International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

New Strategies in Comprehensive Melanoma Treatment: Applications, Potential, and Challenges of Hydrogels

Qiang Jin, Shi-Qi Lin, Xiang-Jie Xue, Li-Li Wang, Miao-Yun Jiang, Ji Wang, Su-Fan Wu, Yan-Yan Hu

Center for Plastic & Reconstructive Surgery, Department of Plastic & Reconstructive Surgery, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Yan-Yan Hu, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Road, Hangzhou, Zhejiang Province, People's Republic of China, Email 11818077@zju.edu.cn

Abstract: With the rising incidence and mortality rates of melanoma, the limitations of traditional treatment methods have become increasingly evident. These approaches often lack precision, cause systemic toxicity, or fail to prevent recurrence, falling short of current treatment needs such as efficacy, safety, and long-term tumor control. Melanoma progression involves complex biological features such as uncontrolled proliferation, immune evasion, and metastasis, which are crucial for understanding clinical behavior and guiding treatment design. Hydrogels have recently emerged as a promising platform in the field of cancer therapy due to their tunable physicochemical properties, biocompatibility, and capacity for localized, controlled drug delivery. To provide a comprehensive and methodologically sound overview, we systematically searched the PubMed database using the keywords "hydrogel" and "melanoma" for studies published up to December 2024. Studies were screened based on relevance, originality, and experimental support. This review focuses on hydrogel-based strategies for melanoma treatment, highlighting: (1) recent advances in hydrogel design and functionality; (2) their integration with therapeutic approaches such as immunotherapy, chemotherapy, and photothermal therapy; and (3) their potential in postoperative wound management. In addition, we discuss the role of material selection in hydrogel performance and explore how the combination of distinct therapeutic approaches within hydrogel systems can synergistically improve treatment outcomes. Finally, we address the current challenges facing clinical translation, including safety, efficacy, and regulatory hurdles, while outlining potential pathways to overcome these barriers. This review aims to support future research and clinical innovation by providing a structured, up-to-date overview of hydrogel applications in melanoma therapy.

Plain Language Summary:

1. Advances in hydrogel applications for melanoma treatment are reviewed.
2. Synergistic therapeutic effects of hydrogels for melanoma are summarized.
3. Improvements in hydrogel design for enhanced efficacy and reduced side effects are highlighted.
4. Challenges in clinical translation and scalability of hydrogel-based therapies are discussed.

Keywords: hydrogel, melanoma, drug delivery system, synergistic therapy

Introduction

Melanoma originates from the malignant transformation and uncontrolled proliferation of melanocytes, primarily manifesting on the skin.[1] However, it can also be present in other anatomical sites, including the ocular uvea,[2] gastrointestinal tract,[3] genitourinary system,[4] reproductive tract,[4] and meninges.[5] Melanoma is characterized by its high degree of malignancy and invasiveness. Despite accounting for only 1% of skin cancers, melanoma is responsible for more than 80% of skin cancer-related fatalities,[6] Furthermore, the incidence of melanoma is steadily increasing worldwide. According to the International Agency for Research on Cancer, by 2040, there will be approximately a 57%

Received: 16 May 2025
Accepted: 11 October 2025
Published: 18 December 2025

increase in global new cases and a 68% increase in related deaths.[7] The etiology of melanoma is multifaceted and not yet fully understood. Various factors contribute to its pathogenesis, including prolonged exposure to UV radiation, skin phototype, presence of nevi, pesticide use, geographic location, genetic predisposition, immune suppression,[1] and obesity.[8]

Current therapeutic modalities for melanoma include five primary strategies: surgical excision, radiotherapy, chemotherapy, targeted therapy, and immunotherapy.[9] Although surgical resection is the primary treatment for early-stage melanoma, it is associated with a high risk of recurrence and the potential for residual tumor tissue.[10] The efficacy of radiotherapy as a treatment for melanoma is limited by its insensitivity.[11] Currently, chemotherapy is the primary therapeutic approach for advanced melanoma with metastasis, utilizing agents such as cisplatin, paclitaxel (PTX), and dacarbazine.[10]

Regarding targeted therapy, BRAF and MEK inhibitors have exhibited some efficacy. Immunotherapy is a current research hotspot. The development of first and second-generation immunotherapies presents novel prospects for addressing malignant melanoma. Immune checkpoint inhibitors have shown superior efficacy in treating metastatic melanoma.[10] Immunotherapy and targeted therapy for melanoma have been clinically investigated extensively; however, their therapeutic outcomes remain modest. Numerous patients exhibit resistance to novel medications or experience transient responses. Moreover, a significant subset of responsive individuals rapidly develop resistance to treatment[10] Consequently, the collective efficacy of the numerous treatment options for melanoma remains unsatisfactory. One of the current mainstream research directions is the development of new drugs and treatment methods to achieve better therapeutic results, including the applications of biomaterials for melanoma treatment.

Hydrogels are a class of biomaterials characterized by a three-dimensional porous network structure and excellent biocompatibility.[12] They are widely applied in various biomedical fields, particularly tumor treatment and tissue engineering. In melanoma research, hydrogels have been extensively investigated for various therapeutic applications: (1) as drug delivery systems to transport anti-tumor agents, enabling targeted accumulation, sustained release, and improvement of the local immune microenvironment; (2) in synergistic phototherapy, including photothermal and photodynamic therapies; and (3) in vaccine formulation, enhancing specific immune responses and other immunotherapeutic strategies. With diverse functionalities and classifications, hydrogels offer several advantages, including improved drug solubility, controlled release, prolonged half-life, synergy with other therapies, enhanced efficacy, reduced dosage, and selective targeting of specific tissues to minimize side effects. Hydrogels are considered an optimal material for treatment purposes.[13]

Building upon these properties, recent advances in stimuli-responsive and functional hydrogels have shown promising potential to address existing treatment challenges. Stimuli-responsive hydrogels, which react to environmental cues such as pH, temperature, or enzymes, enable spatiotemporally controlled drug release, enhancing therapeutic precision and minimizing off-target effects. Functional hydrogels further incorporate bioactive components or targeting ligands to actively modulate the tumor microenvironment or immune system, thereby overcoming drug resistance and improving antitumor efficacy. These smart hydrogels represent a significant step forward in melanoma treatment by integrating multifunctional capabilities to tackle the disease's complexity. However, to date, no registered clinical trials specifically investigating hydrogel-based therapies for melanoma are available in major databases. This gap highlights the urgent need for advancing clinical research and translation in this promising field.

Despite increasing research interest, existing reviews on hydrogel applications in melanoma treatment often focus narrowly on either material design or specific therapeutic strategies, lacking a comprehensive integration of hydrogel types, modification techniques, and their multifaceted therapeutic roles. This review aims to fill this gap by providing a systematic and updated synthesis that encompasses hydrogel compositions, functional modifications, and their applications across diverse therapeutic modalities including drug delivery, phototherapy, immunotherapy, and combination treatments (Figure 1 and Table 1). By bridging these aspects, our work offers a holistic perspective to guide future hydrogel design and translational efforts, addressing challenges and opportunities not fully covered in prior literature.

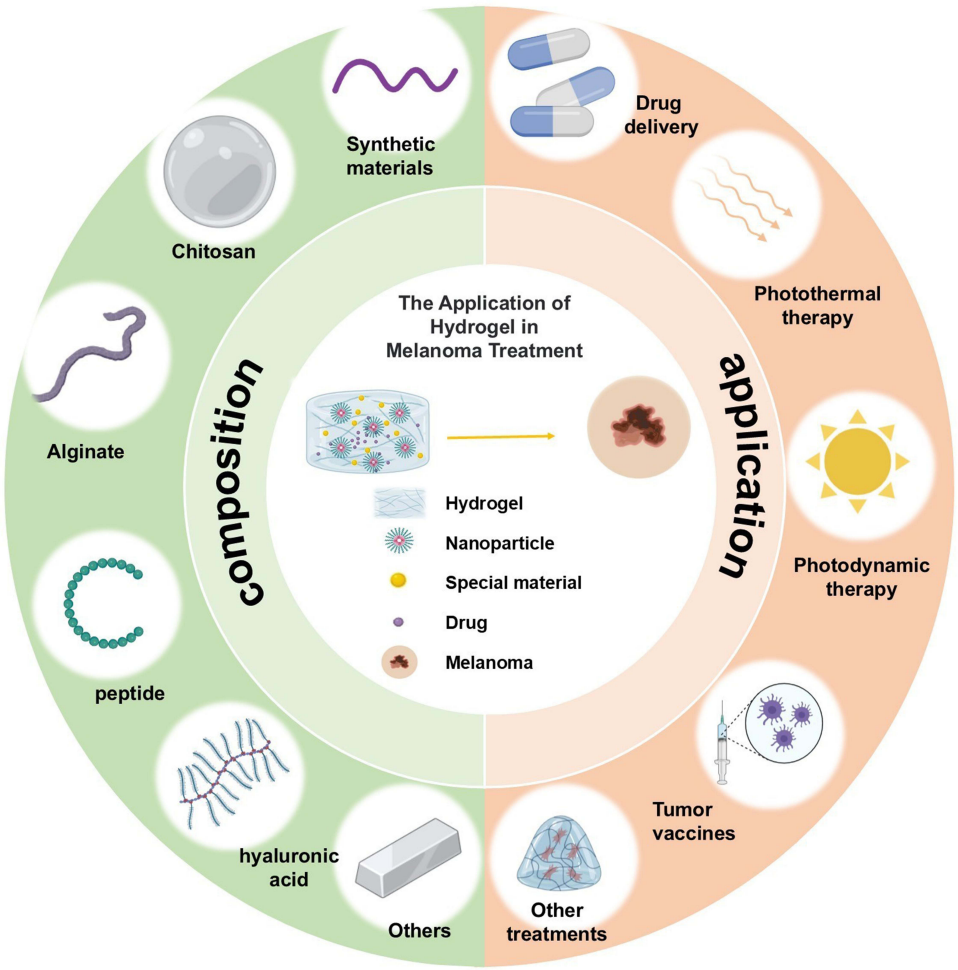

Figure 1 Application of hydrogels with different compositions and functionalities in melanoma treatment. The category "Others" includes polysaccharide-based and metal-based hydrogels. "Other treatments" refer to adjunctive therapies such as gene therapy involving hydrogels.

The Application of Different Types of Hydrogels in Melanoma Treatment

Various hydrogel systems have been investigated in melanoma research for their potential in diverse therapeutic strategies (Figure 2). Researchers strategically select specific hydrogel types and, through rational design, confer them with unique attributes and properties, including biodegradability, mechanical strength, and responsiveness to environmental stimuli such as light, pH, and temperature. Herein, we will discuss the role of various hydrogels in melanoma treatment according to their categories (Table 2).

Table 1 The Applications of Hydrogels in Melanoma Treatment

Type	Author	Year	Cargo	Therapeutics
Alginate	Yongkui Li[14]	2015	Celecoxib, aPD-1	Immunotherapy
	Langtao Xu[15]	2022	PDA, DOX	PTT, Chemotherapy
	Ping Li[16]	2023	PDA, DOX	PTT, Chemotherapy
	Hongshi Ma[17]	2019	OPC	Photothermal therapy
	Zhongcao Wu[18]	2021	Calcium silicate nanowire	PTT
	Jianhui Zhou[17]	2022	TPZ, GOx	PDT, Chemotherapy
	Anna Aihua Li[19]	2006	Myoblast	Gene therapy

(*Continued*)

https://doi.org/10.2147/IJN.S535220

Table 1 (Continued).

Type	Author	Year	Cargo	Therapeutics
CH	Wanqiong Li[20]	2021	OPBP-1	Immunotherapy
	Kejia Xu[21]	2022	Hydroxyapatite nanoparticles	Immunotherapy
	Zhengjie Meng[22]	2022	R837	Immunotherapy
	Ludmilla David de Moura[23]	2021	DTX, Lidocaine	Chemotherapy
	Asif Nawaz[24]	2022	5FU-alginate nanoparticle	Chemotherapy
	Ji Eun Won[25]	2021	DOX	Chemotherapy
	Zahra Pourmanouchehri[26]	2022	5-FU	Chemotherapy
	Xiuqi Liang[27]	2021	EndoFit OVA	Immunotherapy
	Andrew J Highton[28]	2015	Ovalbumin protein, Quil-A adjuvant	Immunotherapy
	Shenqiang Wang[29]	2020	MnO2, DOX	PTT, Chemotherapy
	Daniela N. Céspedes-Valenzuela[30]	2022	rGO-DOX	PTT, Chemotherapy
	Yaling Zheng[31]	2023	CuO2 nanodot, L-Buthionine-(S, R)-sulfoximine	Chemodynamic therapy
	Farnaz Azadikhah[32]	2021	Tannic acid, N, N′-di-(L-alanine)-3,4,9,10-perylene tetracarboxylic diimide	PDT
HA	Quanyin Hu[33]	2021	CAR-T, aPD-L1	Immunotherapy
	Vajihe Akbari[34]	2022	GM-CSF, PTX	Immunotherapy
	Huu Thuy Trang Duong[35]	2020	OVA expressing plasmid, GM-CSF	Immunotherapy
	Yufang Zhao[36]	2016	Cripto-1 receptor antibody	Immunotherapy
	Seungbeom Ko[37]	2019	Gallic acid, Fe3+	PTT
	Lidong Zhang[38]	2023	CaO2, hyaluronic acid-chlorin e6 modified nanoceria	PDT
Peptides	Tianyue Jiang[39]	2018	PTX	Chemotherapy
	Chendan Liu[40]	2021	DTX	Chemotherapy
	Xiaomeng Dai[41]	2020	CAMKII	Immunotherapy
	Honglin Jin[42]	2018	DOX	Chemotherapy
	Shuangjiang Yv[43]	2018	aPD-L1, dextro-1-methyl tryptophan	Immunotherapy
	Yingge Shi[44]	2021	aPD-L1, DOX	Immunotherapy, Chemotherapy
	Yuhan Zhou[45]	2022	HOCl-CDS	Immunotherapy
	Kui Yang[46]	2023	CpG, tumor lysate	Immunotherapy
	Huijuan Song[47]	2018	TCL, TLR3 agonist	
PEG hydrogels	Qiang Lv[48]	2018	DOX, IL-2, IFN-g	Chemotherapy, immunotherapy
	Santiago Correa[49]	2022	CD40 agonist	Immunotherapy
	Weitai Wu[50]	2010	Ag-Au bimetallic NP core, TMC	Chemotherapy, PTT
	Mirela Kremenovic[51]	2022	BCG lysate	Immunotherapy
	Zhu Chen[52]	2022	Nano-hydroxyapatite, GM-CSF	Chemotherapy, Immunotherapy
	Huitong Ruan[53]	2019	aPD1, Zebularine	Immunotherapy
	Xilong Wu[54]	2017	IL-15, cisplatin	Chemotherapy, Immunotherapy
	Muchao Chen[55]	2021	Y27632	Immunotherapy
	Juan Wang[56]	2021	Adv-Flagrp170	Viral immunotherapy
	Huijuan Song[57]	2019	Tumor cell lysates, GM-CSF, aCTLA-4, aPD-1	Immunotherapy
	Yarong Liu[58]	2014	DC, macrophage, cancer antigen	Immunotherapy
	Bin Zheng[59]	2021	SeV	Immunotherapy
	Xia Dong[60]	2019	CpG self-crosslinked Nanoparticle, IR820	Immunotherapy, PTT

(*Continued*)

Table 1 (Continued).

Type	Author	Year	Cargo	Therapeutics
NON-PEG synthetic polymer hydrogels	Mario Casolaro[61]	2011	CISPLATIN	Chemotherapy
	Hongmei Xu[62]	2020	PTX	Chemotherapy
	Xing Huang[63]	2023	Timosaponin AIII	Chemotherapy
	Sergey V. Abkin[64]	2015	Phloretin, HSP70	Immunotherapy
	Sushma Havanur[65]	2019	DOX	Chemotherapy
	Hui Wang[66]	2014	Bifunctional nanoparticle, curcumin	PTT, chemotherapy
	Syed Baseeruddin Alvi[67]	2021	DOX	Chemotherapy
	Cong Wang[68]	2016	Tungsten oxide	PTT
COS and LA	Mengqi Jia[69]	2023	LA, COS	Chemotherapy
Dialdehyde starch and β-cyclodextrin	Behzad Pourbadi[70]	2023	Azobenzene derivative, N-isopropyl acrylamide	PTX
Oxidativedextran and diselenide	Xiaoran Ding[71]	2023	TPZ	Glutathione consumption-enhanced cancer therapy
5-amino-1,10-phenanthroline, NSAIDs and $Zn(NO_3)_2$	Sourabh Bera[72]	2023	5-amino-1,10-Phenanthroline, $Zn(NO_3)_2$	Chemotherapy

Abbreviations: aPD-1, anti-programmed cell death protein 1 checkpoint inhibitor; PTT, Photothermal therapy; PDT, Photodynamic therapy; PDA, Polydopamine; DOX, doxorubicin; OPC, oligomeric proanthocyanidins; TPZ, tirapazamine; Gox, glucose oxidase; CH, Chitosan; OPBP-1, an anti-protein hydrolysis D peptide; R837, imiquimod; DTX, docetaxel; 5-FU, 5-fluorouracil; rGO-DOX, doxorubicin-functionalized reduced graphene oxide; HA, Hyaluronic acid; CAR-T, chimeric antigen receptor T cell immunotherapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; PTX, paclitaxel; CAMKII, calmodulin-dependent protein kinase II; aPD-L1, anti-PDL1 blocking antibody; HOCl-CDS, Hypochlorous acid-treated cell-derived secretions; CpG, Cytosine–phosphate–guanine; TCL, tumor cell lysates; PEG, Polyethylene glycol; BCG, intralesional Mycobacterium bovis; Y27632, rho-associated kinase inhibitor; DC, dendritic cell; SeV, Sendai virus; IR820, new Indocyanine Green; HSP70, heat-shock protein 70 kDa; LA, lipoic acid; COS, chitosan oligosaccharides; NSAIDs, Nonsteroidal anti-inflammatory Drugs.

Alginate

Alginate is a naturally derived polyanionic hydrophilic polysaccharide primarily obtained from seaweed and microbes. It is renewable and easy to prepare.[73] Alginate hydrogels, as naturally derived polysaccharides, exhibit superior

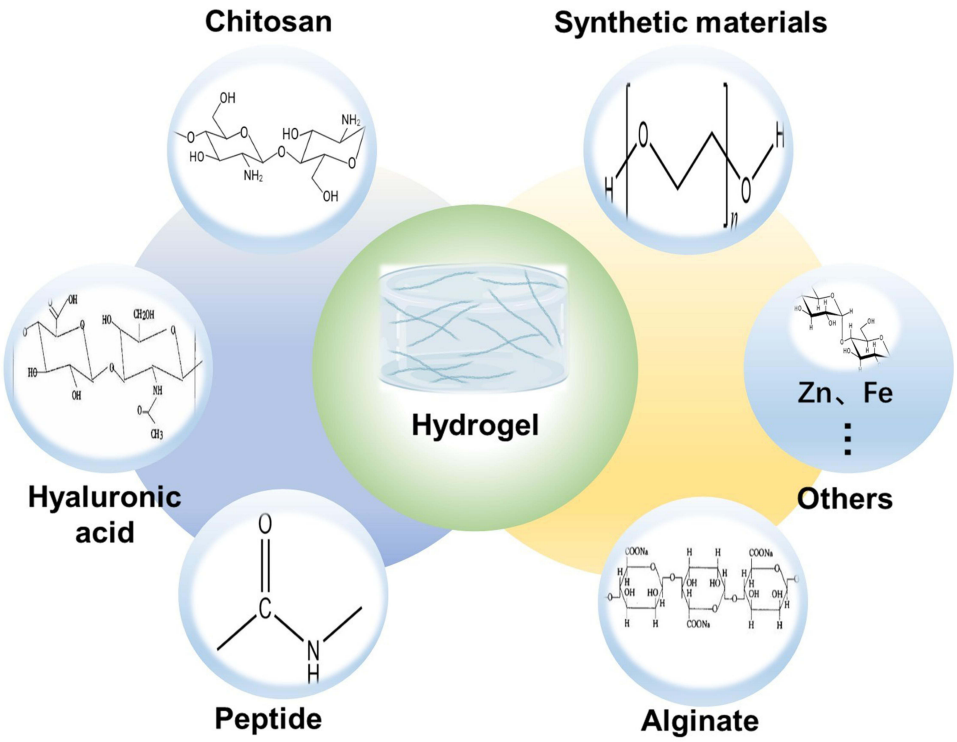

Figure 2 Representative compositions of hydrogels used in melanoma treatment.

https://doi.org/10.2147/IJN.S535220

Table 2 Advantages and Disadvantages of Different Types of Hydrogels Used in Melanoma Research

Hydrogel Type	Advantages	Disadvantages
Alginate	Naturally derived, easy to prepare, excellent biocompatibility and biodegradability; high hydrophilicity improves drug efficacy and safety.	Weak mechanical properties and poor drug retention under shear stress; functional research is still early with reproducibility, cost, and long-term safety issues.
CH	Cationic natural polysaccharide, excellent biocompatibility and biodegradability; hemostatic, antibacterial, cost-effective, and easy to process.	Soft texture with moderate mechanical strength; poor stability, requiring modification or cross-linking, potentially increasing cost and complexity.
HA	Major component of ECM with high bioactivity and modifiability; rich in functional groups for chemical tailoring.	Limited application in melanoma field; still under exploration.
Peptide	High biocompatibility and low toxicity; can self-assemble in response to pH, temperature, or ultrasound; properties can be tailored by amino acid sequences.	Poor mechanical stability; strengthening requires aromatic residues or chemical crosslinking, which may increase complexity and cost.
Synthetic Polymer Hydrogels	Adjustable physicochemical properties with excellent mechanical strength; PEG offers strong hydrophilicity, functional versatility, and stimuli-responsiveness.	Poor native tissue adhesion; mainly passive drug carriers lacking intrinsic bioactivity, requiring combination with responsive systems.
Other Hydrogels	Diverse novel systems with natural sources, low immunogenicity, and tunable mechanical properties.	Mostly experimental, complex formulations, and high cost; need scalable and cost-effective formulations.

biocompatibility, water absorption capacity, and biodegradability compared to many synthetic polymer-based hydrogels.[73] These properties can enhance drug efficacy and reduce adverse reactions. Consequently, they are extensively used in the management of melanoma.

For drug delivery, Li et al loaded celecoxib and anti-programmed cell death protein 1 checkpoint inhibitor (aPD-1) into alginate hydrogels and achieved excellent anti-tumor effects by reshaping the tumor microenvironment (Figure 3a).[14] Additionally, the researchers integrated photothermal therapy (PTT), photodynamic therapy (PDT), and gene therapy into the hydrogel system to achieve multifunctionality. Specifically, Xu et al constructed an alginate-based hydrogel composed of sodium alginate, gelatin, and polydopamine (PDA) nanoparticles. PDA, a biomimetic polymer with excellent photothermal conversion efficiency, was used in this system to enable synergistic photothermal therapy alongside the delivery of doxorubicin (DOX) for melanoma treatment. Xu et al developed hydrogels combining sodium alginate, gelatin, and PDA nanoparticles, enabling the simultaneous delivery of DOX and the implementation of photothermal therapy for melanoma treatment.[15] Furthermore, Ma et al fabricated hydrogels using calcium silicate nanowires and sodium alginate as precursors, incorporating oligomeric proanthocyanidins (OPC) as photothermal agents to enhance photothermal regulation capabilities (Figure 3b).[74] In addition to their application in photothermal therapy, alginate hydrogels can be combined with PDT. Zhou et al developed photoresponsive hydrogels incorporating sodium alginate solution with nanoparticles, hypoxia-responsive tirapazamine (TPZ), and glucose oxidase (GOx). These semiconductor nanoparticles mediated photodynamic reactions and oxygen depletion, while GOx further depleted oxygen, collectively activating TPZ for chemotherapy.[17] Anna Aihua Li et al used sodium alginate hydrogels with non-viral gene therapy to protect exogenous myoblasts from host immune system attacks while allowing the diffusion of nutrients and therapeutic gene products.[19]

Due to their unique biocompatibility, water absorption capacity, and biodegradability, alginate-based hydrogels have become attractive carriers in melanoma treatment research. However, several limitations remain to be addressed. For example, their intrinsic mechanical weakness may hinder retention and sustained drug delivery at the tumor site, especially under physiological shear stress. Furthermore, efforts to integrate alginate with functional components—such as immune adjuvants, gene vectors, or phototherapeutic agents—are still at an early stage and require optimization to ensure therapeutic synergy and stability. For clinical translation, issues such as batch-to-batch reproducibility, cost-efficient fabrication, and long-term biosafety must also be systematically investigated in the context of melanoma therapy.

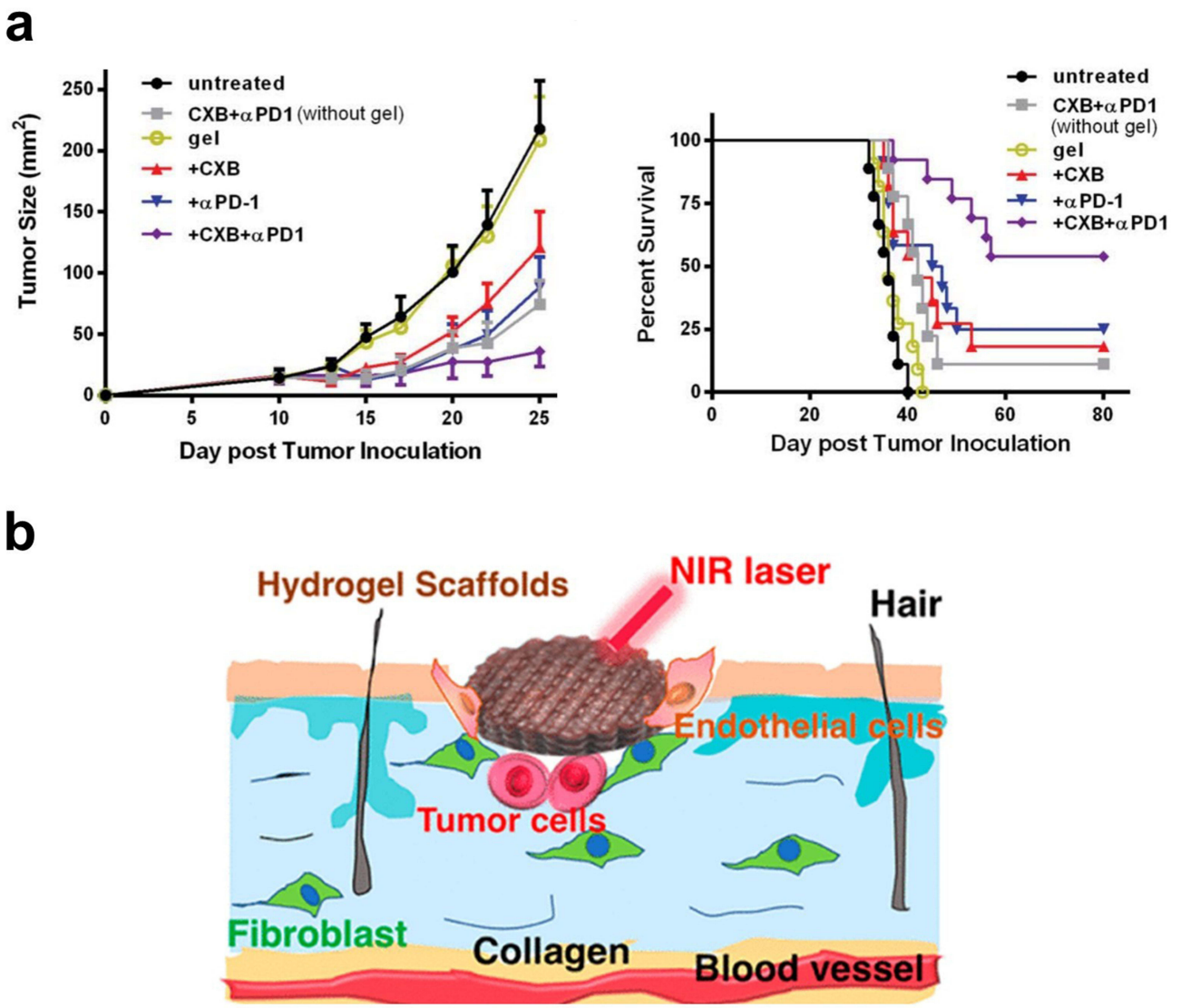

Figure 3 Alginate hydrogel in treating melanoma: photothermal therapy (PTT) and photodynamic therapy (PDT). (**a**) C57BL/6 Mice treated with hydrogels loaded with celecoxib and aPD1 (anti-PD-1 antibody) had significantly reduced tumor size and significantly increased survival. Reproduced from Li Y, Fang M, Zhang J et al. Hydrogel dual delivered celecoxib and anti-PD-1 synergistically improve antitumor immunity. Oncoimmunology. 2015 Aug 12;5(2):e1074374. © 2016 Taylor & Francis Group, LLC.[14] Copyright @ Taylor & Francis (**b**) The controlled high temperature induced by OPC-containing hydrogel scaffolds under NIR (near-infrared) laser irradiation could effectively kill melanoma cells and suppress tumor growth. Reproduced from Ma H, Zhou Q, Chang J, Wu C. Grape Seed-Inspired Smart Hydrogel Scaffolds for Melanoma Therapy and Wound Healing. *ACS Nano.* 2019;13(4):4302–4311.[74] Copyright @ 2019, American Chemical Society.

Chitosan

Chitosan (CH) is the only natural cationic polysaccharide with excellent biocompatibility and biodegradability,[75] and it possesses desirable properties, including adsorption, hemostasis, and antibacterial effects.[76] Due to these properties, CH is considered an optimal biomaterial for formulating hydrogels, which have been extensively investigated for their potential in melanoma research. CH hydrogels are applied in various treatment scenarios by grafting different functional groups to modify the gel's properties.

Chitosan hydrogels are frequently employed for drug delivery melanoma treatment, with the primary goal of reducing systemic drug-related adverse effects and achieving targeted therapy. Xu et al developed a chitosan/alginate hydrogel incorporating rod-shaped hydroxyapatite nanoparticles (HANPs) for the treatment of cutaneous malignant melanoma (CMM). In vitro studies demonstrated that HANPs selectively induced apoptosis in melanoma cells by disrupting mitochondrial function and increasing reactive oxygen species (ROS), while exhibiting minimal toxicity to normal

cells. In vivo, the hydrogel significantly inhibited tumor growth in a CMM mouse model, and histological analysis confirmed its good biocompatibility, with no signs of damage to major organs or systemic toxicity (Figure 4a).[21] Building on these foundational applications, recent advances have focused on the development of smart chitosan hydrogels capable of precise and stimuli-responsive drug release. Nawaz et al showcased that temperature-sensitive chitosan-gelatin hydrogels can effectively deliver 5-fluorouracil (5-FU)-sodium alginate particles. These hydrogels undergo a phase transition (sol-gel transition) at 34 °C, effectively preventing premature and burst release of 5-FU (Figure 4b).[24] Furthermore, this approach facilitates temperature-controlled drug release. In addition to the temperature-controlled drug release system, Won et al developed chitosan hydrogel systems that enable the controlled release of DOX under near-infrared (NIR) irradiation, enhancing the retention time of DOX in tumor tissues.[25] Pourmanouchehri et al designed a pH-sensitive hydrogel incorporating deoxycholic acid micelles and carboxymethyl chitosan, enabling optimal 5-FU release at an environmental pH of 9.[26]

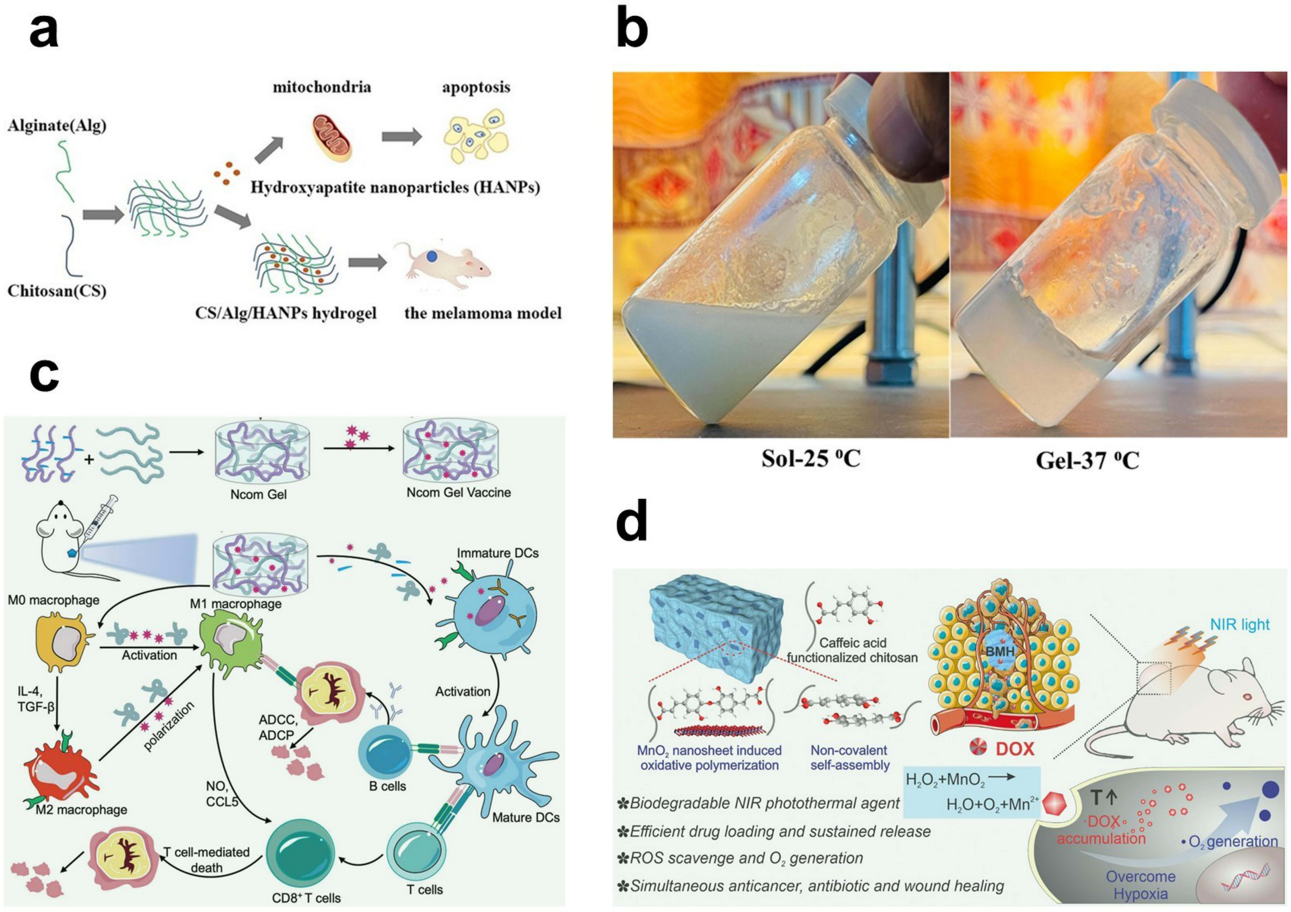

Figure 4 Chitosan hydrogel in melanoma treatment: photothermal therapy, chemotherapy and immunotherapy. (**a**) A chitosan hydrogel containing hydroxyapatite nanoparticles treats melanoma cells by inducing apoptosis of tumor cells. Reproduced from Xu K, Wang Y, Xie Y et al. Anti-melanoma effect and action mechanism of a novel chitosan-based composite hydrogel containing hydroxyapatite nanoparticles, *Regenerative Biomaterials*, Volume 9, 2022, rbac050. *Copyright © 2022, © The Author(s) 2022. Published by Oxford University Press. Creative Commons CC BY licens.*[21] (**b**) Sol–gel transition of 5FU-Alg-Np-HG hydrogel. Reproduced from Nawaz A, Ullah S, Alnuwaiser MA, Rehman FU, Selim S, Al Jaouni SK, Farid A. Formulation and Evaluation of Chitosan-Gelatin Thermosensitive Hydrogels Containing 5FU-Alginate Nanoparticles for Skin Delivery. *Gels*. 2022; 8(9):537. © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[24] (**c**) The innate immune response was amplified through the activation of dendritic cells (DCs) and macrophages after Gel vaccine administration. In addition, innate immune cells launched and maintained a powerful adaptive immune response through the function of the Gel vaccine. Reproduced from Liang X, Li L, Li X et al. A spontaneous multifunctional hydrogel vaccine amplifies the innate immune response to launch a powerful antitumor adaptive immune response. Theranostics. 2021 May 8;11(14):6936–6949. © The author(s). Creative Commons Attribution License.[27] (**d**) The hydrogel can release DOX (doxorubicin) while alleviating the tumor hypoxic microenvironment (TME). It can also be combined with photothermal therapy, promoting in vivo healing of multidrug-resistant wounds. Reproduced from Wang S, Zheng H, Zhou L et al. Injectable redox and light responsive MnO2 hybrid hydrogel for simultaneous melanoma therapy and multidrug-resistant bacteria-infected wound healing. *Biomaterials*. 2020;260:120,314. *© 2020 Elsevier Ltd. All rights reserved.*[29]

In addition to drug delivery, hydrogels have many other applications. Melanoma tumor vaccines have been extensively developed using chitosan hydrogels. Liang et al introduced a CH hydrogel-based vaccine that enhances innate immune responses, leveraging them to initiate and sustain robust adaptive immunity (Figure 4c).[27] CH hydrogels can be combined with other treatment modalities to improve therapeutic effects by serving as effective carriers for specific sensitizers, including photosensitizers. Wang et al prepared a hybrid hydrogel containing MnO_2 for photothermal treatment of melanoma (Figure 4d).[29] Zheng et al demonstrated that CH thermosensitive hydrogels enhance chemotherapy and sonodynamic therapy and have potential applications in photothermal therapy.[31] Furthermore, Farnaz Azadikhah et al developed antioxidant-photosensitive CH hydrogels to regulate the intensity of PDT in cancer therapy.[32]

CH hydrogels have been extensively used in treating malignant melanoma due to their unique three-dimensional network structure, excellent hydrophilicity, good biocompatibility, processability, and low cost. However, CH hydrogels do have some inherent limitations, such as relatively soft texture, moderate mechanical strength, and variable gel stability. Fortunately, many of these aspects can be effectively improved through various modification techniques due to the versatile chemical nature of chitosan. While excessive modifications or addition of materials may increase experimental complexity and cost, a balanced optimization can be achieved between performance and feasibility. Although a multifaceted approach that combines different treatment modalities is essential for tumor therapy, the current applications of most CH hydrogels remain focused on basic drug delivery. Therefore, additional research is warranted to develop stimuli-responsive hydrogels, synergistic photothermal therapy, tumor vaccines, and other innovative applications.

Hyaluronic Acid

Hyaluronic acid (HA), a major component of the extracellular matrix in nearly all mammalian tissues,[77] is a linear glycosaminoglycan composed of alternating units of glucuronic acid and N-acetylglucosamine.[78] Its remarkable biocompatibility, bioactivity, and ease of modification make it widely used in tissue engineering.[79]

Hu et al conducted a study utilizing chimeric antigen receptor T cell (CAR-T cells) immunotherapy and anti-PDL1 blocking antibody (aPD-L1) delivered via HA hydrogels to prevent tumor recurrence after surgery (Figure 5a).[33] In addition, composite hydrogels were synthesized by mixing oxidized HA grafted with the 2B11 antibody and adipic dihydrazide, facilitating the delivery of cripto-1 receptor antibodies. This created an embryonic-like microenvironment that effectively suppressed melanoma growth and transformed B16 melanoma cells into melanocyte-like cells (Figure 5b).[36] Researchers have further advanced the field by creating intelligent HA hydrogel-controlled release systems. HA photoresponsive hydrogels were developed, demonstrating the ability to completely eradicate melanoma under near-infrared light irradiation.[37] Although PDT-mediated oxygen therapy exhibits potential for melanoma ablation, its efficacy is impeded by challenges, including the hydrophobicity of photosensitizers, low tumor selectivity, and oxygen consumption. Researchers have turned to HA hydrogels as a potential solution to overcome these limitations. Zhang et al developed a multifunctional oxygen-producing HA hydrogel, which exhibited significant phototoxicity against B16F10 tumors under near-infrared radiation, effectively alleviating the tumor hypoxic microenvironment and improving PDT efficiency.[38]

HA hydrogels are widely studied in melanoma research due to their inherent biocompatibility and biodegradability. Their molecular structure contains reactive functional groups that facilitate diverse chemical and physical modifications, enabling tailored properties to meet specific therapeutic needs. These properties position HA hydrogels as a promising material for malignant melanoma treatment. However, current research into their application in melanoma therapy remains limited. To fully realize their potential, it is essential to explore and expand the therapeutic use of HA hydrogels in addressing melanoma.

Peptides

Peptide hydrogels are widely used in the biomedical field due to their high biocompatibility and low toxicity. Certain peptide substances can be transformed into hydrogels through simple methods, including thermal manipulation, ultrasonication, and pH adjustment. By manipulating the number of peptide (-CONH-) bonds and the properties of amino

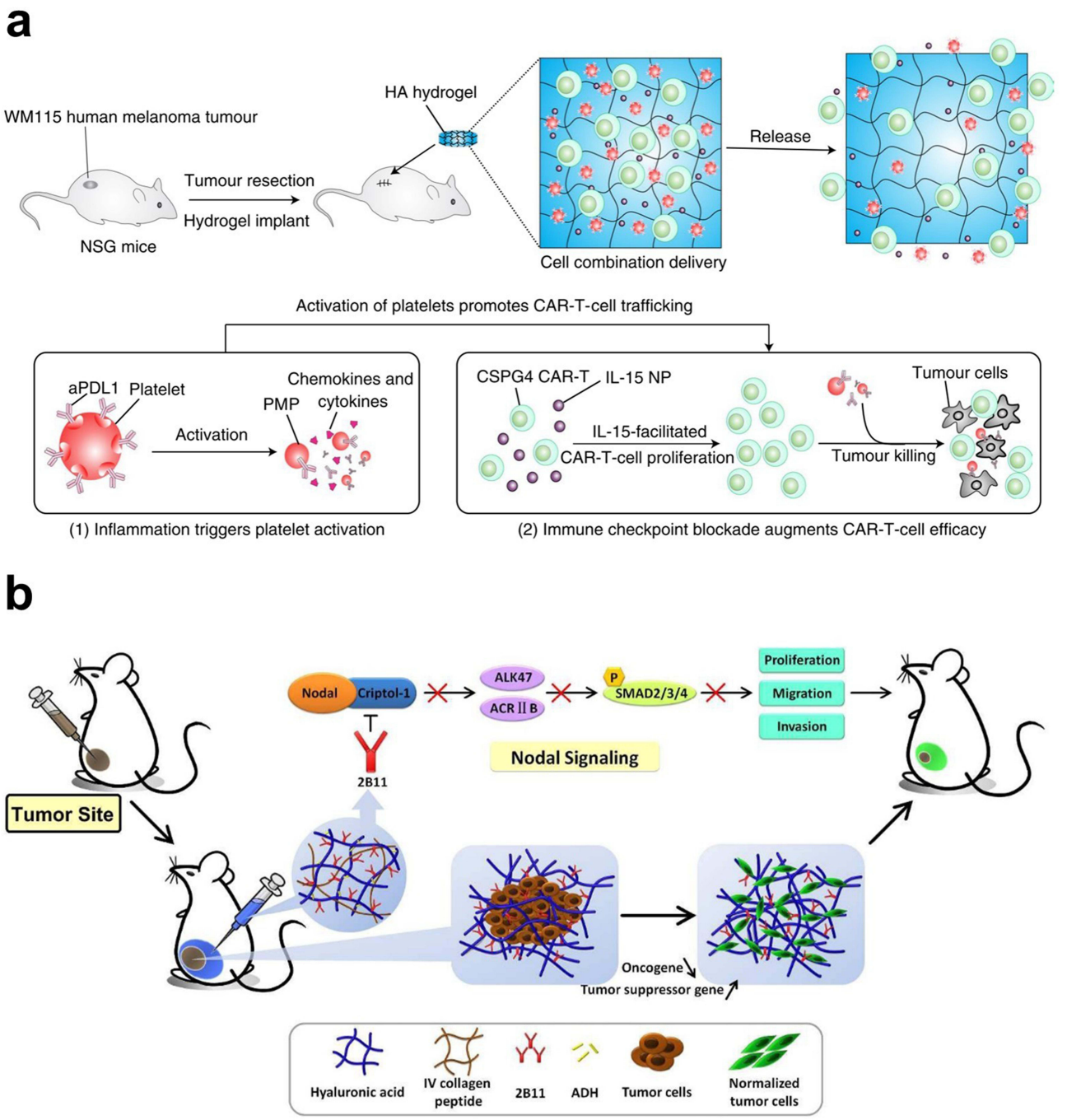

Figure 5 Applications of HA hydrogels in melanoma treatment. (**a**) A hyaluronic acid hydrogel can release chimeric antigen receptor T cell (CAR-T cells) targeting the human chondroitin sulfate proteoglycan 4, polymer nanoparticles encapsulating the cytokine interleukin-15 and platelets conjugated with the checkpoint inhibitor programmed death-ligand 1 into the melanoma cavity of mice with a resected subcutaneous melanoma inhibits the local recurrence of the melanoma. Reproduced from Hu Q, Li H, Archibong E et al. Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets. Nat Biomed Eng. 2021 Sep;5(9):1038–1047. © 2021. The Author(s), under exclusive licence to Springer Nature Limited.[33] (**b**) The injectable bioactive hydrogel system realized the local treatment of mouse melanoma and could powerfully inhibit tumor proliferation, migration, and invasion by blocking Nodal signaling. Reproduced from Zhao Y, Yan H, Qiao S et al. Hydrogels bearing bioengineered mimetic embryonic microenvironments for tumor reversion. *J Mater Chem B*. 2016;4(37):6183–6191.[36] Copyright @ 2016, Royal Society of Chemistry.

acids within peptides and adjusting their hydrophobicity and hydrophilicity, peptides' physical and chemical properties can be modified, allowing their application in various biological scenarios.[80]

In melanoma research, oligopeptide and polypeptide hydrogels have been primarily explored for their potential applications in therapy. Oligopeptides, consisting of short peptide chains formed by connecting more than two but fewer

than twenty peptide bonds, are primarily employed for delivery. Jiang et al demonstrated that oligopeptide hydrogels enhanced the transdermal delivery capacity and prolonged the retention time of paclitaxel (PTX) (Figure 6a).[39] Additionally, delivering docetaxel (DTX) through oligopeptide hydrogels can inhibit postoperative recurrence of malignant melanoma.[40]

Polypeptides characterized by long-chain peptide sequences with 20–50 amide bonds are also primarily used for drug delivery. Jin et al developed a peptide hydrogel that contained DOX and was a hybrid of bee venom peptide and RADA32, effective in the immunotherapeutic treatment of melanoma.[42] Additionally, researchers have produced various intelligent polypeptide hydrogels, including the ROS-responsive polypeptide hydrogel, which releases aPD-L1 and dextro-1-methyl tryptophan in response to ROS levels in the tumor microenvironment (Figure 6b).[43] Shi et al developed an injectable thermosensitive polypeptide hydrogel for delivering aPD-L1 and DOX.[44]

Polypeptide hydrogels have also been used to produce tumor vaccines. Mixed hydrogel vaccines have been developed and are composed of bee venom peptide, self-assembling fusion peptide (RADA32), Cytosine–phosphate–guanine (CpG), and tumor lysates (Figure 6c).[46] Moreover, polypeptide hydrogels have encapsulated tumor cell lysates (TCL) and TLR3 agonists to form hydrogel vaccine formulations.[47]

Peptide hydrogels are primarily employed for the targeted delivery of therapeutic agents in melanoma treatment research. However, their low mechanical strength limits their use. Given the high plasticity of peptide hydrogels, future research may focus on modifying peptide hydrogels. Previous studies have demonstrated that mechanical strength and chemical versatility of peptide hydrogels can be enhanced by modifying peptide linkages and incorporating aromatic residues. For instance, altering amino acid composition to adjust hydrophobicity or hydrophilicity has

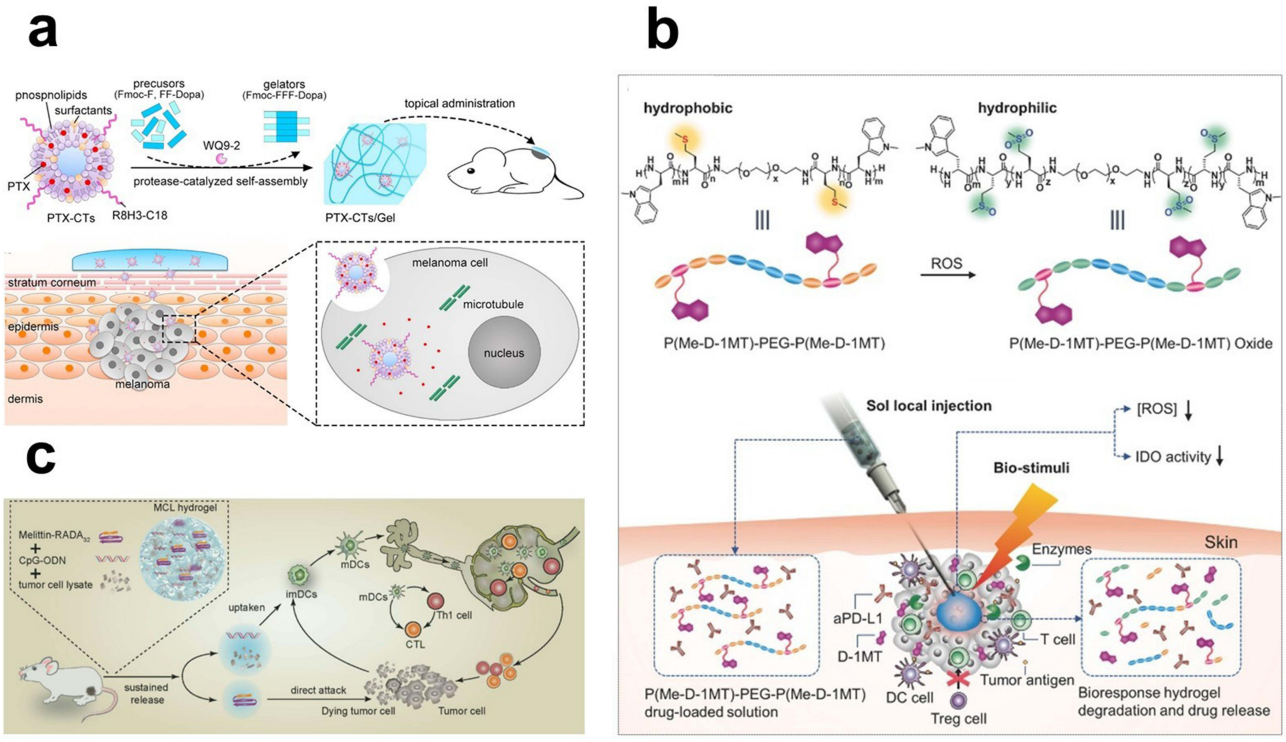

Figure 6 Applications of peptide hydrogels in melanoma treatment. (**a**) An oligopeptide hydrogel containing paclitaxel (PTX) that increases transdermal PTX delivery. Reproduced from Jiang T, Wang T, Li T et al. Enhanced Transdermal Drug Delivery by Transfersome-Embedded Oligopeptide Hydrogel for Topical Chemotherapy of Melanoma. *ACS Nano*. 2018;12(10):9693–9701.[39] Copyright @ 2018, American Chemical Society. (**b**) A polypeptide gel can effectively reduce the local reactive oxygen species (ROS) level and facilitate the release of immunotherapeutics, which results in enhanced anti-melanoma efficacy in vivo. Reproduced from Yu S, Wang C, Yu J et al. Injectable Bioresponsive Gel Depot for Enhanced Immune Checkpoint Blockade. *Advanced Materials*. 2018;30(28):1,801,527.[43] Copyright © 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (**c**) Schematic illustration of the this hydrogel vaccine composed of CpG oligodeoxynucleotide (CpG-ODN) and tumor cell lysate encapsulated in an methacrylate-based hydrogel (MR hydrogel) scaffold. The hydrogel enables sustained release of immune adjuvants and tumor antigens, promotes dendritic cell maturation and T cell activation, and exerts a dual anti-tumor effect for melanoma immunotherapy. Reproduced from Yang K, Zhou Y, Huang B. Sustained release of tumor cell lysate and CpG from an injectable, cytotoxic hydrogel for melanoma immunotherapy. J. Chen, *Nanoscale Adv.*, 2023, 5, 2071.[46] Copyright @ 2023, Royal Society of Chemistry. Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

https://doi.org/10.2147/IJN.S535220

been successfully applied to tune hydrogel properties.[81,82] While these modifications can improve functionality, they often require more complex synthesis processes, which may increase costs and experimental workload. Nevertheless, these structural modification strategies are still regarded as important approaches for developing high-performance, multifunctional peptide hydrogels, which are of great significance for advancing their application in melanoma therapy.

Synthetic Polymer Hydrogels

Synthetic polymer hydrogels exhibit a flexible structure and tunable physicochemical properties, making them more suitable for applications in melanoma treatment than natural polymer hydrogels.[83] Furthermore, the utility of natural polymer hydrogels is frequently limited by their inferior mechanical properties. Conversely, the robust mechanical performance of synthetic polymer hydrogels is attributed to their three-dimensional network structure.[84]

Polyethylene Glycol (PEG) Hydrogels

Polyethylene glycol (PEG)-based hydrogels have emerged as the predominant choice in melanoma treatment research, although numerous high-performance hydrogels have been established. PEG, a typical synthetic monomer, exhibits significant hydrophilicity, favorable biocompatibility, and easy functionalization capabilities. Through precise design and modification, PEG can respond to various stimuli, such as pH, temperature, and redox reactions, enabling the controlled release of drugs in the tumor microenvironment, which makes it a highly promising biomaterial.[85]

PEG hydrogels are used as drug delivery systems for treating malignant melanoma. Lv et al utilized PEG hydrogel to deliver DOX, IL-2, and IFN-γ for local melanoma treatment (Figure 7a).[48] Correa et al prepared polymer nanoparticle-based PEG hydrogels to reduce the dose-limiting toxicity of CD40 agonists while maintaining their effective anticancer effects.[49]

In addition to conventional drug delivery mechanisms, advanced PEG hydrogels have been engineered to exhibit rapid responsiveness to external stimuli. Thermosensitive PEG hydrogels are particularly prevalent. Wu et al combined localized chemotherapy with near-infrared photothermal therapy using a thermo-responsive PEG-based hydrogel containing a core-shell structure of silver and gold bimetallic nanoparticles and temozolomide (TMZ).[50] Moreover, researchers have used PEG to develop block copolymer micelle hydrogels, specifically poly(ethylene glycol)-poly(γ-ethyl-L-glutamate), to deliver interleukin-15 and cisplatin (Figure 7b).[54] Radiofrequency ablation (RFA) is a widely used local therapy that induces tumor coagulative necrosis at high temperatures. However, its effectiveness can be hindered by factors including dendritic cells' inefficient presentation of antigens (DC). Therefore, researchers loaded the rho-associated kinase (ROCK) inhibitor (Y27632) into PLGA-PEG-PLGA hydrogels to enhance DC-mediated antigen presentation, thereby improving the therapeutic efficacy of RFA (Figure 7c).[55]

Additionally, PEG hydrogels have been demonstrated to deliver adenovirus encoding Flagrp170 for viral immunotherapy of malignant melanoma.[56] Song et al have developed an injectable PEG hydrogel for the simultaneous delivery of tumor vaccines, granulocyte-macrophage colony-stimulating factor (GM-CSF), and two immune checkpoint inhibitors, improving the efficacy of tumor immunotherapy. Combination therapy with hydrogels for melanoma immunotherapy has exhibited better outcomes than using vaccines alone or adding a single immune checkpoint blockade.[52] Zheng et al found that the non-pathogenic Sendai virus (SeV) could activate antigen-presenting cells, represented by DCs, and they subsequently designed a PEG hydrogel vaccine containing SeV.[59]

PEG hydrogels can further be combined with photothermal therapy to combat malignant melanoma. By incorporating the new Indocyanine Green (IR820), an infrared blood pool contrast agent, into α-cyclodextrin copolymers and polyethylene glycol, the IR820-loaded hydrogels can be synthesized.[60] Furthermore, combining CpG-loaded self-crosslinking nanoparticles in these hydrogels facilitates a synergistic effect between photothermal therapy and immunotherapy.[60]

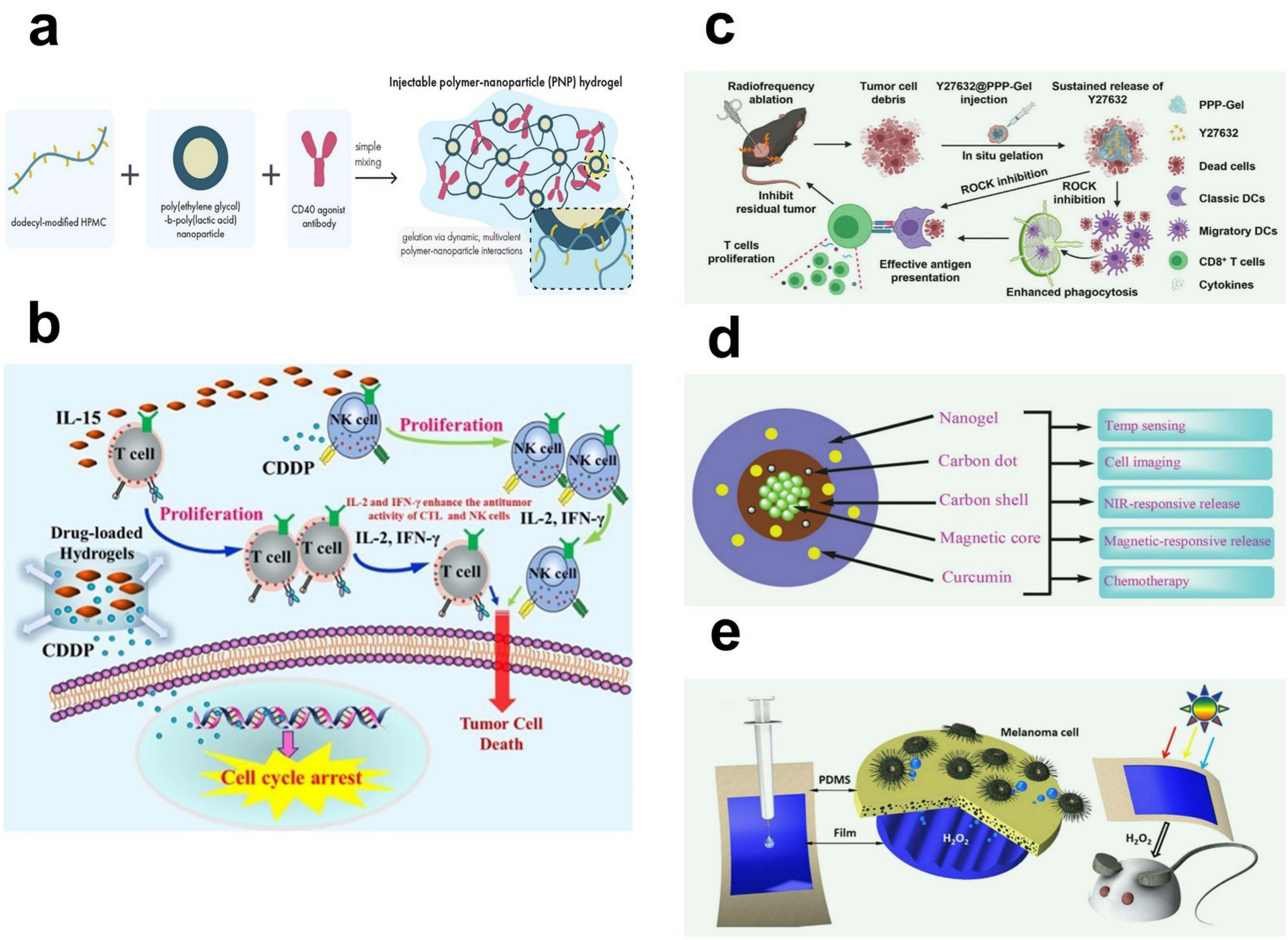

Figure 7 Applications of synthetic polymer hydrogels in melanoma treatment. (**a**) Synthesis method of polyethylene glycol (PEG) hydrogel loaded with CD40 agonist. Reproduced from Correa S, Meany EL, Gale EC et al Injectable Nanoparticle-Based Hydrogels Enable the Safe and Effective Deployment of Immunostimulatory CD40 Agonist Antibodies. Adv Sci (Weinh). 2022 Oct;9(28):e2103677.[49] Copyright @ 2022 The Authors. Advanced Science published by Wiley-VCH GmbH. CC BY. (**b**) Schematic representation of the mechanism for synergistic anti-tumor effects of localized coadministration of IL-15 and cisplatin (CDDP) released from the hydrogels. Reproduced from Wu X, Wu Y, Ye H, Yu S, He C, Chen X. Interleukin-15 and cisplatin co-encapsulated thermosensitive polypeptide hydrogels for combined immuno-chemotherapy. *Journal of Controlled Release*. 2017;255:81–93.[54] Copyright @ 2017 Elsevier B.V. (**c**) Schematic showing the injectable immunotherapeutic thermogel for enhanced immunotherapy post radiofrequency ablation (RFA). A large number of immunogenic tumor debris and "danger signals" are released after RFA, which could trigger robust anti-tumor immune responses together with ROCK inhibitor (Y27632) released from the thermosgel. Reproduced from Chen M, Tan Y, Hu J et al. Injectable Immunotherapeutic Thermogel for Enhanced Immunotherapy Post Tumor Radiofrequency Ablation. *Small*. 2021;17(52):2,104,773.[55] Copyright @ 2021 Wiley-VCH GmbH (**d**) Schematic illustration of multifunctional core–shell hybrid nano-gels. The anticancer drug (curcumin) and bifunctional nanoparticles (BFNP) are coated with an outer poly (NIPAM-AAm)-based gel layer to offer both stability in aqueous media and temperature sensitivity. Reproduced from Wang H, Yi J, Mukherjee S, Banerjee P, Zhou S, Magnetic/NIR-thermally responsive hybrid nanogels for optical temperature sensing, tumor cell imaging and triggered drug release. *Nanoscale*, 2014, **6**, 13,001.[66] Copyright @ 2014 Royal Society of Chemistry (**e**) Hydrogels have adjustable, controlled H_2O_2 release across the entire white spectral range. Reproduced from Wang, C., Gao, Y., Gao, X. et al Synergistic effect of sunlight induced photothermal conversion and H_2O_2 release based on hybridized tungsten oxide gel for cancer inhibition. *Sci Rep* 6, 35,876 (2016).[68] Copyright @ 2016, The Author(s). Creative Commons Attribution 4.0 International License.

Non-PEG Synthetic Polymer Hydrogels

In addition to PEG hydrogels, other synthetic polymer hydrogels are also widely used to treat malignant melanoma. Like PEG hydrogels, the primary application of the majority of synthetic hydrogels is drug delivery. Mario et al synthesized acrylic acid hydrogels as a platform for releasing cisplatin.[61] Additionally, in hydrogels composed of polyacrylic acid, glycerol, and dimethyl sulfoxide, recombinant heat-shock protein 70 kDa (HSP70) molecular chaperones and genistein have been proven effective in treating melanoma.[64] In addition to PEG, other polymer hydrogels can also be engineered into smart hydrogels to achieve on-demand drug release. Havanur et al synthesized poly(N, N-diethyl acrylamide) nanothermosensitive hydrogels capable of temperature-responsive release of DOX.[65] Furthermore, many multifunctional hydrogel systems have been developed, one example is a multifunctional core-shell hybrid nanogel with fluorescence and magnetic properties. This hydrogel, constructed with a thermoresponsive poly(N-isopropylacrylamide-co-acrylamide)

shell containing dual-functional nanoparticles, accomplishes three distinct functions: optical temperature sensing, tumor cell imaging, and acting as magnetic/near-infrared thermal drug carrier (Figure 7d).[66] Alvi et al prepared thermosensitive hydrogels by mixing Pluronic F-127, polyvinyl alcohol, and albumin, achieving a pH-responsive release of DOX.[67] Moreover, synthetic polymer hydrogels can kill malignant melanoma cells by releasing H_2O_2. The synthesis of tungsten oxide and poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) into hydrogels allowed for regulating H_2O_2 release by adjusting light exposure (Figure 7e).[68]

In general, artificially synthesized polymer hydrogels exhibit good biocompatibility and biodegradability. Furthermore, they exhibit strong modifiability, enabling them to make physical and chemical modifications according to different scenarios and requirements. However, polymer hydrogel materials face challenges, including inadequate tissue adhesion, and their utility is predominantly confined to drug delivery. Future research can explore various aspects of optimizing artificially synthesized polymer hydrogels. Polymer hydrogels can be modified with composite materials to enhance their mechanical properties and introduce special features. Moreover, integrating advanced 3D printing techniques allows for the precise formation of hydrogels into specific structures, including microneedles.[86] Besides, developing multi-stimulus-responsive systems can reduce the reliance on singular stimuli, thereby enabling on-demand drug release at various stages of treatment.[87] These advancements will expand the potential applications of polymer hydrogels and provide more comprehensive treatment options for malignant melanoma.

Other Types of Hydrogels: Polysaccharide-Based and Metal-Based Systems

In addition to the hydrogels above, there are various other sugar-based and metal hydrogels. Polysaccharide hydrogels are characterized by their natural origin, ease of functionalization, and low immunogenicity, making them promising candidates for biomedical applications.[88] Jia et al developed a novel hydrogel by combining chitosan oligosaccharide (COS) with lipoic acid (LA), which could continuously release LA and COS. This material has disrupted the "vicious cycle" between residual tumor cells and postoperative inflammation (Figure 8a).[69] Pourbadiei et al integrated an azobenzene derivative and N-isopropyl acrylamide copolymer into starch hydrogel as photosensitive and thermosensitive components, respectively, facilitating the controlled release of PTX.[70] Sugar-based hydrogels have been demonstrated to complement glutathione (GSH) depletion therapy. Ding et al developed a disulfide-crosslinked oxidized dextran hydrogel for enhanced GSH depletion and hypoxia-activated chemotherapy, which can degrade and release drugs in response to increasing pH and H_2O_2 levels.[71] Bera et al discovered that a subcutaneously implanted hydrogel, synthesized by coordinating NSAIDs and 5-AP with Zn (II), exhibited significant anti-tumor effects against melanoma cell (B16-F10)-induced tumors in a C57BL/6 mouse model. The study demonstrated that this hydrogel effectively reduces PGE2 expression, leading to the upregulation of IFN-γ and IL-12, which activate M1 macrophages to stimulate $CD8^+$ T cells and induce tumor cell apoptosis (Figure 8b).[72] Future research should aim to broaden the range of hydrogel types and produce more cost-effective alternatives. Furthermore, incorporating metal hydrogels, known for their superior mechanical properties, in conjunction with other materials can address the mechanical constraints typically associated with hydrogels.

Roles of Hydrogels in Melanoma Therapy

Hydrogel is a versatile component in the treatment of melanoma, exhibiting potent anti-tumor effects when loaded with specific therapeutic agents.[83] In addition to its independent efficacy in melanoma treatment, hydrogel synergistically improves the effectiveness of other therapeutic approaches by establishing an optimal therapeutic environment and facilitating the delivery of multiple treatment modalities.[83] The following section will explore the multifaceted role of hydrogel in melanoma therapy, emphasizing its diverse functions in treating this malignancy (Figure 9).

Drug Delivery

Hydrogels are three-dimensional network-structured materials with high water absorption and biocompatibility, extensively used in melanoma drug delivery.[83] They can absorb large amounts of water, forming a gel-like structure that is an ideal drug carrier, ensuring their stability and effectiveness.

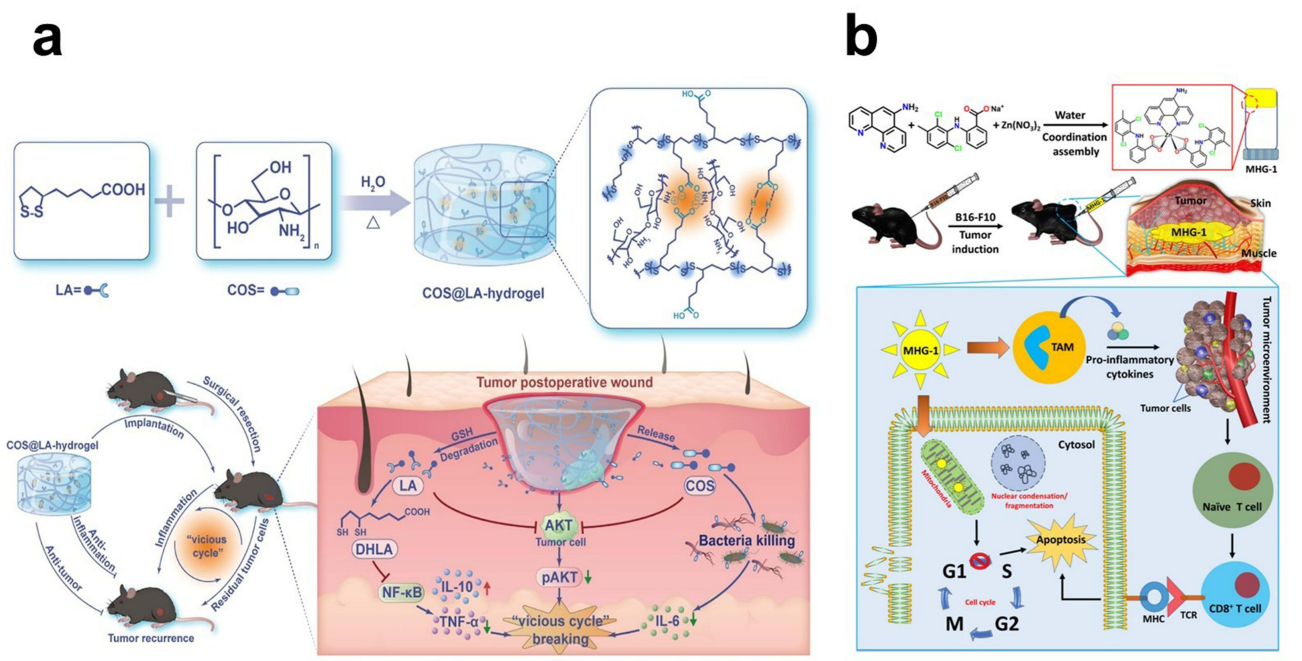

Figure 8 Applications of Other types of hydrogels in melanoma treatment. (**a**) Introducing chito-oligosaccharide into the lipoic acid hydrogel can break the vicious cycle of postoperative melanoma residue and inflammation. Reproduced from Jia M, Lu R, Liu C, Zhou X, Li P, Zhang S. In Situ Implantation of Chitosan Oligosaccharide-Doped Lipoic Acid Hydrogel Breaks the "Vicious Cycle" of Inflammation and Residual Tumor Cell for Postoperative Skin Cancer Therapy. *ACS Appl Mater Interfaces*. 2023;15(27):32,824–32,838.[69] Copyright @ 2023, American Chemical Society. (**b**) Subcutaneous injection of the hydrogel (MHG-1) to the melanoma-induced tumor site in a C57BL/6 mouse model showed a remarkable anti-tumor effect; upregulation of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-12, IL-2 and IL-6) observed in the hydrogel-treated tumor tissue further supported the apoptotic pathway and increased the cytotoxic T cell population. Reproduced from Bera S, Datta HK, Dastidar P, An injectable supramolecular hydrogel as a self-drug-delivery system for local chemoimmunotherapy against melanoma. *Biomater. Sci*., 2023, 11, 5618.[72] Copyright @ 2023, Royal Society of Chemistry.

Abbreviations: TAM, tumor associated macrophages; MHG-1, metallohydrogel-1; MHC, major histocompatibility complex; TCR, T cell receptor.

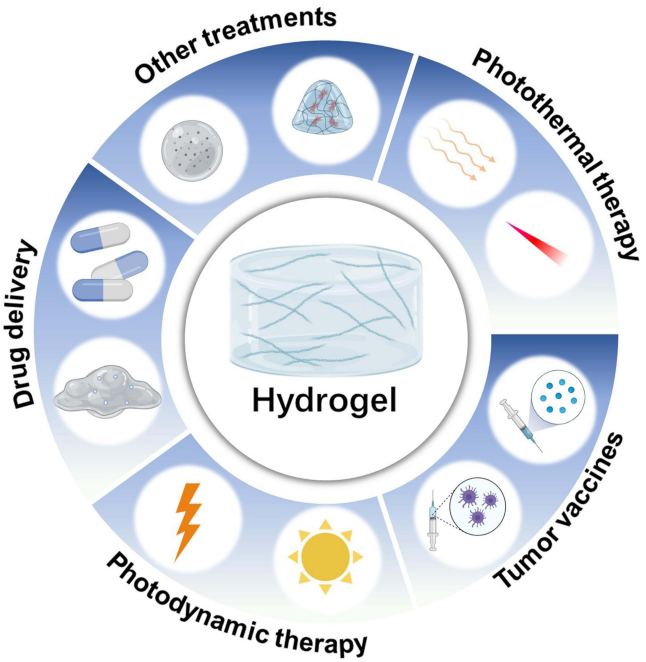

Figure 9 Roles of hydrogels in melanoma therapy.

https://doi.org/10.2147/IJN.S535220

First, hydrogels are frequently used as ideal carriers for chemotherapy drugs, effectively delivering them to target tissues. This helps to increase the local concentration of chemotherapy drugs and reduce their impact on healthy tissues. Researchers have encapsulated PTX in liposomes or transferrin before loading them into hydrogels to construct transdermal drug delivery systems for melanoma therapy.[39,40] Additionally, DOX is a common chemotherapy drug. Won et al developed chitosan hydrogel-containing systems that enable the controlled release of DOX under NIR irradiation and enhance its retention time in tumor tissues (Figure 10a).[25] In addition to the two drugs mentioned above, Asif Nawaz et al prepared a thermosensitive hydrogel containing 5-FU that can continuously deliver 5-FU to the skin.[24]

Cancer immunotherapy aims to provide patients with anticancer immunity, eradicate cancer, and prevent recurrence using the patient's immune system.[90] Currently, multiple studies have used hydrogels as carriers for cancer immunotherapy drugs. Immunotherapy can be divided into four categories: immune checkpoint inhibitors (PD-1/L1), tumor vaccines, CAR-T, and nonspecific immune modulators. Tumor vaccines will be discussed in detail later. This section only discusses the application of hydrogels in the remaining three parts. First, immune checkpoint inhibitors. Li et al used chitosan hydrogels to deliver an anti-protein hydrolysis D peptide (OPBP-1), significantly enhancing the oral bioavailability of peptide drugs, compared with the other experimental groups, the tumor size of the hydrogel group showed a significant reduction (Figure 10b).[20] The tumor microenvironment is an essential factor in treating tumors. According to Yu et al, it releases aPD-L1 and dextro-1-methyl tryptophan in response to ROS levels in the tumor microenvironment.[43] Li et al constructed a dual delivery system of celecoxib and aPD-1 using alginate hydrogels, reshaping tumors' immune, inflammatory, and angiogenic microenvironments.[14]

In addition to immune checkpoint inhibitors, nonspecific immune modulators are frequently used with hydrogels for melanoma treatment. Duong et al developed hydrogels containing functionalized HA with levodopa and polyester, loaded with nano complexes of immune regulatory factors and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Figure 10c).[35] Additionally, some studies have loaded rho-associated kinase inhibitor Y27632, aCD40, timosaponin AIII, recombinant HSP70 molecular chaperone and genipin, intralesional Mycobacterium bovis BCG lysate, and calmodulin-dependent protein kinase II (CAMKII) inhibitor[41,49,51,55,63,64] into hydrogels to enhance anti-tumor immunity. Hydrogels provide an ideal carrier for immune modulators. Hydrogel delivery systems facilitate the integration of two immunotherapy methods, resulting in a synergistic therapeutic effect that surpasses the sum of their components. Hu et al utilized chimeric antigen receptor T cell immunotherapy and aPD-L1 delivered through HA hydrogels to prevent tumor recurrence after surgery.[33] Targeted therapy intervenes in tumor cells' growth, proliferation, or survival mechanisms by interfering with specific cell molecules required for cancer development and tumor growth. Hydrogels can encapsulate targeted drugs, thereby facilitating their slow and sustained release as drug carriers. This release method can maintain the concentration of drugs in tumor tissue, more precisely target tumor cells, and reduce the impact on normal cells. Better treatment for melanoma can be achieved by integrating additional functionalities into targeted therapy. Jia et al developed a novel material combining COS with LA hydrogel to disrupt the "vicious cycle" between residual tumor cells and postoperative inflammation.[69]

Furthermore, hydrogels can combine with metals, such as zinc and silver, to enhance the anti-melanoma effect. Alba Cano-Vicent et al reported an alginate hydrogel cross-linked with calcium and zinc ions, which releases an appropriate amount of zinc to exert anti-melanoma effects (Figure 10d).[89] In addition to zinc ions, Zhao et al incorporated silver nanoparticles into chitosan/starch hybrid hydrogels, conferring significant anti-melanoma capability to the hydrogel.[91]

Moreover, hydrogels provide an ideal carrier for combination therapy involving multiple treatment modalities, synergistically treating melanoma. Lv et al utilized PEG hydrogel to deliver DOX, IL-2, and IFN-γ for local melanoma treatment.[48] Shi et al developed an injectable thermosensitive polypeptide hydrogel for delivering aPD-L1 and DOX (Figure 10e),[44] in addition to immunomodulatory therapy. Chemical dynamic therapy and sonodynamic therapy can be integrated by utilizing hydrogel systems. Zheng et al demonstrated that chitosan thermosensitive hydrogels enhance chemotherapy sonodynamic therapy and have potential applications in photothermal therapy.[31] Finally, Xiaoran Ding et al also developed a multifunctional dextran hydrogel to assist in GSH depletion therapy and chemotherapy. This hydrogel increases GSH consumption and can activate chemotherapy under hypoxic and acidic conditions. With pH and

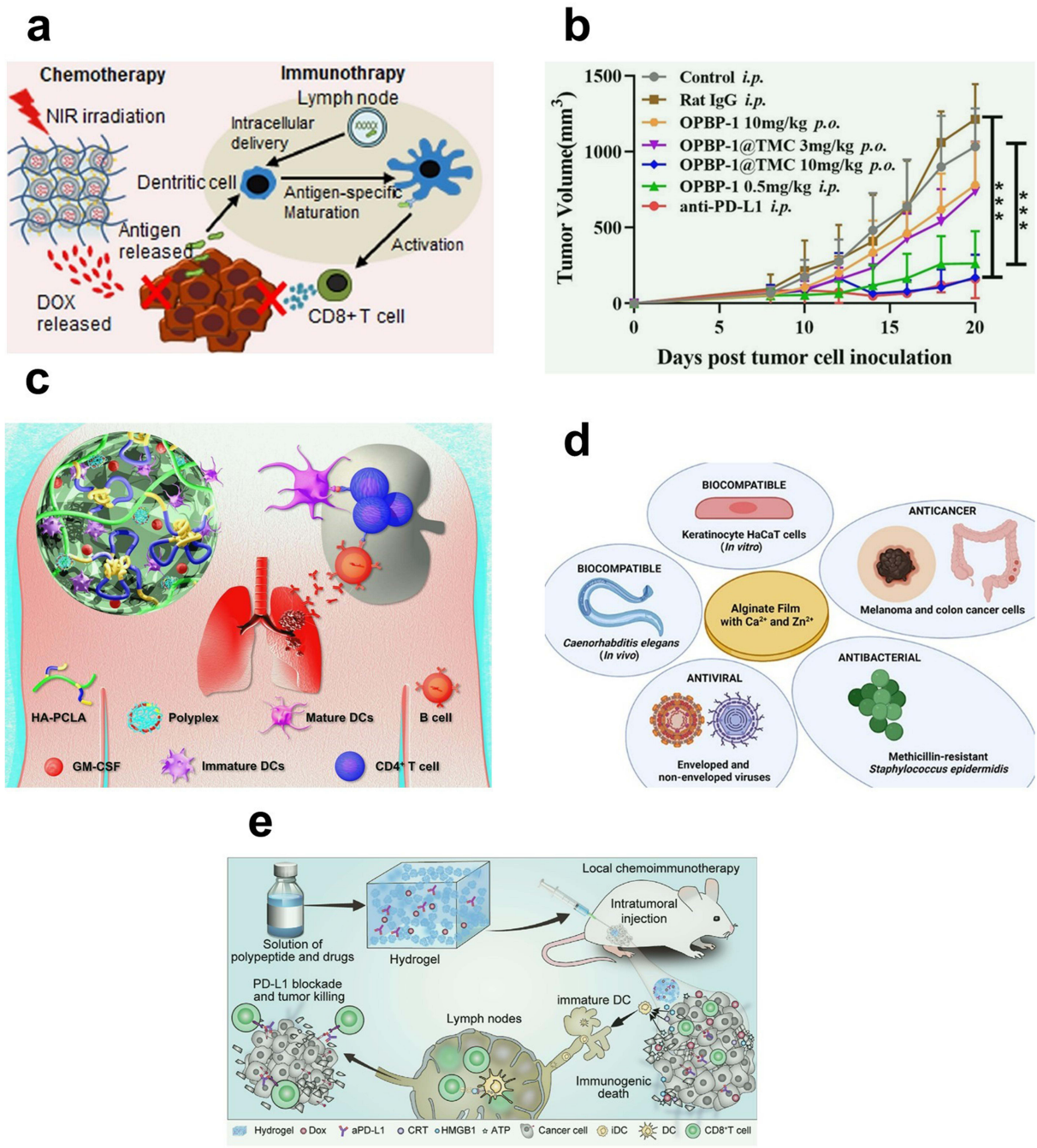

Figure 10 Applications of hydrogels in drug delivery. (**a**) Under external NIR irradiation, chitosan hydrogel containing doxorubicin can control drug release and integrate with immunotherapy. Reproduced from Won JE, Wi TI, Lee CM et al. NIR irradiation-controlled drug release utilizing injectable hydrogels containing gold-labeled liposomes for the treatment of melanoma cancer. *Acta Biomaterialia*. 2021;136:508–518.[25] *© 2021 The Author(s). Published by Elsevier Ltd on behalf of Acta Materialia Inc.* Creative Commons CC-BY-NC-ND license (**b**) The in vivo anti-tumor effects of oral an anti-protein hydrolysis D peptide (OPBP-1) loaded N, N, N-trimethyl chitosan (TMC) hydrogel on CT26 tumor-bearing mice. Data were shown as means ± SD, n = 5 or n = 3. **, P <0.01; ***, P < 0.001. Reproduced from Li W, Zhu X, Zhou X et al. An orally available PD-1/PD-L1 blocking peptide OPBP-1-loaded trimethyl chitosan hydrogel for cancer immunotherapy. *Journal of Controlled Release*. 2021;334:376–388.[20] Copyright @ 2021 Elsevier B.V. (**c**) Schematic of the 3D microenvironment network of injectable smart hydrogels co-loaded with immunomodulatory factor GM-CSF and DNA polyplex. The controlled release of GM-CSF allows the massive invasion of immune cells into the network, and the subsequent transfection of nano-sized immunomodulatory factor-bearing polyplexes allows the maturization of DCs. Subsequently DCs bound with MHCII complex induced the production of tumor-specific antibody to induce antitumor immunity. Reproduced from Duong HTT, Thambi T, Yin Y et al. Degradation-regulated architecture of injectable smart hydrogels enhances humoral immune response and potentiates antitumor activity in human lung carcinoma. *Biomaterials*. 2020;230:119,599.[35] Copyright @ 2019 Elsevier Ltd. (**d**) Calcium alginate hydrogels cross-linked with zinc can release the right amount of zinc to protect against melanoma and have antimicrobial properties. Reproduced from Cano-Vicent A, Tuñón-Molina A, Bakshi H et al. Biocompatible Alginate Film Crosslinked with Ca^{2+} and Zn^{2+} Possesses Antibacterial, Antiviral, and Anticancer Activities. *ACS Omega*. 2023;8(27):24,396–24,405.[89] Copyright @ 2023 The Authors. Published by American Chemical Society. CC-BY 4.0 (**e**) The Peptide hydrogel could co-delivery aPD-L1 and DOX after intratumoral injection. Reproduced from Shi Y, Li D, He C, Chen X. Design of an Injectable Polypeptide Hydrogel Depot Containing the Immune Checkpoint Blocker Anti-PD-L1 and Doxorubicin to Enhance Antitumor Combination Therapy. *Macromolecular Bioscience*. 2021;21(6):2,100,049.[44] Copyright @ 2021 Wiley-VCH GmbH.

https://doi.org/10.2147/IJN.S535220

dual redox response characteristics, this hydrogel can release loaded drugs as pH and H_2O_2 increase, playing a role in local melanoma treatment.[71]

In summary, hydrogels have been extensively investigated and applied in the treatment of melanoma due to their high biocompatibility, water-absorbing capacity, biodegradability, controlled drug release capability, targeted delivery, and multifunctionality. They provide an ideal carrier for local treatment of melanoma and facilitate the combination of various treatment modalities. However, hydrogels also have limitations in drug delivery. When delivering drugs transdermally, especially to deep-seated melanoma cells, hydrogels face challenges posed by multiple layers of tissue. This may affect the distribution and efficacy of drugs. Furthermore, due to the molecular complexity of melanoma, combination therapy is often required to maximize treatment efficacy and avoid resistance mechanisms, resulting in a better long-term prognosis. When used as a carrier for combination therapy, factors including the quantity, type, and proportion of drugs or other materials in the hydrogel should be considered. Finally, future research should focus on improving the delivery efficiency of hydrogels, enhancing their transdermal capabilities, combining hydrogels with novel treatment technologies, evaluating the practical effectiveness and safety of hydrogels in treating malignant melanoma, and designing personalized hydrogels to precisely deliver the required drugs, thereby increasing the personalized treatment.

Photothermal Therapy (PTT)

PTT represents a promising approach for cancer treatment, characterized by excellent anticancer efficacy, high specificity, low invasiveness, and minimal side effects.[92] The principle involves the photothermal agents absorbing photon energy, increasing the surrounding microenvironmental temperature, thereby inducing the death of tumor cells.[93] In addition, PTT can accelerate the depletion of glutathione (GSH), facilitating efficient anti-tumor therapy.[94] However, common adverse reactions associated with photothermal therapy arise from the thermal damage to normal tissues.[95] Incorporating photothermal agents into hydrogels can restrict their localization to tumor sites, thereby reducing the penetration of PTT into normal tissues and alleviating adverse reactions. Furthermore, limitations of PTT include limited penetration depth of light, inability to act on tumor tissues beyond the radiation range, and the inadequacy of a single photothermal treatment to eliminate tumors, potentially leading to tumor recurrence and metastasis. Consequently, introducing hydrogels can enhance the overall therapeutic efficacy by combining PTT with other treatment modalities targeting tumor tissues.

Ma et al fabricated hydrogels utilizing calcium silicate nanowires and sodium alginate as precursors, incorporating OPC to impart superior photothermal regulation capabilities to the hydrogel.[74] Furthermore, hydrogels have been used to deliver manganese-doped calcium silicate nanowires or polydopamine nanoparticles for photothermal therapy-induced tumor cell ablation (Figure 11a).[15,18] PTT can be combined with chemotherapy and immunotherapy in the treatment of melanoma with the help of hydrogels. The intelligent release of DOX and the incorporation of photothermal agents into hydrogels, which employ the pH sensitivity of alginate hydrogels or specially designed hydrogels, achieve synergistic photothermal and chemotherapy. Daniela N. Céspedes-Valenzuela and her team designed a photothermal-responsive hydrogel composed of chitosan methacrylate, porcine small intestine submucosa methacrylate, and reduced graphene oxide-doxorubicin complexes. This hydrogel effectively eliminates residual tumors after surgery by combining NIR-induced photothermal therapy with heat-triggered doxorubicin release (Figure 11b).[30] Xia et al synthesized IR820-conjugated α-cyclodextrin copolymers and polyethylene glycol to form IR820-hydrogels, which, when loaded with immunoadjuvants, achieve the combination of photothermal therapy and immunotherapy through their fusion (Figure 11c).[60] Hydrogels are effective carriers for combining photothermal therapy with other treatments and protect photosensitizers from decomposition, thereby effectively enhancing photothermal conversion effects. Hwang et al encapsulated indocyanine green in hydrogels, endowing them with photothermal properties while protecting indocyanine green from decomposition by the human body.[96]

The introduction of hydrogels significantly enhances the therapeutic efficacy of photothermal therapy and effectively addresses its limitations. However, loading more materials into hydrogels for combined photothermal therapy can affect the efficacy of photosensitizers. Consequently, balancing hydrogel design and final treatment outcomes is crucial for future research. Moreover, in promoting the synergy of photothermal therapy with other treatments, the inadequacy of

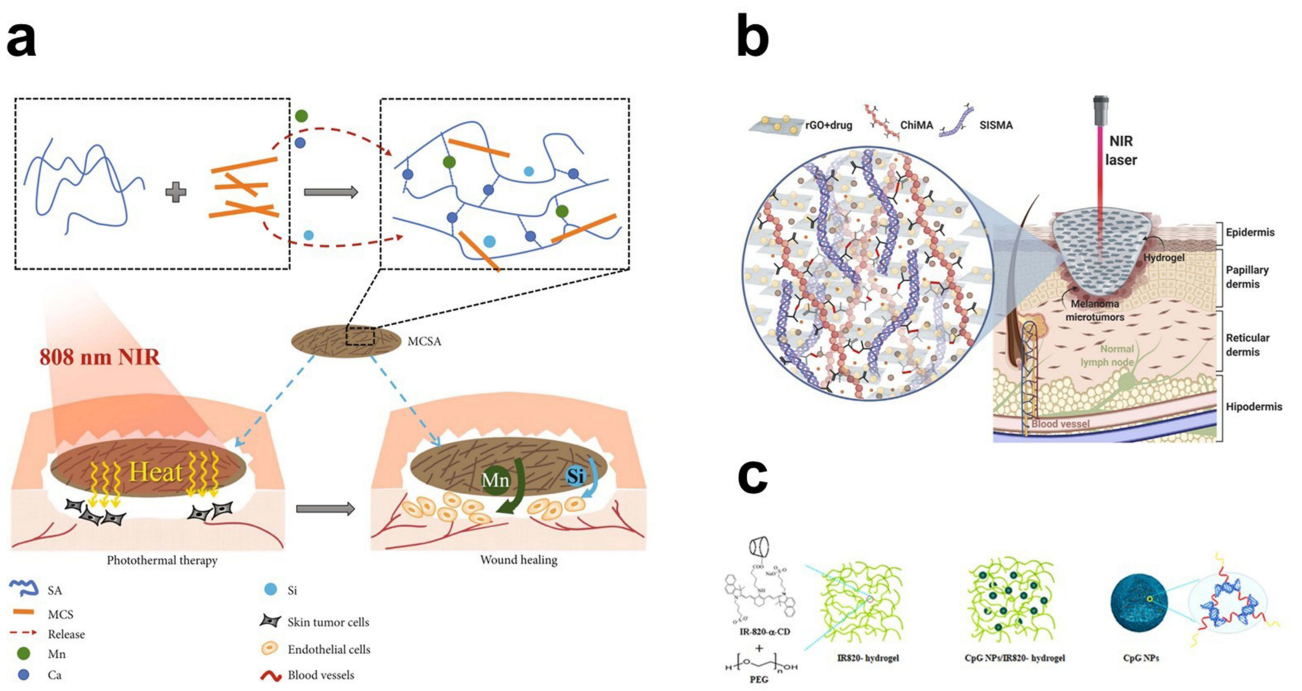

Figure 11 Applications of hydrogels in PTT. (**a**) Photothermal therapy of melanoma and enhanced wound healing based on the composite hydrogels. Reproduced Wu Z, Zhuang H, Ma B et al. Manganese-Doped Calcium Silicate Nanowire Composite Hydrogels for Melanoma Treatment and Wound Healing. *Research*. 2021;2021:2021/9,780,943.[18] Copyright @ 2021 Zhongcao Wu et al (**b**) When stimulated with a NIR laser, the reduced graphene oxide (rGO) in the hydrogel generates local hyperthermia by converting light into heat. Subsequently, DOX is released from the hydrogel, as the increasing temperature breaks the azo bonds that link the anticancer drug to the GO vehicle. Reproduced from Céspedes-Valenzuela DN, Sánchez-Rentería S, Cifuentes J, Gómez SC, Serna JA, Rueda-Gensini L, Ostos C, Muñoz-Camargo C and Cruz JC (2022) Novel Photo- and Thermo-Responsive Nanocomposite Hydrogels Based on Functionalized rGO and Modified SIS/Chitosan Polymers for Localized Treatment of Malignant Cutaneous Melanoma. *Front. Bioeng. Biotechnol.* 10:947,616.[30] © 2022 Céspedes-Valenzuela, Sánchez-Rentería, Cifuentes, Gómez, Serna, Rueda-Gensini, Ostos, Muñoz-Camargo and Cruz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). (**c**) Structure of CpG NPs/IR820-hydrogel. Reproduced from Dong X, Liang J, Yang A, Qian Z, Kong D, Lv F. Fluorescence imaging guided CpG nanoparticles-loaded IR820-hydrogel for synergistic photothermal immunotherapy. *Biomaterials*. 2019;209:111–125. doi:10.1016/j.biomaterials.2019.04.024.[60] Copyright @ 2019 Elsevier Ltd.

single phototherapy cannot be addressed by simply combining multiple treatment modalities. Future research should focus on expanding the synergistic effects of these treatments.

Photodynamic Therapy (PDT)

PDT represents another phototherapy method besides photothermal therapy. The principle of PDT involves the accumulation of photosensitizers in pathological tissues, activating photosensitizers by absorbing light at appropriate wavelengths, selectively destroying tumor cells, or transferring energy from photosensitizers to surrounding oxygen molecules and generating highly reactive singlet oxygen. Singlet oxygen undergoes oxidation reactions with nearby biomolecules, resulting in cytotoxicity and consequently damaging the lesioned cells.[97]

The three essential factors for PDT are light, photosensitizers, and oxygen. However, tumor hypoxia is a common characteristic of solid tumors, making it a crucial factor that must be considered in PDT. Singlet oxygen can only be generated in the presence of oxygen, thereby exerting the tumor-killing effect of PDT. Researchers have addressed the issue of tumor hypoxia in PDT by introducing hydrogels. Zhang et al developed a multifunctional oxygen-producing hydrogel, which exhibited significant phototoxicity against B16F10 tumors under near-infrared radiation, effectively alleviating the tumor hypoxic microenvironment and improving PDT efficiency (Figure 12a).[38] Moreover, the therapeutic effect can be improved by utilizing the hypoxic environment of tumors. Zhou et al developed a photoresponsive hydrogel incorporating sodium alginate solution with nanoparticles, hypoxia-responsive TPZ, and Gox. These semiconductor nanoparticles mediated photodynamic reactions and oxygen depletion, while GOx further depleted oxygen, collectively activating TPZ for chemotherapy (Figure 12b).[17] PDT, like PTT, risks causing damage to normal tissues. Therefore, hydrogels can effectively target tumor cells and control PDT. Farnaz Azadikhah et al developed a novel antioxidant-

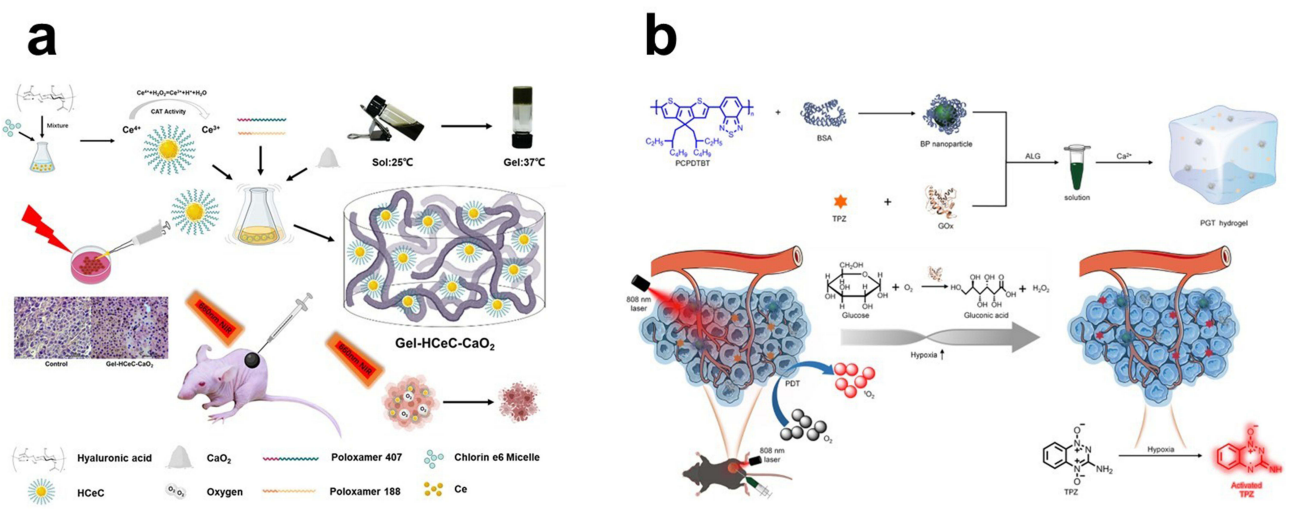

Figure 12 Applications of hydrogels in PDT. (**a**) A multifunctional oxygen-generating hydrogel loaded with hyaluronic acid-chlorin e6 modified nanoceria and calcium peroxide (Gel-HCeC-CaO_2) could alleviate tumor hypoxia microenvironment, prolong drug supply, enhance PDT efficacy, and overcome melanoma. Reproduced from Zhang L, Liu X, Mao Y, Rong S, Chen Y, Qi Y, Cai Z and Li H (2023) Inhibition of melanoma using a nanoceria-based prolonged oxygen-generating phototherapy hydrogel. *Front. Oncol*. 13:1,126,094.[38] Copyright © 2023 Zhang, Liu, Mao, Rong, Chen, Qi, Cai and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). (**b**) An alginate hydrogel containing streptozotocin (STZ) and glucose oxidase (GOx) is used in combination with phototherapy and chemotherapy for melanoma treatment. Reproduced from Zhou J, Liu C, Wang Y et al. Prodrug and Glucose Oxidase Coloaded Photodynamic Hydrogels for Combinational Therapy of Melanoma. *ACS Biomater Sci Eng*. 2022;8(11):4886–4895.[17] Copyright @ 2022, American Chemical Society.

photosensitive hydrogel for controlling PDT activity in cancer treatment. The natural polyphenol antioxidant tannic acid in the hydrogel effectively controls the level of ROS and mitigates damage to healthy cells and tissues by removing singlet oxygen.[32]

The problem of insufficient oxygen in tumors can be addressed by catalyzing excessive hydrogen peroxide within tumors using specially designed hydrogels or by directly releasing oxygen from hydrogels into tumor sites. Moreover, improving the hypoxic microenvironment of tumors inhibits tumor growth and metastasis. Therefore, future research can focus on developing innovative hydrogels that can release oxygen and catalyze hydrogen peroxide. These methods, like PDT and PTT, are also susceptible to the negative effects of inadequate light penetration and tissue damage. Hydrogels can assist PTT in targeting tumor cells and controlling ROS levels. However, research on hydrogels enhancing ROS-excited light penetration is limited. Therefore, additional research can be conducted to improve light penetration, enabling hydrogels to effectively complement PDT for melanoma treatment. Finally, hydrogels can help address the inadequacy of single ROS-based treatments by combining PDT with other treatment methods, making them an ideal delivery system.

Tumor Vaccines

Recently, tumor vaccines have emerged as a promising, minimally toxic, and targeted immunotherapy option. They can effectively treat tumors and induce long-term memory of tumor-specific immune responses, providing protection against recurrence and metastasis.[98] Loading tumor vaccines into hydrogels can facilitate the injection of melanoma vaccines into tumors and provide a platform to combine these vaccines with other treatment methods for melanoma therapy. Hydrogel-assisted treatment of melanoma primarily employs three vaccine platforms: cellular vaccines, viral vector vaccines, and protein vaccines.

Most tumor vaccines are cell-based, which offers the benefit of not requiring antigen-target predetermination. Adding tumor cell lysates to specially designed hydrogels can achieve effective melanoma treatment. Meng et al utilized hydrogels for the delivery of the immunoadjuvant R837 (Figure 13a).[22] Highton et al incorporated ovalbumin antigen and adjuvant Quil-A into thermosensitive chitosan hydrogels, demonstrating the hydrogel's ability to elicit protective $CD8^+$ T cells, thereby exerting both preventative and therapeutic effects on tumors.[28] One advantage of viral vector vaccines is that the immune system can effectively respond to viruses by leveraging the joint action of innate and

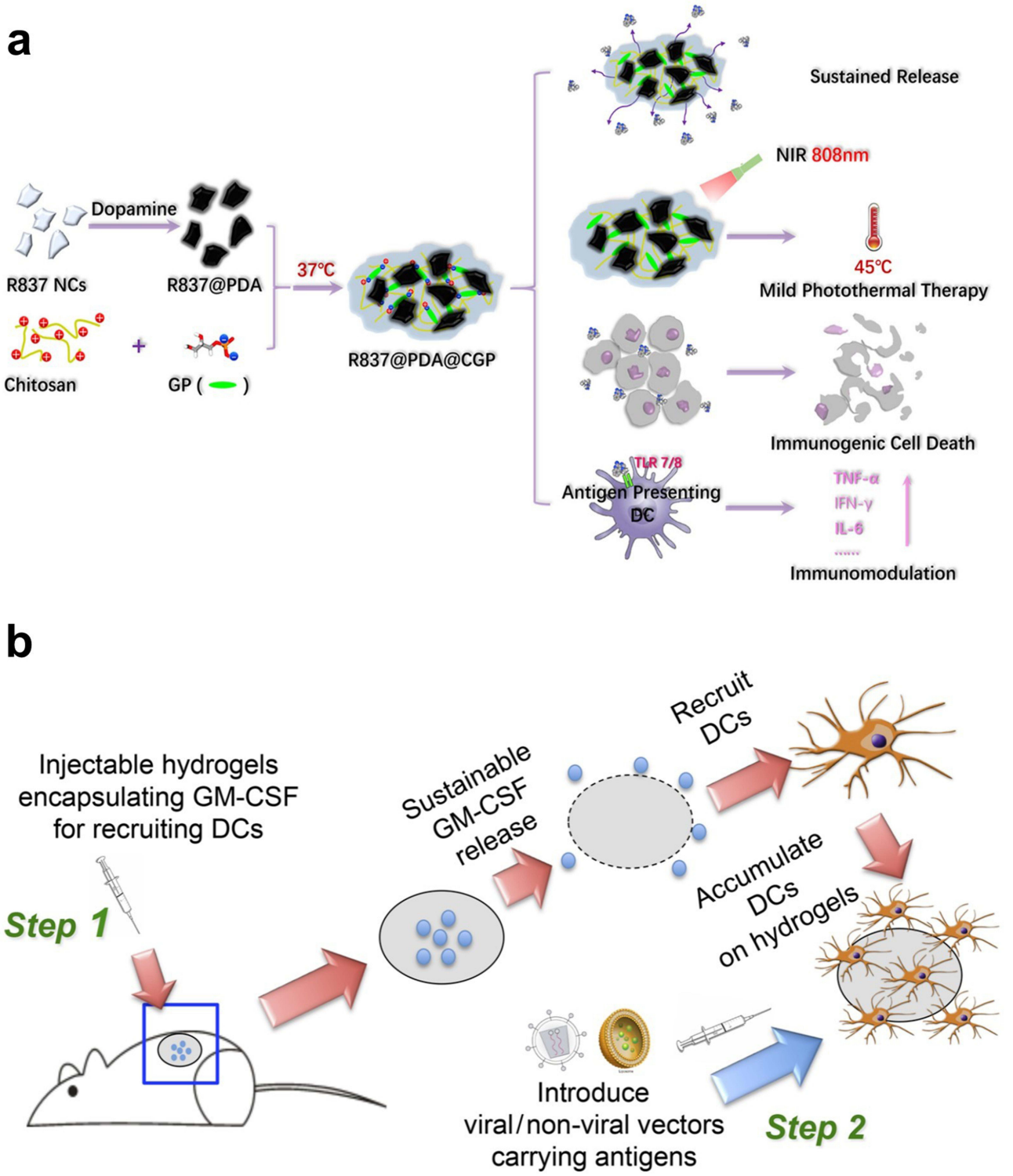

Figure 13 Applications of hydrogels in tumor vaccines. (**a**) The insoluble immune adjuvant imiquimod (R837) was prepared as nanocrystals, coated with PDA to form R837@PDA, and loaded into chitosan hydrogel to combine immunomodulation, induction of immunogenic cell death and immune enhancement. Reproduced from Meng Z, Fang X, Fu B et al. Tumor immunotherapy boosted by R837 nanocrystals through combining chemotherapy and mild hyperthermia. *Journal of Controlled Release*. 2022;350:841–856.[22] Copyright @ 2022 Elsevier B.V. (**b**) The thermosensitive hydrogel first continuously releases GM-CSF to recruit host dendritic cells (DCs) to the administration site, and then the immunogen-carrying vectors can be delivered to the DCs in situ in the hydrogel to improve antigen uptake efficiency. Reproduced Liu Y, Xiao L, Joo KI, Hu B, Fang J, Wang P. In Situ Modulation of Dendritic Cells by Injectable Thermosensitive Hydrogels for Cancer Vaccines in Mice. *Biomacromolecules*. 2014;15(10):3836–3845.[58] Copyright @ 2014 American Chemical Society.

adaptive immune mechanisms, resulting in a robust and enduring response. Liu et al divided the treatment into two steps: first, by releasing granulocyte-macrophage colony-stimulating factor, many DCs were recruited into the hydrogel. Then, antigens were introduced through viral vectors to initiate antigen presentation and trigger immune responses. This two-step strategy produced a high level of tumor-specific immunity, confirmed in both preventive and therapeutic models of melanoma in mice (Figure 13b).[58]

Recently, there has been a significant advancement in the research of tumor vaccines, and their clinical application has also been enhanced. However, tumor vaccines are just one type of immunotherapy. Like other treatment modalities, a single method is insufficient to completely cure melanoma, and it requires to be combined with other treatments. When combining with other treatments, it is important to consider whether adding other substances will affect the release of tumor vaccine antigens, immune adjuvants, and the affinity between antigens and antibodies. Future research should focus on combining tumor vaccines with surgical procedures, chemotherapy, and other treatments through hydrogels to achieve comprehensive treatment.

Hydrogel-Based Therapies in the Comprehensive Management of Melanoma

Hydrogel-based therapies represent an emerging treatment modality for melanoma, providing a versatile platform for transdermal drug delivery and multimodal therapeutic approaches. While their antitumor properties have been validated in numerous studies, hydrogels offer functionalities beyond monotherapy. In the comprehensive management of melanoma, hydrogels present several key advantages, not only enhancing therapeutic efficacy but also improving the patients' quality of life.

As an ideal moist wound dressing, hydrogels play a crucial role in post-surgical wound management. They effectively address wound infections, promote healing, and reduce the likelihood of tumor recurrence after melanoma resection.[69] Moreover, by incorporating tumor-targeting agents, hydrogels can be used in tumor imaging.[50] This functionality aids in determining the tumor's size, location, and metastasis, thereby supporting the formulation of more precise treatment strategies and facilitating the monitoring of therapeutic responses (Figure 14).

Additionally, hydrogels have shown promise in pain management, significantly contributing to an improved quality of life for patients.[23] The versatility and broad applicability of hydrogels in melanoma management underscore their potential for clinical translation, paving the way for innovative and effective therapeutic solutions.

Post-Surgical Wound Management

While hydrogel-based therapies have shown significant potential in melanoma treatment, surgical excision remains the cornerstone of management. However, incomplete tumor resection leaves residual tumor cells that serve as seeds for recurrence. Surgical excision also activates inflammatory pathways, releasing pro-inflammatory mediators that nourish these residual cells and recruit additional inflammatory cells to the tumor microenvironment. This perpetuates a vicious cycle of inflammation and tumor progression, ultimately facilitating recurrence.[69] Moreover, melanoma resection often results in large skin defects, which are highly susceptible to bacterial infections. These infections not only exacerbate inflammation but also increase the risk of tumor relapse. Recent studies have shown that incorporating LA into COS-based hydrogels can effectively disrupt this pathological cycle. The hydrogel gradually degrades at the implantation site, releasing LA and COS to inhibit AKT phosphorylation in the PI3K-AKT signaling pathway, thereby suppressing the proliferation of residual tumor cells. Furthermore, LA exhibits potent anti-inflammatory and antioxidant properties by reducing NF-κB, TNF-α, and ROS levels, while COS provides strong antibacterial effects to mitigate infection-induced inflammation.[69]

In addition to controlling inflammation and preventing recurrence, accelerating post-surgical wound healing is crucial. The large skin defects caused by melanoma resection can lead to chronic, non-healing wounds, severely impacting the patient's quality of life. Studies have shown that loading copper oxide (CuO_2) nanoparticles into chitosan-based hydrogels not only exhibit robust antimicrobial activity but also promote the proliferation of skin cells and angiogenesis, expediting the healing process of infected wounds (Figure 15a).[31] Similarly, hydrogels loaded with procyanidin

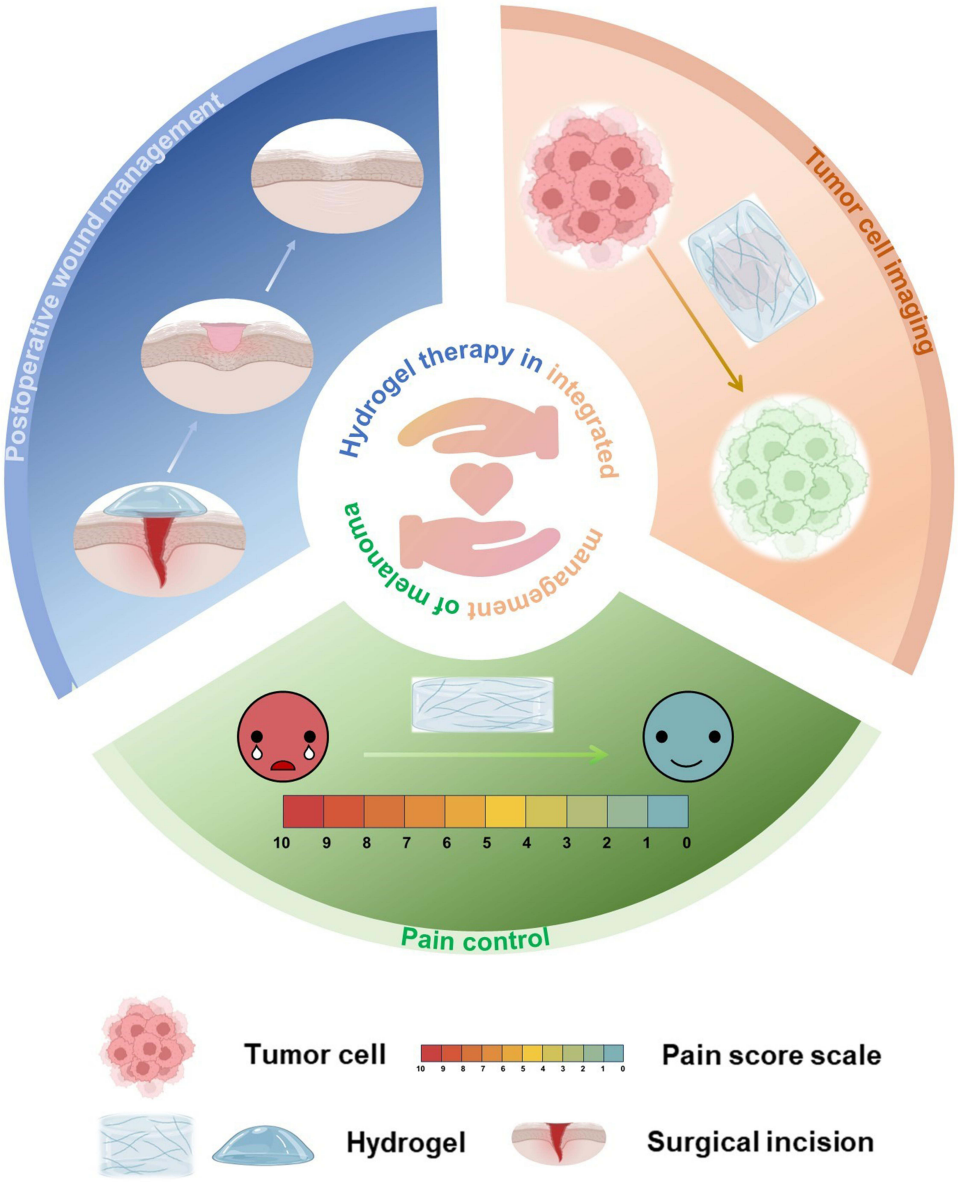

Figure 14 Comprehensive Management of Melanoma with Hydrogel.

oligomers function as a natural photothermal agents and enhance the proliferation and migration of dermal fibroblasts and endothelial cells, stimulating angiogenesis and skin regeneration.[74]

Tumor Cell Imaging

Tumor imaging is critical in cancer research and clinical practice, providing key information on tumor type, stage, and progression. Dynamic imaging, in particular, allows real-time monitoring of treatment outcomes, enabling early detection of recurrence and timely adjustments to therapy, which are essential for advancing precision medicine and follow-up care.

The incorporation of imaging agents, such as nanoparticles, into hydrogels endows these materials with diagnostic capabilities. For example, Wu et al functionalized gold nanoparticles (Ag-Au NPs) with HA and encapsulated them in PEG-based hydrogels. The HA moiety binds to CD44 receptors on B16F10 melanoma cells, promoting hydrogel internalization through receptor-mediated endocytosis. Upon exposure to 405 nm laser irradiation, the nanoparticles emit fluorescence, enabling both temperature sensing and precise tumor cell imaging (Figure 15b).[50] Similarly,

https://doi.org/10.2147/IJN.S535220

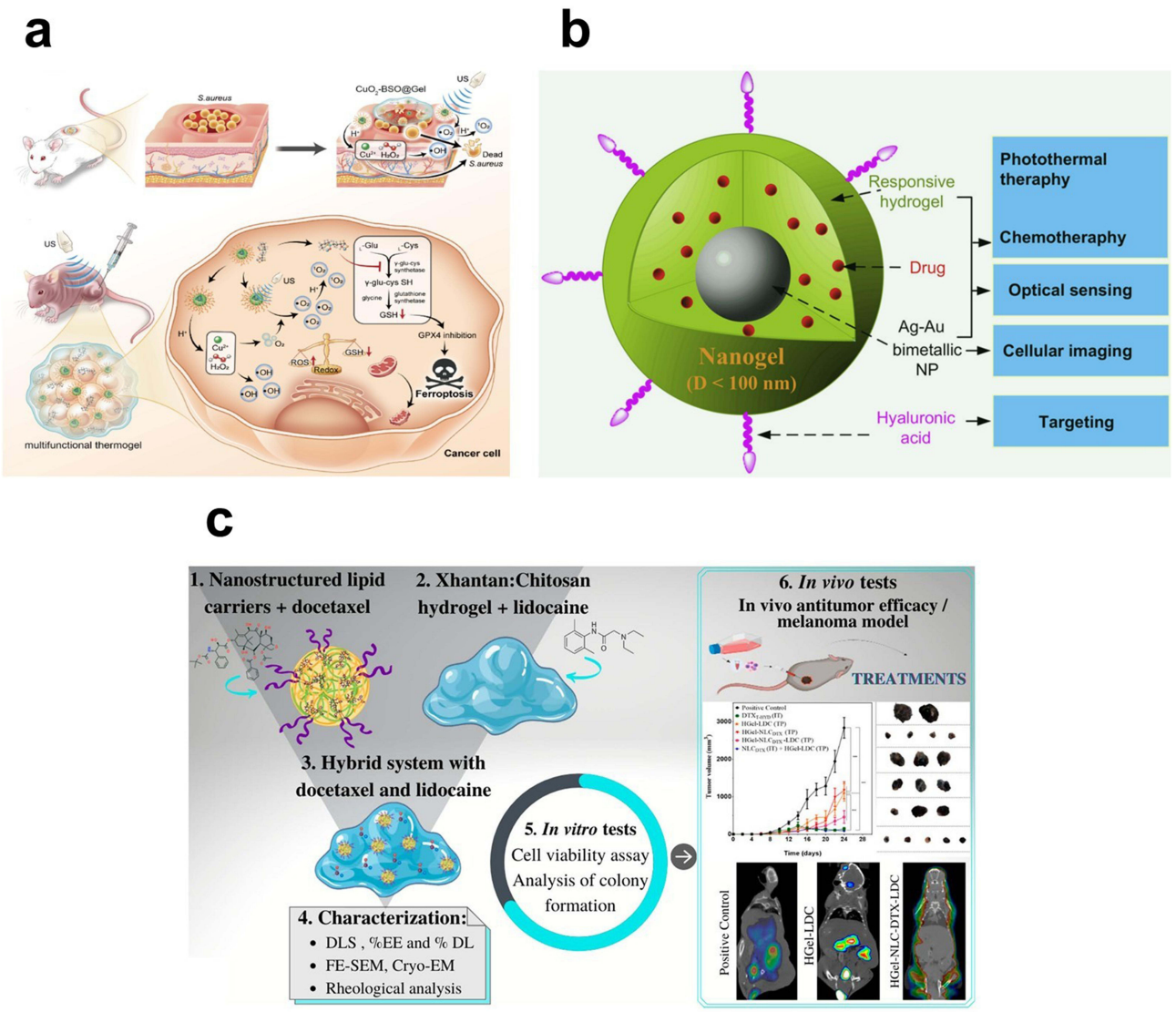

Figure 15 Integrated management of melanoma with hydrogel therapy. (**a**) An injectable CuO_2 nanodots-engineered thermosensitive chitosan hydrogel can enhance melanoma chemo-son dynamic therapy and improve infected wound healing. Reproduced from Zheng Y, Wang W, Gao Y, Wang W, Zhang R, Wu D, Yu L, Chen Y. Nanosonosensitizers-engineered injectable thermogel for augmented chemo-sonodynamic therapy of melanoma and infected wound healing. Mater Today Bio. 2023 Mar 31;20:100,621.[31] Copyright @ 2023 The Authors. Published by Elsevier Ltd. Creative Commons CC-BY-NC-ND license. (**b**) Schematic illustration of multifunctional core–shell hybrid nanogels for targeted drug delivery. The core consists of highly fluorescent and NIR-responsive Ag–Au bimetallic nanoparticles. The outer PEG-based thermoresponsive gel shell regulates fluorescence intensity and enables controlled drug release upon local temperature increase triggered by NIR irradiation. HA, as a targeting ligand, can effectively penetrate the surface gel network within the light penetration depth for enhanced targeting. Reproduced from Wu W, Shen J, Banerjee P, Zhou S. Core–shell hybrid nanogels for integration of optical temperature-sensing, targeted tumor cell imaging, and combined chemo-photothermal treatment. *Biomaterials*. 2010;31(29):7555–7566.[50] Copyright @ 2010 Elsevier Ltd. (**c**) The formulation of nanostructured lipid carriers loaded with docetaxel (NLCDTX) in xanthan-chitosan hydrogel containing lidocaine (LDC) with anticancer and analgesia effects. Reproduced from De Moura LD, Ribeiro LNM, De Carvalho FV et al. Docetaxel and Lidocaine Co-Loaded (NLC-in-Hydrogel) Hybrid System Designed for the Treatment of Melanoma. *Pharmaceutics*. 2021;13(10):1552.[23] © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

multifunctional hybrid nanogels have been developed to cross cellular barriers and enable intracellular imaging, thus broadening the scope of hydrogel-based imaging strategies.[66]

Pain Management

Pain associated with melanoma may arise from a combination of factors, including tumor-induced nerve compression, local inflammation, and surgical trauma. Effective pain management is crucial for improving the patient's quality of life and ensuring adherence to therapeutic regimens. To address this problem, Ludmilla David de Moura et al developed

a hybrid hydrogel system containing docetaxel and lidocaine. This formulation not only inhibits tumor progression but also provides localized analgesia, offering dual therapeutic benefits (Figure 15c).[23] Similarly, Zhang et al incorporated ropivacaine into a Pluronic F127-based hydrogel system used in photothermal therapy. This approach significantly alleviated the acute pain during melanoma ablation.[99] In addition, chemotherapy-induced peripheral neuropathy (CIPNP) remains a major clinical challenge in cancer pain management, often leading to debilitating discomfort. Jiqian Zhang et al addressed this issue by co-delivering ropivacaine and cisplatin using Pluronic F127 hydrogels. Their study found that cisplatin-loaded Pluronic F127 hydrogels induced severe CIPNP, as evidenced by an increased number of pERK-positive neurons in the dorsal root ganglion. Remarkably, the addition of ropivacaine effectively alleviated CIPNP for more than 10 hours. Furthermore, ropivacaine upregulated the expression of major histocompatibility complex class I on tumor cells, facilitating $CD8^+$ T-cell infiltration and enhancing the antitumor efficacy of chemotherapy.[100]

Challenges in the Clinical Translation of Hydrogel-Based Therapies for Melanoma

Unlike conventional melanoma treatments, hydrogel-based therapies offer a flexible platform for integrating multiple therapeutic strategies by carefully selecting and combining materials and drugs. This versatility enables the incorporation of synergistic treatment modalities, potentially improving therapeutic outcomes. However, the clinical translation of these sophisticated hydrogel systems remains challenging, primarily due to the complex interactions between materials and drugs within the hydrogel matrix, which may result in unpredictable effects on therapeutic efficacy and increase the risk of damage to healthy tissues, thereby complicating clinical application. Overcoming these challenges necessitates a thorough investigation of the mechanisms underlying material compatibility and drug interactions. Optimizing the design of hydrogel formulations to ensure effective synergy among components is a key step toward overcoming these challenges. By achieving a harmonious balance between therapeutic efficacy and biocompatibility, hydrogel-based therapies can be better positioned for successful translation into clinical practice.

While preclinical studies provide valuable insights into hydrogel-based melanoma therapies, their relevance to clinical applications is limited due to the complex and dynamic nature of the human physiological and biochemical environment. Factors such as burst drug release, unpredictable enzymatic degradation, cellular infiltration, and fluid exchange significantly impact the behavior of hydrogels in vivo, often diverging from initial expectations.[101] Addressing these challenges requires precise control over drug release kinetics and a thorough understanding of the interactions between hydrogel drug delivery systems and the biological environment.

In addition to challenges in drug delivery control, the long-term safety of hydrogels is a critical concern. Prolonged use can lead to adverse effects such as chronic inflammation, fibrosis, and calcification. For instance, Sarojini et al reported that a PHEMA-based hydrogel showed significant calcification at the injection site after approximately 12 weeks in rabbit corneas, highlighting its insufficient biocompatibility for long-term applications.[102] Similarly, polyethylene glycol (PVA)-based hydrogels have been shown to induce macrophage infiltration and cytokine release, potentially leading to chronic inflammation.[103] Additionally, the local hydrogel injections carry inherent risks of infection and introduces uncertainties in tissue repair processes. Furthermore, complex interactions between hydrogel components and loaded drugs may introduce unpredictable therapeutic effects, further complicating the design of safe and effective formulations. The incorporation of multifunctional agents with both anti-tumor and tissue-regenerative properties, such as curcumin,[104] could simplify hydrogel formulations and reduce concerns about drug interactions. However, the long-term use of such multifunctional systems may still carry a risk of inducing drug resistance, which should be carefully considered.

Moreover, hydrogel-based therapies face significant challenges when applied to extracutaneous lesions, particularly in advanced melanoma cases where tumor cells have metastasized via the bloodstream to distant organs, such as the brain. This limitation primarily arises from the inability of hydrogels and their drug payloads to effectively cross the blood-brain barrier (BBB), resulting in significantly reduced drug delivery efficiency and compromised therapeutic outcomes.[5,105] To address this issue, Bastianich et al proposed a promising solution: encapsulating drugs within hydrogel-based nanocapsules. This approach effectively bypasses the BBB, enabling precise drug delivery to both the primary site

of glioblastoma and intracranial metastatic lesions, thereby significantly enhancing drug targeting and therapeutic efficacy.[106] However, no similar studies have yet been conducted on melanoma brain metastases, underscoring the critical need for further exploration in this area. While the application of nanocarriers demonstrates significant potential in overcoming the limitations of hydrogel-based therapies, current research remains in its infancy, necessitating more extensive preclinical and clinical trials to fully evaluate the safety and efficacy of this innovative approach.

Another critical factor in the clinical translation of hydrogel therapies is inter-patient variability. A formulation that proves effective in one patient may elicit unexpected adverse reactions in another, highlighting the importance of personalized therapeutic approaches. Moreover, many hydrogel formulations remain in the preclinical phase, facing challenges such as low synthesis efficiency, time-consuming preparation processes, and high production costs, which impede large-scale manufacturing.[13] In addition to cost-effectiveness and scalability, practical issues such as storage, transportation, and long-term stability must also be addressed. Establishing standardized manufacturing protocols and quality control processes is essential to ensure consistent product quality for clinical applications.

In conclusion, although hydrogel-based therapies for melanoma hold substantial promise, their clinical translation is hindered by several challenges, including material interactions, drug release control, potential adverse effects, and scalability of production. Advancing our understanding of material interactions and enhancing biocompatibility will be essential to optimize hydrogel formulations, improving therapeutic outcomes and patient comfort. Future research should prioritize the development of multifunctional hydrogels to achieve more effective treatment outcomes and support tissue regeneration. Finally, establishing standardized production and quality control protocols will be critical for the successful clinical application of hydrogel-based therapies.

Conclusions and Future Perspectives

Hydrogels have demonstrated promising potential as a therapeutic modality for melanoma treatment, providing improved targeting and reduced side effects compared to conventional methods. Their advantageous properties, including biocompatibility and biodegradability, allow for gradual drug release within the body, minimizing patient discomfort and trauma. Consequently, hydrogels have been commonly utilized as a platform for integrated therapeutic approaches, including drug release, immunotherapy, photothermal therapy, and photodynamic therapy. Different types of hydrogels provide versatile delivery platforms that facilitate various therapeutic mechanisms for melanoma treatment. They can directly inhibit melanoma growth and metastasis by delivering drugs or bioactive substances, effectively inhibit melanoma occurrence by regulating the tumor microenvironment, and exert anti-tumor effects by enhancing immune responses. Besides, hydrogels can be artificially modified to achieve a wide array of anti-tumor effects. This versatile and multifaceted therapeutic strategy presents multiple options and opportunities for utilizing hydrogels in treating melanoma, thereby expanding the scope for further research and clinical implementation.

However, it is imperative to acknowledge the challenges confronting hydrogels in melanoma treatment, including optimizing drug delivery efficiency, enhancing mechanical properties, and effectively integrating multiple treatment modalities. These challenges not only pose significant obstacles but also offer avenues for innovation. Addressing these challenges and seizing opportunities requires extensive research and development efforts focused on hydrogels in melanoma treatment and continuously exploring novel technologies and methodologies. However, it is imperative to acknowledge the challenges hydrogels encounter in melanoma treatment, including issues with drug delivery efficiency, insufficient mechanical properties, and the integration of various treatment modalities. These challenges present barriers as well as avenues for potential advancement. Addressing these challenges and opportunities requires extensive research and development of hydrogels for melanoma treatment and continually investigating novel technologies and methodologies. Further investigation into the biocompatibility and biodegradability of hydrogels is required to ensure their safety and stability in the human body. Additionally, a deeper exploration of the interactions between hydrogels and drugs is essential to optimize drug release rates and effects and improve the precision and efficacy of treatment. Furthermore, exploring innovative technologies, including biomaterials engineering and nanotechnology, is crucial for precisely regulating the structure and properties of hydrogels to meet different treatment requirements and improve treatment efficacy. In conclusion, it is prudent to capitalize on the carrier properties of hydrogels to optimize the efficacy of combination therapy protocols.

Future research should focus on the following aspects: standardized production of hydrogels, clinical trial validation, and cost-effectiveness analysis. Interdisciplinary collaboration must be strengthened to promote clinical translation. By conducting clinical trials and evaluations and collecting and analyzing treatment data, we can optimize hydrogel treatment systems to ensure their safety and efficacy. Moreover, enhancing patient tracking and monitoring will help promptly address treatment issues and risks, ensure long-term efficacy, and provide personalized and effective treatment options for melanoma patients.

In summary, hydrogels present significant potential as a therapeutic modality for melanoma, offering wide-ranging applications and opportunities for advancement. Future research and development efforts should focus on innovation and exploration to overcome existing challenges and enhance the efficacy and personalization of treatment options for melanoma patients.

While numerous reviews have discussed the use of hydrogels in cancer therapy, few have provided a focused and up-to-date overview specific to melanoma. This review seeks to address this gap by systematically summarizing hydrogel classifications and their therapeutic strategies for melanoma, integrating recent advances across diverse treatment modalities. We hope this work may offer a useful reference for researchers and help guide future exploration in this evolving field.

Funding

This work was supported by National Natural Science Foundation of China (82203602 to J.W).

Disclosure

The authors declare no known conflict of interest.

References

1. Strashilov S, Yordanov A. Aetiology and pathogenesis of cutaneous melanoma: current concepts and advances. *Int J Mol Sci*. 2021;22(12):6395. doi:10.3390/ijms22126395
2. Sayan M, Mamidanna S, Oncel D, et al. Clinical management of uveal melanoma: a comprehensive review with a treatment algorithm. *Radiat Oncol J*. 2020;38(3):162–169. doi:10.3857/roj.2020.00318
3. Zheng Y, Cong C, Su C, Sun Y, Xing L. Epidemiology and survival outcomes of primary gastrointestinal melanoma: a SEER-based population study. *Int J Clin Oncol*. 2020;25(11):1951–1959. doi:10.1007/s10147-020-01759-x
4. Sun XF, Gu YQ, Xie JL, Wang L, Zhou QL. Melanoma of female genital tract: a clinicopathological analysis of 5 cases. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(8):834–836. doi:10.3760/cma.j.cn112151-20191108-007237
5. Machado AKLP, Nunes DBC, Carneiro FRO, Mendes AMD. Primary melanoma of leptomeninge in a patient with giant congenital melanocytic nevus. *Anais Brasileiros de Dermatologia*. 2020;95(3):404–406. doi:10.1016/j.abd.2019.11.002
6. National Cancer Institute Melanoma of the Skin-Cancer Stat Facts. Available from: https://seer.cancer.gov/statfacts/html/melan.html. Accessed November 1, 2025.
7. International Agency for Research on Cancer Cancer Tomorrow. Estimated Number of New Cases from 2020 to 2040 of Melanoma of Skin. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=16&single_unit=50000&group_cancers=1&multiple_cancers=1. Accessed November 1, 2025.
8. Saginala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiology of Melanoma. *Med Sci*. 2021;9(4):63. doi:10.3390/medsci9040063
9. Lopes J, Rodrigues CMP, Gaspar MM, Reis CP. Melanoma management: from epidemiology to treatment and latest advances. *Cancers*. 2022;14(19):4652. doi:10.3390/cancers14194652
10. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biol Ther*. 2019;20(11):1366–1379. doi:10.1080/15384047.2019.1640032
11. Corrie P, Hategan M, Fife K, Parkinson C. Management of melanoma. *Br Med Bul*. 2014;111(1):149–162. doi:10.1093/bmb/ldu019
12. Zhang L, Li K, Xiao W, et al. Preparation of collagen–chondroitin sulfate–hyaluronic acid hybrid hydrogel scaffolds and cell compatibility in vitro. *Carbohydr Polym*. 2011;84(1):118–125. doi:10.1016/j.carbpol.2010.11.009
13. Li X, Xu X, Xu M, Geng Z, Ji P, Liu Y. Hydrogel systems for targeted cancer therapy. *Front Bioeng Biotechnol*. 2023;11:1140436. doi:10.3389/fbioe.2023.1140436
14. Li Y, Fang M, Zhang J, et al. Hydrogel dual delivered celecoxib and anti-PD-1 synergistically improve antitumor immunity. *OncoImmunology*. 2016;5(2):e1074374. doi:10.1080/2162402X.2015.1074374
15. Xu L, Chen Y, Zhang P, et al. 3D printed heterogeneous hybrid hydrogel scaffolds for sequential tumor photothermal-chemotherapy and wound healing. *Biomater Sci*. 2022;10(19):5648–5661. doi:10.1039/D2BM00903J
16. Li P, Li Y, Fu R, Duan Z, Zhu C, Fan D. NIR- and pH-responsive injectable nanocomposite alginate-graft-dopamine hydrogel for melanoma suppression and wound repair. *Carbohydr Polym*. 2023;314:120899. doi:10.1016/j.carbpol.2023.120899
17. Zhou J, Liu C, Wang Y, et al. Prodrug and glucose oxidase coloaded photodynamic hydrogels for combinational therapy of melanoma. *ACS Biomater Sci Eng*. 2022;8(11):4886–4895. doi:10.1021/acsbiomaterials.2c00992

18. Wu Z, Zhuang H, Ma B, et al. Manganese-doped calcium silicate nanowire composite hydrogels for melanoma treatment and wound healing. *Research*. 2021;2021:2021/9780943. doi:10.34133/2021/9780943
19. Li AA, Shen F, Zhang T, Cirone P, Potter M, Chang PL. Enhancement of myoblast microencapsulation for gene therapy. *J Biomed Mater Res*. 2006;77B(2):296–306. doi:10.1002/jbm.b.30342
20. Li W, Zhu X, Zhou X, et al. An orally available PD-1/PD-L1 blocking peptide OPBP-1-loaded trimethyl chitosan hydrogel for cancer immunotherapy. *J Control Release*. 2021;334:376–388. doi:10.1016/j.jconrel.2021.04.036
21. Xu K, Wang Y, Xie Y, et al. Anti-melanoma effect and action mechanism of a novel chitosan-based composite hydrogel containing hydroxyapatite nanoparticles. *Regen Biomater*. 2022;9:rbac050. doi:10.1093/rb/rbac050
22. Meng Z, Fang X, Fu B, et al. Tumor immunotherapy boosted by R837 nanocrystals through combining chemotherapy and mild hyperthermia. *J Control Release*. 2022;350:841–856. doi:10.1016/j.jconrel.2022.09.009
23. De Moura LD, Ribeiro LNM, De Carvalho FV, et al. Docetaxel and lidocaine co-loaded (NLC-in-Hydrogel) hybrid system designed for the treatment of melanoma. *Pharmaceutics*. 2021;13(10):1552. doi:10.3390/pharmaceutics13101552
24. Nawaz A, Ullah S, Alnuwaiser MA, et al. Formulation and evaluation of chitosan-gelatin thermosensitive hydrogels containing 5FU-alginate nanoparticles for skin delivery. *Gels*. 2022;8(9):537. doi:10.3390/gels8090537
25. Won JE, Wi TI, Lee CM, et al. NIR irradiation-controlled drug release utilizing injectable hydrogels containing gold-labeled liposomes for the treatment of melanoma cancer. *Acta Biomater*. 2021;136:508–518. doi:10.1016/j.actbio.2021.09.062
26. Pourmanouchehri Z, Ebrahimi S, Limoee M, et al. Controlled release of 5-fluorouracil to melanoma cells using a hydrogel/micelle composites based on deoxycholic acid and carboxymethyl chitosan. *Int J Biol Macromol*. 2022;206:159–166. doi:10.1016/j.ijbiomac.2022.02.096
27. Liang X, Li L, Li X, et al. A spontaneous multifunctional hydrogel vaccine amplifies the innate immune response to launch a powerful antitumor adaptive immune response. *Theranostics*. 2021;11(14):6936–6949. doi:10.7150/thno.58173
28. Highton AJ, Kojarunchitt T, Girardin A, Hook S, Kemp RA. Chitosan hydrogel vaccine generates protective CD8 T cell memory against mouse melanoma. *Immunol Cell Biol*. 2015;93(7):634–640. doi:10.1038/icb.2015.14
29. Wang S, Zheng H, Zhou L, et al. Injectable redox and light responsive MnO2 hybrid hydrogel for simultaneous melanoma therapy and multidrug-resistant bacteria-infected wound healing. *Biomaterials*. 2020;260:120314. doi:10.1016/j.biomaterials.2020.120314
30. Céspedes-Valenzuela DN, Sánchez-Rentería S, Cifuentes J, et al. Novel photo- and thermo-responsive nanocomposite hydrogels based on functionalized rGO and modified SIS/Chitosan polymers for localized treatment of malignant cutaneous melanoma. *Front Bioeng Biotechnol*. 2022;10:947616. doi:10.3389/fbioe.2022.947616
31. Zheng Y, Wang W, Gao Y, et al. Nanosonosensitizers-engineered injectable thermogel for augmented chemo-sonodynamic therapy of melanoma and infected wound healing. *Mater Today Bio*. 2023;20:100621. doi:10.1016/j.mtbio.2023.100621
32. Azadikhah F, Karimi AR, Yousefi GH, Hadizadeh M. Dual antioxidant-photosensitizing hydrogel system: cross-linking of chitosan with tannic acid for enhanced photodynamic efficacy. *Int J Biol Macromol*. 2021;188:114–125. doi:10.1016/j.ijbiomac.2021.08.006
33. Hu Q, Li H, Archibong E, et al. Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets. *Nat Biomed Eng*. 2021;5(9):1038–1047. doi:10.1038/s41551-021-00712-1
34. Akbari V, Hejazi E, Minaiyan M, Emami J, Lavasanifar A, Rezazadeh M. An injectable thermosensitive hydrogel/nanomicelles composite for local chemo-immunotherapy in mouse model of melanoma. *J Biomater Appl*. 2022;37(3):551–562. doi:10.1177/08853282221098232
35. Duong HTT, Thambi T, Yin Y, et al. Degradation-regulated architecture of injectable smart hydrogels enhances humoral immune response and potentiates antitumor activity in human lung carcinoma. *Biomaterials*. 2020;230:119599. doi:10.1016/j.biomaterials.2019.119599
36. Zhao Y, Yan H, Qiao S, et al. Hydrogels bearing bioengineered mimetic embryonic microenvironments for tumor reversion. *J Mater Chem B*. 2016;4(37):6183–6191. doi:10.1039/C6TB00927A
37. Ko S, Park JY, Oh YK. A microbial siderophore-inspired self-gelling hydrogel for noninvasive anticancer phototherapy. *Cancer Res*. 2019;79(24):6178–6189. doi:10.1158/0008-5472.CAN-19-0975
38. Zhang L, Liu X, Mao Y, et al. Inhibition of melanoma using a nanoceria-based prolonged oxygen-generating phototherapy hydrogel. *Front Oncol*. 2023;13:1126094. doi:10.3389/fonc.2023.1126094
39. Jiang T, Li T, Wang T, et al. Enhanced transdermal drug delivery by transfersome-embedded oligopeptide hydrogel for topical chemotherapy of melanoma. *ACS Nano*. 2018;12(10):9693–9701. doi:10.1021/acsnano.8b03800
40. Liu C, Ma Y, Guo S, He B, Jiang T. Topical delivery of chemotherapeutic drugs using nano-hybrid hydrogels to inhibit post-surgical tumour recurrence. *Biomater Sci*. 2021;9(12):4356–4363. doi:10.1039/D0BM01766C
41. Dai X, Meng J, Deng S, et al. Targeting CAMKII to reprogram tumor-associated macrophages and inhibit tumor cells for cancer immunotherapy with an injectable hybrid peptide hydrogel. *Theranostics*. 2020;10(7):3049–3063. doi:10.7150/thno.42385
42. Jin H, Wan C, Zou Z, et al. Tumor ablation and therapeutic immunity induction by an injectable peptide hydrogel. *ACS Nano*. 2018;12(4):3295–3310. doi:10.1021/acsnano.7b08148
43. Yu S, Wang C, Yu J, et al. Injectable bioresponsive gel depot for enhanced immune checkpoint blockade. *Adv Mater*. 2018;30(28):1801527. doi:10.1002/adma.201801527
44. Shi Y, Li D, He C, Chen X. Design of an injectable polypeptide hydrogel depot containing the immune checkpoint blocker Anti-PD-L1 and doxorubicin to enhance antitumor combination therapy. *Macromol Biosci*. 2021;21(6):2100049. doi:10.1002/mabi.202100049
45. Zhou Y, Ye T, Ye C, et al. Secretions from hypochlorous acid-treated tumor cells delivered in a melittin hydrogel potentiate cancer immunotherapy. *Bioact Mater*. 2022;9:541–553. doi:10.1016/j.bioactmat.2021.07.019
46. Yang K, Zhou Y, Huang B, et al. Sustained release of tumor cell lysate and CpG from an injectable, cytotoxic hydrogel for melanoma immunotherapy. *Nanoscale Adv*. 2023;5(7):2071–2084. doi:10.1039/D2NA00911K
47. Song H, Huang P, Niu J, et al. Injectable polypeptide hydrogel for dual-delivery of antigen and TLR3 agonist to modulate dendritic cells in vivo and enhance potent cytotoxic T-lymphocyte response against melanoma. *Biomaterials*. 2018;159:119–129. doi:10.1016/j.biomaterials.2018.01.004
48. Lv Q, He C, Quan F, Yu S, Chen X. DOX/IL-2/IFN-γ co-loaded thermo-sensitive polypeptide hydrogel for efficient melanoma treatment. *Bioact Mater*. 2018;3(1):118–128. doi:10.1016/j.bioactmat.2017.08.003
49. Correa S, Meany EL, Gale EC, et al. Injectable nanoparticle-based hydrogels enable the safe and effective deployment of immunostimulatory CD40 agonist antibodies. *Adv Sci*. 2022;9(28):2103677. doi:10.1002/advs.202103677

50. Wu W, Shen J, Banerjee P, Zhou S. Core–shell hybrid nanogels for integration of optical temperature-sensing, targeted tumor cell imaging, and combined chemo-photothermal treatment. *Biomaterials*. 2010;31(29):7555–7566. doi:10.1016/j.biomaterials.2010.06.030
51. Kremenovic M, Chan AA, Feng B, et al. BCG hydrogel promotes CTSS-mediated antigen processing and presentation, thereby suppressing metastasis and prolonging survival in melanoma. *J Immunother Cancer*. 2022;10(6):e004133. doi:10.1136/jitc-2021-004133
52. Chen Z, Deng J, Cao J, et al. Nano-hydroxyapatite-evoked immune response synchronized with controllable immune adjuvant release for strengthening melanoma-specific growth inhibition. *Acta Biomater*. 2022;145:159–171. doi:10.1016/j.actbio.2022.04.002
53. Ruan H, Hu Q, Wen D, et al. A dual-bioresponsive drug-delivery depot for combination of epigenetic modulation and immune checkpoint blockade. *Adv Mater*. 2019;31(17):1806957. doi:10.1002/adma.201806957
54. Wu X, Wu Y, Ye H, Yu S, He C, Chen X. Interleukin-15 and cisplatin co-encapsulated thermosensitive polypeptide hydrogels for combined immuno-chemotherapy. *J Control Release*. 2017;255:81–93. doi:10.1016/j.jconrel.2017.04.011
55. Chen M, Tan Y, Hu J, et al. Injectable immunotherapeutic thermogel for enhanced immunotherapy post tumor radiofrequency ablation. *Small*. 2021;17(52):2104773. doi:10.1002/smll.202104773
56. Wang J, Guo C, Wang XY, Yang H. "Double-punch" strategy for delivery of viral immunotherapy with prolonged tumor retention and enhanced transfection efficacy. *J Control Release*. 2021;329:328–336. doi:10.1016/j.jconrel.2020.11.043
57. Song H, Yang P, Huang P, Zhang C, Kong D, Wang W. Injectable polypeptide hydrogel-based co-delivery of vaccine and immune checkpoint inhibitors improves tumor immunotherapy. *Theranostics*. 2019;9(8):2299–2314. doi:10.7150/thno.30577
58. Liu Y, Xiao L, Joo KI, Hu B, Fang J, Wang P. In situ modulation of dendritic cells by injectable thermosensitive hydrogels for cancer vaccines in mice. *Biomacromolecules*. 2014;15(10):3836–3845. doi:10.1021/bm501166j
59. Zheng B, Peng W, Gan L, et al. Sendai virus-based immunoadjuvant in hydrogel vaccine intensity-modulated dendritic cells activation for suppressing tumorigenesis. *Bioact Mater*. 2021;6(11):3879–3891. doi:10.1016/j.bioactmat.2021.04.002
60. Dong X, Liang J, Yang A, Qian Z, Kong D, Lv F. Fluorescence imaging guided CpG nanoparticles-loaded IR820-hydrogel for synergistic photothermal immunotherapy. *Biomaterials*. 2019;209:111–125. doi:10.1016/j.biomaterials.2019.04.024
61. Casolaro M, Barbara DB, Emilia M. Hydrogel containing l-valine residues as a platform for cisplatin chemotherapy. *Colloids Surf B*. 2011;88 (1):389–395. doi:10.1016/j.colsurfb.2011.07.019
62. Xu H, Wen Y, Chen S, Zhu L, Feng R, Song Z. Paclitaxel skin delivery by micelles-embedded Carbopol 940 hydrogel for local therapy of melanoma. *Int J Pharm*. 2020;587:119626. doi:10.1016/j.ijpharm.2020.119626
63. Huang X, He Y, Zhang M, Lu Z, Zhang T, Wang B. GPP-TSAIII nanocomposite hydrogel-based photothermal ablation facilitates melanoma therapy. *Expert Opin Drug Delivery*. 2023;20(9):1277–1295. doi:10.1080/17425247.2023.2200997
64. Abkin SV, Ostroumova OS, Komarova EY, et al. Phloretin increases the anti-tumor efficacy of intratumorally delivered heat-shock protein 70 kDa (HSP70) in a murine model of melanoma. *Cancer Immunol Immunother*. 2016;65(1):83–92. doi:10.1007/s00262-015-1778-1
65. Havanur S, Batish I, Cheruku SP, Gourishetti K, J PE, Kumar N. Poly(N,N-diethyl acrylamide)/functionalized graphene quantum dots hydrogels loaded with doxorubicin as a nano-drug carrier for metastatic lung cancer in mice. *Mater Sci Eng C*. 2019;105:110094. doi:10.1016/j.msec.2019.110094
66. Wang H, Yi J, Mukherjee S, Banerjee P, Zhou S. Magnetic/NIR-thermally responsive hybrid nanogels for optical temperature sensing, tumor cell imaging and triggered drug release. *Nanoscale*. 2014;6(21):13001–13011. doi:10.1039/C4NR03748K
67. Baseeruddin Alvi S, R PS, Begum N, Jogdand AB, Veeresh B, Rengan AK. In situ nanotransformable hydrogel for chemo-photothermal therapy of localized tumors and targeted therapy of highly metastatic tumors. *ACS Appl Mater Interfaces*. 2021;13(47):55862–55878. doi:10.1021/acsami.1c17054
68. Wang C, Gao Y, Gao X, et al. Synergistic effect of sunlight induced photothermal conversion and H2O2 release based on hybridized tungsten oxide gel for cancer inhibition. *Sci Rep*. 2016;6(1):35876. doi:10.1038/srep35876
69. Jia M, Lu R, Liu C, Zhou X, Li P, Zhang S. In situ implantation of chitosan oligosaccharide-doped lipoic acid hydrogel breaks the "Vicious Cycle" of inflammation and residual tumor cell for postoperative skin cancer therapy. *ACS Appl Mater Interfaces*. 2023;15(27):32824–32838. doi:10.1021/acsami.3c03355
70. Pourbadiei B, Adlsadabad SY, Rahbariasr N, Pourjavadi A. Synthesis and characterization of dual light/temperature-responsive supramolecular injectable hydrogel based on host-guest interaction between azobenzene and starch-grafted β-cyclodextrin: melanoma therapy with paclitaxel. *Carbohydr Polym*. 2023;313:120667. doi:10.1016/j.carbpol.2023.120667
71. Ding X, Zang M, Zhang Y, et al. A bioresponsive diselenide-functionalized hydrogel with cascade catalytic activities for enhanced local starvation- and hypoxia-activated melanoma therapy. *Acta Biomater*. 2023;167:182–194. doi:10.1016/j.actbio.2023.06.017
72. Bera S, Datta HK, Dastidar P. An injectable supramolecular hydrogel as a self-drug-delivery system for local chemoimmunotherapy against melanoma. *Biomater Sci*. 2023;11(16):5618–5633. doi:10.1039/D3BM00758H
73. Lee KY, Mooney DJ. Alginate: properties and biomedical applications. *Prog Polym Sci*. 2012;37(1):106–126. doi:10.1016/j.progpolymsci.2011.06.003
74. Ma H, Zhou Q, Chang J, Wu C. Grape seed-inspired smart hydrogel scaffolds for melanoma therapy and wound healing. *ACS Nano*. 2019;13 (4):4302–4311. doi:10.1021/acsnano.8b09496
75. Yang J, Shen M, Luo Y, et al. Advanced applications of chitosan-based hydrogels: from biosensors to intelligent food packaging system. *Trends Food Sci Technol*. 2021;110:822–832. doi:10.1016/j.tifs.2021.02.032
76. Lv S, Zhang S, Zuo J, et al. Progress in preparation and properties of chitosan-based hydrogels. *Int J Biol Macromol*. 2023;242:124915. doi:10.1016/j.ijbiomac.2023.124915
77. Salwowska NM, Bebenek KA, Żądło DA, Wcisło-Dziadecka DL. Physiochemical properties and application of hyaluronic acid: a systematic review. *J Cosmetic Dermatol*. 2016;15(4):520–526. doi:10.1111/jocd.12237
78. Passi A, Vigetti D. Hyaluronan as tunable drug delivery system. *Adv Drug Delivery Rev*. 2019;146:83–96. doi:10.1016/j.addr.2019.08.006
79. Graça MFP, Miguel SP, Cabral CSD, Correia IJ. Hyaluronic acid—Based wound dressings: a review. *Carbohydr Polym*. 2020;241:116364. doi:10.1016/j.carbpol.2020.116364
80. Mondal S, Das S, Nandi AK. A review on recent advances in polymer and peptide hydrogels. *Soft Matter*. 2020;16(6):1404–1454. doi:10.1039/C9SM02127B
81. Zhang S. Fabrication of novel biomaterials through molecular self-assembly. *Nat Biotechnol*. 2003;21(10):1171–1178. doi:10.1038/nbt874

82. Galler KM, Aulisa L, Regan KR, D'Souza RN, Hartgerink JD. Self-assembling multidomain peptide hydrogels: designed susceptibility to enzymatic cleavage allows enhanced cell migration and spreading. *J Am Chem Soc*. 2010;132(9):3217–3223. doi:10.1021/ja910481t
83. Lee KY, Mooney DJ. Hydrogels for tissue engineering. *Chem Rev*. 2001;101(7):1869–1880. doi:10.1021/cr000108x
84. Yan C, Pochan DJ. Rheological properties of peptide-based hydrogels for biomedical and other applications. *Chem Soc Rev*. 2010;39(9):3528. doi:10.1039/b919449p
85. Wang Z, Ye Q, Yu S, Akhavan B. Poly ethylene glycol (PEG)-based hydrogels for drug delivery in cancer therapy: a comprehensive review. *Adv Healthcare Mater*. 2023;12(18):2300105. doi:10.1002/adhm.202300105
86. Yao W, Li D, Zhao Y, et al. 3D printed multi-functional hydrogel microneedles based on high-precision digital light processing. *Micromachines*. 2019;11(1):17. doi:10.3390/mi11010017
87. Liu J, Du C, Huang W, Lei Y. Injectable smart stimuli-responsive hydrogels: pioneering advancements in biomedical applications. *Biomater Sci*. 2024;12(1):8–56. doi:10.1039/d3bm01352a
88. Hu H, Xu FJ. Rational design and latest advances of polysaccharide-based hydrogels for wound healing. *Biomater Sci*. 2020;8(8):2084–2101. doi:10.1039/D0BM00055H
89. Cano-Vicent A, Tuñón-Molina A, Bakshi H, et al. Biocompatible alginate film crosslinked with Ca^{2+} and Zn^{2+} Possesses antibacterial, antiviral, and anticancer activities. *ACS Omega*. 2023;8(27):24396–24405. doi:10.1021/acsomega.3c01935
90. Szeto GL, Finley SD. Integrative approaches to cancer immunotherapy. *Trends Cancer*. 2019;5(7):400–410. doi:10.1016/j.trecan.2019.05.010
91. Zhao Z, Fang L, Lv D, Chen L, Zhang B, Wu D. Design and synthesis of Ag NPs/chitosan-starch nano-biocomposite as a modern anti-human malignant melanoma drug. *Int J Biol Macromol*. 2023;236:123823. doi:10.1016/j.ijbiomac.2023.123823
92. Kong C, Chen X. Combined photodynamic and photothermal therapy and immunotherapy for cancer treatment: a review. *IJN*. 2022;17:6427–6446. doi:10.2147/IJN.S388996
93. Li X, Lovell JF, Yoon J, Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat Rev Clin Oncol*. 2020;17(11):657–674. doi:10.1038/s41571-020-0410-2
94. Kennedy L, Sandhu JK, Harper ME, Cuperlovic-Culf M. Role of glutathione in cancer: from mechanisms to therapies. *Biomolecules*. 2020;10(10):1429. doi:10.3390/biom10101429
95. Deng X, Shao Z, Zhao Y. Solutions to the drawbacks of photothermal and photodynamic cancer therapy. *Adv Sci*. 2021;8(3):2002504. doi:10.1002/advs.202002504
96. Hwang J, Jin JO. Attachable hydrogel containing indocyanine green for selective photothermal therapy against melanoma. *Biomolecules*. 2020;10(8):1124. doi:10.3390/biom10081124
97. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy – mechanisms, photosensitizers and combinations. *Biomed Pharmacother*. 2018;106:1098–1107. doi:10.1016/j.biopha.2018.07.049
98. Kwak M, Leick KM, Melssen MM, Slingluff CL. Vaccine strategy in melanoma. *Surg Oncol Clin North Am*. 2019;28(3):337–351. doi:10.1016/j.soc.2019.02.003
99. Zhang J, Zhu S, Zhao M, et al. Analgesic and potentiated photothermal therapy with ropivacaine-loaded hydrogels. *Theranostics*. 2023;13(7):2226–2240. doi:10.7150/thno.81325
100. Qing X, Dou R, Wang P, et al. Ropivacaine-loaded hydrogels for prolonged relief of chemotherapy-induced peripheral neuropathic pain and potentiated chemotherapy. *J Nanobiotechnol*. 2023;21(1):462. doi:10.1186/s12951-023-02230-5
101. Chen B, Liu J. Advancements in hydrogel-based therapies for ovarian cancer: a review. *Cell Biochem Biophys*. 2024. doi:10.1007/s12013-024-01483-7
102. Vijayasekaran S, V.Chirila T, Robertson TA, et al. Calcification of poly(2-hydroxyethyl methacrylate) hydrogel sponges implanted in the rabbit cornea: a 3-month study. *J Biomater Sci*. 2000;11(6):599–615. doi:10.1163/156856200743896
103. Hou Y, Tian Y, Tian J, et al. Peptide-based double-network hydrogels for melanoma treatment and wound healing promotion. *ACS Appl Mater Interfaces*. 2023;15(25):29927–29938. doi:10.1021/acsami.3c03854
104. Vollono L, Falconi M, Gaziano R, et al. Potential of curcumin in skin disorders. *Nutrients*. 2019;11(9):2169. doi:10.3390/nu11092169
105. Aquib M, Juthi AZ, Farooq MA, et al. Advances in local and systemic drug delivery systems for post-surgical cancer treatment. *J Mater Chem B*. 2020;8(37):8507–8518. doi:10.1039/D0TB00987C
106. Bastiancich C, Bianco J, Vanvarenberg K, et al. Injectable nanomedicine hydrogel for local chemotherapy of glioblastoma after surgical resection. *J Control Release*. 2017;264:45–54. doi:10.1016/j.jconrel.2017.08.019