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Three-dimensional (3D) scaffolds as powerful weapons for tumor immunotherapy

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ABSTRACT

Though increasing understanding and remarkable clinical successes have been made, enormous challenges remain to be solved in the field of cancer immunotherapy. In this context, biomaterial-based immunomodulatory strategies are being developed to boost antitumor immunity. For the local immunotherapy, macroscale biomaterial scaffolds with 3D network structures show great superiority in the following aspects: facilitating the encapsulation, localized delivery, and controlled release of immunotherapeutic agents and even immunocytes for more efficient immunomodulation. The concentrating immunomodulation *in situ* could minimize systemic toxicities, but still exert abscopal effects to harness the power of overall anticancer immune response for eradicating malignancy. To promote such promising immunotherapies, the design requirements of macroscale 3D scaffolds should comprehensively consider their physicochemical and biological properties, such as porosity, stiffness, surface modification, cargo release kinetics, biocompatibility, biodegradability, and delivery modes. To date, increasing studies have focused on the relationships between these parameters and the biosystems which will guide/assist the 3D biomaterial scaffolds to achieve the desired immunotherapeutic outcomes. In this review, by highlighting some recent achievements, we summarized the latest advances in the development of various 3D scaffolds as niches for cancer immunotherapy. We also discussed opportunities, challenges, current trends, and future perspectives in 3D macroscale biomaterial scaffold-assisted local treatment strategies. More importantly, this review put more efforts to illustrate how the 3D biomaterial systems affect to modulate antitumor immune activities, where we discussed how significant the roles and behaviours of 3D macroscale scaffolds towards *in situ* cancer immunotherapy in order to direct the design of 3D immunotherapeutic.

1. Introduction

Since the secrets of immunosuppressive tumor microenvironment (TME) in most cancer patients uncovered, cancer immunotherapy has caught extensive attention and run to the frontier that revolutionized the traditional cancer therapies. Cancer immunotherapy aims to intervene the immune systems, fully evoking host immunity or initiatively manipulating immune activities, to combat tumor cells and even eradicate the malignancies [1,2]. The cancer immunotherapy could likely restrain cancer metastasis and relapse for a long term. However, despite many exceptional advances, in most cases, its therapeutic efficacy towards many different cancer types in clinic is mainly limited [3]. Except the suboptimal patient immune response rate curtailing the therapeutic efficiency, some common immune-associated side effects such as autoimmune reactions, cytokine release syndrome, and vascular leak syndrome severely challenge the safety of this treatment [4]. Besides, major cancer immunotherapies were primarily applied only in hematological malignancies but still unable to break through the tough barriers in solid tumors [4]. And some problems also remain in the current approaches like adoptive cell transfer (ACT) strategies of *ex vivo* cell expansion, involving the generation of low-quality T cells without sustained persistence and minimal adverse toxicity [5].

Multifunctional biomaterial-based drug delivery system (DDS) strategies provide much more feasibility and selectivity to address the limitations in cancer immunotherapy [6,7]. Novel smart delivery systems can effectively payload, efficiently protect the immunotherapeutic cargos and control their fate in designate spatiotemporal manner to increase the target and accumulation within tumors and/or immunocytes of interest, weaken the off-target effects and systemic toxicity [8–11]. Many promising nanoscale and microscale biomaterial-based immunomodulatory strategies reported and reviewed elsewhere

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Abbreviations

aCD47	Anti-CD47 antibody
ACT	Adoptive cell transfer
aCTLA-4	Anti-cytotoxic T lymphocyte-associated antigen 4 antibody
APC	Antigen-presenting cell
aPD-1	Anti-programmed cell death protein ligand 1 antibody
aPD-L1	Anti-programmed cell death protein 1 antibody
Arg	Arginine
CAR-T	Chimeric antigen receptor T
CAT	Catalase
Ce6	Chlorin e6
CpG ODN	Cytosine-phosphodiester-guanine oligonucleotide
CPT	Camptothecin
CS	Chitosan
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
DDS	Drug delivery system
dLN	Draining lymph node
DOX	Doxorubicin
ECM	Extracellular matrix
GEM	Gemcitabine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HA	Hyaluronic acid
HA-MA	Methacrylate-modified hyaluronic acid
ICB	Immune checkpoint blockade
ICD	Immunogenic cell death
ICG	Indocyanine green
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IL	Interleukin
iNOS	Inducible nitric oxide synthase
MB	Methylene blue
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
NIR	Near-infrared
OVA	Ovalbumin
Oxaliplatin	OXA
PCL	Poly(caprolactone)
PEA	Poly(ester amide)
PEG	Poly(ethylene glycol)
PEGDA	Poly(ethylene glycol) diacrylate
PEG-DA	Poly(ethylene glycol) double acrylate
PEI	Polyethylenimine
PLA	Polylactic acid
PLG	Poly(lactide-*co*-glycolide)
PLGA	Poly(lactic-*co*-glycolic acid)
Pluronic-DA	Pluronic diacrylate
PNIPAM	Poly(N-isopropylacrylamide)
PPG	Poly(propylene glcol)
PTX	Paclitaxel
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
TAA	Tumor-associated antigen
TAM	Tumor associated macrophage
TLR	Toll-like receptor
TME	Tumor microenvironment

exemplify the exploration for well-designed cancer immunotherapy [12–14]. Based on the specificity of the cancer cells and TME, nanomaterials for immunotherapy can positively and precisely target the cancer site by modifying targeted molecules, achieve controllable and sustained treatments on demand by inserting smart response “switches” (chemical bonds or functional groups, etc). To some extent, they did resolve few of the abovementioned obstacles during immunotherapy [15–18]. Nevertheless, recent evidence has pointed to non-negligible systemic toxicity and a small percentage lower than 1% tumor accumulation of nanoparticle agents via traditional bolus administration [3,19]. It makes most of micro- and nano-scale drug delivery biomaterials difficult to show satisfactory results in clinics.

Compared to nano and micro biomaterials, the bulk 3D biomaterial platforms show some extraordinary superiorities [20–22]. Aside from excellent biocompatibility and environmental responsiveness, they have many unique features including macroscale volume, 3D porous inner structures, swelling properties, flexibility, and elasticity. These merits will expand the practical applications of cancer immunotherapy. On the one hand, the macroscale injections and implants could be positioned *in situ* at the specific space for regional therapies reducing toxicity related to the systematic administration. Their adaptive shapes better fit irregular lesions. The localized delivery of pharmaceuticals tends to result in magnified immunotherapy at lower per dosage. On the other hand, these macroscale 3D counterparts usually have physiological biomimetic matrix which could act as artificial immune tissues for recruiting, housing, and programming host immunocytes or cell incubation depots for encapsulating, proliferating, modulating engineered immunocytes [23,24]. Currently, 3D scaffold biomaterials have already applied in various applications including tumor immunotherapy, tissue engineering, bone related diseases, infectious diseases, and many others [25–28].

Injectable or implantable hydrogels and scaffolds, representative of 3D macroscale biomaterials, facilitate the controlled delivery and release of therapeutic small molecule reagents, macromolecule biological factors, and even living cells strikingly heightening the vitality of cancer immunotherapy [29]. Unfortunately, clinical translations of 3D macroscale biomaterial-based immunotherapies still develop in a slow graded pace during several decades [30,31]. More and more widely recognized, it is essential for the biomaterial engineering researchers to attain a systematic characterization and comprehensive understanding of the mutual interaction between biomaterials and immune system, including how the physicochemical and mechanical properties of the particular biomaterial system influence the immunologic behaviours, and how immunologic indexes fluctuate towards different biomaterial systems upon timescales, in order to speed up their clinical developments [7,32,33] (Fig. 1).

In this review, the importance of 3D macroscale biomaterial-based cancer immunotherapy will be fully introduced. Firstly, the cancer immunotherapy will be briefly summarized about its principles, mechanisms with some typical methods or techniques. According to existing clinical failures and dilemmas of cancer immunotherapy, the problems and challenges of cancer immunotherapy faced nowadays will be raised. Subsequently, biomaterial-based strategies with a bright prospect to improve the immunotherapeutic effects will be put forward in which the notable advantages of 3D macroscale biomaterials would be highlighted. Due to the indispensability but lack of studies on the relationships between material properties and their behaviours and interactions with the biosystems, this review will put more efforts to profile different properties of macroscale biomaterials influence their functions as immunotherapeutic niches. And the following part will introduce the latest successful trials of 3D macroscale biomaterials for enhanced precise immunotherapy. Finally, the emerging trends together with challenges for future cancer immunotherapies will be critically discussed.

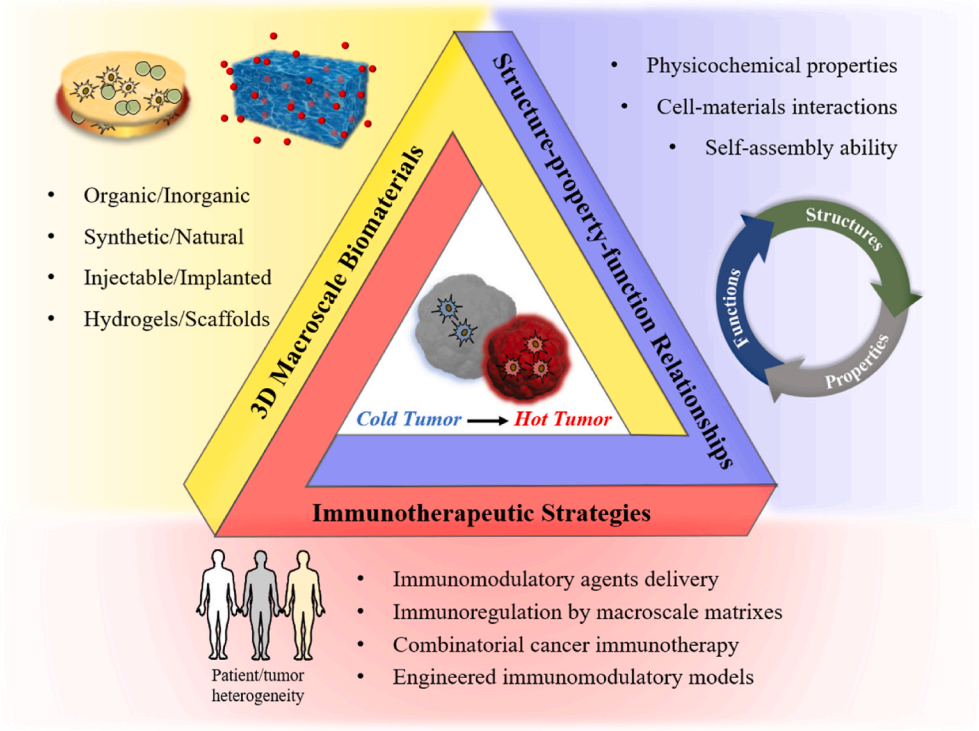

Fig. 1. Versatile 3D macroscale biomaterial scaffolds equipped with multiple personalities meeting a variety of needs in tumor immune treatments.

2. Tumor immunotherapy and 3D scaffold biomaterials: a brief summary

The tumor-imposed immunosuppression is the reason why immune cells scarcely traffic into TME and take actions for immune attacks. The macroscale 3D scaffold-based immunotherapies would help to tip the balance. With the supply of certain matrixes, the immune events can be rearranged to disturb the immune tolerance by imported immunomodulatory molecules or cells or just scaffolds themselves. It will enhance various functions like peripheral programming of immune cells, intratumoral recruiting of effector cells, etc. The strategies based on this kind of materials have shown increasing merits in cancer immunotherapy and preclinical research. In this section, brief introduction of cancer immunobiology (e.g., tumor immune microenvironment modulation, tumor-targeted systematic immune programming) paired with the significance of auxiliary from 3D biomaterials for cancer

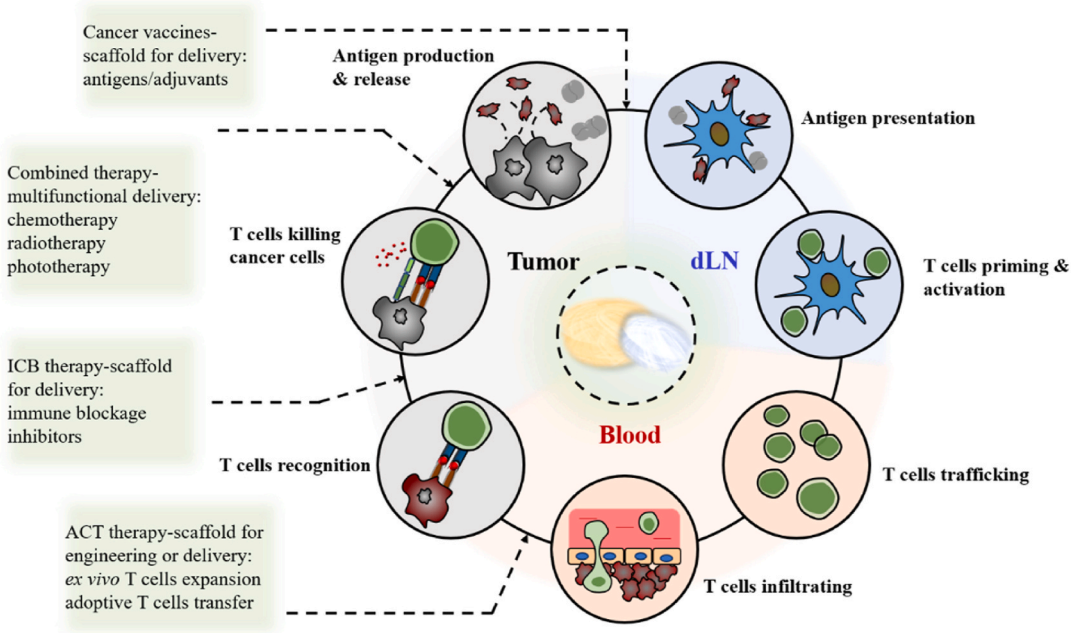

Fig. 2. 3D macroscale biomaterial-based tumor immune microenvironment modulation. (ICB: immune checkpoints blockade; ACT: adoptive cell transfer; dLN: draining lymph node.)

immunotherapy will be initially summed up (Fig. 2).

2.1. Immuno-oncology and current tumor immunotherapy

Before launching into biomaterials, tumor immunology and cancer immunotherapy should be grasped in the first place. Since the confirmation of the role immune system playing in tumor progress a century ago, the viewpoints of cancer nature have been gradually shifted that tumors are no longer merely deemed as crowds of aberrant cells, but as a systemic chaos. The interactions between cancer cells and immunity take place throughout the course of tumor development [34]. The major function of the immune system is to detect threat, sustain homeostasis, and provide precise immunological memory to resist a second invasion. During the period of cancer primary pathological stage, the immune surveillance and immune clearance from the T cells, NK cells and some other immunocytes function [35]. After the endless immune editing improving the immune resistance, the immune escape of tricky cancer cells accelerates their survival and proliferation.

A variety of factors create favourable circumstances for that immunosuppression. First, tumor cells manage to display weak immunogenicity by down-regulating the expression of tumor antigens; releasing soluble antigen molecules to induce tumor antibodies binding tumor antigens; reducing the expression of major histocompatibility complex (MHC)-1 proteins limiting efficient antigen presentation; decreasing the secretion of antigen presentation costimulatory factors, etc. The overriding outcome is a significant drop in the amount of recognition of immune cells [36,37]. Second, tumor cells continue to target the immune cells that still work for recognition to interfere with their immune checkpoints. Cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are the most two characterized. These molecules are self-tolerant under normal physiological contexts but easily powerless by malignancy [38,39]. Cancer cells aim to bind them with self-expressed specific receptors so that antitumor signalling and immune attack will be prevented. Then, sufficient tumor-associated antigen-presenting cells (APCs) and tumor infiltrating T cells will be extremely lacking in TME [40,41]. Although the immune defence never gives up, at the end, it is going to be beyond the diagnosing and fighting abilities of natural immune packages thus failing to reverse the immune abnormality [42].

The immune system and oncogenesis are both intricate biological machineries. The exact analysis of highly heterogeneous tumor immune microenvironment (TIME) is fundamental to design the drug and scaffold combined biomaterials. Since the changes of TIME are reflected mainly in both cancer cells and immune cells, immunomodulation is therefore multifaceted [35]. To come up with a working immunotherapeutic regimen, the following matters in tumor immunology should be taken into account: (a) poor immunogenicity of tumors, (b) serious immunosuppression towards immunocytes, (c) adequate priming, enough numbers and pinpoint phenotypes and antigen-specific actions of effective T cells [42]. In the past decades, significant advancements have been made in cancer immunotherapies, with cancer vaccines, immune checkpoint blockade (ICB) and ACT as representatives. Since increasing the number or quality of antineoplastic effector T cells in TIME alone does not positively correlate with therapeutic outcomes, the fruitful advancements of cancer immunotherapy should also lie in programming immune cells in peripheral tissues or draining lymph nodes (dLNs) and modulating both immune cells and malignant cells in the TIME [43].

Some exciting clinical results seemingly imply that treatment is getting closer to cure, yet far from people' s expectations, cancer immunotherapies cease to go forward due to a few obstructions. To get over these barriers and optimize the curative efficacy, biomaterial-based immunotherapeutic platforms as the interface between biomedical material engineering and immunopathology should be thought highly of [44,45]. Based on the profound understanding of different causes, changes, phases of cancers and different immunity, physical and mental conditions of patients, a comprehensive biomaterial treating systems can be eventually determined.

2.2. Significance and functions of 3D macroscale biomaterials

Biomaterial-derived strategies have been developed into highly customization which empower precise localized distribution, focused dosage concentration, optimized release kinetics of payloads and prolonged administrating periods. Among them, 3D macroscale biomaterials have gained an amenable momentum as one of the most crucial classes superior to other biomaterials [32,46]. The junction of biocompatible macro-materials and cancer immunotherapy is unique and inevitable that may allow for more reliable preclinical outcomes and more effective treatment care [47].

One of the aspects making these 3D macroscale biomaterials stand out needs to be with specialized emphasis on localized anchored adjuvant delivery. Despite a few achievements of preferred soluble injections in many pathological conditions, deficiencies of this administration method to cancer immunotherapies yet emerge. Firstly, off-target effects and rapid renal and hepatic clearance easily occur and therefore the high dosages or frequent doses of soluble therapeutics are necessitated, which often in all probability accumulate systemic toxicities and meanwhile lose patient compliance [48]. Additionally, it is difficult for some immune formulations such as soluble prophylactic vaccines to trigger strong enough native/foreign antitumor immune responses for ideal cancer immunotherapy [49]. The tightly topical arrangement based on macro-biomaterials enables to mitigate some concerns of systemic administrations. Once target position is found out and accessible, the treatment modality of bulk biomaterials can be applied locally through injection or implantation *in situ*, and then closely responsible for regional tumor immunomodulation. It is also worth noting that they are associated with complementary local and systematic cancer immunotherapy as well. As we all know, more than 90% of cancer deaths stem from metastasis and relapse, so the ideal treating approach is not only to direct at TME *in situ*, but to activate the systematic immunity of the body more effectively [50]. Luckily, although local treatment, the "abscopal effect" from such biomaterials could also result in systemic antitumor immune safeguard that is well exemplified by effective prohibition of the tumor disseminated metastasis and distant ectopic recurrence after local immunotherapy [51]. On the one hand, the encapsulated therapeutic molecular or cellular agents would enter and transport within the systemic circulation to expand antitumor effects beyond the primary site; on the other hand, a great number of the effector T cells, or antibodies originated from the foremost immune response primed by macroscale delivery vehicles can also be automatically manipulated for systemic deployment.

Another outstanding feature refers to the advantages of their macrosizes and microstructures. The scaffold structures of macroscale bulk materials upgrade the interaction between biomaterials and cells. They could prompt encapsulation of immune cells for further immunocyte functionalization which lays a solid foundation to build up *in vitro* 3D experimental models [52]. Compared to *in vivo* animal models and *in vitro* 2D models, 3D frameworks not only possess structurally and functionally physiological environment-mimic matrixes but also permit hierarchical control of biological processes in multidimensions which is extremely required in the explanation of immunomodulatory molecular and cellular mechanisms [53–55]. Moreover, suitable scaffolds can serve as cell harbour or the entrepot for co-delivering other chemical agents and biologic factors to support engineered cell cultivation [45,56,57]. No matter scientific research or clinical trials, macroscale biomaterial-manufactured 3D models could be utilized for the exploration of immune dysfunction and function at various biological levels as well as spatiotemporal scales. In the sense, they could pioneer a new era for the design and development of cancer immunotherapies.

In a word, recent cancer immunotherapies depending on the application of local delivery systems outperform systemic administration due

to better therapeutics stability, higher "effective" doses, and less side effects. Besides, local immunomodulatory scaffolds play an important role in establishment of *in vitro* 3D models flourishing the researching tools for cancer immunotherapies. And it also makes sense that in addition to the functionality as conscientious loading carriers, the active immunomodulatory capability of 3D macroscale biomaterials themselves deserves to be investigated [58].

3. Behaviours and interactions of 3D biomaterials in tumor immunomodulation-related biosystems

The properties of materials usually make a great impact on their practical applications. For example, poly (lactide-*co*-glycolide) (PLG)-derived polymeric scaffolds suffer from drawbacks of brittleness which might make them too fragile to be implanted onto tumor resection bed or solid tumor neighbourhood [59]. By contrast, the injectable routes can partially optimize the available implantable methods. However, injection based on the needle can be adopted only if the biomaterials at the state of liquid or gel which significantly limits the types of applied materials. For instance, the improved resorbable and soft alginate scaffolds still rely on invasive surgery for implantation [59]. When injection, the rheological properties such as gelation time might adjust the injectability of 3D hydrogels. And the mechanical characteristics like deformation degree might affect the location and distribution of the bulk materials. For example, the surgically inaccessible sites and volume-limited spaces are easy to result in dissatisfactory localization without suitable exogenous materials [59]. In the aspect of biological properties, the systematic adverse effects (e.g., infectious inflammation, foreign body reactions) must be taken into consideration after their persistent presence to normal tissues or organs [60–63]. For example, some published reports demonstrated the observation of pancreatic cell impairments caused by incorrect immune attack during the treatment of alginate-based pancreatic tumor therapies [64].

A comprehensive evaluation of the behaviours and interactions and a thorough explanation of the processes and mechanisms within the material-immune system followed by establishing a bridge between these two systems seem overwhelming. Nevertheless, the feasible design and desirable optionality for materials-based immunotherapeutic strategies have been developed still at the outset stage and immunotherapeutic property-activity relationship-related literatures are that rare. Therefore, this part will try to explore the underlying property-function relationships when 3D macroscale biomaterials applied in the cancer immunotherapy particularly from the view of materials science and engineering (Fig. 3).

3.1. Physicochemical properties influencing the immunotherapeutic behaviours

Implantation and injection are the two of the most widespread-applied ways in 3D macroscale biomaterial-based immunotherapy. Implantable and injectable scaffolds or gels have some common regulatable physicochemical properties, mainly containing hydrophilicity, electric charge, mechanical strength, thermal stability, biodegradation rate, and controlled payload release which can be adjusted by the types, quantity, ratios and modification of the components or the fabrication techniques [65,66]. Alternatively, in terms of injectable soft gel-like biomaterials for higher spatiotemporal precision, other features namely injectability (e.g., a shear-thinning ability/a high compression strain), gelation duration and swelling ratio should also be regarded [51].

The accurate operation of physicochemical properties of materials is of utmost significance. The electrostatic interaction (positively/negatively charged) and hydrophobic effect (hydrophilicity/hydrophobicity) quite affect the loading efficiency of immunotherapeutic agents. Thus, the coordination among the pharmaceuticals and materials will elevate the potent encapsulation in defined doses. The implantable hydrogels in the form of tablets or pills are likely to be confronted with the brittle problems [67]. Therefore, the appropriate moulding mechanism needs to be determined in specific cases. For example, the physically crosslinked hydrogels usually exhibit lower mechanical strength than the chemically crosslinked hydrogels [51]. As for the controlled payload release, it is supposed to have some intrinsic connection with biodegradation rate of biomaterials which can be fundamentally ascribed to materials design. As tools to direct the immune reactions, 3D biomaterial scaffolds can be engineered with the physicochemical properties to augment the immune responses temporally and spatially [36]. Indeed, many experts have made many contributions to illuminating how the physicochemical properties influence the immunotherapeutic behaviours in order to motivate a potent immune response to defeat most of the immune-susceptible diseases especially cancers.

Injectable hydrogels require applicable gelling characteristics, related to the thermodynamic and rheological properties of 3D biomaterials. Thermo-responsiveness is one of the promising candidates whose gel windows should cover the physiological temperature. Many

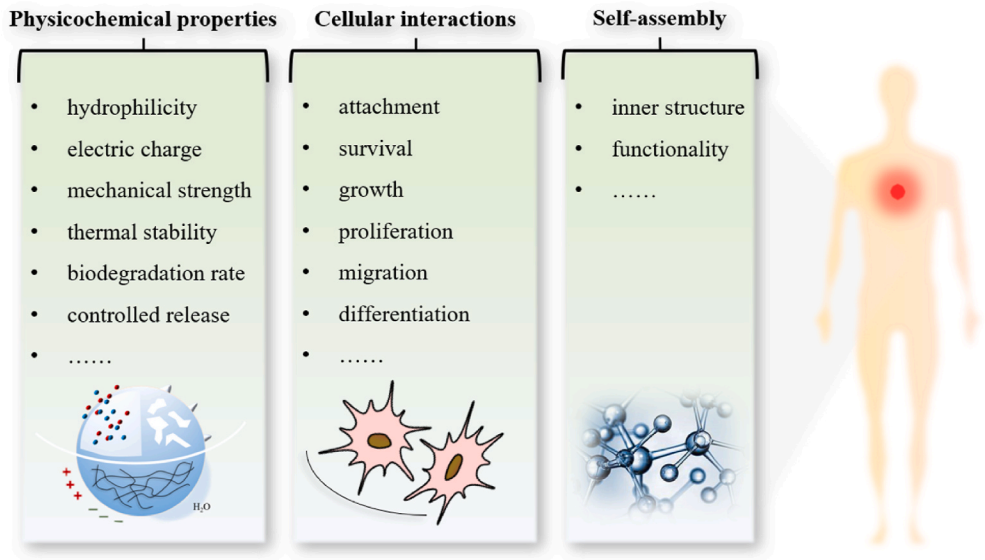

Fig. 3. Properties and interactions of 3D macroscale biomaterials influencing the tumor immunomodulation efficiency.

synthetic polymers can be easily endowed with that. Take an example, Kyle Brewer et al. synthesized an array of thermo-responsive copolymers from poly (caprolactone) (PCL), poly (ethylene glycol) (PEG) and poly (propylene glycol) (PPG) by varying the proportion of PEG/PPG for cell therapies [68]. The percentage of PEG/PPG in the copolymers could change the specific phase transition temperature of copolymers. When the products with PEG:PPG in ratio of 1:2, they enabled to accomplish sol-gel transition at 28 °C and gelatinize when body temperature (37 °C) adequate for *in vivo* applications. $CD4^+$ T-cells could be encapsulated in that copolymer-gelatinized 3D scaffolds. After injected to the target site, effector T-cells will be controllably released after lipase-based enzymatical degradation which makes the copolymers as potential delivery carriers for ACT.

In comparation, natural biomaterials are more suitable as easily degradation-regulatable implantable scaffolds. Long Ren et al. constructed macroporous scaffolds by combining two different components, stable methacrylate-modified hyaluronic acid (HA-MA) and readily hydrolysed derivatives methacrylate-modified oxidized hyaluronic acid (oxHA-MA) [69]. The *in vivo* degradation rate can be varied from 10 to 28 days via adjusting the blending ratios of HA-MA/oxHA-MA. Different antitumor agents including paclitaxel (PTX), R837 agonists, aCTLA-4 and anti-OX40 monoclonal antibody (mAb) were selected for combined cancer immunotherapy towards 4T1 breast cancer. Each of them could achieve spatiotemporal controlled release, therefore, the conversion of immunosuppressive TME in 4T1 breast cancer can be segmented and long-term. Hathaichanok Phuengkham et al. fabricated a cross-linked collagen-HA scaffold with both resiquimod and doxorubicin (DOX) loaded [70]. The degradability of the matrix can be modulated directly by the w/w ratio of collagen to HA. Under the condition that the w/w ratio of collagen to HA is 5:5, the matrix degradation sustained longest over four weeks, most advantageous for long-acting immunoregulation (Fig. 4. A-F). To facilitate higher accurate and intelligent control, Sangeetha Srinivasan et al. used auxiliary mathematical modelling to conduct temporal release of one or more immunomodulators [71]. The porous agarose scaffold with immunomodulator-loaded gelatin microparticles was generated from the empirical mathematical model based on the Weibull equation and the Bayesian approach. The release profile data of specific molecules could be mimicked and modified in advance. This smart scaffold design strategy will sufficiently improve the materials properties and instructionally enhance the generation of endogenous regulatory dendritic cells (DCs) phenotype *in vivo*.

As the upgradation of single component 3D scaffolds, the incorporation of new components or multi-strand network usually improve the mechanical properties of 3D macroscale substrates and it might award more intelligence to the biomaterials for morphological changes or performance activation to external stimuli [72]. For example, Sandeep T. Koshy et al. designed a series of nanocomposite alginate cryogels for protein drug delivery [73]. In the study, the entrapped Laponite nanoplatelets could slow the release of immune-related proteins with various size, charge, and functions because of electrostatic interaction whilst the electrostatic interaction between Laponite and alginate would result in the embrittlement of cryogels. Higher concentrations of Laponite attracted much stronger interaction variating the crosslinking and swelling levels inside the hydrogels so that the brittle gels will irreversibly deformable and fragmented hardly to be injected. Therefore, a moderate content of Laponite nanoplatelets in the system should be found to balance the slow release of protein drugs and feasible injectability of cryogels.

3.2. Cellular interactions supporting the immunotherapeutic functions

The size advantages of 3D macroscale biomaterials open more opportunities for immunotherapies targeting to the cell level. The cytocompatibility of these materials are basic for successful cellular adherence and survival. Natural or synthetic, organic or inorganic, newly-developed or long-studied biomaterials themselves are likely to accompany with acute inflammatory responses or even chronic foreign body reactions increasing the risk of systemic toxicity [74]. Post-processing like surficial modification might improve the biocompatibility of 3D scaffolds [75,76]. However, it is still questionable whether their degradation by-products would cause these adverse reactions in a long time. Then, a steady and safe space sponsored by inner

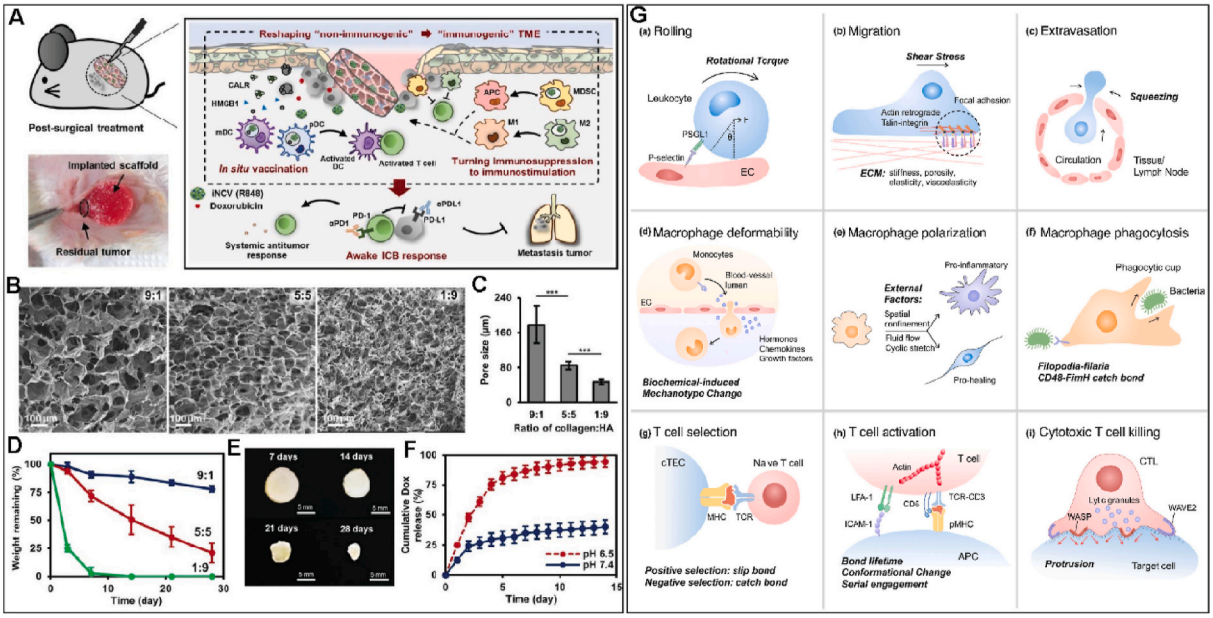

Fig. 4. Physicochemical properties and cellular interactions influencing the immunotherapeutic efficiency. (A) The scaffold co-delivering iNCVs (R848), DOX, and ICB molecules (aPD-L1/aPD-1) to induce an immunogenic tumor phenotype. (B) SEM analysis of the morphology and (C) pore size of collagen/HA scaffolds prepared in different collagen:HA ratios. (D) *In vitro* (1:9, 5:5, and 9:1) and (E) *in vivo* degradation tests of the scaffold (5:5). (F) *In vitro* profile of DOX release from the scaffold in an enzyme-containing buffer (pH 7.4 or 6.5). Reproduced with permission from Ref. [70]. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA. (G) Different mechanical factors in cell-material/cell-cell interactions regulating immune cell morphologies, behaviours, and functions. Reproduced with permission from Ref. [92]. Copyright 2020 Elsevier.

microstructure is of necessity for cellular growth, proliferation, and migration. Generally, there usually exist enough porous structures in cryogels and some inorganic scaffolds suitable for cell migration and accommodation, but less porous hydrogels can realize cell encapsulation and attachment and co-delivery with immunomodulatory agents [77–79]. Besides, the inner properties like hydrophilicity, electric charge, ionic strength could also affect the habitus of immune cells. The hydrophilic and positive-charged surfaces are relatively apt to cellular contact, but excessively positive charges are bound to be lethal for immunocytes [80]. More importantly, during immunotherapy, the polarization of immune cells into competent phenotype for effective immune responses is vital. The immunologically inert 3D biomaterials could also have the potential capability to induce the T cell functionalization or macrophage polarization [81]. On this occasion, various effects on generating subtle and intricate interactions between materials and immune cells should be further recognized.

Koyal Garg et al. studied the functional polarization of macrophages in response to distinct fiber diameter and pore size of electrospun scaffolds [82]. The research firstly indicated that the pore size of a scaffold was a more decisive in the macrophage polarization compared to the fiber diameter. The thinner fibrous scaffolds yielded from lower polydioxanone (PDO) concentrations intend to have smaller pore sizes and porosity which is likely to induce the M1 type of macrophages. In immunosuppressive TME, the transition of tumor associated macrophages (TAMs) from the pro-tumor (M2) phenotype to anti-tumor (M1) phenotype is critical [83]. Hence, the PDO electrospun scaffolds with smaller pore size and less porosity can be regarded as promising platform for directional TAM polarization [84]. Other attempts like tunable hydrophilicity and ionic strength have also been carried out for cellular modulation. Jun Wu and coworkers used arginine-based unsaturated poly (ester amide) (Arg-UPEA) and Pluronic diacrylate (Pluronic-DA) forming a library of hybrid hydrogels [85]. The hydrophilicity and ionic strength were accurately commanded by changing the length of carbon chains in Arg-UPEA and feeding ratios of Arg-UPEA:Pluronic-DA, respectively. These data are instructive for the design of macroscale immune-functionalized scaffolds and subsequent studies on detailed molecular immunological principles should be followed up.

Differential biomaterials can bring about differentiated immune responses, therein diversifying phenotype of DCs and directing T cells polarization. Jaehyung Park et al. tried to coculture biomaterial films made of alginate, agarose, chitosan (CS), HA, or 75:25 poly (lactic-*co*-glycolic acid) (PLGA) with DCs and autologous T cells [86]. The results demonstrated that these pretreatments dictated distinct presentation of DCs, producing non-identical T cells. It was supposed that the substrate stiffness and surface smoothness might be the potential physicochemical influence cues for cell growth [87]. Matthew H. W. Chin et al. therefore investigated how these biophysical factors modulated immune cells [88]. By tuning the concentrations of the cross-linkers or coating antibodies, the substrate stiffness and ligand density of the 2D polyacrylamide hydrogels can be set in a wide range. The results indicated that softer substrate and higher ligand density could harness a synergistic interaction for Jurkat T cell activation and interleukin secret. The stress reaction process of immune cells has tried to be labelled, recorded and monitored in real time in order to better target the function of immune cells, particularly DCs, macrophages and T lymphocytes [89].

With the recognition of the effects from both the tissue and biomaterial rigidity in cancer treatment, mechano-based therapies or mechanomedicines come up clinically [90]. It is undeniable that the immunocytes should have certain mechanical sensitivity towards matrix materials first to produce the associated cellular response [87]. Nearly all mechanical signals outside the cells such as interstitial flow, cyclical forces, stretching, spatial confinement and matrix stiffness, can be propagated through cell membrane and further reorganize intracellular structures (e.g., cytoskeleton, nucleoskeleton) to induce cellular deformation and functionalization [91]. The mechanobiology of immune cells is therefore gradually unraveled [92,93]. 3D scaffolds with optimal porosity, matrix stiffness, antigen presentation and biophysical cues inside the tumor immune microenvironment would influence the activation and polarization of immunocytes (Fig. 4. G). The mechanotransduction is found in both innate and adaptive immunity, short-term immune attack, and long-term immune memory. These important physical parameters will inspire the design of biomaterial innovation to establish robust biomedical engineering tools for cancer immunotherapy [90,92].

3.3. Others

The self-assembly capability of some biomacromolecule-derived materials (typically nucleic acids and peptides) facilely endeavours to spontaneously organize into the 3D scaffolds with rational and variable microstructures and disorganize for therapeutic release upon external stimulus.

The base complementary pairing guarantees precise and efficient self-assembly of DNA. The varied and adjustable DNA sequences lead to the strict and controllable structures. Tomoya Yata et al. reported a sort of composite gold nanoparticle (Au NP)-DNA hydrogels for immunostimulatory tumor photothermal immunotherapy [94]. The DNA hydrogels were composed of hexapod-like structured DNA (hexapodna) with CpG sequences and Au nanospheres or nanorods (Au NSs/Au NRs). The formation of structure-specific Au NP-DNA hydrogels resulted from complementary pairing bases of designed hexapodna and directional oligonucleotide (ODN)-modified Au NPs. These well-ordered Au NP-DNA hydrogels displayed the release of immunostimulatory hexapodna under laser irradiation. The inner connection manners made a difference on the thermal stability of the combination of hexapodna and ODN-Au NPs which varied the efficiency of immunotherapeutic disruption behaviour.

The peptide hydrogels are another one of the common self-assembly hydrogels. Due to the variety and number of amino acids in peptide, these hydrogels are not only of many classes, but also have excellent designability in structure and performance. Since each amino acid have own hydrophilicity/hydrophobicity, positively/negatively charge and chemical groups in side chains, it was acknowledged that a lot of mutual effects, more than hydrophobic forces, electrostatic interaction, hydrogen-bonding, and steric repulsion, could master the gelatinization and denature destinies of self-assembled peptide hydrogels [95]. A good command of structure-activity correlation in peptide hydrogels will also benefit materials design on demand.

Otherwise, some factors like drug formulation, injection technique and delivery mode could also influence the treating efficacy of cancer immunotherapy (Table 1) [96]. For example, in the study of Jianghua

Table 1
Contrasts of typical macroscale biomaterials for cancer immunotherapies.

	Implantable scaffolds	Injectable scaffolds	Transdermal microneedles
Advantages	✓ Provide physical structures for immunoregulators/cells ✓ *In situ* immunocytes activation ✓ Controlled release profiles	✓ No surgery required ✓ Minimally invasive ✓ Controlled release profiles ✓ Shape flexibility	✓ Simple to apply ✓ Minimally invasive ✓ High patient compliance ✓ Sustained release ✓ Low required doses
Limitations	• Need to confirm specific immunoregulators in advance • Require surgery • Potential translocation	• Suitable gelation period and properties • Require large gauge needle	• Limited treating area and cancer types (better for superficial tumors) • Unknown bioavailability • Complex manufacturing

Wang et al., CpG-modified nanovaccines (CNVs) were designed into three different delivery modes: mono-pulse staggered-pulse, and gel-confined. The former two nano vaccinations passively drain to LNs due to their size; in the inverse scenario, gel-confined CNVs were actively delivered to LNs. After entering the dLNs, these three CNVs exhibited three different spatiotemporal distribution and utilization. The interaction of DCs with T cells were subsequently changed, leading to individualized T cell-mediated antitumor immune response [97].

The properties of engineered materials that can edit cancer immunobiology and the responses of immune system exerted by specific interventions are numerous. A better understanding of material-immune system interactions will clarify the underlying interface modes between these two counterparts which is constructive for affording a set of biomaterials design criteria for effective immunotherapies. Indeed, the development of such an integrated guideline is exceptionally elementary and elusive so that more energies need to be devoted to learning the property-function relationships. This will enable prevalent applications of immunotherapeutic 3D macroscale biomaterial strategies for more intractable cancers.

4. Modern immunotherapeutic strategies based on 3D macroscale biomaterials

The 3D macroscale biomaterial immunotherapeutic platforms are multitudinous that can be classified according to their components, preparation methods, administration routes or immunomodulation principles. They are generally constituted of natural components or synthetic polymers (e.g., collagen, alginates, HA; PEG, PLGA, mesoporous silica, etc.). The 3D macroscale constructs can be established by *in vitro* simple crosslinking, *in vivo* rapid sol-gel phase transition, *in situ* chemically polymerized assembly or advanced 3D printing and self-assembly techniques, etc [98]. With tumor antigens and adjuvants, immunostimulatory or immunosuppressive molecules, and even bioactive immune cells embraced in, these 3D scaffolds or hydrogels become versatile and easy to be implanted or injected into patient hosts to operate immunomodulation. As macroscale delivery systems, 3D scaffolds can be further loaded with other chemotherapeutic drugs and photo-/sono-/thermo-/magneto-sensitizers to mediate combinational immunotherapeutic strategies. Higher spatiotemporal controllability, immune reaction, and therapeutic efficacy will be obtained due to the attendance of 3D macroscale biomaterials [5,99,100]. In addition, since 3D *in vitro* models are considerable in scientific research, 3D macroscale scaffolds have been considered to develop as biomimetic organoids, in which dynamic biological and therapeutic processes can be evaluated simultaneously [101]. Each immunotherapy regimen would present its own virtues when executed appropriately in particular cases. In this section, the modern immunotherapeutic strategies based on 3D macroscale biomaterials will be categorized and discussed according to the objects exercising immunomodulatory functions and some remarkable immunotherapeutic paradigms will be enumerated (Fig. 5).

4.1. Delivery of immunomodulatory agents by 3D macroscale platforms

The 3D macroscale platforms have been widely investigated as drug delivery systems [102,103]. Different kinds of immunomodulatory agents could be simply incorporated into them via gentle procedures. Small immunotherapeutic drugs, such as pathway modulators, can be encapsulated in quantities, locally applied, and durably released. For example, interleukin (IL). It is short half-life *in vivo* and high doses-dependent toxicity to normal organs. The localized single long-term administration by 3D therapeutic biomaterials enhances efficacy and lessens side effects which makes 3D scaffolds outperform conventional systematic delivery of IL [104]. For macromolecular immunomodulatory drugs, such as antigens and antibodies, 3D macroscale platforms can help to sustain their special biological activity and increase their bioavailability in physiological circumstances [105]. For example, protein or nucleic acid-derived antigens and immune adjuvants. They are fragile to experience inactivation and denaturation during circulation. Hence, prolonging their lifespan by 3D macroscale biomaterials will ensure them work as effective cancer vaccines [36,106]. 3D scaffold materials also extend delivery business to cellular level promoting ACT therapy. The immune cells can combine with immunomodulatory molecules, concentrated and carried by 3D macroscale vehicles for synergistic therapies. Therefore, sufficient modulation of

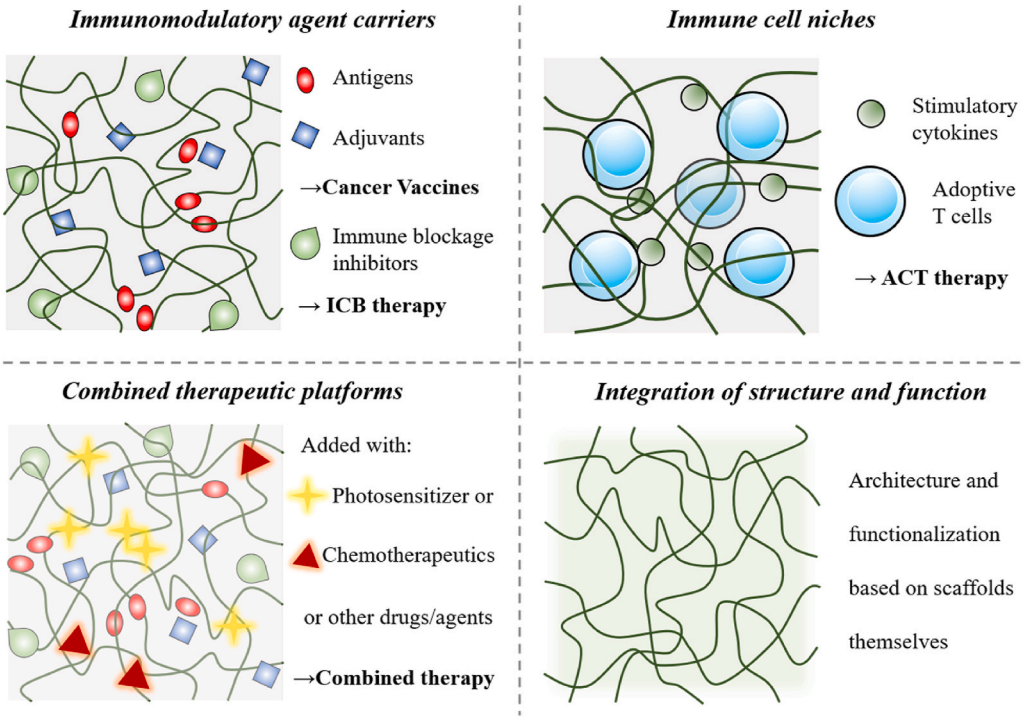

Fig. 5. Some classical immunotherapeutic strategies based on 3D macroscale biomaterial platforms. 3D macroscale biomaterials can load and deliver bioactive molecules as well as immune-related cells to achieve immunotherapy in tumor sites. They can also be further loaded with other cancer therapeutic agents for more efficient cancer combination therapy. In addition to supporting 3D structures as a carrier platform, part of the 3D bioscaffolds themselves can play a significant immunomodulatory role to treat tumors without any loading or further modification.

immune performances will be provoked in this localizable way [107] (Fig. 6).

There are many successful design of 3D scaffold-based cancer vaccines and immune checkpoint blocking. For instance, Bin Zheng et al. prepared an injectable hydrogel vaccine from PLGA-PEG-PLGA [108]. NIR-triggered antigens and non-pathogenic Sendai virus adjuvants could recruit and stimulate DCs, boost antigen presentation, activate anticancer immunity and induce immune memory. Yimou Gong et al. fabricated injectable reactive oxygen species (ROS)-responsive covalently crosslinked hydrogels [109]. The hydrogels can intelligently release aPD-L1 antibodies blocking suppressive immune recognition of B16F10 melanoma cells. Most recently, in the research of Chun Gwon Park et al. the crucial role of hydrogel in its mediated immunoregulatory strategy has been highlighted and further revealed [110]. The 3D hydrogels made from thiol-modified HA and poly (ethylene glycol) diacrylate (PEGDA) were used to load antibodies (aCTLA-4, aPD-1), cytokines (IL-15sa), or small molecules [lenalidomide, celecoxib, 2′3′-c-di-AM(PS)2 (Rp,Rp) ("STING-RR"), R848] and implanted into the tumor resection site. The extended release and immunotherapeutic effects of several different payloads have been studied for perioperative immunotherapy. Although extended regional release of these agents was realized in the adjacent to tumors, the most durable perioperative immune response presented when administering the agonists of innate immunity-loaded hydrogels (STING-RR and R848) which accounted for converting an immunosuppressive post-resection TME into an immunostimulatory type. Next, the researchers managed to confirm that these

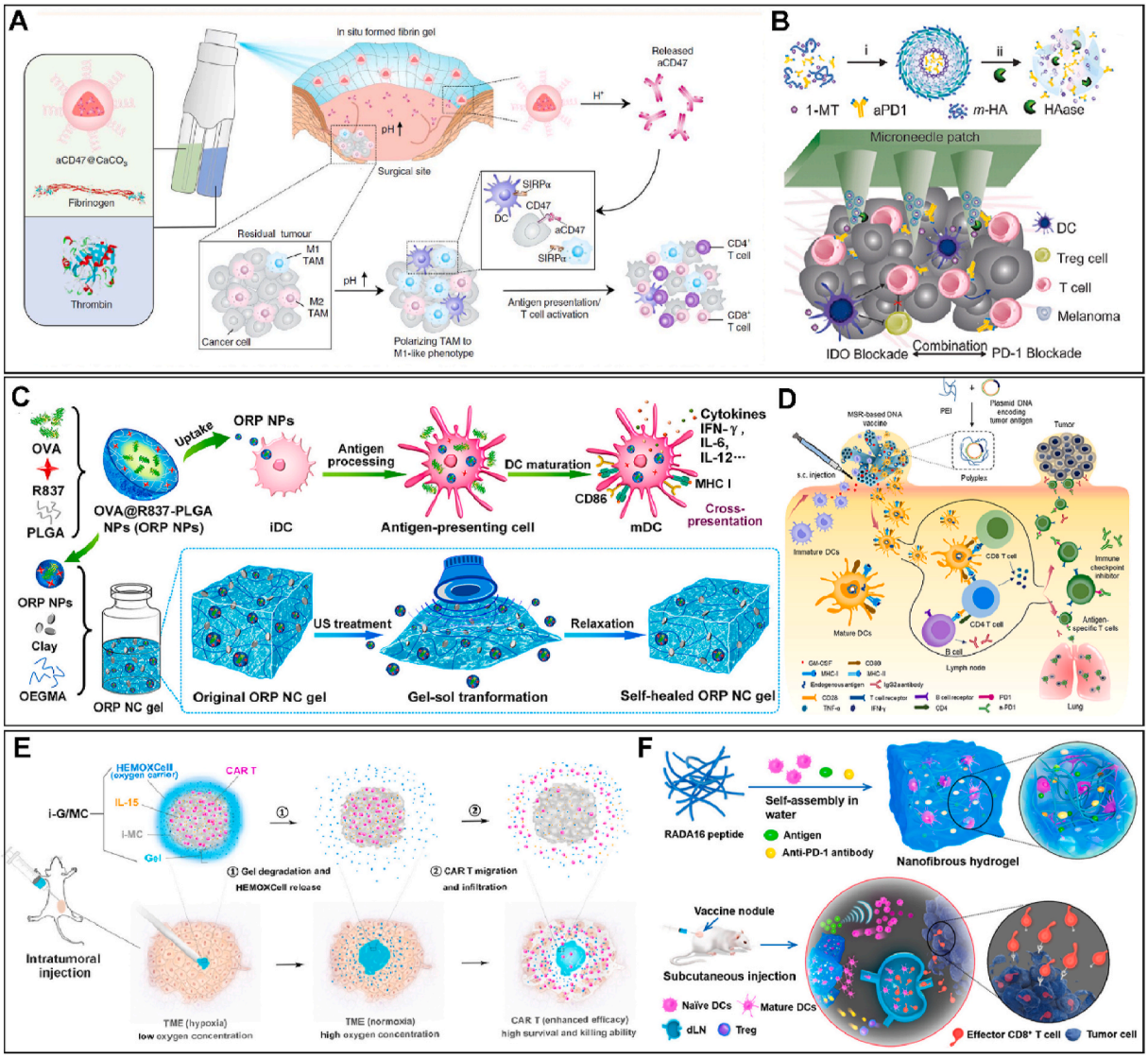

Fig. 6. 3D macroscale platforms for immunomodulatory molecules and cells delivery. (A) The *in situ* sprayed bioresponsive fibrin gel containing aCD47@$CaCO_3$ NPs within the post-surgery tumor bed, promoting both polarization of TAM to an M1-like phenotype and blockade of the 'don't eat me' signal in cancer cells. Reproduced with permission from Ref. [114]. Copyright 2018 The Author(s), under exclusive licence to Springer Nature Limited. (B) The microneedle-based transcutaneous platform loaded with self-assembled m-HA NPs for encapsulation and release of immunotherapeutic indoleamine 2,3-dioxygenase (IDO) inhibitor 1-MT and aPD-1. Reproduced with permission from Ref. [115]. Copyright 2016 American Chemical Society. (C) The fabrication of OVA@R837-PLGA NPs for immune stimulation as a nanovaccine and ultrasound-triggered release of NPs from the self-healing nanocomposite gel. Reproduced with permission from Ref. [116]. Copyright 2021 American Chemical Society. (D) Subcutaneous injection of chemokine-attracting DCs loaded in mesoporous silica microrods mixed with DNA-encoding tumor antigen polyplexes resulting in the formation of a 3D macroporous scaffold. Reproduced with permission from Ref. [117]. Copyright 2020 American Chemical Society. (E) A porous scaffold with oxygen reservoirs enhancing CAR-T cell immunotherapy of solid tumors by intratumoral injection. Reproduced with permission from Ref. [118]. Copyright 2020 American Chemical Society. (F) The formation and immune action mechanism of a peptide nanofibrous hydrogel self-assembled with tumor antigens, aPD-1 antibodies and exogenous DCs. Reproduced with permission from Ref. [119]. Copyright 2018 American Chemical Society.

agonists of innate immunity were effective only when released locally from the hydrogel. By contrasting the groups of blank controls, empty hydrogel controls, R848-loaded hydrogels, weekly intravenous injection (free R848), weekly intraperitoneal injection (free R848), and local delivery of R848 solution (single dose), the facts indicated that perioperative delivery of R848 from hydrogels conferred more survival benefit in most mice. The immunotherapeutic efficacy was also substantiated in spontaneous lung metastasis models. All these experimental results have demonstrated the outstanding functions of the engineered hydrogel strategies for cancer immunotherapy which could not only prevent recurrence but also avoid metastases of residual tumor tissues.

The porous and hydrophilic 3D networks of macroscale biomaterials are promising for cellular therapeutics. Afeng Yang et al. designed α-cyclodextrin and PEG co-crosslinked hydrogels for DC cancer vaccines [111]. The co-laden DOX/CpG nanoparticles as prodrugs offered DOX-stimulated tumor antigens and immunoadjuvants rising the antigen presentation levels of DCs. The implantation of exogenous DCs was compensatory to the insufficiency of endogenous DCs. Therefore, this 3D biomaterial-mediated cell vaccine could remarkably maximize T cell infiltration and killing to reverse intratumoral immune insensitivity. ACT is another hopeful strategy in cancer immunotherapy, yet its immune reactions are always limited by several major constraints, including high costs but low rates of *ex vivo* cell "training", poor functionality, and fragile vitality of transplanted cell products [112]. The interaction between immunocytes and macroscale scaffolds will be advantageous for cell encapsulation, viability or orientational differentiation. Sirkka B Stephan et al. successfully fabricated a kind of new hydrogels by alginate with collagen-mimetic peptide GFOGER which could carry T cells and implant *in situ* for adoptive T-cell transfer [113]. In both 4T1 mouse breast tumor resection model and advanced-stage inoperable tumor models, scaffold-delivered lymphocytes could maximize the immune interventions halting cancer aggravation. By comparing the groups treating with intravenous injection, intracavitary injection (with or without superagonist/antibody prestimulation), and scaffold delivery, respectively, using the same dose of T cells, the scaffold delivery did produce more antitumor effectiveness than that of conventional injection. Further cell trace found that intravenously injected lymphocytes tended to accumulate in the spleen and the liver, while peritoumorally injected T cells tended to rapidly exhaust functions, both ineffective for ACT. Differentially, the scaffold-supported T cells could deal with those above problems and offer the possibility for high-speed and high-yield cell proliferation.

As far, codelivery of over one single therapeutic agent in an appropriately defined pattern has become the mainstream trend in cancer immunotherapy. 3D macroscale materials can accomplish this task. Therein, multiple therapeutics would strike synergistic or additive effects overcoming the limitations of one component and improving overall therapeutic efficacy [120]. Yingge Shi et al. developed an injectable polypeptide hydrogel depot with both DOX and aPD-L1 delivered [121]. DOX elicits immunogenic cell death (ICD) to produce tumor-specifc antigens as cancer vaccines and meanwhile aPD-L1 antibodies inhibits PD-1/PD-L1 pathway for immune checkpoint blocking suppressing tumorigenesis in high efficiency. The spatiotemporal accuracy of immunotherapy can also be improved by 3D macroscale biomaterials since biomaterials are easier to be functionalized with stimuli-responsiveness [122,123]. For instance, a new kind of ultrasound-responsive self-healing hydrogel platform for nano-vaccine delivery was brought up by Zhouqi Meng et al. [116]. Based on the easy-to-operate remotely controlled ultrasound treatment, the system could go through gel-sol transition for individualized vaccine release, and self-heal to gel in the preset time for termination. After a single hypodermic injection, the smart hydrogel could achieve repeated vaccine burst release under multiple ultrasound treatments. The established B16-OVA tumor-bearing animal experiments suggested that this new system could elicit antitumor immune responses and obtain good *in vivo* therapeutic effects combined with ICB. As prophylactic vaccine, the hydrogels could arouse a long-term immune memory effect and further prevent postoperative metastases and recurrence.

With decades of hard efforts, several breakthroughs of 3D scaffold-based cancer immunotherapy have been achieved with exciting preclinical responses applied for immune checkpoint inhibition, cancer vaccines, and chimeric antigen receptor T (CAR-T) cells transfer. Some representatives of recently reported choreographed 3D macroscale biomaterial depots for delivery of immunomodulatory agents are summarized in Table 2.

P (Me-D-1MT)-PEG-P (Me-D-1MT): poly (L-methionine-dextro-1-methyl tryptophan)-poly (ethylene glycol)-poly (L-methionine-dextro-1-methyl tryptophan) triblock copolymer; Zeb: Zebularine; MA-alginate: methacrylated alginate; MA-PEG: methacrylated poly (ethylene glycol); GO: graphene oxide; PCL-PEG-PCL: poly (caprolactone)-poly (ethylene glycol)-poly (caprolactone); PDLLA-PEG-PDLLA: poly (D, L-lactide)-poly (ethylene glycol)-poly (D, L-lactide); ODEX: oxidized dextran; PECT: Poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone)-poly (ethylene glycol)-poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone); EAASc: poly (ethylene glycol)-*b*-poly (2-amino ethyl methacrylate)-*b*-poly (2-(hexamethylene imino) ethyl methacrylate-*co*-2-(dibutyl amino) ethyl methacrylate); α-CD: α-cyclodextrin; MIT: mitoxantrone; Gel-PEG-Cys: thiolated gelatin poly (ethylene glycol); LPS: Lipopolysaccharide; IMQ: Imiquimod; CDNs: cyclic dinucleotide, dithio-(Rp,Rp)-[cyclic [A (2′,5′)pA (3′,5′)p]]; BBN: N-Butyl-N-(4-hydroxybutyl) nitrosamine.

4.2. Immunoregulatory effects sponsored by 3D macroscale matrixes

The immune stimulation from 3D materials themselves navigates a novel direction for cancer immunotherapy. The scaffolds self-assembled by nucleic acids (viz. DNA and RNA) or peptides appear as a budding branch. Unlike common hydrogels/scaffolds made from polysaccharides and proteins, they are active in immunity by self-participation which might be applicable as cancer vaccines [146,147]. Such 3D biomaterials should not only provide a macroscale structure for immune agent delivery or immune cell expansion but act as a functional entity like cancer antigens or APCs to activate antitumor immunity [148–150]. They can be inserted to the available place by an easy or less invasive way. And if possible, these 3D biomaterials can move and spread to anywhere conformed to locally improve the stromal immunotherapeutic efficacy [151].

The DNAs represent the components that are both constructional and functional units. Yu Shao et al. put forward an unmethylated CpG supramolecular hydrogel vaccine (DSHV) system with a T-helper cell epitope peptide antigen [152]. The well-built injectable hydrogels have rigid network and mimetic function as LNs. By antigens triggering strong immune effects and CpG arousing synergistic immune stimulation, the APCs can be efficiently recruited and activated locally to induce high concentration of specific antibodies for constant recognition and defeat of target tumor cells (Fig. 7. A). Yuka Umeki et al. additionally incorporated tumor antigens as well as immune cells into the self-assembling DNA hydrogels to boost antitumor immunity [153]. The biocompatible and immunostimulatory hydrogels did not affect the cell viability but efficiently activated the DCs and macrophages for antigen-specific responses. Lately, Jaiwoo Lee et al. improved the DNA hydrogels with more precise liberation and higher immunocyte filtration of therapeutic DNAs [154]. The novel PD-1 DNA polyaptamer hydrogels were engineered with Cas9/sgRNA editability from which the free PD-1 aptamer sequences can be released after designated cut. Afterwards, the tumor cell survival could be hugely threatened with the T cell activity exacerbating.

Alternatively, antigenic peptides are also available for co-assembled hydrogels. Huaimin Wang et al. tried to develop a co-assembly molecular hydrogel with peptide gelators and OVA protein introduced into [155]. The hydrogels formed by phosphatase catalysed were supposed to be efficient vaccine adjuvants for optimizing the humoral immune

Table 2
Recently reported 3D macroscale biomaterial depots for delivery of immunomodulatory agents for cancer immunotherapy.

Therapeutic strategies	Scaffold composition	Gelling/Assembly mechanisms	Immunomodulatory agents	Administration routes	Tumor models	Ref.
ICB	Fibrin	Enzyme catalysis crosslinking (fibrinogen with thrombin)	aCD47/$CaCO_3$ NPs	Spray into the tumor resection cavity	C57BL/6 mice; B16F10 melanoma cells	[114]
	HA modified with 1-methyl-DL-tryptophan (1-MT)	Microneedle patch [124]	aPD-1	Transcutaneous administration	C57BL/6 mice; B16F10 melanoma cells	[115]
	PVA	Chemical conjugation (phenylboronic acid and the *cis*-1,3-diol in PVA)	aPD-1/$CaCO_3$ NPs and Zeb	Peritumoral injection	C57BL/6 mice; B16F10 melanoma cells	[125]
	P (Me-D-1MT)-PEG-P (Me-D-1MT)	Thermo-responsive	aPD-L1	Intratumoral injection	C57BL/6 mice; B16F10 melanoma cells	[126]
Vaccines	MA-alginate	Cryogelation technique and ionic crosslinking	CpG ODNs and GM-CSF	Subcutaneous injection	BALB/cJ mice; HER2/neu-overexpressing DD breast cancer cells	[127]
	MA-alginate and MA-PEG	Cryo-polymerization technique	CpG ODNs, GM-CSF and one or multiple antigens	Subcutaneous injection	C57BL/6 mice; MLL-AF9 AML cells	[128]
	MA-alginate and RGD peptides	Cryogelation technique	CpG ODNs and GM-CSF	Subcutaneous injection	C57BL/6 mice; B16F10 melanoma cells	[129]
	HA	Microneedle patch	Whole tumor lysate (with melanin) and GM-CSF	Intradermal administration	C57BL/6 J mice with $BRAF^{V600E}$-mutated BP melanoma; BALB/cJ mice with triple-negative breast cancer 4T1 carcinoma	[130]
	GO and PEI	Electrostatic interaction	mOVA (mRNA) and R848	Subcutaneous injection	C57BL/6 mice; mycoplasma-free B16-OVA cells and lung metastasis	[131]
	PCL-PEG-PCL	Thermo-responsive	OVA NPs and GM-CSF	Subcutaneous injection	C57BL/6 mice	[132]
	PDLLA-PEG-PDLLA	Thermo-responsive	CpG ODNs, GM-CSF, and tumor cell lysates	Subcutaneous injection	C57BL/6 J or Balb/c mice; B16F10 or C26 tumor cells	[133]
	8-arm-PEG and ODEX	Covalent crosslinking	Tumor lysate protein antigens (OVA) and CpG@PEI	Peritumoral/ Subcutaneous injection	BALB/c mice with postoperative MC38 tumor; C57BL/6 mice with B16-OVA tumor	[134]
	α-CD and PEG	Covalent crosslinking	CpG/DOX modified B16 cells and DCs	Subcutaneous injection	C57BL/6 mice; B16 melanoma cells	[135]
	Mesoporous silica microrods	Self-assembly	pOVA@PEI polyplex (pDNA encoding tumor antigen)	Subcutaneous injection	C57BL/6 mice; mycoplasma-free B16-OVA cells	[117]
	PECT NPs and EAASc NPs	Self-assembly	Curcumin; CpG ODN and peptide	*In situ* injection at the postoperative location	Balb/c mice; 4T1 cells; lung metastasis	[136]
ACT	HA-MA/oxHA-MA	Free radicals-based cryogelation	Human natural killer cells	Implantation *in situ*	BALB/c mice with incompletely resected MDA-MB-231 tumor	[137]
	Alginate	Ionic crosslinking and cryogelation	Human activated T cells	*In vitro* static transduction of T Cells	NSG mice with lymphoma xenograft model using the FFLuc-labelled $CD19^{+}$ human Daudi tumor cells	[138]
	Polyisocyano-peptide (PIC)	Thermo-responsive	Pre-activated T cells	Subcutaneous injection	C57BL/6 J mice	[139]
	Decellularized lymph node	Formic acid, acetic acid, or citric acid treatment	Dendritic cells	Implantation	C57BL/6 mice with E.G7-OVA tumor	[140]
Combined	HEMOXCell (marine hemoglobin) and alginate microspheres on Teflon plates	Ionic crosslinking	CAR T cells; IL-15	Intratumoral injection	Combined immune deficiency NPG/Vst mice; SKOV-3 (GFP+) cells	[118]
	RADA16 peptides	Self-assembly	DCs, aPD-1 and tumor antigens	Subcutaneous injection	C57BL/6 mice subcutaneously injected EG7-OVA lymphoma cells	[119]
	Oligopeptide precursors	Enzyme-assisted self-assembly	MIT and siIDO1 coloaded ZIF-8 nano-carriers; glioma-associated macrophage membrane	Intracavity injection	$GL261^{R132H}$-bearing mice with postoperative glioma	[141]
	HA-MA	Photo-crosslinking	aPD-L1-conjugated platelets and CAR-T cells	Implantation	NOD-*scid* $Il2rg^{null}$ (NSG) mice; WM115 human melanoma post-surgery	[142]
	PEGDA/Gel-PEG-Cys	Photo-crosslinking	M1 macrophages; LPS and IFN-γ	Subcutaneous injection	Athymic nude mice (BALB/c nu/nu) with subcutaneous MHCC97L xenograft	[143]
Others	Pluronic F-127	Thermal-responsive	IMQ/liposomes	*In situ* injection	Mice with 4T1 breast cancer	[144]
	N6-(1-iminoethyl)-L-lysine-Multidomain Peptides	Self-assembly	CDNs	Intratumoral injection	C57BL/6 mice with MOC1 oral tumor cells	[145]

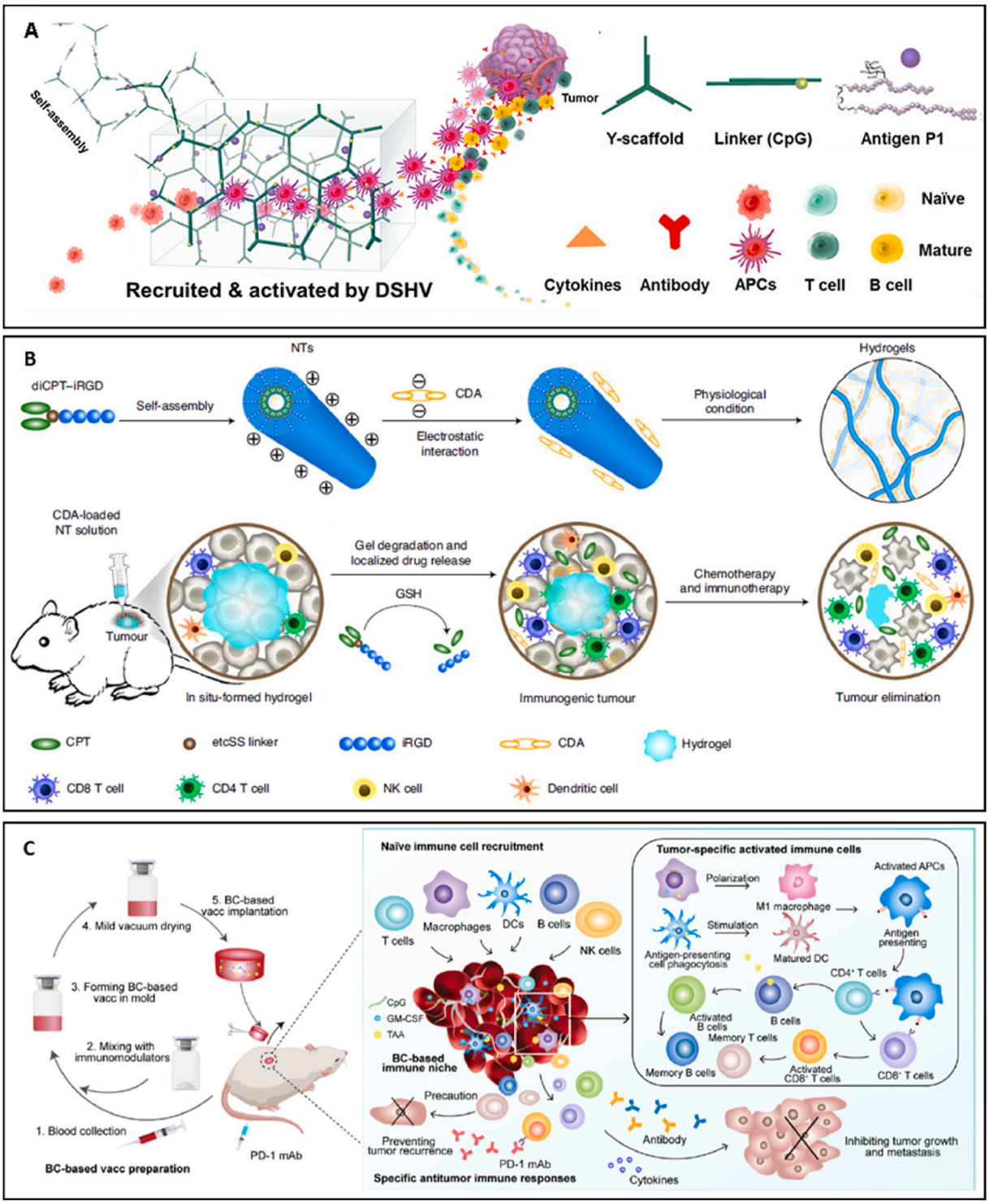

Fig. 7. 3D macroscale matrixes directly exerting immunoregulatory effects. (A) The injectable DNA supramolecular hydrogel vaccine (DSHV) system could be fabricated through the self-assembly of Y-scaffold, linker (both formed by specific DNA sequences), and antigen, for recruiting and activating naive APCs. Reproduced with permission from Ref. [152]. Copyright 2018 American Chemical Society. (B) The *in situ*-formed camptothecin (CPT)-based nanotube supramolecular hydrogel for localized CPT and STING agonist [c-di-AMP (CDA)] delivery to regulate TME. Reproduced with permission from Ref. [160]. Copyright 2020 The Author(s), under exclusive licence to Springer Nature Limited. (C) The innovative implantable blood clot vaccines that enhance the immune response *in vivo*. Reproduced with permission from Ref. [165]. Copyright 2020 The Author(s), under exclusive licence to American Association for the Advancement of Science.

reactions. The study also emphasized that the D-peptide hydrogel was more promising adjuvant activating immunity than the L-peptide while the exact mechanisms still needed to keep exploration. Xinxin Li et al. opted for another two potential stimulating peptides and combined them into new supramolecules (Nap-G^{D}F^{D}F^{D}YTKPR) which could self-assemble into either nanofiber scaffolds or hydrogels [156]. The derivative instruments intended to govern antitumor CD8^{+} T immune responses by increasing macrophages phagocytosis, expediting DCs maturation, promoting antigen presentation and stimulating cytokines secretion.

The nucleic acids and peptides share a common characteristic that their constituent units (either bases or amino acids) are minimalistic, countable, and highly specific so that there have existed mature technologies to produce them in large-scale [157]. This will contribute to the applications of these 3D scaffolds as immunomodulatory matrixes for clinical immunotherapy.

A minority of small molecules have also been used in the design of 3D scaffolds with only a few trials reported. Muchao Chen et al. selected steroid drugs to self-assemble carrier-free nanofiber hydrogels [158]. The anti-inflammatory betamethasone phosphate disodium (BetP) mixed with calcium ions could transform into gel for local delivery of aPD-L1 antibodies. As a functional immune-reprogramming machine, this system can not only reverse the immunosuppressive TME by the active scaffold, but also synergistically release aPD-L1 to stimulate the antitumor immune activity. Feihu Wang and coworkers successfully constructed drug-based supramolecular hydrogelator for local ICB therapy [159]. In the system, amphiphilic prodrug, diCPT-PLGLAG-iRGD were synthesized by two camptothecin (CPT) petals and hydrophilic iRGD parts conjugated with a both redox and matrix metalloproteinase 2 (MMP-2) responsive linker (PLGLAG peptide). This prodrug gelator could first spontaneously assemble into supramolecular nanotubes and then gelatinize via quick sol-gel transition. The small-molecule prodrugs with unique structures acted as both chemotherapeutic and aPD-1 carrier for responsive combination chemoimmunotherapy. The *in vivo* results revealed that this versatile carrier induced complete regression of GL-261 brain tumors and robust and durable systemic immunity inhibiting cancer recurrence and metastasis. Similarly, these researchers continued to use the diCPT-iRGD backbones and electrostatically complexed with STING agonists (c-di-AMP, CDA) for self-assembly as a local reservoir [160]. The hydrogels resulted in the extended release of CDA immunomodulators and CPT chemo-drugs to awaken both the innate and adaptive antitumor immunity (Fig. 7. B).

For “inert” biomaterials (3D delivery vehicles without immunomodulatory effects themselves), with the post-conjugation or modification, they can be allowed to function like biomimetic extracellular matrixes (ECM), as immune regulators rather than mere delivery tools. It is of practical significance especially in cellular immunotherapy. A biomimetic synthetic APCs matrix for T lymphocytes stimulation is by far one of the most feasible approaches for cancer immunotherapeutic applications. The ideal microenvironments should exhibit pores with diameter of 50–500 μm for cell migration and cell activity maintaining [161]. After specific antigen decorated onto the ECM-like 3D scaffolds, signal ligand-mediated communication will enable cell differentiation and expansion improving the functionality and quantity of antigen-specific T cells [162]. The therapeutic T-cell *ex vivo* expansion of high quality is one of the most vital portions in ACT. The group of David J. Mooney have described an inorganic system and summarized into a detailed protocol [163,164]. The system was comprised of biodegradable mesoporous silica microrods coated with liposomes-formed lipid bilayer which can be assembled into a bracket with a spatial structure by interacting with T cells. The fluid lipid bilayer can be inset with membrane-bound ligands (e.g., antibodies, cytokines) for T cell activation and the mesoporous silica enable sustained release of soluble paracrine cues like mitogenic factors. Compared to some conventional methods or commercial products, the scaffold facilitates *ex vivo* cell manipulation of ACT in low cost, rapid speed, and high efficiency, which can be assembled in approximately 4 h for several-fold greater expansion or faster enrichment of rare T-cell clones within 2 weeks.

In stead of abovementioned artificial formulations which usually requires high cost or multiple synthetic steps, Qin Fan et al. innovatively took advantage of coagulation or clotting, a natural process, to get a gel-like material [165]. The novel blood clot 3D scaffold can be formed using autologous blood, reducing adverse immunogenicity. In the blood clot scaffold, the main components are hydrated fibrous network and trapped red blood cells (RBCs). It makes the blood clot an ideal immune niche. RBCs in different states such as oxidized, damaged, or senescent periods, can implement important immune modulation in the innate immune system, including promoting DC maturity, macrophage polarization and T cells proliferation, which deserve to be concerned as potential cancer vaccines (Fig. 7. C). Furthermore, in company with tumor-associated antigen and adjuvant plus ICB, it has been confirmed that the blood clot vaccine could elicit an effective anticancer immune response in both B16F10 and 4T1 tumor models. It is a very interesting idea, harnessing human’s own natural physiological processes for immunotherapy, that will light a new orientation of immunotherapeutic matrixes.

4.3. Multifunctional 3D macroscale biomaterials for combined immunotherapy

The unsatisfactory immunotherapeutic outcomes in clinics usually come from weak and short-lasting anti-tumor immunity. The combination of multiple tumor therapies is expected to significantly improve the intensity and period of tumor immunotherapy. 3D macroscale scaffolds have strong competence to store different cancer therapeutics. Therefore, 3D biomaterial-assisted cancer immune treatments can undergo the cooperation from chemotherapy, radiotherapy, photothermal or photodynamic therapy and other therapeutic techniques. It will promise enhanced and prolonged immune responses to fortify the caner therapeutic efficiency [166].

Chemotherapy-induced cell death is one of the most common ways to increase tumor immunogenicity. Many studies have shown that chemotherapeutic agents do not entirely depend on their cytotoxicity to kill tumors. Some chemotherapeutic drugs also induce ICD, during which apoptotic cells release immune-related signals to initiate tumor-specific immune responses [167,168]. Synthetic polymeric scaffolds with prominent physiochemical performances have been developed for immunochemotherapy, lots of which have thermosensitive injectability and stimuli-responsive drug delivery [74,169,170]. Qiang Lv et al. developed triblock-copolymer hydrogels from poly (*g*-ethyl--L-glutamate)-poly (ethylene glycol)-poly (*g*-ethyl-L-glutamate) (PELG--PEG-PELG) for local treatment of melanoma [171]. DOX, IL-2 and IFN-γ were encapsulated in this chemoimmunotherapeutic system which could not only accelerate cell apoptosis but improve population of CD3+/CD4+ and CD3+/CD8+ T cells. Lei Jiang et al. also designed a thermosensitive injectable hydrogel based on PLGA-PEG-PLGA triblock copolymers as a delivery matrix [172]. The incorporated NPs can be controllably released for sustained tumor regression which carried the anticancer drugs DOX inside and made their outer arginine-rich molecules as inducible nitric oxide synthase (iNOS) substrate polarizing macrophages to M1 type. And Farrukh Vohidov et al. selected polylactic acid (PLA), PEG, and poly (N-isopropylacrylamide) (PNIPAM) as triblock to synthesize bottlebrush copolymer-based injectable hydrogels. After intratumoral rapid formation of the hydrogels, both PTX and toll-like receptor (TLR) 7/8 agonist resiquimod could be delivered to the tumor *in situ* [173]. Based on the cancer immunochemotherapy, CT26-bearing mice suffered from enhanced therapeutic effects compared to the administration with each drug alone. Chao Wang et al. engineered an *in situ*-forming and TME ROS-degradable PVA scaffold, allowing the local delivery of gemcitabine (GEM) and aPD-L1 antibody in a programmed fashion [174]. This bioresponsive aPD-L1-GEM scaffolds promised combined chemoimmunotherapy with GEM promoting immunogenic tumor phenotype and ICB prohibiting PD-1/PD-L1 pathway for immune-mediated tumor destruction.

Many biocompatible naturally occurring biomacromolecule are used to construct 3D scaffolds, mostly to treat poorly immunogenic TME for immunochemotherapy [175–177] (Fig. 8. A). Kosuke Ueda et al. investigated the synergistic anticancer effects of sorafenib and IFN-α with HA-tyramine (HA-Tyr) hydrogels as delivery platforms in human RCC-xenografted nude mice [178]. The HA-Tyr hydrogels addressed some problems including immune tolerability and dose limitation in the IFN-α therapy for metastatic renal cell carcinoma. Hathaichanok

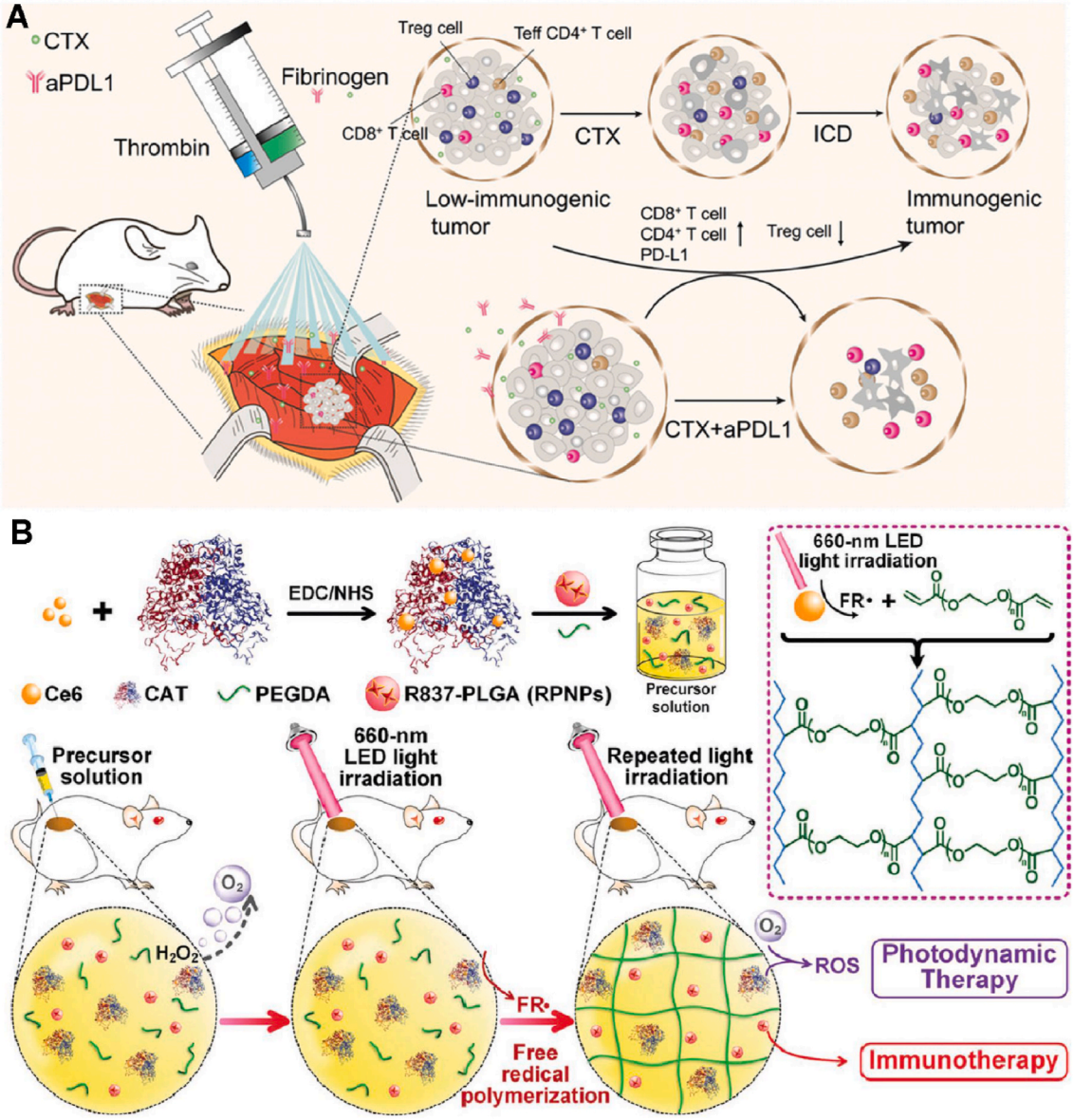

Fig. 8. Multifunctional 3D macroscale scaffolds for combined cancer immunotherapy. (A) The *in situ* formed fibrin scaffold delivering both cyclophosphamide and aPD-L1 for cancer chemoimmunotherapy to prohibit cancer recurrence at low-immunogenetic surgical site. Reproduced with permission from Ref. [177]. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA. (B) The light-triggered *in situ* gelation of Ce6-CAT/PEGDA hydrogel enabling repeated stimulations for robust photodynamic-immunotherapy. Reproduced with permission from Ref. [192]. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA.

Phuengkham et al. reported a multifunctional implantable scaffold made of collagen and HA which was designed to bring synergistic immunomodulatory actions to postoperative tumor resection bed [179]. In this system, GEM served as a myeloid-derived suppressor cell (MDSC)-depleting agent rising the immunogenicity in TME and cancer vaccines comprising whole tumor lysates-based antigens and poly (I:C) loaded nanogels-based adjuvants could elicit tumor-specific immune attack. This immune niche showed desirable treating efficacy even for the advanced stage 4T1 breast tumors. Another injectable alginate cryogels were prepared by Tomás Bauleth-Ramos et al. [180]. The cryogels could be loaded with GM-CSF, CpG ODNs, and ICD-induced p53 activator Nutlin-3a (Nut-3a) in the package of spermine-modified acetalated dextran NPs (Sp-AcDEX NPs). The antitumor immune responses will be initiated by the specific T-cell activation. Recently, Yu Chao et al. developed a kind of localized cocktail chemoimmunotherapy for robust immune trigger [181]. The injectable alginate could undergo gelation in the presence of Ca^{2+} in TME. A series of chemotherapeutic drugs (DOX or OXA), immune adjuvants (R837), and immune checkpoint inhibitors (aPD-L1) in the alginate excipients could be released in a sustained way to further amplify the antitumor immunity. This therapeutic cocktail formulations optimized current therapeutics and the authors claimed that it would be hopefully pushed into clinical trials in nearly 3 years. Furthermore, Hongjuan Zhao et al. developed an implantable drug-built scaffold with bioresponsive nanoarrays [182]. DOX as chemotherapeutics and JQ1 as epigenetic modulators were loaded into HA-modified polydopamine NPs. Another part of free JQ1 mixed with NPs conjugated with ROS-responsive linker molecules to fabricate immunotherapeutic nanoarray. It was confirmed that this strategy could change “cold tumors” into “hot tumors” and facilitate systematic immunogenicity inhibiting potential tumor recurrence or metastasis post surgery.

In the latest decades, with the good use of exogenous energy sources, tunor dynamic therapies have been prevailing, such as photodynamic therapy (PDT), sonodynamic therapy (SDT) and chemodynamic therapy (CDT) [183–187]. After site-specific exposure, high level ROS could be generated leading to damage-associated molecular patterns (DAMP) in tumor sites. The accumulation of tumor-associated antigens (TAA) then

arouses enhanced anti-cancer immunity [188–190]. Such immunostimulatory features make dynamic therapies amplify therapeutic potential of conventional immunotherapy. Based on 3D macroscale biomaterials, several decent platforms have been practiced in cancer combinational photodynamic immunotherapy [191]. Zhouqi Meng et al. synthesized poly (ethylene glycol) double acrylate (PEG-DA) for *in situ* light-crosslinking gelation [192]. Photosensitizer-modified catalase (CAT) and nano-adjuvant NPs were introduced into the hybrid hydrogels together for combined photodynamic immunotherapy. The single-dose injection can accomplish stimulations for several times. The repeated PDT will ensure intensive enough antitumor immune activities. More singlet oxygen was generated which significantly promoted tumor cell apoptosis, inhibited tumor growth and distant metastasis by means of PDT-mediated immunogenic improvement (Fig. 8. B). To boost personalized immunotherapy, Lei Fang et al. optimized autologous tumor cell-based vaccine (ATV) system with tumor target and on-demand gelation [193]. The ATV using oxidized autologous tumor cells was coated with 9-fluorenyl methoxycarbonyl (Fmoc)-KCRGDK--phenylboronic acid (FK-PBA) hydrogels which could target overexpressed sialic acid on residue tumor cell surfaces. Polyethylenimine-conjugated chlorin e6 (PEI-Ce6) in the gels supported the PDT. The peptide-based scaffold could self-assemble into hydrogels in Na_2CO_3 solution so that the gelation process could be fairly controlled as required. This powerful strategy of engineered ATVs could also provide an alternative avenue for other cell-based antigens to resist specific tumor postoperative relapse.

In addition, photonic hyperthermal-assisted immunotherapy could perform immunoadjuvant-like effects to mobilize tumor-attacking immunity [194,195]. The common photothermal immunomodifiers consist of Au-derived nanomaterials, near-infrared (NIR) dye small molecules and others [196,197]. For example, Tingting Wang et al. came up with a multifunctional personalized idea for postsurgical combined immunotherapy [198]. Tumor-penetrable peptide (Fmoc-KCRGDK) was designed to self-assemble into hydrogels with a BRD4 inhibitor JQ1 and indocyanine green (ICG) coloaded. After intratumoral injection, upon the NIR irradiation, ICG as photothermal inducer elevated temperature in tumors to release JQ1 for PD-L1 immune checkpoint blockage and generate tumor-specific antigens by ICD for cancer vaccines. This smart immunotherapeutic hydrogel system established long-term immune-memory and guarded effectively against post-operational tumor relapse and distant metastasis which can also be mirrored in other cancers or different patients. Enci Mei et al. achieved photothermal immunotherapy by an injectable photothermal drug methylene blue (MB) and TLR agonist R837 co-encapsulated collagen/alginate hydrogel [199]. When eliminating primary tumors, PTT also produced TAAs to gain additive or synergistic immune response with R837 elevating the therapeutic efficiency. Lately, Chao He et al. designed an R837 immune adjuvant-loaded 3D-printing bioglass scaffold. Niobium carbide (Nb2C) MXene as a new kind of thermo-active 2D agents coated with a mesoporous silica layer modified the biodegradable scaffolds [200]. The multifunctional therapeutic scaffold can not only direct immune-activation in TME combined with aPD-L1 ICB therapy, but also effectively conquer the bone metastasis and even prompt the injured bone regeneration. This system gives a high prospect to solve clinical problems on bone metastasis of breast cancer.

Many other combined therapies have been witnessed in recent few years. The group of Liu Zhuang made good use of aforementioned alginate-Ca^{2+} *in situ* gelling system for combinatorial radiotherapy and immunotherapy [201]. With ^{131}I radioisotope labelled CAT for radiotherapy, CpG ODNs as cancer vaccines and aCTLA-4 antibodies for ICB therapy, the local treatment has imparted potent systemic antitumor responses in many types of late-stage solid tumors. In the future clinical trials, more therapies, especially like traditional Chinese medicine are anticipated to be took into practice [202].

4.4. Engineered immunomodulatory models for further cancer immunotherapeutic research and clinical transformation

The shortage of tumor models that resemble the real *in vivo* TME has greatly slowed down the advancements of cancer immunotherapy into the clinic. Since the humanized *in vivo* animal model building remains imperfect, a wider range of animal species is urgently demanded, but it puts more pressures onto the costs of both funds and time [20]. The *ex vivo* 3D scaffolds can be equipped with spatial constructions similar to the physiological microenvironment and permit many exterior controls useful for imitating *in vivo* human responses or managing dynamic immunocyte activities [52]. The construction of ideal preclinical researching model is one of the most crucial steps in immunotherapy.

Natural polymers are very suitable for the preparation of 3D scaffold models. In comparation, the polymers from flora are better than those of fauna origin. Their high repeatability and tunability can make those 3D structures used to study cell-cell interactions with robust reproducibility [203,204]. Alginate, on behalf of the plant derivatives, is lacking native chemical sites bonding to mammalian cells whose inertness relieves the redundant conditioning of the bioactive media on cell fate. Stephen J. Florczyk et al. developed a 3D chitosan-alginate (CA) scaffold with the goal to study the interactions of cancer cells and lymphocytes *in vitro* [205]. Evaluated by SEM, immunohistochemistry, confocal fluorescence microscopy and flow cytometry, it was evident to conclude that the CA scaffolds prolonged the co-culture of prostate cancer cells and human peripheral blood lymphocytes for 55 days. They supported the *ex vivo* interaction of cancer cells with tumor-infiltrating B cells, T lymphocytes, and natural killer cells, and timely supervised *in situ* for screening immunotherapies, much better than Matrigel or other hydrogels did. Alessandra Marrella et al. also proposed an alginate-derived 3D hydrogel as convenient platform to investigate the neuroblastoma immunization and susceptibility to some unprecedented therapeutics [204]. It can be validated in a reliable way that the cytokine therapy could upregulate the expression of the immune checkpoint ligands on cell surface correlating with NK cell-mediated immune killing.

The acellular scaffolds as naturally derived scaffolds with self-existent 3D networks have revealed initial clinical promise. Some previous studies have confirmed that more engineerability should be employed to that scaffold for promoting the optimal phenotype of the cells [81]. Matthew T. Wolf et al. started a research on whether the immune microenvironment created by the biologic decellularized extracellular matrix, an implanted urinary bladder matrix (UBM) scaffold, encouraged tissue regeneration to develop tumors or not [206]. It was observed that an activated type 2 like wound-healing immune responses potentiated $CD4^+$ T cells and macrophages and affected sensitivity to PD-1 and PD-L1 ICBs, as a signature for tumor inhibition. Therefore, engineering the TME into type 2 wound-healing immune state by 3D scaffolds might improve tumor immunogenicity for targeting.

In addition to *in vitro* models for the basic studies of oncology, immunology and biology, biomimetic scaffold models as artificial living immune tissues/organs are also imperative for cancerous immune-related tissue engineering [207]. The *ex vivo* thymus or lymph nodes are anticipated to mimic natural lymphoid organs setting up a site for engineering immunocytes. They can attempt to turn into effective mediators employed for synthetic artificial APCs presenting antigens, generation and expansion of target-reactive effector cells for ACT [101]. However, the structural complexity of the immune organs undoubtedly strengthens the difficulties. Complicated parameters should be individually or collectively taken into concern at various stages. New breakthroughs in immune tissue engineering need to be made for prospective cancer immunotherapy.

5. Conclusions and prospects

Cancer immunotherapy has been universally perceived as a vigorous

force in cancer treatments. To date, anti-cancer immunotherapies have gotten a few exciting grades, whereas some distinct limitations suggest more valid settlements be behoved [208]. The elaborate biomaterial tools with emerging opportunities and potentials provide alternative ways to improve immunotherapeutic outcomes. Many of the delivery strategies delineated are endowed with preload, protection, delivery, and controlled release of imbedded substances. The 3D macroscale biomaterial-assisted delivery technologies can additionally realize local administration and cellular storage. Moreover, the self-assembly of some biomaterials not only offers 3D construction for targeted transportation of cargos, but forms functional matrixes for direct anticancer immunity. 3D scaffolds can be further equipped with drugs and external power-responsive agents to mediate dual or triple combinational tumor immunotherapy. Although such cancer immunotherapeutic platforms are just in the infant step, continuous and speedy growth for higher design flexibility will contribute to the broader clinical applications [209,210]. There is a hopeful vision of 3D scaffold-based cancer immunotherapies in the foreseeable future, but there is still a long way to go to address several leftover issues.

First and foremost, the inherent heterogeneity among every individual, different tumors and their district microenvironment is one of the key players that vary the responses to a specific therapeutic regimen [211,212]. Overcoming these limitations requires more detailed understanding of cancer immunobiology, after which the personalized treatment will allow more precise and efficacious immune reactions in the patient. In the recent few decades, a large range of patient-specific genes, signal factors, biomarkers, or neoantigens are long waiting for being discovered and identified [213,214]. The attractive technologies of computer aid and big data information may hasten this development [20].

The tailored biomaterial systems are equally essential for circumventing the failure of immunization. The physiochemical and biological properties of 3D macroscale biomaterials, involving but not limited to mechanical strength and brittleness, volume sensitivity and morphological deformation, viscoelasticity-dependent movement or *in situ* orientation, biodegradability, and long-term biosafety, deserve further lucubration and optimization [29,59,98]. And the potential in promoting the tumor growth of ECM-like environment should also be concerned. More importantly, how to achieve effective tumor tissue suppression and rapid regeneration of normal tissue in the meantime needs to be emphasized [215]. The research on the property-function relationships of biomaterials themselves could offer many guidelines for the design of 3D materials. Devotions to explaining the mysterious entanglement between immune and material systems seem tremendously requisite. In another words, it must be fully aware of the specific immune response clinically needed to define corresponding immunotherapeutic projects and then objectively analyse the associated organismal feedbacks for tuning design afterwards [210]. Collaboration in the fields of biology, medicine and engineering will improve the universality of 3D scaffold-based tumor immunotherapy.

After immunotherapeutic breadth, the therapeutic depth is another intractable issue. Although 3D scaffolds could solve the problems of nanoparticles hard to infiltrate solid tumors after systematic administration, it may still be a difficulty to accurately insert 3D scaffolds into deep tissues which might require imaging assistant [216]. Besides, the tissue penetration of external stimuli when combinational immunotherapy is also depth-dependent [217,218]. However, the mouse models used in most of the preclinical researches are not physiologically analogical to human patients in both size and depth. Therefore, more larger animals should be considered to build up both superficial and deep-seated tumor models at humanlike level, but it is always costly [59,219].

3D macroscale scaffolds can be developed as preliminary researching models. By emulation 3D to 4D modelling of *ex vivo* immune tissues or organs, the dynamic interaction processes between biomaterials and creatures are possible to be observed in order to facilitate adjustment of several parameters at any time [206,207]. From the aspect of techniques, the leap from 3D printing to 3D bioprinting technique overturns traditional 3D scaffold preparation [220,221]. Cells such as immunocytes are hoped to be directly used as bio-ink for additive manufacturing [222–224]. What's more, advanced 4D printing adds a new dimension time based on 3D structures. With smart bioactive materials combined, shapes or functions of 3D bioscaffolds could be transformed over time in response to microenvironmental stimulus. Therefore, dynamic immunotherapeutic intervention at different periods is expected to be achieved [225,226]. However, up to now, the field of model construction and immunotherapeutic applications by this way have rarely been set foot in.

As a product with both clinical transformation significance and commercial transformation value, 3D macroscale scaffolds also need to think about mass production and patient compliance [37,227]. Going forward, the 3D macroscale biomaterial-based immunotherapies with great translational potential will open more avenues of modulating the immune responses against more sophisticated diseases.

Declaration of competing interest

The authors declare no conflicts of interest.

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References

[1] Q. Sun, M. Barz, B.G. De Geest, M. Diken, W.E. Hennink, F. Kiessling, T. Lammers, Y. Shi, Nanomedicine and macroscale materials in immuno-oncology, Chem. Soc. Rev. 48 (1) (2019) 351–381.
[2] J. Tang, A. Shalabi, V.M. Hubbard-Lucey, Comprehensive analysis of the clinical immuno-oncology landscape, Ann. Oncol. 29 (1) (2018) 84–91.
[3] P.S. Hegde, D.S. Chen, Top 10 challenges in cancer immunotherapy, Immunity 52 (1) (2020) 17–35.
[4] Z.W. Zhao, L.Y. Zheng, W.Q. Chen, W. Weng, J.J. Song, J.S. Ji, Delivery strategies of cancer immunotherapy: recent advances and future perspectives, J. Hematol. Oncol. 12 (1) (2019).
[5] R.G. Majzner, C.L. Mackall, Clinical lessons learned from the first leg of the CAR T cell journey, Nat. Med. 25 (9) (2019) 1341–1355.
[6] O.S. Fenton, K.N. Olafson, P.S. Pillai, M.J. Mitchell, R. Langer, Advances in biomaterials for drug delivery, Adv. Mater. 30 (29) (2018) 1705328.
[7] S.N. Lee, S.M. Jin, H.S. Shin, Y.T. Lim, Chemical strategies to enhance the therapeutic efficacy of toll-like receptor agonist based cancer immunotherapy, Acc. Chem. Res. 53 (10) (2020) 2081–2093.
[8] N.A. Hotaling, L. Tang, D.J. Irvine, J.E. Babensee, Biomaterial strategies for immunomodulation, in: M.L. Yarmush (Ed.), Annual Review of Biomedical Engineering 17, 2015, pp. 317–349.
[9] J.M. Caster, C. Callaghan, S.N. Seyedin, K. Henderson, B. Sun, A.Z. Wang, Optimizing advances in nanoparticle delivery for cancer immunotherapy, Adv. Drug Deliv. Rev. 144 (2019) 3–15.
[10] J. Liu, R. Zhang, Z.P. Xu, Nanoparticle-based nanomedicines to promote cancer immunotherapy: recent advances and future directions, Small 15 (32) (2019), 1900262.
[11] R. Toy, K. Roy, Engineering nanoparticles to overcome barriers to immunotherapy, Bioengineering & Translational Medicine 1 (1) (2016) 47–62.
[12] Z. Yang, Y. Ma, H. Zhao, Y. Yuan, B.Y.S. Kim, Nanotechnology platforms for cancer immunotherapy, Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology 12 (2) (2020).
[13] Z. Zhao, L. Zheng, W. Chen, W. Weng, J. Song, J. Ji, Delivery strategies of cancer immunotherapy: recent advances and future perspectives, J. Hematol. Oncol. 12 (1) (2019).
[14] J. Nam, S. Son, K.S. Park, W. Zou, L.D. Shea, J.J. Moon, Cancer nanomedicine for combination cancer immunotherapy, Nat. Rev. Mater. 4 (6) (2019) 398–414.
[15] L. Xiao, Y. Huang, Y. Yang, Z. Miao, J. Zhu, M. Zhong, C. Feng, W. Tang, J. Zhou, L. Wang, X. Zhao, Z. Wang, Biomimetic cytomembrane nanovaccines prevent breast cancer development in the long term, Nanoscale 13 (6) (2021) 3594–3601.

[16] H. Xu, M. Hu, M. Liu, S. An, K. Guan, M. Wang, L. Li, J. Zhang, J. Li, L. Huang, Nano-puerarin regulates tumor microenvironment and facilitates chemo- and immunotherapy in murine triple negative breast cancer model, Biomaterials 235 (2020) 119769.
[17] M. Liu, W. Song, L. Huang, Drug delivery systems targeting tumor-associated fibroblasts for cancer immunotherapy, Cancer Lett. 448 (2019) 31–39.
[18] R.H. Fang, A.V. Kroll, L. Zhang, Nanoparticle-based manipulation of antigen-presenting cells for cancer immunotherapy, Small 11 (41) (2015) 5483–5496.
[19] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (5) (2016) 12.
[20] P.S. Huang, X.L. Wang, X.Y. Liang, J. Yang, C.N. Zhang, D.L. Kong, W.W. Wang, Nano-, micro-, and macroscale drug delivery systems for cancer immunotherapy, Acta Biomater. 85 (2019) 1–26.
[21] J. Li, Y. Luo, B. Li, Y. Xia, H. Wang, C. Fu, Implantable and injectable biomaterial scaffolds for cancer immunotherapy, Front. Bioeng. Biotechnol. 8 (2020), 612950.
[22] M. Niazi, E. Alizadeh, A. Zarebkohan, K. Seidi, M.H. Ayoubi-Joshaghani, M. Azizi, H. Dadashi, H. Mahmudi, T. Javaheri, M. Jaymand, M.R. Hamblin, R. Jahanban-Esfahlan, Z. Amoozgar, Advanced Bioresponsive Multitasking Hydrogels in the New Era of Biomedicine, Advanced Functional Materials 41st, 31, Wiley, 2021, 2104123.
[23] S.Y. Han, K.Q. Huang, Z.P. Gu, J. Wu, Tumor immune microenvironment modulation-based drug delivery strategies for cancer immunotherapy, Nanoscale 12 (2) (2020) 413–436.
[24] W. Park, K.H. Song, J. Lim, C.G. Park, J. Doh, D.K. Han, Biomaterial-based strategies to prime dendritic cell-mediated anti-cancer immune responses, Int. Mater. Rev. 65 (7) (2020) 445–462.
[25] X. Zhang, L. Li, J. Ouyang, L. Zhang, J. Xue, H. Zhang, W. Tao, Electroactive electrospun nanofibers for tissue engineering, Nano Today 39 (2021) 101196.
[26] X. Zhang, S. Koo, J.H. Kim, X. Huang, N. Kong, L. Zhang, J. Zhou, J. Xue, M. B. Harris, W. Tao, J.S. Kim, Nanoscale materials-based platforms for the treatment of bone-related diseases, Matter 4 (9) (2021) 2727–2764.
[27] Z. Tang, N. Kong, X. Zhang, Y. Liu, P. Hu, S. Mou, P. Liljestrom, J. Shi, W. Tan, J. S. Kim, Y. Cao, R. Langer, K.W. Leong, O.C. Farokhzad, W. Tao, A materials-science perspective on tackling COVID-19, Nat. Rev. Mater. (2020) 1–14.
[28] A.J. Najibi, D.J. Mooney, Cell and tissue engineering in lymph nodes for cancer immunotherapy, Adv. Drug Deliv. Rev. 161 (2020) 42–62.
[29] M.O. Dellacherie, B.R. Seo, D.J. Mooney, Macroscale biomaterials strategies for local immunomodulation, Nat. Rev. Mater. 4 (6) (2019) 379–397.
[30] O.T. Shofolawe-Bakare, L.D. Stokes, M. Hossain, A.E. Smith, T.A. Werfel, Immunostimulatory biomaterials to boost tumor immunogenicity, Biomaterials Science 8 (20) (2020) 5516–5537.
[31] Y. Shi, Clinical translation of nanomedicine and biomaterials for cancer immunotherapy: progress and perspectives, Advanced Therapeutics 3 (9) (2020). UNSP 1900215.
[32] A.S. Cheung, D.J. Mooney, Engineered materials for cancer immunotherapy, Nano Today 10 (4) (2015) 511–531.
[33] X. You, Z. Gu, J. Huang, Y. Kang, C.C. Chu, J. Wu, Arginine-based poly(ester amide) nanoparticle platform: from structure-property relationship to nucleic acid delivery, Acta Biomater. 74 (2018) 180–191.
[34] L. Chiossone, P.Y. Dumas, M. Vienne, E. Vivier, Natural killer cells and other innate lymphoid cells in cancer, Nat. Rev. Immunol. 18 (11) (2018) 671–688.
[35] K. Adu-Berchie, D.J. Mooney, Biomaterials as local niches for immunomodulation, Acc. Chem. Res. 53 (9) (2020) 1749–1760.
[36] G.A. Roth, V. Picece, B.S. Ou, W. Luo, B. Pulendran, E.A. Appel, Designing spatial and temporal control of vaccine responses, Nat. Rev. Mater. (2021) 1–22.
[37] J. Liu, S.S. Liew, J. Wang, K. Pu, Bioinspired and biomimetic delivery platforms for cancer vaccines, Adv. Mater. (2021), e2103790.
[38] X. Li, C. Shao, Y. Shi, W. Han, Lessons learned from the blockade of immune checkpoints in cancer immunotherapy, J. Hematol. Oncol. 11 (1) (2018) 31.
[39] Q. Li, Z. Zhao, X. Qin, M. Zhang, Q. Du, Z. Li, Y. Luan, A checkpoint-regulatable immune niche created by injectable hydrogel for tumor therapy, Adv. Funct. Mater. 31 (37) (2021), 2104630.
[40] A. Isser, N.K. Livingston, J.P. Schneck, Biomaterials to enhance antigen-specific T cell expansion for cancer immunotherapy, Biomaterials 268 (2021), 120584.
[41] Z.S. Dunn, J. Mac, P. Wang, T cell immunotherapy enhanced by designer biomaterials, Biomaterials (2019) 217, 119265.
[42] H. Phuengkham, L. Ren, I. Shin, Y.T. Lim, Nanoengineered immune niches for reprogramming the immunosuppressive tumor microenvironment and enhancing cancer immunotherapy, Adv. Mater. 31 (34) (2019), 1803322.
[43] S.T. Koshy, D.J. Mooney, Biomaterials for enhancing anti-cancer immunity, Curr. Opin. Biotechnol. 40 (2016) 1–8.
[44] C. Yang, N.T. Blum, J. Lin, J. Qu, P. Huang, Biomaterial scaffold-based local drug delivery systems for cancer immunotherapy, Sci. Bull. 65 (17) (2020) 1489–1504.
[45] A. Kurum, M. Gao, L. Tang, Synthetic 3D scaffolds for cancer immunotherapy, Curr. Opin. Biotechnol. 65 (2020) 1–8.
[46] F. Yang, K. Shi, Y.-p. Jia, Y. Hao, J.-r. Peng, Z.-y. Qian, Advanced biomaterials for cancer immunotherapy, Acta Pharmacol. Sin. 41 (7) (2020) 911–927.
[47] A. Singh, N.A. Peppas, Hydrogels and scaffolds for immunomodulation, Adv. Mater. 26 (38) (2014) 6530–6541.
[48] N. Oliva, J. Conde, K. Wang, N. Artzi, Designing hydrogels for on-demand therapy, Acc. Chem. Res. 50 (4) (2017) 669–679.
[49] Y. Zhao, Y. Guo, L. Tang, Engineering cancer vaccines using stimuli-responsive biomaterials, Nano Res. 11 (10) (2018) 5355–5371.
[50] M. Wang, X. Cheng, L. Luo, Y. Liu, F. Cao, S. Zhao, H. Peng, C. Hong, L. Jin, L. Deng, H. Xin, X. Wang, A multi-effective and long-acting immunotherapy through one single hydrogel based injection, Biomaterials Science 9 (4) (2021) 1374–1380.
[51] K.W. Lei, L. Tang, Surgery-free injectable macroscale biomaterials for local cancer immunotherapy, Biomaterials Science 7 (3) (2019) 733–749.
[52] S. Kim, S.B. Shah, P.L. Graney, A. Singh, Multiscale engineering of immune cells and lymphoid organs, Nat. Rev. Mater. 4 (6) (2019) 355–378.
[53] C. Jensen, Y. Teng, Is it time to start transitioning from 2D to 3D cell culture? Frontiers in Molecular Biosciences 7 (2020) 33.
[54] P. Datta, M. Dey, Z. Ataie, D. Unutmaz, I.T. Ozbolat, 3D bioprinting for reconstituting the cancer microenvironment, Npj Precision Oncology 4 (1) (2020) 18.
[55] M. Tang, J.N. Rich, S. Chen, Biomaterials and 3D bioprinting strategies to model glioblastoma and the blood-brain barrier, Adv. Mater. 33 (5) (2021), 2004776.
[56] R.-Z. Tang, Z.-Z. Liu, S.-S. Gu, X.-Q. Liu, Multiple local therapeutics based on nano-hydrogel composites in breast cancer treatment, J. Mater. Chem. B 9 (6) (2021) 1521–1535.
[57] C. Liu, T. Zhang, L. Chen, Y. Chen, The choice of anti-tumor strategies based on micromolecules or drug loading function of biomaterials, Cancer Lett. 487 (2020) 45–52.
[58] A. Fakhari, J.A. Subramony, Engineered in-situ depot-forming hydrogels for intratumoral drug delivery, J. Contr. Release 220 (2015) 465–475.
[59] D.G. Leach, S. Young, J.D. Hartgerink, Advances in immunotherapy delivery from implantable and injectable biomaterials, Acta Biomater. 88 (2019) 15–31.
[60] W. Wang, Q. Zhang, M. Zhang, X. Lv, Z. Li, M. Mohammadniaei, N. Zhou, Y. Sun, A novel biodegradable injectable chitosan hydrogel for overcoming postoperative trauma and combating multiple tumors, Carbohydr. Polym. 265 (2021), 118065.
[61] F.-j. Zhu, Y.-l. Tong, Z.-y. Sheng, Y.-m. Yao, Role of dendritic cells in the host response to biomaterials and their signaling pathways, Acta Biomater. 94 (2019) 132–144.
[62] C. Chu, J. Deng, X. Sun, Y. Qu, Y. Man, Collagen membrane and immune response in guided bone regeneration: recent progress and perspectives, Tissue Eng. B Rev. 23 (5) (2017) 421–435.
[63] C. Chu, L. Liu, S. Rung, Y. Wang, Y. Ma, C. Hu, X. Zhao, Y. Man, Y. Qu, Modulation of foreign body reaction and macrophage phenotypes concerning microenvironment, J. Biomed. Mater. Res. 108 (1) (2020) 127–135.
[64] T.T. Smith, H.F. Moffett, S.B. Stephan, C.F. Opel, A.G. Dumigan, X.Y. Jiang, V. G. Pillarisetty, S.P.S. Pillai, K.D. Wittrup, M.T. Stephan, Biopolymers codelivering engineered T cells and STING agonists can eliminate heterogeneous tumors, J. Clin. Invest. 127 (6) (2017) 2176–2191.
[65] A.A. Nada, E.A. Ali, A.A.F. Soliman, Biocompatible chitosan-based hydrogel with tunable mechanical and physical properties formed at body temperature, Int. J. Biol. Macromol. 131 (2019) 624–632.
[66] A. Ajovalasit, M.A. Sabatino, S. Todaro, S. Alessi, D. Giacomazza, P. Picone, M. Di Carlo, C. Dispenza, Xyloglucan-based hydrogel films for wound dressing: structure-property relationships, Carbohydr. Polym. 179 (2018) 262–272.
[67] S.A. Chew, S. Danti, Biomaterial-based implantable devices for cancer therapy, Advanced Healthcare Materials 6 (2) (2017), 1600766.
[68] K. Brewer, B. Gundsambuu, P.F. Marina, S.C. Barry, A. Blencowe, Thermoresponsive poly(epsilon-caprolactone)-poly(ethylene/propylene glycol) copolymers as injectable hydrogels for cell therapies, Polymers 12 (2) (2020) 367.
[69] L. Ren, Y.T. Lim, Degradation-regulatable Architectured implantable macroporous scaffold for the spatiotemporal modulation of immunosuppressive microenvironment and enhanced combination cancer immunotherapy, Adv. Funct. Mater. 28 (47) (2018), 1804490.
[70] H. Phuengkham, C. Song, Y.T. Lim, A designer scaffold with immune nanoconverters for reverting immunosuppression and enhancing immune checkpoint blockade therapy, Adv. Mater. 31 (42) (2019), 1903242.
[71] S. Srinivasan, J.E. Babensee, Controlled delivery of immunomodulators from a biomaterial scaffold niche to induce a tolerogenic phenotype in human dendritic cells, ACS Biomater. Sci. Eng. 6 (7) (2020) 4062–4076.
[72] Y. Shi, C. Ma, L. Peng, G. Yu, Conductive “smart” hybrid hydrogels with PNIPAM and nanostructured conductive polymers, Adv. Funct. Mater. 25 (8) (2015) 1219–1225.
[73] S.T. Koshy, D.K.Y. Zhang, J.M. Grolman, A.G. Stafford, D.J. Mooney, Injectable nanocomposite cryogels for versatile protein drug delivery, Acta Biomater. 65 (2018) 36–43.
[74] S.J. Yu, C.L. He, X.S. Chen, Injectable hydrogels as unique platforms for local chemotherapeutics-based combination antitumor therapy, Macromol. Biosci. 18 (12) (2018), 1800240.
[75] C. Chu, L. Liu, Y. Wang, R. Yang, C. Hu, S. Rung, Y. Man, Y. Qu, Evaluation of epigallocatechin-3-gallate (EGCG)-modified scaffold determines macrophage recruitment, Mater Sci Eng C Mater Biol Appl 100 (2019) 505–513.
[76] C. Chu, L. Liu, Y. Wang, S. Wei, Y. Wang, Y. Man, Y. Qu, Macrophage phenotype in the epigallocatechin-3-gallate (EGCG)-modified collagen determines foreign body reaction, Journal of Tissue Engineering and Regenerative Medicine 12 (6) (2018) 1499–1507.
[77] L.J. Eggermont, Z.J. Rogers, T. Colombani, A. Memic, S.A. Bencherif, Injectable cryogels for biomedical applications, Trends Biotechnol. 38 (4) (2020) 418–431.
[78] A. Memic, T. Colombani, L.J. Eggermont, M. Rezaeeyazdi, J. Steingold, Z. J. Rogers, K.J. Navare, H.S. Mohammed, S.A. Bencherif, Latest advances in cryogel Technology for biomedical applications, Advanced Therapeutics 2 (4) (2019), 1800114.
[79] M.O. Dellacherie, A. Li, B.Y. Lu, C.S. Verbeke, L. Gu, A.G. Stafford, E.J. Doherty, D.J. Mooney, Single-shot mesoporous silica rods scaffold for induction of humoral responses against small antigens, Adv. Funct. Mater. 30 (38) (2020), 2002448.

[80] L.J. Luo, J.Y. Lai, Amination degree of gelatin is critical for establishing structure-property-function relationships of biodegradable thermogels as intracameral drug delivery systems, Mater Sci Eng C Mater Biol Appl 98 (2019) 897–909.
[81] S.H. Kelly, L.S. Shores, N.L. Votaw, J.H. Collier, Biomaterial strategies for generating therapeutic immune responses, Adv. Drug Deliv. Rev. 114 (2017) 3–18.
[82] K. Garg, N.A. Pullen, C.A. Oskeritzian, J.J. Ryan, G.L. Bowlin, Macrophage functional polarization (M1/M2) in response to varying fiber and pore dimensions of electrospun scaffolds, Biomaterials 34 (18) (2013) 4439–4451.
[83] Y. Yang, Y. Yang, M. Chen, J. Chen, J. Wang, Y. Ma, H. Qian, Injectable shear-thinning polylysine hydrogels for localized immunotherapy of gastric cancer through repolarization of tumor-associated macrophages, Biomaterials Science 9 (19) (2021) 6597–6608.
[84] E. Prince, E. Kumacheva, Design and applications of man-made biomimetic fibrillar hydrogels, Nat. Rev. Mater. 4 (2) (2019) 99–115.
[85] J. Wu, D. Wu, M.A. Mutschler, C.-C. Chu, Cationic hybrid hydrogels from amino-acid-based poly(ester amide): fabrication, characterization, and biological properties, Adv. Funct. Mater. 22 (18) (2012) 3815–3823.
[86] J. Park, M.H. Gerber, J.E. Babensee, Phenotype and polarization of autologous T cells by biomaterial-treated dendritic cells, J. Biomed. Mater. Res. 103 (1) (2015) 170–184.
[87] O. Chaudhuri, J. Cooper-White, P.A. Janmey, D.J. Mooney, V.B. Shenoy, Effects of extracellular matrix viscoelasticity on cellular behaviour, Nature 584 (7822) (2020) 535–546.
[88] M.H.W. Chin, M.D.A. Norman, E. Gentleman, M.-O. Coppens, R.M. Day, A hydrogel-integrated culture device to interrogate T cell activation with physicochemical cues, ACS Appl. Mater. Interfaces 12 (42) (2020) 47355–47367.
[89] H. Wang, M.C. Sobral, D.K.Y. Zhang, A.N. Cartwright, A.W. Li, M.O. Dellacherie, C.M. Tringides, S.T. Koshy, K.W. Wucherpfennig, D.J. Mooney, Metabolic labeling and targeted modulation of dendritic cells, Nat. Mater. 19 (11) (2020) 1244–+.
[90] J. Zhang, C.A. Reinhart-King, Targeting tissue stiffness in metastasis: mechanomedicine improves cancer therapy, Cancer Cell 37 (6) (2020) 754–755.
[91] B. Ozkale, M.S. Sakar, D.J. Mooney, Active biomaterials for mechanobiology, Biomaterials 267 (2021) 120497.
[92] X. Zhang, T.-H. Kim, T.J. Thauland, H. Li, F.S. Majedi, C. Ly, Z. Gu, M.J. Butte, A. C. Rowat, S. Li, Unraveling the mechanobiology of immune cells, Curr. Opin. Biotechnol. 66 (2020) 236–245.
[93] J.K. Kim, Y.J. Shin, L.J. Ha, D.H. Kim, D.H. Kim, Unraveling the mechanobiology of the immune system, Adv Healthc Mater 8 (4) (2019), e1801332.
[94] T. Yata, Y. Takahashi, M.M. Tan, H. Nakatsuji, S. Ohtsuki, T. Murakami, H. Imahori, Y. Umeki, T. Shiomi, Y. Takakura, M. Nishikawa, DNA nanotechnology-based composite-type gold nanoparticle-immunostimulatory DNA hydrogel for tumor photothermal immunotherapy, Biomaterials 146 (2017) 136–145.
[95] B. Hu, W. Sun, H. Li, H. Sui, S. Li, Systematic modifications of amino acid-based organogelators for the investigation of structure-property correlations in drug delivery system, Int. J. Pharm. 547 (1–2) (2018) 637–647.
[96] N.M. Munoz, M. Williams, K. Dixon, C. Dupuis, A. McWatters, R. Avritscher, S. Z. Manrique, K. McHugh, R. Murthy, A. Tam, A. Naing, S.P. Patel, D. Leach, J. D. Hartgerink, S. Young, P. Prakash, P. Hwu, R.A. Sheth, Influence of injection technique, drug formulation and tumor microenvironment on intratumoral immunotherapy delivery and efficacy, Journal for immunotherapy of cancer 9 (2) (2021), e001800.
[97] J. Wang, S. Wang, T. Ye, F. Li, X. Gao, Y. Wang, P. Ye, S. Qing, C. Wang, H. Yue, J. Wu, W. Wei, G. Ma, Choice of nanovaccine delivery mode has profound impacts on the intralymph node spatiotemporal distribution and immunotherapy efficacy, Adv. Sci. 7 (19) (2020), 2001108.
[98] C. Wang, Y.Q. Ye, Q.Y. Hu, A. Bellotti, Z. Gu, Tailoring biomaterials for cancer immunotherapy: emerging trends and future outlook, Adv. Mater. 29 (29) (2017), 1606036.
[99] J.J. Havel, D. Chowell, T.A. Chan, The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy, Nat. Rev. Cancer 19 (3) (2019) 133–150.
[100] Z. Hu, P.A. Ott, C.J. Wu, Towards personalized, tumour-specific, therapeutic vaccines for cancer, Nat. Rev. Immunol. 18 (3) (2018) 168–182.
[101] H. Lin, Q. Li, O. Wang, J. Rauch, B. Harm, H.J. Viljoen, C. Zhang, E. Van Wyk, C. Zhang, Y. Lei, Automated expansion of primary human T cells in scalable and cell-friendly hydrogel microtubes for adoptive immunotherapy, Advanced Healthcare Materials 7 (15) (2018), 1701297.
[102] H. Ma, C. He, X. Chen, Injectable hydrogels as local depots at tumor sites for antitumor immunotherapy and immune-based combination therapy, Macromol. Biosci. 21 (6) (2021), 2100039.
[103] R. Cui, Q. Wu, J. Wang, X. Zheng, R. Ou, Y. Xu, S. Qu, D. Li, Hydrogel-by-design: smart delivery system for cancer immunotherapy, Front. Bioeng. Biotechnol. 9 (2021), 723490.
[104] Y. Zhang, N. Li, H. Suh, D.J. Irvine, Nanoparticle anchoring targets immune agonists to tumors enabling anti-cancer immunity without systemic toxicity, Nat. Commun. 9 (1) (2018) 6.
[105] D. Wen, G.J. Chen, Q. Chen, P.Y. Li, H. Cheng, Z. Gu, Engineering protein delivery depots for cancer immunotherapy, Bioconjugate Chem. 30 (3) (2019) 515–524.
[106] H. Zhang, X. You, X. Wang, L. Cui, Z. Wang, F. Xu, M. Li, Z. Yang, J. Liu, P. Huang, Y. Kang, J. Wu, X. Xia, Delivery of mRNA vaccine with a lipid-like material potentiates antitumor efficacy through Toll-like receptor 4 signaling, Proc. Natl. Acad. Sci. U. S. A. 118 (6) (2021), e2005191118.
[107] Y. Chao, Q. Chen, Z. Liu, Smart injectable hydrogels for cancer immunotherapy, Adv. Funct. Mater. 30 (2) (2020), 1902785.
[108] B. Zheng, W. Peng, L. Gan, M. Guo, S. Wang, X.-D. Zhang, D. Ming, Sendai virus-based immunoadjuvant in hydrogel vaccine intensity-modulated dendritic cells activation for suppressing tumorigenesis, Bioactive Materials 6 (11) (2021) 3879–3891.
[109] Y. Gong, M. Chen, Y. Tan, J. Shen, Q. Jin, W. Deng, J. Sun, C. Wang, Z. Liu, Q. Chen, Injectable reactive oxygen species-responsive SN38 prodrug scaffold with checkpoint inhibitors for combined chemoimmunotherapy, ACS Appl. Mater. Interfaces 12 (45) (2020) 50248–50259.
[110] C.G. Park, C.A. Hartl, D. Schmid, E.M. Carmona, H.J. Kim, M.S. Goldberg, Extended release of perioperative immunotherapy prevents tumor recurrence and eliminates metastases, Sci. Transl. Med. 10 (433) (2018), eaar1916.
[111] A. Yang, X. Dong, Y. Bai, S. Sheng, Y. Zhang, T. Liu, D. Zhu, F. Lv, Doxorubicin/CpG self-assembled nanoparticles prodrug and dendritic cells co-laden hydrogel for cancer chemo-assisted immunotherapy, Chem. Eng. J. 416 (2021), 129192.
[112] T.R. Abreu, N.A. Fonseca, N. Goncalves, J.N. Moreira, Current challenges and emerging opportunities of CAR-T cell therapies, J. Contr. Release 319 (2020) 246–261.
[113] S.B. Stephan, A.M. Taber, I. Jileaeva, E.P. Pegues, C.L. Sentman, M.T. Stephan, Biopolymer implants enhance the efficacy of adoptive T-cell therapy, Nat. Biotechnol. 33 (1) (2015) 97–U277.
[114] Q. Chen, C. Wang, X. Zhang, G. Chen, Q. Hu, H. Li, J. Wang, D. Wen, Y. Zhang, Y. Lu, G. Yang, C. Jiang, J. Wang, G. Dotti, Z. Gu, In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment, Nat. Nanotechnol. 14 (1) (2019) 89–97.
[115] Y.Q. Ye, J.Q. Wang, Q.Y. Hu, G.M. Hochu, H.L. Xin, C. Wang, Z. Gu, Synergistic transcutaneous immunotherapy enhances antitumor immune responses through delivery of checkpoint inhibitors, ACS Nano 10 (9) (2016) 8956–8963.
[116] Z. Meng, Y. Zhang, J. She, X. Zhou, J. Xu, X. Han, C. Wang, M. Zhu, Z. Liu, Ultrasound-mediated remotely controlled nanovaccine delivery for tumor vaccination and individualized cancer immunotherapy, Nano Lett. 21 (3) (2021) 1228–1237.
[117] N. Thanh Loc, Y. Yin, Y. Choi, J.H. Jeong, J. Kim, Enhanced cancer DNA vaccine via direct transfection to host dendritic cells recruited in injectable scaffolds, ACS Nano 14 (9) (2020) 11623–11636.
[118] Z. Luo, Z. Liu, Z. Liang, J. Pan, J. Xu, J. Dong, Y. Bai, H. Deng, S. Wei, Injectable porous microchips with oxygen reservoirs and an immune-niche enhance the efficacy of CAR T cell therapy in solid tumors, ACS Appl. Mater. Interfaces 12 (51) (2020) 56712–56722.
[119] P.X. Yang, H.J. Song, Y.B. Qin, P.S. Huang, C.N.A. Zhang, D.L. Kong, W.W. Wang, Engineering dendritic-cell-based vaccines and PD-1 blockade in self-assembled peptide nanofibrous hydrogel to amplify antitumor T-cell immunity, Nano Lett. 18 (7) (2018) 4377–4385.
[120] H. Ruan, L. Bu, Q. Hu, H. Cheng, W. Lu, Z. Gu, Strategies of combination drug delivery for immune checkpoint blockades, Adv Healthc Mater 8 (4) (2019), e1801099.
[121] Y. Shi, D. Li, C. He, X. Chen, Design of an injectable polypeptide hydrogel depot containing the immune checkpoint blocker anti-PD-L1 and doxorubicin to enhance antitumor combination therapy, Macromol. Biosci. 21 (6) (2021), 2100049.
[122] L. Li, Z. Yang, X. Chen, Recent advances in stimuli-responsive platforms for cancer immunotherapy, Acc. Chem. Res. 53 (10) (2020) 2044–2054.
[123] D. Li, R. Zhang, G. Liu, Y. Kang, J. Wu, Redox-responsive self-assembled nanoparticles for cancer therapy, Adv Healthc Mater 9 (20) (2020), e2000605.
[124] Z.M. Zhao, A. Ukidve, A. Dasgupta, S. Mitragotri, Transdermal immunomodulation: principles, advances and perspectives, Adv. Drug Deliv. Rev. 127 (2018) 3–19.
[125] H.T. Ruan, Q.Y. Hu, D. Wen, Q. Chen, G.J. Chen, Y.F. Lu, J.Q. Wang, H. Cheng, W. Y. Lu, Z. Gu, A dual-bioresponsive drug-delivery depot for combination of epigenetic modulation and immune checkpoint blockade, Adv. Mater. 31 (17) (2019), 1806957.
[126] S.J. Yu, C. Wang, J.C. Yu, J.Q. Wang, Y. Lu, Y.Q. Zhang, X.D. Zhang, Q.Y. Hu, W. J. Sun, C.L. He, X.S. Chen, Z. Gu, Injectable bioresponsive gel depot for enhanced immune checkpoint blockade, Adv. Mater. 30 (28) (2018), 1801527.
[127] T.Y. Shih, S.O. Blacklow, A.W. Li, B.R. Freedman, S. Bencherif, S.T. Koshy, M. C. Darnell, D.J. Mooney, Injectable Tough alginate cryogels as cancer vaccines, Advanced Healthcare Materials 7 (10) (2018), 1701469.
[128] N.J. Shah, A.J. Najibi, T.Y. Shih, A.S. Mao, A. Sharda, D.T. Scadden, D.J. Mooney, A biomaterial-based vaccine eliciting durable tumour-specific responses against acute myeloid leukaemia, Nat Biomed Eng 4 (1) (2020) 40–51.
[129] S.A. Bencherif, R. Warren Sands, O.A. Ali, W.A. Li, S.A. Lewin, T.M. Braschler, T. Y. Shih, C.S. Verbeke, D. Bhatta, G. Dranoff, D.J. Mooney, Injectable cryogel-based whole-cell cancer vaccines, Nat. Commun. 6 (2015) 7556.
[130] Y.Q. Ye, C. Wang, X.D. Zhang, Q.Y. Hu, Y.Q. Zhang, Q. Liu, D. Wen, J. Milligan, A. Bellotti, L. Huang, G. Dotti, Z. Gu, A melanin-mediated cancer immunotherapy patch, Science Immunology 2 (17) (2017), eaan5692.
[131] Y. Yin, X. Li, H. Ma, J. Zhang, D. Yu, R. Zhao, S. Yu, G. Nie, H. Wang, In situ transforming RNA nanovaccines from polyethylenimine functionalized graphene oxide hydrogel for durable cancer immunotherapy, Nano Lett. 21 (5) (2021) 2224–2231.
[132] Z.T. Sun, J. Liang, X. Dong, C. Wang, D.L. Kong, F. Lv, Injectable hydrogels coencapsulating granulocyte-macrophage colony-stimulating factor and ovalbumin nanoparticles to enhance antigen uptake efficiency, ACS Appl. Mater. Interfaces 10 (24) (2018) 20315–20325.
[133] F. Yang, K. Shi, Y. Jia, Y. Hao, J. Peng, L. Yuan, Y. Chen, M. Pan, Z. Qian, A biodegradable thermosensitive hydrogel vaccine for cancer immunotherapy, Applied Materials Today 19 (2020), 100608.

[134] Z. Yu, Y. Xu, H. Yao, X. Si, G. Ji, S. Dong, J. Zhao, Z. Tang, X. Fang, W. Song, X. Chen, A simple and general strategy for postsurgical personalized cancer vaccine therapy based on an injectable dynamic covalent hydrogel, Biomater. Sci. 9 (2021) 6879–6888.
[135] A. Yang, Y. Bai, X. Dong, T. Ma, D. Zhu, L. Mei, F. Lv, Hydrogel/nanoadjuvant-mediated combined cell vaccines for cancer immunotherapy, Acta Biomater. 133 (2021) 257–267.
[136] X. Liu, Z. Feng, C. Wang, Q. Su, H. Song, C. Zhang, P. Huang, X.-J. Liang, A. Dong, D. Kong, W. Wang, Co-localized delivery of nanomedicine and nanovaccine augments the postoperative cancer immunotherapy by amplifying T-cell responses, Biomaterials (2020) 230.
[137] Y.H. Ahn, L. Ren, S.M. Kim, S.H. Seo, C.R. Jung, D.S. Kim, J.Y. Noh, S.Y. Lee, H. Lee, M.Y. Cho, H. Jung, S.R. Yoon, J.E. Kim, S.N. Lee, S. Kim, I.W. Shin, H. S. Shin, K.S. Hong, Y.T. Lim, I. Choi, T.D. Kim, A three-dimensional hyaluronic acid-based niche enhances the therapeutic efficacy of human natural killer cell-based cancer immunotherapy, Biomaterials 247 (2020) 119960.
[138] P. Agarwalla, E.A. Ogunnaike, S. Ahn, F.S. Ligler, G. Dotti, Y. Brudno, Scaffold-mediated static transduction of T cells for CAR-T cell therapy, Advanced Healthcare Materials 9 (14) (2020), 2000275.
[139] J. Weiden, D. Voerman, Y. Dolen, R.K. Das, A. van Duffelen, R. Hammink, L. J. Eggermont, A.E. Rowan, J. Tel, C.G. Figdor, Injectable biomimetic hydrogels as tools for efficient T cell expansion and delivery, Front. Immunol. 9 (2018) 2798.
[140] H.J. Lin, W. Wang, Y.Y. Huang, W.T. Liao, T.Y. Lin, S.Y. Lin, D.Z. Liu, Decellularized lymph node scaffolding as a carrier for dendritic cells to induce anti-tumor immunity, Pharmaceutics 11 (11) (2019) 533.
[141] J. Zhang, C. Chen, A. Li, W. Jing, P. Sun, X. Huang, Y. Liu, S. Zhang, W. Du, R. Zhang, Y. Liu, A. Gong, J. Wu, X. Jiang, Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection, Nat. Nanotechnol. 16 (2021) 538–548.
[142] Q. Hu, H. Li, E. Archibong, Q. Chen, H. Ruan, S. Ahn, E. Dukhovlinova, Y. Kang, D. Wen, G. Dotti, Z. Gu, Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and nnti-PDL1-conjugated platelets, Nat. Biomed. Eng. 5 (2021) 1038–+.
[143] A.D. Guerra, O.W.H. Yeung, X. Qi, W.J. Kao, K. Man, The anti-tumor effects of M1 macrophage-loaded poly (ethylene glycol) and gelatin-based hydrogels on hepatocellular carcinoma, Theranostics 7 (15) (2017) 3732–3744.
[144] H.C. Tsai, H.Y. Chou, S.H. Chuang, J.Y. Lai, Y.S. Chen, Y.H. Wen, L.Y. Yu, C.L. Lo, Preparation of immunotherapy liposomal-loaded thermal-responsive hydrogel carrier in the local treatment of breast cancer, Polymers 11 (10) (2019) 1592.
[145] D.G. Leach, N. Dharmaraj, T.L. Lopez-Silva, J.R. Venzor, B.H. Pogostin, A. G. Sikora, J.D. Hartgerink, S. Young, Biomaterial-facilitated immunotherapy for established oral cancers, ACS Biomater. Sci. Eng. 7 (2) (2021) 415–421.
[146] J. Gacanin, C.V. Synatschke, T. Weil, Biomedical applications of DNA-based hydrogels, Adv. Funct. Mater. 30 (4) (2020), 1906253.
[147] M.M. Li, X.R. Zhao, J.F. Dai, Z.L. Yu, Peptide therapeutics and assemblies for cancer immunotherapy, Science China-Materials 62 (11) (2019) 1759–1781.
[148] X. Huang, J.Z. Williams, R. Chang, Z. Li, C.E. Burnett, R. Hernandez-Lopez, I. Setiady, E. Gai, D.M. Patterson, W. Yu, K.T. Roybal, W.A. Lim, T.A. Desai, DNA scaffolds enable efficient and tunable functionalization of biomaterials for immune cell modulation, Nat. Nanotechnol. 16 (2020) 214–223.
[149] K. Huang, J. Wu, Z. Gu, Black phosphorus hydrogel scaffolds enhance bone regeneration via a sustained supply of calcium-free phosphorus, ACS Appl. Mater. Interfaces 11 (3) (2019) 2908–2916.
[150] J.W. Hickey, Y. Dong, J.W. Chung, S.F. Salathe, H.C. Pruitt, X.W. Li, C. Chang, A. K. Fraser, C.A. Bessell, A.J. Ewald, S. Gerecht, H.Q. Mao, J.P. Schneck, Engineering an artificial T-cell stimulating matrix for immunotherapy, Adv. Mater. 31 (23) (2019), 1807359.
[151] A. Johansson, J. Hamzah, R. Ganss, More than a scaffold: stromal modulation of tumor immunity, Biochim. Biophys. Acta Rev. Canc 1865 (1) (2016) 3–13.
[152] Y. Shao, Z.Y. Sun, Y.J. Wang, B.D. Zhang, D.S. Liu, Y.M. Li, Designable immune therapeutical vaccine system based on DNA supramolecular hydrogels, ACS Appl. Mater. Interfaces 10 (11) (2018) 9310–9314.
[153] Y. Umeki, K. Mohri, Y. Kawasaki, H. Watanabe, R. Takahashi, Y. Takahashi, Y. Takakura, M. Nishikawa, Induction of potent antitumor immunity by sustained release of cationic antigen from a DNA-based hydrogel with adjuvant activity, Adv. Funct. Mater. 25 (36) (2015) 5758–5767.
[154] J. Lee, Q.V. Le, G. Yang, Y.K. Oh, Cas9-edited immune checkpoint blockade PD-1 DNA polyaptamer hydrogel for cancer immunotherapy, Biomaterials 218 (2019), 119359.
[155] H.M. Wang, Z. Luo, Y.C.Z. Wang, T. He, C.B. Yang, C.H. Ren, L.S. Ma, C.Y. Gong, X.Y. Li, Z.M. Yang, Enzyme-catalyzed formation of supramolecular hydrogels as promising vaccine adjuvants, Adv. Funct. Mater. 26 (11) (2016) 1822–1829.
[156] X.X. Li, Y.Z. Wang, S.W. Wang, C.H. Liang, G.J. Pu, Y.X. Chen, L. Wang, H. Xu, Y. Shi, Z.M. Yang, A strong CD8(+) T cell-stimulating supramolecular hydrogel, Nanoscale 12 (3) (2020) 2111–2117.
[157] Q. Su, H. Song, P. Huang, C. Zhang, J. Yang, D. Kong, W. Wang, Supramolecular co-assembly of self-adjuvanting nanofibrious peptide hydrogel enhances cancer vaccination by activating MyD88-dependent NF-kappa B signaling pathway without inflammation, Bioactive Materials 6 (11) (2021) 3924–3934.
[158] M. Chen, Y. Tan, Z. Dong, J. Lu, X. Han, Q. Jin, W. Zhu, J. Shen, L. Cheng, Z. Liu, Q. Chen, Injectable Anti-inflammatory nanofiber hydrogel to achieve systemic immunotherapy post local administration, Nano Lett. 20 (9) (2020) 6763–6773.
[159] F. Wang, D. Xu, H. Su, W. Zhang, X. Sun, M.K. Monroe, R.W. Chakroun, Z. Wang, W. Dai, R. Oh, H. Wang, Q. Fan, F. Wan, H. Cui, Supramolecular prodrug hydrogelator as an immune booster for checkpoint blocker-based immunotherapy, Sci. Adv. 6 (18) (2020), eaaz8985.
[160] F. Wang, H. Su, D. Xu, W. Dai, W. Zhang, Z. Wang, C.F. Anderson, M. Zheng, R. Oh, F. Wan, H. Cui, Tumour sensitization via the extended intratumoural release of a STING agonist and camptothecin from a self-assembled hydrogel, Nature Biomedical Engineering 4 (11) (2020) 1090–+.
[161] J. Weiden, J. Tel, C.G. Figdor, Synthetic immune niches for cancer immunotherapy, Nat. Rev. Immunol. 18 (3) (2018) 212–219.
[162] V. Kafil, A.A. Saei, M.R. Tohidkia, J. Barar, Y. Omidi, Immunotargeting and therapy of cancer by advanced multivalence antibody scaffolds, J. Drug Target. 28 (10) (2020) 1018–1033.
[163] D.K.Y. Zhang, A.S. Cheung, D.J. Mooney, Activation and expansion of human T cells using artificial antigen-presenting cell scaffolds, Nat. Protoc. 15 (2020) 773–798.
[164] A.S. Cheung, D.K.Y. Zhang, S.T. Koshy, D.J. Mooney, Scaffolds that mimic antigen-presenting cells enable ex vivo expansion of primary T cells, Nat. Biotechnol. 36 (2) (2018) 160–+.
[165] Q. Fan, Q. Ma, J. Bai, J. Xu, Z. Fei, Z. Dong, A. Maruyama, K.W. Leong, Z. Liu, C. Wang, An implantable blood clot-based immune niche for enhanced cancer vaccination, Sci. Adv. 6 (39) (2020), eabb4639.
[166] Q. Chen, M. Chen, Z. Liu, Local biomaterials-assisted cancer immunotherapy to trigger systemic antitumor responses, Chem. Soc. Rev. 48 (22) (2019) 5506–5526.
[167] F. Yang, K. Shi, Y. Hao, Y. Jia, Q. Liu, Y. Chen, M. Pan, L. Yuan, Y. Yu, Z. Qian, Cyclophosphamide loaded thermo-responsive hydrogel system synergize with a hydrogel cancer vaccine to amplify cancer immunotherapy in a prime-boost manner, Bioactive Materials 6 (10) (2021) 3036–3048.
[168] X. Xiong, J. Zhao, R. Su, C. Liu, X. Guo, S. Zhou, Double enhancement of immunogenic cell death and antigen presentation for cancer immunotherapy, Nano Today 39 (2021), 101225.
[169] M. Liu, Z. Cao, R. Zhang, Y. Chen, X. Yang, Injectable supramolecular hydrogel for locoregional immune checkpoint blockade and enhanced cancer chemo-immunotherapy, ACS Appl. Mater. Interfaces 13 (29) (2021) 33874–33884.
[170] L. Huang, Y. Zhang, Y. Li, F. Meng, H. Li, H. Zhang, J. Tu, C. Sun, L. Luo, Time-programmed delivery of sorafenib and anti-CD47 antibody via a double-layer-gel matrix for postsurgical treatment of breast cancer, Nano-Micro Lett. 13 (1) (2021) 141.
[171] Q. Lv, C.L. He, F.L. Quan, S.J. Yu, X.S. Chen, DOX/IL-2/IFN-gamma co-loaded thermo-sensitive polypeptide hydrogel for efficient melanoma treatment, Bioactive Materials 3 (1) (2018) 118–128.
[172] L. Jiang, Y. Ding, X.L. Xue, S.S. Zhou, C. Li, X.K. Zhang, X.Q. Jiang, Entrapping multifunctional dendritic nanoparticles into a hydrogel for local therapeutic delivery and synergetic immunochemotherapy, Nano Res. 11 (11) (2018) 6062–6073.
[173] F. Vohidov, L.E. Milling, Q. Chen, W. Zhang, S. Bhagchandani, H.V.T. Nguyen, D. J. Irvine, J.A. Johnson, ABC triblock bottlebrush copolymer-based injectable hydrogels: design, synthesis, and application to expanding the therapeutic index of cancer immunochemotherapy, Chem. Sci. 11 (23) (2020) 5974–5986.
[174] C. Wang, J.Q. Wang, X.D. Zhang, S.J. Yu, D. Wen, Q.Y. Hu, Y.Q. Ye, H. Bomba, X. L. Hu, Z. Liu, G. Dotti, Z. Gu, In situ formed reactive oxygen species-responsive scaffold with gemcitabine and checkpoint inhibitor for combination therapy, Sci. Transl. Med. 10 (429) (2018), eaan3682.
[175] H. Wang, A.J. Najibi, M.C. Sobral, B.R. Seo, J.Y. Lee, D. Wu, A.W. Li, C. S. Verbeke, D.J. Mooney, Biomaterial-based scaffold for in situ chemo-immunotherapy to treat poorly immunogenic tumors, Nat. Commun. 11 (1) (2020) 5696.
[176] L. Sun, F. Shen, L. Tian, H. Tao, Z. Xiong, J. Xu, Z. Liu, ATP-responsive smart hydrogel releasing immune adjuvant synchronized with repeated chemotherapy or radiotherapy to boost antitumor immunity, Adv. Mater. 33 (18) (2021), 2007910.
[177] L. Zhang, J.H. Zhou, L.Z. Hu, X. Han, X.W. Zou, Q. Chen, Y.G. Chen, Z. Liu, C. Wang, In situ formed fibrin scaffold with cyclophosphamide to synergize with immune checkpoint blockade for inhibition of cancer recurrence after surgery, Adv. Funct. Mater. 30 (7) (2019), 1906922.
[178] K. Ueda, J. Akiba, S. Ogasawara, K. Todoroki, M. Nakayama, A. Sumi, H. Kusano, S. Sanada, S. Suekane, K.M. Xu, K.H. Bae, M. Kurisawa, T. Igawa, H. Yano, Growth inhibitory effect of an injectable hyaluronic acid-tyramine hydrogels incorporating human natural interferon-alpha and sorafenib on renal cell carcinoma cells, Acta Biomater. 29 (2016) 103–111.
[179] H. Phuengkham, C. Song, S.H. Um, Y.T. Lim, Implantable synthetic immune niche for spatiotemporal modulation of tumor-derived immunosuppression and systemic antitumor immunity: postoperative immunotherapy, Adv. Mater. 30 (18) (2018), 1706719.
[180] T. Bauleth-Ramos, T.Y. Shih, M.A. Shahbazi, A.J. Najibi, A.S. Mao, D. Liu, P. Granja, H.A. Santos, B. Sarmento, D.J. Mooney, Acetalated dextran nanoparticles loaded into an injectable Alginate cryogel for combined chemotherapy and cancer vaccination, Adv. Funct. Mater. 29 (35) (2019) 1903686.
[181] C.L. Yu Chao, Huiquan Tao, Yaran Du, Di Wu, Ziliang Dong, Qiutong Jin, Guobin Chen, Jun Xu, Zhisheng Xiao, Qian Chen, Chao Wang, Jian Chen, Zhuang Liu, Localized cocktail chemoimmunotherapy after in situ gelation to trigger robust systemic antitumor immune responses, Sci. Adv. 6 (2020), eaaz4204.
[182] H. Zhao, Q. Song, C. Zheng, B. Zhao, L. Wu, Q. Feng, Z. Zhang, L. Wang, Implantable bioresponsive nanoarray enhances postsurgical immunotherapy by activating pyroptosis and remodeling tumor microenvironment, Adv. Funct. Mater. 30 (51) (2020), 2005747.

[183] Y. Zhang, X. Zhang, H. Yang, L. Yu, Y. Xu, A. Sharma, P. Yin, X. Li, J.S. Kim, Y. Sun, Advanced biotechnology-assisted precise sonodynamic therapy, Chem. Soc. Rev. 50 (20) (2021) 11227–11248.
[184] J. Yao, F. Zheng, C. Yao, X. Xu, O.U. Akakuru, T. Chen, F. Yang, A. Wu, Rational design of nanomedicine for photothermal-chemodynamic bimodal cancer therapy, Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology 13 (3) (2021), e1682.
[185] X. Wang, X. Zhong, Z. Liu, L. Cheng, Recent progress of chemodynamic therapy-induced combination cancer therapy, Nano Today 35 (2020), 100946.
[186] Q. Zhang, C. Bao, X. Cai, L. Jin, L. Sun, Y. Lang, L. Li, Sonodynamic therapy-assisted immunotherapy: a novel modality for cancer treatment, Cancer Sci. 109 (5) (2018) 1330–1345.
[187] M. Liu, A.R. Khan, J. Ji, G. Lin, X. Zhao, G. Zhai, Crosslinked self-assembled nanoparticles for chemo-sonodynamic combination therapy favoring antitumor, antimetastatic management and immune responses, J. Contr. Release 290 (2018) 150–164.
[188] Y. Li, J. Xie, W. Um, D.G. You, S. Kwon, L. Zhang, J. Zhu, J.H. Park, Sono/photodynamic nanomedicine-elicited cancer immunotherapy, Adv. Funct. Mater. 31 (12) (2021), 2008061.
[189] C. Xu, K. Pu, Second near-infrared photothermal materials for combinational nanotheranostic, Chem. Soc. Rev. 50 (2) (2021) 1111–1137.
[190] Q. Tian, F. Xue, Y. Wang, Y. Cheng, L. An, S. Yang, X. Chen, G. Huang, Recent advances in enhanced chemodynamic therapy strategies, Nano Today 39 (2021), 101162.
[191] H. Kobayashi, P.L. Choyke, Near-infrared photoimmunotherapy of cancer, Acc. Chem. Res. 52 (8) (2019) 2332–2339.
[192] Z.Q. Meng, X.F. Zhou, J. Xu, X. Han, Z.L. Dong, H.R. Wang, Y.J. Zhang, J.L. She, L. G. Xu, C. Wang, Z. Liu, Light-triggered in situ gelation to enable robust photodynamic-immunotherapy by repeated stimulations, Adv. Mater. 31 (24) (2019), 1900927.
[193] L. Fang, Z. Zhao, J. Wang, P. Zhang, Y. Ding, Y. Jiang, D. Wang, Y. Li, Engineering autologous tumor cell vaccine to locally mobilize antitumor immunity in tumor surgical bed, Sci. Adv. 6 (25) (2020), eaba4024.
[194] V. Revuri, S.K. Rajendrakumar, M.-S. Park, A. Mohapatra, S. Uthaman, J. Mondal, W.K. Bae, I.-K. Park, Y.-K. Lee, Heat-confined tumor-docking reversible thermogel potentiates systemic antitumor immune response during near-infrared photothermal ablation in triple-negative breast cancer, Advanced Healthcare Materials 10 (21) (2021), 2100907.
[195] X. Ye, X. Liang, Q. Chen, Q. Miao, X. Chen, X. Zhang, L. Mei, Surgical tumor-derived personalized photothermal vaccine formulation for cancer immunotherapy, ACS Nano 13 (3) (2019) 2956–2968.
[196] X.-l. Hou, X. Dai, J. Yang, B. Zhang, D.-h. Zhao, C.-q. Li, Z.-y. Yin, Y.-d. Zhao, B. Liu, Injectable polypeptide-engineered hydrogel depot for amplifying the anti-tumor immune effect induced by chemo-photothermal therapy, J. Mater. Chem. B 8 (37) (2020) 8623–8633.
[197] Y.P. Jia, K. Shi, F. Yang, J.F. Liao, R.X. Han, L.P. Yuan, Y. Hao, M. Pan, Y. Xiao, Z. Y. Qian, X.W. Wei, Multifunctional nanoparticle loaded injectable thermoresponsive hydrogel as NIR controlled release platform for local photothermal immunotherapy to prevent breast cancer postoperative recurrence and metastases, Adv. Funct. Mater. 30 (25) (2020), 2001059.
[198] T.T. Wang, D.G. Wang, H.J. Yu, B. Feng, F.Y. Zhou, H.W. Zhang, L. Zhou, S. Jiao, Y.P. Li, A cancer vaccine-mediated postoperative immunotherapy for recurrent and metastatic tumors, Nat. Commun. 9 (2018) 1532.
[199] E.C. Mei, S.K. Li, J.W. Song, R.R. Xing, Z.M. Li, X.H. Yan, Self-assembling Collagen/Alginate hybrid hydrogels for combinatorial photothermal and immuno tumor therapy, Colloids Surf. A Physicochem. Eng. Asp. 577 (2019) 570–575.
[200] C. He, L. Yu, H. Yao, Y. Chen, Y. Hao, Combinatorial photothermal 3D-printing scaffold and checkpoint blockade inhibits growth/metastasis of breast cancer to bone and accelerates osteogenesis, Adv. Funct. Mater. 31 (10) (2020), 2006214.
[201] Y. Chao, L.G. Xu, C. Liang, L.Z. Feng, J. Xu, Z.L. Dong, L.L. Tian, X. Yi, K. Yang, Z. Liu, Combined local immunostimulatory radioisotope therapy and systemic immune checkpoint blockade imparts potent antitumour responses, Nature Biomedical Engineering 2 (8) (2018) 611–+.
[202] Y. Xiang, Z. Cuo, P. Zhu, J. Chen, Y. Huang, Traditional Chinese medicine as a cancer treatment: modern perspectives of ancient but advanced science, Cancer Medicine 8 (5) (2019) 1958–1975.
[203] F. Zamboni, S. Vieira, R.L. Reis, J.M. Oliveira, M.N. Collins, The potential of hyaluronic acid in immunoprotection and immunomodulation: chemistry, processing and function, Prog. Mater. Sci. 97 (2018) 97–122.
[204] A. Marrella, A. Dondero, M. Aiello, B. Casu, D. Olive, S. Regis, C. Bottino, D. Pende, R. Meazza, G. Caluori, R. Castriconi, S. Scaglione, Cell-laden hydrogel as a clinical-relevant 3D model for analyzing neuroblastoma growth, immunophenotype, and susceptibility to therapies, Front. Immunol. 10 (2019) 1876.
[205] S.J. Florczyk, G. Liu, F.M. Kievit, A.M. Lewis, J.D. Wu, M.Q. Zhang, 3D porous chitosan-alginate scaffolds: a new matrix for studying prostate cancer cell-lymphocyte interactions in vitro, Advanced Healthcare Materials 1 (5) (2012) 590–599.
[206] M.T. Wolf, S. Ganguly, T.L. Wang, C.W. Anderson, K. Sadtler, R. Narain, C. Cherry, A.J. Parrillo, B.V. Park, G.N. Wang, F. Pan, S. Sukumar, D.M. Pardoll, J. H. Elisseeff, A biologic scaffold-associated type 2 immune microenvironment inhibits tumor formation and synergizes with checkpoint immunotherapy, Sci. Transl. Med. 11 (477) (2019), eaat7973.
[207] A. Singh, Biomaterials innovation for next generation ex vivo immune tissue engineering, Biomaterials 130 (2017) 104–110.
[208] J.Y. Sun, X.J. Lu, Cancer immunotherapy: current applications and challenges, Cancer Lett. 480 (2020) 1–3.
[209] L.A. Emens, P.A. Ascierto, P.K. Darcy, S. Demaria, A.M.M. Eggermont, W. L. Redmond, B. Seliger, F.M. Marincola, Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape, Eur. J. Cancer 81 (2017) 116–129.
[210] S. Correa, A.K. Grosskopf, H. Lopez Hernandez, D. Chan, A.C. Yu, L.M. Stapleton, E.A. Appel, Translational applications of hydrogels, Chem. Rev. 121 (18) (2021) 11385–11457.
[211] I. Vitale, E. Shema, S. Loi, L. Galluzzi, Intratumoral heterogeneity in cancer progression and response to immunotherapy, Nat. Med. 27 (2) (2021) 212–224.
[212] I. Dagogo-Jack, A.T. Shaw, Tumour heterogeneity and resistance to cancer therapies, Nat. Rev. Clin. Oncol. 15 (2) (2018) 81–94.
[213] X. Zhao, X. Pan, Y. Wang, Y. Zhang, Targeting neoantigens for cancer immunotherapy, Biomark Res 9 (1) (2021) 61.
[214] A. Garcia-Garijo, C.A. Fajardo, A. Gros, Determinants for neoantigen identification, Front. Immunol. 10 (2019) 1392.
[215] C. He, L. Yu, H. Yao, Y. Chen, Y. Hao, Combinatorial photothermal 3D-printing scaffold and checkpoint blockade inhibits growth/metastasis of breast cancer to bone and accelerates osteogenesis, Adv. Funct. Mater. 31 (10) (2021), 2006214.
[216] Z. Xie, J. Shen, H. Sun, J. Li, X. Wang, Polymer-based hydrogels with local drug release for cancer immunotherapy, Biomed. Pharmacother. 137 (2021), 111333.
[217] F. Wang, J. Gao, S. Wang, J. Jiang, Y. Ye, J. Ou, S. Liu, F. Peng, Y. Tu, Near infrared light activation of an injectable whole-cell cancer vaccine for cancer immunoprophylaxis and immunotherapy, Biomaterials Science 9 (11) (2021) 3945–3953.
[218] G. Shu, W. Zhu, Y. Jiang, X. Li, J. Pan, X. Zhang, X. Zhang, S.-K. Sun, Persistent luminescence immune hydrogel for photodynamic-immunotherapy of tumors in vivo, Adv. Funct. Mater. 31 (36) (2021), 2104472.
[219] S. Pozzi, A. Scomparin, S.I. Dangoor, D.R. Ajamil, P. Ofek, L. Neufeld, A. Krivitsky, D. Vaskovich-Koubi, R. Kleiner, P. Dey, S. Koshrovski-Michael, N. Reisman, R. Satchi-Fainaro, Meet me halfway: are in vitro 3D cancer models on the way to replace in vivo models for nanomedicine development? Adv. Drug Deliv. Rev. 175 (2021), 113760.
[220] Y. Zhang, J. Xu, Z. Fei, H. Dai, Q. Fan, Q. Yang, Y. Chen, B. Wang, C. Wang, 3D Printing Scaffold Vaccine for Antitumor Immunity, Advanced Materials, Deerfield Beach, Fla., 2021, e2106768-e2106768.
[221] Z. Jin, X. Li, X. Zhang, P. Desousa, T. Xu, A. Wu, Engineering the fate and function of human T-Cells via 3D bioprinting, Biofabrication 13 (3) (2021), 035016.
[222] M. Rafiee, R.D. Farahani, D. Therriault, Multi-material 3D and 4D printing: a survey, Adv. Sci. 7 (12) (2020) 1902307.
[223] F. Mota, L. Braga, L. Rocha, B. Cabral, 3D and 4D bioprinted human model patenting and the future of drug development, Nat. Biotechnol. 38 (6) (2020) 689–694.
[224] Y. Luo, X. Lin, B. Chen, X. Wei, Cell-laden four-dimensional bioprinting using near-infrared-triggered shape-morphing alginate/polydopamine bioinks, Biofabrication 11 (4) (2019), 045019.
[225] M. Champeau, D.A. Heinze, T.N. Viana, E.R. de Souza, A.C. Chinellato, S. Titotto, 4D printing of hydrogels: a review, Adv. Funct. Mater. 30 (31) (2020) 1910606.
[226] C.M. González-Henríquez, M.A. Sarabia-Vallejos, J. Rodriguez-Hernandez, Polymers for additive manufacturing and 4D-printing: materials, methodologies, and biomedical applications, Prog. Polym. Sci. 94 (2019) 57–116.
[227] S.M. Rossi, T. Murray, L. McDonough, H. Kelly, Loco-regional drug delivery in oncology: current clinical applications and future translational opportunities, Expet Opin. Drug Deliv. 18 (5) (2021) 607–623.