Materials Today Advances 8 (2020) 100087

Contents lists available at ScienceDirect

Materials Today Advances

journal homepage: www.journals.elsevier.com/materials-today-advances/

Localized nanotheranostics: recent developments in cancer nanomedicine

R. Prasad [a, ***], N.K. Jain [a], J. Conde [b, c, *], R. Srivastava [a, **]

[a] Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai, India
[b] NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, 1169-056 Lisboa, Portugal
[c] Centre for Toxicogenomics and Human Health, Genetics, Oncology and Human Toxicology, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, 1169-056 Lisboa, Portugal

ARTICLE INFO

Article history:
Received 18 March 2020
Received in revised form
26 May 2020
Accepted 26 May 2020
Available online xxx

Keywords:
Biomaterials
Nanotherapeutics
Clinical oncomedicine
Imaging

ABSTRACT

Since decades, conventional diagnosis and treatment strategies for cancer have been practiced widely despite their expensive and time-consuming process. These conventional contrast and therapeutic agents suffer from various side-effects such as low radiodensity and image resolution, rapid clearance, non-specific biodistribution, poor tumor accumulation, high-dose and multiple-dose requirements, nephrotoxicity, uncontrolled exposure of high electromagnetic radiations, whole-body scans, and so on. Therefore, nanosized imaging and therapeutic probes have been proposed recently owing to their promising efficacy and negligible side-effects. However, these nanoplatforms are struggling deeply to find their clinical translational relevance. Integrating targeting ligands with diagnostic and therapeutic agents within a single system at the nanoscale resulted in localized nanotheranostics. Furthermore, the conceptualized nanotheranostics has been recognized as a clinical 'weapon' for localized cancer nanomedicine. In this review, we have covered a wide spectrum of recent developments in cancer nanotheranostics. Numerous examples of functional nanohybrids and clinical relevant materials with their multimode imaging and therapeutics have been addressed here. On the other hand, the importance of combination therapies, imaging-guided tumor regression, deep tissue visualization, localized diagnosis and tumor ablation, manipulation of the tumor microenvironment, and so on have been discussed here. Overall, localized and stimuli responsive nanosized multifunctional platforms have proved their superiority over conventional diagnosis and therapies.

1. Introduction

Over the past decades, the cost of diagnostics and therapeutics has been rising impulsively throughout the world [1–5]. Even today, conventional diagnostics and treatment strategies, which are being practiced commonly, have gained much attention [1,5]. These conventional options include the combination or stand-alone approaches of radiation therapy, chemotherapy, and surgery [6–17]. However, high doses and high power of electromagnetic radiations come with numerous side-effects and remain as major concerns of these approaches [1,14–16]. Conventional diagnostics depend on the administration of large volumes of contrast media, into the patient's body for evaluating tumor location and volume [11–21]. Nevertheless, non-specific biodistribution, poor accumulation in the tumor area, poor image resolution, rapid excretion, high and multiple doses, and nephrotoxicity are critical issues of these contrast agents [22–25]. Importantly, a correlation between intense reduction in disease related deaths and regular rise in costs has been widely noticed. Thus, developing safe and cost-effective imaging and therapeutic agents has become a priority to overcome the aforementioned limitations [1]. Notably, a gradual shift from the traditional approach to personalized and targeted medicine has been observed in recent years [26–36]. In addition, understanding and manipulating the tumor microenvironment are another interesting area of biomedical research [26]. Subsequently, the rapid growth of new blood vessels in the tumor area, known as angiogenesis, increases the proliferation of endothelial cells with abnormality [37–40]. Heterogeneity with dense vascularization in

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: rpmeena@iitb.ac.in (R. Prasad), joao.conde@nms.unl.pt (J. Conde), rsrivasta@iitb.ac.in (R. Srivastava).

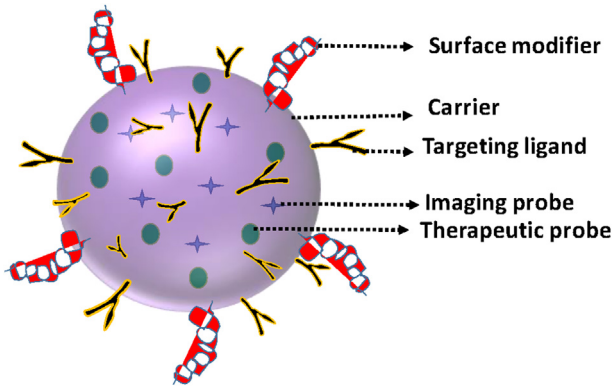
https://doi.org/10.1016/j.mtadv.2020.100087

tumor areas is a significant mark that helps in supplying oxygen and nutrients for rapid growth of the tumor [41–43]. In contrast, a heterogeneous solid tumor has a highly acidic environment, with glutathione, peroxides, and so on, compared with normal tissues [43–48]. Therefore, it is important to understand the tumor microenvironment to design safe contrast and therapeutic agents [49–55]. So far, various technologies have been commonly practiced in hospitals today. Among them, nanobiological technologies have potential impact and have gained much attention for safe and cost-effective diagnosis and treatments over the existing one [56–61]. Moreover, localized treatment strategies demonstrate promising advantages such as site-selective or site-specific binding ability of the injected substance at the desired area without affecting the surrounding healthy tissues owing to the miniature size of the injected probes (imaging and therapeutic agents). For example, the uptake of hybrid materials/nanoparticles into the tumor environment through enhanced permeability and retention (EPR) effect is a well-documented concept [62–64]. In addition, it has also been studied that mature vascularization enhances the uptake/delivery of nanoparticles into the tumor environment compared with prevascularized regions of the tumor [65–67]. But localized distribution and enhanced accumulation of the injected nanosized hybrids in the tumor microenvironment is still being questioned and is an ongoing discussion in cancer nanomedicine [68,69]. To resolve these obstacles, various strategies have been proposed for imaging-guided treatment, followed by single-dose and minimum dose administration of diagnostics and therapeutics [60,70–75]. Furthermore, integrating targeting ligands (bind to the receptors present on cancer cells) with diagnostic and therapeutic agents within a single system at the nanoscale, known as localized nanotheranostics, is a recent concept in cancer medicine. Thus, proposing the integrated theranostics platform has significant impact on cancer nanomedicine with reduced toxicity, other side-effects, time-consuming procedures, and overall cost [56,76–80]. In recent years, various conjugated systems such as bioorganic, bioinorganic, functional inorganic and organic, biological nanoparticles, and so on have been developed and applied for localized nanomedicine due to their better contrasting and therapeutic ability [81–90]. Moreover, these systems have better multimode contrasting ability (emissive nature and radiodensity) for deep tissue visualization, a large surface area to load therapeutic molecules, easy surface functionalization, high biocompatibility, smooth and easy circulation, specific biodistribution, high tumor-binding ability, and so on [91–94]. Our review focuses on the recent developments in diagnostic and therapeutic agents and their modalities. In addition, we also have covered the novel concept and advantages of nanosized theranostics demonstrating enhanced contrast imaging of the localized area.

2. Nanomedicine and nanotheranostics

Few decades ago, surface-engineered nanosized (1- to 100-nm) materials have been proposed for biomedical and sensing applications owing to their specific physicochemical properties at the nanoscale level [1]. Furthermore, nanosized platforms have proved their potential impact for various reasons such as (1) better accumulation and binding on specific sites owing to small dimensions, (2) tunable physicochemical properties (morphology, size, shape, stability, and surface charge), (3) high surface area and volume for large drug payload and their controlled delivery, (4) easy surface functionalization with targeting ligands and biomolecules, and (5) multifunctionality and modality for imaging and therapeutics. Thus, a nanosized platform is always advantageous for biomedical purposes owing to its ability to carry large payload than a small molecule (a conventional platform), while retaining its smooth circulation through the bloodstream. Moreover, these nanomaterials have been classified into three major classes such as metallic, non-metallic, and biological, showing their versatile medical properties for better health care called nanomedicine. These nanosized materials 'nanomedicines' are playing major roles in cost-effective diagnostics and therapeutics. Indeed, these nanomaterials are capable enough to demonstrate their easy uptake and homogeneous distribution in the heterogeneous tumor microenvironment owing to their tiny size. However, these nanomedicines are limited with various disadvantages such as (1) easy aggregation, (2) sometimes too large in size to enter into tumor and too small for easy uptake into cells, (3) non-specific distribution, (4) long-term retention in the body that may cause side-effects, (5) poor image resolution due to low accumulation in desired tissues/tumor, (6) slow degradation, (7) time-consuming procedures for diagnosis and treatments, and (8) high concentration requirement. Therefore, surface engineering and integration of diagnostic and therapeutic agents in a single platform at the nanoscale level, 'known as nanotheranostics,' have been realized as a necessary need to overcome the aforementioned concerns.

On the other hand, an ideal vision of next-generation medicine depends on theranostics representation and its operation in the future. Overall, nanoengineered theranostics has major advantages for site-specific imaging and treatment in short time with minimum dose requirement. But maintaining the effectiveness and efficiency of imaging and therapeutic probes during nanoengineering of theranostics has been another critical challenge so far. Scheme 1 demonstrates the integration of targeting ligand, imaging and therapeutic probes within one platform, which was also explained in 2002 by John Funkhouser, the president of PharmaNetics. The theranostic medicines can reduce the overall expense, prolonged diagnosis and treatment procedures, side-effects, and so on. Recently, nanoscale engineering of theranostics, known as nanotheranostics, has become an ideal trend in biomedical applications especially for multimode imaging and combined therapeutics [1,2]. These smart nanotheranostics have displayed many advantages such as targeting, response to multiple stimuli, controlled delivery, better contrast and treatment efficacy, improved transport efficiency, and so on. Hence, such 'all-in-one' functionality with their multimodality has immense potential, but ultimately they must be adapted for clinical usage. As a result, researchers from various fields are trying to design clinically suitable theranostics by improving the synthesis procedures without losing the efficacy of the fabricated platforms. Recently, developed functional nanotheranostics and their critical challenges have been highlighted in Table 1.



Scheme 1. Schematic illustration of a nanotheranostic system.

Table 1
Nanotheranostics with their critical challenges [1,2].

Nanotheranostics	Testing level	Critical concerns
Metallic	*In vitro* and *in vivo*	Slow degradation and toxicity
Non-metallic	*In vitro* and *in vivo*	Premature release of payload
Biological	*In vitro* and *in vivo*	Site-specific targeting
Quantum dots	*In vitro* and *in vivo*	Rapid clearance and toxicity

3. Nanomedicine for localized infarction of tumor vessels

Profusion of capillaries within tumor angiogenesis causes tumor vascular infarction, which is one of the most efficient ways to inhibit tumor growth. Remarkably, a single blood clot could be sufficient for blocking a single vessel that causes the death of thousand cells. Tumor vasculature inhibition can be achieved through antiangiogenic and site-specific vascular disruption of antitumor molecules [57]. Coagulation factor–induced tumor vessel infarction is a novel approach in vascular targeting applications. Nonspecific bio-distribution of conventional chemotherapeutic drugs result in inadequate therapeutic levels inside the cancer cells where tumor vascular system has direct contact with vascular endothelial cells. Moreover, various anticancer drugs and antiangiogenic and vascular disrupting agents have been tried to inhibit tumor progression and block tumor blood supply. Among several fusion proteins, truncated tissue factor (tTF)-NGR retains its thrombogenic activity and binds to its specific targets on endothelial cells during intravenous infusion, which induces thrombosis in blood vessels, showing perfect tumor growth regression. Conjugated peptide assemblies, viz, tTF-RGD, Cys-Arg-Glu-Lys-Ala, and tumor-homing pentapeptide, are popular approaches in vessel infarction especially in breast and lung cancer. However, poor targeting and high-dose administration limit the applicability of these agents. Thus, nanomedicine-based strategies with better therapeutic efficacy and safety have proved their suitability for localized infarction of tumor vessels in targeted cancer therapy. Targeted tumor vasculature, especially nucleic acid–integrated nanohybrids, is a recent development in onconanomedicine [95–100]. In addition, conductive hydrogel with hydrogen sulpfide release and hydrogel crosslinked with tetraaniline nanoparticles have been tried for localized infarction of vessels. Furthermore, engineering of smart nanotherapeutics has been proposed according to the specific structural and functional features of tumor vasculature. Importantly, nanohybrids that selectively blocks blood supply to the tumor with significant cell death has been studied successfully in treating vessel infarction in a solid tumor (Fig. 1a and b). Vascular infarction and tumor necrosis have been observed via delivering thrombin-loaded DNA nanorobots and polyethylene glycol–conjugated retargeted tissue factor into tumor vessels [95,96].

In brief, DNA-integrated nanoassemblies known as nanorobotics have been tested for targeted imaging, biosensing, and cargo delivery applications, as shown in Fig. 1a [96]. These DNA-based nanohybrids have become much popular for selective occlusion of tumor blood vessels by reducing the nutrient and oxygen level in the tumor environment that induces cancer cell death. In this approach, platelet activation and fibrinogen-to-fibrin conversion occur with obstreperous thrombosis via regulation of platelet aggregation. However, naked thrombin is short-lived in the circulation inducing coagulation events but not yet explored extensively for cancer treatment. Therefore, it is necessary and critical to precisely deliver thrombin solely to tumor sites in a highly controllable manner to reduce its side-effects in healthy tissues. Overall, DNA nanorobotic systems have the possibility to inspire new design of cancer therapeutics by delivery of small interfering Ribonucleic acid (siRNA), and chemotherapeutic anticancer or peptide drugs. Moreover, combinations of these DNA nanorobotic systems with other therapeutic strategies may help to accomplish the eradication of solid tumors [96,101].

On the other hand, polymeric poly(lactic-*co-glycolic acid)*–cofunctionalized nanoplatelets (platelet membranes are extracted from whole blood of mice in this case) are chemically conjugated with the thrombolytic drug, recombinant tissue plasminogen activator (rtPA), which is further evaluated for localized infarction of tumor vessels, as explained in Fig. 1b [102]. Thus, the platelet supported polymeric nanoparticles (nanoplatelets) are considered recently developed targeted delivery systems. These engineered hybrids have been tested for delivery of the thrombolytic drug, rtPA. Surprisingly, these tailored nanoplatelets demonstrate better thrombolysis activity and therapeutic efficacy than free rtPA, indicating their low risk of bleeding complications at the *in vivo* level. Moreover, these platelets support to maintain the integrity of the damaged endothelium and avoid critical challenges of active targeting keynotes to thrombolytic agents because of the inherent targeting molecules on the plasma membrane. Consequently, nanoplatelets gained superiority over the existing molecularly targeted thrombolytic nanotherapeutics. Overall, these hybrid biomimetic nanoplatelets demonstrated a promising solution for better efficacy and reduced bleeding risk of thrombolytic therapy in a wide spectrum of thrombotic diseases.

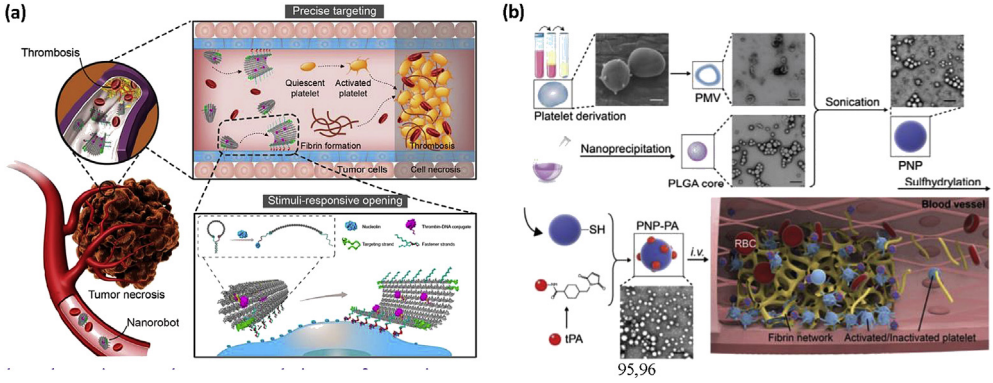


Fig. 1. (a) Localized infarction of tumor vessels using thrombin-loaded DNA nanohybrids (known as nanorobots). Reproduced with permission from ref Mehwish et al [95] and Li et al [96] Copyright of ACS Publishing Group published in 2019 and Nature Publishing Group published in 2018. (b) Schematic illustration and proposed mechanism of polymeric nanoplatelet design and its microscopic images. Reproduced with permission from Xu et al [102] Copyright of Wiley Publishing Group published in 2019. tPA = tissue plasminogen activator; PLGA = poly(lactic-*co-glycolic acid); NP = nanoparticle; RBC = red blood cell*; PMV = *platelet membrane vehicles; SH = represent the thiol groups present on the surface of nanohybrids.*

However, poor targeting ability, short half-lives, and uncontrolled bleeding complications are some of the remaining hurdles of these nanosized platforms.

4. Nanocontrast agents for localized imaging

Early-stage and site-specific diagnosis are major challenges in biomedical research. For decades, small molecule–based conventional contrast agents have been widely used for imaging although they are associated with several potential drawbacks such as nephrotoxicity, rapid clearance, non-specific biodistribution, poor image resolution, poor uptake in the tumor microenvironment, and low biocompatibility [11,103–105]. In the past few years, owing to the high atomic number, density, and radio-contrasting and deep tissue penetration ability, various imaging agents such as Ba, U, Gd, Dy, Yb, W, Pb, Cu, Lu, Ta, Bi, Au, and organic dyes have been tried for bioimaging applications. However, these imaging probes have limitations such as poor uptake and high toxicity issue [11]. To overcome these hurdles, integrating the aforementioned imaging agents in soft/hard matrixes at nanoscale or engineering themselves in nanoformulations has been proposed that are recognized as a versatile approach for better imaging and high resolution of a specific and abnormal area, as shown in Fig. 2a–f. A wide range of functional contrast agents and their advantages and disadvantages has been addressed in this review, as highlighted in Table 2. Specifically, small-sized gold nanorod–encapsulated silica nanohybrids as a diagnostic agent are discussed here as an example. In detail, the designed gold nanorod-silica nanohybrids has been proposed as safe contrast agents for X-ray computed tomography (X-ray CT) imaging owing to the high atomic number and electron density of embedded gold nanorods. The silica overcoating have multiple advantages for gold nanorods such as (1) reduced aggregation, (2) improved biocompatibility, (3) enhanced stability, and (4) circulation. In addition, the silica surface is available for easy surface functionalization. Effective distribution of gold nanorods in silica nanoparticles is recently achieved, as shown in Fig. 2a. On the other hand, small gold nanoparticles are decorated with a silica core, as shown in Fig. 2b. Apart from X-ray CT imaging, these gold-silica nanohybrids are also a promising approach for photoacoustic (PA) imaging owing to better optical absorption and surface plasmon resonance (see Fig. 2c). Importantly, the engineered silica-coated gold nanorod hybrid is decorated with folic acid as a targeting ligand and applied as a safe contrast agent for solid tumor diagnosis and specific biodistribution followed by X-ray CT imaging, as shown in Fig. 2d and e. Similarly, the functional magnetic nanohybrid has been applied for localized imaging of the liver, followed by magnetic resonance imaging (MRI) (see Fig. 2f). Overall, these nanosized structures have potential impact for localized bioimaging and tumor diagnosis [3,11,106–109]. However, the mechanism of interaction between solid tumor and solid nanoparticles is under investigation and is an ongoing discussion in onconanomedicine [109]. Apart from this, so far, various nanostructures such as self-assembled soft nanoparticles, organic nanohybrids, inorganic nanocomposites/hybrids, and bioinorganic/bioorganic nanoparticles have been proposed for deep tissue visualization and targeted tumor imaging owing to their specific binding ability, high contrast ability (radiodensity, emissive nature, stimulus response), and improved accumulation [3,109,110]. Especially, nanosized inorganic hybrids/composites are more chemically stable and widely used in biomedical imaging owing to high X-ray absorption coefficients, high atomic numbers and electron density, noninvasive modalities, high spatial control ability, and so on [11,110]. It has been observed that high electron coefficients, electron density, and electron delocalization decide the brightness and contrast ability of nanoscale hybrid materials to obtain significant comparison between normal and abnormal tissues under the exposure of electromagnetic radiations [105].

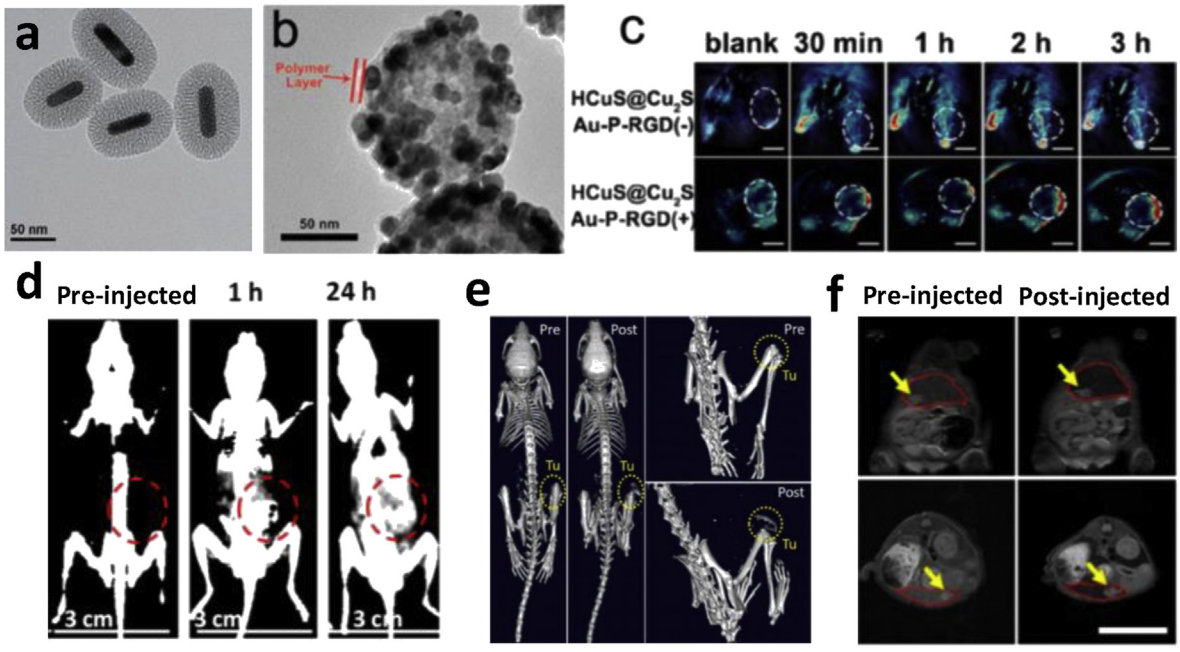


Fig. 2. TEM images of engineered gold-silica nanocontrast agents (a and b), photoacoustic (PA) imaging of the U87MG tumor-bearing mice with and without low power density (50 mW cm^{-2}) pretreatment at different time intervals after intravenous injection of the nanohybrids (c), X-ray computed tomography imaging of tumor-bearing mice using gold-silica nanohybrids and gold nanoparticles as the contrast agent (d and e) and magnetic resonance imaging (MRI) scans of pre-injection and 1 h post-injection of IO cluster C3 or ferumoxytol at a region in the liver (red dotted circle, f). Reproduced with permission from Lim et al [3], Prasad et al [71], Patra et al [106], Deng et al [109], and Zhao et al [110] Copyright of ACS Publishing Group published in 2012, 2015, 2017 and 2018. TEM = transmission electron miscroscopy.

Table 2
Functional contrast agents with their advantages and disadvantages [1–3,106–110]].

Contrast agent	Advantages	Disadvantages	Imaging modality
Iodinated contrast (iohexol, iodixanol, iothalamate, and so on)	1. Cost-effective 2. Better image resolution 3. Higher signal-to-noise and contrast-to-noise ratios	1. Non-specific interactions 2. Rapid clearance 3. Multiple- and high-dose requirement 4. High viscosity 5. Nephrotoxicity	X-ray CT imaging
^{124}I-labeled cRGDY silica	1. Better photo stability and biocompatibility 2. Specific binding ability 3. Long circulation 4. High resolution 5. Easy in surface modification	1. Slow biodegradation 2. Low product yield 3. Low tumor accumulation 4. Easy particle aggregation 5. Long-term retention in the body 6. Complicated synthesis	PET imaging
Plasmonic nanoparticles (Au, Ag, Pt)	1. Easy synthesis, surface engineering, and large production 2. Good stability and biocompatibility 3. High image resolution and deep penetration due to high X-ray attenuation and atomic number 4. Strong tumor-binding and high accumulation ability 5. Better circulation and specific bio distribution ability 6. Minimum dose requirement	1. Easy aggregation and slow degradation 2. Expensive synthesis procedures and high cost of contrast 3. Inflammation of major organs 4. long-time retention in the body 5. High accumulation in the liver and spleen	X-ray CT imaging
Cyanine 5.5, fluorescein isothiocyanate, indocyanine green	1. Easily soluble 2. Biocompatible 3. Deep tissue penetration	1. Poor photo stability 2. Poor circulation 3. Rapid excretion 4. Non-specific biodistribution	Optical and fluorescent imaging
Superparamagnetic iron oxide nanoparticles, macrocyclic compounds chelated with paramagnetic metal ions like gadolinium (Gd^{3+}) and manganese (Mn^{2+}), MnO nanoparticles	1. Better image contrast due to high rotational correlation time and low relaxivity 2. Biocompatible 3. Strong and better tumor accumulation ability 4. Better dispersibility 5. High surface-to-volume ratio	1. Complicated synthesis and low product yield 2. Non-specific biodistribution 3. High concentration need for high image resolution 4. Requirement of high magnetic field 5. Low circulation 6. Slow degradation	MR imaging
Carbon nanotubes, gold nanorods, gold-silica nanohybrids, organic dyes, porphyrin-phospholipid–coated upconversion nanoparticles, silicon nanoparticles	1. Simple design and high photostability 2. Deep tissue penetration ability 3. Enhanced surface plasmon resonance 4. Good biocompatibility 5. High optical absorbance	1. Low conversion efficiency due to poor absorption 2. Slow degradation in case of inorganic hybrids 3. Low sensitivity 4. Low tumor accumulation and binding ability 5. High accumulation of nanoparticles in the liver (30–99%)	PA imaging

CT = computed tomography; MR = magnetic resonance; PA imaging = photoacoustic imaging.

On the other hand, several imaging techniques such as PA imaging, X-ray CT, MRI, positron emission tomography, ultrasound (US), and fluorescence molecular tomography have been established for clinical imaging applications [110,111]. Each imaging modality has its unique merits and limitations. However, these imaging techniques require nanosized contrast agents to improve data visualization. Thus, single-nanostructure–based contrast media can be used for multiple imaging modalities to take major advantages of the promising benefits of such hybrid imaging techniques, and several examples are documented in the literature [105]. Interestingly, surface engineering and functionalization of proposed nanosized contrast agents improve the specific biodistribution, tumor accumulation ability, and localized tumor diagnosis with better resolution. The slightly larger size and surface functionalization also enhances blood circulation and biocompatibility of the injected nanosized contrast agent compared with conventional contrast media [11,109]. Moreover, the conventional contrast agents are limited with poor surface modification and engineering; therefore, they induce high toxicity and poor image quality. Hence, proposing nanosized imaging probes could have a potential impact for targeted tumor imaging and should be considered as major developments in nanobioimaging applications [105].

5. Nanotherapeutic agents for imaging-guided cancer therapy

Traditionally used chemotherapeutic drugs show non-specific distribution and are therefore associated with high toxicity and side-effects [112]. In addition, these drug molecules are unable to differentiate between healthy and cancer cells owing to their molecular size and easy penetration into the cellular interior [101,113–115]. Consequently, nanocarriers were proposed to make them specific and carry drugs to the targeted site of the tumor/cells because of easy surface functionalization, have a large surface area, and large cargo capacity of engineered nanostructures [70,107]. Identification of specific receptors on the cell membrane is essential to promote high accumulation of modified nanoconjugates into the tumor cell by surface modification with targeting ligands. In fact, surface modification enhances biocompatibility and blood circulation of the injected nanohybrids and prevents direct contact of the loaded drugs with red blood cells and other healthy cells/tissues [101,107]. Overall, surface-modified nanohybrids have a strong binding ability toward cancer cells but not with healthy cells owing to the interaction between specific targeting ligands and receptors on the cancer cell membrane

Table 3
Functional therapeutic agents with their advantages and disadvantages [116–134].

Therapeutic agent	Advantages	Disadvantages	Therapeutic modality
Porous silica, DOX-liposome, DOX-PLGA, DOX-graphene oxide, gold nanoshell, silica-gold nanohybrids, quantum dot–gated mSilica, WS_2	1. Large surface area and cargo capacity 2. Smooth circulation 3. Easy preparation and reproducibility 4. Better stability 5. Easy surface modification	1. Premature cargo release 2. Poor tumor accumulation 3. Non-specific biodistribution 4. Slow degradation 5. Long-term toxicity	Chemotherapy
Gold nanorods, nanocages, gold-liposomes, graphene oxide–wrapped liposomes, gold nanorod–encapsulated silica, copper sulfide, plasmonic nanoshell, ICG-mSilica spheres, PEGylated silica-gold nanoshells	1. Easy preparation 2. Good optical property 3. Enhanced surface plasmonic property 4. Good biocompatibility and smooth circulation 5. Good photothermal response 6. Easy biodegradation (in case of gold-liposome and graphene oxide–wrapped liposome)	1. Easy aggregation 2. Long-term exposure (10–30 min) and high power (3–20 W/cm^2) requirement of NIR light 3. Uncontrolled photothermal damage of surrounding healthy tissues 4. Slow excretion 5. Low tumor-binding ability	Photothermal therapy
Quantum dots, organic dye–based photosensitizer (indocyanine green toluidine blue, methylene blue, hypericin), porphyrin, chlorine 6, dye-conjugated gold nanorods and 2D Mxene, dye-loaded liposomes, $NaYF_4$:Yb^{3+}, Er^3, metal-organic framework, copper bismuth sulfide	1. Easy synthesis 2. High product yield 3. Better optical property 4. High production and rapid effect of ROS 5. Easy and high tumor-binding ability 6. Smooth circulation and good biocompatibility 7. Easy excretion	1. High cost 2. Non-specific ROS distribution 3. Uncontrolled oxidative stress on healthy tissue/cells 4. Low stability 5. Uncontrolled particle size (in case of inorganic hybrids) 6. High power density requirement of NIR light	Photodynamic therapy
Drug-loaded plasmonic nanoshell, DOX-loaded graphene oxide–wrapped liposome, DOX@single-wall carbon nanotubes@BSA@Au–S-PEGFA, DOX@GNR-mSilica, DOX-graphene oxide, DOX-AuNRs@liposomal nanohybrids	1. High cargo capacity and thermal conversion efficiency 2. Good biocompatibility 3. Controlled drug release and therapeutic ability 4. Significant tumor reduction and cancer cell death 5. Better reproducibility 6. Minimum NIR light exposure requirement with low power (0.5–2.0 W/cm^2) 7. Easy degradation ability	1. Non-specific biodistribution 2. Side-effect on the surrounding healthy tissues 3. Poor blood circulation 4. Uncontrolled side-effect of the released chemotherapeutic drugs 5. Long-term side-effects 6. Expensive process	Combined chemo-photothermal therapy

NIR = near-infrared; ROS = reactive oxygen species.

(Fig. 3). On the other hand, EPR effect and nanohybrid accumulation in the tumor microenvironment have been widely studied so far [116,117]. The EPR effect helps in improving the delivery of cargo carriers and drug molecules to the tumor area wherein vascularization is well matured. Importantly, low vascularized areas in tumors reduce the entry of injected nanohybrids/drug molecules, which can prevent cytotoxic effect on cancer cells, which can lead to tumor recurrence after treatment [2]. Second, the acidic environment of cancer cells/solid tumor offers resistance to anticancer drugs and prevents their movement across the cell membrane. Third, non-specific distribution and poor uptake of chemotherapeutic drugs results in cytotoxicity and various side-effects on major organs, mainly on the liver, kidneys, and spleen [2,117]. To resolve the aforementioned critical issues of cancer therapy, current research is focused on developing nanohybrids called as 'nanotheranostics'-based therapeutic approaches, for localized/targeted treatment [110,118], which presents improved eradication of solid tumor/cancer cells (Fig. 4a–d). Recently, developed nanomedicines are being engineered to deliver anticancer/therapeutic drugs exclusively to the tumor with a more effective concentration, without damaging the surrounding healthy tissues (see Table 3).

Fig. 4a shows the diagrammatic representation of a functional nanotherapeutic design along with its surface engineering. In recent years, nanosized systems have been proposed for manipulating the tumor microenvironment owing to the biocatalytic and specific biological properties of the administered small-sized particles (widely studied for 10–500 nm) compared with larger particles (more than 1000 nm), as shown in Fig. 4b [119]. After entering into cancer cells and into the tumor microenvironment, these nanoparticles produce reactive oxygen species (ROS), heat, and sound waves upon exposure to external stimuli. This can be attribute to their specific properties such as light to heat response or light to sound response to targeted the treated cancer cells [2,71,119]. Apart from this, the irradiation of external stimuli induces the triggered release of loaded therapeutic agents/drugs from the fabricated nanohybrids [71]. Functional nanohybrids have been applied for an external stimuli active multimode imaging and therapeutics, as shown in Fig. 4c and d. Overall, nanosized platforms can be engineered according to the need for internal (pH, H_2O_2, glutathione, and so on) and external (heat, temperature, magnetic field, US, light, and so on) stimulus conditions that mimick the cancer cell cytoplasm/tumor microenvironment, demonstrating their bioresponsive nature for safe nanomedicine [120]. With respect to the aforementioned stimuli, some targeted nanotherapeutics has been designed for safe treatment. Specially, some of the targeted therapies have been tested and established at the preclinical/clinical level with promising therapeutic response without showing any side-effects on healthy cells and tissues, which is due to their site-selective ability. Recently proposed cancer therapies using nanomedicines as safe treatments are discussed in the following sections.

5.1. Near-infrared light–mediated photothermal therapy

Light-mediated photothermal therapy (PTT) using photothermal active nanohybrids has attracted a much attention for tumor

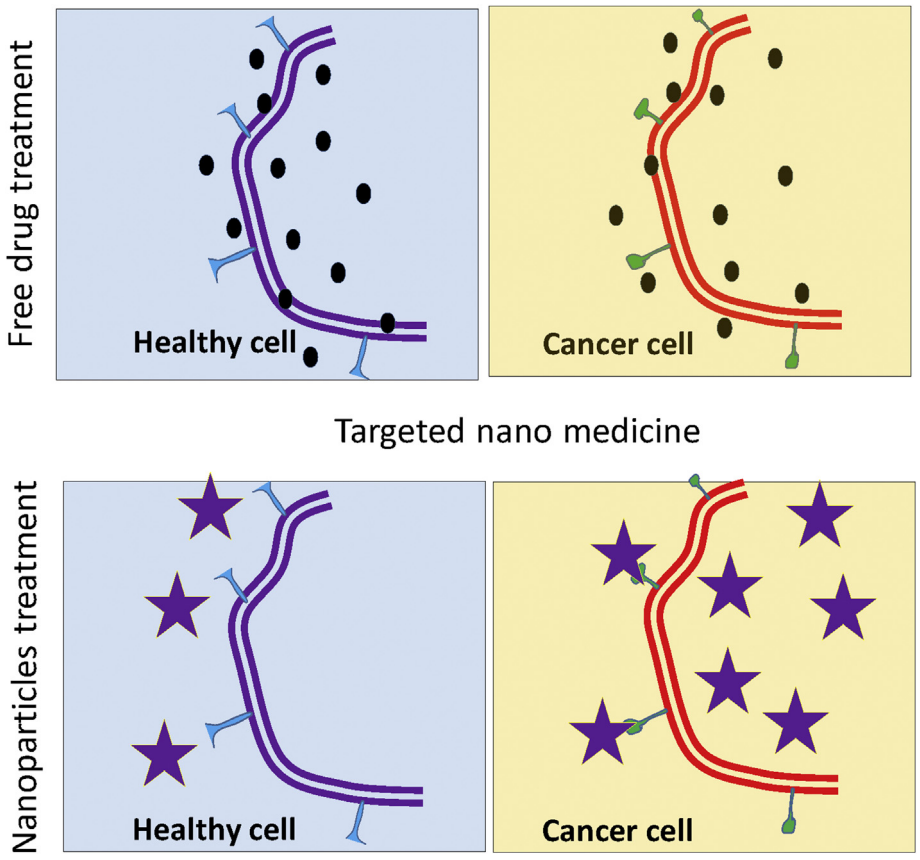


Fig. 3. Distribution of free drugs (black dots) and targeting ability of surface-functionalized nanohybrids (star size) with healthy (sky-colored receptors) and cancer cells (green-colored receptors) demonstrating the impact of the targeting ligand.

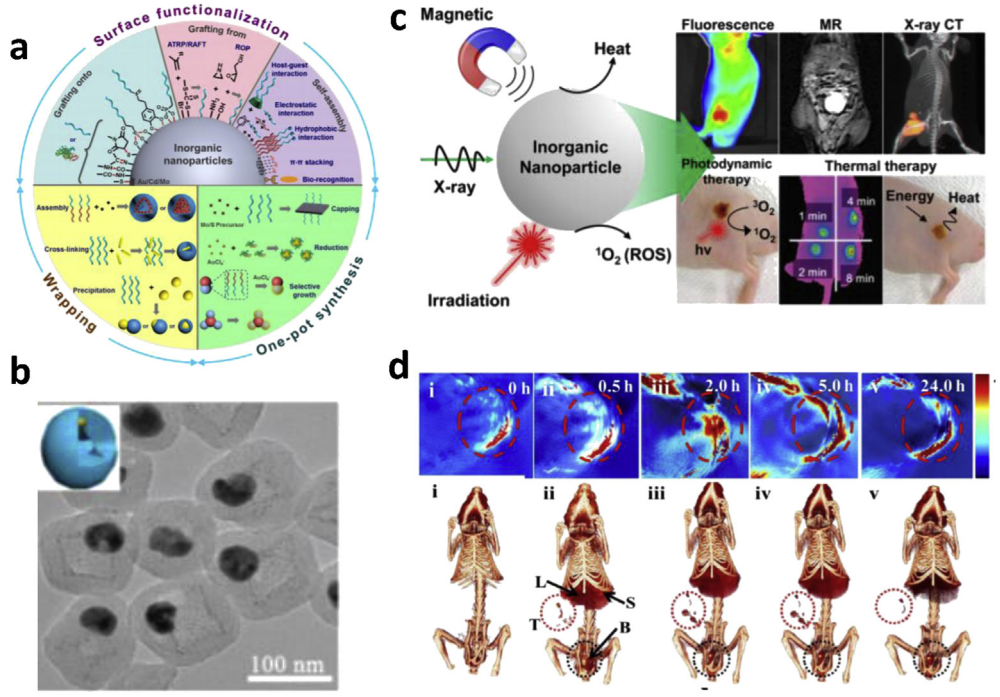


Fig. 4. Engineering the nanotherapeutic agents (a), TEM image of nanotherapeutics agent (b), image guided tumor regression or ablation using nanotherapeutic agent under external stimuli conditions (c), localized tumor diagnosis in animal model at various time points upon injection of nanotherapeutic agent (d). Reproduced with permission from ref 110,118, and 119. Copyright of Wiley and ACS Publishing Group published in 2015, 2017, and 2018.

reduction owing to its non-invasiveness and high selectivity [1,2,71,109,116–121]. Moreover, PTT has been recognized as a promising treatment for cancer therapy owing to deep penetration power of exposed near-infrared (NIR) light, high photothermal conversion efficiency, and low absorption ability by healthy tissue [109,122–124]. Thus, the generated photothermal heat demonstrates its selective effect in tumor regions (photothermal agent–accumulated area) during NIR light irradiation without affecting the surrounding healthy tissues/cells [122,123]. So far, various nanosized photothermal platforms such as organic dyes, gold-silica nanohybrids, gold-liposome nanostructures, CuS_{NC}, $CuS@MnO_2$ hybrids, plasmonic gold nanorods, 2D nanosheets (graphene oxide, MoS_2, WS_2, MXene, and so on), plasmonic nanoshell, gold nanorod–encapsulated polymeric nanohybrids, and so on have been proposed for localized tumor ablation [2,3,71,125–129]. Some recent observations of localized PTT have been explained in Fig. 5a–d. Furthermore, the strong absorbance of these nanostructures in the tissue-transparent NIR optical window (650–900 nm) makes them suitable candidates for photothermal cancer therapy [127,130]. The first window of the NIR range (650–900 nm) is widely studied for plasmonic PTT for localized tumor ablation [3,71,124,128,129,131–133]. Particularly, different types of gold nanoparticles (nanoshells, nanorods, and nanocages) have been validated for PTT owing to better surface plasmon resonance and phototransduction property [132,134,135]. Interestingly, NIR light–mediated PTT has been investigated for preclinical and clinical studies that demonstrate its potential impact for tumor regression [133]. For example, surface-engineered gold nanorod structures have been evaluated for localized PTT, as shown in Fig. 5c and d. During NIR light exposure, the promising photothermal response from the tumor area is indicative of easy accumulation and homogeneous distribution of small-sized nanorods in the tumor environment (see Fig. 5c). Furthermore, the generated heat enhances the photothermal damage of tumor cells, which is validated in animal studies. A comprehensive *in vivo* examination (tested up to 25 days) demonstrated significant tumor reduction in case of surface-modified nanorods compared with parent nanorods, exhibiting the potential impact of localized therapy, as shown in Fig. 5d. Interestingly, good penetration power of NIR light enhances the homogeneous photothermal effect in the whole tumor environment and damages the nucleic acid of the targeted cancer cells [132]. However, ROS are observed recently as the second major product of PTT that damage cancer cells and healthy cells via oxidative stress and oxidation of the cell membrane [55]. The non-specific distribution of ROS induces various toxic effects in healthy cells/tissues by affecting their cellular interior. To the best of our knowledge, the potential validation of PTT depends on (1) localizing these produced ROS toward cancer cells or (2) scavenging these produced ROS to reduce the oxidative damage of healthy tissues/cells. Therefore, nanoscavengers (bimetallic plasmonic gold nanorods) have been proposed recently for targeted cancer cell elimination [52]. Apart from these concerns, slow degradation, poor tumor accumulation, low binding ability, non-specific biodistribution, slow clearance, long-term toxicity, and so on are the remaining challenges for inorganic photothermal agents, which need to be resolved for safe onconanomedicine. Therefore, dye-conjugated organic soft nanosized platforms have been conceptualized as safe and potential photothermal agents for targeted nanomedicine, but low photostability and poor reproducibility are major concerns of these systems [136].

Hence, engineering bioresponsive nanohybrids could resolve the aforementioned limitations and fulfill the requirements of safe therapeutic platforms in PTT. For example, liposomes and polymeric nanohybrids represent major achievements in cancer nanomedicine owing to their good biocompatibility, high capacity to carry photothermal agents, high tumor accumulation, and easy surface modification with targeting molecules [137–140]. Second, nanoscavengers are also another recent example of photothermal therapeutics in onconanomedicine [52].

5.2. Photodynamic cancer therapy

NIR light–mediated photodynamic therapy (PDT) is another promising approach for selective tumor reduction, especially photosensitizer (PS)-based PDT [141–144] (see Fig. 6a–d). In PDT, toxic oxygen species, viz, ROS produced from PS molecules during light exposure, destroys the tissue environment and kills selective cancer cells. Localized and efficient delivery of NIR light (both the first and second optical window) improves the effectiveness of PSs in PDT, showing promising oxidative stress and toxicity for targeted cancer cells/tumors [145–154]. However, poor site selectivity is the critical concern with most PSs which results in its wide distribution to healthy tissues and cells instead accumulating into tumor microenvironment [148,149]. In addition, the non-specific distribution of produced ROS in healthy tissues especially in skin causes various side-effects [151–154]. Furthermore, light-activated PSs can penetrate deep into biological tissues, which plays an important role in PDT using lasers, halogen and arc lamps, and light-emitting diodes [152]. Absorption of clinically approved PSs (e.g. porphyrin and its derivatives) in the visible region limits light penetration, which reduces the efficiency of PDT [155–157]. Developing NIR absorption PSs could be a potential solution to overcome the limitation of PDT for deep tumor treatment [158,159]. Therefore, two-photon excitation is the best way to shift the absorption ability of PSs toward the NIR range (700–1100 nm), which demonstrates a higher deep penetration power (up to 5-mm depth) for improved PDT effect [160–164]. Interestingly, two-photon excitation is consistently better than one-photon excitation owing to high spatial control of PS activation in three dimensions during PDT treatment and the high signal-to-background ratio [162,163]. Apart from phototoxicity toward healthy tissues, these PSs suffer from poor photostability, low circulation, poor binding and accumulation ability, and rapid quenching process, which results in low efficacy of ROS generation and poor PDT performance [165]. The rapid growth in nanobiotechnology and nanomedicine opens adaptable opportunities to overcome the limitations of conventional PDT by integrating multiple components in a single therapeutic strategy. Furthermore, to overcome the whole body circulation of injected PSs that cause phototoxicity, nanohybrids have been proposed to carry these PSs to make them site selective. The carrier systems such as liposomes, porous carbon, porous silica, polymeric matrix, and so on prevent the direct interaction between PSs and the healthy cellular/tissue environment [166–168]. For example, liposomal nanostructures are recently proposed for PDT applications, as shown in Fig. 6a and b. Folic acid as a targeting ligand has been attached to the exterior surface of these PEGylated liposomal nanohybrids (1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) named as DSPE-PEG liposomes), which are validated for *in vitro* and *in vivo* anticancer activity. A significant tumor reduction (more than 64%) is observed during NIR light irradiation, indicating the site-specific delivery of the produced ROS and their oxidative stress on the tumor microenvironment (see Fig. 6b). Hence, nanosized platforms have a major role in the current strategies of PDT, followed by active and passive targeting pathways, as shown in Fig. 6c and d [146,169–172]. The EPR effect enhances the passive targeting and high accumulation ability of nanohybrids in the deep tumor environment, whereas surface modification with a specific targeting ligand improves the active binding ability of these nanosized systems. Moreover, these carriers enhance the biocompatibility, photostability, site-selective tumor-binding ability, and bioresponsive delivery of PSs. In some cases,

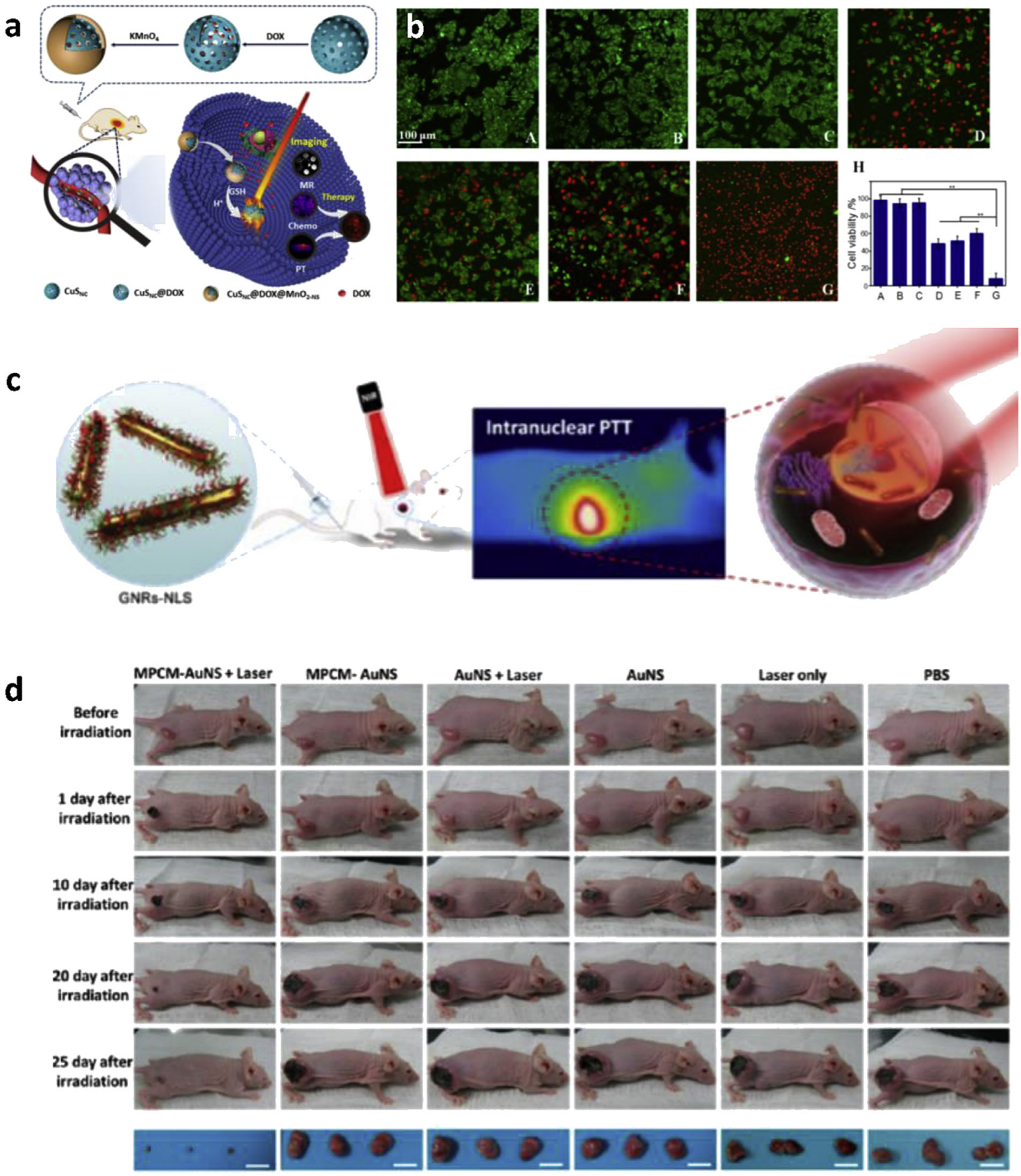


Fig. 5. Engineering the photothermal active nanotherapeutic agents (a), *in vitro* validation using various formulations of photoresponsive nanohybrids (A to G groups) for plasmonic photothermal therapy followed by live-dead cell staining and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (b), planning for *in vivo* tumor ablation under NIR light exposure (c), time-dependent *in vivo* examinations of localized tumor reduction during localized photothermal cancer therapy (d). Reproduced with permission from Pan et al [131], Xuan et al [132], and Lin et al [133] Copyright of Wiley and ACS Publishing Group published in 2015, 2017 and 2018. NIR = near-infrared; AuNS = gold nanorod structure; PTT = photothermal therapy; PBS = phosphate-buffered saline.

nanoparticles are exposed to X-rays as an energy source to initiate PDT against solid tumors, which aids in localized diagnosis and radiation therapy [173].

5.3. Targeted cancer immunotherapy

Today, targeted cancer immunotherapy has evolved as an authoritative effective strategy in cancer treatment [185]. Multitier immunosuppressive mechanisms hamper the immune system of patients with cancer [174–177]. The tumor-specific immune response is observed in cancer immunotherapy, which has received tremendous attention today [178]. Weak immunogenicity of cancer antigens creates negative regulatory pathways and poor infiltration of T cells into the tumor, and thus, tumor-immunosuppressive microenvironments promote cancer-immunity cycles [179–186]. Recently, chimeric antigen receptor (CAR)–reprogrammed T cells, known as CAR-T cells, represent breakthrough modalities in treating blood cancers such as B-cell

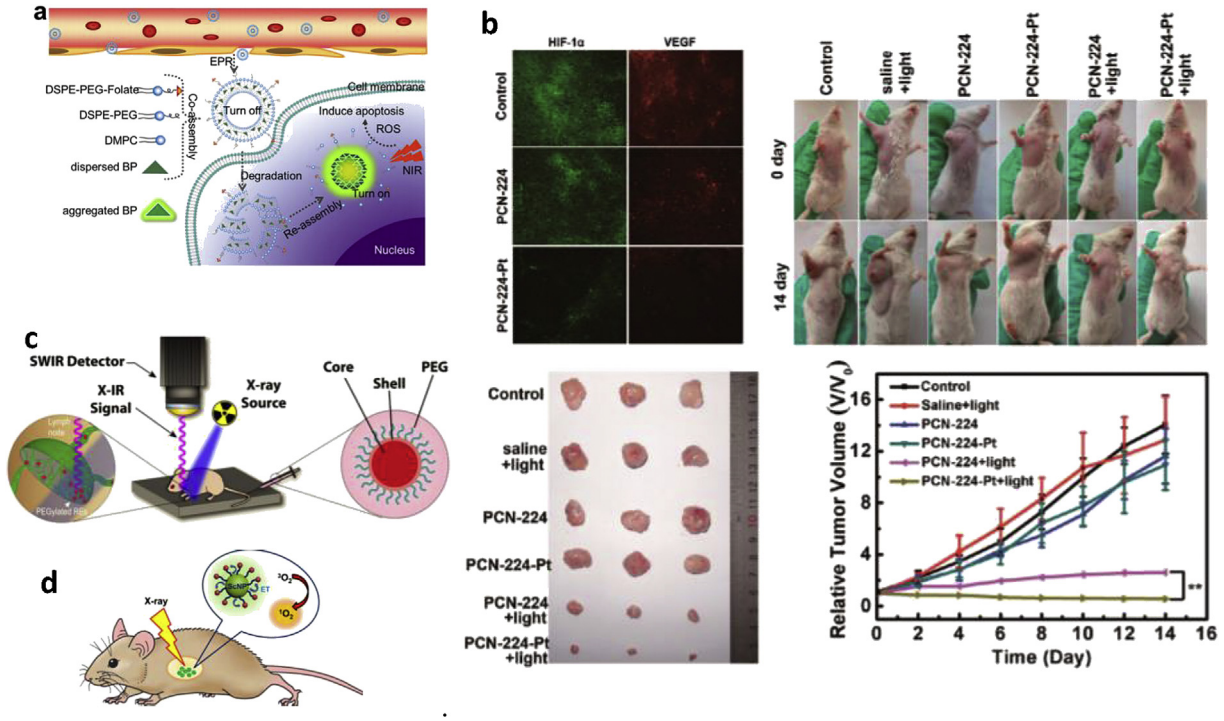


Fig. 6. Illustration of NIR light–activated PDT planning using assembled AIE-PS@liposomes as targeted PS for PDT (a), NIR light–mediated *in vivo* PDT observations of Zr-MOF nanoparticle by intratumoral injection in a subcutaneous tumor model (b), X-ray–induced PDF in animal models using nanohybrids (c and d). Reproduced with permission from Kamkaew et al [146], Naczynski et al [170], Yang et al [171], and Zhang et al [172] Copyright of ACS Publishing Group published in 2015, 2018, and 2019. PDT = photodynamic therapy; NIR = near-infrared; PS = photosensitizer; EPR = enhanced permeability and retention; ROS = reactive oxygen species; PEG = poly(ethylene glycol).

leukemia via direct reorganization of cancer cell surface antigens instead of using antigen peptide–targeting moieties [187–189], as shown in Fig. 7a–f. However, some major concerns of immunotherapy related to their good efficacy and reduced side effects remain unaddressed. For example, longer HA rods have been evaluated for prolonged Alex Fluor 647-OVA retention and cell accumulation around the injection site at the *in vivo* level, as shown in Fig. 7a and b. Furthermore, the accumulation is validated with *in vivo* imaging and various other characteristics, as shown in Fig. 7c and d. Overall, activation and proliferation of T cells are mandatory in cancer immunotherapy, to kill the tumor cells effectively [189]. In addition, TAA-relevant pMHC complexes and OVA-HBc nanocages have been tested for cancer immunotherapy (see Fig. 7e and f). Importantly, cytokines, antigens, and antibodies are immune boosters, and these agents involve mostly peptides/or proteins that moderate the host immune cells via binding toll-like receptors (TLR) on dendritic cells (DCs) and T-cell receptors [190–192]. Inefficient delivery of these therapeutic agents to tumor sites is still being questioned, which needs to be resolved. Second, oral administration of protein- and peptide-based drugs is associated with poor circulation and low biocompatibility [193]. As a result, biomaterial-based therapeutic systems are required to minimize the clearance and degradation of these drugs [194]. Moreover, these biomaterial-based systems improve the biocompatibility and targeted delivery of these drugs on the specific site of tumor via conjugation with precise targeting ligands. So far, a number of bioresponsive hybrid materials have been designed to deliver a variety of immunomodulators, engineered without genetic modification [195]. For example, a protein nanostructure 'in the form of nanocage' is recently applied as a potential functional platform for nanomedicine. Multiple functionalities have been integrated in the nanocage form, followed by genetic and chemical modification, such as OVA peptide, which is conjugated with the hepatitis B core protein nanocage (OVA-HBc), as shown in Fig. 8a–e. The designed OVA-HBc nanostructure demonstrates good effectiveness of epitopes, which can induce bone marrow–derived DC maturation effectively. Furthermore, OVA-HBc nanohybrids as a potential nanovaccine demonstrate better immunity against tumor and significant tumor growth inhibition. These biomaterial-based platforms can minimize the dose and the concentration of the administered drugs, which are the major advantages in current cancer nanomedicine.

5.4. Targeted combination therapies

So far, it has been observed that stand-alone chemotherapy, phototherapy and radiation therapy remain the dominant treatment for a variety of cancers [196–199]. Among them, PTT and chemotherapy have become popular research topics individually and represent emerging and promising approaches for cancer therapy [200–203]. However, they are far from achieving a complete reduction or elimination of various tumors before translating to the clinical level. Overall, it is well studied and documented in the literature that stand-alone cancer therapies such as chemotherapy, phototherapy, PDT, or radiation therapy are unable to reduce the tumor significantly [70]. Hence, it is believed that the combination of these strategies could be more beneficial for significant tumor regression [203]. Recently, numerous combinations of functional agents such as photothermal agents, chemotherapeutics drugs, and PSs in a single platform have been conceptualized for a targeted safe therapy [2,204], as shown in Fig. 9. To the best of our opinion, developing a tumor microenvironment–responsive theranostics platform with multimode imaging–guided combination therapeutics can solve some of the major challenges of localized cancer nanomedicine

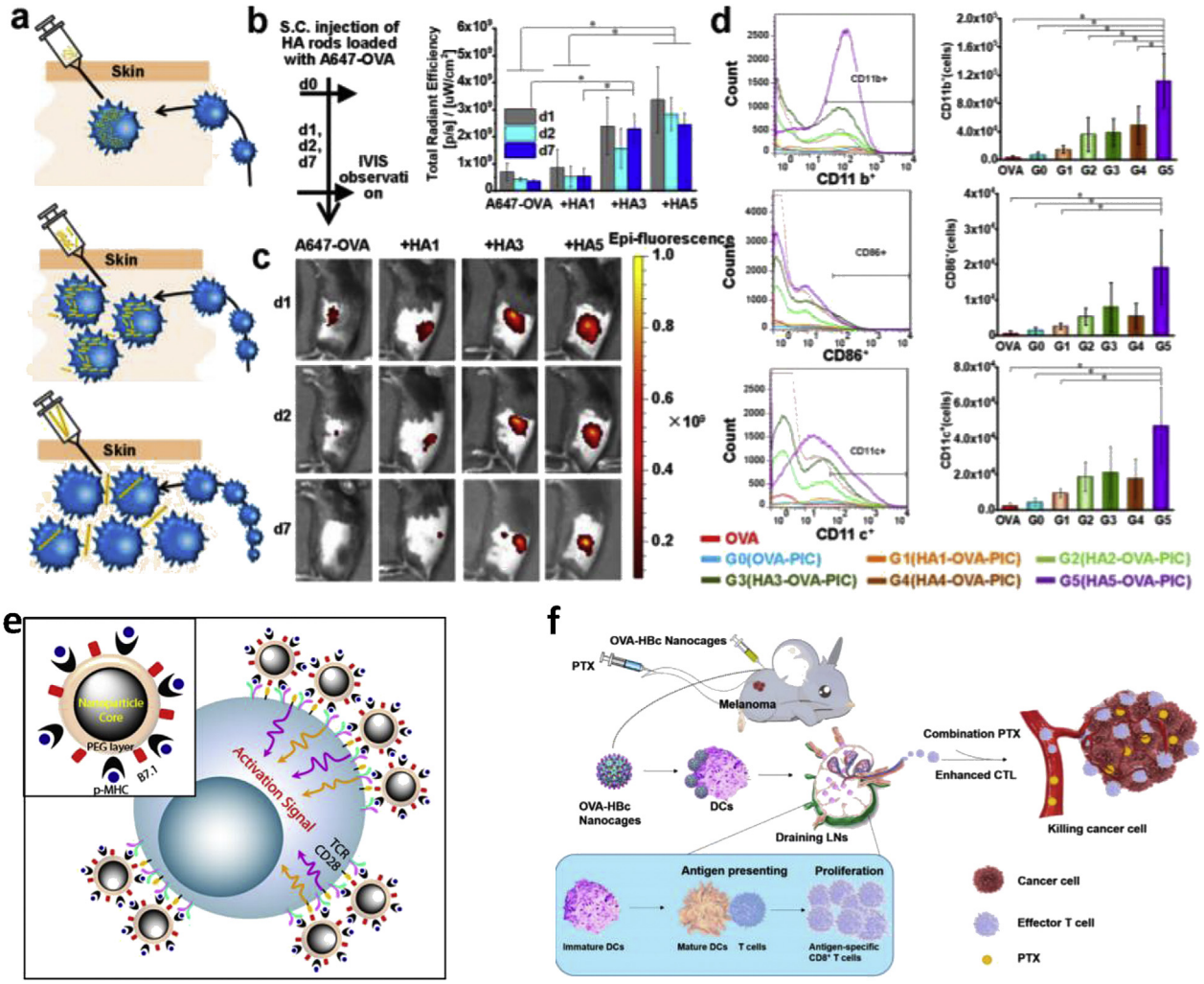


Fig. 7. Longer HA rods significantly prolong Alex Fluor 647-OVA retention and promote $CD11b^+$, $CD86^+$, and $CD11c^+$ cell accumulation around the injection site *in vivo* (a and b), experimental procedure (left) and total radiant efficiency around the injection site (c), *in vivo* imaging system (IVIS) images of mice 1, 2, and 7 d after subcutaneous injection (d), $CD11b^+$, $CD86^+$, and $CD11c^+$ cell accumulation around the injection site *in vivo* for various hydroxyapatite (HA) rods (c and d), direct T-cell-triggering microparticle/nanoparticle structures displaying TAA-relevant pMHC complexes and T-cell costimulatory molecules (anti-CD28 mAb) for T-cell activation (e), and schematic showing the OVA-HBc nanocage-mediated antitumor immunity in cancer immunotherapy (f). Reproduced with permission from ref Wang et al [179], Shao et al [185], and Shan et al [186] Copyright of ACS Publishing Group published in 2015 and 2019. DC = dendritic cell; TCR = T-cell receptor.

[2]. During integration of multiple therapeutics in a single system, nanohybrids face several limitations such as loss of their unique therapeutic abilities in the tumor microenvironment or even before reaching the target site, time-consuming and complicated process, reduction in the surface area leading to low cargo-loading capacity and uncontrolled particle size distribution, easy aggregation, poor degradation, and so on. Hence, several nano-sized hybrids/composites based on lipid soft assemblies, organic assemblies, polymeric particles, micelles, drug-conjugated polymeric nanohybrids, PS-tagged drug-loaded polymeric spheres, organic dye–loaded liposomes and polymers, drug-loaded liposome-gold, drug-loaded silica-gold, drug-loaded conjugated graphene-silica, and so on have been proposed for combination therapies, known as chemo-photothermal therapy, photothermal-photodynamic therapy, chemo-photodynamic therapy, and a triple combination of PTT, PDT, and chemotherapy [205–209]. However, non-specific biodistribution, low tumor accumulation ability of the injected nanomedicines, slow degradation, significant tumor size reduction, inflammation, and poor circulation are critical limitations of these proposed nanohybrids and treatment strategies [55,71,210–212].

For example, a novel structure of gold nanorod–encapsulated silica nanohybrids loaded with anticancer drug has been proposed for synergistic chemo-photothermal therapy, as shown in Fig. 9. The designed nanostructures exhibit strong absorption ability in the NIR range and show their deep penetration ability owing to localized surface plasmon resonance (LSPR) and high electron coefficient. Significant photothermal response of nanohybrids is achieved owing to better LSPR that enhances cancer cell death induced by photothermal heat, as shown in Fig. 9a–c. Fig. 9d shows the effective photothermal response of the nanohybrid-injected animal model demonstrating the potential effect of plasmonic nanohybrids for light-mediated therapy, which is further validated by several *in vitro* and *in vivo* measurements (see Fig. 9e–l). The simple nanoengineering of multifunctional plasmonic gold nanorod–based nanohybrids for combined cancer therapeutics has been demonstrated in Fig. 9m and n. Overall, engineering nanosized medicines in light of features of tumor microenvironment conditions (hypoxia, enzymes, ROS, acidity, and glutathione) has become a recent trend in onconanomedicine [55,213–219]. Thus, these designed nanomedicines demonstrate their potential impact under cellular conditions that exhibit

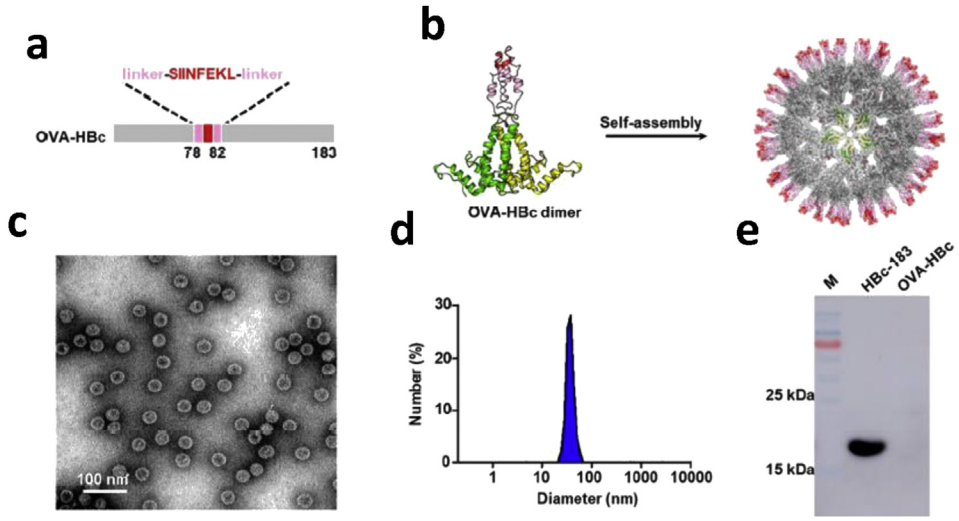


Fig. 8. A novel design of the immunotherapeutic nanoagent. Schematic representation (a), 3D assembly (b), transmission electron microscopy image (c), and dynamic light scattering analysis (d) of the genetic fusion (OVA-HBc). Protein-antibody activity is confirmed by Western blot analysis (e). Reproduced with permission from Shan et al [186] Copyright of ACS Publishing Group published in 2019.

significant death of cancer cells/tumor cells and prevent their premature effect in the physiological environment (known as the extracellular environment) [219]. These bioresponsive stimulus help nanohybrids to trace cancer cells and perform their ability in the cancer-mimicked environment (Fig. 9). Thus, a rational design of the combination of different therapeutic modalities in a single nanoplatform may be a potential approach for enhanced therapeutic response, especially for synergistic therapeutic effects on tumor reduction. Despite the various advantages of combined therapeutics, these strategies suffer from several limitations, such as the fact that combined photodynamic-photothermal therapies not only produce heat and ROS that destroy cancer cells [55] but also have non-specific uptake by normal tissues during the therapeutic process, which not only reduces phototherapeutic efficacy but also causes undesired damage to normal tissues/cells [55,220–222].

6. Nanomaterials into the solid tumor environment

Effective penetration and delivery of diagnostic and therapeutic nanomaterials into solid tumors is essential to decide the smartness of cancer nanomedicines [122,223–227] (see Fig. 10). Studies from earlier reports have suggested that tumor vasculature and the extracellular medium modulate the transvascular and interstitial transportation of nanohybrids, and both are critical for effectively delivering nanohybrids into the solid tumor environment [228–230]. Moreover, morphology of blood vessels and the tumor microenvironment exhibits extensive permeability of nanoparticles, as shown in Fig. 10a–c [231–233]. Ineffective delivery of nanohybrids/composites into solid tumors is recognized as one of the major challenges in cancer nanomedicine [230]. Interestingly, the physicochemical properties of the administered nanoparticles play a major role in biodistribution, targeting efficiency, therapeutic outcomes, and safety in biological systems, which allow utilization of the advantages of nanohybrids in onconanomedicine [230,234]. On the other hand, in cancer nanomedicine, the passive targeting of nanoparticles is an easiest known pathway for solid tumor targeting, which occurs by the EPR effect [64,230,234–237]. In EPR, nanocarriers often do not travel owing to slow diffusion within the tumor and increased interstitial fluid pressure [2,230]. For example, biotin-PEGylated gold nanoparticles have been examined for specific biodistribution and tumor accumulation, as shown in Fig. 10d. In addition, the observed dense extracellular matrix in tumor tissues also induces slow diffusion of nanoparticles as a result of which transportation of nanohybrids into tumor tissues is often regulated to perivascular regions [230]. More importantly, the heterogeneous vasculature perfusion is notable in solid tumors that have several regions with poor vessel perfusion and necrosis. However, the clear mechanism of the reaction between nanoparticles and the tumor microenvironment is less explored [2]. So far, external stimulus–based approaches have been proposed to improve nanoparticle penetration into tumors; especially, nanoparticles that reduce their size in the tumor microenvironment have been used to improve diffusion into the interstitial space [2,230]. These aforementioned concerns have been validated through the outcomes of radiation and US therapeutic modalities but are suffering from various limitations [238–242]. Overall, it has been understood that the designed nanoparticle must have a long circulation time to avoid the physical and biological barriers in the tumor microenvironment, which helps for their tumor uptake [243,244]. Nevertheless, only few studies have described the fundamental physicochemical properties of injected nanoparticles that greatly influence their blood circulation, specific biodistribution, localized tumor targeting, and smooth clearance [242–248].

On the other hand, recently, it has been reported that the entry of a nanoparticle through the gaps between endothelial cells (gaps were reported to be up to 2 μm) in the tumor blood vessel that are molded during angiogenesis is a central pattern in cancer nanomedicine, as shown in Fig. 10a and b [230,247]. But, recently, it is realized and reported that these interendothelial gaps are not responsible for the transportation of nanoparticles into the solid tumor environment. The recent report demonstrates that about 97% of nanoparticles enter the solid tumor environment through endothelial cells, followed by active uptake process [230].

7. Clearance pathways of nanotheranostics

So far, nanotheranostics has been realized as a versatile approach in nanomedicine applications, especially for precise diagnosis and treatment, which have attracted much attention today [249,250]. Interestingly, several nanosized systems such as liposomes, gold-liposome hybrids, gold-silica, doxorubicin-liposome, albumin, and

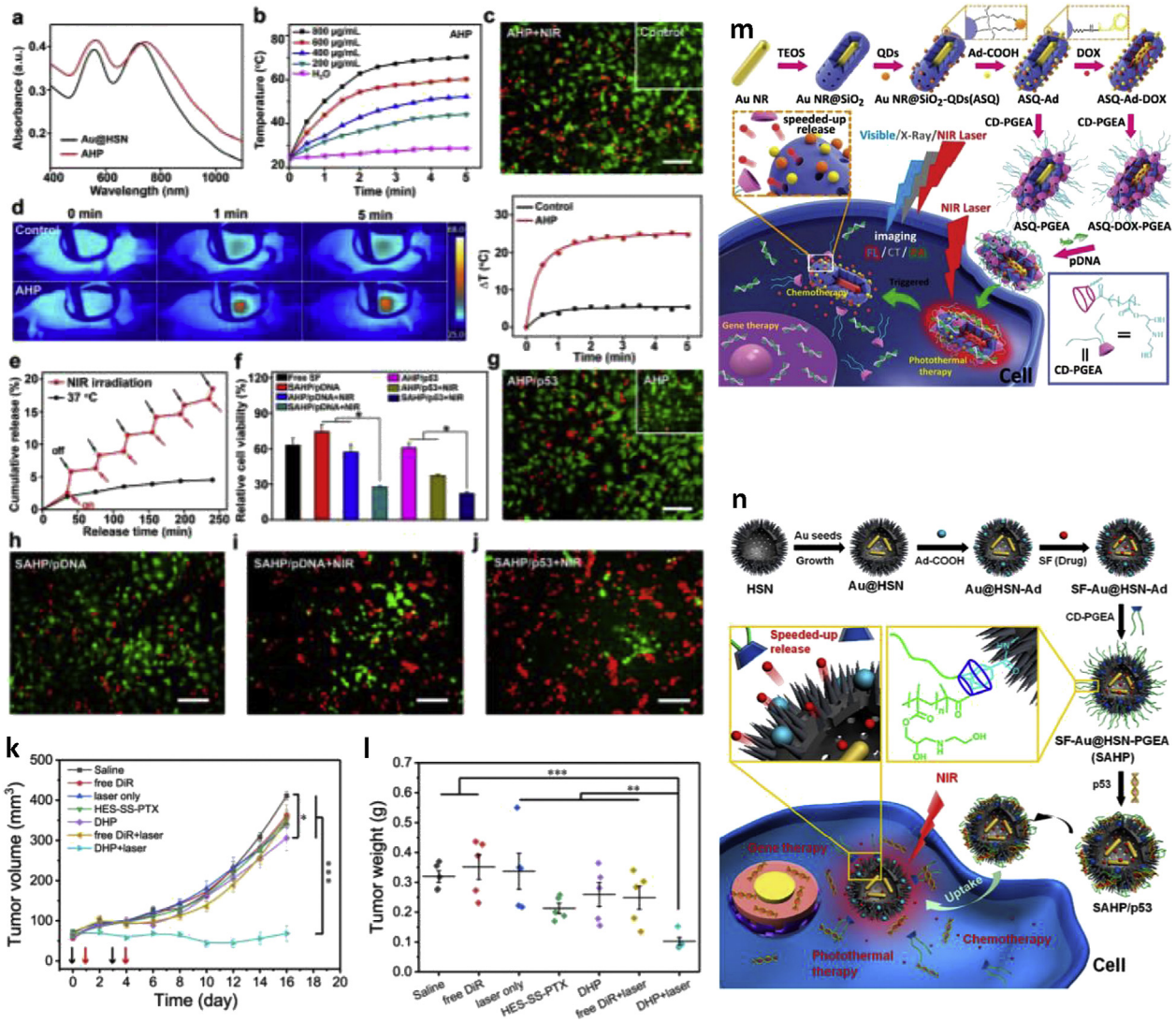


Fig. 9. Absorption spectra of designed nanohybrids (a), temperature response during NIR irradiation (b), FDA-PI–stained fluorescent image of HepG2 cells treated with an NIR laser (c), photothermal images and temperature response of postinjected tumor-bearing mice (d), release profile of SF under NIR irradiation (e), biocompatibility MTT assay of engineered nanohybrids for combination therapy (f), FDA-PI–stained fluorescent images of HepG2 cells treated with nanohybrids in various therapeutic conditions (g–j), tumor reduction measurements in terms of tumor volume and weight observed during combination therapy (k and l), and schematic illustration proposed design of combination therapies (m and n). Reproduced with permission from Chen et al [210], Li et al [211], and Duan et al [212] Copyright of ACS and Wiley Publishing Group published in 2017, 2018 and 2019. NIR = near-infrared.

various others have been successfully applied in preclinical/clinical applications, demonstrating their potential role in cancer nanomedicine [55,60,70,71] (see Fig. 11a–d).

Degradation, biological response, and smooth circulation of the administered nanosized platforms are major concerns [1,2]. Remarkably, once injected, nanoparticles are easily taken by the reticuloendothelial system that leads to toxicity via long-term retention and may hamper practical application [70,251]. Therefore, the Food and Drug Administration (FDA) has classified those injected diagnostic and therapeutic agents as agents that need to be completely cleared within a rational time period after the mode of action [238,252]. Thus, the nanosized medicine can reach up to clinical translation if they fulfill the aforementioned requirements. As a result, degradation and renal clearance have become a major priority for removal of nanoparticles from the body [253]. So far, the internal (pH, H_2O_2, glutathione named as GSH, ROS) and external stimulus (NIR light, heat, radiofrequency, external fields, and so on) have been widely evaluated to understand the degradation of the injected theranostics/nanomedicine before their application in animal studies (see Fig. 11a–c). For example, gold nanorod–decorated liposomal nanohybrids have been recently conceptualized for cancer theranostics application, particularly targeted imaging and combined chemo-photothermal therapy. Furthermore, the degradation/disintegration of these bioinorganic nanohybrids has been evaluated during NIR light irradiation, as shown in Fig. 11b. After localized diagnosis and treatment, the disintegrated nanohybrids are easily cleared from the tested animal body that ensured the high survival rate, which is a major deciding factor of safe nanomedicine (see Fig. 11d). Moreover, ultrasmall nanoparticles with less than 5.5 nm in size can be easily cleared through the renal pathway, which is widely studied and well documented in the literature [254–258]. However, ultrasmall nanoparticles (5–7 nm in diameter) [254,256] are rapidly cleared through the renal pathway that have very short circulation time that reduces the possibility for better diagnosis and treatment within the short time available, and also demonstrate non-specific

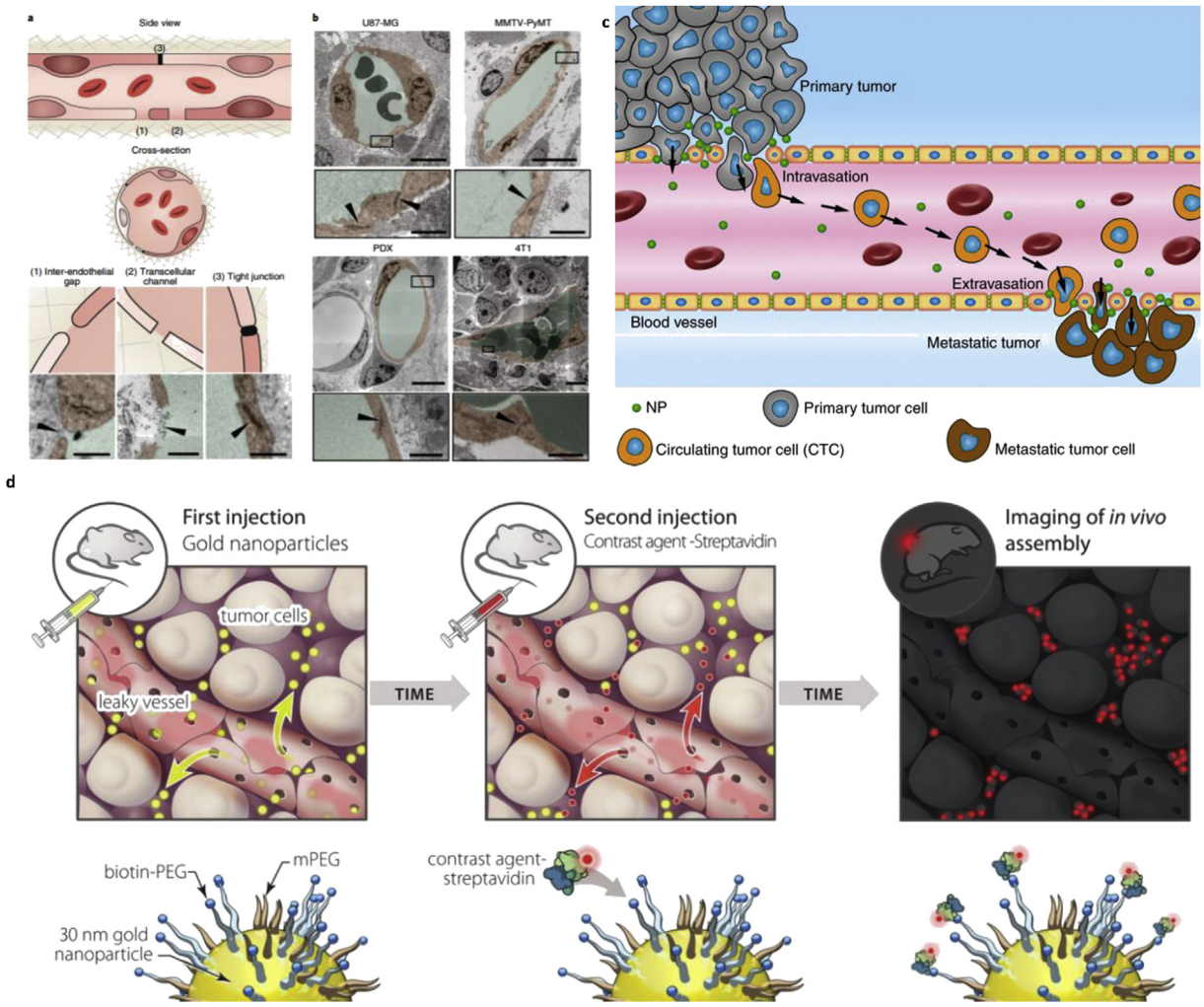


Fig. 10. Schematic design of nanoparticle entry pathways in the tumor microenvironment in various conditions (a–d). Reproduced with permission from Sindhwani et al [230], Perrault and Chan [245], and Peng et al [246] Copyright of Nature and PNAS Publishing Group published in 2010, 2019 and 2020.

biodistribution. On the other hand, large-sized nanoparticles (more than 25-nm size) not only have longer circulation time but also have potential site-selective targeting property and high drug-loading capacity [259,260]. However, the reduced kidney filtration force for nanoparticles increases their retention time in RES that can lead to potential toxicity for the biological system [261–263]. Therefore, it has been noticed that degradation of larger particles is a promising approach to develop safe nanomedicines, having sufficient time to perform precise diagnosis and treatment [253]. These decomposed particles are easily removed from the body (see Table 3).

8. Clinical status of nanomedicines

Several nanosized hybrids/composite materials have been applied to localized imaging and targeted therapies, especially PDT, PTT, and chemotherapy in cancer treatments [264–268] (see Figs. 12a–j and 13). Various nanohybrids such as PEGylated gold nanoparticles, gold-silica nanoparticles, ruthenium nanoparticles, liposome-based nanoparticles, and many others have been developed for imaging and therapies up to clinical level owing to their high biocompatibility, specific biodistribution, localized and site-selective tumor-binding ability, smooth circulation, and easy excretion (see Table 4) [269–276]. In addition, soft and biocompatible molecules such as folic acid, doxorubicin, indocyanine green named as ICG, and so on have been used for diagnosis and therapeutics in clinical studies [212,277–281]. Importantly, application of NIR-responsive nanomedicine extends to diagnostics of tumor and therapeutics such as triggerable drug or gene delivery. Among them, light-based therapeutic modalities, known as photothermal and photodynamic cancer therapy, are realized as the most promising targeted treatments [282–285]. One of the most recently developed nanomedicines known as gold-silica nanoshells (GSNs) (AuroShells) is composed of a silica core and a gold shell with a size of ~150 nm, which are designed to maximally absorb NIR light and convert it to significant heat with high tissue transparency, which have gained particular interest in biomedical applications [270]. These particles absorb the exposed light and generate significant amount of heat that induces highly localized hyperthermia for effective PTT of cancer, resulting in cell death and tumor reduction that has been tested in preclinical animal models, as shown in Fig. 12h and i. Other nanoparticles such as gold nanorods, gold-liposome nanoparticles, gold nanocages, and so on have been tested at the *in vitro* and *in vivo* level and are believed to be tested soon in clinical trials [55,70,286]. Based on our survey and knowledge, we have noticed that nanobiotechnology-based materials known as nanomedicine required several years of clinical trials to gain patients' confidence and trust.

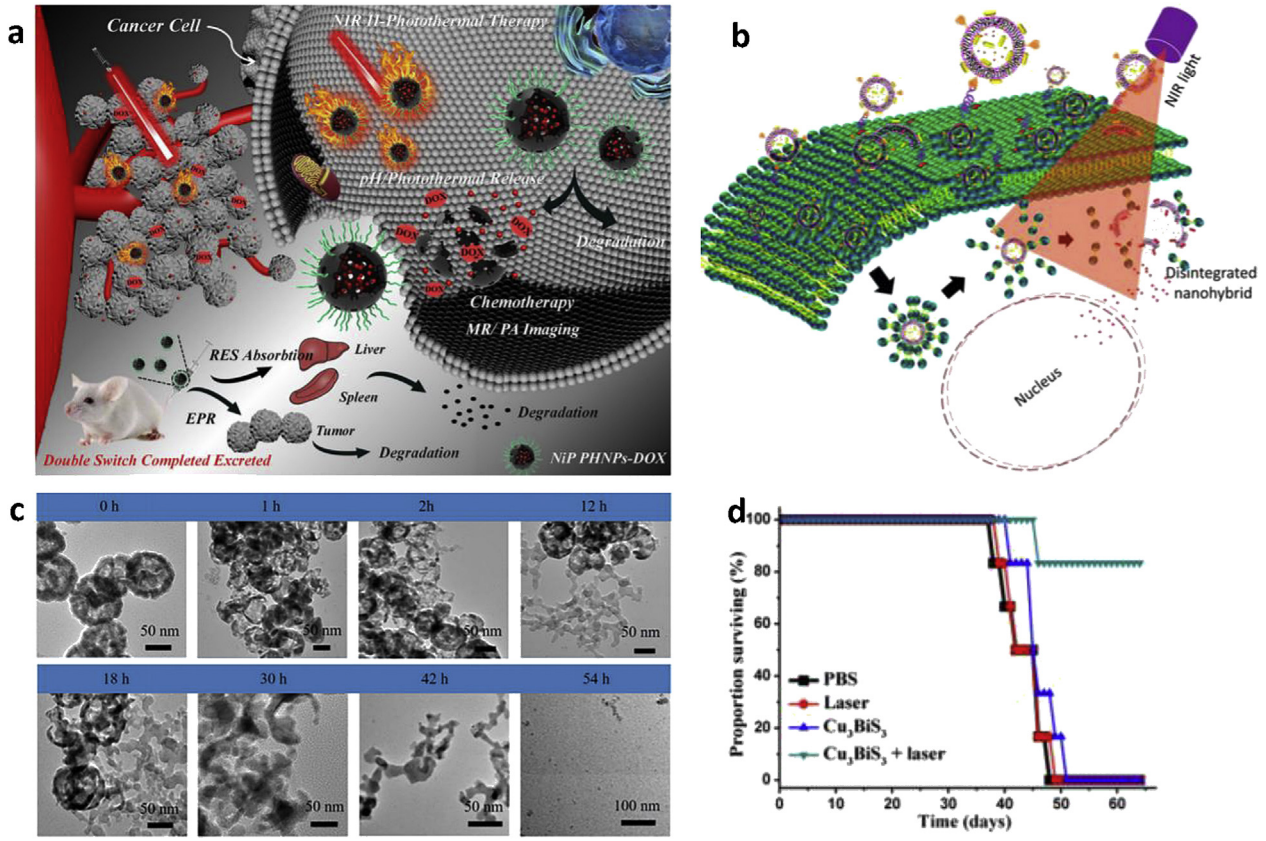


Fig. 11. Schematic design of degradation/disintegration of inorganic and bioinorganic nanohybrids during therapeutic conditions (a and b), TEM imaging measurements of the nanohybrid degradation (c), and surviving fraction of nanohybrid-treated animals (d). Reproduced with permission from Chauhan et al [70] and Liu et al [251,253] Copyright of ACS Publishing Group published in 2016, 2018 and 2019. TEM = transmission electron miscroscopy; NIR = near-infrared; EPR = enhanced permeability and retention; PA imaging = photoacoustic imaging.

A recent study by University College London reports that about 51% of patients could have been considered for focal prostate ablation of their index lesion, that is, the treatment of localized prostate cancer with minimum side-effects of whole-gland treatments [287]. Moreover, high-intensity focused US, specific cryotherapy, irreversible electroporation, laser interstitial thermal therapy, and PDT have been developed [288–290]. Recently, a clinical trial using laser-excited GSNs was applied in combination with magnetic resonance-US fusion imaging to focally ablate low- to intermediate-grade tumors within the prostate by intravenous delivery of injected nanotheranostics [270]. This pilot study has been realized in 16 cases of patients diagnosed with intermediate-risk localized prostate cancer. To examine the successive reduction in tumor volume, the multiparametric MRI/US targeted fusion biopsies and imaging are performed at various time points. Overall, from this treatment, 94% successful outcomes of GSN-mediated focal laser ablation are achieved in 15 of 16 patients, without any significant difference in the International Prostate Symptom Score or Sexual Health Inventory for Men [270].

Moreover, within a short period, the anticancer drug doxorubicin loaded liposomal–based nanosized formulation has been recognized as the first FDA-approved nanomedicine [278]. Doxorubicin liposomal nanomedicine, known as Doxil, and about 30 liposomal or lipid nanoparticle–based therapeutic agents are currently being considered in clinical investigation [291]. The designed formulations have been tested for the preclinical and clinical level of gastric, breast, lung, ovarian, and other types of cancers. In the first clinical trial, a larger size of Doxil (300–500 nm) has been applied on 32 patients suffering from liver cancer (see Fig. 12j). It is noted that the Doxil formulation had a much smaller volume of distribution (4 L) and slow clearance compared with the free doxorubicin (254 L) dose. Subsequently, different formulations of liposomes have been tried with various dose administration (30, 45, 60, and 90 mg/m^2), and it has been noticed that hematologic toxicity occurs at the doses of 60 and 90 mg/m^2. Overall, today's pursuit is for developing tumor-targeted localized therapies [5,292,293]. In this regard, a few strategies have been proposed: (1) Imaging agents can be selectively blocked that materialize for overexpressed in malignant cells and (2) Binding of targeting ligand precisely to a receptor that is articulated on malignant cells. In brief, targeting ligand-drug conjugates can deliver the therapeutic agent precisely into the cancer cells and thereby preventing the unsolicited collateral damage to receptor negative tissues/cells. Thus, specific ligands can be simply exploited to convert non-specific cytotoxic drugs into localized tumor-specific weapons. Low-molecular-weight peptide, oligopeptides, vitamins, folic acid, monoclonal antibodies, oligosaccharides, and so on have been proposed for receptor-binding tumor targeting [277,294–297]. For example, folic acid is a vitamin that is widely explored as a targeting ligand for folate receptor–overexpressed cancer cells and also has properties for the proliferation and maintenance of all cells [277]. The folic acid–targeting ligand has significant impact on targeted imaging at the *in vitro* and *in vivo* level and has also been recognized as a potential targeting candidate for clinical examinations recently.

9. Conclusion and perspectives

Characteristics of smart nanotheranostics have been discussed in this review. We have covered a wide range of nanocontrast and therapeutic agents and their advantages and disadvantages. A

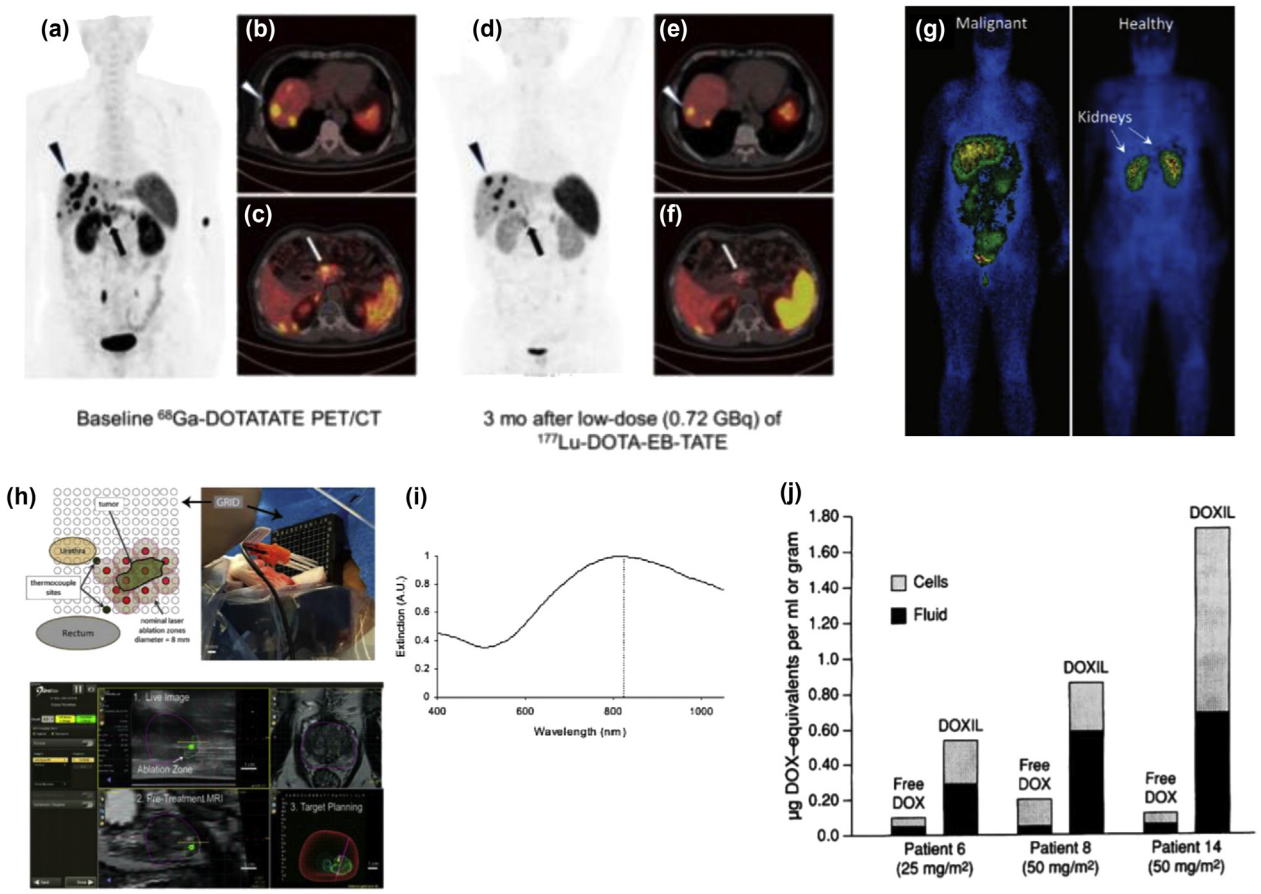


Fig. 12. Clinical examination of a patient having primary pancreatic tumor and metastatic liver disease using ^{68}Ga-DOTA-TATE contrast for PET/CT images of a neuroendocrine tumour (NET) patient (a–c) before and (d–f) after a single low-dose (0.72 GBq) injection of contrast ^{177}Lu-DOTA-EB-TATE, clinical diagnosis and study of a comparison of [^{111}In] DTPA-folate uptake in a patient with stage III ovarian cancer (left) and a healthy volunteer (right) (g), clinical approach for photothermal therapy using gold nanoshells. (h) Figure showing an axial view of the prostate tumor ablation zone and the nearby urethra and rectum overlaid with a rectangular transperineal grid (3-mm spacing). The ablation zone is penetrated with the introducer trocars (red) through the targeting grid, allowing for the 4- to 5-mm treatment radius (tan). Laser introducers (orange hub) placed with the thermocouple (black) through the transperineal grid. (c) UroNav MR/US fusion guidance for trocar placement with real-time ultrasound imaging. (1) Live US and fusion image in which the purple horizontal line is the planned path for the trocars through the virtual target (ablation zone). (2) Pretreatment MRI denoting the prostate (purple), the ablation zone region of interest. (3) Targeting screen allows planning for treatment and trocar placement. (scale bar: b, 9 mm; c, 1 cm), absorption spectrum of the designed gold nanoshell that has been applied for clinical photothermal therapy (i) and clinical chemotherapeutic measurements using doxorubicin liposomal nanoformulation known as Doxil (j). Reproduced with permission from Min et al [5], Rastinehad et al [270], Xia and Low [277], Srinivasarao and Low [295], and Lau et al [296] Copyright of ACS Nature, wiley and PNAS Publishing Group published in 2010, 2015, 2019 and 2020. PET = positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; US = ultrasound.

common trend of traditional diagnosis and therapies and their critical concerns has been highlighted. Owing to expensive and time-consuming complicated process, these traditional methods are realized as outdated strategies that need a better replacement for safe and effective cancer treatment. Even today, these conventional diagnosis and treatments are limited with non-specific biodistribution of the injected contrast and therapeutics agents, poor image resolution, rapid clearance, high-dose and multiple-dose requirements, nephrotoxicity, and so on. Therefore, in the past few years, nanobiotechnology-based nanomedicine has gained much attention for engineering the multifunctional safe materials for localized imaging and therapy of cancer. In fact, precise imaging of diseased area with deep visualization and its potential treatment describes the concept of localized therapy. Prolonged procedure of diagnosis and treatment and high-dose requirement hamper the advantages of stand-alone imaging and therapeutics. Therefore, the concept of nanosized theranostics has been noticed as promising for localized imaging and tumor reduction significantly along with the complete biocompatibility of injected nanohybrids 'nanomedicines.' In nanotheranostics, the fabricated materials have their intrinsic properties for showing their multifunctionality in terms of multimode imaging and therapy. However, integrating targeting moieties, nanocontrast and therapeutic agents, without losing their functionality has been considered a major challenge. Apart from this, various approaches of nanomaterials for cancer treatment have been addressed here. More importantly, individually, the nanosized imaging and therapeutic agents have been successfully tested at the preclinical level for cancer treatment and further translated to clinical studies. Several new nanohybrids are currently in the developing phase, indicating a new hope for better diagnosis and treatment. In addition, we have covered the well-studied site-specific tumor ablation/reduction by photothermal and oxidative stress, without damaging the surrounding healthy tissues. Different functional nanosystems and their advantages and disadvantages for imaging and therapy have been explained in this review. However, major concerns have been noticed in nanomedicines for cancer diagnosis and safe treatment as follows: (1) we are still in the premature stages of the preclinical and clinical development of nanobiotechnology-based diagnosis and treatment, (2) newly developed nanomedicines are still facing the critical issues of localized imaging and complete elimination of solid tumor, (3) non-specific biodistribution and long-term toxicity

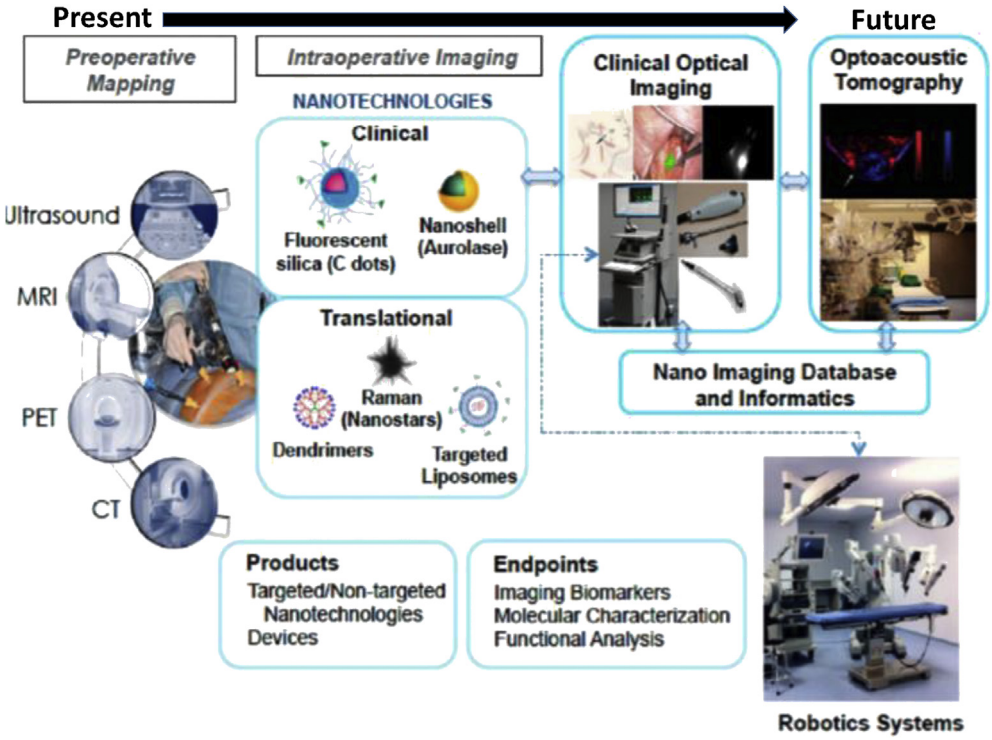


Fig. 13. Present and future of nano-oncology planning for imaging-guided treatments with illustrative translational probes and devices for future clinical use. Reproduced with permission from Liu et al [80] Springer Publishing Group published in 2018. MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography.

Table 4
Functional nanohybrids translated for clinical studies [1,2,57].

Type of cancer	Nanohybrids	Diagnostics and therapeutic modality	Status of the clinical trial
Solid tumor	Ruthenium NPs (NKP-1339)	Targeted therapy	Phase I (2012)
Solid tumor	PEGylated gold nanoparticles	Targeted therapy	Phase I (2012)
Breast cancer	DOX@Liposomal	Targeted therapy	Phase II/III
Breast cancer	CdS/ZnS quantum dots	Diagnosis and therapy	Phase I started
Head and neck, and breast cancer	cRGDY-PEGCy5.5-C dots	Imaging	Phase II ongoing
Prostate cancer	Hafnium oxide NPs	Targeted radiotherapy	Phase I & II ongoing
Leukemia	Liposomal vincristine sulfate	Targeted therapy	Approved
Hepatocellular carcinoma	Carboxydextran-coated SPIO	Imaging	Approved
Ovarian cancer	Poly-ʟ-glutamic acid (poliglumex) conjugate with paclitaxel	Therapy	Phase III
Pancreatic and prostate cancer	Aminosilane-coated SPIO	Therapy	Phase I
Head and neck cancer	NIR active gold nanoshell	Photothermal therapy	Phase 0

NIR = near-infrared; NP = nanoparticle.

of nanomedicines are being questioned, (4) the interaction between the solid tumor microenvironment and injected theranostics agent is still unclear, (5) solid tumors are not significantly reduced in newly proposed targeted therapies, (6) biodegradation and safe clearance of the injected nanotheranostic probes are also being questioned, which is an ongoing discussion in onconanomedicine. Overall, addressing the site-selective targeting, short- and long-term toxicity, and degradation ability of nanomaterials have become a prior need before approaching for FDA approval of nanosized theranostics and nanomedicine. Various examples of clinical translational nanomaterials and their clinical status have been discussed here.

Finally, it has been observed that various researchers and research projects in onconanomedicine and targeted cancer theranostics are promising and successful so far. The success and efficacy of proposed nanotheranostics are determined from the treatment outcomes and advantages provided to cancer patients. Engineering of clinically relevant safe nanosized medicine would be our expectation to continue the onconanomedicine research, wherein nanodiagnostics and combination therapies play a major role through localized nanotheranostics for better health care.

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.

Acknowledgments

This work was supported by the Department of Biotechnology, Government of India. J.C. thanks ERC-2019-STG for financial support. N.K.J. is also grateful for the support of the DST INSPIRE fellowship.

References

[1] I. Brigger, C. Dubernet, P. Couvreur, Nanoparticles in cancer therapy and diagnosis, Adv. Drug Deliv. Rev. 64 (2012) 24–36.
[2] A.S. Thakor, S.S. Gambhir, Nanooncology: the future of cancer diagnosis and therapy, CA. Canc. J. Clin. 63 (6) (2013) 395–418.
[3] 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 (1) (2015) 327–394.
[4] H.Y. Yoon, S. Jeon, D.G. You, J.H. Park, I.C. Kwon, H. Koo, K. Kim, Inorganic nanoparticles for image-guided therapy, Bioconjugate Chem. 28 (1) (2017) 124–134.
[5] Y. Min, J.M. Caster, M.J. Eblan, A.Z. Wang, Clinical translation of nanomedicine, Chem. Rev. 115 (19) (2015) 11147–11190.
[6] A. Ediriwickrema, W.M. Saltzman, Nanotherapy for cancer: targeting and multifunctionality in the future of cancer therapies, ACS Biomater. Sci. Eng. 1 (2) (2015) 64–78.
[7] B.A. Chabner, T.G. Roberts, Chemotherapy and the war on cancer, Nat. Rev. Canc. 5 (1) (2005) 65–72.
[8] V.T. DeVita, E. Chu, A history of cancer chemotherapy, Canc. Res. 68 (21) (2008) 8643–8653.
[9] T. Stylianopoulos, R.K. Jain, Design considerations for nanotherapeutics in oncology, Nanomed. Nanotechnol. Biol. Med. 11 (8) (2015) 1893–1907.
[10] M. Montanari, F. Fabbri, E. Rondini, G.L. Frassineti, R. Mattioli, S. Carloni, E. Scarpi, W. Zoli, D. Amadori, G. Cruciani, Phase II trial of non-pegylated liposomal doxorubicin and low-dose prednisone in second-line chemotherapy for hormone-refractory prostate cancer, Tumori J 98 (6) (2012) 696–701.
[11] N. Lee, S.H. Choi, T. Hyeon, Nano sized CT contrast agents, Adv. Mater. 25 (19) (2013) 2641–2660.
[12] C. Hollander-Mieritz, J. Johansen, C. Johansen, I.R. Vogelius, C.A. Kristensen, H. Pappot, Comparing the patients' subjective experiences of acute side effects during radiotherapy for head and neck cancer with four different patient-reported outcomes questionnaires, Acta Oncol. (Madr.) 58 (5) (2019) 603–609.
[13] A.-K. Wennstig, Long-Term Side Effects of Radiotherapy in Breast Cancer: Studies in Ischemic Heart Disease and Lung Cancer, Umea Universitet, 2020.
[14] G. Cavaletti, D.R. Cornblath, I.S.J. Merkies, T.J. Postma, E. Rossi, P. Alberti, J. Bruna, A.A. Argyriou, C. Briani, R. Velasco, Patients' and physicians' interpretation of chemotherapy induced peripheral neurotoxicity, J. Peripher. Nerv. Syst. 24 (1) (2019) 111–119.
[15] H.C. Lehmann, N.P. Staff, A. Hoke, Modeling chemotherapy induced peripheral neuropathy (CIPN) in vitro: prospects and limitations, Exp. Neurol. (2019) 113140.
[16] E. Pedziwiatr-Werbicka, K. Horodecka, D. Shcharbin, M. Bryszewska, Nanoparticles in combating cancer: opportunities and limitations. A brief review, Curr. Med. Chem. 27 (6) (2020), https://doi.org/10.2174/0929867327666200130101605.
[17] F. Wirsdorfer, S. De Leve, V. Jendrossek, Combining radiotherapy and immunotherapy in lung cancer: can we expect limitations due to altered normal tissue toxicity? Int. J. Mol. Sci. 20 (1) (2019) 24.
[18] S. Ichikawa, N. Fukuhara, S. Hatta, M. Himuro, K. Nasu, K. Ono, Y. Okitsu, M. Kobayashi, Y. Onishi, M. Ri, Anaplastic multiple myeloma: possible limitations of conventional chemotherapy for long-term remission, J. Clin. Exp. Hematop. 58 (1) (2018) 39–42.
[19] S. Kawamoto, M.K. Fuld, D. Laheru, P. Huang, E.K. Fishman, Assessment of iodine uptake by pancreatic cancer following chemotherapy using dual-energy CT, Abdom. Radiol. 43 (2) (2018) 445–456.
[20] S. Fu, C.-F. Wu, M. Wang, D.R. Lairson, Cost effectiveness of transplant, conventional chemotherapy, and novel agents in multiple myeloma: a systematic review, Pharmacoeconomics 1–29 (2019).
[21] T. Jain, M.B. Sonbol, B. Firwana, K.R. Kolla, D. Almader-Douglas, J. Palmer, R. Fonseca, High-dose chemotherapy with early autologous stem cell transplantation compared to standard dose chemotherapy or delayed transplantation in patients with newly diagnosed multiple myeloma: a systematic review and meta-analysis, Biol. Blood Marrow Transplant. 25 (2) (2019) 239–247.
[22] A.-L. Faucon, G. Bobrie, O. Clement, Nephrotoxicity of iodinated contrast media: from pathophysiology to prevention strategies, Eur. J. Radiol. 116 (2019) 231–241.
[23] T.E. Schultz, A.C. Lynch, Intravenous radiographic contrast administered prior to high-dose methotrexate and subsequent toxicity requiring the use of glucarpidase, J. Oncol. Pharm. Pract. 25 (4) (2019) 993–997.
[24] J. Huang, Y. Lyu, J. Li, P. Cheng, Y. Jiang, K. Pu, A renal clearable duplex optical reporter for real time imaging of contrast induced acute kidney injury, Angew. Chem. 131 (49) (2019) 17960–17968.
[25] L. Zhang, Z. Liu, Y. Liu, Y. Wang, P. Tang, Y. Wu, H. Huang, Z. Gan, J. Liu, D. Wu, Ultrathin surface coated water-soluble cobalt ferrite nanoparticles with high magnetic heating efficiency and rapid in vivo clearance, Biomaterials 230 (2020) 119655.
[26] M.L. Etheridge, S.A. Campbell, A.G. Erdman, C.L. Haynes, S.M. Wolf, J. McCullough, The big picture on nanomedicine: the state of investigational and approved nanomedicine products, Nanomed. Nanotechnol. Biol. Med. 9 (1) (2013) 1–14.
[27] E. Boisselier, D. Astruc, Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity, Chem. Soc. Rev. 38 (6) (2009) 1759–1782.
[28] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat. Rev. Clin. Oncol. 7 (11) (2010) 653–664.
[29] K. Guidolin, G. Zheng, Nanomedicines lost in translation, ACS Nano 13 (12) (2019) 13620–13626.
[30] Q. Haseeb, S.D.A. Hamdani, A. Akram, D.A. Khan, T.A. Rajput, M.M. Babar, Nanobiotechnology: paving the way to personalized medicine, in: Nano-BioMedicine, Springer, Singapore; Springer, 2020, pp. 17–32.
[31] M. Piffoux, A. Nicolas-Boluda, V. Mulens-Arias, S. Richard, G. Rahmi, F. Gazeau, C. Wilhelm, A.K.A. Silva, Extracellular vesicles for personalized medicine: the input of physically triggered production, loading and theranostic properties, Adv. Drug Deliv. Rev. 138 (2019) 247–258.
[32] D. Singh, F. Dilnawaz, S.K. Sahoo, Challenges of moving theranostic nanomedicine into the clinic, Nanomedicine (Lond.) 15 (2) (2020) 111–114.
[33] R. van der Meel, E. Sulheim, Y. Shi, F. Kiessling, W.J.M. Mulder, T. Lammers, Smart cancer nanomedicine, Nat. Nanotechnol. 14 (11) (2019) 1007–1017.
[34] C. Fornaguera, M.J. Garcia-Celma, Personalized nanomedicine: a revolution at the nanoscale, J. Personalized Med. 7 (4) (2017) 12.
[35] 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 (2) (2017) 159–171.
[36] J. Shi, P.W. Kantoff, R. Wooster, O.C. Farokhzad, Cancer nanomedicine: progress, challenges and opportunities, Nat. Rev. Canc. 17 (1) (2017) 20.
[37] J. Shi, A.R. Votruba, O.C. Farokhzad, R. Langer, Nanotechnology in drug delivery and tissue engineering: from discovery to applications, Nano Lett. 10 (9) (2010) 3223–3230.
[38] K. Hida, N. Maishi, C. Torii, Y. Hida, Tumor angiogenesis—characteristics of tumor endothelial cells, Int. J. Clin. Oncol. 21 (2016) 206–212.
[39] W.Y. Wang, D. Lin, E.H. Jarman, W.J. Polacheck, B.M. Baker, Functional angiogenesis requires microenvironmental cues balancing endothelial cell migration and proliferation, Lab Chip 20 (6) (2020) 1153–1166.
[40] S. Matsushima, A. Shimizu, M. Kondo, H. Asano, N. Ueno, H. Nakayama, N. Sato, M. Komeno, H. Ogita, M. Kurokawa-Seo, Anosmin-1 activates vascular endothelial growth factor receptor and its related signaling pathway for olfactory bulb angiogenesis, Sci. Rep. 10 (1) (2020) 1–15.
[41] B. Wirthl, J. Kremheller, B.A. Schrefler, W.A. Wall, Extension of a multiphase tumour growth model to study nanoparticle delivery to solid tumours, PloS One 15 (2) (2020), e0228443.
[42] M.R. Tomaszewski, I.Q. Gonzalez, J.P.B. O'Connor, O. Abeyakoon, G.J.M. Parker, K.J. Williams, F.J. Gilbert, S.E. Bohndiek, Oxygen enhanced optoacoustic tomography (OE-OT) reveals vascular dynamics in murine models of prostate cancer, Theranostics 7 (11) (2017) 2900.
[43] C. Viallard, B. Larrivdee, Tumor angiogenesis and vascular normalization: alternative therapeutic targets, Angiogenesis 20 (4) (2017) 409–426.
[44] L. Wang, M. Huo, Y. Chen, J. Shi, Tumor microenvironment enabled nanotherapy, Adv. Healthc. Mater. 7 (8) (2018), 1701156.
[45] C. Liu, D. Wang, S. Zhang, Y. Cheng, F. Yang, Y. Xing, T. Xu, H. Dong, X. Zhang, Biodegradable biomimic copper/manganese silicate nanospheres for chemodynamic/photodynamic synergistic therapy with simultaneous glutathione depletion and hypoxia relief, ACS Nano 13 (4) (2019) 4267–4277.
[46] 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 (11) (2018) 10636–10664.
[47] Z. Wang, Y. Zhang, E. Ju, Z. Liu, F. Cao, Z. Chen, J. Ren, X. Qu, Biomimetic nanoflowers by self-assembly of nanozymes to induce intracellular oxidative damage against hypoxic tumors, Nat. Commun. 9 (1) (2018) 1–14.
[48] R. Chen, Z. Ma, Z. Xiang, Y. Xia, Q. Shi, S.C. Wong, J. Yin, Hydrogen peroxide and glutathione dual redox responsive nanoparticles for controlled DOX release, Macromol. Biosci. 20 (2) (2019), 1900331.
[49] A. Punjabi, X. Wu, A. Tokatli-Apollon, M. El-Rifai, H. Lee, Y. Zhang, C. Wang, Z. Liu, E.M. Chan, C. Duan, Amplifying the red-emission of upconverting nanoparticles for biocompatible clinically used prodrug-induced photodynamic therapy, ACS Nano 8 (10) (2014) 10621–10630.
[50] E.K. Chow, X.-Q. Zhang, M. Chen, R. Lam, E. Robinson, H. Huang, D. Schaffer, E. Osawa, A. Goga, D. Ho, Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment, Sci. Transl. Med. 3 (73) (2011), 73ra21-73ra21.
[51] W.-P. Li, C.-H. Su, Y.-C. Chang, Y.-J. Lin, C.-S. Yeh, Ultrasound-induced reactive oxygen species mediated therapy and imaging using a fenton reaction activable polymersome, ACS Nano 10 (2) (2016) 2017–2027.
[52] M. Aioub, S.R. Panikkanvalappil, M.A. El-Sayed, Platinum-coated gold nanorods: efficient reactive oxygen scavengers that prevent oxidative damage toward healthy, untreated cells during plasmonic photothermal therapy, ACS Nano 11 (1) (2017) 579–586.
[53] T. Wang, D. Wang, J. Liu, B. Feng, F. Zhou, H. Zhang, L. Zhou, Q. Yin, Z. Zhang, Z. Cao, Acidity-triggered ligand-presenting nanoparticles to overcome sequential drug delivery barriers to tumors, Nano Lett. 17 (9) (2017) 5429–5436.
[54] W. Jiang, C.A. Von Roemeling, Y. Chen, Y. Qie, X. Liu, J. Chen, B.Y.S. Kim, Designing nanomedicine for immuno-oncology, Nat. Biomed. Eng. 1 (2) (2017) 1–11.
[55] R. Prasad, D.S. Chauhan, A.S. Yadav, J. Devrukhkar, B. Singh, M. Gorain, M. Temgire, J. Bellare, G.C. Kundu, R. Srivastava, A biodegradable fluorescent

nanohybrid for photo-driven tumor diagnosis and tumor growth inhibition, Nanoscale 10 (40) (2018) 19082–19091.
[56] Y. Liu, P. Bhattarai, Z. Dai, X. Chen, Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer, Chem. Soc. Rev. 48 (7) (2019) 2053–2108.
[57] 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 (3) (2020) 2585–2627.
[58] G. Yu, T.Y. Cen, Z. He, S.P. Wang, Z. Wang, X.W. Ying, S. Li, O. Jacobson, S. Wang, L. Wang, Porphyrin nanocage embedded single molecular nanoparticles for cancer nanotheranostics, Angew. Chem. Int. Ed. 58 (26) (2019) 8799–8803.
[59] B.L. Faintuch, S. Faintuch, Nanotheranostics in oncology and drug development for imaging and therapy. Precision Medicine for Investigators, Practitioners and Providers, Elsevier, 2020, pp. 453–458.
[60] R. Prasad, A.S. Yadav, M. Gorain, D.S. Chauhan, G.C. Kundu, R. Srivastava, K. Selvaraj, Graphene oxide supported liposomes as red emissive theranostics for phototriggered tissue visualization and tumor regression, ACS Appl. Bio. Mater. 2 (8) (2019) 3312–3320.
[61] Y. jing Zhao, L. Xie, Potential role of exosomes in cancer therapy, Precis. Radiat. Oncol. 3 (2) (2019) 59–64.
[62] D. Kalyane, N. Raval, R. Maheshwari, V. Tambe, K. Kalia, R.K. Tekade, Employment of enhanced permeability and retention effect (EPR): nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer, Mater. Sci. Eng. C 98 (2019) 1252–1276.
[63] A. Tahmasbi Rad, C.-W. Chen, W. Aresh, Y. Xia, P.-S. Lai, M.-P. Nieh, Combinational effects of active targeting, shape, and enhanced permeability and retention for cancer theranostic nanocarriers, ACS Appl. Mater. Interfaces 11 (11) (2019) 10505–10519.
[64] G. Bort, F. Lux, S. Dufort, Y. Cremillieux, C. Verry, O. Tillement, EPR-mediated tumor targeting using ultrasmall-hybrid nanoparticles: from animal to human with theranostic AGuIX nanoparticles, Theranostics 10 (3) (2020) 1319.
[65] R.K. Jain, J.D. Martin, V.P. Chauhan, D.G. Duda, Tumor microenvironment: vascular and extravascular compartment, in: Abeloff's Clinical Oncology, Elsevier, 2020, pp. 108–126.
[66] J.K. Tee, L.X. Yip, E.S. Tan, S. Santitewagun, A. Prasath, P.C. Ke, H.K. Ho, D.T. Leong, Nanoparticles' interactions with vasculature in diseases, Chem. Soc. Rev. 48 (21) (2019) 5381–5407.
[67] E.A. Sykes, Q. Dai, C.D. Sarsons, J. Chen, J.V. Rocheleau, D.M. Hwang, G. Zheng, D.T. Cramb, K.D. Rinker, W.C.W. Chan, Tailoring nanoparticle designs to target cancer based on tumor pathophysiology, Proc. Natl. Acad. Sci. USA 113 (9) (2016) E1142–E1151.
[68] X. Meng, L. Gao, K. Fan, X. Yan, Nanozyme-based tumor theranostics, in: Nanozymology, Springer, 2020, pp. 425–457.
[69] C.O. Silva, J.O. Pinho, J.M. Lopes, A.J. Almeida, M.M. Gaspar, C. Reis, Current trends in cancer nanotheranostics: metallic, polymeric, and lipid-based systems, Pharmaceutics 11 (1) (2019) 22.
[70] D.S. Chauhan, R. Prasad, J. Devrukhkar, K. Selvaraj, R. Srivastava, Disintegrable NIR light triggered gold nanorods supported liposomal nanohybrids for cancer theranostics, Bioconjugate Chem. 29 (5) (2017) 1510–1518.
[71] R. Prasad, S.B. Agawane, D.S. Chauhan, R. Srivastava, K. Selvaraj, In vivo examination of folic acid-conjugated gold-silica nanohybrids as contrast agents for localized tumor diagnosis and biodistribution, Bioconjugate Chem. 29 (12) (2018) 4012–4019.
[72] V.F. Cardoso, A. Francesko, C. Ribeiro, M. Banobre Lopez, P. Martins, S. Lanceros Mendez, Advances in magnetic nanoparticles for biomedical applications, Adv. Healthc. Mater. 7 (5) (2018) 1700845.
[73] Z. Liu, Y. Li, W. Li, C. Xiao, D. Liu, C. Dong, M. Zhang, E. Makila, M. Kemell, J. Salonen, Multifunctional nanohybrid based on porous silicon nanoparticles, gold nanoparticles, and acetalated dextran for liver regeneration and acute liver failure theranostics, Adv. Mater. 30 (24) (2018) 1703393.
[74] G. Chauhan, V. Chopra, A. Tyagi, G. Rath, R.K. Sharma, A.K. Goyal, "Gold nanoparticles composite-folic acid conjugated graphene oxide nanohybrids" for targeted chemo-thermal cancer ablation: in vitro screening and in vivo studies, Eur. J. Pharmaceut. Sci. 96 (2017) 351–361.
[75] M.-A. Shahbazi, L. Faghfouri, M.P.A. Ferreira, P. Figueiredo, H. Maleki, F. Sefat, J. Hirvonen, H.A. Santos, The versatile biomedical applications of bismuth-based nanoparticles and composites: therapeutic, diagnostic, biosensing, and regenerative properties, Chem. Soc. Rev. 49 (2020) 1253–1321.
[76] A. Zottel, A. Videti Paska, I. Jov evska, Nanotechnology meets oncology: nanomaterials in brain cancer research, diagnosis and therapy, Materials (Basel) 12 (10) (2019) 1588.
[77] 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.
[78] H. Chen, W. Zhang, G. Zhu, J. Xie, X. Chen, Rethinking cancer nanotheranostics, Nat. Rev. Mater. 2 (7) (2017) 1–18.
[79] N.Z. Knezevi, G.N. Kalu erovi, Silicon-based nanotheranostics, Nanoscale 9 (35) (2017) 12821–12829.
[80] C.H. Liu, P. Tandon, L.M. Russell, Translational nanodiagnostics for in vivo cancer detection, in: Nanotheranostics for Cancer Applications, Springer, 2019, pp. 133–162.
[81] R. Sharma, N. Mody, S.P. Vyas, Bioinspired nanotheranostics for cancer management, in: Biopolymer-Based Composites, Elsevier, 2017, pp. 269–288.
[82] Y. Zhou, X. Liang, Z. Dai, Porphyrin-loaded nanoparticles for cancer theranostics, Nanoscale 8 (25) (2016) 12394–12405.
[83] X. Yue, Z. Dai, Liposomal nanotechnology for cancer theranostics, Curr. Med. Chem. 25 (12) (2018) 1397–1408.
[84] X. Li, L. Liu, S. Li, Y. Wan, J.-X. Chen, S. Tian, Z. Huang, Y.-F. Xiao, X. Cui, C. Xiang, Biodegradable-conjugated oligomer nanoparticles with high photothermal conversion efficiency for cancer theranostics, ACS Nano 13 (11) (2019) 12901–12911.
[85] P. Das, P. Fatehbasharzad, M. Colombo, L. Fiandra, D. Prosperi, Multifunctional magnetic gold nanomaterials for cancer, Trends Biotechnol. 37 (9) (2019) 995–1010.
[86] Y.-T. Liao, C.-H. Liu, Y. Chin, S.-Y. Chen, S.H. Liu, Y.-C. Hsu, K.C.-W. Wu, Biocompatible and multifunctional gold nanorods for effective photothermal therapy of oral squamous cell carcinoma, J. Mater. Chem. B 7 (28) (2019) 4451–4460.
[87] G. Su, D. Miao, Y. Yu, M. Zhou, P. Jiao, X. Cao, B. Yan, H. Zhu, Mesoporous silica-coated gold nanostars with drug payload for combined chemo-photothermal cancer therapy, J. Drug Target. 27 (2) (2019) 201–210.
[88] H. Liu, C. Li, Y. Qian, L. Hu, J. Fang, W. Tong, R. Nie, Q. Chen, H. Wang, Magnetic-induced graphene quantum dots for imaging-guided photothermal therapy in the second near-infrared window, Biomaterials 232 (2020), 119700.
[89] Y. Li, Z. Miao, Z. Shang, Y. Cai, J. Cheng, X. Xu, A visible and NIR light responsive photothermal therapy agent by chirality dependent MoO3- x nanoparticles, Adv. Funct. Mater. 30 (4) (2020), 1906311.
[90] I.-L. Lu, T.-I. Liu, H.-C. Lin, S.-H. Chang, C.-L. Lo, W.-H. Chiang, H.-C. Chiu, IR780-Loaded zwitterionic polymeric nanoparticles with acidity-induced agglomeration for enhanced tumor retention, Eur. Polym. J. 122 (2020), 109400.
[91] A. Lahooti, S. Sarkar, S. Laurent, S. Shanehsazzadeh, Dual nano sized contrast agents in PET/MRI: a systematic review, Contrast Media Mol. Imaging 11 (6) (2016) 428–447.
[92] L.A. Kunz-Schughart, A. Dubrovska, C. Peitzsch, A. Ewe, A. Aigner, S. Schellenburg, M.H. Muders, S. Hampel, G. Cirillo, F. Iemma, Nanoparticles for radiooncology: mission, vision, challenges, Biomaterials 120 (2017) 155–184.
[93] S. Hossen, M.K. Hossain, M.K. Basher, M.N.H. Mia, M.T. Rahman, M.J. Uddin, Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: a review, J. Adv. Res. 15 (2019) 1–18.
[94] N. Mehwish, X. Dou, Y. Zhao, C.-L. Feng, Supramolecular fluorescent hydrogelators as bio-imaging probes. *Mater*, Horizons 6 (1) (2019) 14–44.
[95] Z. Li, C. Di, S. Li, X. Yang, G. Nie, Smart nanotherapeutic targeting of tumor vasculature, Acc. Chem. Res. 52 (9) (2019) 2703–2712.
[96] S. Li, Q. Jiang, S. Liu, Y. Zhang, Y. Tian, C. Song, J. Wang, Y. Zou, G.J. Anderson, J.-Y. Han, A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo, Nat. Biotechnol. 36 (3) (2018) 258.
[97] S. Li, Q. Jiang, B. Ding, G. Nie, Anticancer activities of tumor-killing nanorobots, Trends Biotechnol. 37 (6) (2019) 573–577.
[98] R.K. Jain, Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia, Canc. Cell 26 (5) (2014) 605–622.
[99] S. Zhao, F. Duan, S. Liu, T. Wu, Y. Shang, R. Tian, J. Liu, Z.-G. Wang, Q. Jiang, B. Ding, Efficient intracellular delivery of RNase A using DNA origami carriers, ACS Appl. Mater. Interfaces 11 (12) (2019) 11112–11118.
[100] F.M. Anastassacos, Z. Zhao, Y. Zeng, W.M. Shih, Glutaraldehyde crosslinking of oligolysines coating DNA origami greatly reduces susceptibility to nuclease degradation, J. Am. Chem. Soc. 142 (7) (2020) 3311–3315.
[101] C. Ouyang, S. Zhang, C. Xue, X. Yu, H. Xu, Z. Wang, Y. Lu, Z.-S. Wu, Precision guided missile-like DNA nanostructure containing warhead and guidance control for aptamer-based targeted drug delivery into cancer cells in vitro and in vivo, J. Am. Chem. Soc. 142 (3) (2020) 1265–1277.
[102] J. Xu, Y. Zhang, J. Xu, G. Liu, C. Di, X. Zhao, X. Li, Y. Li, N. Pang, C. Yang, et al., Engineered nanoplatelets for targeted delivery of plasminogen activators to reverse thrombus in multiple mouse thrombosis models, Adv. Mater. 32 (4) (2020) 1–14.
[103] H. Li, H. Li, A. Wan, Luminescent gold nanoclusters for: in vivo tumor imaging, Analyst 145 (2) (2020) 348–363.
[104] J. Wallyn, N. Anton, S. Akram, T.F. Vandamme, Biomedical imaging: principles, technologies, clinical aspects, contrast agents, limitations and future trends in nanomedicines, Pharm. Res. 35 (part 1) (2019) 540–554.
[105] B.R. Smith, S.S. Gambhir, Nanomaterials for in vivo imaging, Chem. Rev. 117 (3) (2017) 901–986.
[106] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M. del Pilar Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (1) (2018) 71.
[107] Z. Zhang, L. Wang, J. Wang, X. Jiang, X. Li, Z. Hu, Y. Ji, X. Wu, C. Chen, Mesoporous silica-coated gold nanorods as a light-mediated multifunctional theranostic platform for cancer treatment, Adv. Mater. 24 (11) (2012) 1418–1423.
[108] Y. Li, T. Lin, Y. Luo, Q. Liu, W. Xiao, W. Guo, D. Lac, H. Zhang, C. Feng, S. Wachsmann-Hogiu, A smart and versatile theranostic nanomedicine platform based on nanoporphyrin, Nat. Commun. 5 (1) (2014) 1–15.
[109] X. Deng, K. Li, X. Cai, B. Liu, Y. Wei, K. Deng, Z. Xie, Z. Wu, P. Ma, Z. Hou, et al., A hollow-structured CuS@Cu 2 S@Au nanohybrid: synergistically enhanced photothermal efficiency and photoswitchable targeting effect for cancer theranostics, Adv. Mater. 29 (36) (2017) 1701266.

[110] N. Zhao, L. Yan, X. Zhao, X. Chen, A. Li, D. Zheng, X. Zhou, X. Dai, F.J. Xu, Versatile types of organic/inorganic nanohybrids: from strategic design to biomedical applications, Chem. Rev. 119 (3) (2019) 1666–1762.
[111] Q. Fu, R. Zhu, J. Song, H. Yang, X. Chen, Photoacoustic imaging: contrast agents and their biomedical applications, Adv. Mater. 31 (6) (2019) 1805875.
[112] R.A. Fouad, G.M. Kamal, S.M. Awad, Side effects of chemotherapy on the molecular structure of rat's retina and the possible protective role of antioxidants, J. Sci. Res. Sci. 35 (part 1) (2020) 540–554.
[113] H. Attarwala, Role of antibodies in cancer targeting, J. Nat. Sci. Biol. Med. 1 (1) (2010) 53.
[114] M. Nurunnabi, Z. Khatun, A.Z.M. Badruddoza, J.R. McCarthy, Y.K. Lee, K.M. Huh, Biomaterials and bioengineering approaches for mitochondria and nuclear targeting drug delivery, ACS Biomater. Sci. Eng. 5 (4) (2019) 1645–1660.
[115] D. Pentak, M. Maciążek-Jurczyk, Nonspecific nanocarriers for doxorubicin and cytarabine in the presence of fatted and defatted human albumin. Part I, J. Mol. Liq. 278 (2019) 115–123.
[116] J. Park, Y. Choi, H. Chang, W. Um, J.H. Ryu, I.C. Kwon, Alliance with EPR effect: combined strategies to improve the EPR effect in the tumor microenvironment, Theranostics 9 (26) (2019) 8073.
[117] W. He, S. Wang, J. Yan, Y. Qu, L. Jin, F. Sui, Y. Li, W. You, G. Yang, Q. Yang, Self assembly of therapeutic peptide into stimuli responsive clustered nanohybrids for cancer targeted therapy, Adv. Funct. Mater. 29 (10) (2019), 1807736.
[118] R. Wang, N. Zhao, F.J. Xu, Hollow nanostars with photothermal gold caps and their controlled surface functionalization for complementary therapies, Adv. Funct. Mater. 27 (23) (2017), 1700256.
[119] Y. Yong, X. Cheng, T. Bao, M. Zu, L. Yan, W. Yin, C. Ge, D. Wang, Z. Gu, Y. Zhao, Tungsten sulfide quantum dots as multifunctional nanotheranostics for in vivo dual-modal image-guided photothermal/radiotherapy synergistic therapy, ACS Nano 9 (12) (2015) 12451–12463.
[120] R.A. Revia, Z.R. Stephen, M. Zhang, Theranostic nanoparticles for RNA-based cancer treatment, Acc. Chem. Res. 52 (6) (2019) 1496–1506.
[121] L. Zou, H. Wang, B. He, L. Zeng, T. Tan, H. Cao, X. He, Z. Zhang, S. Guo, Y. Li, Current approaches of photothermal therapy in treating cancer metastasis with nanotherapeutics, Theranostics 6 (6) (2016) 762.
[122] Q. Cheng, Z.H. Li, Y.X. Sun, X.Z. Zhang, Controlled synthesis of a core-shell nanohybrid for effective multimodal image-guided combined photothermal/photodynamic therapy of tumors, NPG Asia Mater. 11 (1) (2019) 1–15.
[123] J. Chen, C. Ning, Z. Zhou, P. Yu, Y. Zhu, G. Tan, C. Mao, Nanomaterials as photothermal therapeutic agents, Prog. Mater. Sci. 99 (2019) 1–26.
[124] K. Deng, C. Li, S. Huang, B. Xing, D. Jin, Q. Zeng, Z. Hou, J. Lin, Recent progress in near infrared light triggered photodynamic therapy, Small 13 (44) (2017) 1702299.
[125] X. Liu, X. Wu, Y. Xing, Y. Zhang, X. Zhang, Q. Pu, M. Wu, J.X. Zhao, Reduced graphene oxide/mesoporous silica nanocarriers for PH-triggered drug release and photothermal therapy, ACS Appl. Bio. Mater. 3 (5) (2020) 2577–2587.
[126] S. Liu, X. Pan, H. Liu, Two-dimensional nanomaterials for photothermal therapy, Angew. Chem. 59 (15) (2020) 5890–5900.
[127] M. Xie, M. Yang, X. Sun, N. Yang, T. Deng, Y. Li, H. Shen, WS2 nanosheets functionalized by biomimetic lipids with enhanced dispersibility for photothermal and chemo combination therapy, J. Mater. Chem. B 8 (11) (2020) 2331–2342.
[128] H. Lin, S. Gao, C. Dai, Y. Chen, J. Shi, A two-dimensional biodegradable niobium carbide (MXene) for photothermal tumor eradication in NIR-I and NIR-II biowindows, J. Am. Chem. Soc. 139 (45) (2017) 16235–16247.
[129] T. Nagy-Simon, M. Potara, A.-M. Craciun, E. Licarete, S. Astilean, IR780-Dye loaded gold nanoparticles as new near infrared activatable nanotheranostic agents for simultaneous photodynamic and photothermal therapy and intracellular tracking by surface enhanced resonant Raman scattering imaging, J. Colloid Interface Sci. 517 (2018) 239–250.
[130] J. Conde, N. Oliva, M. Atilano, H.S. Song, N. Artzi, Self-assembled RNA-triple-helix hydrogel scaffold for MicroRNA modulation in the tumour microenvironment, Nat. Mater. 15 (3) (2016) 353–363.
[131] L. Pan, J. Liu, J. Shi, Nuclear-targeting gold nanorods for extremely low NIR activated photothermal therapy, ACS Appl. Mater. Interfaces 9 (19) (2017) 15952–15961.
[132] M. Xuan, J. Shao, L. Dai, J. Li, Q. He, Macrophage cell membrane camouflaged Au nanoshells for in vivo prolonged circulation life and enhanced cancer photothermal therapy, ACS Appl. Mater. Interfaces 8 (15) (2016) 9610–9618.
[133] X. Lin, Y. Fang, Z. Tao, X. Gao, T. Wang, M. Zhao, S. Wang, Y. Liu, Tumor-microenvironment-induced all-in-one nanoplatform for multimodal imaging-guided chemical and photothermal therapy of cancer, ACS Appl. Mater. Interfaces 11 (28) (2019) 25043–25053.
[134] M.R.K. Ali, M.A. Rahman, Y. Wu, T. Han, X. Peng, M.A. Mackey, D. Wang, H.J. Shin, Z.G. Chen, H. Xiao, et al., Efficacy, long-term toxicity, and mechanistic studies of gold nanorods photothermal therapy of cancer in xenograft mice, Proc. Natl. Acad. Sci. USA 114 (15) (2017) E3110–E3118.
[135] C. Zhan, Y. Huang, G. Lin, S. Huang, F. Zeng, S. Wu, A gold nanocage/cluster hybrid structure for whole-body multispectral optoacoustic tomography imaging, EGFR inhibitor delivery, and photothermal therapy, Small 15 (33) (2019), 1900309.
[136] M. Abbas, Q. Zou, S. Li, X. Yan, Self assembled peptide and protein based nanomaterials for antitumor photodynamic and photothermal therapy, Adv. Mater. 29 (12) (2017), 1605021.
[137] Z. Meng, F. Wei, R. Wang, M. Xia, Z. Chen, H. Wang, M. Zhu, NIR laser switched in vivo smart nanocapsules for synergic photothermal and chemotherapy of tumors, Adv. Mater. 28 (2) (2016) 245–253.
[138] D. Zhu, Z. Wang, S. Zong, Y. Zhang, C. Chen, R. Zhang, B. Yun, Y. Cui, Investigating the intracellular behaviors of liposomal nanohybrids via SERS: insights into the influence of metal nanoparticles, Theranostics 8 (4) (2018) 941.
[139] M. Gautam, R.K. Thapa, B. Gupta, Z.C. Soe, W. Ou, K. Poudel, S.G. Jin, H.-G. Choi, C.S. Yong, J.O. Kim, Phytosterol-loaded CD44 receptor-targeted PEGylated nano-hybrid phyto-liposomes for synergistic chemotherapy. *Expert opin*, Drug Deliv. 17 (3) (2020) 423–434.
[140] W. Yan, S.S.Y. Leung, K.K.W. To, Updates on the use of liposomes for active tumor targeting in cancer therapy, Nanomedicine 15 (3) (2020) 303–318.
[141] S.A. McFarland, A. Mandel, R. Dumoulin-White, G. Gasser, Metal-based photosensitizers for photodynamic therapy: the future of multimodal oncology? Curr. Opin. Chem. Biol. 56 (2020) 23–27.
[142] B. Mansoori, A. Mohammadi, M.A. Doustvandi, F. Mohammadnejad, F. Kamari, M.F. Gjerstorff, B. Baradaran, M.R. Hamblin, Photodynamic therapy for cancer: role of natural products, Photodiagnosis Photodyn. Ther. 26 (2019) 395–404.
[143] M. Zhang, Z. Cui, R. Song, B. Lv, Z. Tang, X. Meng, X. Chen, X. Zheng, J. Zhang, Z. Yao, SnWO4-Based nanohybrids with full energy transfer for largely enhanced photodynamic therapy and radiotherapy, Biomaterials 155 (2018) 135–144.
[144] T. Michy, T. Massias, C. Bernard, L. Vanwonterghem, M. Henry, M. Guidetti, G. Royal, J.-L. Coll, I. Texier, V. Josserand, Verteporfin-loaded lipid nanoparticles improve ovarian cancer photodynamic therapy in vitro and in vivo, Cancers (Basel) 11 (11) (2019) 1760.
[145] X. Li, S. Lee, J. Yoon, Supramolecular photosensitizers rejuvenate photodynamic therapy, Chem. Soc. Rev. 47 (4) (2018) 1174–1188.
[146] A. Kamkaew, F. Chen, Y. Zhan, R.L. Majewski, W. Cai, Scintillating nanoparticles as energy mediators for enhanced photodynamic therapy, ACS Nano 10 (4) (2016) 3918–3935.
[147] U. Chilakamarthi, L. Giribabu, Photodynamic therapy: past, present and future, Chem. Rec. 17 (8) (2017) 775–802.
[148] D. Van Straten, V. Mashayekhi, H.S. De Bruijn, S. Oliveira, D.J. Robinson, Oncologic photodynamic therapy: basic principles, current clinical status and future directions, Cancers (Basel). 9 (2) (2017) 19.
[149] X. Sun, Z. Cao, K. Mao, C. Wu, H. Chen, J. Wang, X. Wang, X. Cong, Y. Li, X. Meng, Photodynamic therapy produces enhanced efficacy of antitumor immunotherapy by simultaneously inducing intratumoral release of sorafenib, Biomaterials 240 (2020) 119845.
[150] R.R. Cheruku, J. Cacaccio, F.A. Durrani, W.A. Tabaczynski, R. Watson, A. Marko, R. Kumar, M.E. El-Khouly, S. Fukuzumi, J.R. Missert, Epidermal growth factor receptor-targeted multifunctional photosensitizers for bladder cancer imaging and photodynamic therapy, J. Med. Chem. 62 (5) (2019) 2598–2617.
[151] R. Vankayala, K.C. Hwang, Near infrared light activatable nanomaterial mediated phototheranostic nanomedicines: an emerging paradigm for cancer treatment, Adv. Mater. 30 (23) (2018), 1706320.
[152] J.E. Roberts, Techniques to improve photodynamic therapy, Photochem. Photobiol. 96 (3) (2020) 524–528.
[153] F.A. Bal, I. Ozkocak, B.H. Cadirci, E.S. Karaarslan, M. Cakdinleyen, M. Agaccioglu, Effects of photodynamic therapy with indocyanine green on Streptococcus mutans biofilm, Photodiagnosis Photodyn. Ther. 26 (2019) 229–234.
[154] F. Borgia, R. Giuffrida, E. Caradonna, M. Vaccaro, F. Guarneri, S.P. Cannavo, Early and late onset side effects of photodynamic therapy, Biomedicines 6 (1) (2018) 12.
[155] X. Jiang, Z. Zhou, H. Yang, C. Shan, H. Yu, L. Wojtas, M. Zhang, Z. Mao, M. Wang, P.J. Stang, Self-assembly of porphyrin-containing metalla-assemblies and cancer photodynamic therapy, Inorg. Chem. 59 (11) (2020) 7380–7388.
[156] Y. Baglo, B.J. Liang, R.W. Robey, S.V. Ambudkar, M.M. Gottesman, H.-C. Huang, Porphyrin-lipid assemblies and nanovesicles overcome ABC transporter-mediated photodynamic therapy resistance in cancer cells, Canc. Lett. 457 (2019) 110–118.
[157] S. Bouramtane, L. Bretin, A. Pinon, D. Leger, B. Liagre, L. Richard, F. Bregier, V. Sol, V. Chaleix, Porphyrin-xylan-coated silica nanoparticles for anticancer photodynamic therapy, Carbohydr. Polym. 213 (2019) 168–175.
[158] J. Dai, Y. Li, Z. Long, R. Jiang, Z. Zhuang, Z. Wang, Z. Zhao, X. Lou, F. Xia, B.Z. Tang, Efficient near-infrared photosensitizer with aggregation-induced emission for imaging-guided photodynamic therapy in multiple xenograft tumor models, ACS Nano 14 (1) (2019) 854–866.
[159] Y. Liu, N. Song, Z. Li, L. Chen, Z. Xie, Near-infrared nanoparticles based on aza-BDP for photodynamic and photothermal therapy, Dyes Pigments 160 (2019) 71–78.
[160] L.K. McKenzie, H.E. Bryant, J.A. Weinstein, Transition metal complexes as photosensitisers in one-and two-photon photodynamic therapy, Coord. Chem. Rev. 379 (2019) 2–29.
[161] J.H. Liang, Y. Zheng, X.W. Wu, C.P. Tan, L.N. Ji, Z.W. Mao, A tailored multifunctional anticancer nanodelivery system for ruthenium based photosensitizers: tumor microenvironment adaption and remodeling, Adv. Sci. 7 (1) (2020), 1901992.

[162] S. Siriwibool, N. Kaekratoke, K. Chansaenpak, K. Siwawannapong, P. Panajapo, K. Sagarik, P. Noisa, R.-Y. Lai, A. Kamkaew, Near-infrared fluorescent PH responsive probe for targeted photodynamic cancer therapy, Sci. Rep. 10 (1) (2020) 1–10.
[163] F.J. Civantos, B. Karakullukcu, M. Biel, C.E. Silver, A. Rinaldo, N.F. Saba, R.P. Takes, V. Vander Poorten, A. Ferlito, A review of photodynamic therapy for neoplasms of the head and neck, Adv. Ther. 35 (3) (2018) 324–340.
[164] C. Shirata, J. Kaneko, Y. Inagaki, T. Kokudo, M. Sato, S. Kiritani, N. Akamatsu, J. Arita, Y. Sakamoto, K. Hasegawa, Near-infrared photothermal/photodynamic therapy with indocyanine green induces apoptosis of hepatocellular carcinoma cells through oxidative stress, Sci. Rep. 7 (1) (2017) 1–8.
[165] P.-C. Lo, M.S. Rodriguez-Morgade, R.K. Pandey, D.K.P. Ng, T. Torres, F. Dumoulin, The unique features and promises of phthalocyanines as advanced photosensitisers for photodynamic therapy of cancer, Chem. Soc. Rev. 49 (4) (2020) 1041–1056.
[166] H. Wang, X. Pan, X. Wang, W. Wang, Z. Huang, K. Gu, S. Liu, F. Zhang, H. Shen, Q. Yuan, Degradable carbon-silica nanocomposite with immunoadjuvant property for dual-modality photothermal/photodynamic therapy, ACS Nano 14 (3) (2020) 2847–2859.
[167] H. Xu, B. Chen, W. Gong, Z. Yang, J. Qu, Nanoliposomes Co encapsulating photoswitchable probe and photosensitizer for super resolution optical imaging and photodynamic therapy, Cytometry Part A 97 (1) (2020) 54–60.
[168] P. Loganathan, M.M. Magzoub, PH responsive upconversion mesoporous silica nanoparticles for targeted photodynamic and photothermal cancer therapy, Biophys. J. 118 (3) (2020) 477a.
[169] C.A. Kruger, H. Abrahamse, Utilisation of targeted nanoparticle photosensitiser drug delivery systems for the enhancement of photodynamic therapy, Molecules 23 (10) (2018) 2628.
[170] D.J. Naczynski, C. Sun, S. Tu rkcan, C. Jenkins, A.L. Koh, D. Ikeda, G. Pratx, L. Xing, X-Ray-Induced shortwave infrared biomedical imaging using rare-earth nanoprobes, Nano Lett. 15 (1) (2015) 96–102.
[171] Y. Yang, L. Wang, H. Cao, Q. Li, Y. Li, M. Han, H. Wang, J. Li, Photodynamic therapy with liposomes encapsulating photosensitizers with aggregation-induced emission, Nano Lett. 19 (3) (2019) 1821–1826.
[172] Y. Zhang, F. Wang, C. Liu, Z. Wang, L. Kang, Y. Huang, K. Dong, J. Ren, X. Qu, Nanozyme decorated metal-organic frameworks for enhanced photodynamic therapy, ACS Nano 12 (1) (2018) 651–661.
[173] W. Sun, Z. Zhou, G. Pratx, X. Chen, H. Chen, Nanoscintillator-mediated X-ray induced photodynamic therapy for deep-seated tumors: from concept to biomedical applications, Theranostics 10 (3) (2020) 1296.
[174] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (1) (2013) 1–10.
[175] X. Wang, X. Li, A. Ito, Y. Watanabe, N.M. Tsuji, Rod-shaped and fluorine-substituted hydroxyapatite free of molecular immunopotentiators stimulates anti-cancer immunity in vivo, Chem. Commun. 52 (44) (2016) 7078–7081.
[176] G. Zhu, F. Zhang, Q. Ni, G. Niu, X. Chen, Efficient nanovaccine delivery in cancer immunotherapy, ACS Nano 11 (3) (2017) 2387–2392.
[177] W. Song, A.C. Anselmo, L. Huang, Nanotechnology intervention of the microbiome for cancer therapy, Nat. Nanotechnol. 14 (12) (2019) 1093–1103.
[178] H. Phuengkham, L. Ren, I.W. Shin, Y.T. Lim, Nanoengineered immune niches for reprogramming the immunosuppressive tumor microenvironment and enhancing cancer immunotherapy, Adv. Mater. 31 (34) (2019), 1803322.
[179] X. Wang, S. Ihara, X. Li, A. Ito, Y. Sogo, Y. Watanabe, A. Yamazaki, N.M. Tsuji, T. Ohno, Rod-scale design strategies for immune-targeted delivery system toward cancer immunotherapy, ACS Nano 13 (7) (2019) 7705–7715.
[180] H.T. Marshall, M. Djamgoz, Immuno-oncology: emerging targets and combination therapies, Front. Oncol. 8 (2018) 315.
[181] Q. Li, D. Zhang, J. Zhang, Y. Jiang, A. Song, Z. Li, Y. Luan, A three-in-one immunotherapy nanoweapon via cascade-amplifying cancer-immunity cycle against tumor metastasis, relapse, and postsurgical regrowth, Nano Lett. 19 (9) (2019) 6647–6657.
[182] N.R. Maimela, S. Liu, Y. Zhang, Fates of CD8+ T cells in tumor microenvironment, Comput. Struct. Biotechnol. J. 17 (2019) 1–13.
[183] B. Ye, C.M. Stary, X. Li, Q. Gao, C. Kang, X. Xiong, Engineering chimeric antigen receptor-T cells for cancer treatment, Mol. Canc. 17 (1) (2018) 32.
[184] Q. Song, Y. Yin, L. Shang, T. Wu, D. Zhang, M. Kong, Y. Zhao, Y. He, S. Tan, Y. Guo, Tumor microenvironment responsive nanogel for the combinatorial antitumor effect of chemotherapy and immunotherapy, Nano Lett. 17 (10) (2017) 6366–6375.
[185] K. Shao, S. Singha, X. Clemente-Casares, S. Tsai, Y. Yang, P. Santamaria, Nanoparticle-based immunotherapy for cancer, ACS Nano 9 (1) (2015) 16–30.
[186] W. Shan, H. Zheng, G. Fu, C. Liu, Z. Li, Y. Ye, J. Zhao, D. Xu, L. Sun, X. Wang, Bioengineered nanocage from HBc protein for combination cancer immunotherapy, Nano Lett. 19 (3) (2019) 1719–1727.
[187] H. Harjunpaa, M. Llort Asens, C. Guenther, S.C. Fagerholm, Cell adhesion molecules and their roles and regulation in the immune and tumor microenvironment, Front. Immunol. 10 (2019) 1078.
[188] E.A. Gosselin, H.B. Eppler, J.S. Bromberg, C.M. Jewell, Designing natural and synthetic immune tissues, Nat. Mater. 17 (6) (2018) 484.
[189] D. Alka, K. Atharva, G. Sarbari, R. Afrin, P. Rahul, Lymphocytes in cellular therapy: functional regulation of CAR T cells, Front. Immunol. 9 (2019) 3180.
[190] J.A. Marin-Acevedo, A.E. Soyano, B. Dholaria, K.L. Knutson, Y. Lou, Cancer immunotherapy beyond immune checkpoint inhibitors, J. Hematol. Oncol. 11 (1) (2018) 8.
[191] A. Aiello, F. Farzaneh, G. Candore, C. Caruso, S. Davinelli, C.M. Gambino, M.E. Ligotti, N. Zareian, G. Accardi, The immunosenescence and its hallmarks: how to oppose ageing strategically? A review of potential options for therapeutic intervention, Front. Immunol. 10 (2019) 2247.
[192] Andrea, M.; Weinschenk, T.; Schoor, O.; Fritsche, J.; Singh, H.; Stevermann, L. Novel peptides and combination of peptides for use in immunotherapy against various tumors. US 2016/0280738A1, Sept. 29 2016.
[193] M. Lim, A.Z.M. Badruddoza, J. Firdous, M. Azad, A. Mannan, T.A. Al-Hilal, C.-S. Cho, M.A. Islam, Engineered nanodelivery systems to improve DNA vaccine technologies, Pharmaceutics 12 (1) (2020) 1–29.
[194] J.R. Campos, P. Severino, A. Santini, A.M. Silva, R. Shegokar, S.B. Souto, E.B. Souto, Solid lipid nanoparticles (SLN): prediction of toxicity, metabolism, fate and physicochemical properties, in: Nanopharmaceuticals, Elsevier, 2020, pp. 1–15.
[195] J.M. Patel, K.S. Saleh, J.A. Burdick, R.L. Mauck, Bioactive factors for cartilage repair and regeneration: improving delivery, retention, and activity, Acta Biomater. 93 (2019) 222–238.
[196] F. Di Xia, B.S. Ferket, V. Huang, R.S. Stern, P.A. Wu, Local radiation and phototherapy are the most cost-effective treatments for stage IA mycosis fungoides: a comparative decision analysis model in the United States, J. Am. Acad. Dermatol. 80 (2) (2019) 485–492.
[197] W. Ma, Y. Hu, H. Yang, Y. Zhang, J. Ding, L. Chen, Au-aided reduced graphene oxide-based nanohybrids for photo-chemotherapy, Mater. Sci. Eng. C 95 (2019) 256–263.
[198] B. Mai, M. Jia, S. Liu, Z. Sheng, M. Li, Y. Gao, X. Wang, Q. Liu, P. Wang, Smart hydrogel-based DVDMS/BFGF nanohybrids for antibacterial phototherapy with multiple damaging-sites and accelerated wound healing, ACS Appl. Mater. Interfaces 12 (9) (2020) 10156–10169.
[199] M. Chang, M. Wang, Y. Chen, M. Shu, Y. Zhao, B. Ding, Z. Hou, J. Lin, Self-assembled CeVO 4/Ag nanohybrid as photoconversion agents with enhanced solar-driven photocatalysis and NIR-responsive photothermal/photodynamic synergistic therapy performance, Nanoscale 11 (20) (2019) 10129–10136.
[200] H. Guan, T. Ding, W. Zhou, Z. Wang, J. Zhang, K. Cai, Hexagonal polypyrrole nanosheets from interface driven heterogeneous hybridization and self-assembly for photothermal cancer treatment, Chem. Commun. 55 (30) (2019) 4359–4362.
[201] C.-C. Chen, D.-Y. Chang, J.-J. Li, H.-W. Chan, J.-T. Chen, C.-H. Chang, R.-S. Liu, C.A. Chang, C.-L. Chen, H.-E. Wang, Investigation of biodistribution and tissue penetration of PEGylated gold nanostars and their application for photothermal cancer treatment in tumor-bearing mice, J. Mater. Chem. B 8 (1) (2020) 65–77.
[202] S. Chen, Q. Lei, W.-X. Qiu, L.-H. Liu, D.-W. Zheng, J.-X. Fan, L. Rong, Y.-X. Sun, X.-Z. Zhang, Mitochondria-targeting “nanoheater” for enhanced photothermal/chemo-therapy, Biomaterials 117 (2017) 92–104.
[203] Y. Cao, J. Yi, X. Yang, L. Liu, C. Yu, Y. Huang, L. Sun, Y. Bao, Y. Li, Efficient cancer regression by a thermosensitive liposome for photoacoustic imaging-guided photothermal/chemo combinatorial therapy, Biomacromolecules 18 (8) (2017) 2306–2314.
[204] R. Xing, Q. Zou, C. Yuan, L. Zhao, R. Chang, X. Yan, Self assembling endogenous biliverdin as a versatile near infrared photothermal nanoagent for cancer theranostics, Adv. Mater. 31 (16) (2019), 1900822.
[205] T. Appidi, D.B. Pemmaraju, R.A. Khan, S.B. Alvi, R. Srivastava, M. Pal, N. Khan, A.K. Rengan, Light-triggered selective ROS-dependent autophagy by bioactive nanoliposomes for efficient cancer theranostics, Nanoscale 12 (3) (2020) 2028–2039.
[206] A. Carvalho, A.R. Fernandes, P.V. Baptista, Nanoparticles as delivery systems in cancer therapy: focus on gold nanoparticles and drugs, in: Applications of Targeted Nano Drugs and Delivery Systems, Elsevier, 2019, pp. 257–295.
[207] Z. Yang, L. Li, A. Jin, W. Huang, X.S. Chen, Rational design of semiconducting polymer brushes as cancer theranostics, Mater. Horizons 7 (6) (2020) 1474–1494.
[208] S. Rajkumar, M. Prabaharan, Multi-functional FITC-silica@gold nanoparticles conjugated with guar gum succinate, folic acid and doxorubicin for CT/fluorescence dual imaging and combined chemo/PTT of cancer, Colloids Surf. B Biointerfaces 186 (2020) 110701.
[209] H. Yang, H.S. Liu, W. Hou, J.X. Gao, Y. Duan, D. Wei, X.Q. Gong, H.J. Wang, X.L. Wu, J. Chang, An NIR-responsive mesoporous silica nanosystem for synergetic photothermal-immunoenhancement therapy of hepatocellular carcinoma, J. Mater. Chem. B 8 (2) (2020) 251–259.
[210] X. Chen, Q. Zhang, J. Li, M. Yang, N. Zhao, F.J. Xu, Rattle-structured rough nanocapsules with in-situ-formed gold nanorod cores for complementary gene/chemo/photothermal therapy, ACS Nano 12 (6) (2018) 5646–5656.
[211] Y. Li, Y. Wu, J. Chen, J. Wan, C. Xiao, J. Guan, X. Song, S. Li, M. Zhang, H. Cui, et al., A simple glutathione-responsive turn-on theranostic nanoparticle for dual-modal imaging and chemo-photothermal combination therapy, Nano Lett. 19 (8) (2019) 5806–5817.
[212] S. Duan, Y. Yang, C. Zhang, N. Zhao, F.J. Xu, NIR-responsive polycationic gatekeeper-cloaked hetero-nanoparticles for multimodal imaging-guided triple-combination therapy of cancer, Small 13 (9) (2017), 1603133.

[213] B. Hou, L. Zhou, H. Wang, M. Saeed, D. Wang, Z. Xu, Y. Li, H. Yu, Engineering stimuli-activatable boolean logic prodrug nanoparticles for combination cancer immunotherapy, Adv. Mater. (2020), 1907210.
[214] Z. Su, Y. Xu, Y. Wang, W. Shi, S. Han, X. Shuai, A PH and reduction dual-sensitive polymeric nanomicelle for tumor microenvironment triggered cellular uptake and controlled intracellular drug release, Biomater. Sci. 7 (9) (2019) 3821–3831.
[215] Z. He, Y. Zhang, N. Feng, Cell membrane-coated nanosized active targeted drug delivery systems homing to tumor cells: a review, Mater. Sci. Eng. C 106 (2020) 110298.
[216] B. Chen, W. Dai, B. He, H. Zhang, X. Wang, Y. Wang, Q. Zhang, Current multistage drug delivery systems based on the tumor microenvironment, Theranostics (2017) 538–558.
[217] T. Lang, X. Dong, Z. Zheng, Y. Liu, G. Wang, Q. Yin, Y. Li, Tumor microenvironment-responsive docetaxel-loaded micelle combats metastatic breast cancer, Sci. Bull. 64 (2) (2019) 91–100.
[218] H. Gao, Z. Yang, S. Zhang, Z. Pang, Q. Liu, X. Jiang, Study and evaluation of mechanisms of dual targeting drug delivery system with tumor microenvironment assays compared with normal assays, Acta Biomater. 10 (2) (2014) 858–867.
[219] Y. Zhang, P. Dosta, J. Conde, N. Oliva, M. Wang, N. Artzi, Prolonged local in vivo delivery of stimuli-responsive nanogels that rapidly release doxorubicin in triple-negative breast cancer cells, Adv. Healthc. Mater. (2020), 1901101.
[220] S. Talebian, J. Foroughi, S.J. Wade, K.L. Vine, A. Dolatshahi-Pirouz, M. Mehrali, J. Conde, G.G. Wallace, Biopolymers for antitumor implantable drug delivery systems: recent advances and future outlook, Adv. Mater. 30 (31) (2018), 1706665.
[221] C. Ann Kruger, H. Abrahamse, Targeted photodynamic therapy as potential treatment modality for the eradication of colon cancer, in: Multidisciplinary Approach for Colorectal Cancer, 2019.
[222] X. Dai, T. Du, K. Han, Engineering nanoparticles for optimized photodynamic therapy, ACS Biomater. Sci. Eng. 5 (12) (2019) 6342–6354.
[223] J. Liu, Q. Chen, W. Zhu, X. Yi, Y. Yang, Z. Dong, Z. Liu, Nanoscale-coordination-polymer-shelled manganese dioxide composite nanoparticles: a multistage redox/PH/H2O2-responsive cancer theranostic nanoplatform, Adv. Funct. Mater. 27 (10) (2017), 1605926.
[224] S. Sowmya, Nanohybrid scaffold structures for smart drug delivery applications, in: Biomimetic Nanoengineered Materials for Advanced Drug Delivery, Elsevier Inc., 2019, pp. 53–59.
[225] D. Rosenblum, N. Joshi, W. Tao, J.M. Karp, D. Peer, Progress and challenges towards targeted delivery of cancer therapeutics, Nat. Commun. 9 (1) (2018) 1–12.
[226] X. Huang, J. Hu, Y. Li, F. Xin, R. Qiao, T.P. Davis, Engineering organic/inorganic nanohybrids through RAFT polymerization for biomedical applications, Biomacromolecules 20 (12) (2019) 4243–4257.
[227] R. Prasad, N.K. Jain, A.S. Yadav, D.S. Chauhan, J. Devrukhkar, M. kumar Kumawat, S. Shinde, M. Gorain, A.S. Thakor, J. Conde, et al., Liposomal nanotheranostics for multimode targeted in vivo bioimaging and near-infrared light mediated cancer therapy, Commun. Biol. 3 (284) (2020) 1–14.
[228] Y.L. Su, S.H. Hu, Functional nanoparticles for tumor penetration of therapeutics, Pharmaceutics 10 (4) (2018) 193.
[229] L.L. Israel, A. Galstyan, E. Holler, J.Y. Ljubimova, Magnetic iron oxide nanoparticles for imaging, targeting and treatment of primary and metastatic tumors of the brain, J. Contr. Release 320 (2020) 45–62.
[230] S. Sindhwani, A.M. Syed, J. Ngai, B.R. Kingston, L. Maiorino, J. Rothschild, P. MacMillan, Y. Zhang, N.U. Rajesh, T. Hoang, et al., The entry of nanoparticles into solid tumours, Nat. Mater. (2020) 1–10.
[231] Q. Guo, X. He, C. Li, Y. He, Y. Peng, Y. Zhang, Y. Lu, X. Chen, Y. Zhang, Q. Chen, et al., Dandelion-like tailorable nanoparticles for tumor microenvironment modulation, Adv. Sci. 6 (21) (2019) 1901430.
[232] S. Kunjachan, S. Kotb, R. Pola, M. Pechar, R. Kumar, B. Singh, F. Gremse, R. Taleeli, F. Trichard, V. Motto-Ros, et al., Selective priming of tumor blood vessels by radiation therapy enhances nanodrug delivery, Sci. Rep. 9 (1) (2019) 1–14.
[233] W. Liu, G. Zhang, J. Wu, Y. Zhang, J. Liu, H. Luo, L. Shao, Insights into the angiogenic effects of nanomaterials: mechanisms involved and potential applications, J. Nanobiotechnol. 18 (1) (2020) 1–22.
[234] D.S. Chauhan, B.P.K. Reddy, S.K. Mishra, R. Prasad, M. Dhanka, M. Vats, G. Ravichandran, D. Poojari, O. Mhatre, A. De, et al., A comprehensive evaluation of degradable and cost effective plasmonic nanoshells for localized photothermolysis of cancer cells, Langmuir 35 (24) (2019) 7805–7815.
[235] R. Ngoune, A. Peters, D. von Elverfeldt, K. Winkler, G. Pütz, Accumulating nanoparticles by EPR: a route of No return, J. Contr. Release 238 (2016) 58–70.
[236] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (5) (2016) 1–12.
[237] S.K. Golombek, J.-N. May, B. Theek, L. Appold, N. Drude, F. Kiessling, T. Lammers, Tumor targeting via EPR: strategies to enhance patient responses, Adv. Drug Deliv. Rev. 130 (2018) 17–38.
[238] J.L. Paris, M. Manzano, M.V. Cabañas, M. Vallet-Regí, Mesoporous silica nanoparticles engineered for ultrasound-induced uptake by cancer cells, Nanoscale 10 (14) (2018) 6402–6408.
[239] A.L. Papa, N. Korin, M. Kanapathipillai, A. Mammoto, T. Mammoto, A. Jiang, R. Mannix, O. Uzun, C. Johnson, D. Bhatta, et al., Ultrasound-sensitive nanoparticle aggregates for targeted drug delivery, Biomaterials 139 (2017) 187–194.
[240] C.G. Dariva, J.F.J. Coelho, A.C. Serra, Near infrared light-triggered nanoparticles using singlet oxygen photocleavage for drug delivery systems, J. Contr. Release 294 (2019) 337–354.
[241] F.F. Inagaki, A. Furusawa, P.L. Choyke, H. Kobayashi, Enhanced nanodrug delivery in tumors after near-infrared photoimmunotherapy, Nanophotonics 8 (10) (2019) 1673–1688.
[242] G. Jin, R. He, Q. Liu, M. Lin, Y. Dong, K. Li, B.Z. Tang, B. Liu, F. Xu, Near-infrared light-regulated cancer theranostic nanoplatform based on aggregation-induced emission luminogen encapsulated upconversion nanoparticles, Theranostics 9 (1) (2019) 246–264.
[243] D. Lombardo, M.T. Caccamo, S. Magazu, M.A. Kiselev, P. Calandra, Enhancement of colloidal stability of drug nanocarriers in complex biological environment, Atti della Accad. Peloritana dei Pericolanti-Classe di Sci. Fis. Mat. e Nat. 97 (S2) (2019) 25.
[244] A.K. Barui, J.Y. Oh, B. Jana, C. Kim, J. Ryu, Cancer-targeted nanomedicine: overcoming the barrier of the protein corona, Adv. Ther. 3 (1) (2020) 1900124.
[245] S.D. Perrault, W.C.W. Chan, In vivo assembly of nanoparticle components to improve targeted cancer imaging, Proc. Natl. Acad. Sci. USA 107 (25) (2010) 11194–11199.
[246] F. Peng, M.I. Setyawati, J.K. Tee, X. Ding, J. Wang, M.E. Nga, H.K. Ho, D.T. Leong, Nanoparticles promote in vivo breast cancer cell intravasation and extravasation by inducing endothelial leakiness, Nat. Nanotechnol. 14 (3) (2019) 279–286.
[247] H. Hashizume, P. Baluk, S. Morikawa, J.W. McLean, G. Thurston, S. Roberge, R.K. Jain, D.M. McDonald, Openings between defective endothelial cells explain tumor vessel leakiness, Am. J. Pathol. 156 (4) (2000) 1363–1380.
[248] W.C.W. Chan, Nanomedicine 2.0, Acc. Chem. Res. 50 (3) (2017) 627–632.
[249] D. Cialla-May, X.S. Zheng, K. Weber, J. Popp, Recent progress in surface-enhanced Raman spectroscopy for biological and biomedical applications: from cells to clinics, Chem. Soc. Rev. 46 (13) (2017) 3945–3961.
[250] L. Li, H. Xing, J. Zhang, Y. Lu, Functional DNA molecules enable selective and stimuli-responsive nanoparticles for biomedical applications, Acc. Chem. Res. 52 (9) (2019) 2415–2426.
[251] J. Liu, P. Wang, X. Zhang, L. Wang, D. Wang, Z. Gu, J. Tang, M. Guo, M. Cao, H. Zhou, et al., Rapid degradation and high renal clearance of Cu3BiS3 nanodots for efficient cancer diagnosis and photothermal therapy in vivo, ACS Nano 10 (4) (2016) 4587–4598.
[252] J.K. Phillips, M.A. Ford, R.J. Bonnie, National Academies of Sciences, Engineering, M. Opioid Approval and Monitoring by the US Food and Drug Administration, Pain Manag. Opioid Epidemic Balanc. Soc. Individ. Benefits Risks Prescr, Opioid Use. Natl. Acad. Press, 2017.
[253] Y. Liu, W. Zhen, Y. Wang, J. Liu, L. Jin, T. Zhang, S. Zhang, Y. Zhao, N. Yin, R. Niu, et al., Double switch biodegradable porous hollow trinickel monophosphide nanospheres for multimodal imaging guided photothermal therapy, Nano Lett. 19 (8) (2019) 5093–5101.
[254] M. Yu, J. Xu, J. Zheng, Renal clearable luminescent gold nanoparticles: from the bench to the clinic, Angew. Chem. Int. Ed. 58 (13) (2019) 4112–4128.
[255] W. Poon, Y.N. Zhang, B. Ouyang, B.R. Kingston, J.L.Y. Wu, S. Wilhelm, W.C.W. Chan, Elimination pathways of nanoparticles, ACS Nano 13 (5) (2019) 5785–5798.
[256] H. Zhou, J. Ge, Q. Miao, R. Zhu, L. Wen, J. Zeng, M. Gao, Biodegradable inorganic nanoparticles for cancer theranostics: insights into the degradation behavior, Bioconjugate Chem. 31 (2) (2020) 315–331.
[257] X. Yu, A. Li, C. Zhao, K. Yang, X. Chen, W. Li, Ultrasmall semimetal nanoparticles of bismuth for dual-modal computed tomography/photoacoustic imaging and synergistic thermoradiotherapy, ACS Nano 11 (4) (2017) 3990–4001.
[258] G. Yang, S.Z.F. Phua, A.K. Bindra, Y. Zhao, Degradability and clearance of inorganic nanoparticles for biomedical applications, Adv. Mater. 31 (10) (2019) 1805730.
[259] W.H. Chen, G.F. Luo, X.Z. Zhang, Recent advances in subcellular targeted cancer therapy based on functional materials, Adv. Mater. 31 (3) (2019) 1802725.
[260] J.G. Dancy, A.S. Wadajkar, N.P. Connolly, R. Galisteo, H.M. Ames, S. Peng, N.L. Tran, O.G. Goloubeva, G.F. Woodworth, J.A. Winkles, et al., Decreased nonspecific adhesivity, receptor-targeted therapeutic nanoparticles for primary and metastatic breast cancer, Sci. Adv. 6 (3) (2020), eaax3931.
[261] S.M. Hossain, S.A.Z. Abidin, E.H. Chowdhury, Krebs cycle intermediate-modified carbonate apatite nanoparticles drastically reduce mouse tumor burden and toxicity by restricting broad tissue distribution of anticancer drugs, Cancers (Basel) 12 (1) (2020) 161.
[262] Y. Zhao, D. Sultan, Y. Liu, Biodistribution, excretion, and toxicity of nanoparticles, in: Theranostic Bionanomaterials, Elsevier Inc., 2019, pp. 27–53.
[263] G. Chen, I. Roy, C. Yang, P.N. Prasad, Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy, Chem. Rev. 116 (5) (2016) 2826–2885.
[264] E. Huynh, G. Zheng, Cancer nanomedicine: addressing the dark side of the enhanced permeability and retention effect, Nanomedicine 10 (13) (2015) 1993–1995.

[265] H. Nakamura, F. Jun, H. Maeda, Development of next-generation macromolecular drugs based on the EPR effect: challenges and pitfalls, Expet Opin. Drug Deliv. 12 (1) (2015) 53–64.
[266] J. Wolfram, M. Ferrari, Clinical cancer nanomedicine, Nano Today 25 (2019) 85–98.
[267] H. He, L. Liu, E.E. Morin, M. Liu, A. Schwendeman, Survey of clinical translation of cancer nanomedicines - lessons learned from successes and failures, Acc. Chem. Res. 52 (9) (2019) 2673–2683.
[268] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, Pharm. Res. 33 (10) (2016) 2373–2387.
[269] Y. Barenholz, Doxil® - the first FDA-approved nano-drug: lessons learned, J. Contr. Release 160 (2) (2012) 117–134.
[270] A.R. Rastinehad, H. Anastos, E. Wajswol, J.S. Winoker, J.P. Sfakianos, S.K. Doppalapudi, M.R. Carrick, C.J. Knauer, B. Taouli, S.C. Lewis, et al., Gold nanoshell-localized photothermal ablation of prostate tumors in a clinical pilot device study, Proc. Natl. Acad. Sci. USA 116 (37) (2019) 18590–18596.
[271] J. Lao, J. Madani, T. Puértolas, M. Álvarez, A. Hernández, R. Pazo-Cid, Á. Artal, A. Antón Torres, Liposomal doxorubicin in the treatment of breast cancer patients: a review, J. Drug Deliv. 2013 (2013) 1–12.
[272] C. Oerlemans, W. Bult, M. Bos, G. Storm, J.F.W. Nijsen, W.E. Hennink, Polymeric Micelles in Anticancer Therapy: Targeting, Imaging and Triggered Release, Pharmaceutical Research, 2010, pp. 2569–2589.
[273] J. Hrkach, D. Von Hoff, M.M. Ali, E. Andrianova, J. Auer, T. Campbell, D. De Witt, M. Figa, M. Figueiredo, A. Horhota, et al., Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile, Sci. Transl. Med. 4 (128ra39) (2012).
[274] N. Senzer, J. Nemunaitis, D. Nemunaitis, C. Bedell, G. Edelman, M. Barve, R. Nunan, K.F. Pirollo, A. Rait, E.H. Chang, Phase i study of a systemically delivered P53 nanoparticle in advanced solid tumors, Mol. Ther. 21 (2013) 1096–1103.
[275] M. Benezra, O. Penate-Medina, P.B. Zanzonico, D. Schaer, H. Ow, A. Burns, E. DeStanchina, V. Longo, E. Herz, S. Iyer, et al., Multimodal silica nanoparticles are effective cancer-targeted probes in a model of human melanoma, J. Clin. Invest. 121 (7) (2011) 2768–2780.
[276] S. Park, A. Aalipour, O. Vermesh, J.H. Yu, S.S. Gambhir, Towards clinically translatable in vivo nanodiagnostics, Nat. Rev. Mater. 2 (5) (2017) 17014.
[277] W. Xia, P.S. Low, Folate-targeted therapies for cancer, J. Med. Chem. 53 (19) (2010) 6811–6824.
[278] J. Szebeni, F. Muggia, Y. Barenholz, Case study: complement activation related hypersensitivity reactions to PEGylated liposomal doxorubicin – experimental and clinical evidence, mechanisms and approaches to inhibition, Handbook of Immunological Properties of Engineered Nanomaterials, Front. Nanobiomed. Res. 6 (2016) 331–361.
[279] M. Zhao, X. feng Ding, J. yu Shen, X. ping Zhang, X. wen Ding, B. Xu, Use of liposomal doxorubicin for adjuvant chemotherapy of breast cancer in clinical practice, J. Zhejiang Univ. - Sci. B 18 (1) (2017) 15–26.
[280] J.A. Carr, D. Franke, J.R. Caram, C.F. Perkinson, M. Saif, V. Askoxylakis, M. Datta, D. Fukumura, R.K. Jain, M.G. Bawendi, Shortwave infrared fluorescence imaging with the clinically approved near-infrared dye indocyanine green, Proc. Natl. Acad. Sci. USA 115 (17) (2018) 4465–4470.
[281] N.N. Nystrom, L.C.M. Yip, J.J.L. Carson, T.J. Scholl, J.A. Ronald, A human photoacoustic imaging reporter gene using the clinical dye indocyanine green, bioRxiv (2019) 537100.
[282] D.M. Ozog, A.M. Rkein, S.G. Fabi, M.H. Gold, M.P. Goldman, N.J. Lowe, G.M. Martin, G.S. Munavalli, Photodynamic therapy: a clinical consensus guide, Dermatol. Surg. 42 (7) (2016) 804–827.
[283] K. Nguyen, A. Khachemoune, An update on topical photodynamic therapy for clinical dermatologists, J. Dermatol. Treat. 30 (8) (2019) 732–744.
[284] J. He, C.L. Li, B.C. Wilson, C.J. Fisher, S. Ghai, R.A. Weersink, A clinical prototype transrectal diffuse optical tomography (TRDOT) system for in vivo monitoring of photothermal therapy (PTT) of focal prostate cancer, IEEE Trans. Biomed. Eng. 67 (7) (2019) 2119–2129.
[285] P. Zhang, C. Hu, W. Ran, J. Meng, Q. Yin, Y. Li, Recent progress in light-triggered nanotheranostics for cancer treatment, Theranostics 6 (7) (2016) 948.
[286] H. Peng, R.E. Borg, L.P. Dow, B.L. Pruitt, I.A. Chen, Controlled phage therapy by photothermal ablation of specific bacterial species using gold nanorods targeted by chimeric phages, Proc. Natl. Acad. Sci. USA 117 (4) (2020) 1951–1961.
[287] M. Karavitakis, M. Winkler, P. Abel, N. Livni, I. Beckley, H.U. Ahmed, Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy, Prostate Cancer Prostatic Dis. 14 (1) (2011) 46–52.
[288] F. Ting, M. Tran, M. Böhm, A. Siriwardana, P.J. Van Leeuwen, A.M. Haynes, W. Delprado, R. Shnier, P.D. Stricker, Focal irreversible electroporation for prostate cancer: functional outcomes and short-term oncological control, Prostate Cancer Prostatic Dis. 19 (1) (2016) 46–52.
[289] F. Lee, D.K. Bahn, R.A. Badalament, A.B. Kumar, D. Klionsky, G.M. Onik, D.O. Chinn, C. Greene, Cryosurgery for prostate cancer: improved glandular ablation by use of 6 to 8 cryoprobes, Urology 54 (1) (1999) 135–140.
[290] A. Kawczyk-Krupka, K. Wawrzyniec, S.K. Musiol, M. Potempa, A.M. Bugaj, A. Sieroń, Treatment of localized prostate cancer using WST-09 and WST-11 mediated vascular targeted photodynamic therapy-A review, Photodiagnosis Photodyn. Ther. 12 (4) (2015) 567–574.
[291] H.A. Havel, Where are the nanodrugs? An industry perspective on development of drug products containing nanomaterials, AAPS J. 18 (6) (2016) 1351–1353.
[292] A. Gabizon, T. Peretz, A. Sulkes, S. Amselem, R. Ben-Yosef, N. Ben-Baruch, R. Catane, S. Biran, Y. Barenholz, Systemic administration of doxorubicin-containing liposomes in cancer patients: a phase I study, Eur. J. Cancer Clin. Oncol. 25 (12) (1989) 1795–1803.
[293] U. Bulbake, S. Doppalapudi, N. Kommineni, W. Khan, Liposomal formulations in clinical use: an updated review, Pharmaceutics 9 (2) (2017) 12.
[294] V. Constantin, Uglea and marcel Popa. Targeting moieties, in: Polymeric Nanomedicines, Bentham Science Publishers, 2013, pp. 144–189.
[295] M. Srinivasarao, P.S. Low, Ligand-targeted drug delivery, Chem. Rev. 117 (19) (2017) 12133–12164.
[296] J. Lau, O. Jacobson, G. Niu, K.S. Lin, F. Bénard, X. Chen, Bench to bedside: albumin binders for improved cancer radioligand therapies, Bioconjugate Chem. 30 (3) (2019) 487–502.
[297] J. Zang, X. Fan, H. Wang, Q. Liu, J. Wang, H. Li, F. Li, O. Jacobson, G. Niu, Z. Zhu, et al., First-in-Human study of 177Lu-EB-PSMA-617 in patients with metastatic castration-resistant prostate cancer, Eur. J. Nucl. Med. Mol. Imag. 46 (1) (2019) 148–158.