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Emerging strategies in developing multifunctional nanomaterials for cancer nanotheranostics

Melgious Jin Yan Ang [a,b], Siew Yin Chan [c], Yi-Yiing Goh [a,b], Zichao Luo [a], Jun Wei Lau [a], Xiaogang Liu [a,b,*]

[a] Department of Chemistry, National University of Singapore, Singapore 117543, Singapore
[b] NUS Graduate School (ISEP), National University of Singapore, Singapore 119077, Singapore
[c] Institute of Materials Research and Engineering, Agency for Science, Technology, and Research, Singapore 138634, Singapore

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ABSTRACT

Cancer involves a collection of diseases with a common trait – dysregulation in cell proliferation. At present, traditional therapeutic strategies against cancer have limitations in tackling various tumors in clinical settings. These include chemotherapeutic resistance and the inability to overcome intrinsic physiological barriers to drug delivery. Nanomaterials have presented promising strategies for tumor treatment in recent years. Nanotheranostics combine therapeutic and bioimaging functionalities at the single nanoparticle level and have experienced tremendous growth over the past few years. This review highlights recent developments of advanced nanomaterials and nanotheranostics in three main directions: stimulus-responsive nanomaterials, nanocarriers targeting the tumor microenvironment, and emerging nanomaterials that integrate with phototherapies and immunotherapies. We also discuss the cytotoxicity and outlook of next-generation nanomaterials towards clinical implementation.

Contents

Abbreviations: ACQ, Aggregation caused quenching; ADV, Acoustic droplet vaporization; AIE, Aggregation-induced emission; AMF, Alternating magnetic field; APCs, Antigen presentation cells; ATP, Adenosine triphosphate; AUNP, Gold nanoparticles; BPNS, Black phosphorous nanosheets; CA4P, Combretastatin A4 phosphate; CD, Cluster of differentiation; Ce6, Chlorin E6; cGAMP, 2′3′-cyclic guanosine monophosphate-adenosine monophosphate; COF, Covalent organic framework; CPT, Camptothecin; CSC, Cancer stem cells; CT, Computed tomography; CTC, Circulating tumor cells; CTL, $CD8^+$ cytotoxic T lymphocyte; CtsB, Cysteine protease cathepsin B; CTX, Cabazitaxzxel; Cy, Cyanine; DC, Dendritic cell; dECM, Dense extracellular matrix; DF-PEG, Dibenzaldehyde-functionalized polyethylene glycol; DNA, Deoxyribonucleic acid; DOX, Doxorubicin; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DTX, Doxcetaxel; EGFR, Epidermal growth factor receptor; EMT, Epithelial-to-mesenchymal transition; EPR, Enhanced permeability and retention effect; GDR, Galactosyl dextran-retinal; GO, Graphene oxide; HIF-1a, Hypoxia-inducible factor 1a; hSOD, Human superoxide dismutase 1; ICG, Indocyanine green; IFNγ, Interferon-gamma; IL, Interluekin; IMD, Imiquimod; IR, Infrared; MC-540, Merocyanine 540; MDR, Multidrug resistance; MET, Mesenchymal-to-epithelial transition; MHC, Major histocompatibility class; MIP, Molecularly imprinted polymer; MMPs, Matrix metalloproteinases; MNPs, Magnetic nanoparticles; MOF, Metal-organic frameworks; mPEG, Methoxypolyethylene; MPS, Mononuclear phagocyte system; MRI, Magnetic resonance imaging; mRNA, Messenger ribonucleic acid; MSR, Mesoporous silica micro-rod; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NIR, Near-infrared; NLRP3, NLR family pyrin domain containing 3; NOXs, Nicotinamide adenine dinucleotide phosphate oxidase; NPN, Nano-pathogenoid; OMV, Outer membrane vesicle; OVA, Ovalbumin; PAHy, Polyaspartylhydrazide; PAMP, Pathogen-associated molecular patterns; PCNH, Pegylated carbon nanohorn; PD-1, Programmed cell death protein 1; PDI, Perylene diimide; PDT, Photodynamic therapy; PEG, Poly(ethylene) glycol; PEI, Polyethyleneimines; PES, Poly(3,4-ethylenedioxythiophene):poly(4-styrenes ulfonate); PFC, Perfluorocarbon; PGDAs, Polypeptide-glycosylated poly(amidoamine) dendron amphiphiles; P-gp, P-glycoprotein; PI3K, Phosphatidylinositol 3-kinase; PLGA, Poly(lactide-co-glycolide); PLGA, Poly(D, L-glycolide); pMBs, Porphyrin microbubbles; pNPs, Porphyrin nanoparticles; PPa, Pyropheophorbide-a; PS, Photosensitizer; PTA, Photothermal agent; PTT, Photothermal therapy; RBC, Red blood cell; RNA, Ribonucleic Acid; ROS, Reactive Oxygen Species; SeaMac, Self-adjuvanted molecular activator; siRNA, Small interfering ribonucleuic acid; STING, Stimulator of interferon genes; TAMs, M2 tumor-associated macrophages; TGF-β, Transforming growth factor beta; TLR, Toll-like receptors; TME, Tumor Microenvironment; TNF-α, Tumor necrosis factor-alpha; TRV2, Transient receptor potential vanilloid family 2; TSDs, Thermal-sensitive droplets; TTA, Triplet-triplet annihilation; UCNP, Lanthanide-doped upconversion nanoparticles; VISA, VP16-GAL4-WPRE integrated systemic amplifier; ZnPc, Zinc phthalocyanine.

* Corresponding author at: Department of Chemistry, National University of Singapore, Singapore 117543, Singapore (X. Liu).
E-mail address: chmlx@nus.edu.sg (X. Liu).

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1. Introduction

Nanomedicine presents an enormous potential for targeted, efficacious, and safe therapeutics in cancer. The development of nanotheranostics, a concept that combines therapy and diagnostics in one package, has recently gained traction [1]. Imaging-guided diagnostics are critical in understanding the extent of tumor progression, and the therapeutic function facilitates tumor treatment. Real-time dynamic data of the biodistribution, release, targeted treatment of chemotherapeutics are essential for discovering new strategies in personalized medicine. With the advent of high precision nanomedicine, many drug delivery issues can be overcome, including non-specific targeting, over-or under-dosing regimen, uneven biodistribution, and adverse biological effects.

The primary rationale for developing cancer nanotheranostics is integrating multiple capabilities into a single nanotechnology-based, multifunctional system for drug delivery and cancer imaging. It could mean a relatively more effective way to treat tumors by improving drug delivery across various physiological barriers, developing novel therapeutic strategies, and having superior performance that responds quickly to changes in the external stimulus or internal tumor microenvironment (TME). It has been envisioned by many in the biopharmaceutical industry that such nanotheranostics are significant in current tumor management. Notably, engineering and manufacturing of surface-modified, multifunctional nanomaterials with superior optical, magnetic, thermal, and TME-responsive properties can revamp current treatment patterns and cancer survivorship [2]. Prospective drugs can be formulated and encapsulated within these nanomaterials, and research studies have shown high potential in overcoming fundamental limitations faced by conventional chemotherapy [3]. These include low drug stability and solubility as well as complex biological side effects. Nanomaterials can carry photosensitizers, photo-absorbers, genetically modified materials, therapeutic proteins, and even antigens or adjuvants. This multifunctional capacity expands the repertoire of potential treatments, either in a unimodal or synergistic multimodal form, with improved therapeutic efficacy against various cancers. The recent emergence of nanotheranostic strategies has tremendously enhanced clinical prognoses and greatly expedites therapeutic decisions that physicians have to make. Further exploration of these innovations would overcome notable challenges in enhancing nanotheranostic efficacy.

Several excellent recent reviews have presented innovative cancer nanotheranostic research, but they often focus on one direction [2,4-9]. In this review, we summarize key emerging nanomaterials and nanotheranostic strategies from organic, inorganic, and a hybrid of both in three major directions that would provide readers with current state-of-the-arts of their impact in various cancer applications. The first is emerging strategies used in stimulus-responsive cancer nanotheranostics; the second involves nanotechnological carriers targeting the TME; and the third deals with nanotheranostic strategies related to phototherapy and immunotherapy. We believe that continual developments at these scientific frontiers would provide opportunities for clinical translation. We also highlight the toxicity issue and challenges towards clinical implementation and discuss strategies and outlooks for designing next-generation nanomaterials for cancer nanotheranostics.

2. Stimulus-responsive cancer nanomaterials

In general, nanomaterials are designed in the "on" state, and detection and release of their cargoes can occur upon their administration in animal models [4]. On the other hand, a personalized examination of the number of drugs that have been successfully delivered to cancer sites can be obtained by designing nanocarriers with "on-off" theranostic functionalities [10]. Therefore, this rationale has spurred the development of stimulus-responsive nanomaterials, expanding many opportunities to enhance and control the treatment dose and repetitive drug delivery [11]. The common mechanisms of various stimulus-responsive nanomaterials often involve constructing chemical-sensitive linkers, functional molecules, or moieties [12]. Another design basis is to incorporate a moiety or structure directly into nanomaterials responsive to stimulation within the TME. Moreover, we highlight emerging innovations of using chemical, physical or biological stimuli in nanomaterials and nanotheranostics. These includes changes to the pH of TME, differential changes in protein expression levels within tumor cells, and rises in oxidative stress within the intracellular TME as well as varied situations due to external stimuli such as near-infrared stimulation, magnetic and ultrasound manipulation. A combination of two or more stimuli is also plausible, providing opportunities to expand the repertoire of advanced stimulus-responsive nanomaterials and nanotheranostics.

2.1. Acid-responsive nanomaterials

The TME pH is considered one key parameter for discrimination between cancer and healthy tissues. Metabolism in cancer cells differs from healthy cells because cancer cells have relatively high glucose uptake. This leads to lactic acid fermentation in cytosol instead of undergoing glycolysis at a relatively low rate and pyruvate oxidation in the mitochondria for most healthy cells. This modified cellular metabolism is known as the Warburg effect [13]. Furthermore, endocytosis of nanomaterials into tumor cells often leads to a series of trafficking into endolysosomal compartments with a pH of around 5 [14]. Thus, the combination of these organelles and the TME pH can be a targetable strategy for cancer theranostic applications.

2.1.1. pH-sensitive linkers

One approach for acid-responsive nanotheranostics is the use of pH-sensitive linkers such as the acotinyl group. For instance, Zhu *et al.* constructed a pH-sensitive, dendrimer-coupled nanotheranostic platform for computed tomography imaging [15]. They functionalized dendrimers with folic acid for active targeting. Importantly, when conjugated to dendrimers using *cis*-aconitic anhydride, chemotherapeutic doxorubicin (Dox) molecules released more rapidly in the acidic TME than under physiological conditions. In another example, Kulhari and co-workers used pluronic F68-*cis*-acotinyl linked-cabazitaxel (CTX) and F68-succinoyl linked-CTX to form micelles encapsulating CTX drug for prostate cancer treatment [16]. The F68-*cis*-acotinyl linked-CTX enhanced pH sensitivity and controlled drug release, resulting in a better apoptotic effect. Other pH-sensitive chemical bonds have also been reported for pH-stimulated drug release. These include functional groups such as β-thiopropionate, citraconic amide, acetal, orthoester, carbamate, cyclic acetal, hydrazone, ketal, imine, and benzoic-imines. For instance, Gawali *et al.* reported the encapsulation of pH-labile, ascorbic acid-coated magnetic nanoconstructs with Dox for treatment against mouse skin fibrosarcoma, MCF-7 breast cancer, and A549 lung cancer [17]. Notably, they covalently conjugated Dox to the nanoconstructs through carbamate and hydrazone bonds. These nanoconstructs exhibited gradual and protracted chemotherapeutic release under acidic conditions within tumor cell lines but not under physiological pH conditions (Fig. 1**A-B).**

2.1.2. pH-sensitive nanomaterials

Another approach to developing pH-responsive nanotheranostics involves nanomaterials that degrade rapidly under acidic conditions upon delivery into tumors. This approach has been applied to various tumor models because of intrinsically low physiological pH values (4 to 6) in tumor organelles, such as endosomes and lysosomes. A slightly acidic TME (pH 6.5 to 6.8) can also be used to distinguish between healthy tissues and tumors. Therefore, these pH-sensitive stimuli can be utilized to control drug release or prodrug cargo activation. An important class is calcium carbonate ($CaCO_3$), which has been employed for various nanotheranostic applications [18]. $CaCO_3$ nanoparticles are generally stable, but

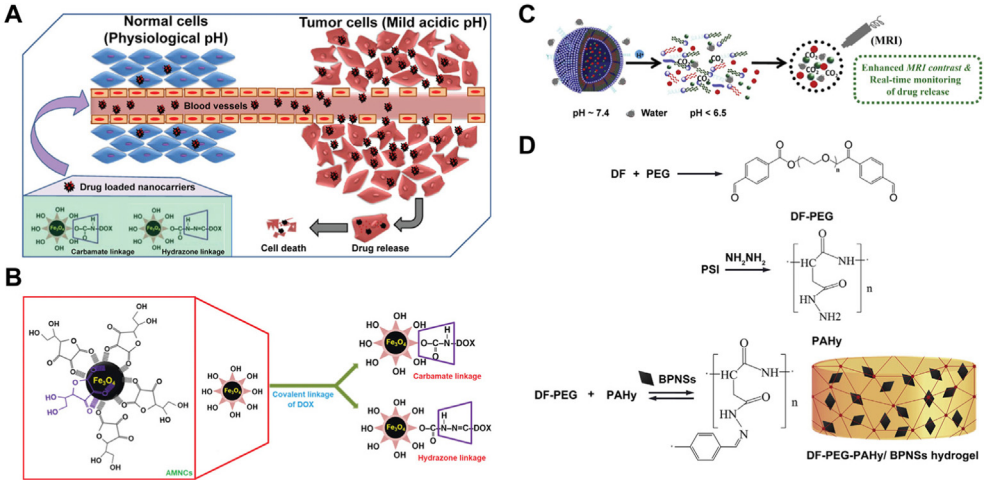

Fig 1. Acidic pH-sensitive linkers and acidic-sensitive nanomaterials. (A) Schematic of acidic pH-responsive nanotheranostics in tumors but not in healthy cells. (B) Schematic of Dox conjugation to the nanoconstruct via acidic-sensitive carbamate and hydrazone bonds [17]. (C) Schematic design of pH-responsive, $CaCO_3$-containing nanotheranostics for controlled pH-dependent T1 signal enhancement and real-time monitoring of drug release [19]. (D) Schematic of pH-sensitive DF-PEG-PAHy/BPNSs hydrogel synthesis [20]. Adapted with permission from [17], American Chemical Society; [19,20], Elsevier.

within an acidic TME, they degrade rapidly into calcium ions and carbon dioxide and discharge cargo payloads in a controlled manner. For example, Liu and co-workers designed a pegylated $CaCO_3$ nanotheranostic platform encapsulating Ce6(Mn) photosensitizer-coupled Dox drug (Fig. 1**C**) [19]. Importantly, Ce6 (Mn) controlled-release enabled pH-dependent T1 signal enhancement for magnetic resonance imaging and real-time monitoring of drug release. These nanocarriers also enhanced cellular uptake in the TME and enabled synergistic chemo-photodynamic therapy.

Expanding on the idea of generalizability, Wu *et al.* reported a pH-sensitive hydrogel integrating black phosphorus nanosheets (BPNSs), dibenzaldehyde-functionalized polyethylene glycol (DF-PEG), and polyaspartylhydrazide (PAHy) polymers (Fig. 1**D**) [20]. This hydrogel was encapsulated with Dox to provide treatment and bioimaging capacities. Notably, their approach harnessed near-infrared (NIR) excitation for controlled drug release and photothermal therapy. They demonstrated that nanotheranostic stimulation by chemical linkers and materials sensitive to acidic pH within the TME could perform on-demand therapy and imaging. However, given the complexity of TME, there is a need to utilize other stimuli to expand controlled release strategies for cancer nanotheranostics.

2.2. Reactive oxygen species (ROS)-responsive nanomaterials

The intrinsic environment of cancer has been demonstrated to elevate intracellular ROS due to high metabolic activity and cell proliferation growth [21]. Thus, the TME can be used as a biological stimulus to perform ROS-responsive nanotheranostics. Moreover, ROS generation can be catalyzed directly from nanoparticles in tumors within a hypoxic environment. By way of illustration, Sun *et al.* designed a nanotheranostic system that integrates ROS-responsive pegylated hyperbranched polyphosphates and Dox-containing thioketal linkers [22]. Upon irradiation at 660 nm, singlet oxygen species were generated, inducing improved drug release and tumor apoptosis. These nanomaterials can also generate photoacoustic signals from Ce6 and magnetic resonance from Gd^{3+} for bimodal tumor imaging. This approach was efficacious in resolving Dox resistance *in vitro* in a breast cancer cell line (MCF-7/ADR) with high P-glycoprotein levels. This nanotheranostic system also showcased great tumor accumulation due to enhanced permeability and retention. Crucially, this study enabled controlled spatiotemporal treatment with minimal toxicity to the kidney and liver.

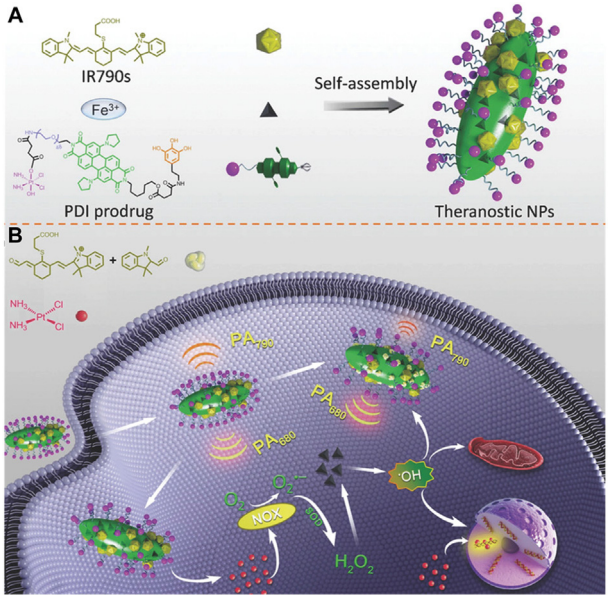

Fig. 2. An example of ROS-responsive nanotheranostic. (A) Schematic nanotheranostics through self-assembly of semiconducting perylene-diimide (PDI) and IR790 [24]. (B) Schematic of cisplatin release in U87-MG cells due to the reductive environment, which activates NOXs and results in cascade catalytic formation of H_2O_2 and superoxide from O_2. Through the Fenton reaction, ferric ions catalyze H_2O_2 into highly cytotoxic •OH, leading to tumor cell death. Adapted with permission from [24], Wiley.

Another example of enhancing drug release using ROS-responsive nanomaterials was reported by Zong and co-workers, who constructed self-assembled, paclitaxel nanoparticles containing cleavable thioketal linkers [23]. When exposed to ultrasound stimulation, paclitaxel nanoparticles generated many ROS that induced cell deaths in U87-MG human glioma while enhancing drug release. The combined effect resulted in a significant tumor inhibition with negligible toxicity. In a similar case, Qiao *et al.* constructed a nanotheranostic platform based on RNAi-based immunomodulation to improve the anti-glioma efficacy of temozolomide by regressing the TME immunosuppressive function upon siRNA inhibition of TGF-β expression *in vitro* and *in vivo.* Intracellular ROS-induced oxidation of benzylboronic acid changed the overall charge of nanocarriers from positive to negative, triggering payload release.

On a parallel development, Yang *et al.* utilized probe IR790 to synthesize perylene diimide-IR790-Fe/Pt nanoparticles. They performed *in vivo* ratiometric photoacoustic imaging of these nanoparticles to monitor ROS levels (Fig. 2) [24]. Upon irradiation at both 680 and 790 nm, real-time monitoring of ROS generation was achieved by ratiometric photoacoustic imaging because IR790 is cleavable by ROS. ROS generation was enabled by cisplatin drug molecules conjugated to nanoparticle surfaces. Upon endocytosis into U87-MG tumor cells, the reductive environment exerted control over cisplatin release. Subsequent activation of nicotinamide adenine dinucleotide phosphate oxidase (NOXs) enzymes facilitated the catalysis of intrinsic O_2 to hydrogen peroxide H_2O_2 and superoxide. Ferric ions then catalyzed H_2O_2 into highly cytotoxic •OH via the Fenton reaction, leading to enhanced oxidation and suppressed tumor cell growth. As demonstrated from the above examples, research into ROS-responsive nanotheranostics has highlighted great opportunities in the preclinical testing of biological stimuli for cancer treatment. It has also lent insight into developing *in vivo* nanosensors predesigned to measure intracellular ROS levels. Furthermore, ROS-stimulated nanotheranostics can be harnessed to establish modern ultrasound diagnostic approaches based on carbon dioxide sensing.

2.3. Enzyme-responsive nanomaterials

In a cellular environment, enzymes can catalyze vital substrates in biological and metabolic processes. Uncontrolled regulation of enzymatic expression and related activities have also been identified as underlying pathological issues in many diseases, including cancer [25,26]. Developments of nanomaterials with enzyme-responsive moieties may find broad utility in nanotheranostics under mild conditions. Moreover, theranostic functions can be precisely controlled because of the superior selectivity and specificity of enzymes. For instance, Ren *et al.* constructed hyaluronic acid ultrastructures as nanocarriers for Ce6 and Dox [27]. High levels of hyaluronidase expression within the TME degraded hyaluronic acid bonds, resulting in the release of Ce6 and Dox and thus enhanced antitumor effects on adenocarcinoma human alveolar basal epithelial cells. Notably, this strategy was also extended to tap into the acidic TME for controlled drug release. However, further in-depth *in vivo* studies are required to ascertain therapy efficacy.

Another important enzyme for nanotheranostics is matrix metalloproteinases (MMPs). Their overexpression in tumors plays an essential role in tumor invasiveness, metastasis, and angiogenesis and affects many signaling cascade pathways within the TME [28,29]. Zhao *et al.* reported dual-stimulus-responsive nanocarriers were fabricated for tumor targeting and fluorescence-guided photothermal therapy [30]. For demonstration, they modified nanocarriers with asymmetric cyanine and glycosyl groups, as well as MMP-specific peptides as linkers. These functional nanocarriers enable *in vitro* and *in vivo* precision theranostics against mouse squamous cell carcinoma (SCC-7). In another example, Van rijt *et al.* reported silica nanoparticles that utilized overexpressed MMP9 to trigger drug release. These nanoparticles are mesoporous, capped with avidin molecules, and conjugated to sequence-specific peptide linkers [31]. Upon endocytosis into H1299 and A549 cell lines, site-specific delivery of cisplatin and bortezomib improved antitumor efficacy.

Ai *et al.* presented another example of enzyme-responsive nanotheranostics [32]. They constructed Nd^{3+}-doped upconversion nanoparticles and modified nanoparticle surfaces with enzyme-responsive peptides using thiol-ene click chemistry. These nanoparticles were also modified with folic acid for active targeting and Ce6 for photodynamic therapy. Overexpression of cysteine protease cathepsin B (CtsB) within the lysosome organelle in the human colorectal adenocarcinoma cell line (HT-29) cleaved the peptide sequence, exposing the 1,2-aminothiol group in cysteine for condensation reactions. Consequently, they achieved selective tumor localization in the HT-29 cell line but not in CtsB-deficient NIH/3T3 mouse fibroblast cells. The enhanced tumor localization was further evident *in vitro* and *in vivo*, which showed significant enhancement in singlet oxygen generation, fluorescence, and photoacoustic signals.

Although enzyme-responsive nanotheranostics has shown promise in precisely controlling drug release in the TME, its widespread adaption requires searching for a broad spectrum of enzymes that can undergo overexpression in various tumors. A critical point to note is that tumors often progress over several stages and present different pathological conditions, which regulate expression levels in different enzymes. Careful deliberation on the chosen enzyme and the design of enzyme-responsive nanomaterials must be appropriate and relevant to the tumor of interest.

2.4. NIR-responsive nanomaterials

The complexity of biological tumor environments in animals and humans imposes careful deliberation in selecting light wavelengths. The chosen wavelength must have limited photon scattering, minimized absorption by endogenous substrates, and negligible autofluorescence in order to permeate through skin barriers and achieve deep-tissue penetration [33]. Therefore, several tissue optical windows have been demarcated for practical use: NIR-I (700–900 nm) and NIR-II (1000–1700 nm). Ultraviolet and visible light excitation can instigate photodamage to biological tissues and possess limited tissue penetration. For that very reason, recent research has delved into developing NIR-responsive nanomaterials.

A recent example was reported by Wang *et al.*, who demonstrated NIR- and TME-responsive nanocapsules comprising a polymer matrix and Fe/FeO nanocrystals [34]. These nanocapsules were loaded with indocyanine green (ICG) and Dox for multimodal photothermal therapy, chemotherapy, fluorescence imaging, and magnetic resonance imaging. Upon 808-nm irradiation for 5 min at pH 6.5, the nanocapsule size reduced from 220 to 54 nm over 48 h and eventually decomposed without causing any cytotoxicity. The researchers also demonstrated controlled ROS release for synergistic improvement for *in vitro* and *in vivo* therapy. Pu and co-workers reported polymer-functionalized ceria nanoparticles in another excellent work that achieved self-regulated NIR photodynamic therapy [35]. The NIR-absorbing semiconducting polymer was used for fluorescence imaging, whereas the nanoceria was a regulator for adjusting ROS generation under physiological conditions or acidic TME.

Another notable example was demonstrated by Zhang and co-workers, who reported the use of upconversion superballs, which were programmable by photoactivation at 808 and 980 nm, to improve the therapeutic efficacy in HeLa cells (Fig. 3) [36]. This NIR-responsive nanotheranostic system was loaded with zinc phthalocyanine (ZnPc) photosensitizer for PDT and human superoxide dismutase 1 (hSOD) siRNA. NIR stimulation at two wavelengths offered dual-modal activation. First, the 980-nm excitation enabled the nanoparticles to undergo cellular endosomal escape via photochemical internalization; this enhanced cellular uptake because recycling endosomes was prevented. Second, upon 808-nm photoactivation, the gene knockdown of hSOD occurred, making HeLa cells susceptible to ROS. Finally, a synergistic therapeutic efficacy was observed upon 980-nm excitation, by which upconverted red emission could photoactivate ZnPc for PDT.

2.5. Magnetic, thermal, and ultrasound-responsive nanomaterials

Magnetic-responsive nanotheranostics offer dual benefits because they can induce magnetic fields for tumor targeting and generate local hyperthermia in tumors under alternating magnetic fields. For instance, Yan *et al.* reported a nanoconstruct by combining magnetic hyperthermia and photothermal therapy [37]. The nanoconstruct was composed of magnetic nanoparticles (MNPs), poly(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate), cyanine 7, and 2-deoxyglucose-polyethylene glycol. The combination of photo-magnetic hyperthermia and a concurrent trimodal imaging platform inhibited tumor cell growth, both *in vitro* and *in vivo*. Interestingly, this nanoconstruct also prolonged second-phase systemic circulation with a half-life of approximately 20 h. In another

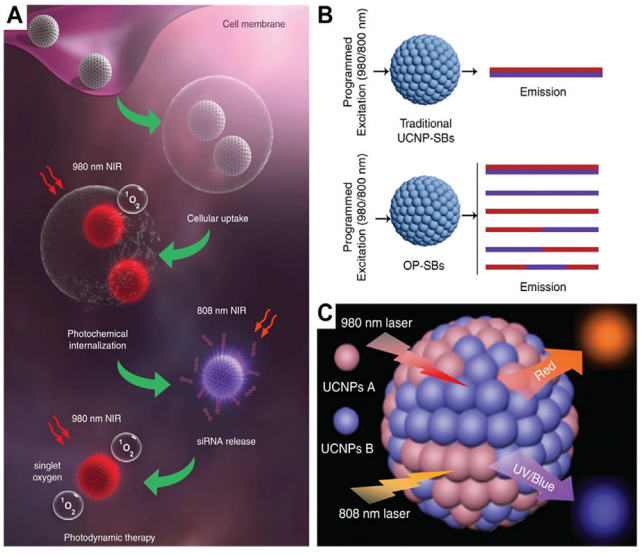

Fig. 3. A NIR-responsive nanotheranostic. (A) Schematic of orthogonal photoexcitation using upconversion superballs for endosomal escape, siRNA release, and PDT [36]. (B) Emission profile comparison between upconversion nanoparticle-superballs (UCNP-SBs) and orthogonal photoactivatable-superballs (OP-SBs). (C) Illustration of emission at UV/Blue and red wavelengths upon excitation with 808 and 980 nm lasers, as taken from a camera. Adapted with permission from [36], Springer Nature.

important study by Shin, Cheon, and co-workers, it was shown that novel MNPs enabled remotely controlled, noninvasive tumor killing [38]. These MNPs were made of zinc-doped iron oxide and surface-modified with antibodies targeting the overexpressed death receptor 4 of DLD-1 colon tumors. Upon applying a magnetic field, nanoparticle aggregation occurred, enhancing apoptotic signaling pathways and tumor death. Interestingly, they also demonstrated the operation of magnetic nanoconstructs at a micrometer length scale and a proof-of-concept application using an *in vivo* zebrafish tumor model.

Thermal-responsive nanotheranostic tools have also been devised for chemotherapeutic drug delivery. They are often integrated with other external stimuli, such as NIR light or ultrasound. These thermal-responsive cancer nanoconstructs maintain their structures at temperatures below 37 °C but undergo conformation change at above 40 °C. An emerging thermal-responsive nanotheranostic example was reported by Tang *et al.* (Fig. 4**A**) [39]. They synthesized organic semiconducting photoacoustic nanodroplets, and further stabilized them with perfluorocarbon and perylene diimide. The perylene diimide acts in a dual role as a photo-absorber and a photoacoustic molecular agent. This nanoconstruct was further encapsulated with $ZnF_{16}Pc$ molecules as photosensitizers. Upon 671-nm excitation, perylene diimide underwent energy conversion into heat, vaporized perfluorocarbon, and induced hypothermia, thereby enabling the simultaneous implementation of ultrasound imaging and photothermal therapy. The perfluorocarbon can also provide molecular oxygen to overcome hypoxia in the TME, whereas the $ZnF_{16}Pc$ molecule serves as an energy acceptor to transfer the energy to molecular oxygen that subsequently generates cytotoxic ROS for PDT.

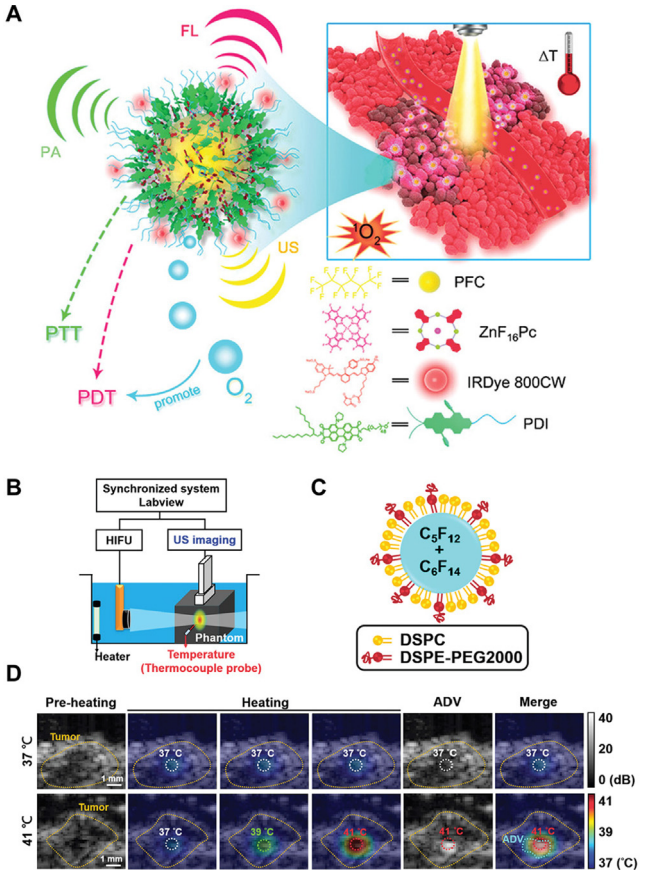

Fig. 4. A thermal and ultrasound-responsive nanotheranostic. (A) Schematic of laser-activatable ultrasound imaging and combinational cancer therapy [39]. (B) Schematic of high-power, ultrasound imaging-guided platform [41]. (C) Schematic of the TSD structure. (D) *In vivo* preclinical solid tumor imaging showing the potential of ultrasound imaging to estimate ADV therapy's treatment position. Adapted with permission from [39], American Chemical Society; [41], Elsevier.

On the other hand, ultrasound-responsive cancer nanotheranostics have also been applied to various tumors. Typically, high-frequency sound waves were used to control drug release upon nanocarrier delivery into the TME. The range of frequency used would be less than 20 kHz for low ultrasound imaging applications, while greater than 20 kHz can be applied to disrupt ultrasound nanocarriers to control the release of intended cargos. Importantly, several ultrasound-responsive cancer theranostics have been commercialized in recent years, such as Optison, Definity, Albunex, Senazoid, and Levovist [40]. However, several shortcomings, including large sizes (1–10 μm), low stability, and short half-lives, have impeded the widespread use of these ultrasound-responsive nanoconstructs for cancer applications. One notable work was performed by Yeh and co-workers, who constructed thermal-sensitive droplets (TSDs) comprising an encapsulated mixture of C_6F_{14} and C_5F_{12} together with DSPC and DSPE-PEG2000 biopolymers, which could be vaporized upon exposure to ultrasound in a mild hyperthermia environment (40 to 43 °C) (Fig. 4**B-D**) [41]. Doxorubicin was co-loaded into TSDs. Ultrasound imaging, tumor heating, and TSD vaporization are achieved by focused ultrasound scanning. Remarkably, their study showed potential in estimating the *in vivo* treatment location of acoustic droplet vaporization (ADV).

In another work, Huynh et al. developed a nanoconstruct based on microbubble formation by low-frequency ultrasound [42]. These microbubbles comprise a gaseous perfluoropropane core and a bacteriochlorophyll-lipid shell. The porphyrin groups in the shell provide fluorescence ultrasound imaging capabilities. Importantly, they demonstrated microbubble conversion into small nanoparticles in tumor-bearing mice with comparable optical performance upon ultrasound scanning. They hypothesized that the *in situ* conversion of microbubbles to nanoparticles could bypass the EPR effect for delivery into tumors.

2.6. Clinical trials and outlook of stimulus-responsive nanomaterials and nanotheranostics

Because developments of stimulus-responsive nanomaterials for cancer nanotheranostics started many years ago, it is crucial to outline and monitor those successfully implemented for clinical use. Several types of these nanomaterials have surpassed expectations. These achievements arise from improvements in magnetic, temperature, and pH-responsive nanotheranostics. However, a few challenges must be addressed before a high level of clinical translation can be sustained. First, preclinical tumor models drastically differ from tumor patients because of tumor heterogeneity issues and the difference in the TME. Moreover, stimulus-responsive cancer nanotheranostics face potential organ or tissue toxicity, biodegradability, and interactions of degraded molecules with organs. Thus, studies toward understanding nanomaterial toxicity effects should be examined. Another area where there could be progress is the colloidal stability of nanotheranostics *in vivo*, which is often neglected. Although no nanotheranostic materials have been approved for personalized medicine by the US Food and Drug Administration (FDA), many clinical trials in various phases are currently underway. Most clinical trials involve the use of remotely controlled stimulation on iron and gold nanomaterials that offer multimodal imaging capabilities [43,44].

3. Targeting the TME

It is believed that the TME enables cellular differentiation niches for various developments of clonal subpopulations of cells

with unique genotypes and phenotypes. Consequently, these existing varied populations of cells retain divergent biological behaviors, which give rise to tumor heterogeneity [45]. Accumulating evidence-based studies over recent years has demonstrated that acellular and cellular elements in the TME can reprogram various aspects of the critical pathways involved in tumors [46]. These include tumor invasion, growth, initiation, metastasis, and even tumor responses to therapies. Many studies have shown that this intrinsic complexity of the TME in various tumors resulted in poor conventional tumor therapeutic strategies. Nanotheranostics have recently been proposed to tackle these major challenges, and here, we present key aspects of the emerging strategies targeting the TME.

3.1. Targeting cancer stem cells

Within a malignant tumor or among circulating cancerous cells, cancer cells can vary from each other. It is generally hard to identify their genotypes and phenotypes. The stem cell theory proposes a few cells within the tumor that act like stem cells to continue reproducing themselves and nurture cancer, contributing to cancer recurrence and metastasis. These stubborn culprits of cancer are known as cancer stem cells (CSCs). CSCs, first discovered in leukemia in 1997, possess the ability to differentiate, proliferate, and self-renew as they can transfer leukemia from sick mice to healthy mice [47,48]. They are a highly dynamic cell population that can undergo mesenchymal-to-epithelial transition and epithelial-to-mesenchymal transition in differentiation, proliferation, and replenishment, which confers resistance to traditional therapies [49]. Thus, detecting CSCs has emerged as a critical clinical target for early diagnosis, treatment, and cancer removal.

To deal with the persistence of CSC populations in the breast tumors, Shen *et al.* co-loaded nanoparticles with all-trans retinoic acid as a differentiation-inducing agent and camptothecin (CPT) as a chemotherapeutic drug to provide a dual strategy for killing CSCs [50]. These dually loaded nanoparticles reduce stemness-related drug resistance and enhanced chemotherapeutic response. Under hypoxic conditions, all-trans retinoic acid can be released to differentiate CSCs, triggering ROS generation. The presence of ROS subsequently prompts the release of CPT to kill CSCs. The breast cancer mouse model also demonstrated that the convergent nanotherapeutic approach inhibited tumor growth and avoided post-surgical tumor relapse and metastasis. Sun *et al.* also demonstrated the effectiveness of the convergent nanotherapeutic approach in the *in vitro* model of breast cancer by incorporating autophagy inhibitors (chloroquine) and chemotherapeutic drugs (doxorubicin or docetaxel) [51]. The convergent delivery systems prolonged the circulation half-time and improved the delivery of drugs into tumor tissues, inhibiting tumor growth by eliminating bulk tumor cells and CSCs. On a different note, Lin *et al.* developed a non-viral targeting vector, VP16-GAL4-WPRE integrated systemic amplifier. They constructed an hTERT-promoter-based VISA vector that drives transgene expression in treating breast cancer [52]. The researchers subsequently incorporated mRNA miR-34a (TV-miR-34a) for delivery to the breast tumor site to induce high throughput miR-34a expression in breast CSCs to suppress proliferation. In breast cancer cells and CSCs, mIR-34a is downregulated compared with healthy breast cells. Combining TV-miR-34a with a chemotherapeutic agent, docetaxel, the convergent therapeutic approach synergistically enhanced therapeutic response on breast CSCs. Notably, the convergent therapeutic approaches have potential in eliminating CSCs and may conquer CSC-related chemotherapeutic resistance.

The incorporation of PTT in clinical treatments also has potential in CSC elimination and metastasis inhibition and may improve the long-term survival of cancer patients. Paholak *et al.* demonstrated that PTT mediated by highly crystalline iron oxide nanoparticles can eliminate CSCs in triple-negative breast cancer mouse models by reducing metastasis to lung and lymph nodes [53]. This effective treatment is most likely because PTT inhibits the self-renewal of CSC through reduction of mammosphere formation. Apart from the convergent nanotherapeutic approach and PTT coupling, other engineered nanomaterial designs have great potential in cancer treatment. Geng *et al.* reported dual-functional gold nanoparticles (AuNP) that can perform the therapeutic intervention and sensing of CSC differentiation into non-CSC phenotype upon increasing intracellular ROS levels (Fig. 5**A**) [49]. By incorporating this sensing system, they were able to identify the effect of nanoparticle structures on CSC differentiation by rapidly collecting phenotypic information. Excitingly, the unreported differentiated non-CSC phenotype triggered by AuNPs was more susceptible to drug treatment than CSCs or non-CSCs, as demonstrated by the breast cancer cell model. On the other hand, Yu *et al.* further integrated the nanomaterial design with genetic engineering and fabricated photoactive nanocarbon complexes that could eliminate cancer cells and regulate the stemness of cancer cells, particularly those overexpressing transient receptor potential vanilloid family type 2 (TRV2) receptors (Fig. 5**B**) [54]. The photothermogenetic nanocomplexes inhibited cancer stemness via calcium-mediated dysregulation of the Wnt/β-catenin signaling pathway. This again demonstrates nanomaterial technological concepts that could lead us to tackle the issues of refractory cancers.

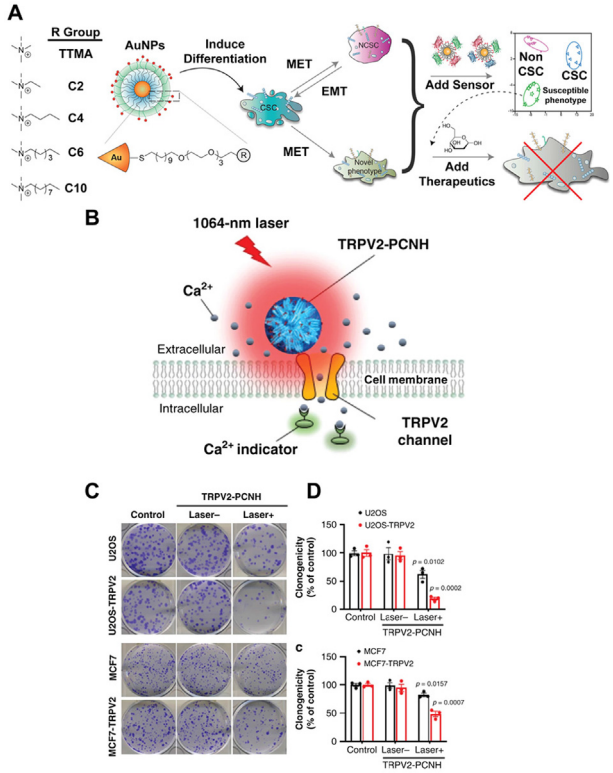

Fig. 5. Strategic approaches to target cancer stem cells. (A) Schematics of the process involving the approach to synthesize various nanoparticles using hypothesis-free sensing to characterize nanoparticles to differentiate CSCs into non-CSC phenotypes [49]. MET: Mesenchymal-to-epithelial transition, EMT: Epithelial-to-mesenchymal transition. (B) Schematic showing the PTT activation of transient receptor potential vanilloid family type 2-mediated Ca^{2+} influx into cancer cells [54]. (C) Effectiveness of laser irradiation on transient receptor potential vanilloid family type 2 (TRV2)-pegylated carbon nanohorn (PCNH) treatments. (D) Bar diagram showing to quantify the treatment effectiveness. Adapted with permission from [49], American Chemical Society; [54], Springer Nature.

In recent years, there has been an overwhelming use of nanomaterials to target and eradicate CSCs. However, there are still major challenges ahead. It is necessary to understand the successful delivery and homing to CSC populations within the tumor population, which can be difficult because of arduous barriers that nanomaterials or nanotheranostics must circumvent before entering CSCs. CSCs are also scarce within a tumor, making delivery a great challenge because of nanomaterial impeding factors, such as high tumor interstitial fluid pressure and random distribution within tumor regions due to tumor heterogeneity [55,56]. At the designing level for nanomaterials, an improved understanding of the fundamental mechanisms governing the epigenetic regulation of CSC self-renewal and non-CSC reprogramming is invaluable for enhancing CSC-targeting therapies for various tumors. Next-generation nanomaterials targeting CSCs have to resolve the outlined challenges before considering clinical translations.

3.2. Cancer-targeting biomimetic nanomaterials

Biological systems have existed for billions of years; evolution inevitably occurs in nature with ingenious adaptation and optimization. Nature may already have created solutions for existing challenges, inspiring us to innovate solutions through biomimicry. In general, the major challenges faced by nanoparticle systems for cancer diagnosis, treatment, and prevention are drug burst release, non-specific absorption, and elimination of nanoparticles during circulation [57,58]. To overcome *in vivo* barriers, stealth functionalization of nanoparticles with surfactants and hydrophilic polymers, such as poly(ethylene glycol) (PEG) and polydopamine, have been established for enhancing biocompatibility and therapeutic efficacy [59,60]. PEG remains the gold standard and has found its way into many clinical products [61]. However, surveillance of anti-PEG immunological response has prompted a further assessment of its biological relevance [62]. Unlike PEG binding with water via hydrogen bonding, zwitterionic materials such as poly(carboxybetaine) [63], poly(phosphorylcholine) [64], and poly(sulfobetaine) [65], possess a stronger hydration ability via ion–dipole bonding, providing promising alternatives for PEG. To date, phosphorylcholine-based material is the only zwitterionic material that gains recognition from the FDA [66,67]. Most zwitterionic materials for biomedical applications are still in the development phase, and it can be lengthy for them to be translated into clinical applications. Alternatively, the development of biomimetic nanoparticles via the incorporation of natural, functional components onto nanoparticle surfaces has the potential to endow them with biocompatibility, immune escaping ability, and targeting functionality. This section briefly reviews the vital roles of cell membranes, exosomes, and proteins in preparing biomimetic nanoparticles.

3.2.1. Cell membrane-based biomimetic nanomaterials

Nanomaterials can be disguised or conferred with a specific targeting ability by utilizing cell membranes derived from non-nucleus-containing cells (e.g., red blood cells and platelets) and nucleus-containing cells (e.g., white blood cells and cancer cells) [68]. A cell membrane mainly functions as a barrier or gate, regulating the exchange of materials and information between the cytoplasm and the external environment [69]. Its phospholipid bilayer and membrane proteins play vital roles in cellular communication and signal transduction [70]. In general, nanoparticles cloaked with cell membranes mimic the cell membrane functions of origins [71]. In other words, cell membranes could protect nanoparticles from the immune system and prevent them from being exposed nonspecifically to the external environment, which provides superior coatings for improved delivery.

Red blood cells, also known as erythrocytes, are the most utilized cell membranes for cloaking nanoparticles. They are the most populated and available human body cells, ranging between 20 and 30 trillion and accounting for ~ 70% of the total cell count in an adult individual [72,73]. They have a lifespan of approximately 100–120 days in humans [74] and are regarded as natural long-circulating delivery vehicles [75]. Therefore, erythrocytes as sheaths have the potential to enhance biocompatibility and prolong the circulation period for exogenous materials. Erythrocyte cell membranes express various immunomodulatory markers, such as CD47 and CD59 [76], and allow cloaked nanoparticles to be recognized by the immune system as endogenous materials, preventing them from being captured and eliminated. It has been demonstrated by erythrocyte-cloaked nanocrystals loaded with docetaxel (NC-DTX@RBC) with a 6-fold higher systemic retention time compared with commercial docetaxel (DTX) in a pharmacokinetics study [77]. Moreover, all mice administered with NC-DTX@RBC survived at a dosage of 25 mg DTX/kg, but it was not the case for commercial DTX [77]. By incorporating tumor-targeting peptide c(RGDyK) (RGD) onto erythrocytes, the resulting compound NC-DTX@RBC-RGD demonstrated enhanced accumulation at the tumor site and therapeutic efficacy for subcutaneous tumor and orthotopic glioma models [77]. Generally, sheath functionalization of nanoparticles by erythrocytes can lengthen the circulation time and improve compound or drug safety for diagnostics, treatment, theranostics, and vaccination [57,58,78-80]. Although erythrocytes have great utility for bestowing biocompatibility, they generally cannot target tumors specifically. However, through minor surface modification with targeting entities such as peptides [79] or antibodies [78], erythrocytes can be conferred with tumor-targeting abilities.

Platelets, also known as thrombocytes, are indispensable in hemostasis and thrombosis of the immune system. More experimental and clinical evidence supports that platelet activation protects circulating tumor cells (CTC) and promotes cancer progression [81,82]. Therefore, platelets can be used as sheaths for detecting and killing cancer cells [82,83]. A microfluidic chip equipped with a biologically interfaced platelet-cloaked surface can capture and detect cancer-derived exosomes of different types (e.g., prostate, lung, bladder, and breast) from ultrasmall volumes (1 μL) of human plasma samples [83]. The interaction of platelets and cancer-derived exosomes induces plasma clotting and platelet aggregation, but the molecular mechanism remains unclear [83]. As platelets can be activated upon tissue injuries, they can be used to target cancer cells in combination with photothermal therapy. Rao *et al.* demonstrated that platelet-cloaked gold nanorods enhanced photothermal therapy of head and neck squamous cell carcinoma *in vivo* [84]. P-selectin is overexpressed on platelet membranes and was discovered to enable platelets aggregation around cancer cells because it can bind to upregulated CD44 receptors on tumors. Based on this natural occurrence, Wang *et al.* cloaked bufalin-loaded, hollow, manganese dioxide (MnO_2) nanoparticles with platelet membranes to facilitate their aggregation around cancer cells intended for further stimulation by the TME for MRI-monitoring and chemo-photodynamic therapies [85].

White blood cells, also dubbed as leukocytes, are the immune system's strength for protection against invaders. The presence of leukocytes represents a major barrier for nanoparticle delivery [86]. Considering that leukocytes target exogenous materials, they can also be used to disguise nanoparticles for avoiding elimination from the system, as demonstrated by leukocyte-cloaked graphene nanosheets with magnetic nanoparticles [87]. Further conjugating CTC-targeting antibodies on leukocyte-based biomimetic nanoparticles confers the targeting ability, allowing specific capture of CTCs via phospholipid extraction for cancer diagnostics [87]. Most of the cells (~98.0%) captured remained viable and were recultured [87].

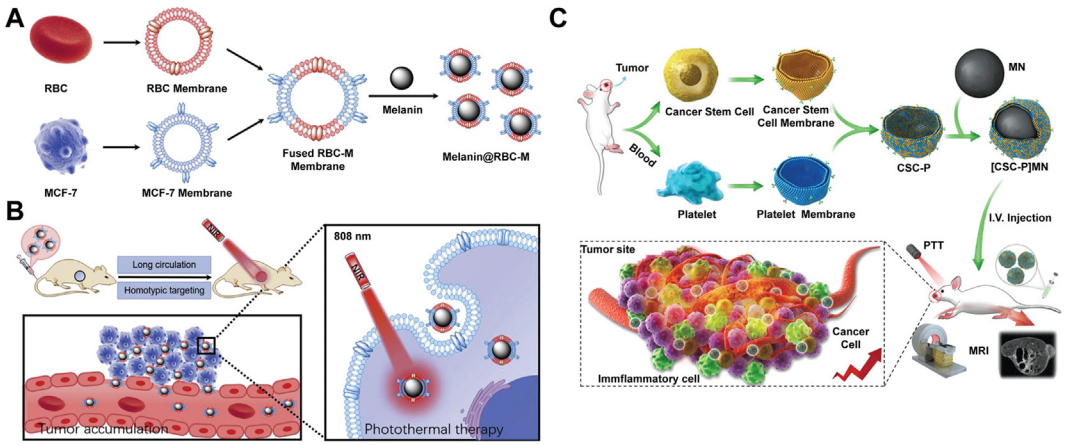

Fig. 6. Cell-membrane-based biomimetic nanomaterials enhance antitumor efficacy. (A) Schematic of the synthetic route to access Melanin@RBC-M nanomaterials [95]. (B) Schematic of improving PTT on tumors by improving pharmacokinetics. (C) Schematic of integrative use of CSCs and platelet fusion of Fe_3O_4 for enhanced intratumor accumulation and improved phototherapy [96]. Adapted with permission from [95], Elsevier; and [96], Wiley.

This leukocyte-cloaking cancer diagnostic method was successfully implemented on clinical samples with good reproducibility (mean relative standard deviation: 8.7 ± 5.6%), having a great capacity for clinical use in cancer diagnosis and CTC isolation [87]. Furthermore, an aptamer-functionalized, leukocyte-cloaked microfluidic chip could enhance affinity by 4 orders of magnitude and capture efficiency by 7-fold compared with the chip functionalized with only monovalent aptamers [88]. Accordingly, leukocytes are ideal candidates for cell-based liquid biopsy. That may be attributed to leukocytes' fluidic nature that enables lateral rearrangement of recognition ligands for high-affinity binding.

Leukocytes are resistant to blood cells, considerably reducing the non-specific absorption of blood cells [88]. Considering the role of leukocytes in combating the immune system, leukocyte-cloaked magnetosomes, functionalized with PD-1 antibody and iron oxide (Fe_3O_4), were used to create and provoke the immunogenic TME, synergizing ferroptosis/immunomodulation in cancer [89]. Disguising with cancer cells allows recognition and aggregation with homotypic cells as they have specific expressions of various surface antigens, such as E-cadherin, anti-epithelial cell adhesion molecule (EpCAM), and Thomsen-Friendenreich antigen [90]. Receptors such as CD47 allow them to escape from the immune system [91]. Therefore, cancer cell-cloaked compounds have simultaneously sustained circulation and homotypic targeting capability [90,92-94]. Cancer cell cloaking can also accumulate these cloaked compounds in tumor sites [92-94], benefiting cancer-targeted therapies. Cancer cell-cloaked NIR-II fluorescent silver telluride (Ag_2Te) quantum dots (Ag2Te@CC) was studied for *in vivo* homotypic tumor imaging and afforded the brightest and most stable fluorescence compared with other polymer-modified quantum dots [90]. Given that this may be attributed to the phospholipid bilayer protection of cancer cell membranes [90], cancer cell-cloaking has great potential for *in vivo* tumor imaging.

Current research has focused mainly on individual cell membrane-functionalized nanoparticles but progressed gradually to multifunctional hybrid membrane materials of different types. The erythrocyte-cancer hybrid membrane was developed by cell fusion and retained both parent erythrocyte and cancer cell (MCF-7) membrane proteins (Fig. 6**A, B**) [95]. This bestows nanoparticles with longer circulation and homotypic targeting to MCF-7 cells simultaneously, essential for overcoming various physiological barriers after systematic administration [95]. CSCs exist deep in tumor sites and are difficult to target, which is often regarded as the culprit for tumor progression and relapse. As such, targeting CSCs is therapeutically vital for next-generation nanotherapeutics. Bu *et al.* developed a fused CSC-platelet membrane with superior characteristics of tumor targeting and immune evading for enhanced photothermal therapy (Fig. 6**C**) [96]. Given that the complexity of biological entities with different membranes can be jointly integrated, versatile biomimetic nanoparticle systems with high specificity can be developed, offering more possibilities for cell membrane-based biomimetic nanoparticles. In particular, enhancing antitumor efficacies in the complex TME is highly advantageous for subsequent clinical trials.

3.2.2. Exosome-based biomimetic nanomaterials

Exosomes are the smallest, naturally secreted extracellular vesicles (30 to 160 nm) of organisms ranging from prokaryotes to eukaryotes [97,98]. Within plasma membranes, exosomes comprise nucleic acids, proteins, lipids, and metabolites [99]. They play vital roles in mediating intercellular communication between health and diseases [99]. In particular, exosomes derived from cancer cells play critical roles in cancer progression and drug resistance [98]. They display efficient cellular uptake and homotypic targeting capabilities by possessing specific membrane proteins such as tetraspanin CD9 and CD81, promoting the fusion of exosomes and cells [87]. Receptors, such as CD47, CD55, and CD59, protect exosomes from being captured and eliminated by the immune system. Liu *et al.* presented that cancer cell-derived exosome-cloaked poly(lactic-*co*-glycolic acid) nanoparticles showed superior immune evading ability and homotypic targeting capability, paving the way for targeted delivery of therapeutic agents or other compounds to tumor sites [91]. Yong *et al.* further demonstrated that cancer cell-derived exosome-cloaked doxorubicin-loaded, porous silicon nanoparticles displayed improved tumor accumulation and deep penetration into tumor sites, which considerably reduced CSCs in subcutaneous, orthotopic, and metastatic tumor models [100]. Excitingly, these exosome-based nanoparticles display strong cross-reactive cellular uptake, overcoming the requirement of specific markers for targeting CSC in different tumors [100]. Increased P-glycoprotein expression (P-gp) is regarded as the main cause of cancer drug resistance and remains a major challenge for developing effective cancer therapies [101]. Exosome-based nanoparticles also significantly reduced P-gp expression in CSC, enriching doxorubicin retention in CSC to overcome drug resistance [100]. Besides cancer cell-derived exosomes, bacteria-secreted exosomes have been used to disguise nanoparticle systems [102]. Inspired by neutrophils battling invading pathogens, Li *et al.* developed a pathogen-mimicking system using *Escherichia coli*-derived exosomes to

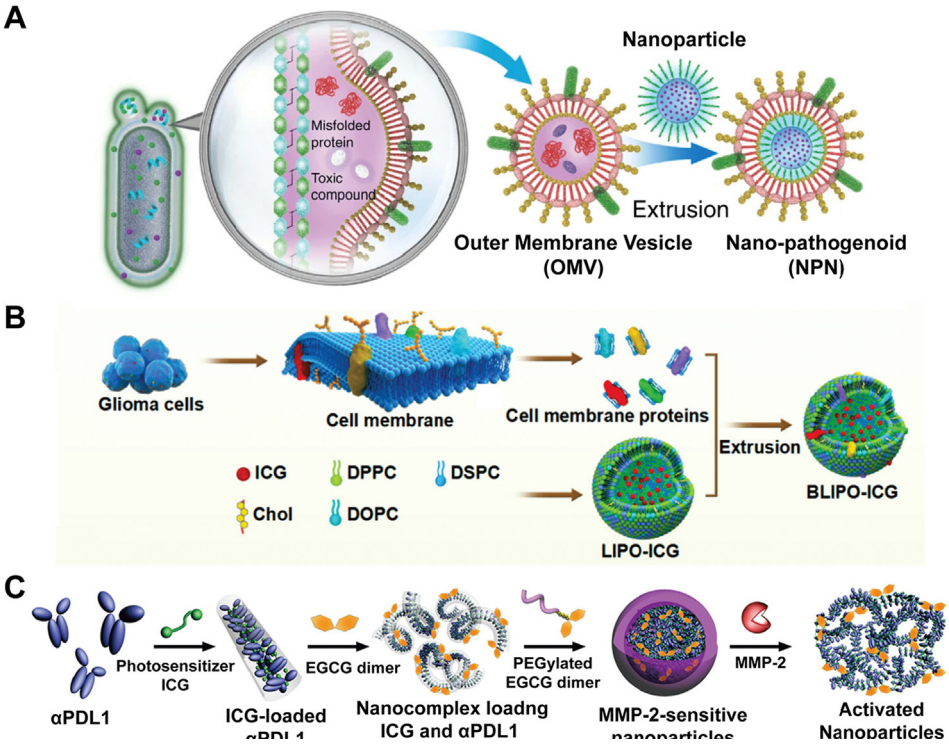

Fig. 7. Exosome-based and protein-based biomimetic nanomaterials enhance antitumor efficacy. (A) An exosome-based biomimetic nanomaterial utilizes chemotaxis-driven delivery to eliminate tumors after phototherapy [102]. (B) Schematic of protein-based biomimetic nanomaterials for enhanced antitumor efficacy. BLIPO-ICG nanoparticles are used to cross the highly stringent blood–brain barrier and achieve active-homing to the *in vivo* orthotopic glioma mouse model [105]. DOPC: 1,2-dioleoyl-*sn*-glycero-3-phosphocholine, DPPC: 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine, Chlo: cholesterol, BLIPO-ICG: biomimetic ICG-loaded liposome. (C) Schematic of another protein-based biomimetic nanomaterial for enhanced antitumor efficacy [112]. TME-responsive, anti-PDL antibody nanoparticles are synthesized for synergistic immunotherapy that curbs or enhances tumor immunological tolerance. PDL1: programmed death ligand 1, EGCG: (−)-epigallocatechin-3-O-gallate, MMP-2: matrix metalloproteinase-2. Adapted with permission from [102], Springer Nature; [105], American Chemical Society; [112], American Association for the Advancement of Science (AAAS).

in situ hitchhike circulating neutrophils for improved cancer therapy (Fig. 7**A**) [102]. As neutrophils target pathogens by recognizing pathogen-associated molecular patterns (PAMP), bacteria-secreted exosomes acquire PAMP from their parent bacteria [102]. Through PAMP recognition, neutrophils can actively take in *E. coli*-derived, exosome-cloaked nanoparticles until further inflammatory stimulation with photothermal therapy for migration, penetration, and release of nanoparticles [102]. In summary, exosome-based biomimetic nanoparticles are still in their early stages, but several promising research studies have shown their great potential to combat cancer.

3.2.3. Protein-based biomimetic nanomaterials

Proteins are the most diverse biomolecules with vast variations of structures and functions. As sheaths for nanoparticles, proteins participate in various roles, from enhancing biocompatibility and encoding functionality to regulating nucleation and growth of nanoparticles. For that reason, many metal-based nanoparticles have been constructed using proteins as sheaths [103]. Xiong *et al.* cloaked Bi_2S_3/FeS_2 with folic acid-functionalized bovine serum albumin nanocages for enhanced biocompatibility and efficient targeting capability [103]. While effective as computed tomography/magnetic resonance dual-mode imaging contrast agents, these nanocages can also suppress tumor growth when coupled with photothermal therapy [103].

On a separate note, studies have shown that S-layers of prokaryotes possess inherent adjuvant property and the capability of displaying epitopes on cell surfaces [104]. Inspired by that notion, Wu *et al.* assembled S-layer proteins from lactobacilli with cancer cell membranes as the sheath for nanoparticles to potentiate immune response and improve biostability [104]. The experimental result demonstrated that incorporating the S-layer enhanced the immune response against tumors by triggering lymphocyte proliferation and cytokine secretion, representing a promising cancer immunotherapy strategy [104]. Moreover, proteins can be incorporated to overcome physiological barriers to cancer diagnostics and treatment. Cancer cell membrane proteins were embedded into liposome nanoparticles for camouflaging purposes to cross the blood–brain-barrier (BBB) [105]. Cancer cell membrane proteins also endowed them with homotypic targeting capability in the orthotopic glioma model (Fig. 7**B**) [105]. Similarly, Gao *et al.* provided a promising solution for penetrating nanoparticles into hypoxic tumor sites by cloaking MnO_2 with ferritin nanocage, a universal protein found in all living organisms except yeast [106,107]. This nanozyme can overcome intratumoral barriers and generate oxygen with high efficiency through catalytic reactions in response to the TME [106]. Besides proteins, peptides can be incorporated as templates on nanoparticles to faciliate cell interactions or regulate physiological conditions [108]. Zhang *et al.* proved that peptide-based nanoparticles can be engineered to block blood vessels *in situ* [109]. These peptide-based nanoparticles are peptide formulations to be delivered to blood vessels in tumors [109]. By responding to TME, the peptide formulation can form occlusion in tumor blood vessels via laminin fibrillogenesis, a process to construct fibrous networks [109]. On another note, Rangel *et al.* employed a highly conserved peptide, Asp1-Trp2-Val3-Ile4-Pro5-Pro6-Ile7, as an epitope to prepare molecularly imprinted polymer (MIP) nanoparticles for cadherins adhesion [108]. Cadherins are cell-surface proteins that mediate cell–cell adhesion and play a major role in cancer metastasis [110]. The MIP nanoparticles designed by Rangel *et al.* block cadherins to prevent cancer cell adhesion, as demonstrated in a cervical cancer model [108]. This

research has unleashed a new, promising direction for cancer treatment.

Antibodies are Y-shaped proteins that recognize and neutralize foreign antigens and elicit a different immune response. Monoclonal antibodies have been mainly used for specific tumor targeting, while some may have therapeutic potential for cancer treatment. As biodistribution control upon intravenous injection is crucial for efficient targeting, Chen *et al.* designed a delivery system (^{89}Zr-labeled anti-human epidermal growth factor receptor 2 (HER2)-targeted ultrasmall silica nanoparticle immunoconjugate) to measure the biodetection of breast tumors with overexpressed HER2 gene. This approach combines the advantages of favorable biodistribution profiles and renal clearable attribute that prevents rapid hepatic clearance [111]. Incorporation of antibody fragment of HER2 bestows this nanoparticle system with high tumor-targeting capability [111], showing the effectiveness of antibodies as targeting agents. With the emergence of multidrug resistance (MDR), Suo *et al.* targeted P-gp with anti-P-gp antibody-functionalized carbon nanotubes for enhanced tumor targeting and loco-regional photothermal therapy to combat against MDR [101]. While stringent conditions have hindered conventional cancer treatments, therapeutic monoclonal antibodies have transformed the way cancer is treated. Wang *et al.* conjugated antibodies against programmed death-ligand 1 (PDL1) with matrix metalloproteinase protein 2 (MMP-2)-sensitive nanoparticles for combined photothermal therapy and immunotherapy (Fig. 7**C**) [112]. These antibody-based nanoparticles can be activated in tumors *in situ*. Localized near-infrared radiation induces reactive oxygen species production via a loaded photosensitizer, which fosters the intratumoral infiltration of cytotoxic T lymphocytes from the immune system and provokes PDL1 blockade therapy [112]. This research has provided a solution for overcoming tumors' immunological tolerance, offering hopes for fighting cancers with our immune systems.

3.2.4. Challenging prospects for tumor treatments

The emergence of biomimetic nanoparticles for cancer theragnostic platforms has expanded beyond material engineering boundaries and offers many advantages in cancer diagnosis and treatment, including increased nanoparticle stability, prolonged circulation, specific cancer targeting, improved biocompatibility, and reduced toxicity. Although enormous progress has been made in biomimetic nanoparticle engineering for oncology, there are various challenges ahead of clinical translation. Under the ideal conception of the EPR effect, long-circulating biomimetic nanoparticles and those with hydrodynamic diameter sizes above the renal threshold can be extravasated and accumulated in tumor cells for cancer diagnosis and treatment. However, the kinetics of biomimetic nanoparticles entering solid tumors remain confounding, and there is no clear evidence revealing the mechanisms underlying biomimetic delivery systems. In situations where biomimetic nanoparticles are not extravasated but remain in body circulation, there may be some effects detrimental to the body. Even in the case of complete extravasation into tumor cells, no clearance data are available for these biomimetic nanoparticles. Accordingly, noninvasive imaging could be a promising approach for deducing the clearance of biomimetic nanoparticles.

Although the synthesis of biomimetic nanoparticles is not covered herein, it is worth noting that precise control of surface structures and compositions on biomimetic nanoparticles remains challenging. More effective and specific cancer-targeting can be achieved by precise surface modification. More intriguingly, biomimetic nanoparticles with optimal clearance characteristics, which can regulate nanoparticle circulation and retention, can be designed and developed to minimize toxicity. In brief, understanding the molecular pathways of ingesting and digesting biomimetic nanoparticles in tumor cells and solid tumors is essential to evaluate their efficacy and safety risk. Long-term safety and toxicity assessments of biomimetic nanoparticles are vital to minimize the risk for adverse immunologic reactions and avoid undesirable effects. It is also critical to study genetic variations in cancer and normal cells while introducing biomimetic nanoparticles to understand the potential long-term impact of biomimetic delivery systems on mutation and therapeutic resistance. Leaving aside the main interaction of nanoparticles with the TME, the involvement of the immune system in cancer diagnosis and treatment with biomimetic nanoparticles is complex. The immune system certainly contributes greatly to the intratumoral distribution of nanoparticles. By uncovering the complex interaction, biomimetic delivery systems with immunotherapy can be designed and combined to improve cancer treatment. Beyond safety and efficacy issues of biomimetic nanoparticles, scalable synthesis is critical before clinical applications. In light of the difficulties in translation, we recommend that collaborative research between various science and medicine branches must bring forth advancements in biomimetic nanoparticles for oncology use.

3.3. Targeting solid tumors

Solid tumors present a different set of challenges for nanomaterials and nanotheranostics to target and deliver. Several key characteristics of solid tumors are outlined. First, studies have shown that intratumoral blood vessels are uniquely perforated with wide pores between neighboring endothelial cells and a discontinuous basement membrane [113]. Moreover, tumors would secrete pro-angiogenic growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and platelet-derived growth factor (PDGF), and increase their corresponding receptor overexpression because of the high demand for nutrients and oxygen supplies [114]. Numerous intratumoral blood endothelia can form rapidly, and their morphological architecture structures are often tortuous and not anastomosed [113]. Consequently, this leads to high intratumoral vascular density and poor intratumoral blood circulation and limits adequate delivery within solid tumors, causing elevated interstitial fluid pressure, relatively slow intratumoral blood circulation, and excessive acidosis and hypoxia [115]. Finally, poor lymphatic drainage is also a typical characteristic. Studies have shown that the lymphatic drainages in tumor tissues are either partly or entirely blocked, affecting the transport of macromolecules away from various parts of body tissues to the bloodstream [116]. A recent study has also demonstrated and analyzed that a mere 0.7% of systemically administered nanomaterials were found localized in solid tumors regardless of passive or active targeting strategies [117]. Therefore, new approaches are needed to improve the successful delivery of nanomaterials to solid tumors.

3.3.1. Enhancing blood flow rates for effective delivery

One of the earliest approaches was to use drugs to affect the vascular network in terms of permeability, normalization, and disruption. These methods were designed to increase blood circulation, enable effective nanoparticle delivery, and enhance nanomaterial accumulation in solid tumors. To enhance vascular permeability, vasodilators and inflammatory cytokines can be used to expand endothelial pores. These include bradykinin, tumor necrosis factor-alpha (TNF-α), serotonin, or histamine. For instance, Eggermont *et al.* harnessed isolated limb perfusion to administer TNF-α, melphalan, and interferon-gamma (IFNγ) and treat patients with soft tissue sarcoma. In another work, Jiang and co-workers harnessed vasodilator captopril to widen the blood vessels, which improved tumor perfusion and boost nanomaterial delivery into U87-MG glioblastoma solid tumors (Fig. 8**A**) [118].

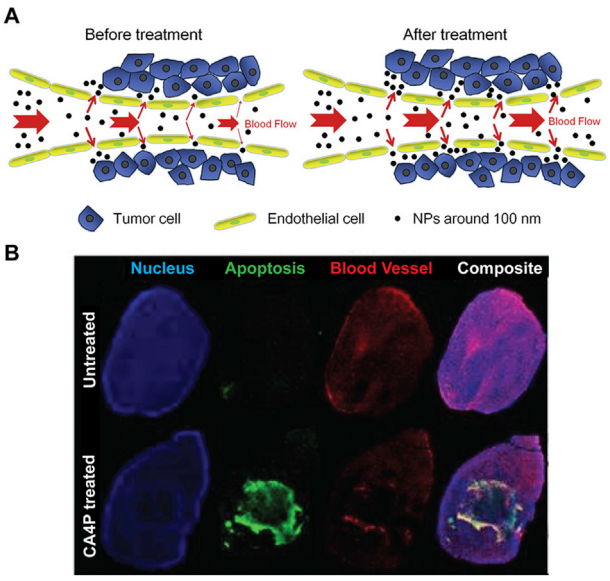

Fig. 8. Effective nanomaterial delivery into solid tumors based on the vascular network for enhanced blood circulation. (A) Blood vessel dilation before and after captopril treatment [118]. (B) Microscopy imaging of the nucleus, apoptosis, blood vessel, and composite of samples before and after CA4P treatment, showing disrupted blood vessels and enhanced delivery of nanomaterials into UMUC3/3T3 solid tumors [126]. Adapted with permission from [118], Elsevier; [126], Ivyspring International Publisher.

Notably, they used a semi-quantitative analysis involving tomato lectin and tumor vessel staining and demonstrated a ~ 2-fold increase in functional vessels.

Vascular normalization is another strategic approach to improve nanomaterial delivery into solid tumors. Several studies have shown that tumor vascular architecture and network are tumultuous and abnormal because of a lack of balance between pro-angiogenic and anti-angiogenic factors [119]. Usually, low-dose anti-angiogenic therapeutics are utilized to restore these vascular abnormalities. They have partially proven effective in regaining the tumor vasculature functionalities and lowering interstitial fluid pressure [120]. For example, Batchelor *et al.* reported an in-depth mechanistic study by combining chemoradiation and cediranib in patients newly diagnosed with glioblastoma. They showed concrete evidence of enhanced blood perfusion and improved delivery, resulting in prolonged patient survival [121]. However, vascular normalization provides the evidence of enhanced delivery for small-molecule chemotherapeutics and small nanomaterials around 10 nm [55]. It was clearly shown by Chauhan *et al.*, who reported that 10-nm Abraxane was delivered at the tumor site more than 100-nm Doxil after the tumor blood vessels were normalized by an anti-VEGFR2 antibody DC101 [55]. While there has been great potential for this approach, several studies have shown that it is transitory for a short duration and the effectiveness of tumor normalization relies on a complex range of parameters involving dose, treatment schedule, and the type of treatment administered [122]. In addition, solid tumors were found to have a dense extracellular matrix (dECM), which could severely restrict nanomaterial permeation and extravasation. Thus, the importance of alleviating the dECM barrier can be a possible direction to improve the delivery of nanomaterials into solid tumors.

Vasculature disruption can be another viable approach for enhancing nanomaterial accumulation in intended tumor sites. These can be achieved using a blood vessel-disrupting drug such as combretastatin A4 phosphate (CA4P) or by applying mechanical stimuli [123-125]. For example, Satterlee *et al.* utilized CA4P to treat blood vessels before systemic administration of lutetium-loaded lipid-calcium-phosphate nanomaterials (Lu-LCP) in various preclinical tumor models (ovarian, B16 melanoma, and orthotopic 4 T1 breast cancer) (Fig. 8**B**) [126]. Interestingly, the use of lutetium benefitted both treatments and enabled quantification of the number of Lu-LCP in the tumor region. Their results also showed that pre-treatment with CA4P improved treatment and inhibited tumor growth in UMUC3/3T3 stroma-rich bladder cancer relative to the control group without CA4P treatment.

Physical method-based treatments are effective in enhancing blood flow. In general, they provide a non-invasive approach, which is highly advantageous and readily deployable in clinical settings. These physical methods, such as hyperthermia, radiotherapy, and sonoporation, can be readily employed because of their portability and ease of setup. In hyperthermia, microwaves use ultrasound and radiofrequency electromagnetic waves to generate heat, widening the tumor blood vasculature. Several studies have also shown the proof-of-concept that various tumors are sensitive to more chemo-radiotherapies under mild hyperthermia [127]. Ishikawa and co-workers examined a novel antitumor effect of using a concurrent hyperthermia-chemotherapy approach on μ-oxo *N,N′*-bis(salicylidene)ethylenediamine iron (Fe(Salen)) nanoparticles [128]. Notably, they showed that the as-synthesized nanoparticles caused tumor apoptosis, and further utilization of an alternating magnetic field (AMF) resulted in enhanced antitumor activity in a preclinical rabbit tongue cancer model.

Radiotherapy is another physical treatment that can improve nanomaterial delivery into solid tumors besides its primary purpose of exerting non-invasive antitumor effects. Given the widespread use of radiotherapy treatments in tumor patients, several other investigations have also shown that drug and nanomaterial penetration and accumulation were enhanced in tumors after radiotherapy because radiotherapy-induced endothelial cell apoptosis and upregulate expression of vasoactive mediators enhanced tumor vessel permeability [129,130]. For example, Tannous and co-workers reported using radiotherapy on an intracranial glioblastoma mouse model to enhance the systemic transportation of iRGD-mediated solid lipid nanoparticles co-loaded with PDL1 siRNA and EGFR (Fig. 9**A**) [131]. Importantly, the synergistic dual-modal therapeutic effects from radioimmunotherapy improved glioblastoma regression and extended the survival of glioma mice. They reasoned that the efficacy was boosted because the radiotherapy exposure improved nanomaterial delivery and accumulation in glioma regions.

High-intensity focused ultrasound has gained traction to dilate blood vessels and improve nanomaterial permeability into tumor tissues. The mechanisms in action are likely caused by rapid compression and expansion of gas-filled microbubbles. These microbubbles undergo cavitation and subsequent implosion, impairing endothelial cell membranes [132,133]. For instance, Kiessling, Lammers and co-workers reported using ultrasound and microbubbles to examine the outcome of sonoporation effects on the delivery of PEGylated liposomes labeled with fluorophores in two preclinical tumor models [132]. They showed an enhanced delivery of functionalized liposomes to the tumor regions of A431 epidermoid xenografts and highly stromal BxPC-3 pancreatic carcinoma xenografts. In another recent work, Jang *et al.* reported ultrasound modulation of a nanomedicine-microbubble complex for trimodal chemo-photodynamic-gene therapies against mouse squamous cell carcinoma (SCC-7) subcutaneous model (Fig. 9**B**) [134]. Notably, they showed that sonoporation improved *in vitro* and *in vivo* delivery of Dox-encapsulating anti-VEGF siRNA nanoparticles co-loaded with Ce6.

In general, drugs, as mentioned earlier, and physical methods, have shown promise in improving nanomaterial delivery into solid

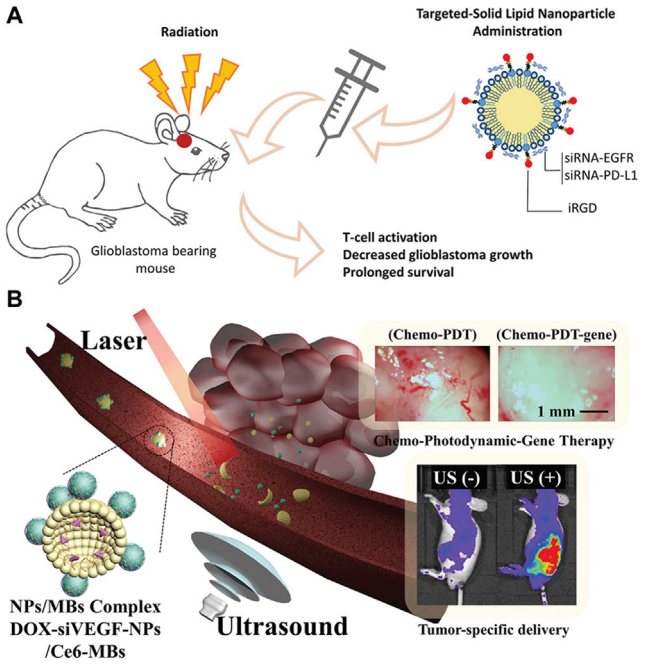

Fig. 9. Effective nanomaterial delivery into solid tumors based on the vascular network for enhanced blood circulation for. (A) Lipid-based nanoparticle radiotherapy for improved drug delivery [131]. (B) The sonoporation process that involves delivery of microbubbles and high-intensity-focused ultrasound signals to enhance nanomaterial delivery [134]. Adapted with permission from [131], Americal Chemical Society and [134], Elsevier.

tumors. However, caution is needed before their widespread adoption for preclinical tumor studies because of the downstream effects of disrupting the blood vessels of the TME. In addition, fenestration of the affected endothelial barrier can harm transportation events. For instance, the metastatic process in which disseminating tumor cells circulating from the tumor origin into other parts of the healthy tissues in the body is often a fundamental problem in cancers, especially those at more advanced stages. Therefore, the ability to control dilation spatiotemporally in the desired regions of blood vessels is highly sought after for enhanced nanomaterial delivery.

3.3.2. Ligand engineering

A recent study by Warren and co-workers has challenged the importance of the EPR effect for the successful delivery of nanomaterials into solid tumors. Notably, they discovered that as many as 97% of nanomaterials enter into solid tumors using an active-targeting process through endothelial cells in various human tumor xenografts and patient samples [135]. As such, the delivery of nanomaterials into solid tumors remains challenging. In light of the limitation in nanomaterial accumulation, active-targeting nanomaterials have gained widespread attention. Many active targeting ligands have been utilized to target tumor-related epitopes, and peptides are one such class of ligands because of their ease of synthesis, relatively low immunogenicity and the ability to conjugate onto nanomaterial surfaces without causing steric hindrance [136]. A single targeting ligand has been utilized for many years and has achieved promising results for potential translational studies. However, most of these tumor-related epitopes are confined to various types of tumor species. They are overexpressed and downplay nanomaterial effectiveness with a single targeting ligand, resulting in off-targeting to other cellular populations. For example, the pathological tumor state often showed targeted epitopes with overly different and dynamic expression profiles [137].

Research studies have recently suggested that functionalizing nanomaterials with two or more types of targeting ligands could provide an effective strategy to improve nanomaterial delivery and augment chemotherapeutic efficacy against various tumors. This strategy is crucial in treating glioblastoma, a lethal tumor with a low prognosis. The fundamental basis for the proposed strategy is that concrete evidence has demonstrated that glioblastoma is heterogeneous and highly variable in their genomic states. Moreover, glioblastoma cells display a diverse range of biomarker expression levels, essential for active targeting [138,139]. Studies showed that the unbalanced expression of transferrin receptors in glioma was only three- to five-fold higher than in normal cells, presenting technical challenges for delivering mono-ligand-modified nanoparticles [140,141]. The scientific community has rapidly adopted multiple ligands for targeting brain glioma. For instance, Gao and co-workers reported using PEG-poly(ε-caprolactone) nanomaterials to cross stringent BBB and target glioma [142]. These nanomaterials were coated with phage-displayed TGN peptide AS1411 aptamer and docetaxel. *In vivo* findings showed substantial tumor regression and prolonged survival of glioma-bearing mice. In a similar work, Chen *et al.* utilized a screening platform to systematically narrow down a list of six widely used peptide ligands [143]. It was confirmed that a pair of optimized ligands enhanced nanomaterial delivery into tumors (Fig. 10**A**). Notably, Peptide-22 and c(RGDfk) surface-modified liposomes co-loaded with Dox enhanced accumulation in the brains of U87-MG bearing mice, improved glioma apoptosis, and extended the overall survival by ~ 5 days compared with mono-ligand liposome controls.

Breast cancer belongs to solid tumors in which dual ligand-modified nanomaterials can be used extensively. For instance, Karathanasis and co-workers examined the outcome of using organic-based liposomes conjugated with peptides that selectively bind to P-selectin and αvβ3 integrin receptors in breast and triple-negative breast rodent models (Fig. 10**B, C**) [144]. Notably, they discovered that dual-peptide ligand nanoparticles had superior advantages because tumors displayed spatiotemporal dynamic changes in the TME, for example, the changes in expression levels

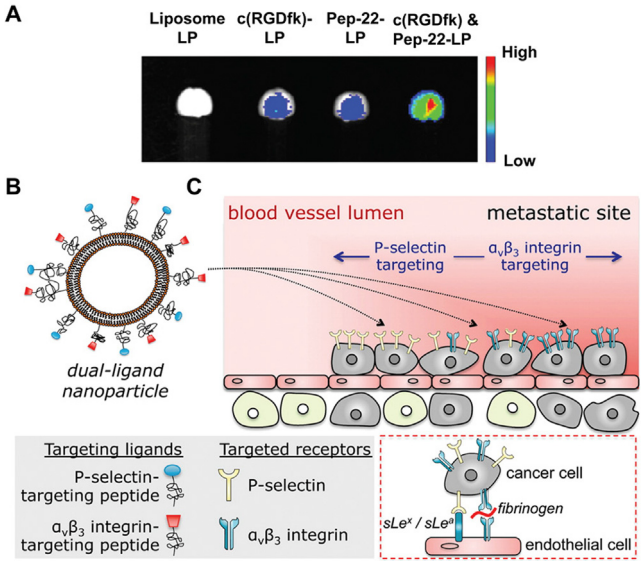

Fig. 10. Ligand engineering using multiple ligands for enhanced nanomaterial delivery into solid tumors. (A) Dual-ligand, liposome-modified nanoparticles against glioma, enabling selective BBB crossing and targeting of implanted U87-MG tumors [143]. (B, C) Dual-ligand, liposome-modified nanoparticles against breast and triple-negative breast cancers [144]. Adapted with permission from [143], Americal Chemical Society and [144], Elsevier.

of targetable cell surface receptors. Both P-selectin and αvβ3 integrin receptors were also functionally associated with different development stages of metastatic cancer of the same animal, which is crucial for using dual ligand liposomes to capture different metastatic sites. In another work, Tang *et al.* reported dual-ligand, lipid-based nanomaterials co-loaded with siRNA, which were surface modified with both folic acid and EGFR-specific antibodies to improve accumulation and transfection efficiency in both *in vitro* and *in vivo* triple-negative mouse tumor models [145]. Peiris *et al.* also designed and reported a novel multi-ligand nanomaterial for improving the targeting delivery of lung metastasis in a 4 T1 rodent model of breast cancer metastasis [146]. They showed that the dual-ligand strategy enabled a 2-fold targeting improvement in targeting lung metastases than the mono-ligand control. Significantly, the four-ligand approach contributed to a 3-fold enhancement in lung metastases than the mono-ligand control. Recently, multiple-ligand modified nanomaterials have exhibited enhanced accumulation in other solid tumors. For example, Kokkoli and co-workers further explored a dual-ligand-conjugated liposome targeting $\alpha_5\beta_1$ and $\alpha_6\beta_4$. They presented a mechanistic study of valency and avidity effects on nanoparticle delivery into a series of tumor cell lines [147]. They constructed a theoretical kinetic model to support their experimental findings. Notably, using a systematic assessment of crucial binding parameters, the researchers showed that developing a dual-ligand liposome with an equal ratio of ligand valencies enhanced selectivity and binding toward tumors with similar and overexpressed levels of receptors. These findings were validated in human ovarian cancer SKOV3 cell lines in which intracellular accumulation of encapsulated DNA was improved. Nonetheless, caution must be taken here because two studies have shown discrepancies in the dual-ligand strategy. In the first study, Ma and co-workers reported that the physicochemical characteristics and surface distribution of dual ligands on nanomaterial surfaces would affect cellular uptake. Of note, they showed that the enhancement in cellular uptake efficiency by dual-ligand targeting nanomaterials is impossible if there is a nonspecific interaction or a length mismatch between the dual ligands [148]. Another major finding was reported by Colombo and colleagues, who showed that the increase in surface-functionalized ligands might not necessarily improve targeting and therapeutic efficacy [149]. Notably, they showed that gold nanoparticles conjugated with two trastuzumab antibodies enhanced homing *in vitro*, but mono-ligand functionalized nanoparticles improved targeting in a subcutaneous breast preclinical model. The dual-ligand strategy may involve a series of complicated parameters, such as the ligand ratio, the ligand density, the length match, and the intrinsic ligand nature that considerably alters the nanomaterial cellular uptake.

The conjugation of multiple ligands on nanomaterial surfaces has the potential to enhance nanoparticle delivery into various solid tumors, such as brain, breast, and even ovarian tumors. The physicochemical properties and the spatial orientation of these targeting ligands on nanomaterial surfaces have also been studied by simulating dissipative particle dynamics. Notably, findings suggest that spontaneous rearrangements of dual ligands on nanomaterial surfaces can facilitate cellular uptake [148]. Also, short ligand length limits reshuffling and short-ligand-conjugated nanomaterials cannot thoroughly wrap exterior cell membranes. Another outlook is that the use of dual or multiple ligands remains controversial because of steric hindrance or interference between adjacent ligands, receptors, and various targeting ligands on nanoparticle surfaces. More fundamental studies are required, especially in understanding how targeting ligands, such as peptides or small molecules coated with a layer of the protein corona, interact with corresponding tumor receptors at the molecular level, and understanding the time-dependent cellular uptake of nanomaterials into the cellular matrix. Lauster *et al.* recently reported using both cryo-electron tomography and computational modeling to probe phage capsid nanoparticles and the effects of ligand arrangement on binding interactions.

4. Incorporating phototherapy and immunotherapy

PDT and PTT are emerging therapeutic strategies that have gained considerable attention for malignant tumor treatment because of their non-invasiveness and high spatial selectivity. Concurrently, there has been a rapid growth in the application of nanomaterials for immunotherapeutic applications. Thus, the attributes of nanomaterials have spurred widespread adoption that may help overcome traditional obstacles. Here, we outline recent strategies that enable the integration of phototherapies and immunotherapy in nanomaterials.

4.1. Fundamental considerations

Nanomaterials are commonly used to potentiate PDT and PTT in cancer treatment [150-152]. PDT operation requires irradiation of photosensitizers (PS) at specific wavelengths, generating various ROS due to interactions between PS and molecular oxygen. ROS signaling occurs via two pathways, both of which start with PS excitation to singlet-excited states upon light irradiation. The PS can undergo non-radiative intersystem crossing, which forms triplet-excited states (^{3}PS*). The ^{3}PS* can proceed through an electron/hydrogen transfer photochemical reaction (type I) or an energy transfer process (type II) to produce ROS [153]. In the type, I reaction, ^{3}PS* can accept an electron to form an anion radical, which reacts with nearby substrates to form various ROS, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals (Fig. 11) [154]. Alternatively, the type II reaction could also occur whereby 3PS* can transfer energy to triplet molecular oxygen to form highly reactive singlet oxygen $^1O_2$ [153]. The ROS induces local oxidative stress and cell death via apoptosis or necrosis mechanisms [155]. On the other hand, PTT utilizes photothermal agents (PTA). PTA release energy via a non-radiative decay after light excitation in their excited states, leading to local hyperthermia and cell death (Fig. 11) [156,157]. In principle, the efficacies of PDT and PTT are mainly governed by three factors: the number of photons reaching PS/PTA; the amount of PS/PTA within the tumor cell; and the efficacy in producing ROS or heat. In this subsection, we discuss how various recent classes of nanomaterials integrating PDT/PTT can improve one or more of these factors through unique design and enhanced therapeutic killing of tumors.

4.1.1. Increasing energy harvesting rate of photons to PS/PTA

One important consideration would be the number of photons available for absorption by PS or PTA to improve therapeutic

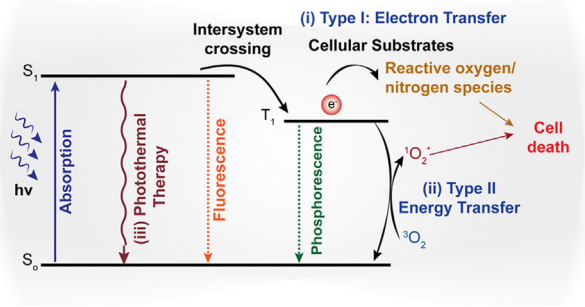

Fig. 11. A typical PDT and PTT energy transfer mechanisms. The energy transfer mechanisms lead to the generation of reactive oxygen species or reactive nitrogen species for PDT and heat for PTT.

efficiency. Light scattering and absorption in biological tissues, including saltwater, melanin, hemoglobin, and various body proteins, lead to light dispersion in the tissues and eventual attenuation in energy density with increasing depth [158]. In a non-biological setting, this challenge can be solved by increasing the power of the light source. However, for biological applications, thermal overheating due to high laser power can cause damage to healthy tissues [159,160]. The solution lies in designing new PS and PTA that absorb in a spectral range where the maximal light penetration is available. Many light attenuation studies in human tissues have been carried out over the years, with three biological optical windows identified between 650 and 950 nm, 1100–1350 nm, and 1600–1870 nm. In these wavelength ranges, scattering and absorption by biological tissues are minimal [161-163]. These biological windows fall within the NIR-I (750–900 nm) and NIR-II (1000–1700 nm) regions, while many commercial PS absorbs in the visible [164]. Recently, research has been placed on developing novel PDT drugs with large absorption in the NIR-I or NIR-II window. This has prompted the advancement of many NIR-absorbing, organic dye-based nanoparticles. These organic nanoparticles include cyanine [165], porphyrin [166,167] and BODIPY derivatives [168,169], semiconductor polymers [170,171] and aggregation-induced emission (AIE) dyes [172,173]. However, these NIR-absorbing dyes have weeker singlet-oxygen generation than visible-absorbing PS [174]. Two-photon PDT was proposed as a practical strategy to resolve this issue [175]. PS agents were activated by two low-energy NIR photons simultaneously, exciting an electron from the ground state to the excited state with an energy gap about two times the energy of the irradiated photon. Various nanomaterials have been designed to optimize two-photon absorption for more effective PDT applications [176,177]. However, two-photon absorption possesses a low upconversion quantum yield as a nonlinear optical process and requires a high-energy pulsed laser as the excitation source [178].

Another solution proposed is using lanthanide-doped upconversion nanoparticles (UCNPs), which can convert two or more low-energy photons into a single high-energy photon. Low-energy NIR excitation on UCNPs could harvest excitation energy before transferring it to commercial visible-absorbing PS, thereby enabling NIR-based PDT. In 2007, Scholfield and co-workers demonstrated this concept [179]. Five years later, Idris *et al.* demonstrated *in vivo* PDT of B16-F10 melanoma tumor cells using mesoporous silica-coated $NaYF_4$:Yb/Er UCNPs loaded with MC-540 and ZnPc dyes, which could absorb upconverted green and red emissions from UCNPs upon 980 nm emission [180]. A few years later, Lin's group took one step further and demonstrated overheat mitigation in biological tissues by coupling UCNPs with two types of 808 nm-absorbing PS (Fig. 12**A**) [181]. Notably, this study achieved *in vivo* reduction of U14 tumors using these UCNPs, whereas the control with a single component of PS only showed growth retardation (Fig. 12**B, C**). UCNPs also imbue therapeutic systems with various imaging capabilities, such as magnetic resonance imaging, computerized tomography, and optical tomography [182,183]. However, in those conventional designs, imaging and therapeutic modalities operate concurrently, which is not desirable in certain situations where only the therapy modality needs to be performed. Skripka *et al.* designed and fabricated elegant UCNPs with an inert shell that could separate neodymium ions from ytterbium ions, enabling decoupling of the diagnostic wavelength (806 nm) and the therapeutic wavelength (980 nm) [184]. This engineering approach allows tissue imaging and temperature sensing to be carried out without phototherapy interference.

Most therapeutic agents for PTT absorb irradiation at 808 nm [185,186]. Although NIR-I light penetrates much deeper in tissues than the visible, NIR-II light could provide additional improvements in penetration depth [187,188]. Many research studies have focused on PTA that absorb NIR-II light. The first NIR-II PTA was reported by Tsai *et al.*, who designed sub-100 nm, rod-in-shell Au nanorods with two distinct absorption bands at 1100 and 1280 nm (Fig. 12**D**) [189]. Upon PTT using a 1064 nm laser, they managed to achieve effective tumor suppression in an *in vivo* LLC/LLC2 lung cancer mice model (Fig. 12**E, F**). In the years that follow, a series of inorganic nanomaterials such as copper manganese sulfide nanoplates [190], silicon oxide nanoparticles [191], and Cu_3BiS_3 nanorods [192] have been reported as effective NIR-II PTA against tumors. Despite enticing prospects, inorganic materials often encounter challenges associated with biocompatibility issues, raising safety concerns in clinical trials [193]. In 2018, Liu and co-workers designed NIR-II conjugated polymer nanoparticles for PTT application [194]. The highly penetrating 1064 nm excitation enabled PTT through the scalp and skull in a U87-MG glioma mice model, with a 50% survival rate at day 40.

4.1.2. Enhancing the intratumoral distribution

The following parameter that affects PDT/PTT efficacy is the PS/PTA concentration in tumor cells. This concentration can be affected by various factors, such as improved PS/PTA delivery. An enhanced delivery thus improves therapeutic efficacy. However, a major limitation is insufficient PS/PTA-loaded nanomaterials

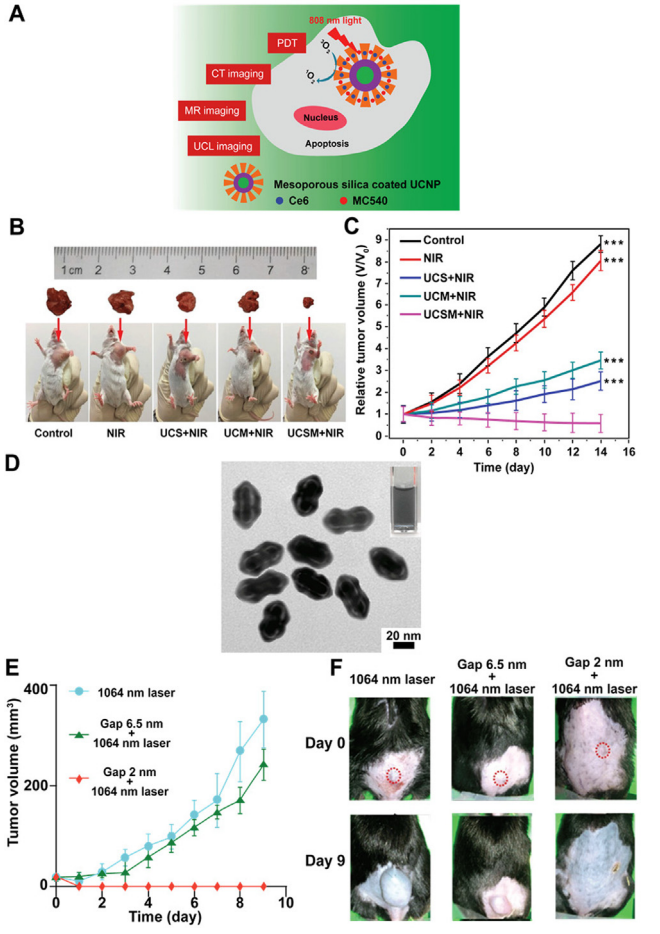

Fig. 12. Increasing energy harvesting using NIR-activatable nanomaterials. (A) NIR-activatable, lanthanide-doped nanoparticles for enhanced PDT and imaging-guided PDT [181]. (B, C) Representative photographs and relative tumor volume of various treatment arms. (D) NIR-activatable gold rod-in-shell nanoparticles for enhanced PTT and imaging-guided PTT. (E, F) Representative photographs and relative tumor volume of various treatment arms [189]. Adapted with permission from [181,189], Americal Chemical Society.

reaching the tumor site. In various preclinical animal models, circulating nanomaterials are rapidly cleared by the mononuclear phagocyte system (MPS) or consumed by Kupffer cells in the liver [195]. Furthermore, nanomaterials are also susceptible to non-specific distribution. They may reside in other healthy organs, especially when the primary mechanism involves passive targeting through enhanced permeability and retention (EPR) [56]. A recent study by Chan's group showed that nanoparticles entered tumors via an active process through endothelial cells, highlighting the inadequacies of the EPR effect for passive targeting [135]. Nanomaterials targeting CD142 [196,197], integrins [198-200], and receptors [201-206] in the TME have been actively researched, providing a powerful platform to enhance the targeted delivery of PS/PTA into tumors.

By way of illustration, Wu's group designed silica-coated, mesoporous $LiLuF_4$:Yb/Er@$LiGdF_4$ UCNPs conjugated with photosensitizer MC540 and surface-functionalized with neuropeptide YY ligands that target overexpressed neuropeptide YY_1 receptors in breast cancer cells [207]. The concentration of ligand-conjugated UCNPs in the tumor was two times higher than those without the targeting ligand. Treatment of MCF-7 tumor-bearing mice with ligand-conjugated UCNPs exhibited prolonged survival. Although tumor-specific targeting strategies have greatly improved PDT efficacy, recent studies revealed that targeting specific organelles can cause cell deaths [208,209]. In 2014, Wei and co-workers designed graphene oxide-based nanocomposites conjugated with pyropheophorbide-a (PPa) and $\alpha_v\beta_3$ monoclonal antibodies, which enabled lysosomal escape with 80% of the nanocomposites accumulated at the mitochondria membrane [210]. Targeting mitochondria, especially vulnerable to oxidative stress, achieved 70% cell death in integrin αvβ3 positive U87-MG cells, compared to 50% for the PPa-free control. Li *et al.* recently designed hollow gold nanospheres and hemoglobin liposomes, modified with endoplasmic reticulum-targeting pardaxin, for endoplasmic reticulum-specific PDT and PTT (Fig. 13) [211]. Introducing stress at the endoplasmic reticulum could induce immunogenic cell death to a greater extent, as evidenced by significant inhibition and increased survival time for both CT-26 and B16 tumor models treated with pardaxin-free nanocomposites.

Another parameter affecting intratumoral distribution is the drug loading efficiency of the nanocarrier. For most nanocarriers, loading efficiency is usually less than 10%, with few therapeutic components reaching tumor cells [212]. In recent years, novel

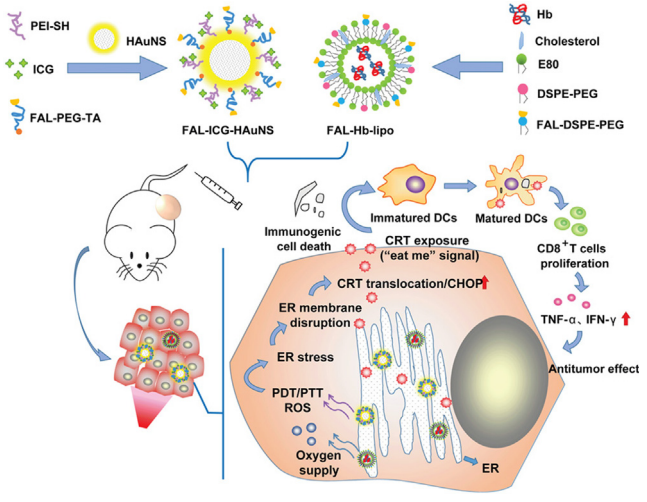

Fig. 13. Schematic of the mechanism underlying the improved immunogenic tumor cell death and antitumor effect of FAL-ICG-HAuNS plus FAL-Hb-lipo nanomaterials [211]. Adapted with permission from [211], Springer Nature.

nanoparticle designs have been proposed to improve high drug loading. One major design strategy is self-assembly. In 2017, Li *et al.* developed self-assembled nanoparticle superstructures from ICG and epirubicin for PTT and chemotherapy [213]. Their nanocarriers allowed 92.4 wt% loading capacity with 30.7 wt% of ICG. Moreover, they demonstrated tumor eradication, and no tumor recurrence was observed for 21 days in a 4 T1 breast cancer murine model. Shortly afterward, Yoon's group developed a simple synthetic method for phthalocyanine nanovesicles by inducing self-assembly through mono-substitution of ZnPc PS with 4-sulfonatophenoxyl functional groups [214]. The high PS concentration in these nanovesicles triggered aggregation-caused quenching (ACQ), making them photoinactive. However, upon reaction with large amounts of albumin proteins in tumor tissues, nanovesicles dissociated and released PS molecules for PDT. One drawback is that albumin proteins are also present in significant quantities around the body, which could cause non-target dissociation of nanovesicles. Luo *et al.* proposed self-assembled nanoparticles using a thioester-linked PPa/paclitaxel (PTX) dimer, which enabled 27.6 wt% PPa loading capacity [215]. Their design was similar to Yoon's, but nanoparticles dissociated to release PS molecules, ameliorating the ACQ effect. However, this dissociation was induced by highly overexpressed ROS in tumor cells. Combining superior loading efficiency and selective dissociation in the tumor resulted in excellent efficacy on both human epidermoid carcinoma and 4 T1 murine breast cancer xenografts. In a separate study, Tong *et al.* designed and integrated phthalocyanine PS into a two-dimensional covalent organic framework (COF), which provided adequate separation between PS molecules even under high loadings [216]. Notably, the ACQ effect was not observed at a PS-to-COF mass ratio of 30%. This led to superior PDT efficacy compared with free PS in the CT26 colorectal cancer mouse model. Taken together, the strategies mentioned above have provided insights into delivering PTA and PS into the TME for effective PTT and PDT in various preclinical tumor models.

4.1.3. Improving ROS and heat production

The efficacy of ROS after photoexcitation in PDT depends on three main factors: the availability of the substrate, the photocatalytic ability of PS to convert the substrate to ROS, and the ROS lifetime. In many type I and II reactions, the substrate is O_2, which lacks in the hypoxic TME [217]. Recently, research strategies have been devoted to nanoparticle design that can alleviate hypoxic conditions. One strategy is using oxygen-transporting moieties, such as hemoglobins or perfluorocarbons [218-220]. This was illustrated by Zhang and co-workers, who demonstrated a light-stimulated oxygen delivery system for PDT in an *in vivo* U87-MG glioblastoma subcutaneous model [221]. By encapsulating core–shell UCNPs, loaded with hypoxic probes and rose bengal, into a red blood cell, the researchers controlled oxygen release into the TME upon 980 nm excitation. Although this study showed an enhanced PDT efficacy, tumor hypoxia and loading efficiency issues remain to be addressed.

In recent years, *in situ* generation of oxygen has gained traction among nanomaterial designs to combat tumor hypoxia. This method utilizes H_2O_2 overexpression in the TME and incorporates various catalysts for H_2O_2 decomposition. One critical catalyst is catalase that is present in many living organisms and protects them from oxidative damage. However, catalase cannot be directly administered because of its vulnerability toward proteases during systemic circulation. In that regard, various nanoparticle designs have recently been developed for catalase integration [222-224]. Major challenges have been outlined in the literature, such as complex synthetic processes and a significant reduction in enzymatic activity upon nanoparticle conjugation [225-228]. To overcome these challenges, Liu *et al.* utilized hydrophobic paclitaxel

molecules to induce co-assembly of catalase and human serum albumin proteins that formed a nanoparticle platform with improved catalase stability against proteases and unaltered enzymatic activity [229]. Another efficacious approach is to use catalase-like catalysts. These include manganese oxides (MnO_2) that can be incorporated into various nanomaterials, including carbon dots [230], metal–organic frameworks (MOFs) [231] and lanthanide-doped nanoparticles [8].

Alternatively, taking advantage of the excellent pH sensitivity of MnO_2, Liu's group developed MnO_2 nanoshell-based therapeutics [232]. In an acidic TME, the MnO_2 nanoshell dissociates to Mn^{2+} ions, allowing efficient drug release and relief from hypoxia (Fig. 14**A**). Their study showed a significant tumor inhibition compared with the control without MnO_2 in a 4 T1 mice model. Moreover, other metal ions such as iron complexes can also be used to decompose H_2O_2 [233,234]. However, those reported catalysts need co-loading with photosensitizers, which complicates nanoparticle design. Yao *et al.* proposed the use of mesoporous cerium oxide-coupled UCNPs for PDT and anti-hypoxia therapy [235]. Cerium oxide acts as a catalyst for H_2O_2 conversion into oxygen and as the photosensitizer for upconverted UV emission from UCNPs.

Another approach to combat hypoxic environments in the TME is targeting excessive oxygen consumption in tumor cells with high mitochondrial activity [236-238]. Instead of supplementing oxygen in the TME, nanomaterial designs can decrease cellular respiration rates and thus improves hypoxic conditions. To validate this hypothesis, Yang *et al.* incorporated metformin into poly(ε-capro lactone)-polyethylene glycol (PEG)-IR780 nanoparticles, which decreased cellular respiration and enabled continuous anti-hypoxia activity both *in vitro* and *in vivo* [239]. Consequently, their protocol led to tumor growth twice smaller than the control without metformin. In the same year, Teng's group encapsulated metformin and IR780 in platelet membranes [240]. Experimental results in an *in vivo* 4 T1 mouse model showed tumor growth approximately four times smaller than the control without metformin. Together, these studies have validated the effects of reduced cellular respiration and improved ROS generation on enhanced PDT efficacy.

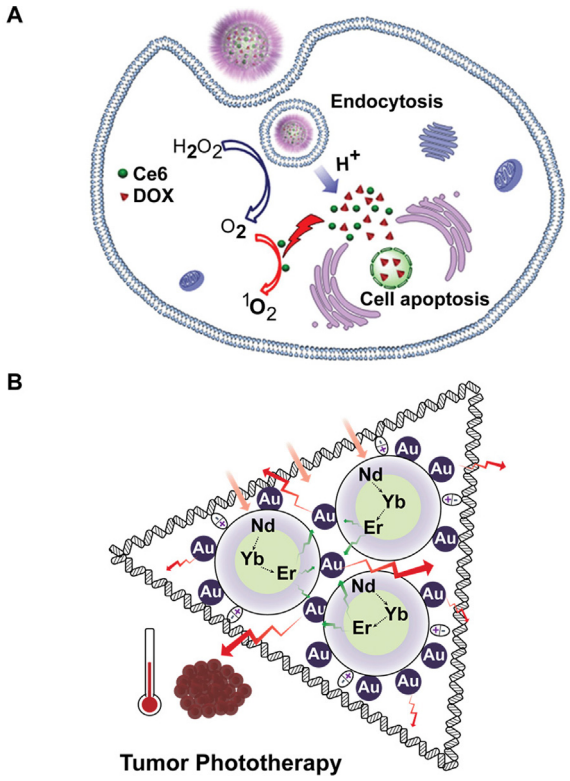

Fig. 14. Nanomaterial-mediated ROS and heat generation. (A) Schematic of pH-responsive drug delivery and oxygen-enhanced PDT [232]. (B) Schematic of NIR-stimulated PTT using hybrid organic–inorganic nanomaterials [258]. Adapted with permission from [232], Springer Nature, and [258], Wiley.

An additional factor affecting the PDT efficacy is the capacity of photosensitizers for ROS production. The main problem in many nanoparticle designs is the ACQ effect due to photosensitizers proximal to each other. Park et al. used Zr-MOF nanoparticles with spatially separated porphyrin linkers to resolve this problem, almost doubling the PDT efficacy relative to the control without the spatial separation [241]. Alternatively, Li's group used an AIE dye with increased photoactivity upon aggregation for achieving more efficient ROS production than the traditional Ce6 [242]. A second reason for low ROS production is low upconversion efficiencies in connection with various upconversion mechanisms [243-245]. As an innovative design for improving upconversion efficiency, Xing's group equipped UCNPs with 2-cyanobenzothiazole peptide molecules that could cleave upon reaction with overexpressed cathepsin B in tumor cells [32]. This peptide-mediated cleavage exposed 1,2-aminothiol groups, which underwent condensation with the nitrile group of 2-cyanobenzothiazole to induce nanoparticle aggregation at the tumor site. This protocol enhanced PDT and significantly inhibited *in vivo* HT-29 colon carcinoma growth compared with the non-conjugated nanoparticle control.

In 2020, Lin and Chang examined distance-dependent luminescence resonance energy transfer (LRET) between Er^{3+} sensitizers and rose bengal photosensitizers in core–shell nanoparticles [246]. By placing Er^{3+} ions in the shell instead of the core, the distance between Er^{3+} and rose bengal was decreased with increased LRET efficiency, thus boosting killing efficiency in MDA-MB-231 breast cancer cells. In addition to UCNP-mediated ROS production, much progress has been made to achieve photon upconversion through two-photon absorption (TPA) or triplet–triplet annihilation (TTA) [174,247-250]. In 2019, Cao and co-workers encapsulated tetraphenylporphyrin photosensitizers with poly[9,9′-bis (6″-bromohexyl)fluorene-2,7-ylenevinylene-co-alt-1,4-phenylene] with a large TPA cross-section, forming conjugated polymer nanoparticles [251]. Conjugation of these nanoparticles with Au nanorods improved singlet oxygen generation by 772-fold, achieving 53% killing efficiency of HeLa cells. In the same year, Zhang *et al.* presented a solution for improved TTA-based PDT [252]. By doping pentacene into tetracene nanorods, intermediate states were formed between the S_0 and S_1 energy levels of the tetracene. These intermediate states have small energy gaps with T_1, resulting in improved intersystem crossing and increased $^1O_2$ generation by 173%. Tetracene/pentacene nanorods exhibited 1.5 times greater inhibition in a B16F10 melanoma mouse model than the tetracene nanorods alone.

ROS lifetime greatly dictates the PDT efficacy. One main reason for the short ROS lifetime is the high levels of antioxidants in cancer cells, especially glutathione (GSH) [253]. Various nanoparticle designs have been proposed to reduce the GSH concentration in tumors. Tang and his co-workers designed MOFs with active Cu^{2+} centers for GSH adsorption and demonstrated marked improvements in *in vitro* and *in vivo* anti-tumor activity [254]. In another work, Wang *et al.* reported FeOOH-coated core–shell UCNPs that react with intratumoral GSH [233]. A major strategy for enhancing light absorption is through localized surface plasmon resonance that is present in gold nanostructures [230,255]. Apart from gold nanostructures, localized surface plasmon resonance has been found in Ti_3C_2 Mxenes, as reported by Dong and co-workers [256]. These Ti_3C_2 Mxenes gave rise to plasmon-induced $Al(OH)_4^-$

anions and achieved a superior photothermal conversion efficiency of 58.3% under 808 nm irradiation. This excellent photothermal effect led to complete tumor ablation in the *in vivo* HCT-116 colon cancer murine model. Instead of using conventional dyes for PTT, Liu *et al.* synthesized organic PTT nano-drugs from non-pigmented peptides and iridoids, which improved nonradiative efficiency [257]. Their protocol improved tumor ablation with a 22-day tumor-free period in an MCF-7 breast cancer mouse model. Alternatively, Yang's group demonstrated improved photothermal efficacy by using a DNA-UCNP-Au hydrogel (Fig. 14**B**) [258]. Incorporation of DNA significantly altered the terrain of the hydrogel, thereby generating a porous, interconnected architecture. This hydrogel renders nanoparticles with a confined, concentrated environment, generating a high photothermal efficiency of 42.7% and a temperature higher than that of the UCNP-Au hydrogel.

Despite the broadly appreciated importance of PDT and PTT, therapeutic efficacy in an orthotopic model remains to be measured. Moreover, the main hurdle remains the insufficient penetration depth of excitation sources. Many existing NIR-II-emitting nanomaterials have reportedly only shown ROS/heat generation at a maximal tissue depth of 20 mm [259,260]. To date, NIR-II light has been demonstrated to reach an 8-cm tissue depth in *ex vivo* models [261]. However, a study carried out by Li *et al.* reported ~ 10-fold reduction in the photoacoustic signal of a 1064-nm probe, placed underneath a 3.5-cm deep chicken breast tissue [262].

Chen *et al.* conceptualized deep-tissue PDT by combining X-ray-excitable scintillators or persistent luminescent nanoparticles with photosensitizers [263]. Following this work, many nanomaterials capable of X-ray-induced PDT have proven effective in a multitude of cancer models [264-268]. However, one main criticism of using X-rays in PDT is the cytotoxic pathway, unlike conventional PDT under non-cytotoxic visible/NIR irradiation. To circumvent the potential X-ray phototoxicity to healthy cells, Zhang's group devised chemiluminescence excitation using Ce6-Luminol-PEG nanoparticles [269]. They demonstrated H_2O_2-induced chemiluminescence resonance energy transfer from luminol to Ce6 for PDT, bypassing the need for external excitation. Retardation of 4 T1 tumor growth and subsequent lung metastasis was also achieved. An alternative excitation source that overcomes the shallow penetration depth is ultrasound, which offers deep penetration depths due to its low attenuation in biological tissues. Using $C_{18}GR_7$-RGDS-ICG nanomicelles, Liu *et al.* conducted sonodynamic therapy after PDT and PTT [270]. They achieved higher *in vivo* efficacy in MDA MB-231 breast adenocarcinoma tumor-xenografted rodents than the PDT/PTT group, suggesting a potential therapeutic alternative for PDT/PTT.

4.2. Improving cancer immunotherapy

Cancer immunotherapy evokes a patient's immune system to fight tumors and it is considered the fourth pillar of cancer treatment, in addition to surgery, chemotherapy, and radiotherapy [271]. Due to the induction of tumor-specific immunity, cancer immunotherapy can reduce severe side effects associated with chemotherapy and radiotherapy. Notably, cancer immunotherapy has shown great promise in inducing an abscopal effect that efficiently inhibits and eradicates tumor metastases [272]. Despite significant advances, cancer immunotherapy also has limitations, including low immune response rates, autoimmune induction, the development of immune tolerance, the need for additional biomarkers, and high treatment costs [273]. Recently, nanotechnology and bioengineering afford new strategies for improving the safety and the efficacy of cancer immunotherapy. These nanomaterials can activate immune cells, facilitate cell-targeting delivery, improving diagnostics and biomarker monitoring, as well as enhancing TME-responsive delivery [274]. This section classifies the nanomaterials for cancer immunotherapy into two main types: self-adjuvants nanomaterials and non-adjuvanted nanomaterials, based on the criterion whether nanomaterials themselves can serve as adjuvants. We review recent achievements in nanomaterial-based tumor immunotherapy and also the challenges that needed to be addressed before clinical translation.

4.2.1. Self-adjuvanted nanomaterials

Cancer vaccines can potently activate $CD8^+$ cytotoxic T lymphocyte (CTL) response to inhibit tumor growth for cancer immunotherapy. This process is essentially associated with major histocompatibility class I (MHC-I) antigen presentation of exogenous antigens [275]. Three signal pathways determine MHC-I antigen presentation: the maturation status of antigen-presentation cells (APCs), such as dendritic cell (DCs) and macrophages; the location of antigen processed in APCs; and cytokines and chemokines produced by APCs. Usually, cancer vaccines weakly induce $CD8^+$ CTL due to the low MHC-I antigen presentation, caused by weak signal pathways.

To improve the anticancer efficacy of vaccines, self-adjuvanted nanomaterials have been developed. For example, Wang *et al.* developed a unique nanomaterial that is both amphiphilic and pH-sensitive to form hydrogel-based vaccines comprising galactosyl dextran-retinal (GDR) that enhanced DC maturation, promoted MHC-I antigen presentation, and improved IL-12 production (Fig. 15**A, B**) [276]. The strategy of strengthening three signal pathways simultaneously inhibited B16-F10 tumor growth and prolonged the survival of tumor-bearing mice. Notably, the authors demonstrated that accumulation of cellular ROS in DCs promoted MHC-I antigen presentation, indicating a clever strategy for boosting antitumor immunity. Another self-adjuvanted polymer, named

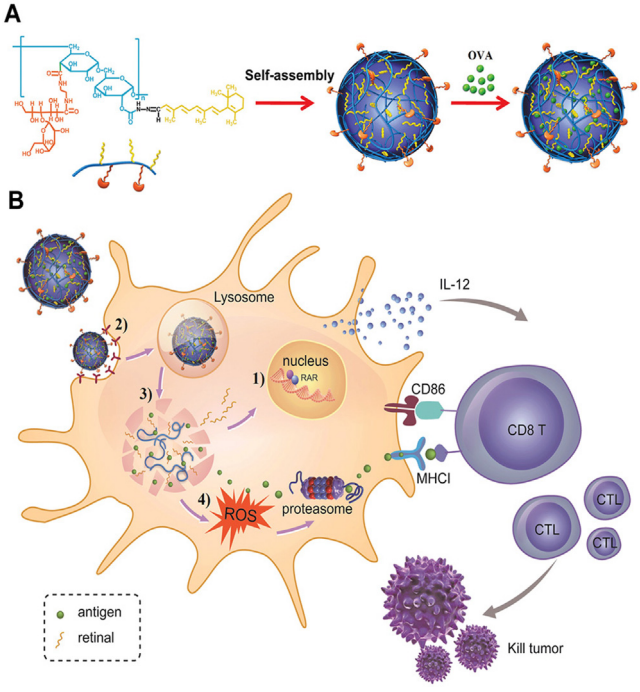

Fig. 15. Self-adjuvanted nanomaterials for immunotherapy. (A) Schematic design of the GDR nanogel and GDR/OVA nanovaccine for immunotherapy [276]. (B) Schematic of the antitumor immune effects of GDR-enhanced cancer vaccine. GDR promotes dendritic cells, as mediated by the RAR signalling pathway. GDR improves dendritic cell-targeted vaccine delivery. GDR improves cytosolic antigen release by activating lysosoma rupture, and GDR-activated lysosome rupture directly generates reactive oxygen species to augment proteasome activity and MHC-1 antigen presentation. Adapted with permission from [276], Elsevier.

p(Man-TLR7), was developed through polymerization of mannose-binding receptor monomers that could agonize Toll-like receptors 7 (TLR7) [277]. This polymer was then conjugated to antigen proteins using a self-immolative linker, enabling antigen release rapidly upon endocytosis. This antigen-p(Man-TLR7)-based nanovaccine significantly induced anti-ovalbumin (OVA)-specific humoral and cellular immunity, showing the potential as an adjuvant for a clinically advanced malaria vaccine. Unlike other formulations that may damage encapsulated antigens upon loading and release, this strategy involves a minimal biomaterial footprint and enables antigen release without chemical or recombinant modification. As an added benefit, it can incorporate other antigens or TLR receptors to generate specific nano-vaccines for various applications.

Recently, self-adjuvanted, pH-sensitive PC7A polymer nanoparticles have been employed to deliver model OVA antigens or MHC-I peptides as a cancer vaccine. This vaccine induced potent cytotoxic T cell response, significantly inhibiting various stages of tumor growth [278]. This antitumor effect was attributed to the adjuvant effect of PC7A nanoparticles on the activating stimulator of interferon genes (STING) as well as enhanced antigen MHC-I presentation. Given that conventional STING agonists, such as 2′3′-cyclic guanosine monophosphate–adenosine monophosphate (cGAMP), are usually intratumorally administrated to achieve superior therapeutic efficacy. By comparison, this current study presents a novel STING agonist, PC7A nanoparticles, suitable for tumor immunotherapy by systemic injection. Another promising STING-activating lipid nanoparticles were identified and selected from over 1000 lipid-based nanoparticle candidates using a one-step three-component reaction [279]. When these nanoparticles were used as mRNA vaccine delivery vehicles, significant suppression in tumor growth and prolonged survival occurred in melanoma and human papillomavirus E7 tumor models due to activation in STING-dependent immune response.

Nanomaterials can directly activate dendritic cells by recognizing pattern recognition receptors, such as Toll-like receptor (TLR) and NLR family pyrin domain containing 3 (NLRP3). This approach has been applied to cancer immunotherapy with potential clinical translation. For instance, Xu *et al.* reported self-adjuvanted, fluoroalkane-grafted polyethyleneimines that could induce DC maturation via Toll-like receptor 4 and promote antigen MHC-I presentation by facilitating antigen transportation in the cytosol [280]. This nanovaccine potently inhibited B16-OVA melanoma growth. Gong *et al.* developed a self-adjuvanted, polymer-based nanovaccine by conjugating antigen peptides on p($DMAEMA_{22}$-$OGEMA_4$)-b-p$(MAVE)_{30}$ via an acid-cleavable linker, potently inhibiting tumor growth in B16-OVA and human papillomavirus-E6/E7 tumor models [281]. The antitumor effect could be attributed to the robust stimulation of $CD8^+$ T cells by the nanovaccine. The polymer activated DC maturation via the NLRP3-inflammasome pathway and facilitated cytosolic delivery of antigens. Importantly, both nanovaccines, as discussed above, showed a synergetic anti-tumor effect with immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-L1, showing a high level of evidence for potential clinical utility.

Neoantigens from non-synonymous mutations and genetic alterations without expression in healthy tissues have been widely selected and applied to cancer immunotherapy in order to improve the response rate of cancer immunotherapeutics. Recently, self-adjuvanted molecular activator (SeaMac) nanovaccines were designed to enhance cancer immunotherapy (Fig. 16**A-E**) [282]. These SeaMac nanoparticles harvested neoantigens from perished cells following PDT, which subsequently induced DC maturation, presented neoantigens to T cells with high efficiency, and augmented the effect of $CD8^+$ CTL activation. SeaMac nanovaccines have proven their strong efficacy in inhibiting primary and distant tumor growth, as well as in extending the survival of tumor-bearing mice in both B16 and CT26 preclinical models.

4.2.2. Immunogen delivery

Nanomaterials have been applied to delivering multiple moieties to tackle the limitation of cancer immunotherapy. These include antigens, peptides, adjuvants, or monoclonal antibodies that can activate the immune response and reduce the immunosuppressive TME [283]. Nanomaterial-based delivery systems can improve cancer immunotherapy due to enhanced stability and biocompatibility, improved EPR effect, and active targeting of various overexpressed tumor epitopes with high precision. For this reason, many nanomaterials have been developed for tumor immunotherapy, including polymer nanoparticles, hydrogel nanoparticles, lipid-based nanoparticles, and inorganic nanocrystals.

Polymeric nanoparticles have attracted considerable attention as cargo carriers in the biomedical arena because they feature high biocompatibility, large loading capacity, precise control over drug release kinetics, and facile surface modification [284]. Many types of polymeric nanoparticles, such as poly(D,L-glycolide) (PLG), poly (lactide-co-glycolide) (PLGA), chitosan, and polyethyleneimines, have exhibited enhanced cancer immunotherapy. In particular, PLGA possesses outstanding biodegradability and has been approved for tumor immunotherapy by U.S. FDA [285]. Owing to their natural capacity for DC targeting, PLGA nanoparticles have been used to deliver tumor antigens and adjuvants. For example, Kim *et al.* found that PLGA nanoparticles loaded with TLR7/8 agonists and OVA induced more potent antitumor efficacy than adjuvants alone [286]. Surface modification of PLGA nanoparticles

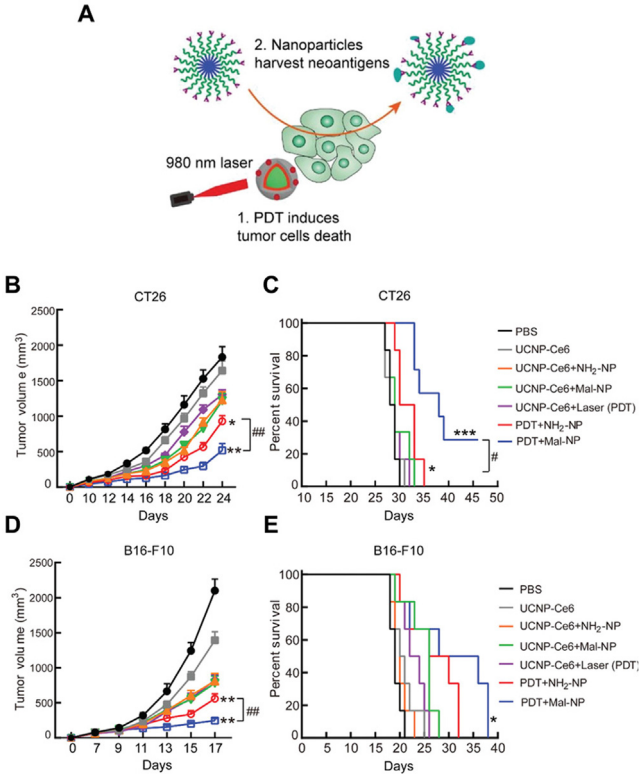

Fig. 16. Self-adjuvanted molecular activators (SeaMac) for immunotherapy. (A) Schematic showing the capture of neoantigens by NH_2-NPs and Mal-NPs [282]. (B) Effectiveness of Mal-NPs to cause tumor regression in CT26 rodent model *in vivo*. (C) Survival rate of different treatment arms in CT26 rodent model *in vivo*. (D) Effectiveness of Mal-NPs to cause tumor regression in B16-F10 rodent model *in vivo*. (E) Survival rate of different treatment arms in B16-F10 rodent model *in vivo*. Adapted with permission from [282], Wiley.

with a spectrum of targeting ligands, such as mannose, DEC-205 antibody, or CD11c antibody, also enhanced nanoparticle uptake by DCs and immunotherapy efficacy [287-289]. A serial of functional groups was modified on PLGA nanoparticle surfaces to capture neoantigens following apoptotic cell-induced radiotherapy, including aminopolyethylene glycol (NH_2-PEG), 1,2-dioleoyloxy-3-(trimethylammonium)propane (DOTAP), maleimide polyethylene glycol (Mal-PEG), or methoxypolyethylene (mPEG). In combination with anti-PD-1, Mal-PLGA nanoparticle formulation induced a remarkable abscopal effect in the B16-F10 melanoma model and generated a 20% cure rate compared with 0% for the control.

Besides surface modification, functionalization of polymers with pH-, UV-, or ROS-responsivity represents a powerful means to improve tumor immunotherapy. For instance, pH-sensitive PEG-b-P[DEAMA-co-BMA-co-PDSMA] polymers were employed to encapsulate 2′3′-cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), STING activating agonists, forming STING-nanoparticle formulation [290]. This polymer material showed a potent enhancement in the therapeutic efficacy of cGAMP following intratumor injection, which could be ascribed to enhanced immune response via STING signal activation in the TME. Hu *et al.* designed ROS-responsive polymer nanoparticles, loaded with doxorubicin and Ce6, for inducing a cascade reaction of chemo-PDT, which inhibited tumor growth. In combination with anti-PD-L1 antibodies, polymer nanoparticle-based chemo-PDT evoked remarkable anti-tumor immunity, generating an abscopal effect in the 4 T1 tumor model [291]. Song *et al.* developed UV-responsive polymers (polypeptide-glycosylated poly(amidoamine) dendron amphiphiles, PGDA) for delivering model antigen OVA. Upon 365 nm irradiation, the polymersomes of PGDA-OVA promoted OVA uptake, endolysosomal escape, and TNF-α production by RAW 264.7 cells [292]. However, the risks of particle aggregation and toxicity with polymer nanoparticles need to be extensively assessed.

Hydrogel nanomaterials are promising drug carriers for cancer immunotherapy because of their unique features, such as high cargo loading capacity, controlled release, and good biocompatibility. For example, Chen *et al.* designed immunotherapeutic bioresponsive hydrogels by combining a thrombin solution and a solution of fibrinogen-containing calcium carbonate nanoparticles, pre-loaded with anti-CD47 antibodies [293]. These *in situ*-forming hydrogels potently polarized immunosuppressive M2 macrophages to immunologically active M1 macrophages. Activated M1 macrophages significantly promoted antigen presentation and $CD8^+$ T cell activation, thereby inhibiting local tumor recurrence and potential metastatic spread post-surgery. Similarly, a hydrogel-based, personalized cancer vaccine (PVAX) was developed by integrating JQ1 (a BRD4 inhibitor) and ICG-co-loaded tumor cells with hydrogels containing tumor-penetrable peptides (Fmoc-KCRGDK, FK) [294]. Upon irradiation at 808 nm, PVAX evoked a significant antitumor effect and patient-specific memory immune response to prevent tumor recurrence and metastasis following tumor surgery.

Lipid nanoparticles, a promising class of FDA-approved nanomedicines, are common for tumor immunotherapy because they offer many advantages, such as preparation simplicity, self-assembly feasibility, high biocompatibility and bioavailability, and large surface areas that can be readily modified with different functional groups. Lipid-based nanoparticles usually contain two subsets: liposomes for drug delivery and lipid nanoparticles for nucleic acid delivery. Kranz *et al.* reported a lipid nanoparticle-based RNA vaccine (RNA-lipoplexes, RNA-LPX) encoded by viral or mutant neoantigens or endogenous self-antigens [295]. This RNA-LPX vaccine induced strong effector and memory T-cell responses and mediated significant IFN-α-dependent inhibition of progressive tumors through systemic administration. Owing to the good therapeutic effect of the RNA-LPX vaccine in rodents, a phase 1 clinical trial (NCT02410733) has begun in melanoma patients, showing robust immune response to tumor-associated antigens [296].

Lipid nanoparticles have also been used to deliver CRISPR/cas9 genome editing, messenger RNA (mRNA), small interfering RNA (siRNA) for tumor immunotherapy, significantly inhibiting tumor growth. For instance, Rosenblum *et al.* used lipid nanoparticles to co-deliver Cas9 mRNA- and sgRNA-targeting PLK1 to glioblastoma cells, resulting in ~ 70% gene editing, tumor growth inhibition by ~ 50%, and improvement in survival by ~ 30% [297]. A lipid nanoparticle formula of lipid-PEG, PLGA, and G0-14 was applied to prostate cancer treatment by delivering phosphatase and tensin homolog deleted on chromosome 10 mRNA. This mRNA significantly inhibited PC3 tumor growth after systemic injection through the phosphatidylinositol 3-kinase (PI3K)-AKT pathway [298]. Shobaki *et al.* designed pH-sensitive CL4H6 lipid nanoparticles and their utility in delivering signal transducer and activator of transcription 3 siRNA and hypoxia-inducible factor 1a siRNA to M2 tumor-associated macrophages [299]. This formulation significantly inhibited tumor growth by polarizing M1 macrophages in the TME. Despite successful demonstrations, the utility of lipid nanoparticles remains challenging because of low drug loading and high biodistribution in unwanted organs, such as the liver and spleen.

Inorganic carbon nanoparticles, silica nanoparticles, metal nanomaterials, MOFs, and lanthanide-doped nanoparticles have been widely used in two directions for cancer immunotherapy. The first direction is to serve as nanocarriers to deliver immune activators, such as adjuvants, antigens, or antibodies, into immune cells. The other direction is integration as an additional therapeutic tool for radiotherapy, PDT, and PTT. As proof of this versatility, tumor-targeting, peptide-functionalized graphene oxides were coated with photosensitizers. Upon laser irradiation, these functional graphene oxides activated cytotoxic $CD8^+$ T cells and potently suppressed subcutaneous and metastatic tumor growth [300]. Moreover, a personalized nanovaccine was prepared by coating mesoporous silica microrods with peptide antigens and polyethyleneimine [301]. One single injection of this vaccine largely eradicated TC-1 tumors in 80% of mice and evoked long-term memory immune response. This therapeutic effect was further confirmed in B16-F10 and CT26 tumor models and synergized with anti-CTLA-4 therapy. Bovine serum (BSA)-bioinspired gold nanorods in conjugation with immunoadjuvant imiquimod R837 have also been used for tumor photothermal therapy and immunotherapy [302]. Upon 1064 nm irradiation, these gold nanorods significantly inhibited tumor lung metastasis and prolonged the survival of tumor-bearing mice, resulting from the activation of $CD8^+$ T cells and enhanced infiltration of DCs at tumor sites.

Nanoscale MOFs and inorganic hybrid nanomaterials comprising metal building blocks and bridging ligands have potential applications in radiotherapy and immunotherapy due to their structural tunability, high porosity, and biocompatibility. For instance, in 2018, Ni *et al.* designed two Hf-based MOFs with two different secondary building units (Hf_6-DBA and Hf_{12}-DBA) for enhanced anti-PD-L1 antibody radiotherapy [303]. After X-ray irradiation, Hf_{12}-DBA showed more potent inhibition of tumor growth than Hf_6-DBA because Hf_{12}-DBA absorbs more X-rays and generates a higher ROS level than its Hf6-DBA counterpart. When combined with anti-PD-L1 antibodies, Hf_{12}-DBA-based radiotherapy potently evoked the abscopal effect due to systemic antitumor immunity. Meanwhile, MOFs can be used as carriers to deliver immune imiquimod (IMD) modifiers for macrophage modulation and anti-CD47 antibodies for reversal immunosuppression in tumors [304]. Coupling anti-PD-L1 antibodies with IMD@Hf-DBP/

anti-CD47 potently induced cellular immunity and significant M2-to-M1 macrophage polarization, resulting in complete eradication of both primary and distant CT26 tumors.

Owing to their deep-tissue imaging capability and long excited-state lifetimes, lanthanide-doped nanoparticles have also been applied to cancer immunotherapy, such as real-time fluorescence imaging in immunotherapy and PDT/PTT-induced immunotherapy. For example, Mao et al. combined UCNPs with aggregation-induced emission luminous to form multifunctional nanoprobes for PDT-induced tumor immunotherapy. Upon high-power NIR irradiation of nanoprobe-treated tumor tissues and low-power laser irradiation of lymph nodes, potent inhibition of tumor recurrence and distant tumor growth occurred, which could be attributed to the dual-mode, ROS-activated immune response [305]. Drawing inspiration from previous seminal work on UCNP-based immunotherapy, Yan *et al.* employed photosensitizer-loaded UCNPs with a dual-PDT/PTT effect [306]. Under 980 nm irradiation, the UCNP-based formulation induced potent systemic and humoral anti-tumor immune responses, significantly inhibiting 4 T1 tumor growth. In particular, when combined with anti-PD-1 antibodies, this synergistic phototherapy showed a remarkable effect on tumor relapse and metastasis in two tumor models, indicating augmented antitumor immune response. Despite their therapeutic potential, developing functional lanthanide-doped nanoparticles with minimal long-term *in vivo* cytotoxicity requires considerable effort.

In summary, the literature survey has revealed the enticing prospects of using nanomaterials for various aspects of immunotherapy. However, the design of next-generation, nanomaterial-based anticancer immunotherapy requires a systematic and thorough knowledge of how these synthetic nanomaterials interact with the immune system. For these nanomaterials to translate into cancer immunotherapy, their long-term efficacy and chronic toxicity, as well as intricate mechanisms at work, need to be carefully studied. A probable aspect could be comparatively metronomic low-dosing schedules, which can maintain adequate therapeutic efficacy and concurrently reduce potential toxicities.

5. Preclinical and clinical studies

The ability to translate proof-of-concept nanomaterials in various tumor applications to clinical trials requires rigorous testing of the experimental data in several settings to support the claims of efficacy and low toxicity relative to the control groups. Fortunately, several cancer nanomedicines have since found their way into the clinics, either in clinical trials or commercialized for human cancer patients. However, numerous challenges require more fundamental studies to be performed to improve our understanding of using these nanomedicines. Here, we present the key aspects of emerging preclinical and clinical studies of various tumor nanomaterials.

5.1. Biological barriers and biodistribution

The systemic administration of nanoparticle carriers often encounters a deficiency in achieving potent drug delivery efficiency and effective biodistribution as they are confronted with physical and biological barriers. These include aggregation, protein adsorption, sequestration by phagocytic cells, and renal clearance. The myriad of these so-called barriers has vastly limited the accessibility of the nanoparticle to reach the targeted therapeutic site [307]. Once eluded from the barriers mentioned above, the nanocarriers then pose an opportunity to interact with the tumor site. Two distinguished biological systems are known as the MPS, and the renal clearance pathway enacts pivotal roles in competing with the tumor for the circulating nanocarriers. Notably, the liver or spleen area containing abundant MPS phagocytic cells would incline to take up the nanocarriers. The kidney possessing the renal system can also potentially excrete nanocarriers with a hydrodynamic meter of less than 5.5 nm [308,309]. Hence, nanoparticle delivery efficiency is a population of these systemically administered nanoparticles to cross these barriers to interact with the tumor regions [310]. Depending on the administration route, varying degrees of the tumor progression, disparate biological barriers are encountered by these nanocarriers. In light of these physiological, environmental factors, appropriate design and modulation of the nanocarriers' physicochemical compositions should not be overlooked. An alteration in one simple characteristic of the nanoparticle could inevitably decide the fate of the nanocarriers, which can potentially induce toxicity to healthy tissues and organs. To address the nanocarriers' biodistribution and their potential toxicity to the tissue environment, physicochemical properties such as size, zeta potential, nanoparticles' morphology, and surface chemistry should be profoundly comprehended better to accelerate the translation of nanoplatforms in clinical applications [311]. In the modulation of clinical nanomaterials, it is crucial to analyze compromising factors between attenuating the rapid renal clearance of nanoparticles for potent therapeutic efficiency and the justifiable nanomaterial clearance from the body to prevent accumulative toxicity. Worth mentioning is that patients with renal impairments might increase the complexity of the renal clearance profile and the need to perform several assessments of disparate nanomaterials [312].

5.2. Mechanisms of cellular and tissue transport

Plasma membrane as a spatially dynamic biological structure holds vital capacity to sustain the cellular environment's integrity, affected by the gradient of surrounding molecular components, extracellularly or intracellularly. The essential small molecule could effortlessly traverse through the plasma membrane with the aid of integral membrane proteins or ion channels. On the other hand, macromolecules or nanoparticles rely essentially on endocytosis, where particles would be enclosed in membrane-bound vesicles invaginated by the associated fragments of the plasma membrane to be translocated to the intracellular milieu. Two main nanoparticle transportation pathways include phagocytosis, where large particles are usually uptaken, pinocytosis, where nearby solutes or fluid are assimilated. Four basic mechanisms were categorized under pinocytosis, namely macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated endocytosis, clathrin, and caveolae dependent and independent endocytosis, respectively (Fig. 17) [313-315]. Precisely, the nanoparticles' physicochemical properties could substantially influence the pathway to be endocytosed.

5.3. Toxicity effects

Nanoparticle circulation in the bloodstream is often exposed to rapid excretion, uptake by phagocytic cells, blood flow, and formation of coronas, affecting the efficacy and stability of nanoparticles [311]. In terms of size, small nanoparticles with a diameter of less than 10 nm can be rapidly eliminated by kidneys, while those larger than 200 nm might activate the immune complement system and then be eliminated from the bloodstream [316]. Studies on gold nanoparticles have been carried out to understand the effect of particle size on cellular internalization. Results reveal that approximately 40–50 nm nanoparticles induce better membrane receptor internalization, which ameliorates the downregulation of gene expression. Herceptin-modified gold nanoparticles greater than 60 nm did not show any cytoplasmic localization. Gold nanoparticles of 40–50 nm in diameters set the critical guideline

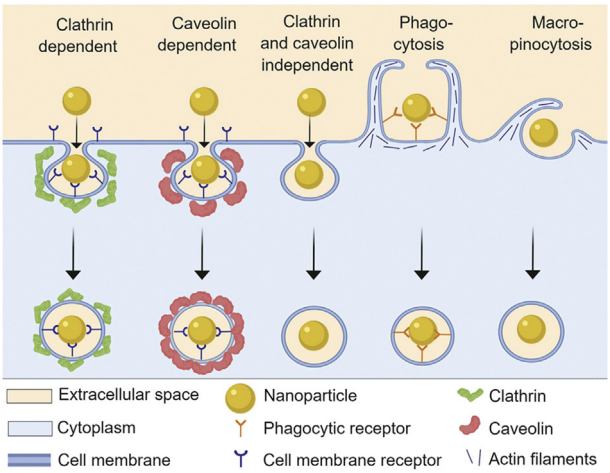

Fig. 17. Schematic of nanomaterial cellular uptake into tumor cells [314]. Adapted with permission from [314], Elsevier.

for receptor-mediated internalization [317]. Moreover, nanoparticle toxicity is size-dependent. Rapid cell death by necrosis was induced by gold nanoparticles of 1.4-nm diameter within 12 h, whereas 15-nm nanoparticles displayed lower toxicity, irrespective of cell type and surface ligands [318,319]. In principle, smaller nanoparticles often possess larger surface areas, which may boost ROS generation and induce cellular injury [320].

Apart from the size factor affecting toxicity, diverse nanoparticle morphologies have shown disparate *in vitro* responses. Zhao and co-workers extensively studied the influence of varying hydroxyapatite shapes on cell cytotoxicity. Needle-like, platelet, spherical, and rod-shaped nanoparticles were synthesized, and needle and platelet nanoparticles induced more toxicity than others, as supported by the high level of IL-6 expression [321]. Studies also demonstrate that spherical silver nanoparticles have little impact on cells, whereas silver nanowires trigger specific cellular cytotoxicity and activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated cell-repairing mechanisms. The nanowire's length is a dominant factor inhibiting complete permeability into the cell intracellular milieu, thus damaging cell membranes [322].

The surface chemistry of nanomaterials should also be considered an essential component for balancing protein functions and cytotoxicity to normal tissues. Depending on the specific nature of the surface modification, surface groups may initiate protein adsorption onto nanoparticle surfaces, forming a protein corona. Consequently, the protein corona can alter the net surface charge, the hydrodynamic diameter, and the characteristics of nanoparticle aggregation. Similarly, upon adsorption onto surface-functionalized nanoparticles, native proteins could also undergo a conformational change, diminishing their native function and potentially disrupting the homeostasis of biological processes [323]. Positively charged polystyrene nanoparticles exert greater toxicity than their negatively charged counterparts. Mitochondrial dysfunction and cell membrane disruption may cause inadequate energy supply and lower cell proliferation rates, resulting in a prolonged G0/G1 phase [324]. The perceived distinctive toxicity level difference between the positive and negative charged nanoparticles was proposed to be mediated by the electrostatic attraction between the negatively charged cell membrane potential with the positively charged nanoparticles, but not with negative or neutral charged nanoparticles [325].

Apart from direct cytotoxicity assays, nanoparticle safety can be evaluated by measuring nanoparticle distribution across biological barriers in the body. These barriers exist diversely in organisms, including the blood–brain barrier, the placental barrier, the corneal epithelial barrier, and the gastrointestinal tract. Their main function is to prevent the invasion of pathogens and harmful allergens [326]. Nanoparticles residing within the barriers also indirectly influence the health of neighboring cells, akin to radiation-induced bystander effects [327]. Bhabra *et al.* reported that incorporating cobalt-chromium (CoCr) nanoparticles into multilayered BeWo cell barriers damaged human fibroblast cells to a greater extent than the control without the cell barrier [328]. The intricate network of epithelial-cell junctions, tight junctions, gap junctions, and desmosomes within BeWo cells can participate in intercellular communication and signaling. The fibroblast DNA damage is likely induced by adenosine triphosphate (ATP) secretion from CoCr nanoparticles and then traverses through the BeWo cellular barrier, followed by cross-talk between upregulated intracellular calcium messengers and receptors and cell junctions. Different barrier layers exist at different stages in systems. As a case in point, bilayer gap junctions interconnecting trophoblast cells exist in the first trimester of human pregnancy, with a cytotrophoblast layer lying underneath the superficial syncytiotrophoblast. During the gestation period, progressive reduction in cytotrophoblast leads to predominant monolayered syncytiotrophoblast, and gap junction signaling may vary significantly depending on the barrier layers at different pregnancy stages [329,330]. Indeed, across multilayered trophoblast and corneal barriers, indirect DNA damage was observed, but not in the single-layered barriers. CoCr nanoparticles can also indirectly induce cytokine and chemokine immunoexpression across corneal barriers, but monolayer cell barriers give a negative response, further proving the concept of barrier thickness-dependent toxicity associated with nanoparticles [331].

Another dimension of nanomaterials is that they can bind immunocompetent cells and stimulate immunotoxicity. Direct damage to immune cells using nanoparticles leads to apoptosis and necrosis. Nanomaterial interactions with the immune response can alter adaptive immune signaling pathways, which result in changes in immune cell function that are measurable by the expression of surface markers, cytokine production, cell differentiation, and immune activation. Physicochemical properties of nanoparticles can be used to determine nanoparticle susceptibility to undesirable interactions with blood constituents after intravenous administration. A small change in nanoparticle property can easily alter the immunological profile and make assessment more challenging as a specific toxicity assay is required. To illustrate, the disruption of the hemostatic balance in the coagulation system can cause disseminated intravascular coagulation and abnormal hemorrhaging or intravascular thrombosis [332,333]. Once introduced *in vivo*, nanoparticles are promptly covered with opsonins, triggering phagocytosis and clearance response.

Moreover, the immune complement system can be activated when the nanoparticle goes through the opsonization process, resulting in inflammation, immune cell activation, and even enhanced tumor progress. An expansion of opsonization is protein corona, which refers to the nanoparticles' specific biological properties and protein binding to their surface. These disparate interactions make it difficult to implement the induction or avoid the suppression or stimulation of the immunotoxin effects [334]. Many nanoparticles have been reported to induce red blood cell damages or hemolysis. Cationic polyamidoamine dendrimers strongly interact with red blood cells, triggering hemoglobin released into the bloodstream and causing iron deficiency anemia and renal failure [335]. Similarly, interactions of nanoparticles such as iron oxide nanoparticles, quantum dots, or mesoporous silica nanoparticles with red blood cells can produce adverse hemolytic effects [336-338]. Pegylated nanoparticle modification with immunoregulatory agents, which provide anti-inflammatory effects and vaccination, or avoid the immune system, may induce endotoxin contamination

and immunotoxicity. Unintentional galvanization of cytokine production and ROS may recruit pro-inflammatory cells such as macrophages, dendritic cells and neutrophils, potentially causing asthma, bronchitis, and damages to lung, liver and kidney tissues [339].

To alleviate immunotoxicity in nanomedicine practice, standardized immunotoxicity evaluation of interferences for endotoxin-free nanoparticles with minimum unregulated immune stimulation must be established. Reduced infusion rates, co-administration of antihistamines or corticosteroids, and properly routed administration modes or advanced surface engineering can be conducted to minimize immunotoxic effects [340,341]. Importantly, predictive tests in nanomedicine to stratify patients with affordable and flexible platforms will greatly improve reproducibility and clinical translation. As the immunostimulatory effect is closely associated with cellular DNA damage, nanoparticle-induced toxicity across cellular barriers may provoke neuronal DNA damage and neurotoxicity through interleukin-6 immunoexpression. When CoCr nanoparticles were exposed to cellular barriers, an elevated p53 expression level proved oxidative stress-driven autophagic flux and consequently promoted the full release of interleukin-6, instigating neuronal and astrocytic DNA damage. Astrocytes are near neurons for neuronal network remodeling. Perturbation of the neuroglial signaling between astrocytes and neurons may elicit neurodevelopmental abnormalities. *In vivo* results also demonstrated that brain pathologies are predominantly mediated by astrocytes [326].

Several systems for nanoparticle-based drug delivery have been examined in cancer patients. Many more are in the pipeline as they undergo a thorough assessment to evaluate the efficacy and toxicity in various preclinical models and clinical trials. While there is still much work ahead to transit these nanomaterials and nanotheranostics into clinical use, myriad bioapplications have shown immense potential. Nonetheless, research gaps from chronic toxicity and nanomaterial degradation pathways to therapeutic efficacy and biomarker validation remain unanswered. The majority of preclinical tumor models are often used in immunocompromised rodent models, which neglects crucial interactions and the effect of the immune system. Fundamental research needs to be improvised before clinical trials to accommodate the TMEcomplexity, the interplay between the immune system and designed nanotheranostics, and long-term chronic toxicity studies. Also worth mentioning are metabolites upon nanomaterial degradation. These studies include that nondegradable inorganic or hybrid nanomaterials, mechanistic understanding of how they are removed from the host, and potential toxicity effects on tissues, organs, and the immune systems.

6. Conclusions and outlook

Research on nanomaterials for cancer nanotheranostics has gained considerable momentum in both fundamental studies and proof-of-concept applications in the past ten years. Extensive *in vitro* cellular, *in vivo* subcutaneous, and orthotopic animal studies have demonstrated promising results for clinical trials. This review has highlighted three major directions in which emerging nanotheranostic strategies involving multifunctional nanomaterials are focused. Each of these directions has been well explored, but more fundamental studies need to be done to address future challenges and research gaps. Vital issues in developing next-generation nanomaterials for clinical translation include the following: i) use of tumor models that closely resemble patient-derived tumors, (ii) long-term study of toxicity effects of nanomaterials on organs and tissues from preclinical animal models, iii) long-term assessment of therapeutic efficacy for cancer remission, and iv) evaluation of metabolites after nanomaterial degradation and their effects on tissue and organ functions. An integrated multidisciplinary and holistic examination of new findings and techniques on rationally designed nanomaterials for cancer nanotheranostics will substantially impact clinical trials and beyond.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] E.K. Lim, T. Kim, S. Paik, S. Haam, Y.M. Huh, K. Lee, Nanomaterials for theranostics: recent advances and future challenges, Chem Rev 115 (2015) 327–394.
[2] M. Izci, C. Maksoudian, B.B. Manshian, S.J. Soenen, The Use of Alternative Strategies for Enhanced Nanoparticle Delivery to Solid Tumors, Chem Rev 121 (2021) 1746–1803.
[3] Y. Chen, L. Liu, Modern methods for delivery of drugs across the blood-brain barrier, Adv Drug Deliv Rev 64 (2012) 640–665.
[4] H. Chen, H. Jia, H.P. Tham, Q. Qu, P. Xing, J. Zhao, S.Z.F. Phua, G. Chen, Y. Zhao, Theranostic Prodrug Vesicles for Imaging Guided Codelivery of Camptothecin and siRNA in Synergetic Cancer Therapy, ACS Appl Mater Interfaces 9 (2017) 23536–23543.
[5] C. Roma-Rodrigues, I. Pombo, L. Raposo, P. Pedrosa, A.R. Fernandes, P.V. Baptista, Nanotheranostics Targeting the Tumor Microenvironment, Front Bioeng Biotechnol 7 (2019) 197.
[6] A. Parodi, M. Rudzinska, S. Leporatti, Y. Anissimov, A.A. Zamyatnin Jr., Smart Nanotheranostics Responsive to Pathological Stimuli, Front Bioeng Biotechnol 8 (2020) 503.
[7] X.Y. Wong, A. Sena-Torralba, R. Alvarez-Diduk, K. Muthoosamy, A. Merkoci, Nanomaterials for Nanotheranostics: Tuning Their Properties According to Disease Needs, ACS Nano 14 (2020) 2585–2627.
[8] J. Xu, R. Shi, G. Chen, S. Dong, P. Yang, Z. Zhang, N. Niu, S. Gai, F. He, Y. Fu, J. Lin, All-in-One Theranostic Nanomedicine with Ultrabright Second Near-Infrared Emission for Tumor-Modulated Bioimaging and Chemodynamic/Photodynamic Therapy, ACS Nano 14 (2020) 9613–9625.
[9] P. Mi, Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics, Theranostics 10 (2020) 4557–4588.
[10] G. Yu, B.C. Yung, Z. Zhou, Z. Mao, X. Chen, Artificial Molecular Machines in Nanotheranostics, ACS Nano 12 (2018) 7–12.
[11] Z. Fan, L. Sun, Y. Huang, Y. Wang, M. Zhang, Bioinspired fluorescent dipeptide nanoparticles for targeted cancer cell imaging and real-time monitoring of drug release, Nat Nanotechnol 11 (2016) 388–394.
[12] M. Karimi, A. Ghasemi, P. Sahandi Zangabad, R. Rahighi, S.M. Moosavi Basri, H. Mirshekari, M. Amiri, Z. Shafaei Pishabad, A. Aslani, M. Bozorgomid, D. Ghosh, A. Beyzavi, A. Vaseghi, A.R. Aref, L. Haghani, S. Bahrami, M.R. Hamblin, Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems, Chem Soc Rev 45 (2016) 1457–1501.
[13] R.J. DeBerardinis, N.S. Chandel, We need to talk about the Warburg effect, Nat Metab 2 (2020) 127–129.
[14] J. Wang, S.R. MacEwan, A. Chilkoti, Quantitative Mapping of the Spatial Distribution of Nanoparticles in Endo-Lysosomes by Local pH, Nano Lett 17 (2017) 1226–1232.
[15] J. Zhu, G. Wang, C.S. Alves, H. Tomas, Z. Xiong, M. Shen, J. Rodrigues, X. Shi, Multifunctional Dendrimer-Entrapped Gold Nanoparticles Conjugated with Doxorubicin for pH-Responsive Drug Delivery and Targeted Computed Tomography Imaging, Langmuir 34 (2018) 12428–12435.
[16] A.K.P. Jangid, D.; Jain, P.; Rompicharla, S.V.K.; Ramesan, S.; Kulhari, H., A nanoscale, biocompatible and amphiphilic prodrug of cabazitaxel with improved anticancer efficacy against 3D spheroids of prostate cancer cells, Materials Advances, 1 (2020) 738-748.
[17] S.L. Gawali, K.C. Barick, N.G. Shetake, V. Rajan, B.N. Pandey, N.N. Kumar, K.I. Priyadarsini, P.A. Hassan, pH-Labile Magnetic Nanocarriers for Intracellular Drug Delivery to Tumor Cells, ACS Omega 4 (2019) 11728–11736.

[18] M.L.P.D. Vaidallon, A.M.; Quek, A.; Mcliesh, H.; Kaslin, J.; Tabor, R.F.; Bishop, A.I.; Teo, B.M. , Gas-Generating, pH-Responsive Calcium Carbonate Hybrid Particles with Biomimetic Coating for Contrast-Enhanced Ultrasound Imaging, Particle & Particle Systems Characterization, 37 (2020) 1900471.
[19] Z. Dong, L. Feng, W. Zhu, X. Sun, M. Gao, H. Zhao, Y. Chao, Z. Liu, CaCO3 nanoparticles as an ultra-sensitive tumor-pH-responsive nanoplatform enabling real-time drug release monitoring and cancer combination therapy, Biomaterials 110 (2016) 60–70.
[20] R.S. Wu, J. Lin, Y.M. Xing, Z.L. Dai, L.W. Wang, X.P. Zhang, pH-Sensitive Black Phosphorous-Incorporated Hydrogel as Novel Implant for Cancer Treatment, J Pharm Sci 108 (2019) 2542–2551.
[21] D. Trachootham, J. Alexandre, P. Huang, Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach?, Nat Rev Drug Discov 8 (2009) 579–591
[22] C.Y. Sun, Z. Cao, X.J. Zhang, R. Sun, C.S. Yu, X. Yang, Cascade-amplifying synergistic effects of chemo-photodynamic therapy using ROS-responsive polymeric nanocarriers, Theranostics 8 (2018) 2939–2953.
[23] P. Wu, W. Dong, X. Guo, X. Qiao, S. Guo, L. Zhang, M. Wan, Y. Zong, ROS-Responsive Blended Nanoparticles: Cascade-Amplifying Synergistic Effects of Sonochemotherapy with On-demand Boosted Drug Release During SDT Process, Adv Healthc Mater 8 (2019) e1900720.
[24] Z. Yang, Y. Dai, C. Yin, Q. Fan, W. Zhang, J. Song, G. Yu, W. Tang, W. Fan, B.C. Yung, J. Li, X. Li, X. Li, Y. Tang, W. Huang, J. Song, X. Chen, Activatable Semiconducting Theranostics: Simultaneous Generation and Ratiometric Photoacoustic Imaging of Reactive Oxygen Species In Vivo, Adv Mater 30 (2018) e1707509.
[25] M.A. Khan, H. Zubair, S. Anand, S.K. Srivastava, S. Singh, A.P. Singh, Dysregulation of metabolic enzymes in tumor and stromal cells: Role in oncogenesis and therapeutic opportunities, Cancer Lett 473 (2020) 176–185.
[26] H.A. Coller, Is cancer a metabolic disease?, Am J Pathol 184 (2014) 4–17
[27] Q. Ren, Z. Liang, X. Jiang, P. Gong, L. Zhou, Z. Sun, J. Xiang, Z. Xu, X. Peng, S. Li, W. Li, L. Cai, J. Tang, Enzyme and pH dual-responsive hyaluronic acid nanoparticles mediated combination of photodynamic therapy and chemotherapy, Int J Biol Macromol 130 (2019) 845–852.
[28] K. Kessenbrock, V. Plaks, Z. Werb, Matrix metalloproteinases: regulators of the tumor microenvironment, Cell 141 (2010) 52–67.
[29] M. Egeblad, Z. Werb, New functions for the matrix metalloproteinases in cancer progression, Nat Rev Cancer 2 (2002) 161–174.
[30] X. Zhao, C.X. Yang, L.G. Chen, X.P. Yan, Dual-stimuli responsive and reversibly activatable theranostic nanoprobe for precision tumor-targeting and fluorescence-guided photothermal therapy, Nat Commun 8 (2017) 14998.
[31] S.H. van Rijt, D.A. Bolukbas, C. Argyo, S. Datz, M. Lindner, O. Eickelberg, M. Konigshoff, T. Bein, S. Meiners, Protease-mediated release of chemotherapeutics from mesoporous silica nanoparticles to ex vivo human and mouse lung tumors, ACS Nano 9 (2015) 2377–2389.
[32] X. Ai, C.J. Ho, J. Aw, A.B. Attia, J. Mu, Y. Wang, X. Wang, Y. Wang, X. Liu, H. Chen, M. Gao, X. Chen, E.K. Yeow, G. Liu, M. Olivo, B. Xing, In vivo covalent cross-linking of photon-converted rare-earth nanostructures for tumour localization and theranostics, Nat Commun 7 (2016) 10432.
[33] G.A. Hong, A.L.; Dai, H. , Near-infrared fluorophores for biomedical imaging, Nature Biomedical Engineering, 1 (2017) 0010.
[34] Z. Wang, Y. Ju, Z. Ali, H. Yin, F. Sheng, J. Lin, B. Wang, Y. Hou, Near-infrared light and tumor microenvironment dual responsive size-switchable nanocapsules for multimodal tumor theranostics, Nat Commun 10 (2019) 4418.
[35] H. Zhu, Y. Fang, Q. Miao, X. Qi, D. Ding, P. Chen, K. Pu, Regulating Near-Infrared Photodynamic Properties of Semiconducting Polymer Nanotheranostics for Optimized Cancer Therapy, ACS Nano 11 (2017) 8998–9009.
[36] Z. Zhang, M.K.G. Jayakumar, X. Zheng, S. Shikha, Y. Zhang, A. Bansal, D.J.J. Poon, P.L. Chu, E.L.L. Yeo, M.L.K. Chua, S.K. Chee, Y. Zhang, Upconversion superballs for programmable photoactivation of therapeutics, Nat Commun 10 (2019) 4586.
[37] H.S. Yan, W.; Sun, X.; Zhao, L.; Wang, J.; Xiong, Z.; Yuan, J.; Zhang, R.; Huang, Q.; Wang, K.; Li, B.; Tian, J.; Kang , F.; Feng, S-S. , "All-in-One" Nanoparticles for Trimodality Imaging-Guided Intracellular Photo-magnetic Hyperthermia Therapy under Intravenous Administration, Advanced Functional Materials, 28 (2018) 1705710.
[38] M.H. Cho, E.J. Lee, M. Son, J.H. Lee, D. Yoo, J.W. Kim, S.W. Park, J.S. Shin, J. Cheon, A magnetic switch for the control of cell death signalling in in vitro and in vivo systems, Nat Mater 11 (2012) 1038–1043.
[39] W. Tang, Z. Yang, S. Wang, Z. Wang, J. Song, G. Yu, W. Fan, Y. Dai, J. Wang, L. Shan, G. Niu, Q. Fan, X. Chen, Organic Semiconducting Photoacoustic Nanodroplets for Laser-Activatable Ultrasound Imaging and Combinational Cancer Therapy, ACS Nano 12 (2018) 2610–2622.
[40] S.M. Son, HS.; You, GD.; Kim, BS.; K, IC., Echogenic nanoparticles for ultrasound technologies: Evolution from diagnostic imaging modality to multimodal theranostic agent, Nano Today, 9 (2014) 525-540.
[41] Y.J. Ho, C.C. Wu, Z.H. Hsieh, C.H. Fan, C.K. Yeh, Thermal-sensitive acoustic droplets for dual-mode ultrasound imaging and drug delivery, J Control Release 291 (2018) 26–36.
[42] E. Huynh, B.Y. Leung, B.L. Helfield, M. Shakiba, J.A. Gandier, C.S. Jin, E.R. Master, B.C. Wilson, D.E. Goertz, G. Zheng, In situ conversion of porphyrin microbubbles to nanoparticles for multimodality imaging, Nat Nanotechnol 10 (2015) 325–332.
[43] P. Pedrosa, R. Vinhas, A. Fernandes, P.V. Baptista, Gold Nanotheranostics: Proof-of-Concept or Clinical Tool?, Nanomaterials (Basel) 5 (2015) 1853–1879
[44] S. Nardecchia, P. Sanchez-Moreno, J. Vicente, J.A. Marchal, H. Boulaiz, Clinical Trials of Thermosensitive Nanomaterials: An Overview, Nanomaterials (Basel) 9 (2019).
[45] R. Fisher, L. Pusztai, C. Swanton, Cancer heterogeneity: implications for targeted therapeutics, Br J Cancer 108 (2013) 479–485.
[46] M.Z. Jin, W.L. Jin, The updated landscape of tumor microenvironment and drug repurposing, Signal Transduct Target Ther 5 (2020) 166.
[47] D. Bonnet, J.E. Dick, Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell, Nature Medicine 3 (1997) 730–737.
[48] R. Misra, S. Kandoi, S. Varadaraj, S. Vijayalakshmi, A. Nanda, R.S. Verma, Nanotheranostics: A tactic for cancer stem cells prognosis and management, Journal of Drug Delivery Science and Technology 55 (2020) 101457.
[49] Y. Geng, J.J. Amante, H.L. Goel, X. Zhang, M.R. Walker, D.C. Luther, A.M. Mercurio, V.M. Rotello, Differentiation of Cancer Stem Cells through Nanoparticle Surface Engineering, ACS Nano 14 (2020) 15276–15285.
[50] S. Shen, X. Xu, S. Lin, Y. Zhang, H. Liu, C. Zhang, R. Mo, A nanotherapeutic strategy to overcome chemotherapeutic resistance of cancer stem-like cells, Nature Nanotechnology 16 (2021) 104–113.
[51] R. Sun, S. Shen, Y.-J. Zhang, C.-F. Xu, Z.-T. Cao, L.-P. Wen, J. Wang, Nanoparticle-facilitated autophagy inhibition promotes the efficacy of chemotherapeutics against breast cancer stem cells, Biomaterials 103 (2016) 44–55.
[52] X. Lin, W. Chen, F. Wei, B.P. Zhou, M.-C. Hung, X. Xie, Nanoparticle Delivery of miR-34a Eradicates Long-term-cultured Breast Cancer Stem Cells via Targeting C22ORF28 Directly, Theranostics 7 (2017) 4805–4824.
[53] H.J. Paholak, N.O. Stevers, H. Chen, J.P. Burnett, M. He, H. Korkaya, S.P. McDermott, Y. Deol, S.G. Clouthier, T. Luther, Q. Li, M.S. Wicha, D. Sun, Elimination of epithelial-like and mesenchymal-like breast cancer stem cells to inhibit metastasis following nanoparticle-mediated photothermal therapy, Biomaterials 104 (2016) 145–157.
[54] Y. Yu, X. Yang, S. Reghu, S.C. Kaul, R. Wadhwa, E. Miyako, Photothermogenetic inhibition of cancer stemness by near-infrared-light-activatable nanocomplexes, Nature Communications 11 (2020) 4117.
[55] V.P. Chauhan, T. Stylianopoulos, J.D. Martin, Z. Popovic, O. Chen, W.S. Kamoun, M.G. Bawendi, D. Fukumura, R.K. Jain, Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner, Nat Nanotechnol 7 (2012) 383–388.
[56] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nature biotechnology 33 (2015) 941–951.
[57] S. Ye, F. Wang, Z. Fan, Q. Zhu, H. Tian, Y. Zhang, B. Jiang, Z. Hou, Y. Li, G. Su, Light/pH-Triggered Biomimetic Red Blood Cell Membranes Camouflaged Small Molecular Drug Assemblies for Imaging-Guided Combinational Chemo-Photothermal Therapy, Acs Applied Materials & Interfaces 11 (2019) 15262–15275.
[58] L. He, T. Nie, X. Xia, T. Liu, Y. Huang, X. Wang, T. Chen, Designing Bioinspired 2D MoSe2 Nanosheet for Efficient Photothermal-Triggered Cancer Immunotherapy with Reprogramming Tumor-Associated Macrophages, Advanced Functional Materials 29 (2019).
[59] Y. Li, J. Lin, P. Wang, Q. Luo, H. Lin, Y. Zhang, Z. Hou, J. Liu, X. Liu, Tumor Microenvironment Responsive Shape Reversal Self-Targeting Virus-Inspired Nanodrug for Imaging-Guided Near-Infrared-II Photothermal Chemotherapy, Acs Nano 13 (2019) 12912–12928.
[60] H. Wang, Q. Lin, L. Yin, Y. Yang, Y. Qiu, C. Lu, H. Yang, Biomimetic Design of Hollow Flower-Like g-C3N4@PDA Organic Framework Nanospheres for Realizing an Efficient Photoreactivity, Small 15 (2019).
[61] G.T. Kozma, T. Shimizu, T. Ishida, J. Szebeni, Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals, Advanced Drug Delivery Reviews 154–155 (2020) 163–175.
[62] P. Zhang, F. Sun, S. Liu, S. Jiang, Anti-PEG antibodies in the clinic: Current issues and beyond PEGylation, Journal of Controlled Release 244 (2016) 184–193.
[63] X. Yao, S. Ma, S. Peng, G. Zhou, R. Xie, Q. Jiang, S. Guo, Q. He, W. Yang, Zwitterionic Polymer Coating of Sulfur Dioxide-Releasing Nanosystem Augments Tumor Accumulation and Treatment Efficacy, Advanced Healthcare Materials 9 (2020) 1901582.
[64] D. She, H. Huang, J. Li, S. Peng, H. Wang, X. Yu, Hypoxia-degradable zwitterionic phosphorylcholine drug nanogel for enhanced drug delivery to glioblastoma, Chemical Engineering Journal 127359 (2020).
[65] S. Peng, B. Ouyang, Y. Men, Y. Du, Y. Cao, R. Xie, Z. Pang, S. Shen, W. Yang, Biodegradable zwitterionic polymer membrane coating endowing nanoparticles with ultra-long circulation and enhanced tumor photothermal therapy, Biomaterials 231 (2020) 119680.
[66] B. Li, P. Jain, J. Ma, J.K. Smith, Z. Yuan, H.-C. Hung, Y. He, X. Lin, K. Wu, J. Pfaendtner, S. Jiang, Trimethylamine N-oxide–derived zwitterionic polymers: A new class of ultralow fouling bioinspired materials, Science, Advances 5 (2019) eaaw9562.
[67] E. van Andel, S.C. Lange, S.P. Pujari, E.J. Tijhaar, M.M.J. Smulders, H.F.J. Savelkoul, H. Zuilhof, Systematic Comparison of Zwitterionic and Non-Zwitterionic Antifouling Polymer Brushes on a Bead-Based Platform, Langmuir 35 (2019) 1181–1191.

[68] J.M. Spanjers, B. Stadler, Cell Membrane Coated Particles, Advanced Biosystems 4 (2020).
[69] S. Toyokuni, Y. Ikehara, F. Kikkawa, M. Hori (Eds.), Chapter 4 - Regulation of Cell Membrane Transport by Plasma, Plasma Medical Science, Academic Press, 2019, pp. 173–247.
[70] M. Schmick, Philippe I.H. Bastiaens, The Interdependence of Membrane Shape and Cellular Signal Processing, Cell 156 (2014) 1132–1138.
[71] R.H. Fang, A.V. Kroll, W. Gao, L. Zhang, Cell Membrane Coating Nanotechnology, Advanced Materials 30 (2018) 1706759.
[72] H.L. Anderson, I.E. Brodsky, N.S. Mangalmurti, The Evolving Erythrocyte: Red Blood Cells as Modulators of Innate Immunity, The Journal of Immunology 201 (2018) 1343–1351.
[73] R. Sender, S. Fuchs, R. Milo, Revised Estimates for the Number of Human and Bacteria Cells in the Body, PLOS Biology 14 (2016) e1002533.
[74] L. Koleva, E. Bovt, F. Ataullakhanov, E. Sinauridze, Erythrocytes as Carriers: From Drug Delivery to Biosensors, Pharmaceutics 12 (2020) 276.
[75] C.-M.J. Hu, L. Zhang, S. Aryal, C. Cheung, R.H. Fang, L. Zhang, Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform, Proceedings of the National Academy of Sciences 108 (2011) 10980–10985.
[76] C.H. Villa, A.C. Anselmo, S. Mitragotri, V. Muzykantov, Red blood cells: Supercarriers for drugs, biologicals, and nanoparticles and inspiration for advanced delivery systems, Advanced Drug Delivery Reviews 106 (2016) 88–103.
[77] Z. Chai, D. Ran, L. Lu, C. Zhan, H. Ruan, X. Hu, C. Xie, K. Jiang, J. Li, J. Zhou, J. Wang, Y. Zhang, R.H. Fang, L. Zhang, W. Lu, Ligand-Modified Cell Membrane Enables the Targeted Delivery of Drug Nanocrystals to Glioma, Acs Nano 13 (2019) 5591–5601.
[78] S.-Y. Sung, Y.-L. Su, W. Cheng, P.-F. Hu, C.-S. Chiang, W.-T. Chen, S.-H. Hu, Graphene Quantum Dots-Mediated Theranostic Penetrative Delivery of Drug and Photolytics in Deep Tumors by Targeted Biomimetic Nanosponges, Nano Letters 19 (2019) 69–81.
[79] W. Jiang, Z. Zhang, Q. Wang, J. Dou, Y. Zhao, Y. Ma, H. Liu, H. Xu, Y. Wang, Tumor Reoxygenation and Blood Perfusion Enhanced Photodynamic Therapy using Ultrathin Graphdiyne Oxide Nanosheets, Nano Letters 19 (2019) 4060–4067.
[80] E.M. Reuven, S.L. Ben-Arye, H. Yu, R. Duchi, A. Perota, S. Conchon, S.B. Abramovitch, J.-P. Soulillou, C. Galli, X. Chen, V. Padler-Karavani, Biomimetic Glyconanoparticle Vaccine for Cancer Immunotherapy, Acs Nano 13 (2019) 2936–2947.
[81] S. Mezouar, C. Frère, R. Darbousset, D. Mege, L. Crescence, F. Dignat-George, L. Panicot-Dubois, C. Dubois, Role of platelets in cancer and cancer-associated thrombosis: Experimental and clinical evidences, Thrombosis Research 139 (2016) 65–76.
[82] Z. Li, S. Hu, K. Cheng, Platelets and their biomimetics for regenerative medicine and cancer therapies, Journal of Materials Chemistry B 6 (2018) 7354–7365.
[83] S. Kumar, J.-A. Han, I.J. Michael, D. Ki, V. Sunkara, J. Park, S. Gautam, H.K. Ha, L. Zhang, Y.-K. Cho, Human Platelet Membrane Functionalized Microchips with Plasmonic Codes for Cancer Detection, Advanced Functional Materials 29 (2019).
[84] L. Rao, L.-L. Bu, L. Ma, W. Wang, H. Liu, D. Wan, J.-F. Liu, A. Li, S.-S. Guo, L. Zhang, W.-F. Zhang, X.-Z. Zhao, Z.-J. Sun, W. Liu, Platelet-Facilitated Photothermal Therapy of Head and Neck Squamous Cell Carcinoma, Angewandte Chemie International Edition 57 (2018) 986–991.
[85] H. Wang, D.H. Bremner, K. Wu, X. Gong, Q. Fan, X. Xie, H. Zhang, J. Wu, L.-M. Zhu, Platelet membrane biomimetic bufalin-loaded hollow MnO2 nanoparticles for MRI-guided chemo-chemodynamic combined therapy of cancer, Chemical Engineering Journal 382 (2020).
[86] J.L. Betker, D. Jones, C.R. Childs, K.M. Helm, K. Terrell, M.A. Nagel, T.J. Anchordoquy, Nanoparticle uptake by circulating leukocytes: A major barrier to tumor delivery, Journal of Controlled Release 286 (2018) 85–93.
[87] X. Zhou, B. Luo, K. Kang, Y. Zhang, P. Jiang, F. Lan, Q. Yi, Y. Wu, Leukocyte-Repelling Biomimetic Immunomagnetic Nanoplatform for High-Performance Circulating Tumor Cells Isolation, Small 15 (2019).
[88] L. Wu, H. Ding, X. Qu, X. Shi, J. Yang, M. Huang, J. Zhang, H. Zhang, J. Song, L. Zhu, Y. Song, Y. Ma, C. Yang, Fluidic Multivalent Membrane Nanointerface Enables Synergetic Enrichment of Circulating Tumor Cells with High Efficiency and Viability, Journal of the American Chemical Society 142 (2020) 4800–4806.
[89] F. Zhang, F. Li, G.-H. Lu, W. Nie, L. Zhang, Y. Lv, W. Bao, X. Gao, W. Wei, K. Pu, H.-Y. Xie, Engineering Magnetosomes for Ferroptosis/Immunomodulation Synergism in Cancer, Acs Nano 13 (2019) 5662–5673.
[90] J.-J. Zhang, Y. Lin, H. Zhou, H. He, J.-J. Ma, M.-Y. Luo, Z.-L. Zhang, D.-W. Pang, Cell Membrane-Camouflaged NIR II Fluorescent Ag2Te Quantum Dots-Based Nanobioprobes for Enhanced In Vivo Homotypic Tumor Imaging, Advanced Healthcare Materials 8 (2019).
[91] C. Liu, W. Zhang, Y. Li, J. Chang, F. Tian, F. Zhao, Y. Ma, J. Sun, Microfluidic Sonication To Assemble Exosome Membrane-Coated Nanoparticles for Immune Evasion-Mediated Targeting, Nano Letters 19 (2019) 7836–7844.
[92] L. Zhang, X. Zhang, G. Lu, F. Li, W. Bao, C. Song, W. Wei, G. Ma, Cell Membrane Camouflaged Hydrophobic Drug Nanoflake Sandwiched with Photosensitizer for Orchestration of Chemo-Photothermal Combination Therapy, Small 15 (2019).
[93] W. Xie, W.-W. Deng, M. Zan, L. Rao, G.-T. Yu, D.-M. Zhu, W.-T. Wu, B. Chen, L.-W. Ji, L. Chen, K. Liu, S.-S. Guo, H.-M. Huang, W.-F. Zhang, X. Zhao, Y. Yuan, W. Dong, Z.-J. Sun, W. Liu, Cancer Cell Membrane Camouflaged Nanoparticles to Realize Starvation Therapy Together with Checkpoint Blockades for Enhancing Cancer Therapy, Acs Nano 13 (2019) 2849–2857.
[94] H. Min, J. Wang, Y. Qi, Y. Zhang, X. Han, Y. Xu, J. Xu, Y. Li, L. Chen, K. Cheng, G. Liu, N. Yang, Y. Li, G. Nie, Biomimetic Metal-Organic Framework Nanoparticles for Cooperative Combination of Antiangiogenesis and Photodynamic Therapy for Enhanced Efficacy, Advanced Materials 31 (2019).
[95] Q. Jiang, Y. Liu, R. Guo, X. Yao, S. Sung, Z. Pang, W. Yang, Erythrocyte-cancer hybrid membrane-camouflaged melanin nanoparticles for enhancing photothermal therapy efficacy in tumors, Biomaterials 192 (2019) 292–308.
[96] L.-L. Bu, L. Rao, G.-T. Yu, L. Chen, W.-W. Deng, J.-F. Liu, H. Wu, Q.-F. Meng, S.-S. Guo, X.-Z. Zhao, W.-F. Zhang, G. Chen, Z. Gu, W. Liu, Z.-J. Sun, Cancer Stem Cell-Platelet Hybrid Membrane-Coated Magnetic Nanoparticles for Enhanced Photothermal Therapy of Head and Neck Squamous Cell Carcinoma, Advanced Functional Materials 29 (2019).
[97] S. Rayamajhi, N. Tuyen Duong Thanh, R. Marasini, S. Aryal, Macrophage-derived exosome-mimetic hybrid vesicles for tumor targeted drug delivery, Acta Biomaterialia, 94 (2019) 482-494.
[98] J. Dai, Y. Su, S. Zhong, L. Cong, B. Liu, J. Yang, Y. Tao, Z. He, C. Chen, Y. Jiang, Exosomes: key players in cancer and potential therapeutic strategy, Signal Transduction and Targeted Therapy 5 (2020) 145.
[99] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (2020) eaau6977.
[100] T. Yong, X. Zhang, N. Bie, H. Zhang, X. Zhang, F. Li, A. Hakeem, J. Hu, L. Gan, H. A. Santos, X. Yang, Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy, Nature Communications 10 (2019).
[101] X. Suo, B.N. Eldridge, H. Zhang, C. Mao, Y. Min, Y. Sun, R. Singh, X. Ming, P-Glycoprotein-Targeted Photothermal Therapy of Drug-Resistant Cancer Cells Using Antibody-Conjugated Carbon Nanotubes, ACS Applied Materials & Interfaces 10 (2018) 33464–33473.
[102] M. Li, S. Li, H. Zhou, X. Tang, Y. Wu, W. Jiang, Z. Tian, X. Zhou, X. Yang, Y. Wang, Chemotaxis-driven delivery of nano-pathogenoids for complete eradication of tumors post-phototherapy, Nature Communications 11 (2020).
[103] Y. Xiong, F. Sun, P. Liu, Z. Yang, J. Cao, H. Liu, P. Liu, J. Hu, Z. Xu, S. Yang, A biomimetic one-pot synthesis of versatile Bi2S3/FeS2 theranostic nanohybrids for tumor-targeted photothermal therapy guided by CT/MR dual-modal imaging, Chemical Engineering Journal 378 (2019).
[104] M. Wu, X. Liu, H. Bai, L. Lai, Q. Chen, G. Huang, B. Liu, G. Tang, Surface-Layer Protein-Enhanced Immunotherapy Based on Cell Membrane-Coated Nanoparticles for the Effective Inhibition of Tumor Growth and Metastasis, Acs Applied Materials & Interfaces 11 (2019) 9850–9859.
[105] Y. Jia, X. Wang, D. Hu, P. Wang, Q. Liu, X. Zhang, J. Jiang, X. Liu, Z. Sheng, B. Liu, H. Zheng, Phototheranostics: Active Targeting of Orthotopic Glioma Using Biomimetic Proteolipid Nanoparticles, Acs Nano 13 (2019) 386–398.
[106] F. Gao, J. Wu, H. Gao, X. Hu, L. Liu, A.C. Midgley, Q. Liu, Z. Sun, Y. Liu, D. Ding, Y. Wang, D. Kong, X. Huang, Hypoxia-tropic nanozymes as oxygen generators for tumor-favoring theranostics, Biomaterials 230 (2020).
[107] F. Palombarini, E. Di Fabio, A. Boffi, A. Macone, A. Bonamore, Ferritin Nanocages for Protein Delivery to Tumor Cells, Molecules 25 (2020) 825.
[108] P.X. Medina Rangel, E. Moroni, F. Merlier, L.A. Gheber, R. Vago, B. Tse Sum Bui, K. Haupt, Chemical Antibody Mimics Inhibit Cadherin-Mediated Cell-Cell Adhesion: A Promising Strategy for Cancer Therapy, Angewandte Chemie International Edition 59 (2020) 2816–2822.
[109] K. Zhang, P.-P. Yang, P.-P. He, S.-F. Wen, X.-R. Zou, Y. Fan, Z.-M. Chen, H. Cao, Z. Yang, K. Yue, X. Zhang, H. Zhang, L. Wang, H. Wang, Peptide-Based Nanoparticles Mimic Fibrillogenesis of Laminin in Tumor Vessels for Precise Embolization, Acs Nano 14 (2020) 7170–7180.
[110] A.M. Bossi, Plastic antibodies for cancer therapy?, Nature Chemistry 12 (2020) 111–112
[111] F. Chen, K. Ma, B. Madajewski, L. Zhuang, L. Zhang, K. Rickert, M. Marelli, B. Yoo, M.Z. Turker, M. Overholtzer, T.P. Quinn, M. Gonen, P. Zanzonico, A. Tuesca, M.A. Bowen, L. Norton, J.A. Subramony, U. Wiesner, M.S. Bradbury, Ultrasmall targeted nanoparticles with engineered antibody fragments for imaging detection of HER2-overexpressing breast cancer, Nature Communications 9 (2018) 4141.
[112] D. Wang, T. Wang, H. Yu, B. Feng, L. Zhou, F. Zhou, B. Hou, H. Zhang, M. Luo, Y. Li, Engineering nanoparticles to locally activate T cells in the tumor microenvironment, Science Immunology 4 (2019) eaau6584.
[113] P. Khosravi Shahi, I. Fernandez Pineda, Tumoral angiogenesis: review of the literature, Cancer Invest 26 (2008) 104–108.
[114] D. Hanahan, J. Folkman, Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis, Cell 86 (1996) 353–364.
[115] H.S. El-Sawy, A.M. Al-Abd, T.A. Ahmed, K.M. El-Say, V.P. Torchilin, Stimuli-Responsive Nano-Architecture Drug-Delivery Systems to Solid Tumor Micromilieu: Past, Present, and Future Perspectives, ACS Nano 12 (2018) 10636–10664.
[116] G. Helmlinger, P.A. Netti, H.C. Lichtenbeld, R.J. Melder, R.K. Jain, Solid stress inhibits the growth of multicellular tumor spheroids, Nat Biotechnol 15 (1997) 778–783.
[117] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nature Reviews Materials 1 (2016) 16014.

[118] B. Zhang, T. Jiang, Y. Tuo, K. Jin, Z. Luo, W. Shi, H. Mei, Y. Hu, Z. Pang, X. Jiang, Captopril improves tumor nanomedicine delivery by increasing tumor blood perfusion and enlarging endothelial gaps in tumor blood vessels, Cancer Lett 410 (2017) 12–19.
[119] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat Rev Clin Oncol 7 (2010) 653–664.
[120] R.K. Jain, Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy, Science 307 (2005) 58–62.
[121] T.T. Batchelor, E.R. Gerstner, K.E. Emblem, D.G. Duda, J. Kalpathy-Cramer, M. Snuderl, M. Ancukiewicz, P. Polaskova, M.C. Pinho, D. Jennings, S.R. Plotkin, A. S. Chi, A.F. Eichler, J. Dietrich, F.H. Hochberg, C. Lu-Emerson, A.J. Iafrate, S.P. Ivy, B.R. Rosen, J.S. Loeffler, P.Y. Wen, A.G. Sorensen, R.K. Jain, Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation, Proc Natl Acad Sci U S A 110 (2013) 19059–19064.
[122] R.K. Jain, D.G. Duda, J.W. Clark, J.S. Loeffler, Lessons from phase III clinical trials on anti-VEGF therapy for cancer, Nat Clin Pract Oncol 3 (2006) 24–40.
[123] C.J. Thebault, G. Ramniceanu, S. Boumati, A. Michel, J. Seguin, B. Larrat, N. Mignet, C. Menager, B.T. Doan, Theranostic MRI liposomes for magnetic targeting and ultrasound triggered release of the antivascular CA4P, J Control Release 322 (2020) 137–148.
[124] C. Hahn, M.A. Schwartz, Mechanotransduction in vascular physiology and atherogenesis, Nat Rev Mol Cell Biol 10 (2009) 53–62.
[125] G. Nagaiah, S.C. Remick, Combretastatin A4 phosphate: a novel vascular disrupting agent, Future Oncol 6 (2010) 1219–1228.
[126] A.B. Satterlee, J.D. Rojas, P.A. Dayton, L. Huang, Enhancing Nanoparticle Accumulation and Retention in Desmoplastic Tumors via Vascular Disruption for Internal Radiation Therapy, Theranostics 7 (2017) 253–269.
[127] T. Ojha, V. Pathak, Y. Shi, W.E. Hennink, C.T.W. Moonen, G. Storm, F. Kiessling, T. Lammers, Pharmacological and physical vessel modulation strategies to improve EPR-mediated drug targeting to tumors, Adv Drug Deliv Rev 119 (2017) 44–60.
[128] I. Sato, M. Umemura, K. Mitsudo, H. Fukumura, J.H. Kim, Y. Hoshino, H. Nakashima, M. Kioi, R. Nakakaji, M. Sato, T. Fujita, U. Yokoyama, S. Okumura, H. Oshiro, H. Eguchi, I. Tohnai, Y. Ishikawa, Simultaneous hyperthermia-chemotherapy with controlled drug delivery using single-drug nanoparticles, Sci Rep 6 (2016) 24629.
[129] T. Lammers, V. Subr, P. Peschke, R. Kuhnlein, W.E. Hennink, K. Ulbrich, F. Kiessling, M. Heilmann, J. Debus, P.E. Huber, G. Storm, Image-guided and passively tumour-targeted polymeric nanomedicines for radiochemotherapy, Br J Cancer 99 (2008) 900–910.
[130] H.C. Schwickert, M. Stiskal, T.P. Roberts, C.F. van Dijke, J. Mann, A. Muhler, D. M. Shames, F. Demsar, A. Disston, R.C. Brasch, Contrast-enhanced MR imaging assessment of tumor capillary permeability: effect of irradiation on delivery of chemotherapy, Radiology 198 (1996) 893–898.
[131] G. Erel-Akbaba, L.A. Carvalho, T. Tian, M. Zinter, H. Akbaba, P.J. Obeid, E.A. Chiocca, R. Weissleder, A.G. Kantarci, B.A. Tannous, Radiation-Induced Targeted Nanoparticle-Based Gene Delivery for Brain Tumor Therapy, ACS Nano 13 (2019) 4028–4040.
[132] B. Theek, M. Baues, T. Ojha, D. Mockel, S.K. Veettil, J. Steitz, L. van Bloois, G. Storm, F. Kiessling, T. Lammers, Sonoporation enhances liposome accumulation and penetration in tumors with low EPR, J Control Release 231 (2016) 77–85.
[133] I. Lentacker, I. De Cock, R. Deckers, S.C. De Smedt, C.T. Moonen, Understanding ultrasound induced sonoporation: definitions and underlying mechanisms, Adv Drug Deliv Rev 72 (2014) 49–64.
[134] Y. Jang, D. Kim, H. Lee, H. Jang, S. Park, G.E. Kim, H.J. Lee, H.J. Kim, H. Kim, Development of an ultrasound triggered nanomedicine-microbubble complex for chemo-photodynamic-gene therapy, Nanomedicine 27 (2020) 102194.
[135] S. Sindhwani, A.M. Syed, J. Ngai, B.R. Kingston, L. Maiorino, J. Rothschild, P. MacMillan, Y. Zhang, N.U. Rajesh, T. Hoang, J.L.Y. Wu, S. Wilhelm, A. Zilman, S. Gadde, A. Sulaiman, B. Ouyang, Z. Lin, L. Wang, M. Egeblad, W.C.W. Chan, The entry of nanoparticles into solid tumours, Nat Mater 19 (2020) 566–575.
[136] Z. Jiang, J. Guan, J. Qian, C. Zhan, Peptide ligand-mediated targeted drug delivery of nanomedicines, Biomater Sci 7 (2019) 461–471.
[137] Y. Luo, H. Yang, Y.F. Zhou, B. Hu, Dual and multi-targeted nanoparticles for site-specific brain drug delivery, J Control Release 317 (2020) 195–215.
[138] R.A. Burrell, N. McGranahan, J. Bartek, C. Swanton, The causes and consequences of genetic heterogeneity in cancer evolution, Nature 501 (2013) 338–345.
[139] Y. Liu, W. Lu, Recent advances in brain tumor-targeted nano-drug delivery systems, Expert Opin Drug Deliv 9 (2012) 671–686.
[140] Z. Pang, H. Gao, Y. Yu, J. Chen, L. Guo, J. Ren, Z. Wen, J. Su, X. Jiang, Brain delivery and cellular internalization mechanisms for transferrin conjugated biodegradable polymersomes, Int J Pharm 415 (2011) 284–292.
[141] B. Zhang, S. Shen, Z. Liao, W. Shi, Y. Wang, J. Zhao, Y. Hu, J. Yang, J. Chen, H. Mei, Y. Hu, Z. Pang, X. Jiang, Targeting fibronectins of glioma extracellular matrix by CLT1 peptide-conjugated nanoparticles, Biomaterials 35 (2014) 4088–4098.
[142] H. Gao, J. Qian, S. Cao, Z. Yang, Z. Pang, S. Pan, L. Fan, Z. Xi, X. Jiang, Q. Zhang, Precise glioma targeting of and penetration by aptamer and peptide dual-functioned nanoparticles, Biomaterials 33 (2012) 5115–5123.
[143] C. Chen, Z. Duan, Y. Yuan, R. Li, L. Pang, J. Liang, X. Xu, J. Wang, Peptide-22 and Cyclic RGD Functionalized Liposomes for Glioma Targeting Drug Delivery Overcoming BBB and BBTB, ACS Appl Mater Interfaces 9 (2017) 5864–5873.
[144] E. Doolittle, P.M. Peiris, G. Doron, A. Goldberg, S. Tucci, S. Rao, S. Shah, M. Sylvestre, P. Govender, O. Turan, Z. Lee, W.P. Schiemann, E. Karathanasis, Spatiotemporal Targeting of a Dual-Ligand Nanoparticle to Cancer Metastasis, ACS Nano 9 (2015) 8012–8021.
[145] J. Tang, C.B. Howard, S.M. Mahler, K.J. Thurecht, L. Huang, Z.P. Xu, Enhanced delivery of siRNA to triple negative breast cancer cells in vitro and in vivo through functionalizing lipid-coated calcium phosphate nanoparticles with dual target ligands, Nanoscale 10 (2018) 4258–4266.
[146] P.M. Peiris, F. He, G. Covarrubias, S. Raghunathan, O. Turan, M. Lorkowski, B. Gnanasambandam, C. Wu, W.P. Schiemann, E. Karathanasis, Precise targeting of cancer metastasis using multi-ligand nanoparticles incorporating four different ligands, Nanoscale 10 (2018) 6861–6871.
[147] R.M. Levine, E. Kokkoli, Dual-ligand alpha5beta1 and alpha6beta4 integrin targeting enhances gene delivery and selectivity to cancer cells, J Control Release 251 (2017) 24–36.
[148] Q.S. Xia, H.M. Ding, Y.Q. Ma, Can dual-ligand targeting enhance cellular uptake of nanoparticles?, Nanoscale 9 (2017) 8982–8989
[149] M. Colombo, L. Fiandra, G. Alessio, S. Mazzucchelli, M. Nebuloni, C. De Palma, K. Kantner, B. Pelaz, R. Rotem, F. Corsi, W.J. Parak, D. Prosperi, Tumour homing and therapeutic effect of colloidal nanoparticles depend on the number of attached antibodies, Nat Commun 7 (2016) 13818.
[150] L. Cheng, C. Wang, L. Feng, K. Yang, Z. Liu, Functional Nanomaterials for Phototherapies of Cancer, Chemical Reviews 114 (2014) 10869–10939.
[151] D. Jaque, L. Martínez Maestro, B. del Rosal, P. Haro-Gonzalez, A. Benayas, J.L. Plaza, E. Martín Rodríguez, J. García Solé, Nanoparticles for photothermal therapies, Nanoscale 6 (2014) 9494–9530.
[152] S.S. Lucky, K.C. Soo, Y. Zhang, Nanoparticles in Photodynamic Therapy, Chemical Reviews 115 (2015) 1990–2042.
[153] C.S. Foote, DEFINITION OF TYPE I and TYPE II PHOTOSENSITIZED OXIDATION, Photochemistry and Photobiology 54 (1991) 659.
[154] M.S. Baptista, J. Cadet, P. Di Mascio, A.A. Ghogare, A. Greer, M.R. Hamblin, C. Lorente, S.C. Nunez, M.S. Ribeiro, A.H. Thomas, M. Vignoni, T.M. Yoshimura, Type I and Type II Photosensitized Oxidation Reactions: Guidelines and Mechanistic Pathways, Photochemistry and photobiology 93 (2017) 912–919.
[155] T.J. Dougherty, C.J. Gomer, B.W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, Q. Peng, Photodynamic Therapy, JNCI: Journal of the National Cancer Institute 90 (1998) 889–905.
[156] J.R. Melamed, R.S. Edelstein, E.S. Day, Elucidating the Fundamental Mechanisms of Cell Death Triggered by Photothermal Therapy, ACS Nano 9 (2015) 6–11.
[157] R.R. Anderson, J.A. Parrish, Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation, Science 220 (1983) 524.
[158] T. Lister, P. Wright, P. Chappell, Optical properties of human skin, Journal of Biomedical Optics 17 (2012) 090901.
[159] J. Rockwell, R. James ; Goldman, Leon, Research on Human Skin Laser Damage Thresholds, CINCINNATI UNIV OH DEPT OF DERMATOLOGY AND LASER LABS, (1974).
[160] M. DeLisi, M. Schmidt, A. Hoffman, A. Peterson, G. Noojin, A. Shingledecker, A. Boretsky, D. Stolarski, S. Kumru, R. Thomas, Thermal damage thresholds for multiple-pulse porcine skin laser exposures at 1070 nm, Journal of Biomedical Optics 25 (2019) 035001.
[161] L. Sordillo, Y. Pu, S. Pratavieira, Y. Budansky, R. Alfano, Deep optical imaging of tissue using the second and third near-infrared spectral windows, Journal of Biomedical Optics 19 (2014) 056004.
[162] R.R. Anderson, J.A. Parrish, The Optics of Human Skin, Journal of Investigative Dermatology 77 (1981) 13–19.
[163] A.M. Smith, M.C. Mancini, S. Nie, Second window for in vivo imaging, Nature Nanotechnology 4 (2009) 710–711.
[164] A.B. Ormond, H.S. Freeman, Dye Sensitizers for Photodynamic Therapy, Materials 6 (2013) 817–840.
[165] S. Luo, X. Tan, S. Fang, Y. Wang, T. Liu, X. Wang, Y. Yuan, H. Sun, Q. Qi, C. Shi, Mitochondria-Targeted Small-Molecule Fluorophores for Dual Modal Cancer Phototherapy, Advanced Functional Materials 26 (2016) 2826–2835.
[166] D. Pan, P. Liang, X. Zhong, D. Wang, H. Cao, W. Wang, W. He, Z. Yang, X. Dong, Self-Assembled Porphyrin-Based Nanoparticles with Enhanced Near-Infrared Absorbance for Fluorescence Imaging and Cancer Photodynamic Therapy, ACS Applied Bio Materials 2 (2019) 999–1005.
[167] L. Yang, J. Zhou, Z. Wang, H. Li, K. Wang, H. Liu, F. Wu, Biocompatible conjugated porphyrin nanoparticles with photodynamic/photothermal performances in cancer therapy, Dyes and Pigments 182 (2020) 108664.
[168] Y. Liu, N. Song, Z. Li, L. Chen, Z. Xie, Near-infrared nanoparticles based on aza-BDP for photodynamic and photothermal therapy, Dyes and Pigments 160 (2019) 71–78.
[169] N. Song, L. Fu, Y. Liu, Y. Li, L. Chen, X. Wang, S. Liu, Z. Xie, Rational design of BODIPY organic nanoparticles for enhanced photodynamic/photothermal therapy, Dyes and Pigments 162 (2019) 295–302.
[170] J. Li, X. Zhen, Y. Lyu, Y. Jiang, J. Huang, K. Pu, Cell Membrane Coated Semiconducting Polymer Nanoparticles for Enhanced Multimodal Cancer Phototheranostics, ACS Nano 12 (2018) 8520–8530.
[171] J. Li, J. Huang, Y. Lyu, J. Huang, Y. Jiang, C. Xie, K. Pu, Photoactivatable Organic Semiconducting Pro-nanoenzymes, Journal of the American Chemical Society 141 (2019) 4073–4079.
[172] X. Cai, D. Mao, C. Wang, D. Kong, X. Cheng, B. Liu, Multifunctional Liposome: A Bright AIEgen–Lipid Conjugate with Strong Photosensitization, Angewandte Chemie International Edition 57 (2018) 16396–16400.

[173] X. Min, T. Fang, L. Li, C. Li, Z.-P. Zhang, X.-E. Zhang, F. Li, AIE nanodots scaffolded by mini-ferritin protein for cellular imaging and photodynamic therapy, Nanoscale 12 (2020) 2340–2344.
[174] S. Wang, H. Chen, J. Liu, C. Chen, B. Liu, NIR-II Light Activated Photosensitizer with Aggregation-Induced Emission for Precise and Efficient Two-Photon Photodynamic Cancer Cell Ablation, Advanced Functional Materials 30 (2020) 2002546.
[175] W.G. Fisher, W.P. Partridge Jr, C. Dees, E.A. Wachter, Simultaneous Two-Photon Activation of Type-I Photodynamic Therapy Agents, Photochemistry and Photobiology 66 (1997) 141–155.
[176] V. Juvekar, C.S. Lim, D.J. Lee, S.J. Park, G.O. Song, H. Kang, H.M. Kim, An azo dye for photodynamic therapy that is activated selectively by two-photon excitation, Chemical Science 12 (2021) 427–434.
[177] Z. Zheng, H. Liu, S. Zhai, H. Zhang, G. Shan, R.T.K. Kwok, C. Ma, H.H.Y. Sung, I.D. Williams, J.W.Y. Lam, K.S. Wong, X. Hu, B.Z. Tang, Highly efficient singlet oxygen generation, two-photon photodynamic therapy and melanoma ablation by rationally designed mitochondria-specific near-infrared AIEgens, Chemical Science 11 (2020) 2494–2503.
[178] H. Qiu, M. Tan, T.Y. Ohulchanskyy, J.F. Lovell, G. Chen, Recent Progress in Upconversion Photodynamic Therapy, Nanomaterials 8 (2018).
[179] P. Zhang, W. Steelant, M. Kumar, M. Scholfield, Versatile Photosensitizers for Photodynamic Therapy at Infrared Excitation, Journal of the American Chemical Society 129 (2007) 4526–4527.
[180] N.M. Idris, M.K. Gnanasammandhan, J. Zhang, P.C. Ho, R. Mahendran, Y. Zhang, In vivo photodynamic therapy using upconversion nanoparticles as remote-controlled nanotransducers, Nature Medicine 18 (2012) 1580–1585.
[181] J. Xu, P. Yang, M. Sun, H. Bi, B. Liu, D. Yang, S. Gai, F. He, J. Lin, Highly Emissive Dye-Sensitized Upconversion Nanostructure for Dual-Photosensitizer Photodynamic Therapy and Bioimaging, ACS Nano 11 (2017) 4133–4144.
[182] Y. Li, J. Tang, D.-X. Pan, L.-D. Sun, C. Chen, Y. Liu, Y.-F. Wang, S. Shi, C.-H. Yan, A Versatile Imaging and Therapeutic Platform Based on Dual-Band Luminescent Lanthanide Nanoparticles toward Tumor Metastasis Inhibition, ACS Nano 10 (2016) 2766–2773.
[183] R. Lv, P. Yang, F. He, S. Gai, C. Li, Y. Dai, G. Yang, J. Lin, A Yolk-like Multifunctional Platform for Multimodal Imaging and Synergistic Therapy Triggered by a Single Near-Infrared Light, ACS Nano 9 (2015) 1630–1647.
[184] A. Skripka, V. Karabanovas, G. Jarockyte, R. Marin, V. Tam, M. Cerruti, R. Rotomskis, F. Vetrone, Decoupling Theranostics with Rare Earth Doped Nanoparticles, Advanced Functional Materials 29 (2019) 1807105.
[185] X. Song, Q. Chen, Z. Liu, Recent advances in the development of organic photothermal nano-agents, Nano Research 8 (2015) 340–354.
[186] S. Gai, G. Yang, P. Yang, F. He, J. Lin, D. Jin, B. Xing, Recent advances in functional nanomaterials for light–triggered cancer therapy, Nano Today 19 (2018) 146–187.
[187] G. Hong, J.C. Lee, J.T. Robinson, U. Raaz, L. Xie, N.F. Huang, J.P. Cooke, H. Dai, Multifunctional in vivo vascular imaging using near-infrared II fluorescence, Nature Medicine 18 (2012) 1841–1846.
[188] X. Ding, C.H. Liow, M. Zhang, R. Huang, C. Li, H. Shen, M. Liu, Y. Zou, N. Gao, Z. Zhang, Y. Li, Q. Wang, S. Li, J. Jiang, Surface Plasmon Resonance Enhanced Light Absorption and Photothermal Therapy in the Second Near-Infrared Window, Journal of the American Chemical Society 136 (2014) 15684–15693.
[189] M.-F. Tsai, S.-H.G. Chang, F.-Y. Cheng, V. Shanmugam, Y.-S. Cheng, C.-H. Su, C.-S. Yeh, Au Nanorod Design as Light-Absorber in the First and Second Biological Near-Infrared Windows for in Vivo Photothermal Therapy, ACS Nano 7 (2013) 5330–5342.
[190] K. Ke, W. Yang, X. Xie, R. Liu, L.-L. Wang, W.-W. Lin, G. Huang, C.-H. Lu, H.-H. Yang, Copper Manganese Sulfide Nanoplates: A New Two-Dimensional Theranostic Nanoplatform for MRI/MSOT Dual-Modal Imaging-Guided Photothermal Therapy in the Second Near-Infrared Window, Theranostics 7 (2017) 4763–4776.
[191] X. Yu, K. Yang, X. Chen, W. Li, Black hollow silicon oxide nanoparticles as highly efficient photothermal agents in the second near-infrared window for in vivo cancer therapy, Biomaterials 143 (2017) 120–129.
[192] A. Li, X. Li, X. Yu, W. Li, R. Zhao, X. An, D. Cui, X. Chen, W. Li, Synergistic thermoradiotherapy based on PEGylated Cu3BiS3 ternary semiconductor nanorods with strong absorption in the second near-infrared window, Biomaterials 112 (2017) 164–175.
[193] R. Mohammadpour, M.A. Dobrovolskaia, D.L. Cheney, K.F. Greish, H. Ghandehari, Subchronic and chronic toxicity evaluation of inorganic nanoparticles for delivery applications, Advanced Drug Delivery Reviews 144 (2019) 112–132.
[194] B. Guo, Z. Sheng, D. Hu, C. Liu, H. Zheng, B. Liu, Through Scalp and Skull NIR-II Photothermal Therapy of Deep Orthotopic Brain Tumors with Precise Photoacoustic Imaging Guidance, Advanced Materials 30 (2018) 1802591.
[195] E. Sadauskas, H. Wallin, M. Stoltenberg, U. Vogel, P. Doering, A. Larsen, G. Danscher, Kupffer cells are central in the removal of nanoparticles from the organism, Particle and Fibre Toxicology 4 (2007) 10.
[196] J. Duanmu, J. Cheng, J. Xu, C.J. Booth, Z. Hu, Effective treatment of chemoresistant breast cancer in vitro and in vivo by a factor VII-targeted photodynamic therapy, British Journal of Cancer 104 (2011) 1401–1409.
[197] J. Cheng, J. Xu, J. Duanmu, H. Zhou, C.J. Booth, Z. Hu, Effective Treatment of Human Lung Cancer by Targeting Tissue Factor with a Factor VII-Targeted Photodynamic Therapy, Current Cancer Drug Targets 11 (2011) 1069–1081.
[198] O.J. Klein, H. Yuan, N.H. Nowell, C. Kaittanis, L. Josephson, C.L. Evans, An Integrin-Targeted, Highly Diffusive Construct for Photodynamic Therapy, Scientific Reports 7 (2017) 13375.
[199] S.Y.Y. Ha, R.C.H. Wong, C.T.T. Wong, D.K.P. Ng, An integrin-targeting glutathione-activated zinc(II) phthalocyanine for dual targeted photodynamic therapy, European Journal of Medicinal Chemistry 174 (2019) 56–65.
[200] B. Li, H. Xiao, M. Cai, X. Li, X. Xu, Molecular Probe Crossing Blood-Brain Barrier for Bimodal Imaging-Guided Photothermal/Photodynamic Therapies of Intracranial Glioblastoma, Advanced functional materials 30 (2020).
[201] X. Kang, X. Guo, W. An, X. Niu, S. Li, Photothermal therapeutic application of gold nanorods-porphyrin-trastuzumab complexes in HER2-positive breast cancer, Scientific reports 7 (2017).
[202] S. Li, Y. Jin, Y. Su, W. Li, Y. Xing, F. Wang, Z. Hong, Anti-HER2 Affibody-Conjugated Photosensitizer for Tumor Targeting Photodynamic Therapy, Molecular Pharmaceutics 17 (2020) 1546–1557.
[203] Y.-T. Yu, S.-W. Shi, Y. Wang, Q.-L. Zhang, S.-H. Gao, S.-P. Yang, J.-G. Liu, A Ruthenium Nitrosyl-Functionalized Magnetic Nanoplatform with Near-Infrared Light-Controlled Nitric Oxide Delivery and Photothermal Effect for Enhanced Antitumor and Antibacterial Therapy, ACS Applied Materials & Interfaces 12 (2020) 312–321.
[204] T. Kato, C.S. Jin, H. Ujiie, D. Lee, K. Fujino, H. Wada, H.-P. Hu, R.A. Weersink, J. Chen, M. Kaji, K. Kaga, Y. Matsui, B.C. Wilson, G. Zheng, K. Yasufuku, Nanoparticle targeted folate receptor 1-enhanced photodynamic therapy for lung cancer, Lung Cancer 113 (2017) 59–68.
[205] Y. Zhao, W. Liu, Y. Tian, Z. Yang, X. Wang, Y. Zhang, Y. Tang, S. Zhao, C. Wang, Y. Liu, J. Sun, Z. Teng, S. Wang, G. Lu, Anti-EGFR Peptide-Conjugated Triangular Gold Nanoplates for Computed Tomography/Photoacoustic Imaging-Guided Photothermal Therapy of Non-Small Cell Lung Cancer, ACS Applied Materials & Interfaces 10 (2018) 16992–17003.
[206] X. Zhao, M. Li, W. Sun, J. Fan, J. Du, X. Peng, An estrogen receptor targeted ruthenium complex as a two-photon photodynamic therapy agent for breast cancer cells, Chemical Communications 54 (2018) 7038–7041.
[207] Z. Yu, Y. Xia, J. Xing, Z. Li, J. Zhen, Y. Jin, Y. Tian, C. Liu, Z. Jiang, J. Li, A. Wu, Y1-receptor–ligand-functionalized ultrasmall upconversion nanoparticles for tumor-targeted trimodality imaging and photodynamic therapy with low toxicity, Nanoscale 10 (2018) 17038–17052.
[208] D. Dutta, R. Calvani, R. Bernabei, C. Leeuwenburgh, E. Marzetti, Contribution of impaired mitochondrial autophagy to cardiac aging: mechanisms and therapeutic opportunities, Circ Res 110 (2012) 1125–1138.
[209] A.D. Garg, P. Agostinis, ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses, Photochemical & Photobiological Sciences 13 (2014) 474–487.
[210] Y. Wei, F. Zhou, D. Zhang, Q. Chen, D. Xing, A graphene oxide based smart drug delivery system for tumor mitochondria-targeting photodynamic therapy, Nanoscale 8 (2016) 3530–3538.
[211] W. Li, J. Yang, L. Luo, M. Jiang, B. Qin, H. Yin, C. Zhu, X. Yuan, J. Zhang, Z. Luo, Y. Du, Q. Li, Y. Lou, Y. Qiu, J. You, Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death, Nature Communications 10 (2019) 3349.
[212] Y. Liu, G. Yang, S. Jin, L. Xu, C.-X. Zhao, Development of High-Drug-Loading Nanoparticles, ChemPlusChem 85 (2020) 2143–2157.
[213] Y. Li, G. Liu, J. Ma, J. Lin, H. Lin, G. Su, D. Chen, S. Ye, X. Chen, X. Zhu, Z. Hou, Chemotherapeutic drug-photothermal agent co-self-assembling nanoparticles for near-infrared fluorescence and photoacoustic dual-modal imaging-guided chemo-photothermal synergistic therapy, Journal of Controlled Release 258 (2017) 95–107.
[214] X. Li, S. Yu, Y. Lee, T. Guo, N. Kwon, D. Lee, S.C. Yeom, Y. Cho, G. Kim, J.-D. Huang, S. Choi, K.T. Nam, J. Yoon, In Vivo Albumin Traps Photosensitizer Monomers from Self-Assembled Phthalocyanine Nanovesicles: A Facile and Switchable Theranostic Approach, Journal of the American Chemical Society 141 (2019) 1366–1372.
[215] C. Luo, B. Sun, C. Wang, X. Zhang, Y. Chen, Q. Chen, H. Yu, H. Zhao, M. Sun, Z. Li, H. Zhang, Q. Kan, Y. Wang, Z. He, J. Sun, Self-facilitated ROS-responsive nanoassembly of heterotypic dimer for synergistic chemo-photodynamic therapy, Journal of Controlled Release 302 (2019) 79–89.
[216] X. Tong, S. Gan, J. Wu, Y. Hu, A. Yuan, A nano-photosensitizer based on covalent organic framework nanosheets with high loading and therapeutic efficacy, Nanoscale 12 (2020) 7376–7382.
[217] Y. Kim, Q. Lin, P.M. Glazer, Z. Yun, Hypoxic tumor microenvironment and cancer cell differentiation, Curr Mol Med 9 (2009) 425–434.
[218] Z. Luo, M. Zheng, P. Zhao, Z. Chen, F. Siu, P. Gong, G. Gao, Z. Sheng, C. Zheng, Y. Ma, L. Cai, Self-Monitoring Artificial Red Cells with Sufficient Oxygen Supply for Enhanced Photodynamic Therapy, Scientific Reports 6 (2016) 23393.
[219] S. Wang, F. Yuan, K. Chen, G. Chen, K. Tu, H. Wang, L.-Q. Wang, Synthesis of Hemoglobin Conjugated Polymeric Micelle: A ZnPc Carrier with Oxygen Self-Compensating Ability for Photodynamic Therapy, Biomacromolecules 16 (2015) 2693–2700.
[220] Y. Cheng, H. Cheng, C. Jiang, X. Qiu, K. Wang, W. Huan, A. Yuan, J. Wu, Y. Hu, Perfluorocarbon nanoparticles enhance reactive oxygen levels and tumour growth inhibition in photodynamic therapy, Nature Communications 6 (2015) 8785.
[221] P. Wang, X. Li, C. Yao, W. Wang, M. Zhao, A.M. El-Toni, F. Zhang, Orthogonal near-infrared upconversion co-regulated site-specific O2 delivery and photodynamic therapy for hypoxia tumor by using red blood cell microcarriers, Biomaterials 125 (2017) 90–100.

[222] L. Deng, D. Sheng, M. Liu, L. Yang, H. Ran, P. Li, X. Cai, Y. Sun, Z. Wang, A near-infrared laser and H2O2 activated bio-nanoreactor for enhanced photodynamic therapy of hypoxic tumors, Biomaterials Science 8 (2020) 858–870.
[223] S.Z.F. Phua, G. Yang, W.Q. Lim, A. Verma, H. Chen, T. Thanabalu, Y. Zhao, Catalase-Integrated Hyaluronic Acid as Nanocarriers for Enhanced Photodynamic Therapy in Solid Tumor, ACS Nano 13 (2019) 4742–4751.
[224] Z. Luo, M. Li, M. Zhou, H. Li, Y. Chen, X. Ren, Y. Dai, O2-evolving and ROS-activable nanoparticles for treatment of multi-drug resistant Cancer by combination of photodynamic therapy and chemotherapy, Nanomedicine: Nanotechnology, Biology and Medicine 19 (2019) 49–57.
[225] Y. Wang, F. Caruso, Mesoporous Silica Spheres as Supports for Enzyme Immobilization and Encapsulation, Chemistry of Materials 17 (2005) 953–961.
[226] J. Lee, Y. Lee, J.K. Youn, H.B. Na, T. Yu, H. Kim, S.-M. Lee, Y.-M. Koo, J.H. Kwak, H.G. Park, H.N. Chang, M. Hwang, J.-G. Park, J. Kim, T. Hyeon, Simple Synthesis of Functionalized Superparamagnetic Magnetite/Silica Core/Shell Nanoparticles and their Application as Magnetically Separable High-Performance Biocatalysts, Small 4 (2008) 143–152.
[227] L.M. Rossi, A.D. Quach, Z. Rosenzweig, Glucose oxidase–magnetite nanoparticle bioconjugate for glucose sensing, Analytical and Bioanalytical Chemistry 380 (2004) 606–613.
[228] D.-G. Lee, K.M. Ponvel, M. Kim, S. Hwang, I.-S. Ahn, C.-H. Lee, Immobilization of lipase on hydrophobic nano-sized magnetite particles, Journal of Molecular Catalysis B: Enzymatic 57 (2009) 62–66.
[229] Q. Chen, J. Chen, C. Liang, L. Feng, Z. Dong, X. Song, G. Song, Z. Liu, Drug-induced co-assembly of albumin/catalase as smart nano-theranostics for deep intra-tumoral penetration, hypoxia relieve, and synergistic combination therapy, Journal of Controlled Release 263 (2017) 79–89.
[230] X. Zhang, Z. Xi, J.O.a. Machuki, J. Luo, D. Yang, J. Li, W. Cai, Y. Yang, L. Zhang, J. Tian, K. Guo, Y. Yu, F. Gao, Gold Cube-in-Cube Based Oxygen Nanogenerator: A Theranostic Nanoplatform for Modulating Tumor Microenvironment for Precise Chemo-Phototherapy and Multimodal Imaging, ACS Nano, 13 (2019) 5306-5325.
[231] J. Lu, L. Yang, W. Zhang, P. Li, X. Gao, W. Zhang, H. Wang, B. Tang, Photodynamic therapy for hypoxic solid tumors via Mn-MOF as a photosensitizer, Chemical Communications 55 (2019) 10792–10795.
[232] G. Yang, L. Xu, Y. Chao, J. Xu, X. Sun, Y. Wu, R. Peng, Z. Liu, Hollow MnO2 as a tumor-microenvironment-responsive biodegradable nano-platform for combination therapy favoring antitumor immune responses, Nature Communications 8 (2017) 902.
[233] S. Wang, Z. Wei, L. Li, X. Ning, Y. Liu, Luminescence imaging-guided triple-collaboratively enhanced photodynamic therapy by bioresponsive lanthanide-based nanomedicine, Nanomedicine: Nanotechnology, Biology and Medicine 29 (2020) 102265.
[234] A. Sahu, K. Min, J. Jeon, H.S. Yang, G. Tae, Catalytic nanographene oxide with hemin for enhanced photodynamic therapy, Journal of Controlled Release 326 (2020) 442–454.
[235] C. Yao, W. Wang, P. Wang, M. Zhao, X. Li, F. Zhang, Near-Infrared Upconversion Mesoporous Cerium Oxide Hollow Biophotocatalyst for Concurrent pH-/H2O2-Responsive O2-Evolving Synergetic Cancer Therapy, Advanced Materials 30 (2018) 1704833.
[236] R. Moreno-Sánchez, A. Marín-Hernández, E. Saavedra, J.P. Pardo, S.J. Ralph, S. Rodríguez-Enríquez, Who controls the ATP supply in cancer cells?, Biochemistry lessons to understand cancer energy metabolism, The International Journal of Biochemistry & Cell Biology 50 (2014) 10–23
[237] D.R. Grimes, C. Kelly, K. Bloch, M. Partridge, A method for estimating the oxygen consumption rate in multicellular tumour spheroids, Journal of The Royal Society Interface 11 (2014) 20131124.
[238] B. Gallez, M.-A. Neveu, P. Danhier, B.F. Jordan, Manipulation of tumor oxygenation and radiosensitivity through modification of cell respiration. A critical review of approaches and imaging biomarkers for therapeutic guidance, Biochimica et Biophysica Acta (BBA) -, Bioenergetics 1858 (2017) 700–711.
[239] Z. Yang, J. Wang, S. Liu, X. Li, L. Miao, B. Yang, C. Zhang, J. He, S. Ai, W. Guan, Defeating relapsed and refractory malignancies through a nano-enabled mitochondria-mediated respiratory inhibition and damage pathway, Biomaterials 229 (2020) 119580.
[240] X. Mai, Y. Zhang, H. Fan, W. Song, Y. Chang, B. Chen, J. Shi, X. Xin, Z. Teng, J. Sun, G. Teng, Integration of immunogenic activation and immunosuppressive reversion using mitochondrial-respiration-inhibited platelet-mimicking nanoparticles, Biomaterials 232 (2020) 119699.
[241] J. Park, Q. Jiang, D. Feng, L. Mao, H.-C. Zhou, Size-Controlled Synthesis of Porphyrinic Metal-Organic Framework and Functionalization for Targeted Photodynamic Therapy, Journal of the American Chemical Society 138 (2016) 3518–3525.
[242] Y. Gao, Q.C. Zheng, S. Xu, Y. Yuan, X. Cheng, S. Jiang, Q. Kenry, Z. Yu, B. Song, M. Li Liu, Theranostic Nanodots with Aggregation-Induced Emission Characteristic for Targeted and Image-Guided Photodynamic Therapy of Hepatocellular Carcinoma, Theranostics 9 (2019) 1264–1279.
[243] J.C. Goldschmidt, S. Fischer, Upconversion for Photovoltaics – a Review of Materials, Devices and Concepts for Performance Enhancement, Advanced, Optical Materials 3 (2015) 510–535.
[244] T.F. Schulze, T.W. Schmidt, Photochemical upconversion: present status and prospects for its application to solar energy conversion, Energy & Environmental Science 8 (2015) 103–125.
[245] S. Asahi, H. Teranishi, K. Kusaki, T. Kaizu, T. Kita, Two-step photon up-conversion solar cells, Nature Communications 8 (2017) 14962.
[246] S.-L. Lin, C.A. Chang, Optimising FRET-efficiency of Nd3+-sensitised upconversion nanocomposites by shortening the emitter–photosensitizer distance, Nanoscale 12 (2020) 8742–8749.
[247] S. Kuang, L. Sun, X. Zhang, X. Liao, T.W. Rees, L. Zeng, Y. Chen, X. Zhang, L. Ji, H. Chao, A Mitochondrion-Localized Two-Photon Photosensitizer Generating Carbon Radicals Against Hypoxic Tumors, Angewandte Chemie International Edition 59 (2020) 20697–20703.
[248] J. Karges, S. Kuang, F. Maschietto, O. Blacque, I. Ciofini, H. Chao, G. Gasser, Rationally designed ruthenium complexes for 1- and 2-photon photodynamic therapy, Nature Communications 11 (2020) 3262.
[249] Z. Wang, J. Zhao, Bodipy-Anthracene Dyads as Triplet Photosensitizers: Effect of Chromophore Orientation on Triplet-State Formation Efficiency and Application in Triplet-Triplet Annihilation Upconversion, Organic Letters 19 (2017) 4492–4495.
[250] Y. Wei, M. Zhou, Q. Zhou, X. Zhou, S. Liu, S. Zhang, B. Zhang, Triplet–triplet annihilation upconversion kinetics of C60–Bodipy dyads as organic triplet photosensitizers, Physical Chemistry Chemical Physics 19 (2017) 22049–22060.
[251] S. Li, X. Shen, Q.-H. Xu, Y. Cao, Gold nanorod enhanced conjugated polymer/photosensitizer composite nanoparticles for simultaneous two-photon excitation fluorescence imaging and photodynamic therapy, Nanoscale 11 (2019) 19551–19560.
[252] R. Zhang, Y. Guan, Z. Zhu, H. Lv, F. Li, S. Sun, J. Li, Multifunctional Tetracene/Pentacene Host/Guest Nanorods for Enhanced Upconversion Photodynamic Tumor Therapy, ACS Applied Materials & Interfaces 11 (2019) 37479–37490.
[253] S. Singh, A.R. Khan, A.K. Gupta, Role of glutathione in cancer pathophysiology and therapeutic interventions, J Exp Ther Oncol 9 (2012) 303–316.
[254] W. Zhang, J. Lu, X. Gao, P. Li, W. Zhang, Y. Ma, H. Wang, B. Tang, Enhanced Photodynamic Therapy by Reduced Levels of Intracellular Glutathione Obtained By Employing a Nano-MOF with CuII as the Active Center, Angewandte Chemie International Edition 57 (2018) 4891–4896.
[255] D. Yang, G. Yang, P. Yang, R. Lv, S. Gai, C. Li, F. He, J. Lin, Assembly of Au Plasmonic Photothermal Agent and Iron Oxide Nanoparticles on Ultrathin Black Phosphorus for Targeted Photothermal and Photodynamic Cancer Therapy, Advanced Functional Materials 27 (2017) 1700371.
[256] G. Liu, J. Zou, Q. Tang, X. Yang, Y. Zhang, Q. Zhang, W. Huang, P. Chen, J. Shao, X. Dong, Surface Modified Ti3C2 MXene Nanosheets for Tumor Targeting Photothermal/Photodynamic/Chemo Synergistic Therapy, ACS Applied Materials & Interfaces 9 (2017) 40077–40086.
[257] Y. Liu, G. Shen, L. Zhao, Q. Zou, T. Jiao, X. Yan, Robust Photothermal Nanodrugs Based on Covalent Assembly of Nonpigmented Biomolecules for Antitumor Therapy, ACS Applied Materials & Interfaces 11 (2019) 41898–41905.
[258] B. Liu, J. Sun, J. Zhu, B. Li, C. Ma, X. Gu, K. Liu, H. Zhang, F. Wang, J. Su, Y. Yang, Injectable and NIR-Responsive DNA–Inorganic Hybrid Hydrogels with Outstanding Photothermal Therapy, Advanced Materials 32 (2020) 2004460.
[259] Q. Chen, J. Chen, Z. Yang, L. Zhang, Z. Dong, Z. Liu, NIR-II light activated photodynamic therapy with protein-capped gold nanoclusters, Nano Research 11 (2018) 5657–5669.
[260] X. Wu, Y. Suo, H. Shi, R. Liu, F. Wu, T. Wang, L. Ma, H. Liu, Z. Cheng, Deep-Tissue Photothermal Therapy Using Laser Illumination at NIR-IIa Window, Nano-Micro Letters 12 (2020) 38.
[261] X. Dang, N.M. Bardhan, J. Qi, L. Gu, N.A. Eze, C.-W. Lin, S. Kataria, P.T. Hammond, A.M. Belcher, Deep-tissue optical imaging of near cellular-sized features, Scientific Reports 9 (2019) 3873.
[262] S. Li, Q. Deng, Y. Zhang, X. Li, G. Wen, X. Cui, Y. Wan, Y. Huang, J. Chen, Z. Liu, L. Wang, C.-S. Lee, Rational Design of Conjugated Small Molecules for Superior Photothermal Theranostics in the NIR-II Biowindow, Advanced Materials 32 (2020) 2001146.
[263] W. Chen, J. Zhang, Using Nanoparticles to Enable Simultaneous Radiation and Photodynamic Therapies for Cancer Treatment, Journal of Nanoscience and Nanotechnology 6 (2006) 1159–1166.
[264] W. Park, S. Cho, D. Kang, J.-H. Han, J.-H. Park, B. Lee, J. Lee, D.-H. Kim, Tumor Microenvironment Targeting Nano-Bio Emulsion for Synergistic Combinational X-Ray PDT with Oncolytic Bacteria Therapy, Advanced Healthcare Materials 9 (2020) 1901812.
[265] X. Zhong, X. Wang, G. Zhan, Y.a. Tang, Y. Yao, Z. Dong, L. Hou, H. Zhao, S. Zeng, J. Hu, L. Cheng, X. Yang, NaCeF4:Gd,Tb Scintillator as an X-ray Responsive Photosensitizer for Multimodal Imaging-Guided Synchronous Radio/Radiodynamic Therapy, Nano Letters, 19 (2019) 8234-8244.
[266] C.-C. Hsu, S.-L. Lin, C.A. Chang, Lanthanide-Doped Core–Shell–Shell Nanocomposite for Dual Photodynamic Therapy and Luminescence Imaging by a Single X-ray Excitation Source, ACS Applied Materials & Interfaces 10 (2018) 7859–7870.
[267] L. Luo, W. Sun, Y. Feng, R. Qin, J. Zhang, D. Ding, T. Shi, X. Liu, X. Chen, H. Chen, Conjugation of a Scintillator Complex and Gold Nanorods for Dual-Modal Image-Guided Photothermal and X-ray-Induced Photodynamic Therapy of Tumors, ACS Applied Materials & Interfaces 12 (2020) 12591–12599.
[268] S. Clement, W. Chen, A.G. Anwer, E.M. Goldys, Verteprofin conjugated to gold nanoparticles for fluorescent cellular bioimaging and X-ray mediated photodynamic therapy, Microchimica Acta 184 (2017) 1765–1771.
[269] J.G. Fujimoto, C. Pitris, S.A. Boppart, M.E. Brezinski, Optical coherence tomography: an emerging technology for biomedical imaging and optical biopsy 2 (2000) 9–25.

[270] Z. Liu, J. Li, W. Chen, L. Liu, F. Yu, Light and sound to trigger the Pandora's box against breast cancer: A combination strategy of sonodynamic, photodynamic and photothermal therapies, Biomaterials 232 (2020) 119685.
[271] I. Mellman, G. Coukos, G. Dranoff, Cancer immunotherapy comes of age, Nature 480 (2011) 480–489.
[272] W. Ngwa, O.C. Irabor, J.D. Schoenfeld, J. Hesser, S. Demaria, S.C. Formenti, Using immunotherapy to boost the abscopal effect, Nature Reviews Cancer 18 (2018) 313–322.
[273] J. Nam, S. Son, K.S. Park, W. Zou, L.D. Shea, J.J. Moon, Cancer nanomedicine for combination cancer immunotherapy, Nature Reviews Materials 4 (2019) 398–414.
[274] M.S. Goldberg, Improving cancer immunotherapy through nanotechnology, Nature Reviews Cancer 19 (2019) 587–602.
[275] Z. Hu, P.A. Ott, C.J. Wu, Towards personalized, tumour-specific, therapeutic vaccines for cancer, Nature Reviews Immunology 18 (2018) 168.
[276] C. Wang, P. Li, L. Liu, H. Pan, H. Li, L. Cai, Y. Ma, Self-adjuvanted nanovaccine for cancer immunotherapy: role of lysosomal rupture-induced ROS in MHC class I antigen presentation, Biomaterials 79 (2016) 88–100.
[277] D.S. Wilson, S. Hirosue, M.M. Raczy, L. Bonilla-Ramirez, L. Jeanbart, R. Wang, M. Kwissa, J.-F. Franetich, M.A. Broggi, G. Diaceri, Antigens reversibly conjugated to a polymeric glyco-adjuvant induce protective humoral and cellular immunity, Nature materials 18 (2019) 175–185.
[278] M. Luo, H. Wang, Z. Wang, H. Cai, Z. Lu, Y. Li, M. Du, G. Huang, C. Wang, X. Chen, A STING-activating nanovaccine for cancer immunotherapy, Nature nanotechnology 12 (2017) 648.
[279] L. Miao, L. Li, Y. Huang, D. Delcassian, J. Chahal, J. Han, Y. Shi, K. Sadtler, W. Gao, J. Lin, Delivery of mRNA vaccines with heterocyclic lipids increases anti-tumor efficacy by STING-mediated immune cell activation, Nature biotechnology 37 (2019) 1174–1185.
[280] J. Xu, J. Lv, Q. Zhuang, Z. Yang, Z. Cao, L. Xu, P. Pei, C. Wang, H. Wu, Z. Dong, A general strategy towards personalized nanovaccines based on fluoropolymers for post-surgical cancer immunotherapy, Nature Nanotechnology 15 (2020) 1043–1052.
[281] N. Gong, Y. Zhang, X. Teng, Y. Wang, S. Huo, G. Qing, Q. Ni, X. Li, J. Wang, X. Ye, Proton-driven transformable nanovaccine for cancer immunotherapy, Nature nanotechnology 15 (2020) 1053–1064.
[282] Z. Luo, T. He, P. Liu, Z. Yi, S. Zhu, X. Liang, E. Kang, C. Gong, X. Liu, Self-Adjuvanted Molecular Activator (SeaMac), Nanovaccines Promote Cancer Immunotherapy, Advanced Healthcare Materials (2020) 2002080.
[283] R. van der Meel, E. Sulheim, Y. Shi, F. Kiessling, W.J. Mulder, T. Lammers, Smart cancer nanomedicine, Nature nanotechnology 14 (2019) 1007–1017.
[284] C.J. Cheng, G.T. Tietjen, J.K. Saucier-Sawyer, W.M. Saltzman, A holistic approach to targeting disease with polymeric nanoparticles, Nature reviews Drug discovery 14 (2015) 239–247.
[285] F.S. Tabatabaei Mirakabad, K. Nejati-Koshki, A. Akbarzadeh, M.R. Yamchi, M. Milani, N. Zarghami, V. Zeighamian, A. Rahimzadeh, S. Alimohammadi, Y. Hanifehpour, PLGA-based nanoparticles as cancer drug delivery systems, Asian Pacific Journal of Cancer Prevention 15 (2014) 517–535.
[286] H. Kim, D. Sehgal, T.A. Kucaba, D.M. Ferguson, T.S. Griffith, J. Panyam, Acidic pH-responsive polymer nanoparticles as a TLR7/8 agonist delivery platform for cancer immunotherapy, Nanoscale 10 (2018) 20851–20862.
[287] A. Bandyopadhyay, R.L. Fine, S. Demento, L.K. Bockenstedt, T.M. Fahmy, The impact of nanoparticle ligand density on dendritic-cell targeted vaccines, Biomaterials 32 (2011) 3094–3105.
[288] S.S. Saluja, D.J. Hanlon, F.A. Sharp, E. Hong, D. Khalil, E. Robinson, R. Tigelaar, T.M. Fahmy, R.L. Edelson, Targeting human dendritic cells via DEC-205 using PLGA nanoparticles leads to enhanced cross-presentation of a melanoma-associated antigen, International journal of nanomedicine 9 (2014) 5231.
[289] R. Yang, J. Xu, L. Xu, X. Sun, Q. Chen, Y. Zhao, R. Peng, Z. Liu, Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination, Acs Nano 12 (2018) 5121–5129.
[290] D. Shae, K.W. Becker, P. Christov, D.S. Yun, A.K. Lytton-Jean, S. Sevimli, M. Ascano, M. Kelley, D.B. Johnson, J.M. Balko, Endosomolytic polymersomes increase the activity of cyclic dinucleotide STING agonists to enhance cancer immunotherapy, Nature nanotechnology 14 (2019) 269–278.
[291] L. Hu, Z. Cao, L. Ma, Z. Liu, G. Liao, J. Wang, S. Shen, D. Li, X. Yang, The potentiated checkpoint blockade immunotherapy by ROS-responsive nanocarrier-mediated cascade chemo-photodynamic therapy, Biomaterials 223 (2019) 119469.
[292] Y. Song, Y. Chen, P. Li, C.-M. Dong, Photoresponsive Polypeptide-Glycosylated Dendron Amphiphiles: UV-Triggered Polymersomes, OVA Release, and In Vitro Enhanced Uptake and Immune Response, Biomacromolecules (2020).
[293] Q. Chen, C. Wang, X. Zhang, G. Chen, Q. Hu, H. Li, J. Wang, D. Wen, Y. Zhang, Y. Lu, In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment, Nature Nanotechnology 14 (2019) 89–97.
[294] T. Wang, D. Wang, H. Yu, B. Feng, F. Zhou, H. Zhang, L. Zhou, S. Jiao, Y. Li, A cancer vaccine-mediated postoperative immunotherapy for recurrent and metastatic tumors, Nature communications 9 (2018) 1–12.
[295] L.M. Kranz, M. Diken, H. Haas, S. Kreiter, C. Loquai, K.C. Reuter, M. Meng, D. Fritz, F. Vascotto, H. Hefesha, Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy, Nature 534 (2016) 396–401.
[296] U. Sahin, P. Oehm, E. Derhovanessian, R.A. Jabulowsky, M. Vormehr, M. Gold, D. Maurus, D. Schwarck-Kokarakis, A.N. Kuhn, T. Omokoko, L.M. Kranz, M. Diken, S. Kreiter, H. Haas, S. Attig, R. Rae, K. Cuk, A. Kemmer-Brück, A. Breitkreuz, C. Tolliver, J. Caspar, J. Quinkhardt, L. Hebich, M. Stein, A. Hohberger, I. Vogler, I. Liebig, S. Renken, J. Sikorski, M. Leierer, V. Müller, H. Mitzel-Rink, M. Miederer, C. Huber, S. Grabbe, J. Utikal, A. Pinter, R. Kaufmann, J.C. Hassel, C. Loquai, Ö. Türeci, An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma, Nature 585 (2020) 107–112.
[297] D. Rosenblum, A. Gutkin, R. Kedmi, S. Ramishetti, N. Veiga, A.M. Jacobi, M.S. Schubert, D. Friedmann-Morvinski, Z.R. Cohen, M.A. Behlke, CRISPR-Cas9 genome editing using targeted lipid nanoparticles for cancer therapy, Science advances 6 (2020) eabc9450.
[298] M.A. Islam, Y. Xu, W. Tao, J.M. Ubellacker, M. Lim, D. Aum, G.Y. Lee, K. Zhou, H. Zope, M. Yu, Restoration of tumour-growth suppression in vivo via systemic nanoparticle-mediated delivery of PTEN mRNA, Nature biomedical engineering 2 (2018) 850–864.
[299] N. Shobaki, Y. Sato, Y. Suzuki, N. Okabe, H. Harashima, Manipulating the function of tumor-associated macrophages by siRNA-loaded lipid nanoparticles for cancer immunotherapy, Journal of Controlled Release 325 (2020) 235–248.
[300] X. Yu, D. Gao, L. Gao, J. Lai, C. Zhang, Y. Zhao, L. Zhong, B. Jia, F. Wang, X. Chen, Inhibiting metastasis and preventing tumor relapse by triggering host immunity with tumor-targeted photodynamic therapy using photosensitizer-loaded functional nanographenes, ACS nano 11 (2017) 10147–10158.
[301] A.W. Li, M.C. Sobral, S. Badrinath, Y. Choi, A. Graveline, A.G. Stafford, J.C. Weaver, M.O. Dellacherie, T.-Y. Shih, O.A. Ali, A facile approach to enhance antigen response for personalized cancer vaccination, Nature materials 17 (2018) 528–534.
[302] B. Zhou, J. Song, M. Wang, X. Wang, J. Wang, E.W. Howard, F. Zhou, J. Qu, W.R. Chen, BSA-bioinspired gold nanorods loaded with immunoadjuvant for the treatment of melanoma by combined photothermal therapy and immunotherapy, Nanoscale 10 (2018) 21640–21647.
[303] K. Ni, G. Lan, C. Chan, B. Quigley, K. Lu, T. Aung, N. Guo, P. La Riviere, R.R. Weichselbaum, W. Lin, Nanoscale metal-organic frameworks enhance radiotherapy to potentiate checkpoint blockade immunotherapy, Nature communications 9 (2018) 1–12.
[304] K. Ni, T. Luo, A. Culbert, M. Kaufmann, X. Jiang, W. Lin, Nanoscale metal–organic framework co-delivers TLR-7 agonists and anti-CD47 antibodies to modulate macrophages and orchestrate cancer immunotherapy, Journal of the American Chemical Society 142 (2020) 12579–12584.
[305] D. Mao, F. Hu, Z. Yi, K. Kenry, S. Xu, S. Yan, Z. Luo, W. Wu, Z. Wang, D. Kong, AIEgen-coupled upconversion nanoparticles eradicate solid tumors through dual-mode ROS activation, Science advances 6 (2020) eabb2712.
[306] S. Yan, X. Zeng, Y.a. Tang, B.F. Liu, Y. Wang, X. Liu, Activating antitumor immunity and antimetastatic effect through polydopamine-encapsulated core–shell upconversion nanoparticles, Advanced Materials, 31 (2019) 1905825.
[307] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nature Reviews Materials 1 (2016).
[308] M. Yu, J. Zheng, Clearance Pathways and Tumor Targeting of Imaging Nanoparticles, ACS Nano 9 (2015) 6655–6674.
[309] J. Liu, M. Yu, C. Zhou, S. Yang, X. Ning, J. Zheng, Passive tumor targeting of renal-clearable luminescent gold nanoparticles: long tumor retention and fast normal tissue clearance, J Am Chem Soc 135 (2013) 4978–4981.
[310] C.M. Dawidczyk, C. Kim, J.H. Park, L.M. Russell, K.H. Lee, M.G. Pomper, P.C. Searson, State-of-the-art in design rules for drug delivery platforms: lessons learned from FDA-approved nanomedicines, J Control Release 187 (2014) 133–144.
[311] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Engineering precision nanoparticles for drug delivery, Nat Rev Drug Discov (2020).
[312] C. von Roemeling, W. Jiang, C.K. Chan, I.L. Weissman, B.Y.S. Kim, Breaking Down the Barriers to Precision Cancer Nanomedicine, Trends Biotechnol 35 (2017) 159–171.
[313] S.D. Conner, S.L. Schmid, Regulated portals of entry into the cell, Nature 422 (2003) 37–44.
[314] F. Zhao, Y. Zhao, Y. Liu, X. Chang, C. Chen, Y. Zhao, Cellular uptake, intracellular trafficking, and cytotoxicity of nanomaterials, Small 7 (2011) 1322–1337.
[315] N.D. Donahue, H. Acar, S. Wilhelm, Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine, Adv Drug Deliv Rev 143 (2019) 68–96.
[316] N. Hoshyar, S. Gray, H. Han, G. Bao, The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction, Nanomedicine 11 (2016) 673–692.
[317] W. Jiang, B.Y. Kim, J.T. Rutka, W.C. Chan, Nanoparticle-mediated cellular response is size-dependent, Nat Nanotechnol 3 (2008) 145–150.
[318] Y. Pan, A. Leifert, D. Ruau, S. Neuss, J. Bornemann, G. Schmid, W. Brandau, U. Simon, W. Jahnen-Dechent, Gold nanoparticles of diameter 1.4 nm trigger necrosis by oxidative stress and mitochondrial damage, Small 5 (2009) 2067–2076.
[319] Y. Pan, S. Neuss, A. Leifert, M. Fischler, F. Wen, U. Simon, G. Schmid, W. Brandau, W. Jahnen-Dechent, Size-dependent cytotoxicity of gold nanoparticles, Small 3 (2007) 1941–1949.
[320] A. Nel, T. Xia, L. Madler, N. Li, Toxic Potential of Materials at the Nanolevel, Science 311 (2006) 622–627.

[321] X. Zhao, S. Ng, B.C. Heng, J. Guo, L. Ma, T.T. Tan, K.W. Ng, S.C. Loo, Cytotoxicity of hydroxyapatite nanoparticles is shape and cell dependent, Arch Toxicol 87 (2013) 1037–1052.
[322] L.C. Stoehr, E. Gonzalez, A. Stampfl, E. Casals, A. Duschl, V. Puntes, G.J. Oostingh, Shape matters: effects of silver nanospheres and wires on human alveolar epithelial cells, Particle and Fibre Toxicology 8 (2011).
[323] M. Lundqvist, J. Stigler, S. Elia, I. Lynch, T. Cedervall, K.A. Dawson, Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 14265–14270.
[324] Y. Liu, W. Li, F. Lao, Y. Liu, L. Wang, R. Bai, Y. Zhao, C. Chen, Intracellular dynamics of cationic and anionic polystyrene nanoparticles without direct interaction with mitotic spindle and chromosomes, Biomaterials 32 (2011) 8291–8303.
[325] C.M. Goodman, C.D. McCusker, T. Yilmaz, V.M. Rotello, Toxicity of Gold Nanoparticles Functionalized with Cationic and Anionic Side Chains, Bioconjugate Chemistry 15 (2004) 897–900.
[326] S.J. Hawkins, L.A. Crompton, A. Sood, M. Saunders, N.T. Boyle, A. Buckley, A.M. Minogue, S.F. McComish, N. Jimenez-Moreno, O. Cordero-Llana, P. Stathakos, C.E. Gilmore, S. Kelly, J.D. Lane, C.P. Case, M.A. Caldwell, Nanoparticle-induced neuronal toxicity across placental barriers is mediated by autophagy and dependent on astrocytes, Nat Nanotechnol 13 (2018) 427–433.
[327] A. Thubagere, B.M. Reinhard, Nanoparticle-Induced Apoptosis Propagates through Hydrogen-PeroxideMediated Bystander Killing: Insights from a Human Intestinal Epithelium In Vitro Model, ACS Nano 4 (2010) 3611–3622.
[328] G. Bhabra, A. Sood, B. Fisher, L. Cartwright, M. Saunders, W.H. Evans, A. Surprenant, G. Lopez-Castejon, S. Mann, S.A. Davis, L.A. Hails, E. Ingham, P. Verkade, J. Lane, K. Heesom, R. Newson, C.P. Case, Nanoparticles can cause DNA damage across a cellular barrier, Nat Nanotechnol 4 (2009) 876–883.
[329] A. Malassine, L. Cronier, Involvement of gap junctions in placental functions and development, Biochim Biophys Acta 1719 (2005) 117–124.
[330] B. Huppertz, The anatomy of the normal placenta, J Clin Pathol 61 (2008) 1296–1302.
[331] A. Sood, S. Salih, D. Roh, L. Lacharme-Lora, M. Parry, B. Hardiman, R. Keehan, R. Grummer, E. Winterhager, P.J. Gokhale, P.W. Andrews, C. Abbott, K. Forbes, M. Westwood, J.D. Aplin, E. Ingham, I. Papageorgiou, M. Berry, J. Liu, A.D. Dick, R.J. Garland, N. Williams, R. Singh, A.K. Simon, M. Lewis, J. Ham, L. Roger, D.M. Baird, L.A. Crompton, M.A. Caldwell, H. Swalwell, M. Birch-Machin, G. Lopez-Castejon, A. Randall, H. Lin, M.S. Suleiman, W.H. Evans, R. Newson, C.P. Case, Signalling of DNA damage and cytokines across cell barriers exposed to nanoparticles depends on barrier thickness, Nat Nanotechnol 6 (2011) 824–833.
[332] C.F. Jones, R.A. Campbell, A.E. Brooks, S. Assemi, S. Tadjiki, G. Thiagarajan, C. Mulcock, A.S. Weyrich, B.D. Brooks, H. Ghandehari, D.W. Grainger, Cationic PAMAM Dendrimers Aggressively Initiate Blood Clot Formation, ACS Nano 6 (2012) 9900–9910.
[333] R.W. Teh, D.T. Tsoi, Acute disseminated intravascular coagulation in neuroendocrine carcinoma, Case Rep Oncol 5 (2012) 524–529.
[334] C. Corbo, R. Molinaro, A. Parodi, N.E.T. Furman, F. Salvatore, E. Tasciotti, The impact of nanoparticle protein corona on cytotoxicity, immunotoxicity and target drug delivery, Nanomedicine 11 (2016) 81–100.
[335] B. Klajnert, S. Pikala, M. Bryszewska, Haemolytic activity of polyamidoamine dendrimers and the protective role of human serum albumin, Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences 466 (2009) 1527–1534.
[336] U.S. Gaharwar, P. R, Iron Oxide Nanoparticles Induced Oxidative Damage in Peripheral Blood Cells of Rat, Journal of Biomedical Science and Engineering, 08 (2015) 274-286.
[337] M. Fang, M. Chen, L. Liu, Y. Li, Applications of Quantum Dots in Cancer Detection and Diagnosis: A Review, J Biomed Nanotechnol 13 (2017) 1–16.
[338] D.S.T. Martinez, A.J. Paula, L.C. Fonseca, L.A.V. Luna, C.P. Silveira, N. Durán, O.L. Alves, Monitoring the Hemolytic Effect of Mesoporous Silica Nanoparticles after Human Blood Protein Corona Formation, European Journal of Inorganic Chemistry 2015 (2015) 4595–4602.
[339] Y.H. Luo, L.W. Chang, P. Lin, Metal-Based Nanoparticles and the Immune System: Activation, Inflammation, and Potential Applications, Biomed Res Int 2015 (2015) 143720.
[340] K. Maier-Hauff, F. Ulrich, D. Nestler, H. Niehoff, P. Wust, B. Thiesen, H. Orawa, V. Budach, A. Jordan, Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme, J Neurooncol 103 (2011) 317–324.
[341] L. Sercombe, T. Veerati, F. Moheimani, S.Y. Wu, A.K. Sood, S. Hua, Advances and Challenges of Liposome Assisted Drug Delivery, Front Pharmacol 6 (2015) 286.