic acid, fibronectin, methylcellulose, and chitosan, are soft materials that have natural advantages in soft tissue reconstruction [43-46].

Moreover, in surgery, the removal of cancerous tissue often results in tissue defects, affecting the normal function and appearance of the patient's breasts, which can impose a significant psychological burden on the patient [47-50]. In BC surgery, hydrogels' reversible expansion and contraction properties and good fluidity enable them to adequately fill the surgi-

cal cavity. They can be used to repair breast defects and restore the original appearance while preventing tumor recurrence [51]. Hydrogels are a new type of biomaterial with great potential for clinical application in the postoperative treatment of BC, providing an effective solution to the challenges of removing residual tumor cells, combating wound infection, and repairing tissue defects following BC surgery.

Overall, this review discusses and emphasizes the mechanism of BC postoperative recurrence and postoperative inflammation-associated immunosuppression. It highlights hydrogel delivery systems for the postoperative treatment of BC. The purpose is to call more attention to the entire metastatic process of breast tumors. This review aims to offer researchers a broader perspective on postoperative BC therapy and inspire new ideas for the development and use of novel hydrogels.

The process of postoperative metastasis of BC

Effect of surgery on the in situ invasion of BC cells

Postoperative residual BC cells can invade into surrounding normal tissues, involving various changes in migration and cell adhesion molecules. Epithelial-mesenchymal transition (EMT) in tumor cells occurs through the loss of inter-epithelial cell adhesion and the acquisition of mesenchymal features. EMT plays a critical role in all stages of development, including proto-gut embryo formation, neural crest cell formation, and inflammation-induced cellular fibrosis [52-56]. Studies have shown that the EMT process can be initiated by activating multiple pathways, such as transforming growth factor-β (TGF-β), Wnt, and NOTCH, which induce EMT regulators like Twist-1, Zeb-1, Zeb-2, and Snail. This leads to the down-regulation of epithelial markers [e.g., E-cadherin and zonula occludens connexin 1 (ZO-1)] and the up-regulation of mesenchymal markers [e.g., vimentin, fibronectin, and N-cadherin], ultimately resulting in the tumor cells' acquiring invasiveness [55, 56].

Additionally, myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells with immunosuppressive functions, can also promote tumor cell invasion by secreting matrix metalloproteinases (MMPs) [57]. It has been found that surgical stress can enhance the EMT process in tumor cells by increasing the levels of TGF-β, vascular endothelial growth factor (VEGF), and IL-10, as well as promoting the recruitment of MDSCs [58]. However, the EMT process is not the only requirement for breast tumor metastasis to occur [59]. The surgically induced inflammatory response recruits macrophages, which assist BC cells in local invasion by secreting proteases that degrade cell adhesion molecules and extracellular matrix (ECM) and by activating cell chemokines [60, 61].

Effect of surgery on intracellular leakage, circulatory system survival, and extracellular leakage of BC cells

Breast tumor cells can spread by lymphatic and hematogenous routes. These cells secrete colony-stimulating factor 1 (CSF-1), which stimulates the growth of macrophages that are recruited in response to postoperative inflammation. These macrophages then secrete proteases that degrade the vascular basement membrane, allowing tumor cells to enter the circulation [62]. VEGF secreted by macrophages also promotes tumor cell migration. The structure of lymphatic vessels, characterized by a discontinuous basement membrane and a lack of tight inter-endothelial junctions, facilitates the entry of tumor cells into the lymphatic circulation. Lymph node metastasis is a crucial finding for BC staging, as it increases the risk of distant metastasis [63, 64].

Once tumor cells enter the circulatory system, they become CTCs. Studies have shown a significant increase in CTCs after surgery [65]. CTCs face three major challenges in circulation: (1) anoikis (loss of cell-matrix adhesion), (2) physical damage from blood flow shear stress, and (3) immune attack. Breast tumor cells activate signaling pathways such as tropomyosin receptor kinase B (TrkB), EMT, and phosphatidyl-inositol 3-kinase (PI3K) to overcome anoikis [66]. During the repair of tissue damage caused by surgery, the coagulation pathway is activated, initiating the wound-healing process [67]. Activated platelets attach to CTCs to form aggregates through adhesion receptors such as P-Selectin, glycoprotein (GP)Ib-IX-V, and GPIIb-IIIa [68, 69]. GPIIb-IIIa has been shown to interact with the tumor cell receptor $\alpha_v\beta_3$, pro-

moting aggregation between tumor cells and platelets [70, 71]. This aggregation helps retain CTCs within the vessel wall, preventing their destruction by shear generated by blood flow [72].

Surgery promotes the release of inflammatory cytokines [interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF)], which increase fibrinogen production [73]. Surgically induced fibrinogen production and activated platelets cover CTCs, protecting them from natural killer (NK) cells in the circulatory system [74, 75]. TGF-β released by activated platelets downregulates natural killer group 2, member D (NKG2D) expression, thereby inhibiting the anti-tumor activity of NK cells [76]. TGF-β also inhibits NK cells activation and function by suppressing mammalian target of rapamycin (mTOR) activity in NK cells [77]. Additionally, activated platelets can enhance the proliferation of CTCs [78], inhibiting CTCs' death [79], promoting EMT in tumor cells, and facilitating CTC extravasation [54-56].

CTCs must undergo extravasation before they can colonize specific tissues. A significant barrier to CTC extravasation is the structural differences in the vascular system. For example, unlike the highly permeable vasculature of tumors, pulmonary capillaries are tightly structured. Therefore, CTCs must actively disrupt the tight junctions between endothelial cells to accomplish extravasation. Surgically induced ischemia-reperfusion injury (IRI) modifies angiopoietin-like 4 (ANGPTL4) secreted by CTCs, which disrupts the endothelium and facilitates the extravasation of CTCs into the lung parenchyma [80]. The role of macrophages in cancer extravasation has also been demonstrated in BC, where researchers found that macrophage depletion significantly reduces the number of exudative BC tumor cells [81].

Tumor cell colonization and the formation of metastatic foci

Before new metastases can form, tumor cells that extravasate into the parenchyma of distant organs must overcome several challenges, including anti-metastatic signals secreted by stromal cells, attack by immune cells, and the different microenvironment compared to the primary tumor site. For instance, in lung metastasis, genes such as inhibitor of differentiation binding ID-1/3, Tenascin C, chemokine (C-X-C motif) ligand 1 (CXCL1), vascular cell adhesion molecule (VCAM), microRNA-200 (miR-200), and periosteal proteins have been identified as contributors to lung metastasis. Additionally, the interaction between the ECM of the lung tissue and the breast tumor cells entering it is crucial for the establishment of new lung metastases.

Breast tumor cells capable of initiating lung metastasis can activate Wnt signaling by secreting TGF-β, which stimulates lung fibroblasts to produce periostin, ultimately promoting lung metastasis development [82]. The glycoprotein Tenascin C can also enhance the stem cell properties of breast tumor cells by activating the Notch pathway, supporting the initial growth of breast tumor cells [83]. Moreover, VCAM-1 protects breast tumor cells from apoptosis [84]. ID-1 further promotes the development of lung metastases in BC by facilitating the mesenchymal-epithelial transformation (MET), the reverse process of EMT, which is a critical step for lung metastasis formation [85].

Postoperative immunosuppression and changes in the tumor microenvironment

Tumor cells create an immunosuppressive microenvironment that allows them to evade immune surveillance, thereby promoting tumor progression and metastasis [86, 87]. The inflammatory response following surgery can lead to a similar state of systemic immunosuppression. After tumor resection, inflammatory changes at the surgical site cause the release of factors that promote tumor metastasis and recruit various types of immune cells.

BC surgery is associated with a significant increase in various pro-tumor cytokines, including VEGF, IL-1, IL-6, IL-10, monocyte chemotactic protein-1 (MCP-1), and TGF-β, and a significant decrease in interferon-gamma (IFN-γ) [88, 89]. Additionally, surgery can affect immunosuppressive cells, and studies have shown that after surgery, there is an overall decrease in the number of CD8(+) T-cells, along with impaired function, which may promote tumor recurrence [90-92]. NK cells, a major source of IFN-γ, play a crucial role in cancer immune surveillance, and the density of NK cells in tumors correlates with cancer prognosis and morbidity [93-95]. Surgical stress has been shown to affect NK cell function, leading to a significant inhibi-

tion of IFN-γ secretion, with more than 90% of patients having lower than normal INF-γ levels on the first day after surgery, which can persist for up to two months [96].

Regulatory T cells (Tregs) are essential for regulating the immune system and maintaining tolerance to self-antigens to prevent autoimmune disease [97]. After surgery, an increase in Tregs has been observed, which exerts an inhibitory effect on effector T cells and NK cells, thereby promoting tumor cell metastasis [98-101]. Tregs can release inhibitory cytokines such as IL-10, TGF-β and IL-36 to suppress effector T cell function [102-105]. They also release large amounts of granzymes and perforins that induce apoptosis in effector T cells [106].

Neutrophils are a key component of the innate immune system, acting as first responders in the host's defense against external injury, initiating immune regulation, repairing tissue damage, and combating cancer [107-109]. Neutrophils are rapidly recruited to the site of injury within minutes of surgery by a damage-associated molecular pattern (DAMP) released by IRI-induced sterile inflammation [110], and they form neutrophil extracellular traps (NETs) at sites of tissue injury [111]. NETs are complex structures made of DNA, histones, and specific granular enzymes such as neutrophil elastase (NE) and myeloperoxidase (MPO) [112]. Originally recognized for their role in neutrophil-mediated defense against microbes [113], recent research has highlighted their significant involvement in cancer metastasis [114, 115]. A high concentration of matrix metalloproteinase-9 (MMP-9) in NETs promotes tumor progression and metastasis by activating the local immunosuppressive microenvironment of NETs in TGF-β niches [116, 117]. NETs also trigger the release of high-mobility group box 1 (HMGB1), which not only binds platelets by toll-like receptor 4 (TLR4) but also activates the TLR9-dependent pathway in tumor cells, thereby promoting tumor cell growth, adhesion, migration, and invasion following surgical stress [118].

Design of hydrogel drug delivery systems for postoperative BC treatment

Hydrogels have attracted researchers' attention due to their excellent biocompatibility, controlled drug release, and high drug-carrying capacity. Surgical excision combined with hydrogel-based postoperative treatment is a promising treatment a promising option that has been used topically to inhibit BC recurrence after surgery, minimize side effects, and improve efficacy. The hydrogel, when placed in the surgical defect area, can maintain the local drug concentration for an extendedperiod, dramatically reducing the possibility of tumor recurrence after surgery. Currently, hydrogels used for postoperative treatment are mainly categorized into hydrogel drug-carrying systems for encapsulating chemotherapeutic drugs targeting in residual tumor cells, and immunotherapy hydrogel drug-carrying systems targeting the immune system.

Hydrogel for the treatment of local residual BC cells

Postoperative chemotherapy is the cornerstone of treatment after surgery, but the significant side effects of chemotherapy limit its further application. Hydrogel extended-release formulations have reduced side effects, and hydrogel-encapsulated chemotherapeutic agents may be an effective strategy for treating postoperative BC recurrence. Ranran Fan [119] prepared insoluble paclitaxel (PTX) as nanocrystals using wet media milling to improve the solubility and bioavailability of PTX. These nanocrystals were loaded into thermosensitive hydrogels made from Poloxamer 407, Poloxamer 188, and Carbomer 974P to create PTX-NCS-gel thermosensitive hydrogels for localized PTX release. Rheological characterization and *in vitro* dissolution studies showed that PTX-NCS-gel thermosensitive hydrogel have a clear and regular network structure with good temperature sensitivity. They could gel within minutes at 33.1°C, exhibiting good viscoelasticity and self-recovery ability. In a mouse model of postoperative tumor recurrence, PTX-NCS-gel thermosensitive hydrogel provided long-term slow release of PTX, reduced systemic toxicity, and effectively inhibited tumor recurrence in mice with recurrent BC (**Table 1**). The multi-activated thermosensitive hydrogel offers temperature-controlled, precise, and continuous drug release. It demonstrates better biosafety compared to intravenous methods, provided there is a thorough understanding of the synthesized material's various physical properties, pharmacology, and toxicology. Zexiang

Table 1. Hydrogel for the treatment of local residual BC cells

Hydrogel	Features	Advantages	Disadvantages	Rf
PTX-NCS-gel	Mesh-like porous structure, shear-thinning properties, semi-solid at near-body temperature.	Localized drug delivery, strong adhesion, controlled drug release, good rheological properties.	Limited storage and usage conditions, potential biocompatibility issues.	[119]
OHA-Met	pH-responsive drug release, dynamic reversible imine bond connection ensures drug release, reduces cytotoxicity.	Degradability, mechanical stability, good biocompatibility.	Potential initial drug burst release might harm normal cells.	[120]
MSH	Magnetic field control for precise localization and drug release, local hyperthermia enhances efficacy.	Injectable, shape memory and fluid-like properties, good biocompatibility.	Complex preparation process may limit production, long-term safety of Fe3O4 needs further research.	[121]
IR820/Mgel	Multi-porous structure with rough surface, loaded with photothermal and IR820, exhibiting thermal effects.	Injectable, good cell adhesion aids in breast reconstruction.	Potential toxicity of photothermal agents, degradation byproducts may cause inflammation or other side effects.	[128]
PTX/mPECT NPs	Combined release of multiple drugs, controlled drug release mechanism.	Shape plasticity can match irregular wounds, relatively simple preparation.	Potential drug stability issues.	[129]
125I-GNR-RGDY	Dual-network structure with different characteristics, PTT combined therapy.	Good degradation rate, excellent mechanical properties, significant antibacterial properties.	Complex preparation process, high cost, highly cross-linked structure affects material plasticity.	[130]
BGN-Fe-Ag2S	PTT and CDT combined therapy, controllable gelation.	High anti-tumor efficiency, quick response, antibacterial and promotes wound healing.	Potential toxicity risk of metal ion accumulation in the body, complex preparation, high cost.	[132]
HMI@GEL	PTT and PDT combined therapy, controllable drug release.	Combination of PTT and PDT enhances therapeutic effect, providing more treatment options.	Complex synthesis and functionalization process, high difficulty.	[141]

Zheng [120] prepared OHA-Met by covalently grafting metformin (Met) onto oxidized hyaluronic acid (OHA) through imine bonds. Injectable hyaluronic acid hydrogels (CMCS/OHA-Met) that release drugs in response to pH changes were then created by attaching carboxymethyl chitosan (CMCS) to OHA-Met by imine bonds. Under acidic conditions, the hydrogel intelligently releases metformin while maintaining mechanical stability, cytocompatibility, and anti-tumor properties. When directly injected into mice, CMSC/OHA-Met hydrogel facilitates tissue repair and eradication of tumor cells (**Table 1**). Compared to direct administration, CMSC/OHA-Met hydrogel reduces the dosage, frequency, and systemic side effects of Met, showing great potential in prevention postoperative BC recurrence and promoting tissue repair.

A novel drug delivery system utilizing iron-based hydrogel has been developed for the targeted delivery of various chemotherapeutic agents. Haoan Wu [121] designed a magnetic supramolecular hydrogel (MSH) to co-deliver chemotherapy and thermosensitive drugs, aiming to prevent tumor recurrence after BC surgery. The self-assembled MSH consists of polyethylene glycolized iron oxide nanoparticle surface copolymerization and α-cyclodextrin (α-CD) complexation [122, 123]. The hierarchical structure of MSH contains both hydrophilic and hydrophobic structural domains. The hydrophobic molecule PTX is double-loaded into the shell structure of the polyethylene glycolized iron oxide nanoparticles, while the hydrophilic molecule doxorubicin (DOX) is loaded into the gel's aqueous phase, ensuring that both hydrophobic and hydrophilic drugs are loaded and released successively with different release profiles. MSH is injected into the surgical cavity, and under the influence of an alternating current magnetic field (ACMF), the MSH undergoes a magneto-thermal gel-sol transition to achieve precise alignment with the surgical cavity. Magnetic nanoparticle-mediated conductive heat then triggers drug release. MSH combined with thermal chemotherapy offers significant advantages in preventing tumor recurrence after surgery (**Table 1**). Fei Gao [124] developed a novel ferromagnetic vortex-domain iron oxides (FVIOs) hydrogel with optimal adaptive functionality based on difunctional telechelic poly (ethylene glycol) (DT-PEG) and glycol-chitosan. FVIO-functionalized hydrogels overcome the possible side effects of conventional superparamagnetic iron oxide nanoparticles (SPIOs) hydrogels, exhibiting high induction heating and remarkable rheological properties. These adaptive functions allow for the sustainable release of anticancer drugs, and mild hyperthermia under alternating magnetic field (AMF) exposure effectively promotes DOX nuclear internalization. *In vivo* studies in tumor-bearing mice demonstrate that FVIO-functionalized hydrogels effectively prevent local recurrence after primary tumor resection (**Table 1**).

Photothermal therapy (PTT), a non-invasive therapy, uses NIR light-absorbing materials to convert light into heat to ablate and remove tumor tissue [125-127]. PTT-induced hyperthermia prevents DNA self-repair, promotes blood circulation, and improves the hypoxic microenvironment, thereby synergistically enhancing the efficacy of radiotherapy in cancer treatment. Xi Yang [128] developed a thermosensitive and injectable methylcellulose hydrogel platform (IR820/Mgel) by integrating porous microspheres (MPs) and IR820 to prevent recurrence after surgery through photothermal therapy, while also serving as an adjunct in breast reconstruction (**Figure 2**). IR820, known for its excellent photothermal properties, acts as a photothermal agent. The inclusion of MPs enhances the hydrogel's durability, ensuring its long-term functionality *in situ*. Moreover, the porous nature of the MPs provides additional support for the stable attachment of normal breast cells, aiding in breast reconstruction. Experimentally results showed that IR820/Mgel could effectively kill 4T1 cells when heated above 50.0°C under NIR irradiation, making it an excellent therapeutic method for preventing local recurrence. It was well tolerated and biologically safe in mice (**Table 1**).

In recent years, numerous innovative strategies for incorporating PTT have emerged, along with many biomedical applications of bionanomaterials. Meiyan Liu [129] developed an injectable nanocomposite hydrogel platform with multicomponent compatibility and sustainable release of nanomedicines. The diblock copolymer, methoxy-poly(ethylene-glycol)-b-poly (e-caprolactone-co-1,4,8-trioxa-spiro-9-undecanone) (mPECT), was used to create both mPECT-

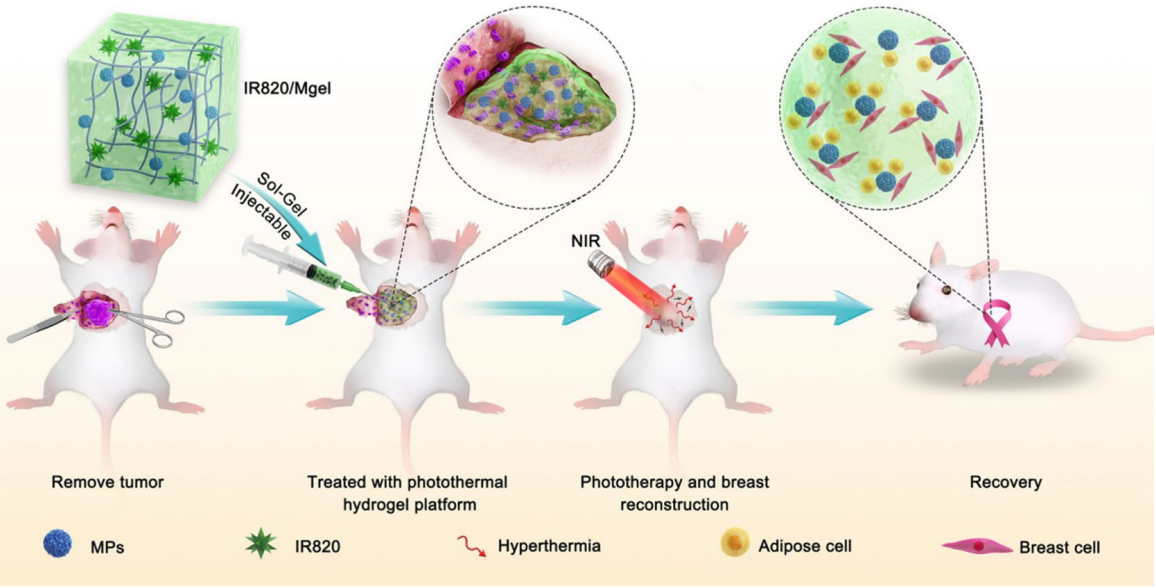

Figure 2. Scheme of hydrogel platform (IR820/Mgel) preparation and its applications for preventing post-surgical tumor recurrence and improving breast reconstruction [128].

modified gold nanorods (AuNR-PECT) and paclitaxel-loaded mPECT nanoparticles (PTX/mPECT NPs). This approach of creating nanocomposite hydrogels through supramolecular assembly for local combination therapy can be easily adapted of various nano theranostic agents. Yuanhao Wu [130] prepared a polyethylene glycol diacrylate (PEGDA)-alginate double-network nanocomposite hydrogel (GPA) embedded with ^{125}I-labeled RGDY peptide-modified gold nanorods (^{125}I-GNR-RGDY) (**Figure 3**). The dual-network (DN) hydrogels were formed by rapid gelation of a GPA precursor solution injected into the cancerous breast cavity of excised mice. Increased temperature under near-infrared light irradiation induced the polymerization of PEGDA and the cross-linking of the second alginate network with endogenous Ca^{2+} around the tumor. The DN hydrogel, with a dense polymer network, tightly immobilizes ^{125}I-GNR-RGDY and exhibits excellent sustained photothermal and radiologic effects. Under NIR irradiation, ^{125}I-GNR-RGNY exhibits a built-in photothermal effect that generates high heat, inhibits the self-repair of damaged DNA, improves the hypoxic environment by promoting blood circulation, and enhances the anti-tumor efficiency of brachytherapy. The isotopic labeling with ^{125}I also provides the hydrogel with long-term isotopic imaging properties [131]. The synergistic effect between the photothermal effect and the real-time brachytherapy effectively prevents recurrence and wound infection after surgery (**Table 1**). Han Huang [132] developed a photoactivatable injectable hydrogel based on a bioactive nanocomposite system by incorporating silver sulfide nanodots coupled with Fe-doped bioactive glass nanoparticles (BGN-Fe-Ag_2S) into a poly (ethylene glycol) PEGDA and 2,2-azobis[2-(2-imidazolidine-2-yl)propane] dihydrochloride (AIPH) solution to inhibit tumor growth, treat bacterial infections, and promote post-injury healing. Silver sulfide nanodots act as photothermal agents [133], and the laser-generated thermotherapy irradiation triggers the decomposition of AIPH to release alkyl radicals, which initiates the polymerization of PEGDA [134]. Given the overexpression of hydrogen peroxide in the inflammatory microenvironment [135-137], BGN-Fe serves as a growth promoter and chemodynamic therapy (CDT) agent for wound tissue to inhibit tumor growth and bacterial proliferation. Simultaneously, the BGN core promotes skin repair by stimulating collagen formation during hydrolysis.

Photodynamic therapy (PDT) is highly selective and non-invasive, causing fatal damage to tumor cells by large amounts of cytotoxic reactive oxygen species (ROS) [138]. The oral hypoglycemic drug Met has shown favorable thera-

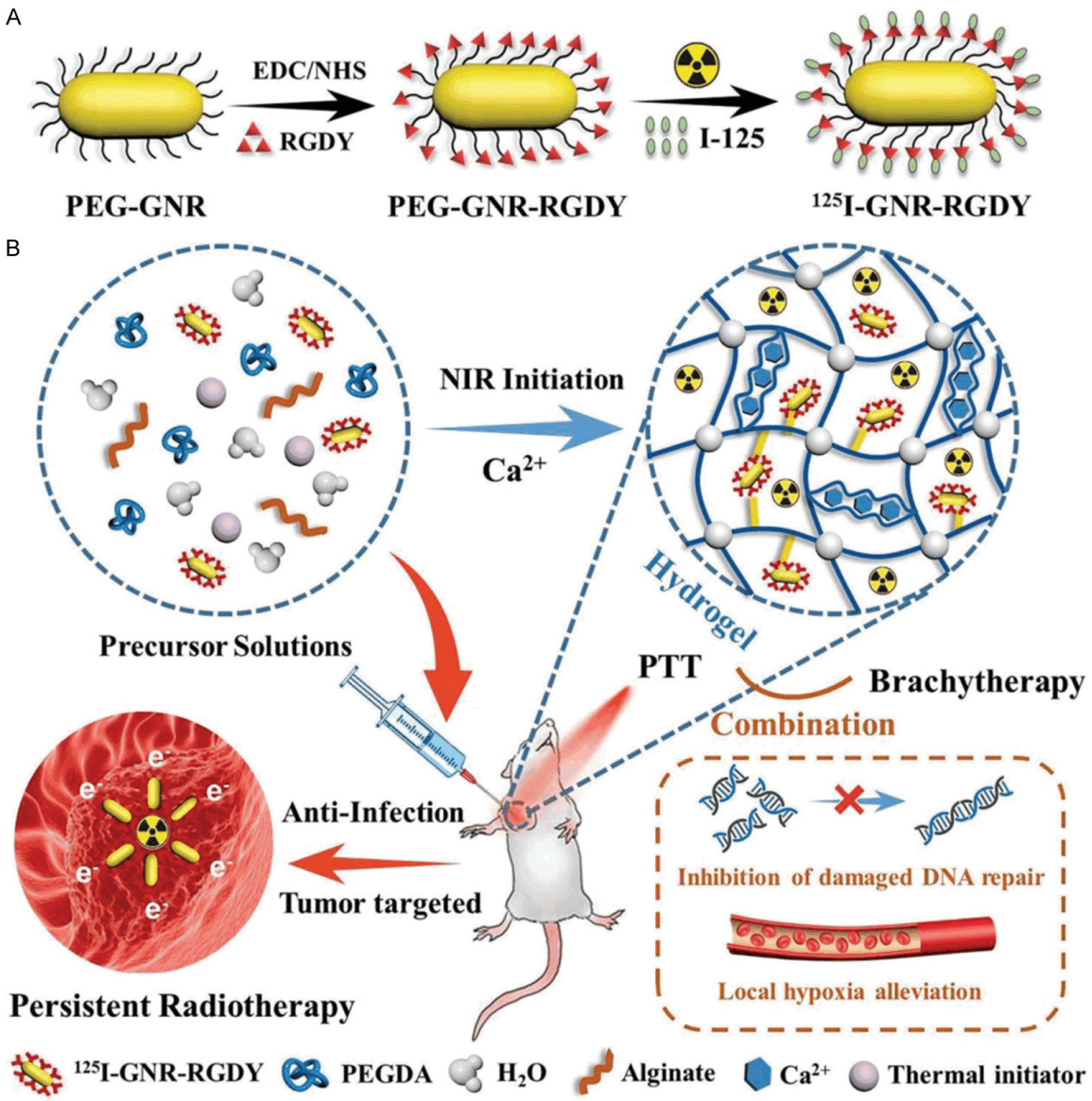

Figure 3. Schematic illustration of the fabrication of (A)^{125}I-GNR-RGDY and (B) nanocomposite double-network GPA hydrogel and their theranostic application for inhibition of postoperative BC recurrence and wound infection through synergistic brachytherapy and photothermal therapy [130].

peutic effects on most types of cancer [139, 140], primarily by inhibiting mitochondrial complex I and thus restricting energy flow to cancer cells. Yanting Sun [141] prepared a smart, photothermally controlled drug-releasing g-quadruplex (G4) hydrogel using 5'-guanosine monophosphate (5'GMP), indocyanine green (ICG), hemin, and Met. Met release was triggered under 808 nm NIR light. This approach significantly reduced mitochondrial oxygen consumption due to dual inhibition of glycolysis and tricarboxylic acid (TCA) cycle through the combined action of hemin and Met. The combition of PTT with the synergistic enhancement of PDT and activated tumor immunotherapy led to significant tumor cell apoptosis and necrosis (**Table 1**).

Systematic immunotherapy hydrogel for preventing postoperative breast tumor recurrence

Compared to traditional treatments, immunotherapy is better tolerated, concentrates the drug at the site of action, and minimizes some of the negative impacts associated with systemic therapy [142]. BC immunotherapy en-

compasses methods such as tumor vaccine therapy, cytokine therapy, monoclonal antibody therapy, and adoptive cell therapy [143].

Immunogenic cell death (ICD) is a specific variant of regulated cell death (RCD), driven by stress-induced pressures, that triggers adaptive immunity against antigens from dead cells. Dinglingge Cao [144] developed a therapeutic-prophylactic (TPV) hydrogel from a matrix combining two types of poly (d,l-lactide-co-glycolide)-b-poly (ethylene glycol)-b-poly (d,l-lactide-co-glycolide) block copolymers, incorporating bioactive inorganic calcium salt and the organic substance R827. R827, serving as an immune adjuvant, is embedded within the TPV hydrogel in microcrystalline form to activate immune responses upon release. The TPV-gel is designed to facilitate both immediate and prolonged dispersion of calcium ions, achieving burst and sustained release through the incorporation of $CaCl_2$ and $CaCO_3$. This mechanism aims to provide effective treatment by ensuring an adequate supply of calcium ions at the residual tumor site, thereby inducing ICD in remaining tumor cells through calcium overload (**Table 2**).

Immunological analysis after the resection of *in situ* breast tumors reveals that the activation of postoperative chemokine receptor 4 (CXCR4) signaling exacerbates immunosuppression and correlates with adaptive upregulation of programmed cell death 1 ligand 1 (PD-L1) in recurrent tumors [145]. Minglu Zhou [146] developed a multifunctional hydrogel integrating CXCR4 inhibition, immunogenic activation, and PD-L1 blockade strategies. This hydrogel includes a methacrylamide copolymer-adriamycin coupling (P-DOX), an antagonist coupling [P-(LV)6], and an anti-PD-L1 antibody. P-DOX naturally accumulates within primary tumors, triggering ICD and attracting anti-tumor T cells. P-(LV)6 specifically targets and binds extensively to CXCR4 receptors, which are overexpressed on cancer cells, leading to significant CXCR4 depletion. This process effectively reduces the migration of immunosuppressive cells into the tumor. Experimental results showed that the hydrogel had a localized inhibitory effect on residual tumor cells and disrupted the pre-metastatic niche (PMN). Additionally, it produced vaccine-like effects and long-lasting anti-tumor memory (**Table 2**). Xiang Liu [147] proposed a unique synergistic approach to cancer immunotherapy by co-localizing cancer nanomedicine delivery to enhance the tumor immunogenicity and incorporating a nano-vaccine to boost antitumor T-cell immunity. They developed an injectable, thermosensitive hydrogel from self-assembling, curcumin-loaded polymeric nanoparticles that encapsulate a nano-vaccine for post-surgical tumor immunotherapy. This nanomedicine effectively promoted ICD in the remaining cancer cells, thereby increasing tumor immunogenicity and making the tumor more susceptible to antitumor T-cell immunity. The cancer nano-vaccine, composed of an antigenic peptide, a toll-like receptor 9 (TLR9) agonist (CpG-ODN), and a cationic polymer nanoparticle, significantly enhanced the maturation of dendritic cells (DCs) and elicited robust, vaccine-specific T-cell immune responses. Administering the hydrogel formulation at the surgical site significantly improved the suppression of local tumor spread to the lungs (**Table 2**).

CD47 is one of the most promising targets in tumor immunotherapy, playing a key role in the immune system's ability to recognize "self". Tumors often exploit CD47 overexpression to achieve immune escape. Tumor cells can evade attack by the immune system through the CD47 "don't eat me" signaling pathway [148]. CD47 antibodies (aCD47) bind to CD47 receptors on the surface of tumor cells, blocking this pathway and triggering macrophage-mediated cellular phagocytosis [149, 150]. Xiaodan Wu [151] designed an injectable hydrogel scaffold infused with engineered exosome mimetics. This innovative approach effectively attracts and reprograms endogenous macrophages *in vivo* into M1 macrophages that bind with the aCD47 antibody (M1-aCD47 macrophages), aimed at enhancing postoperative cancer immunotherapy. The injectable chitosan hydrogel encapsulates M1 macrophage-derived exosome mimetics, co-modified with vesicular stomatitis virus glycoprotein (VSV-G) and anti-CD47 (V-M1EM-aCD47), for targeted delivery. *In vivo* experiments demonstrated that the hydrogel activated of the adaptive immune systems to inhibit postoperative BC recurrence (**Table 2**).

Sorafenib, a small molecule multikinase inhibitor, modulates macrophage polarization and

Table 2. Systematic immunotherapy hydrogel for preventing postoperative breast tumor recurrence

Hydrogel	Mechanism:	Advantages	Disadvantages	Rf
TPV-gel	Induces intracellular Ca^{2+} overload to enhance antigen immune response.	Injectable, good biocompatibility.	Low solubility of the copolymer may limit some applications.	[144]
PVA-TSPBA-gel	Induces ICD, inhibits CXCR4-CXCL12 axis to suppress metastatic microenvironment, blocks PD-L1 receptor binding.	Persistent anti-tumor memory effect, systemic immunity, dual therapy.	Accumulation of degradation products may cause adverse reactions, long-term safety needs to be studied.	[146]
PECT-Cur NPs	Combination of nano-vaccine and nano-drug enhances anti-tumor T cell immunity.	Injectable, good biocompatibility, controllable drug release.	Stability may be affected by body temperature fluctuations.	[147]
V-M1EM-aCD47@CS	Exosome-modified aCD47 recruits and programs M1-type macrophages.	Specific targeting, sustained release, high drug retention.	Potential biocompatibility issues.	[151]
DLG	Sorafenib promotes anti-tumor M1 macrophages, blocks CD47-SIRPα pathway.	Combined immunotherapy, precise temporal programmatic drug release, long-lasting anti-tumor effects.	Complex preparation process, potential inter-patient variability.	[154]
aCD47/Ce6@PPG	Combined ICB and PDT synergistic therapy, targeting CD7.	PDDA framework's ROS scavenging ability protects ICB antibodies, real-time monitoring via Raman imaging.	Complex preparation and application process, long-term safety.	[159]
FK@IQ-4T1	Inhibits PD-L1 to enhance anti-tumor immune response, blocks immune escape.	Personalized treatment for different patients, targeted drug delivery.	Complex preparation process, high cost.	[166]
PTLDH	GM-CSF activates DCs for more effective tumor antigen presentation to T cells.	Regulates immune microenvironment, personalized immune response.	High swelling ratio leads to instability.	[167]
SH@FP@$CaCO_3$	Promotes DC maturation and activates T cells, promotes M1-type macrophage polarization.	Dual action, strong targeting.	Ca^{2+} accumulation from degradation products needs further study.	[168]
PF127-MTL	Specifically targets DCs, activates STING pathway.	Dual action, good biocompatibility.	Trichosanthin as an exogenous protein requires further research on its immunogenicity.	[169]
RIC NPs@PLEL	RIC NPs activate immune response, significantly increasing CD8+ T cells.	PTT and immune stimulation synergistic therapy.	Long-term biocompatibility issues require further study.	[170]
ICG-STING-gel	Activates STING pathway to activate innate immune system.	PTT synergistic therapy.	High swelling ratio structure may be unstable, affecting long-term degradation.	[21]
BPQDs@pNIPAM	Activates and proliferates γδ T cell.	PTT synergistic therapy, reduces limitations of traditional immunotherapy.	Complex preparation process, material stability needs further research.	[171]
CMCS/OHA-Met	Activates immune system through Caspase-3/PARP signaling pathway.	PDT synergistic therapy.	Initial drug burst release might harm normal cells.	[175]

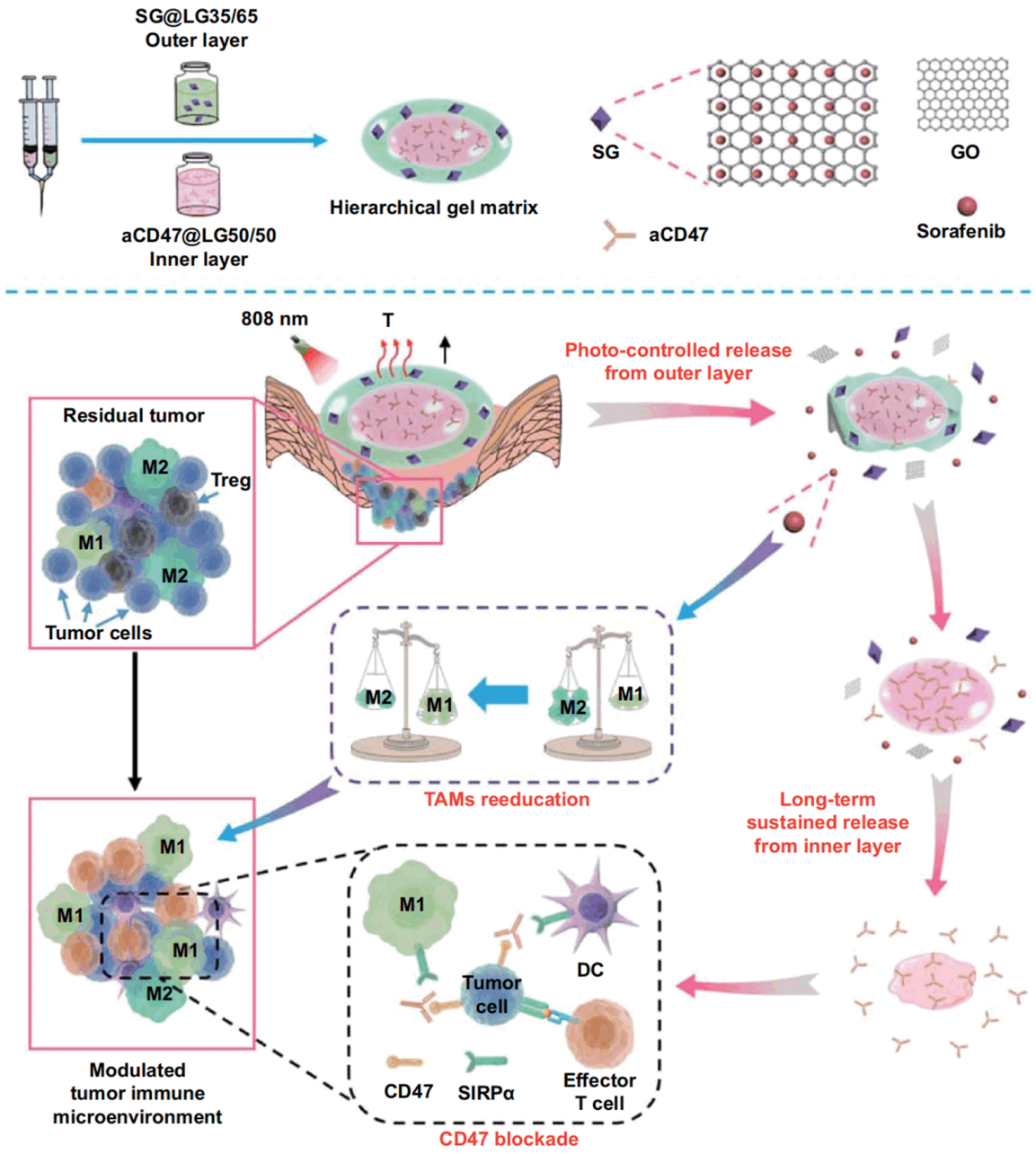

Figure 4. Schematic illustration of time-programmed sequential delivery of combined cancer immunotherapy by a hierarchically structured gel matrix (DLG scaffold) for postsurgical tumor immune microenvironment modulation [154].

influences macrophage involvement in tumor metastasis and formation [152]. Blocking CD47 to activate tumor cell phagocytosis by carrier T cells enhances anti-tumor efficacy [153]. Liping Huang [154] designed an injectable, hierarchically structured gel matrix with a double lipid gel (DLG) layer, where the outer and inner layers consist of different mass ratios of soybean phosphatidylcholine (SPC) and glycerol dioleate (GDO) (**Figure 4**). A binary system of SPC/GDO with a mass ratio of 35/65 was selected as the precursor for the outer lipid gel (LG) layer of the DLG matrix, incorporating sorafenib-loaded graphene oxide (GO) nanoparticles (SG). The inner LG precursor of the DLG matrix is loaded with aCD47, and the outer layer is thermo-responsive, loaded with first-adsorbed GO nanoparticles. The release of these nanoparti-

cles under 808 nm NIR irradiation activates tumor-associated macrophages (TAMs) and improves the immunogenic tumor microenvironment. Subsequent release of aCD47 blocks the CD47 signaling pathway involving the regulatory protein α (SIRPα), providing long-term anti-tumor effects [152, 153]. *In vivo* studies have shown that the DLG can locally reverse immunosuppression, synergistically block CD47-dependent immune evasion, enhance systemic immune response, and effectively prevent tumor recurrence after surgery (**Table 2**).

Combining ICB therapy [155-158] with PDT has excellent potential for treating immunologically "cold" tumors. Yiyi Zhang [159] developed a ROS-responsive, biocompatible hydrogel named PPG, which utilizes cross-linking of conjugated poly (deca-4,6-dienedioic acid) (PDDA) [160] with natural pullulan glycan [161, 162] to simultaneously release ICB antibodies and photosensitizers (PSs), addressing the issue of ROS potentially harming unreleased antibodies. The cluster of differentiation 47 (CD47) antibody (aCD47) and chlorine e6 (Ce6) were loaded into the PPG hydrogel. The degradation of the hydrogel under LED irradiation at 640 nm resulted in sustained release of aCD47 and Ce6. *In vivo* experiments demonstrated that the hydrogel inhibited recurrence in 4T1 tumor-bearing mice (**Table 2**). Additionally, the Raman imaging response of PDDA allowed visualization of the hydrogel degradation process, enabling precise control of drug release [163].

Cancer vaccines developed from tumor cells represent another promising approach to cancer immunotherapy. Autologous tumor cells obtained from patients can release specific antigens for personalized immunotherapy [164, 165]. Tingting Wang [166] developed a personalized cancer vaccine (PVAX) loaded with JQ1 (a BRD4 inhibitor) and ICG within a hydrogel matrix derived from tumor cells. The controlled release of tumor-specific antigens and JQ1, triggered by NIR light, effectively induces anti-tumor immunity and block PD-L1-dependent immune evasion, thereby preventing tumor recurrence after BC surgery (**Figure 5**). Yi Lu [167] introduced an innovative hydrogel vaccine system that incorporates granulocyte-macrophage colony-stimulating factor (GM-CSF) with lysates from surgically excised tumor cells. This personalized tumor lysate-derived hydrogel (PTLDH) was formulated by crosslinking the tumor cell lysates with alginate at low temperatures. GM-CSF is gradually released from the hydrogel, attracting DCs to this unique tumor antigen reservoir. These DCs take up the personalized tumor antigens from PTLAH, effectively initiating multi-antigen specific T cells for the precise elimination of residual tumor cells. The hydrogel enhances the therapeutic effect of αPD-L1 and demonstrates excellent efficacy in preventing tumor recurrence (**Table 2**).

The presence of a large number of suppressor cells and cytokines in TME is detrimental to the activation of immune cells within tumors. Enhancing the immunogenicity of tumor vaccines in a manner that aligns with the TME is key to improving the anti-tumor vaccine response and inhibiting breast tumor recurrence. Wendi Huo [168] developed a $CaCO_3$ biomineralized hydrogel DCs vaccine, incorporating membrane proteins from 4T1cell-DCs fusion cells (FP) into a biomineralized silk fibroin hydrogel framework. This vaccine, labeled SH@FP@$CaCO_3$, enhances immunogenicity by providing a broad array of tumor-associated antigens (TAAs) and ensuring sustained protein release, which is cruical for DCs maturation and T cells activation. Additionally, the inclusion of $CaCO_3$ adjusts the pH level of the TME, facilitating the transition from M2-type to M1-type macrophages. This shift counteracts the immunosuppressive TME and reduces its impact on T cells, offering a dual-mode mechanism to strengthen the immune response against cancer. The biomineralized hydrogel vaccine demonstrates excellent immune activation effects by simultaneously enhancing the immunogenicity and reversing the immunosuppressive TME (**Table 2**).

DCs are the most potent antigen-presenting cells (APCs), and vaccines targeting DCs have the potential to induce strong immunity through the initiation and enhancement pathways. Trichosanthin, a plant-derived protein, has demonstrated cancer immune-stimulation properties. Guihua Chen [169] developed a protein vaccine, termed TLM, incorporating trichostatin as an adjuvant and the legumain domain as a peptidic antigen. Additionally, they chemically modified this vaccine with mannose to specifi-

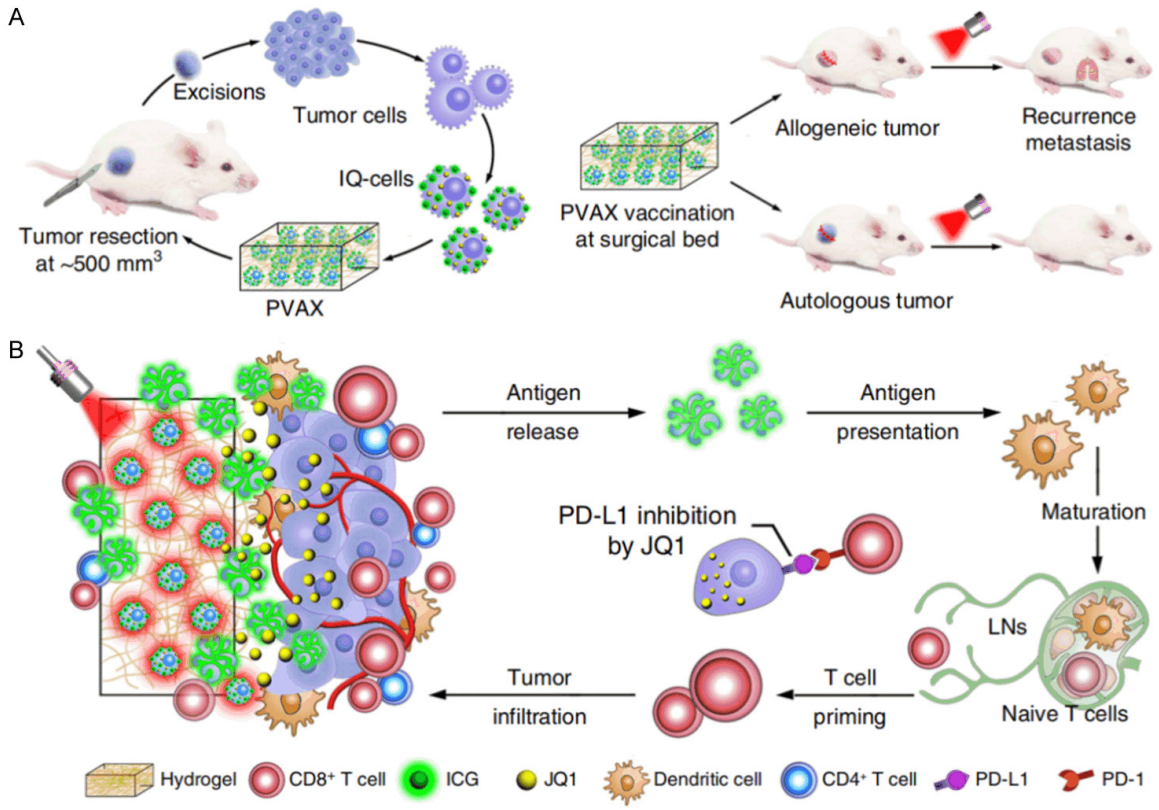

Figure 5. Schematic illustration of fabrication of PVAX for cancer immunotherapy [166].

cally target DCs. The vaccine was then loaded into a temperature-sensitive hydrogel based on Pluronic F127 for implantation at the postoperation site. The PF127-MTL hydrogel, with its temperature-sensitive properties, not only inhibitied tumor recurrence but also prevented lung metastasis of BC (**Table 2**).

Given the immunosuppressive conditions often observed following surgery, combining PTT with immunotherapy holds considerable promise for managing local recurrence and metastasis post-surgery. Yan Peng Jia [170] developed a locally injectable therapeutic platform based on a thermosensitive PDLLA-PEG-PDLLA (PLEL) hydrogel with NIR-stimulated drug release (**Figure 6**). The RIC NIPs, a novel multifunctional nanoparticle formulation, integrates three therapeutic agents: indocyanine green for photothermal action, resiquimod (R848) as a TLR-7/8 stimulant, and CpG ODNs as a TLR-9 activator. These nanoparticles are seamlessly incorporated into a thermosensitive PLEL hydrogel. Upon local injection into the post-surgical tumor cavity, the RIC NPs encapsulated within the PLEL hydrogel (RIC NPs@PLEL) perform targeted photothermal therapy to eradicate residual tumor cells and release tumor-associated antigens. Demonstrating superior biocompatibility both *in vitro* and *in vivo*, this hydrogel, through photothermal ablation and its immunoadjuvant properties, effectively suppresses lung metastasis and stimulates a potent immune defense, thereby preventing BC recurrence (**Table 2**).

Cyclic dinucleotides (CDNs) are a promising class of immunostimulants that activate the stimulator of interferon genes (STING), thereby initiating both innate and adaptive immune responses. Cunguo Chen [21] developed a novel immunotherapy approach using injectable hydrogels that respond to ROS. The hydrogel is designed to release 5,6-dimethylxanthenone-4-acetic acid (DMXAA), an agent that activates the STING pathway, along with ICG, leveraging high ROS levels within the TME. By combining the STING agonist with PTT, this approach not only enhances the biological performance of DMXAA but also transforms the suppressive TME into an immunogenic environment conducive to tumor destruction. The

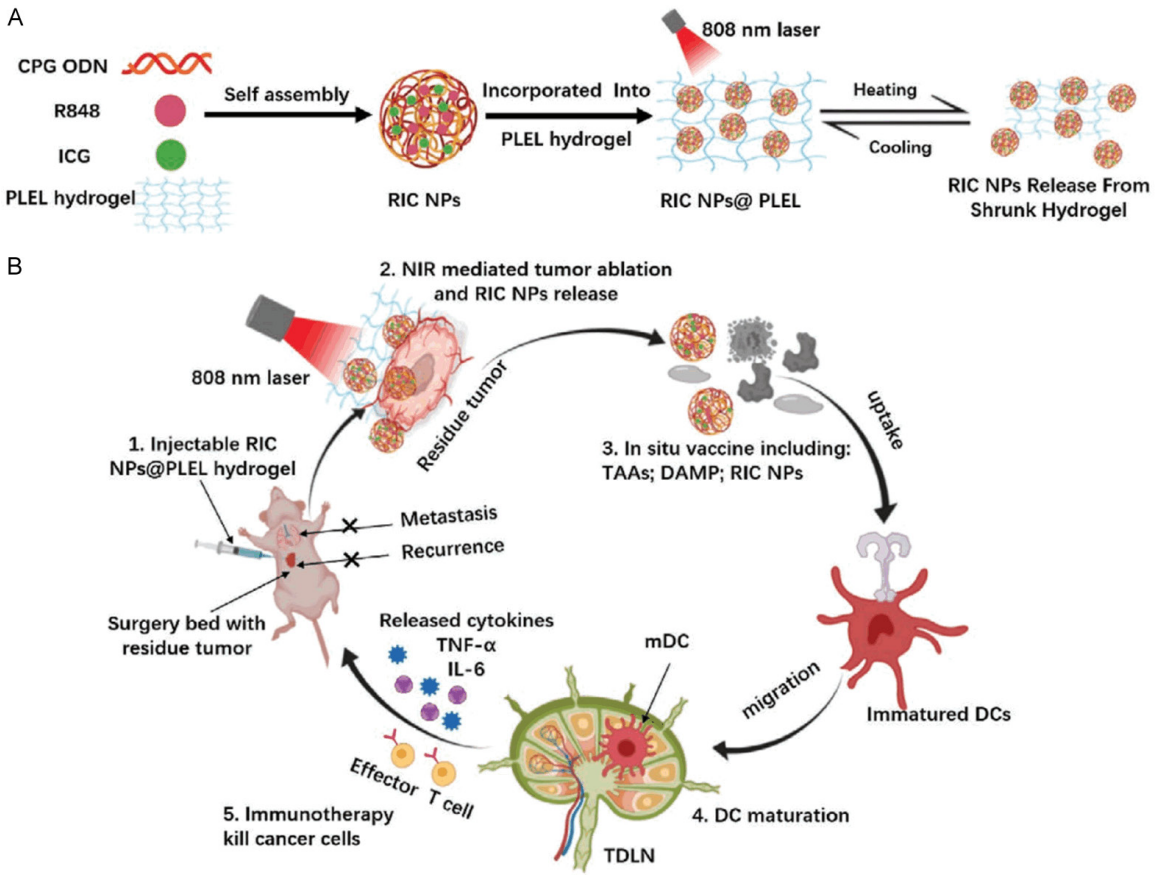

Figure 6. Schematic illustration of (A) the preparation process of RIC NPs@PLEL hydrogels and (B) photothermal-immune therapy to prevent post-surgery tumor recurrence [170].

hydrogels, known for their robust mechanical properties, biocompatibility, and biodegradability, enable a sustained release of therapeutic agents by utilizing the ROS concentration at tumor sites. Integrating this delivery system with physical tumor ablation and immunotherapy may significantly improve clinical response rate (**Table 2**).

Gamma-delta (γδ) T cells, which are part of the innate-like T cell family, have gained recognition as a promising approach for specifically targeting tumors in cancer therapy. Xin Shou [171] developed an innovative hydrogel particle that mimics γδ T cells, showing potential for BC immunotherapy. This particle is created by embedding black phosphorus quantum dots (BPQDs) into a N-isopropyl acrylamide (NIPAM) pre-gel solution, then using this mixture to create a negative of the structure of silica colloidal crystal beads (SCCBs), resulting in a porous scaffold. These BPQDs-doped pNIPAM hydrogel particles, when loaded with zoledronate, not only support the growth and activation of γδ T cells but also significantly reduce tumor size in nude mice experiments, highlighting their potential as a comprehensive platform for cancer treatment (**Table 2**).

Gasdermin E (GSDME) is a tumor suppressor gene associated with pyroptosis-mediated cell death [172]. GSDME converts non-inflammatory apoptosis into inflammatory pyroptosis [173]. The potential of pyroptosis lies in the release of immunogenic molecules that contribute to both the primary and memory anti-tumor immune response [174]. Dandan Mi [175] developed a photopolymerized hydrogel using poly (ethylene glycol) dimethacrylate (PEG-DMA) and sericin methacryloyl (SER-MA) for postoperative BC treatment. The hydrogel, loaded with the DNA methylation inhibitor decitabine (DEC) and gambogic acid (GA) encapsulated in poly (lactic-co-glycolic acid), facilitates rapid DEC release and sustained GA release, inducing GSDME-mediated pyroptosis in tumor cells.

This mechanism not only directly targets tumor cells but also stimulates an immune response that helps prevent tumor recurrence and lung metastasis, making the hydrogel a powerful tool for managing surgical wounds and reducing the risk of cancer recurrence in BC treatment (**Table 2**).

Conclusion

Postoperative treatment of BC still faces significant challenges due to different mechanisms of tumor recurrence. Hydrogel-based cancer therapeutic platforms have gained much attention due to their superior characteristics. This paper reviewed the effects of surgery on promoting postoperative metastasis in BC. Postoperative residual breast tumor cells in situ become more invasive to normal tissues due to EMT and cytokines secreted by macrophages. Various systemic changes induced by surgery can help CTCs survive and metastasize to different degrees. The postoperative inflammatory response creates a state of systemic immunosuppression similar to the tumor microenvironment, enabling tumor cells to evade the immune system. We also summarized various principles and synthetic methods for constructing hydrogels used in postoperative BC treatment, including local chemotherapy, immunotherapy, PTT, PDT, CDT, and multimodal combinations.

In terms of synthetic design of hydrogels, we have found that to achieve injectability, the material composition of most current hydrogels tends to favor organic/inorganic synthesis using known materials. However, the superior biocompatibility and tissue regeneration benefits of natural hydrogels cannot be overlooked. Modifying natural hydrogels can achieve ideal drug delivery properties, allowing the desired structural features to be obtained while retaining the benefits of the natural material. Moreover, most hydrogel drug delivery designs focus primarily on drug loading, with the hydrogel itself serving only as a passive carrier. The functional design of the hydrogel itself (such as responsive drug release) is often neglected. It is noteworthy that hydrogel drug delivery systems for multimodal combination therapy are gaining increasing attention. Various photothermal agents not only enable combined PTT, but also act as a "key" to achieving controlled release of the loaded drug.

Note that when choosing a type of treatment, most chemotherapeutic drugs have serious toxic side effects and can even compromise the body's immune system, making them unsuitable for use in the perioperative period. However, a single short-term dose of cyclophosphamide or anthracycline during the postoperative period has been shown to improve the long-term survival of cancer patients. Researchers should consider the postoperative period when designing a localized chemotherapy hydrogel loaded with a drug, whether the hydrogel is intended for immediate postoperative use or for identifying the appropriate timing for administration through models. Immunotherapy hydrogel avoids the use of chemotherapy drugs during the perioperative period. However, literature indicates that the posttraumatic inflammatory response, inflammation resolution, and tissue repair are sequential processes that provide physiologic protection to the body. Interfering with this process through immunotherapy during the perioperative period may lead to excessive inflammation and its harmful effects. Current hydrogels for immunotherapy primarily focus on activating the immune response by applying immune inhibitors or inducing ICD to activate T cells, DCs, or macrophages. Additionally, NETs play a crucial role in the body's immune response, but NETs-based immunotherapy hydrogels are rarely discussed. In future studies, researchers evaluating the design of hydrogel experiments should not only focus on pharmacodynamics but also consider whether the mechanism of action of the hydrogel affects the body's inflammation resolution and wound repair processes. It is also recommended that they systematically evaluate the mechanism of action at all stages of drug efficacy to fully demonstrate the safety and effcetiveness of their hydrogel designs.

Despite the step-by-step progress made in applying hydrogel technology for BC treatment, further research is required before these technologies can be widely adopted in clinical practice. Currently, most therapeutic strategies involving hydrogels target only specific stages of tumor cell metastasis. To more effectively prevent the spread of breast cancer, it is essential to broaden the focus of research to encompass the entire metastatic process. By leveraging the multi-drug loading capacity of hydrogels, it may possible to inhibit tumor cell metastasis at various stages, thus blocking the spread

more comprehensively. Hydrogel therapy for BC presents a platform with tremendous potential, but correct, rational, and safe application in clinical settings will require improvements in standardization. Furthermore, the successful application of hydrogels depends on a comprehensive understanding of their *in vivo* behavior, including biocompatibility, degradation rate, and the safety of degradation byproducts. Ensuring that hydrogels degrade safely in the body without causing toxicity or immune reactions is crucial for their clinical use. At the same time, the production processes for hydrogels must be scalable to meet clinical demands, while maintaining consistent quality and performance in large-scale manufacturing. Beyond drug delivery, hydrogels can also serve as carriers for gene therapy, immune modulators, or other bioactive substances, allowing for intervention at multiple levels of tumor progression and metastasis. Combining hydrogels with other treatments, such as radiation, chemotherapy, targeted therapies and immunotherapy, could significantly enhance overall treatment outcome and overcome the limitations and resistance associated with monotherapy. Moreover, future research should prioritize the development of personalized hydrogel-based therapies tailored to the unique characteristics of a patient's tumor. This approach may involve integrating biomarker-driven strategies to precisely target metastatic cells while minimizing side effects.

As our understanding of the tumor microenvironment and metastatic pathways deepens, the design of hydrogel systems can evolve not only to deliver chemotherapeutics but also to carry immune modulators, gene therapies, or RNA-based treatments. These advancements may dramatically improve outcomes for BC patients, particularly those with advanced or refractory disease. However, achieving these goals will require rigorous preclinical testing followed by well-designed clinical trials to ensure the safety and efficacy of hydrogel-based interventions across diverse patient populations. Only through a multidisciplinary, integrated approach can hydrogel therapy fulfill its promise.

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Disclosure of conflict of interest

None.

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References

[1] Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. N Engl J Med 2020; 383: 2557-2570.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.

[3] Waks AG and Winer EP. Breast cancer treatment: a review. JAMA 2019; 321: 288-300.

[4] DeSantis CE, Miller KD, Goding Sauer A, Jemal A and Siegel RL. Cancer statistics for African Americans, 2019. CA Cancer J Clin 2019; 69: 211-233.

[5] Demicheli R, Retsky MW, Hrushesky WJ, Baum M and Gukas ID. The effects of surgery on tumor growth: a century of investigations. Ann Oncol 2008; 19: 1821-1828.

[6] Ceelen W, Pattyn P and Mareel M. Surgery, wound healing, and metastasis: recent insights and clinical implications. Crit Rev Oncol Hematol 2014; 89: 16-26.

[7] Al-Sahaf O, Wang JH, Browne TJ, Cotter TG and Redmond HP. Surgical injury enhances the expression of genes that mediate breast cancer metastasis to the lung. Ann Surg 2010; 252: 1037-1043.

[8] Costa A, Kieffer Y, Scholer-Dahirel A, Pelon F, Bourachot B, Cardon M, Sirven P, Magagna I, Fuhrmann L, Bernard C, Bonneau C, Kondratova M, Kuperstein I, Zinovyev A, Givel AM, Parrini MC, Soumelis V, Vincent-Salomon A and Mechta-Grigoriou F. Fibroblast heterogeneity and immunosuppressive environment in human breast cancer. Cancer Cell 2018; 33: 463-479, e10.

[9] Raa ST, Oosterling SJ, Van Der Kaaij NP, Van Den Tol MP, Beelen RH, Meijer S, Van Eijck CH, Van Der Sijp JR, Van Egmond M and Jeekel J. Surgery promotes implantation of disseminated tumor cells, but does not increase growth of tumor cell clusters. J Surg Oncol 2005; 92: 124-129.

[10] Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somer-

field MR and Davidson NE; American Society of Clinical Oncology. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006; 24: 5091-5097.

[11] Fisher B, Slack NH, Cavanaugh PJ, Gardner B and Ravdin RG. Postoperative radiotherapy in the treatment of breast cancer: results of the NSABP clinical trial. Ann Surg 1970; 172: 711-732.

[12] Mehlen P and Puisieux A. Metastasis: a question of life or death. Nat Rev Cancer 2006; 6: 449-458.

[13] Tellini R, Antonelli A, Palumbo C, Veccia A, Furlan M, Tardanico R, Fisogni S and Simeone C. Positive surgical margins predict progression-free survival after nephron sparing surgery for renal cell carcinoma: results from a single centre cohort of almost 500 cases with a minimum follow-up of 5 years. J Urol 2018; 199: E624-E624.

[14] Shi Y and Lammers T. Combining nanomedicine and immunotherapy. Acc Chem Res 2019; 52: 1543-1554.

[15] Xu J, Xu L, Wang C, Yang R, Zhuang Q, Han X, Dong Z, Zhu W, Peng R and Liu Z. Near-infrared-triggered photodynamic therapy with multitasking upconversion nanoparticles in combination with checkpoint blockade for immunotherapy of colorectal cancer. Acs Nano 2017; 11: 4463-4474.

[16] Peng JR, Yang Q, Xiao Y, Shi K, Liu QY, Hao Y, Yang F, Han RX and Qian ZY. Tumor microenvironment responsive drug-dye-peptide nanoassembly for enhanced tumor-targeting, penetration, and photo-chemo-immunotherapy. Adv Funct Mater 2019; 29: 16.

[17] Liu S, Jiang Q, Zhao X, Zhao R, Wang Y, Wang Y, Liu J, Shang Y, Zhao S, Wu T, Zhang Y, Nie G and Ding B. A DNA nanodevice-based vaccine for cancer immunotherapy. Nat Mater 2021; 20: 421-430.

[18] Hu Z, Ott PA and Wu CJ. Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nat Rev Immunol 2018; 18: 168-182.

[19] Wang T, Wang D, Yu H, Feng B, Zhou F, Zhang H, Zhou L, Jiao S and Li Y. A cancer vaccine-mediated postoperative immunotherapy for recurrent and metastatic tumors. Nat Commun 2018; 9: 1532.

[20] Sanchez-Martinez D, Baroni ML, Gutierrez-Aguera F, Roca-Ho H, Blanch-Lombarte O, Gonzalez-Garcia S, Torrebadell M, Junca J, Ramirez-Orellana M, Velasco-Hernandez T, Bueno C, Fuster JL, Prado JG, Calvo J, Uzan B, Cools J, Camos M, Pflumio F, Toribio ML and Menendez P. Fratricide-resistant CD1a-specific CAR T cells for the treatment of cortical T-cell acute lymphoblastic leukemia. Blood 2019; 133: 2291-2304.

[21] Chen C, Hu M, Cao Y, Zhu B, Chen J, Li Y, Shao J, Zhou S, Shan P, Zheng C, Li Z and Li Z. Combination of a STING agonist and photothermal therapy using chitosan hydrogels for cancer immunotherapy. Biomacromolecules 2023; 24: 2790-2803.

[22] Seitz CM, Mittelstaet J, Atar D, Hau J, Reiter S, Illi C, Kieble V, Engert F, Drees B, Bender G, Krahl AC, Knopf P, Schroeder S, Paulsen N, Rokhvarguer A, Scheuermann S, Rapp E, Mast AS, Rabsteyn A, Schleicher S, Grote S, Schilbach K, Kneilling M, Pichler B, Lock D, Kotter B, Dapa S, Miltenyi S, Kaiser A, Lang P, Handgretinger R and Schlegel P. Novel adapter CAR-T cell technology for precisely controllable multiplex cancer targeting. Oncoimmunology 2021; 10: 2003532.

[23] Huang J, Yang B, Peng Y, Huang JS, Wong SHD, Bian LM, Zhu KS, Shuai XT and Han SS. Nanomedicine-boosting tumor immunogenicity for enhanced immunotherapy. Adv Funct Mater 2021; 31: 2011171.

[24] Nam J, Son S, Park KS, Zou WP, Shea LD and Moon JJ. Cancer nanomedicine for combination cancer immunotherapy. Nat Rev Mater 2019; 4: 398-414.

[25] Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, Zhang W, Luoma A, Giobbie-Hurder A, Peter L, Chen C, Olive O, Carter TA, Li S, Lieb DJ, Eisenhaure T, Gjini E, Stevens J, Lane WJ, Javeri I, Nellaiappan K, Salazar AM, Daley H, Seaman M, Buchbinder EI, Yoon CH, Harden M, Lennon N, Gabriel S, Rodig SJ, Barouch DH, Aster JC, Getz G, Wucherpfennig K, Neuberg D, Ritz J, Lander ES, Fritsch EF, Hacohen N and Wu CJ. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017; 547: 217-221.

[26] Rodell CB, MacArthur JW, Dorsey SM, Wade RJ, Wang LL, Woo YJ and Burdick JA. Shear-thinning supramolecular hydrogels with secondary autonomous covalent crosslinking to modulate viscoelastic properties in vivo. Adv Funct Mater 2015; 25: 636-644.

[27] Moses MA, Brem H and Langer R. Advancing the field of drug delivery: taking aim at cancer. Cancer Cell 2003; 4: 337-341.

[28] Omtvedt LA, Kristiansen KA, Strand WI, Aachmann FL, Strand BL and Zaytseva-Zotova DS. Alginate hydrogels functionalized with beta-cyclodextrin as a local paclitaxel delivery system. J Biomed Mater Res A 2021; 109: 2625-2639.

[29] Graham-Gurysh EG, Moore KM, Schorzman AN, Lee T, Zamboni WC, Hingtgen SD, Bachelder EM and Ainslie KM. Tumor responsive and tunable polymeric platform for optimized delivery of paclitaxel to treat glioblastoma. ACS Appl Mater Interfaces 2020; 12: 19345-19356.

[30] Khodadadi M, Alijani S, Montazeri M, Esmaeilizadeh N, Sadeghi-Soureh S and Pilehvar-Soltanahmadi Y. Recent advances in electrospun nanofiber-mediated drug delivery strategies for localized cancer chemotherapy. J Biomed Mater Res A 2020; 108: 1444-1458.
[31] Naahidi S, Jafari M, Logan M, Wang Y, Yuan Y, Bae H, Dixon B and Chen P. Biocompatibility of hydrogel-based scaffolds for tissue engineering applications. Biotechnol Adv 2017; 35: 530-544.
[32] Sun Z, Song C, Wang C, Hu Y and Wu J. Hydrogel-based controlled drug delivery for cancer treatment: a review. Mol Pharm 2020; 17: 373-391.
[33] Miranda CS, Ribeiro ARM, Homem NC and Felgueiras HP. Spun biotextiles in tissue engineering and biomolecules delivery systems. Antibiotics (Basel) 2020; 9: 174.
[34] Shao J, Ruan C, Xie H, Li Z, Wang H, Chu PK and Yu XF. Black-phosphorus-incorporated hydrogel as a sprayable and biodegradable photothermal platform for postsurgical treatment of cancer. Adv Sci (Weinh) 2018; 5: 1700848.
[35] Zhao S, Zhang L, Deng L, Ouyang J, Xu Q, Gao X, Zeng Z and Liu YN. NIR-II responsive hydrogel as an angiogenesis inhibition agent for tumor microenvironment reprogramming. Small 2021; 17: e2103003.
[36] Liang Y, Hao Y, Wu Y, Zhou Z, Li J, Sun X and Liu YN. Integrated hydrogel platform for programmed antitumor therapy based on near infrared-triggered hyperthermia and vascular disruption. ACS Appl Mater Interfaces 2019; 11: 21381-21390.
[37] Wang S, Zhang Z, Wei S, He F, Li Z, Wang HH, Huang Y and Nie Z. Near-infrared light-controllable MXene hydrogel for tunable on-demand release of therapeutic proteins. Acta Biomater 2021; 130: 138-148.
[38] Zheng Y, Wang W, Zhao J, Wu C, Ye C, Huang M and Wang S. Preparation of injectable temperature-sensitive chitosan-based hydrogel for combined hyperthermia and chemotherapy of colon cancer. Carbohydr Polym 2019; 222: 115039.
[39] He Y, Yuan T, Wang X, Shen M, Ding L, Huang L, Wang S, Kong P, Zhou X, Duan Y and Cao J. Temperature sensitive hydrogel for preoperative treatment of renal carcinoma. Mater Sci Eng C Mater Biol Appl 2020; 111: 110798.
[40] Lin CW, Tseng SJ, Kempson IM, Yang SC, Hong TM and Yang PC. Extracellular delivery of modified oligonucleotide and superparamagnetic iron oxide nanoparticles from a degradable hydrogel triggered by tumor acidosis. Biomaterials 2013; 34: 4387-4393.
[41] Wang H, Yi J, Mukherjee S, Banerjee P and Zhou S. Magnetic/NIR-thermally responsive hybrid nanogels for optical temperature sensing, tumor cell imaging and triggered drug release. Nanoscale 2014; 6: 13001-13011.
[42] Zhao Z, Shen J, Zhang L, Wang L, Xu H, Han Y, Jia J, Lu Y, Yu R and Liu H. Injectable postoperative enzyme-responsive hydrogels for reversing temozolomide resistance and reducing local recurrence after glioma operation. Biomater Sci 2020; 8: 5306-5316.
[43] Barros da Silva P, Coelho M, Bidarra SJ, Neves SC and Barrias CC. Reshaping in vitro models of breast tissue: integration of stromal and parenchymal compartments in 3D printed hydrogels. Front Bioeng Biotechnol 2020; 8: 494.
[44] Conci C, Bennati L, Bregoli C, Buccino F, Danielli F, Gallan M, Gjini E and Raimondi MT. Tissue engineering and regenerative medicine strategies for the female breast. J Tissue Eng Regen Med 2020; 14: 369-387.
[45] Jain S, Yassin MA, Fuoco T, Liu H, Mohamed-Ahmed S, Mustafa K and Finne-Wistrand A. Engineering 3D degradable, pliable scaffolds toward adipose tissue regeneration; optimized printability, simulations and surface modification. J Tissue Eng 2020; 11: 20417314-20954316.
[46] Varma DM, Gold GT, Taub PJ and Nicoll SB. Injectable carboxymethylcellulose hydrogels for soft tissue filler applications. Acta Biomater 2014; 10: 4996-5004.
[47] Aquil A, El Kherchi O, El Azmaoui N, Mouallif M, Guerroumi M, Benider A and Elgot A. Predictors of mental health disorders in women with breast and gynecological cancer after radical surgery: a cross-sectional study. Ann Med Surg (Lond) 2021; 65: 102278.
[48] Maass SW, Roorda C, Berendsen AJ, Verhaak PF and de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. Maturitas 2015; 82: 100-108.
[49] Jacob L, Bleicher L, Kostev K and Kalder M. Prevalence of depression, anxiety and their risk factors in German women with breast cancer in general and gynecological practices. J Cancer Res Clin Oncol 2016; 142: 447-452.
[50] Yang YL, Liu L, Wang XX, Wang Y and Wang L. Prevalence and associated positive psychological variables of depression and anxiety among Chinese cervical cancer patients: a cross-sectional study. PLoS One 2014; 9: e94804.
[51] Yang X, Gao L, Wei Y, Tan B, Wu Y, Yi C and Liao J. Photothermal hydrogel platform for prevention of post-surgical tumor recurrence and improving breast reconstruction. J Nanobiotechnology 2021; 19: 307.
[52] Nieto MA. Epithelial plasticity: a common theme in embryonic and cancer cells. Science 2013; 342: 1234850.

[53] Thiery JP, Acloque H, Huang RY and Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell 2009; 139: 871-890.
[54] Kalluri R and Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest 2009; 119: 1420-1428.
[55] Zheng H, Shen M, Zha YL, Li W, Wei Y, Blanco MA, Ren G, Zhou T, Storz P, Wang HY and Kang Y. PKD1 phosphorylation-dependent degradation of SNAIL by SCF-FBXO11 regulates epithelial-mesenchymal transition and metastasis. Cancer Cell 2014; 26: 358-373.
[56] Labelle M, Begum S and Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011; 20: 576-590.
[57] Condeelis J and Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006; 124: 263-266.
[58] Yang L, Huang J, Ren X, Gorska AE, Chytil A, Aakre M, Carbone DP, Matrisian LM, Richmond A, Lin PC and Moses HL. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. Cancer Cell 2008; 13: 23-35.
[59] Gao D, Joshi N, Choi H, Ryu S, Hahn M, Catena R, Sadik H, Argani P, Wagner P, Vahdat LT, Port JL, Stiles B, Sukumar S, Altorki NK, Rafii S and Mittal V. Myeloid progenitor cells in the premetastatic lung promote metastases by inducing mesenchymal to epithelial transition. Cancer Res 2012; 72: 1384-1394.
[60] Clark AG and Vignjevic DM. Modes of cancer cell invasion and the role of the microenvironment. Curr Opin Cell Biol 2015; 36: 13-22.
[61] Lopez-Novoa JM and Nieto MA. Inflammation and EMT: an alliance towards organ fibrosis and cancer progression. EMBO Mol Med 2009; 1: 303-314.
[62] Roussos ET, Condeelis JS and Patsialou A. Chemotaxis in cancer. Nat Rev Cancer 2011; 11: 573-587.
[63] Karaman S and Detmar M. Mechanisms of lymphatic metastasis. J Clin Invest 2014; 124: 922-928.
[64] de Boer M, van Dijck JA, Bult P, Borm GF and Tjan-Heijnen VC. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. J Natl Cancer Inst 2010; 102: 410-425.
[65] Tvedskov TF, Jensen MB, Kroman N and Balslev E. Iatrogenic displacement of tumor cells to the sentinel node after surgical excision in primary breast cancer. Breast Cancer Res Treat 2012; 131: 223-229.
[66] Douma S, Van Laar T, Zevenhoven J, Meuwissen R, Van Garderen E and Peeper DS. Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. Nature 2004; 430: 1034-9.
[67] Mackman N, Tilley RE and Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscler Thromb Vasc Biol 2007; 27: 1687-1693.
[68] Amirkhosravi A, Mousa SA, Amaya M, Blaydes S, Desai H, Meyer T and Francis JL. Inhibition of tumor cell-induced platelet aggregation and lung metastasis by the oral GpIIb/IIIa antagonist XV454. Thromb Haemost 2003; 90: 549-554.
[69] Avtaeva YN, Mel'nikov IS, Saburova OS, Guriya KG, Osidak MC, Domogatsky CP and Gabbasov ZA. Complex interaction of platelets, von Willebrand factor and leukocytes, in whole blood at high shear rates is mediated by platelet GPIIb/IIIa receptor. Bull Exp Biol Med 2021; 171: 588-591.
[70] Nierodzik ML and Karpatkin S. Thrombin induces tumor growth, metastasis, and angiogenesis: evidence for a thrombin-regulated dormant tumor phenotype. Cancer Cell 2006; 10: 355-362.
[71] Nierodzik ML, Klepfish A and Karpatkin S. Role of platelets, thrombin, integrin IIb-IIIa, fibronectin and von Willebrand factor on tumor adhesion in vitro and metastasis in vivo. Thromb Haemost 1995; 74: 282-90.
[72] Gay LJ and Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011; 11: 123-134.
[73] Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, Fabra R and Heinrich PC. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Lett 1989; 242: 237-9.
[74] Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, Jirouskova M and Degen JL. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 2005; 105: 178-185.
[75] Seth R, Tai LH, Falls T, de Souza CT, Bell JC, Carrier M, Atkins H, Boushey R and Auer RA. Surgical stress promotes the development of cancer metastases by a coagulation-dependent mechanism involving natural killer cells in a murine model. Ann Surg 2013; 258: 158-168.
[76] Kopp HG, Placke T and Salih HR. Platelet-derived transforming growth factor-beta down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer Res 2009; 69: 7775-7783.

[77] Viel S, Marcais A, Guimaraes FS, Loftus R, Rabilloud J, Grau M, Degouve S, Djebali S, Sanlaville A, Charrier E, Bienvenu J, Marie JC, Caux C, Marvel J, Town L, Huntington ND, Bartholin L, Finlay D, Smyth MJ and Walzer T. TGF-beta inhibits the activation and functions of NK cells by repressing the mTOR pathway. Sci Signal 2016; 9: ra19.

[78] Cho MS, Bottsford-Miller J, Vasquez HG, Stone R, Zand B, Kroll MH, Sood AK and Afshar-Kharghan V. Platelets increase the proliferation of ovarian cancer cells. Blood 2012; 120: 4869-4872.

[79] Velez J, Enciso LJ, Suarez M, Fiegl M, Grismaldo A, López C, Barreto A, Cardozo C, Palacios P, Morales L, Duque JE, Carmona JU, Konopleva M, Andreeff M and Samudio I. Platelets promote mitochondrial uncoupling and resistance to apoptosis in leukemia cells: a novel paradigm for the bone marrow microenvironment. Cancer Microenviron 2014; 7: 79-90.

[80] Padua D, Zhang XH, Wang Q, Nadal C, Gerald WL, Gomis RR and Massague J. TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell 2008; 133: 66-77.

[81] Qian B, Deng Y, Im JH, Muschel RJ, Zou Y, Li J, Lang RA and Pollard JW. A distinct macrophage population mediates metastatic breast cancer cell extravasation, establishment and growth. PLoS One 2009; 4: e6562.

[82] Malanchi I, Santamaria-Martinez A, Susanto E, Peng H, Lehr HA, Delaloye JF and Huelsken J. Interactions between cancer stem cells and their niche govern metastatic colonization. Nature 2011; 481: 85-9.

[83] Oskarsson T, Acharyya S, Zhang XH, Vanharanta S, Tavazoie SF, Morris PG, Downey RJ, Manova-Todorova K, Brogi E and Massague J. Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. Nat Med 2011; 17: 867-74.

[84] Chen Q, Zhang XH and Massague J. Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. Cancer Cell 2011; 20: 538-549.

[85] Gupta GP, Perk J, Acharyya S, de Candia P, Mittal V, Todorova-Manova K, Gerald WL, Brogi E, Benezra R and Massague J. ID genes mediate tumor reinitiation during breast cancer lung metastasis. Proc Natl Acad Sci U S A 2007; 104: 19506-19511.

[86] Quail DF and Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med 2013; 19: 1423-1437.

[87] Kitamura T, Qian BZ and Pollard JW. Immune cell promotion of metastasis. Nat Rev Immunol 2015; 15: 73-86.

[88] Mathenge EG, Dean CA, Clements D, Vaghar-Kashani A, Photopoulos S, Coyle KM, Giacomantonio M, Malueth B, Nunokawa A, Jordan J, Lewis JD, Gujar SA, Marcato P, Lee PW and Giacomantonio CA. Core needle biopsy of breast cancer tumors increases distant metastases in a mouse model. Neoplasia 2014; 16: 950-960.

[89] Predina J, Eruslanov E, Judy B, Kapoor V, Cheng G, Wang LC, Sun J, Moon EK, Fridlender ZG, Albelda S and Singhal S. Changes in the local tumor microenvironment in recurrent cancers may explain the failure of vaccines after surgery. Proc Natl Acad Sci U S A 2013; 110: E415-24.

[90] Shakhar G and Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann Surg Oncol 2003; 10: 972-992.

[91] Bartal I, Melamed R, Greenfeld K, Atzil S, Glasner A, Domankevich V, Naor R, Beilin B, Yardeni IZ and Ben-Eliyahu S. Immune perturbations in patients along the perioperative period: alterations in cell surface markers and leukocyte subtypes before and after surgery. Brain Behav Immun 2010; 24: 376-386.

[92] Ananth AA, Tai LH, Lansdell C, Alkayyal AA, Baxter KE, Angka L, Zhang J, Tanese de Souza C, Stephenson KB, Parato K, Bramson JL, Bell JC, Lichty BD and Auer RC. Surgical stress abrogates pre-existing protective T cell mediated anti-tumor immunity leading to postoperative cancer recurrence. PLoS One 2016; 11: e0155947.

[93] Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Che X, Iwashige H, Aridome K, Hokita S and Aikou T. Prognostic value of intratumoral natural killer cells in gastric carcinoma. Cancer 2000; 88: 577-583.

[94] Coca S, Perez-Piqueras J, Martinez D, Colmenarejo A, Saez MA, Vallejo C, Martos JA and Moreno M. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer 1997; 79: 2320-2328.

[95] Pasero C, Gravis G, Granjeaud S, Guerin M, Thomassin-Piana J, Rocchi P, Salem N, Walz J, Moretta A and Olive D. Highly effective NK cells are associated with good prognosis in patients with metastatic prostate cancer. Oncotarget 2015; 6: 14360-14373.

[96] Angka L, Martel AB, Kilgour M, Jeong A, Sadiq M, de Souza CT, Baker L, Kennedy MA, Kekre N and Auer RC. Natural killer cell IFN gamma secretion is profoundly suppressed following colorectal cancer surgery. Ann Surg Oncol 2018; 25: 3747-3754.

[97] Sakaguchi S. Regulatory T cells: key controllers of immunologic self-tolerance. Cell 2000; 101: 455-8.
[98] Plitas G and Rudensky AY. Regulatory T cells in cancer. Annu Rev Cancer Biol 2020; 4: 459-477.
[99] Takeuchi Y and Nishikawa H. Roles of regulatory T cells in cancer immunity. Int Immunol 2016; 28: 401-409.
[100] Ohue Y and Nishikawa H. Regulatory T (Treg) cells in cancer: can treg cells be a new therapeutic target? Cancer Sci 2019; 110: 2080-2089.
[101] Bakos O, Lawson C, Rouleau S and Tai LH. Combining surgery and immunotherapy: turning an immunosuppressive effect into a therapeutic opportunity. J Immunother Cancer 2018; 6: 86.
[102] Tumis ME, Sawant DV, Szymczak-Workman AL, Andrews LP, Delgoffe GM, Yano H, Beres AJ, Vogel P, Workman CJ and Vignali DA. Interleukin-35 limits anti-tumor immunity. Immunity 2016; 44: 316-329.
[103] Sawant DV, Yano H, Chikina M, Zhang Q, Liao M, Liu C, Callahan DJ, Sun Z, Sun T, Tabib T, Pennathur A, Corry DB, Luketich JD, Lafyatis R, Chen W, Poholek AC, Bruno TC, Workman CJ and Vignali DAA. Adaptive plasticity of IL-10(+) and IL-35(+) T-reg cells cooperatively promotes tumor T cell exhaustion. Nat Immunol 2019; 20: 724-735.
[104] Grütz G. New insights into the molecular mechanism of interleukin-10-mediated immunosuppression. J Leukoc Biol 2005; 77: 3-15.
[105] Gorelik L, Constant S and Flavell RA. Mechanism of transforming growth factor β-induced inhibition of T helper type 1 differentiation. J Exp Med 2002; 195: 1499-1505.
[106] Cao X, Cai SF, Fehniger TA, Song J, Collins LI, Piwnica-Worms DR and Ley TJ. Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity 2007; 27: 635-646.
[107] de Oliveira S, Rosowski EE and Huttenlocher A. Neutrophil migration in infection and wound repair: going forward in reverse. Nat Rev Immunol 2016; 16: 378-391.
[108] Kruger P, Saffarzadeh M, Weber AN, Rieber N, Radsak M, von Bernuth H, Benarafa C, Roos D, Skokowa J and Hartl D. Neutrophils: between host defence, immune modulation, and tissue injury. PLoS Pathog 2015; 11: e1004651.
[109] Coffelt SB, Wellenstein MD and de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer 2016; 16: 431-446.
[110] Peiseler M and Kubes P. More friend than foe: the emerging role of neutrophils in tissue repair. J Clin Invest 2019; 129: 2629-2639.
[111] de Bont CM, Boelens WC and Pruijn GJM. NETosis, complement, and coagulation: a triangular relationship. Cell Mol Immunol 2019; 16: 19-27.
[112] Sorensen OE and Borregaard N. Neutrophil extracellular traps - the dark side of neutrophils. J Clin Invest 2016; 126: 1612-1620.
[113] Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y and Zychlinsky A. Neutrophil extracellular traps kill bacteria. Science 2004; 303: 1532-1535.
[114] Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, Bourdeau F, Kubes P and Ferri L. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. J Clin Invest 2013; 123: 3446-3458.
[115] Park J, Wysocki RW, Amoozgar Z, Maiorino L, Fein MR, Jorns J, Schott AF, Kinugasa-Katayama Y, Lee Y, Won NH, Nakasone ES, Hearn SA, Kuttner V, Qiu J, Almeida AS, Perurena N, Kessenbrock K, Goldberg MS and Egeblad M. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps. Sci Transl Med 2016; 8: 361ra138.
[116] Erpenbeck L and Schon MP. Neutrophil extracellular traps: protagonists of cancer progression? Oncogene 2017; 36: 2483-2490.
[117] Chen Q, Zhang L, Li X and Zhuo W. Neutrophil extracellular traps in tumor metastasis: pathological functions and clinical applications. Cancers (Basel) 2021; 13: 2832.
[118] Tohme S, Yazdani HO, Al-Khafaji AB, Chidi AP, Loughran P, Mowen K, Wang Y, Simmons RL, Huang H and Tsung A. Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress. Cancer Res 2016; 76: 1367-1380.
[119] Fan R, Sun W, Zhang T, Wang R, Tian Y, Zhang H, Li J, Zheng A and Song S. Paclitaxel-nanocrystals-loaded network thermosensitive hydrogel for localised postsurgical recurrent of breast cancer after surgical resection. Biomed Pharmacother 2022; 150: 113017.
[120] Zheng Z, Yang X, Zhang Y, Zu W, Wen M, Liu T, Zhou C and Li L. An injectable and pH-responsive hyaluronic acid hydrogel as metformin carrier for prevention of breast cancer recurrence. Carbohydr Polym 2023; 304: 120493.
[121] Wu H, Song L, Chen L, Zhang W, Chen Y, Zang F, Chen H, Ma M, Gu N and Zhang Y. Injectable magnetic supramolecular hydrogel with magnetocaloric liquid-conformal property prevents post-operative recurrence in a breast cancer model. Acta Biomater 2018; 74: 302-311.
[122] He H, Chen S, Zhou J, Dou Y, Song L, Che L, Zhou X, Chen X, Jia Y, Zhang J, Li S and Li X. Cyclodextrin-derived pH-responsive nanoparti-

cles for delivery of paclitaxel. Biomaterials 2013; 34: 5344-5358.
[123] Zhang Z, He Z, Liang R, Ma Y, Huang W, Jiang R, Shi S, Chen H and Li X. Fabrication of a micellar supramolecular hydrogel for ocular drug delivery. Biomacromolecules 2016; 17: 798-807.
[124] Gao F, Xie W, Miao Y, Wang D, Guo Z, Ghosal A, Li Y, Wei Y, Feng SS, Zhao L and Fan HM. Magnetic hydrogel with optimally adaptive functions for breast cancer recurrence prevention. Adv Healthc Mater 2019; 8: e1900203.
[125] Leitao MM, de Melo-Diogo D, Alves CG, Lima-Sousa R and Correia IJ. Prototypic heptamethine cyanine incorporating nanomaterials for cancer phototheragnostic. Adv Healthc Mater 2020; 9: e1901665.
[126] Chang M, Hou Z, Wang M, Li C and Lin J. Recent advances in hyperthermia therapy-based synergistic immunotherapy. Adv Mater 2021; 33: e2004788.
[127] Rohaizad N, Mayorga-Martinez CC, Fojtu M, Latiff NM and Pumera M. Two-dimensional materials in biomedical, biosensing and sensing applications. Chem Soc Rev 2021; 50: 619-657.
[128] Yang X, Gao L, Wei Y, Tan B, Wu Y, Yi C and Liao J. Photothermal hydrogel platform for prevention of post-surgical tumor recurrence and improving breast reconstruction. J Nanobiotechnology 2021; 19: 307.
[129] Liu M, Huang P, Wang W, Feng Z, Zhang J, Deng L and Dong A. An injectable nanocomposite hydrogel co-constructed with gold nanorods and paclitaxel-loaded nanoparticles for local chemo-photothermal synergetic cancer therapy. J Mater Chem B 2019; 7: 2667-2677.
[130] Wu Y, Yao Y, Zhang J, Gui H, Liu J and Liu J. Tumor-targeted injectable double-network hydrogel for prevention of breast cancer recurrence and wound infection via synergistic photothermal and brachytherapy. Adv Sci (Weinh) 2022; 9: e2200681.
[131] Hu Y, Chi C, Wang S, Wang L, Liang P, Liu F, Shang W, Wang W, Zhang F, Li S, Shen H, Yu X, Liu H and Tian J. A comparative study of clinical intervention and interventional photothermal therapy for pancreatic cancer. Adv Mater 2017; 29: 9.
[132] Huang H, Wang X, Wang W, Qu X, Song X, Zhang Y, Zhong L, Yang DP, Dong X and Zhao Y. Injectable hydrogel for postoperative synergistic photothermal-chemodynamic tumor and anti-infection therapy. Biomaterials 2022; 280: 121289.
[133] Yang T, Tang Y, Liu L, Lv X, Wang Q, Ke H, Deng Y, Yang H, Yang X, Liu G, Zhao Y and Chen H. Size-dependent Ag2S nanodots for second near-infrared fluorescence/photoacoustics imaging and simultaneous photothermal therapy. Acs Nano 2017; 11: 1848-1857.
[134] Li QZ, Zhang YW, Huang X, Yang DL, Weng LX, Ou CJ, Song XJ and Dong XC. An NIR-II light responsive antibacterial gelation for repetitious photothermal/thermodynamic synergistic therapy. Chem Eng J 2021; 407: 10.
[135] Zhou L, Xi YW, Xue YM, Wang M, Liu YL, Guo Y and Lei B. Injectable self-healing antibacterial bioactive polypeptide-based hybrid nanosystems for efficiently treating multidrug resistant infection, skin-tumor therapy, and enhancing wound healing. Adv Funct Mater 2019; 29: 1806883.
[136] Ouldhnini Y, Atila A, Ouaskit S and Hasnaoui A. Atomistic insights into the structure and elasticity of densified 45S5 bioactive glasses. Phys Chem Chem Phys 2021; 23: 15292-15301.
[137] Kumar A, Murugavel S, Aditya A and Boccaccini AR. Mesoporous 45S5 bioactive glass: synthesis, in vitro dissolution and biomineralization behavior. J Mater Chem B 2017; 5: 8786-8798.
[138] Ding Y, Yang R, Yu W, Hu C, Zhang Z, Liu D, An Y, Wang X, He C, Liu P, Tang Q and Chen D. Chitosan oligosaccharide decorated liposomes combined with TH302 for photodynamic therapy in triple negative breast cancer. J Nanobiotechnology 2021; 19: 147.
[139] Chen L, Zhou L, Wang C, Han Y, Lu Y, Liu J, Hu X, Yao T, Lin Y, Liang S, Shi S and Dong C. Tumor-targeted drug and CpG delivery system for phototherapy and docetaxel-enhanced immunotherapy with polarization toward M1-type macrophages on triple negative breast cancers. Adv Mater 2019; 31: e1904997.
[140] Kamarudin MNA, Sarker MMR, Zhou JR and Parhar I. Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects. J Exp Clin Cancer Res 2019; 38: 491.
[141] Sun Y, Fang K, Hu X, Yang J, Jiang Z, Feng L, Li R, Rao Y, Shi S and Dong C. NIR-light-controlled G-quadruplex hydrogel for synergistically enhancing photodynamic therapy via sustained delivery of metformin and catalase-like activity in breast cancer. Mater Today Bio 2022; 16: 100375.
[142] Wang C, Wang J, Zhang X, Yu S, Wen D, Hu Q, Ye Y, Bomba H, Hu X, Liu Z, Dotti G and Gu Z. In situ formed reactive oxygen species-responsive scaffold with gemcitabine and checkpoint inhibitor for combination therapy. Sci Transl Med 2018; 10: eaan3682.
[143] Bu LL, Yan J, Wang Z, Ruan H, Chen Q, Gunadhi V, Bell RB and Gu Z. Advances in drug delivery for post-surgical cancer treatment. Biomaterials 2019; 219: 119182.
[144] Cao D, Guo W, Cai C, Tang J, Rao W, Wang Y, Wang Y, Yu L and Ding J. Unified therapeutic-

prophylactic vaccine demonstrated with a postoperative filler gel to prevent tumor recurrence and metastasis. Adv Funct Mater 2022; 32: 2206084.
[145] Zhou M, Luo C, Zhou Z, Li L and Huang Y. Improving anti-PD-L1 therapy in triple negative breast cancer by polymer-enhanced immunogenic cell death and CXCR4 blockade. J Control Release 2021; 334: 248-262.
[146] Zhou M, Zuo Q, Huang Y and Li L. Immunogenic hydrogel toolkit disturbing residual tumor "seeds" and pre-metastatic "soil" for inhibition of postoperative tumor recurrence and metastasis. Acta Pharm Sin B 2022; 12: 3383-3397.
[147] Liu X, Feng Z, Wang C, Su Q, Song H, Zhang C, Huang P, Liang XJ, Dong A, Kong D and Wang W. Co-localized delivery of nanomedicine and nanovaccine augments the postoperative cancer immunotherapy by amplifying T-cell responses. Biomaterials 2020; 230: 119649.
[148] Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, Kline J, Roschewski M, LaCasce A, Collins GP, Tran T, Lynn J, Chen JY, Volkmer JP, Agoram B, Huang J, Majeti R, Weissman IL, Takimoto CH, Chao MP and Smith SM. CD47 Blockade by Hu5F9-G4 and rituximab in Non-Hodgkin's lymphoma. N Engl J Med 2018; 379: 1711-1721.
[149] Lakhani NJ, Chow LQM, Gainor JF, LoRusso P, Lee KW, Chung HC, Lee J, Bang YJ, Hodi FS, Kim WS, Santana-Davila R, Fanning P, Squifflet P, Jin F, Kuo TC, Wan HI, Pons J, Randolph SS and Messersmith WA. Evorpacept alone and in combination with pembrolizumab or trastuzumab in patients with advanced solid tumours (ASPEN-01): a first-in-human, open-label, multicentre, phase 1 dose-escalation and dose-expansion study. Lancet Oncol 2021; 22: 1740-1751.
[150] Sikic BI, Lakhani N, Patnaik A, Shah SA, Chandana SR, Rasco D, Colevas AD, O'Rourke T, Narayanan S, Papadopoulos K, Fisher GA, Villalobos V, Prohaska SS, Howard M, Beeram M, Chao MP, Agoram B, Chen JY, Huang J, Axt M, Liu J, Volkmer JP, Majeti R, Weissman IL, Takimoto CH, Supan D, Wakelee HA, Aoki R, Pegram MD and Padda SK. First-in-human, first-in-class phase I trial of the Anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. J Clin Oncol 2019; 37: 946-953.
[151] Wu X, Zhong Z, Li Y, Wang Y, Tian Y, Liu X, Zhang X, Tao W, Wang J, Du Y and Zhang S. Injectable scaffolds for in vivo programmed macrophages manufacture and postoperative cancer immunotherapy. Adv Funct Mater 2023; 33: 2300058.
[152] McCracken MN, Cha AC and Weissman IL. Molecular pathways: activating T cells after cancer cell phagocytosis from blockade of CD47 "Don't eat me" signals. Clin Cancer Res 2015; 21: 3597-3601.
[153] Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, Xu H, Peng H, Fu YX and Xu MM. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. Nat Med 2015; 21: 1209-15.
[154] Huang L, Zhang Y, Li Y, Meng F, Li H, Zhang H, Tu J, Sun C and Luo L. Time-programmed delivery of sorafenib and anti-CD47 antibody via a double-layer-gel matrix for postsurgical treatment of breast cancer. Nanomicro Lett 2021; 13: 141.
[155] Bender E. Editorial. Nature 2017; 552: S61-S61.
[156] Sanmamed MF and Chen LP. A paradigm shift in cancer immunotherapy: from enhancement to normalization. Cell 2018; 175: 313-326.
[157] Ribas A and Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018; 359: 1350-1355.
[158] Zhang J, Chen C, Li A, Jing W, Sun P, Huang X, Liu Y, Zhang S, Du W, Zhang R, Liu Y, Gong A, Wu J and Jiang X. Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection. Nat Nanotechnol 2021; 16: 538-548.
[159] Zhang Y, Tian S, Huang L, Li Y, Lu Y, Li H, Chen G, Meng F, Liu GL, Yang X, Tu J, Sun C and Luo L. Reactive oxygen species-responsive and Raman-traceable hydrogel combining photodynamic and immune therapy for postsurgical cancer treatment. Nat Commun 2022; 13: 4553.
[160] Tian S, Yue Q, Liu C, Li M, Yin M, Gao Y, Meng F, Tang BZ and Luo L. Complete degradation of a conjugated polymer into green upcycling products by sunlight in air. J Am Chem Soc 2021; 143: 10054-10058.
[161] Yuan R, Zheng F, Zhong S, Tao X, Zhang Y, Gao F, Yao F, Chen J, Chen Y and Shi G. Self-assembled nanoparticles of glycyrrhetic acid-modified pullulan as a novel carrier of curcumin. Molecules 2014; 19: 13305-13318.
[162] Ren YL, Li RQ, Cai YR, Xia T, Yang M and Xu FJ. Effective codelivery of lncRNA and pDNA by pullulan-based nanovectors for promising therapy of hepatocellular carcinoma. Adv Funct Mater 2016; 26: 7314-7325.
[163] Fang F, Meng FL and Luo L. Recent advances on polydiacetylene-based smart materials for biomedical applications. Materials Chemistry Frontiers 2020; 4: 1089-1104.
[164] Lee PP, Yee C, Savage PA, Fong L, Brockstedt D, Weber JS, Johnson D, Swetter S, Thompson J, Greenberg PD, Roederer M and Davis MM. Characterization of circulating T cells specific for tumor-associated antigens in melanoma patients. Nat Med 1999; 5: 677-685.

[165] Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, Ha TT and Gajewski TF. Up-regulation of PD-L1, IDO, and T-regs in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med 2013; 5: 200ra116.
[166] Wang T, Wang D, Yu H, Feng B, Zhou F, Zhang H, Zhou L, Jiao S and Li Y. A cancer vaccine-mediated postoperative immunotherapy for recurrent and metastatic tumors. Nat Commun 2018; 9: 1532.
[167] Lu Y, Wu C, Yang Y, Chen X, Ge F, Wang J and Deng J. Inhibition of tumor recurrence and metastasis via a surgical tumor-derived personalized hydrogel vaccine. Biomater Sci 2022; 10: 1352-1363.
[168] Huo W, Yang X, Wang B, Cao L, Fang Z, Li Z, Liu H, Liang XJ, Zhang J and Jin Y. Biomineralized hydrogel DC vaccine for cancer immunotherapy: a boosting strategy via improving immunogenicity and reversing immune-inhibitory microenvironment. Biomaterials 2022; 288: 121722.
[169] Chen G, Xiong W, Gu Z, Gao Y, Hou J, Long L, Wang H, Asrorov AM, Muhitdinov B, Xu Q and Huang Y. Mannosylated engineered trichosanthin-legumain protein vaccine hydrogel for breast cancer immunotherapy. Int J Biol Macromol 2022; 223: 1485-1494.
[170] Jia YP, Shi K, Yang F, Liao JF, Han RX, Yuan LP, Hao Y, Pan M, Xiao Y, Qian ZY and Wei XW. Multifunctional nanoparticle loaded injectable thermoresponsive hydrogel as NIR controlled release platform for local photothermal immunotherapy to prevent breast cancer postoperative recurrence and metastases. Adv Funct Mater 2020; 30: 2001059.
[171] Shou X, Liu Y, Wu D, Zhang H, Zhao Y, Sun W and Shen X. Black phosphorus quantum dots doped multifunctional hydrogel particles for cancer immunotherapy. Chem Eng J 2021; 408: 127349.
[172] Xia X, Wang X, Cheng Z, Qin W, Lei L, Jiang J and Hu J. The role of pyroptosis in cancer: pro-cancer or pro-"host"? Cell Death Dis 2019; 10: 650.
[173] Yu P, Zhang X, Liu N, Tang L, Peng C and Chen X. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther 2021; 6: 128.
[174] Wang Q, Wang Y, Ding J, Wang C, Zhou X, Gao W, Huang H, Shao F and Liu Z. A bioorthogonal system reveals antitumour immune function of pyroptosis. Nature 2020; 579: 421-426.
[175] Mi D, Li J, Wang R, Li Y, Zou L, Sun C, Yan S, Yang H, Zhao M and Shi S. Postsurgical wound management and prevention of triple-negative breast cancer recurrence with a pryoptosis-inducing, photopolymerizable hydrogel. J Control Release 2023; 356: 205-218.