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The effect of low- and high-penetration light on localized cancer therapy

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ABSTRACT

The design of a delivery system allowing targeted and controlled drug release has been considered one of the main strategies used to provide individualized cancer therapy, to improve survival statistics, and to enhance quality-of-life. External stimuli including low- and high-penetration light have been shown to have the ability to turn drug delivery on and off in a non-invasive remotely-controlled fashion. The success of this approach has been closely related to the development of a variety of drug delivery systems – from photosensitive liposomes to gold nanocages – and relies on multiple mechanisms of drug release activation. In this review, we make reference to the two extremes of the light spectrum and their potential as triggers for the delivery of anti-tumor drugs, along with the most recent achievements in preclinical trials and the challenges to an efficient translation of this technology to the clinical setting.

Contents

1. Introduction

The first attempts to eliminate fast dividing somatic cells were reported in the late 40s, when Goodman studied the action of nitrogen mustards against leukemia [1]. Over 70 years later, scientists have come to the conclusion that the challenges to an efficient cancer therapy go beyond the characteristics of the cancer cells *per se*. The same type of cancer can trigger the expression of different genes depending on the patient. Drug effects are subject to interpersonal variations regarding metabolism, immune system, and other biological events that highlight the importance of transitioning from universal to individualized cancer therapy (Fig. 1) [2–7].

In this regard, nanotechnology has emerged as a frontline approach to the design of systems able to diagnose and to react to unique effects of the disease in a particular patient. Drug carriers have been optimized

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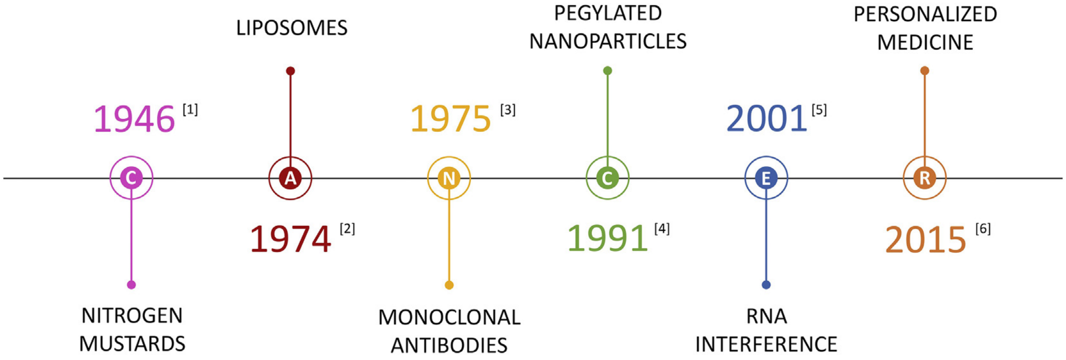

Fig. 1. The evolution of cancer therapy. Over the last 70 years, advances in immunology, drug delivery and genetic modification have opened up the possibilities for therapeutic strategies based on the geno- and phenotypes in a single patient, the so-called personalized medicine [1–6].

in order to respond to biological and physical stimuli, and to combine drug, imaging agents, biomarkers, and genetic material in a single particle [8].

Drug delivery triggered by biological stimuli has often improved tumor growth inhibition and reduced off-target effects in animal models. This approach assesses the characteristics of the tumor tissue and uses them to guide the treatment. Lower pH, redox potential variation, elevated temperature, overexpression of enzymes, and high levels of reactive oxygen species have been studied as potential triggers for drug release from various nanosystems [9–12].

Additionally, physical stimuli have been shown to be critical for the simultaneous diagnoses and treatment of cancer. The emission of light, ultrasound, and electromagnetic waves offer the singular ability to turn drug delivery on and off in a particular site of action. Tunable release of chemotherapeutics and other payloads plays a key role on the development of localized therapies [13].

2. Targeted cancer therapy relies on tunable drug delivery

The intravenous injection of chemotherapeutics has special importance in the treatment of tumors that are not easily accessible for surgical removal or implantation of drug delivery devices. However, this route of administration still faces the drawbacks of an uncontrolled biodistribution of the payloads as well as their interaction with components of the blood. One of the most reported adverse effects of chemotherapy is the production of cytokines and chemokines that generate undesired acute and chronic inflammatory responses in multiple organs of cancer patients [14,15]. Fatigue, anemia, alopecia, and immunosuppression are also common side effects of non-targeted therapies [16].

Effectively targeting a diseased tissue relies on understanding its very specific features in order to allow the development of a tunable drug delivery technology. In the ideal case, the release of the therapeutic agent is turned on only at the site of action, but not in the rest of the body [17]. Such an effect can be remotely controlled by external stimuli or activated by components of the tumor microenvironment. The first approach has unique clinical benefits, since it is less affected by biological variations among tumor types [18]. The most common triggering agents are ultrasound, X-ray, temperature, electric and magnetic field emissions [13].

The efficiency of remotely-triggered delivery systems depends on multiple factors including circulation time, evasion of healthy tissues, escape from the immune system, and most importantly, non-invasive monitoring. The inclusion of imaging modalities to drug carriers allows simultaneous diagnosis and treatment of tumor tissues [19–21]. These systems, called theranostics, are decorated with contrast agents that generate a visual signal with magnetic resonance, ultrasound, computed and positron emission tomographies [22–25].

A broad range of nanoparticles have been developed as theranostic carriers, including, but not limited to, liposomes, micelles, nanocages, dendrimers and vesicles [26–28]. They hold promise for early recognition and elimination of cancer cells. The efficiency of chemotherapeutics is considerably higher when the treatment starts in the first stages of the disease, which reduces the appearance of metastatic sites and consequently improves survival statistics and quality-of-life of patients [13,29].

3. Light penetration in human tissue: Ultraviolet *VERSUS* near-infrared

The selection of the ideal triggering mechanism for a particular theranostic system should consider the physiology of the organs to be treated and the administration routes. A particle circulating in the bloodstream, deposited in the hypoderm or entrapped in an implanted device could react differently to the same signal emitted from outside the body [17].

For over a century, phototherapy has led the application of physical stimuli in medicine. In 1903, the physician, Niels R. Finsen, was awarded the Nobel Prize in Physiology or Medicine for using a UV light source, the Finsen lamp, to treat cutaneous tuberculosis [30]. Nowadays, a wide range of electromagnetic sources, such as lasers, lamps and light emitting diodes (LEDs) have been essential tools for studies in ophthalmology, neurology, cancer, and other disorders [31–33]. In addition to its therapeutic properties, the non-invasive nature of light irradiation has had a great impact in clinical translation and patient compliance [8,13].

Light-sensitive particles are one of the most versatile modalities of theranostics. By using an external light source, one can disrupt the chemical structure of the delivery system and tailor the drug release profile to gain better control over the dose and duration of the treatments [8,13]. The effectiveness of photo-triggered therapies relies on the type of light and its ability to penetrate human tissues. The selection of a specific wavelength determines the structural modifications of the delivery system irradiated [17].

Long wavelength light, or near-infrared (NIR), penetrates deep tissues (up to 10 cm) but cannot cause major chemical modifications in the delivery system [34,35]. Its low excitation energy is absorbed by NIR-sensitive drug carriers and converted into the heat used for photothermal therapies [36]. Short wavelength light, or ultraviolet (UV), has poor tissue penetration (< 10 mm) but high energy [37]. It can induce a variety of effects on organic molecules, such as covalent bond cleavage, conformational changes (cis to trans) and production of reactive oxygen species (Fig. 2) [8,38].

Comparatively, NIR light presents a better safety profile to humans than UV. Absorption of UV light, especially in the UVB region (280 to 320 nm), damages heterocyclic nitrogen bases in the DNA and induces mutation [39]. The acute effects of UV irradiation include sunburn

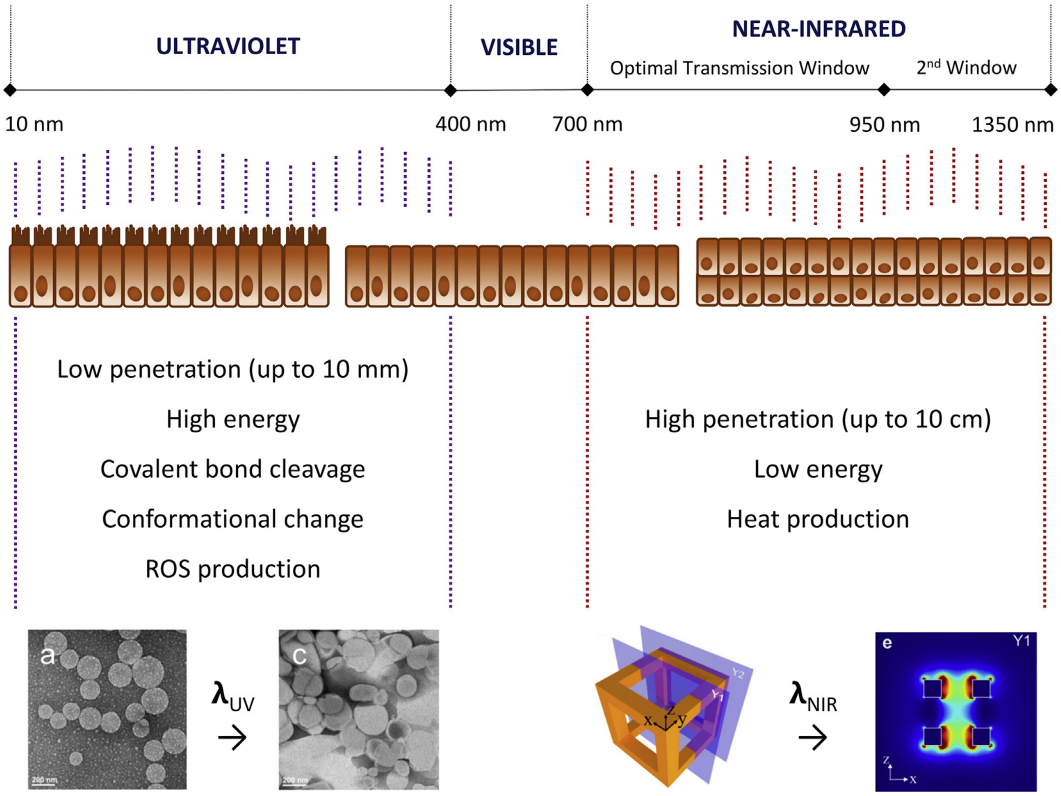

Fig. 2. Characteristics and main effects of UV and NIR light in body tissues. The optimization of endoscopy and laparoscopy techniques allowed the application of light irradiation in multiple types of tissue surface, such as small intestine (LEFT), stomach (CENTER) and urethra (RIGHT) epitheliums [33]. In the figure, the main effects of exposure to UV and NIR light are listed, along with TEM images of UV-sensitive liposomes before and after light exposure (LEFT) and a computational simulation of heat generation in a gold nanocage excited at 800 nm (RIGHT). Adapted with permission from Refs. [55, 117].

inflammation and tanning. Long exposure can cause immunosuppression, skin cancer, cataract, and retinal degeneration. The low penetration of UV light also limits its application to body surfaces (skin, eyes and hair follicles) or areas where endoscopic techniques can reach [40,41].

The composition of the human body affects not only the biological effect of exposure to light, but also the ability of drug carriers to generate imaging signal. Excitation of light-sensitive nanomaterials can produce photons or acoustic energy. In order to reach the detector of imaging systems, these signals must avoid scattering and attenuation by tissues [42,43]. DNA, proteins and other organic molecules in the blood or skin absorb UV–Visible light. The shorter the wavelength, the more efficiently tissue components scatter the light, which reduces penetration depth and imaging quality. If one considers the range of UV (10 to 400 nm) and NIR (700 to 2500 nm) spectrums, it is wiser to choose the second as the triggering stimulus for delivery systems that aim to localize and treat deeper tissues [44,45].

Water also causes significant impact in light absorption. As the most abundant component in the body, it plays a key role in the selection of the best excitation/emission conditions for the use of photo-activated drug carriers and fluorescent contrasts. Water absorbs excitation intensities higher than 950 nm, which leads to local overheating [44]. For this reason, the range of NIR emission from 700 to 950 nm was determined to be the optical transmission window in biological tissues [45]. Even within this range, it is still possible to detect substantial background noise from tissue autofluorescence [46].

Overheating and consequent tissue damage can be avoided when light is emitted through pulsed lasers. The shorter the duration of the pulse (or pulse width), the safer it is to the tissue. Pulsed lasers can achieve high intensity of excitation, but still keep low average power [47]. The optimization of contrast agents for *in vivo* imaging, such as carbon nanotubes, quantum dots and gold nanorods, have led to improvement in the generation of fluorescent signals [48]. More potent NIR cameras have also opened up a second window for optical imaging from 1000 to 1350 nm (NIR-II). However the biocompatibility of many probes responsive to this wavelength range is not suitable for their use in animals [45]. Recently, Wan and collaborators produced non-invasive *in vivo* images of blood flow in mouse brain vessels by encapsulating an organic NIR-II dye (p-FE) in the hydrophobic core of polymeric micelles. The system showed high spatial resolution, low background and high biocompatibility. No liver injury, signs of inflammation or morphological changes in the imaged tissues were detected [49].

4. The triggering effect of UV light

Over the last 40 years, the use of UV light as a trigger of photochemical reactions has provided a unique mechanism to actively control the release of anti-cancer agents [50]. Three main strategies have been extensively described in the most recent studies on tunable drug delivery: photoisomerization, photocleavage and phototargeting (Table 1).

4.1. Reversible Photoisomerization

The first attempts to develop UV-sensitive drug delivery systems date back to the early 1980s. Koji and collaborators demonstrated that the incorporation of azobenzene in a lipid chain allowed modulation of drug release from liposomes exposed to UV light irradiation [50]. Their observation was based on the ability of azobenzene to change from a trans to cis conformational state after exposure to UV light, the so-called photoisomerization [51].

In most cases, a pair of isomers presents different polarity, charge and steric properties. The incorporation of trans azobenzene into the bilayer membrane of liposomes forms a compact organization that prevents the encapsulated content from leaking out of the carrier [30].

Table 1
Examples and main characteristics of UV light-triggered delivery systems used for cancer therapy.

Triggering mechanism	Photosensitive moiety	Carrier	Therapeutic agent	Cancer type	[REF]
Photoisomerization	Dithienylethene	Free prodrug	Platinum (II)	Melanoma (A375) Colorectal adenocarcinoma (SW620)	[59]
	Spiropyran	Polymeric nanoparticles	Merocyanine Gold (III)	Glioma (C6)	[66]
	Azobenzene	Mesoporous silica nanoparticles	Camptothecin	Pancreatic carcinoma (PANC-1) Colorectal adenocarcinoma (SW480)	[69]
Photocleavage	o-NB	Polymeric nanoparticles	Doxorubicin Anti-P-gp siRNA	Breast adenocarcinoma (MCF7/Adr)	[78]
	Coumarin	Free prodrug	Ruthenium (II)	Cervix adenocarcinoma (HeLa) Hepatocellular carcinoma (BEL-7402) Osteosarcoma (MG-63)	[80]
	o-NB Coumarin	Mesoporous silica nanoparticles	Anti-P-gp shRNA Doxorubicin	Hepatocellular carcinoma (HepG2/ADR)	[89]
Phototargeting	o-NB	Polymeric/lipid nanoparticles	Paclitaxel	Malignant papilloma (KB)	[97]

The exposure to UV light stimulates the conversion from trans to cis azobenzene, a bulkier conformation that disrupts the bilayer packing and causes drug release [52,53]. The effect is reversed upon visible light irradiation or heating, which stops drug leakage [54]. Liu and collaborators used azobenzene linkers to decorate the surface of doxorubicin-loaded liposomes with galactosyl groups. <5% of drug release was detected when the system was kept in the dark at 37 °C. After only 10 min of UV irradiation, over 90% of the chemotherapeutic agent was released [55].

Photoisomerization of azobenzene is characterized by the reorganization of a double bond between its two nitrogen atoms. A similar event happens to the double bond between carbons of stilbene [56]. More complex light-induced chemical modifications have also been shown to have the ability to trigger drug delivery (Fig. 3) [57,58].

Spiropyran is hydrophobic photochromatic molecule composed of two cyclic functional groups: benzopyran and indoline. UV light exposure induces opening of the benzopyran ring and formation of merocyanine, a hydrophilic compound that destabilizes and increases the permeability of lipid bilayers. The isomerization can still lead to particle size reduction and enhancement of tissue penetration [57]. Ring opening also provides the mechanistic effect of the light-sensitive dithienylethene [58]. Presa and collaborators designed a series of photoswitchable platinum(II) complexes by attaching the metallodrug to dithienylethene derivatives. UV-light exposure changed the DNA-interacting properties of the isomeric pairs. The open form of the most active compound showed a lower IC_{50} for melanoma (A375) and colorectal adenocarcinoma (SW620) in comparison to the widely used cisplatin. The closed isomer was over 25 times less toxic than its counterpart [59].

These four molecules have also been used for the design of photoactive micelles, where the UV light-sensitive components are covalently attached to the hydrophobic segment of block copolymers [60–63]. The thermodynamic rearrangement of the copolymers in an aqueous environment forces the photoisomerizable moiety to remain in the inner core of the micelle. Upon UV irradiation, the switch to more hydrophilic conformational states causes the disassemble of the polymeric units and consequent release of cargoes [64,65]. The isomerization reaction itself can also trigger biological effects. Rad and collaborators designed gold-decorated polymer nanoparticles in order to enhance photogeneration of reactive oxygen species in the cytoplasm of brain cancer cells (C6 glioma). Upon UV irradiation at 365 nm, spiropyran groups in the core of the particles are converted to merocyanine isomers, which conjugate with gold ions on the surface of the drug carrier and improve antitumor effect by increasing local oxidative stress [66].

Photoisomerization has also been applied to the design of reversible light-sensitive valves in mesoporous silica nanoparticles (MSNs). The photochromic isomer is bound around the pores of MSNs and capped with β-cyclodextrin. It works as a gate-keeper that guarantees the entrapment of payloads. Irradiation with UV light stimulates opening of the pores by isomerizing the photochromic components and releasing the cap (Fig. 4) [67,68]. If attached to the inner core of MSNs, the switch between cis and trans conformations simulates a pump, ejecting the therapeutic agents from the core of the delivery system [69,70]. Photoisomerization of azobenzene derivatives impelled the release of camptothecin from MSNs used to treat PANC-1 (pancreatic carcinoma) and SW480 (colorectal adenocarcinoma) cells. Drug release upon UV light irradiation killed 60% and 86% of the aforementioned cells,

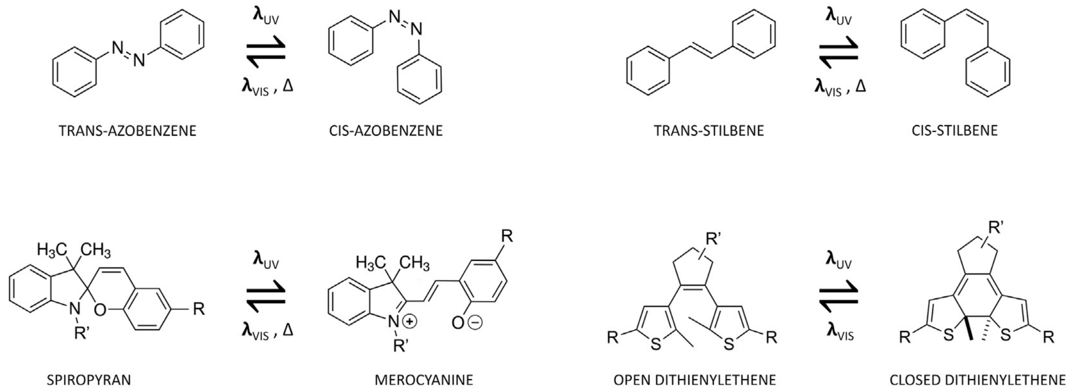

Fig. 3. Photoisomerization reaction of light-sensitive molecules incorporated into drug delivery systems. UV light triggers the switch between conformational states to regulate the release of therapeutic agents entrapped in nanoparticles. Local application of visible light or heat can reverse these reactions [54,56–58].

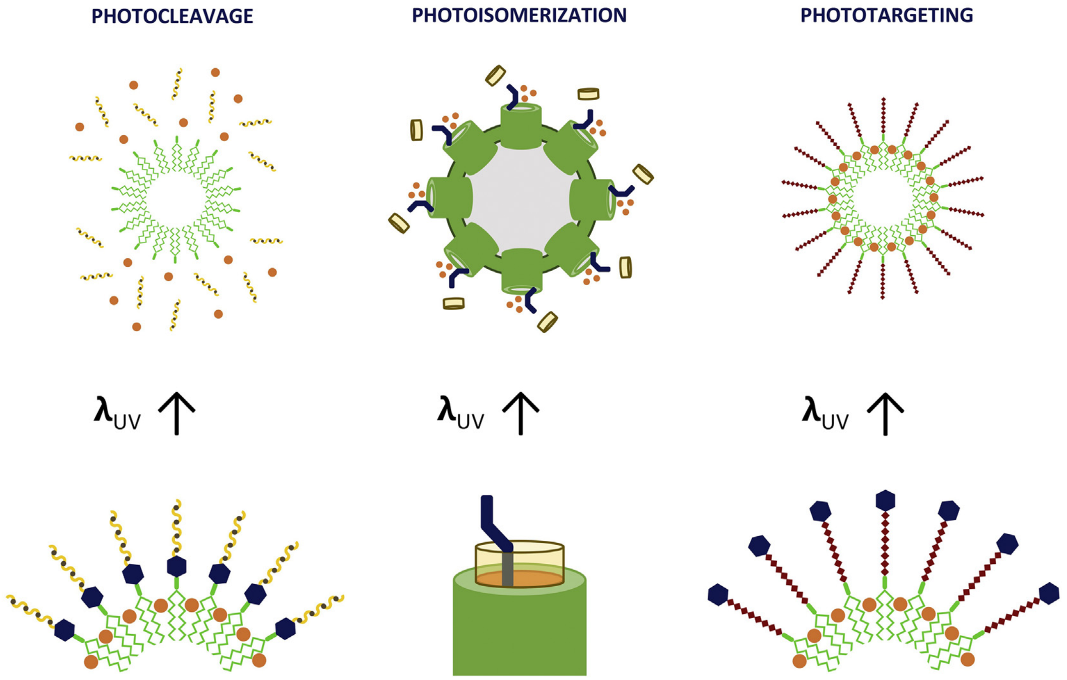

Fig. 4. Schematics of three UV light-sensitive drug delivery systems. (LEFT) UV irradiation cleaves the photolabile groups (blue) in a micelle, leading to detachment of the hydrophilic moiety (yellow) and leakage of the drug (orange); (CENTER) UV irradiation changes the conformational state of the photolabile group (blue), which causes the detachment of β-cyclodextrin cap (yellow) and consequent release of the drug (orange) from the inner core of a mesoporous silica nanoparticle; (RIGHT) UV irradiation cleaves the photolabile groups (blue) on the surface of a micelle and exposes the cell-penetrating peptides (red) for interaction with targeted cells [67,87,96].

respectively [69]. Consecutive rounds of photoisomerization can damage lipid-based carriers, but MSNs are able to promote ON/OFF tunable release for longer time periods [30].

4.2. Irreversible photocleavage

Photo-sensitive “caging” groups have been used to regulate a variety of biological processes. The idea of temporally inactivating a molecule by the attachment of a photolabile group was first tested in the late 70s. Hoffman and collaborators applied light to restore the activity of a modified adenosine triphosphate (ATP) [71]. This reaction, called photocleavage or uncaging, is characterized by the rupture of a covalent bond upon light irradiation [72].

Photocleavable moieties have been widely investigated for their potential to control the delivery of anti-cancer agents. They can form light-sensitive prodrugs or be incorporated into the structure of a drug carrier. In the first case, exposure to UV light stimulates the generation of an active compound. In the second case, light exposure partially or completely destabilizes the delivery system, which leads to the release of encapsulated payloads [30,73].

Ideally, a good photolabile component should be: (1) easy to introduce into the structure of a drug carrier, (2) stable under physiological conditions, and (3) efficiently activated by short exposure to light. It is also important that byproducts of the reaction are biocompatible and do not absorb light in the same wavelength as the caging group [74]. O-nitrobenzyl (o-NB) is one of the most common examples of photocleavable linkers used in drug delivery. It goes through intramolecular rearrangement upon exposure to UV light within the range of 260 to 380 nm [75–77]. Wu and collaborators used o-NB as a linker between doxorubicin and a hydrophobic moiety in order to control the release of the drug from polymeric nanoparticles. Emission of UV light at 365 nm triggered tumor growth inhibition in an animal model of drug-resistant breast adenocarcinoma (MCF7/Adr). The antitumor effect was 3 times higher when anti P-glycoprotein siRNA was complexed on the surface of the delivery system [78].

Coumarin derivatives are also photolabile structures of choice. They are cleaved by light wavelengths as long as 500 nm. For this reason, they present a safer profile for biomedical applications [79]. Two coumarin based Ruthenium(II)-polyimine complexes showed DNA intercalation properties in HeLa (cervix adenocarcinoma), BEL-7402 (hepatocellular carcinoma) and MG-63 (osteosarcoma) cells. Upon irradiation of visible light at 450 nm, the photocleavage reaction induced oxidative stress and disruption of DNA. Both complexes showed IC_{50} around 20 mM in all cancer cell lines studied [80].

The combination of two photocleavable units of distinctive absorption wavelengths allows the control of different properties of the delivery system in a sequential manner. Azagarsamy and collaborators conjugated bone morphogenic proteins (BMP2- and BMP-7) to a hydrogel network *via* o-NB (λ_{EX} 365 nm) and coumarin (λ_{EX} 405 nm) derivatives. The variation of light wavelength, intensity and time of light exposure resulted in selective release of the proteins [81].

The position of the photocleavable group in the structure that forms a drug carrier determines the disruption mechanism through which the payload is released. In some cases, they are part of the hydrophobic core of the particles. Irradiation with UV light breaks the photo-sensitive component and shifts the hydrophobic/hydrophilic balance, which causes disruption of the system [82,83]. Photolabile groups can also be inserted repeatedly within a polymeric chain to completely disassemble micellar structures upon light exposure [84]. In cases where they act as linkers between a hydrophilic and a hydrophobic block, UV light irradiation disconnects both segments and results in loss of amphiphilicity. The encapsulated cargo can be released during the process (Fig. 4) [85–87].

A similar strategy has been used to control drug release from the inner core of MSNs [88]. Wu and collaborators developed light-sensitive mesoporous silica nanoparticles for sequential delivery of short-hairpin RNA (shRNA) and doxorubicin (Dox) to multidrug resistant human hepatocellular carcinoma cells (HepG2/ADR). A photolabile coumarin was used as a linker to attach a cationic polymer to the inner core of the particles. The positively charged microenvironment allowed the complexation of anionic shRNA. An o-NB-modified Dox prodrug was also loaded into the inner pores of the MSNs. Tumor-bearing mice receiving the treatment were first irradiated with UV light at 405 nm to release shRNA and downregulate drug efflux pumps overexpressed in the cancer cells. In the sequence, exposure to UV light at 365 nm triggered the release of free Dox. Selective drug release showed the highest tumor growth inhibition in comparison to single or simultaneous light irradiation treatments [89].

4.3. Phototargeting

The challenge of delivering therapeutic agents to a specific tissue was addressed with the first generations of nanoparticulate drug delivery systems [90]. In some cases, the disease itself induces modifications in the physiology of the tissue that facilitates the penetration of drug carriers based solely on physical events. Tumors and other inflammation zones, for example, receive part of their blood supply from a neovasculature formed of defective endothelial cells with wide fenestrations, which leaves space for nanostructures to passively reach the irrigated tissue [91]. Alternatively, protein expression and the composition of diseased tissues have also been studied to aid the selection of targeting moieties to be attached on the surface of drug carriers that actively bind to a specific location [92,93]. Recently, the use of photolabile groups and light irradiation have helped to precisely control the active targeting of nanocarriers [30].

One common strategy to increase the amount of drug transported to the intracellular microenvironment of cancer cells, for example, is to decorate the delivery system with peptide sequences that show great interaction with the cellular membrane, the so-called cell-penetrating peptides [94]. However, the internalization effect of such peptides is non-specific and could also happen in any tissue. This adverse event can be avoided by covering the targeting components with photocleavable groups [95]. Upon UV light exposure directed specifically to the tumor area, the light-sensitive molecules are disrupted, which makes the drug carrier available for cellular uptake (Fig. 4) [96]. Fan and collaborators used o-NB to mask folic acid targeting groups on the surface of polymer/lipid hybrid nanoparticles. Light illumination exposed the folic acid and triplicated the uptake of paclitaxel-loaded particles by malignant papilloma cells in comparison to non-irradiated particles [97]. More recently, Kim and collaborators designed a photosensitive cell-penetrating peptide. Upon UV irradiation, an azobenzene linker introduced within the peptide sequence undergoes photoisomerization and modifies the α-helical conformation of the material. The effect of light exposure resulted in the formation of multimeric aggregates that showed better penetration into HeLa cells in comparison to the monomeric peptide sequence [98].

5. The triggering effect of NIR light

Despite the potential of UV light to serve as a trigger of drug delivery, disadvantages related to its limited penetration depth and toxicity are daunting, especially when considering the translation from preclinical studies to clinical trials [40,41]. On the other hand, NIR light allows deeper tissue penetration and capture of quantitative optical images up to 10 cm deep in tumor excisional biopsies [35]. Depending on the approach being used, NIR not only creates an imaging signal, but can also induce the elimination of cancer cells by generation of oxygen species (photodynamic therapy), heat production (photothermal therapy) or *in situ* emission of UV light (upconversion) (Table 2) [99,100].

5.1. Photodynamic therapy

NIR light has been extensively used to induce local generation of reactive oxygen species (ROS), a process called photosensitization or photodynamic therapy (PDT). ROS are free radicals derived from molecular oxygen (O_2) produced in both physiological and pathological conditions. They include superoxide ($O_2^{\bullet -}$), peroxide (O_2^{2-}), singlet oxygen ($^1O_2$), and hydroxyl radical (HO•) [101,102]. Studies have found elevated levels of ROS in various types of cancer cells [103]. Alterations in the redox environment of normal *versus* cancer cells have been exploited as targets for the development of alternative approaches to conventional chemotherapy, immunotherapy, and radiotherapy [104–107].

Treatment employing PDT aims to produce exogenous ROS in order to induce apoptosis and necrosis in cancer cells that are reportedly more vulnerable to oxidative stress effects than normal tissues [104–107]. The generation of ROS can be obtained by the excitation of a photosensitizer

Table 2
Examples and main characteristics of NIR light-triggered delivery systems used for cancer therapy.

Triggering mechanism	Photosensitive moiety	Carrier	Therapeutic agent	Cancer type	[REF]
Photodynamic therapy	Bacteriochlorin	Free prodrug	Reactive oxygen species	Murine colon carcinoma (CT26)	[112]
	Gold	Lipid/gold nanoparticles	Anti-SOD1 siRNA Reactive oxygen species	Cervix adenocarcinoma (HeLa) Melanoma (B16-F0)	[118]
	BODIPY	Polymeric nanoparticles	Manganese dioxide Reactive oxygen species	Hepatocellular carcinoma (HepG2) Murine breast adenocarcinoma (4 T1)	[121]
Photothermal therapy	Gold	Nanorods	Heat Anti-EGFR antibody	Breast adenocarcinoma (MDA- MB-231)	[136]
	TBDOPV / DT	Polymeric nanoparticles	Heat	Cervix adenocarcinoma (HeLa) Hepatocellular carcinoma (HepG2)	[145]
	Indocyanine green	Cell membrane capsules	Heat Reactive oxygen species Doxorubicin	Cervix adenocarcinoma (HeLa)	[146]
	Indocyanine green	Lipoprotein-like nanoparticles	Heat Reactive oxygen species Paclitaxel	Lung carcinoma (A549)	[148]
	Copper sulfide	Nanocapsules	Heat Doxorubicin	Hepatocellular carcinoma (SMMC-7721)	[150]
Upconversion	Ytterbium (III) Thulium (III)	$NaYF_4$ nanoparticles	Reactive oxygen species	Breast adenocarcinoma (SK-BR-3) Murine lung carcinoma (LLC1)	[159]
	Ytterbium (III) Thulium (III) Erbium (III)	$NaYF_4$ nanoparticles	Titanium dioxide Chlorin e6 Reactive oxygen species	Breast adenocarcinoma (MCF7)	[160]
	Ytterbium (III) Erbium (III) Copper sulfide Zinc phthalocyanine	Mesoporous silica/ $NaGdF_4$ nanoparticles	Heat Reactive oxygen species Doxorubicin	Cervix adenocarcinoma (HeLa) Murine hepatocellular carcinoma (H22)	[172]

upon light exposure in the presence of oxygen. Before activation, these molecules are considered non-toxic and do not cause cell damage [108]. Photofrin® is a photosensitizer currently approved by the FDA for treatment of esophageal and non-small cell lung cancer. Its applications are limited by low tissue selectivity and the need of high dosages to reach the desired therapeutic effect [109]. Alternatively, other molecules are being investigated, including Redaporfin®, which showed efficient anti-tumor effect in Phase I/IIa clinical trials of patients with head and neck cancer submitted to local PDT (λ_{EX} 749 nm) [110].

Some photosensitizers, such as porphyrin-, chlorin- and bacteriochlorin-based compounds, are commonly applied as single agents of PDT and imaging probes (Fig. 5) [111]. Patel and collaborators synthesized and evaluated the antitumor effect of a series of NIR bacteriochlorin derivatives. After the assessment of tumor growth inhibition and skin phototoxicity in an animal model of colon carcinoma (CT26), the authors identified 3-(1′-butyloxy)ethyl-3-deacetyl-bacteriopurpurin-18-N-butylimide methyl ester as having great PDT potential, imaging capability and safety profile for imaging-guided surgery and cancer phototherapy [112].

Currently, more attractive options involve the incorporation of photosensitizers in the composition of drug delivery systems, including quantum dots, polymeric, carbon and gold nanoparticles. They overcome common drawbacks of free photosensitizers, such as short half-life, poor stability in biological fluids and low tumor accumulation [108,113]. In addition, they offer the opportunity to carry one or more chemotherapeutic agents for light-triggered on-site release [114–117]. Vijayaraghavan and collaborators developed lipid-coated gold nanoparticles that simultaneously deliver siRNA and cause PDT under ultra-low doses of NIR light in the first (λ_{EX} 915 nm) and second (λ_{EX} 1064 nm) biological windows. Light irradiation increased ROS levels in cervix adenocarcinoma (HeLa) cells when compared to a non-irradiated group. The inclusion of siRNA against superoxide dismutase 1, an enzyme responsible for eliminating free radicals, showed even better *in vitro* effect. In a melanoma (B16-F0) mouse model, the combination improved tumor inhibition and animal survival in comparison to the single therapies and treatment with doxorubicin [118].

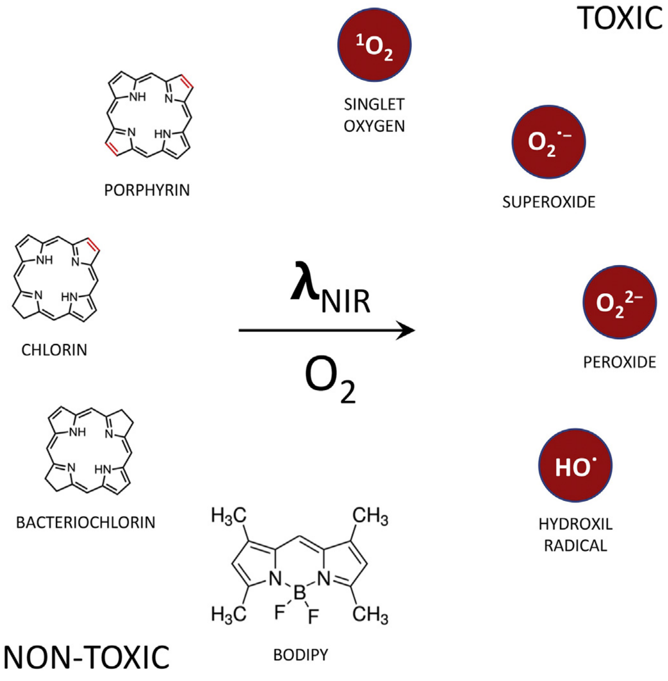

Fig. 5. Agents of photodynamic therapy. Chemical structure of four photosensitizers commonly incorporated into drug delivery systems. Upon NIR light irradiation and in the presence of oxygen, these non-toxic molecules induce generation of reactive oxygen species with great potential to damage cancer cells [111,119].

Among the chemical entities with photosensitization properties, derivatives of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) are one of the most studied. In addition to their ability to produce free radicals, they present resistance to photobleaching, low toxicity, and high absorption/emission of fluorescence signal in the visible range [119,120]. Modifications to their basic structure can also generate molecules with high NIR excitation and emission wavelengths [121,122]. Liu and collaborators designed biocompatible polymeric nanoparticles containing BODIPY and manganese dioxide (MnO_2) in order to evaluate their antitumor effect in human liver carcinoma (HepG2) and murine breast cancer (4 T1) cells upon light irradiation. Since many tumors present hypoxic conditions, the delivery of MnO_2 was intended to generate O_2 when reacting with the endogenous H_2O_2 produced by the tumor cells, which would then form singlet oxygen after light irradiation in the presence of BODIPY. Exposure of the developed nanoparticles to extremely low light energy density (25 mW/cm^2) induced cell suppression under hypoxic conditions. They were also able to light up cancer cells in real-time imaging [121]. The encapsulation of BODIPY in nanoparticles circumvents delivery issues related to its high hydrophobicity [123–125].

5.2. Photothermal therapy

Thermal therapy, also known as hyperthermia, has long been employed to treat cancer, either alone or in combination with chemo- and radiotherapy [126,127]. Local application of heat at the tumor site causes a killing effect by damaging DNA and inducing apoptosis [128]. Heat can be directly applied from an external source or generated by NIR light-triggered devices. Some materials have the ability to absorb NIR light upon excitation and convert it into heat, a process named photothermal therapy (PTT) [129]. Contrary to conventional hyperthermia, PTT is selective to the cells in close contact with the light-sensitive devices, which avoids the occurrence of non-specific effects in surrounding tissues [130].

Gold nanoparticles (AuNPs), carbon nanotubes and copper sulfide nanoparticles are among the main inorganic materials used for PTT [131–133]. Various types and shapes of AuNPs have already been described as NIR-triggered devices, including nanospheres, nanorods, nanocages and nanoshells (Fig. 6) [134,135]. Zhang and collaborators conjugated gold nanorods to antibodies targeting ephidermal growth factor receptors in order to improve the treatment of triple negative breast cancer (MDA- MB-231). The combination of PTT and immunotherapy significantly improved the anti-proliferative and apoptotic effects of the single therapies *in vitro* as well as tumor regression activity *in vivo*. In addition, the particles generated great photoacoustic signal for NIR-guided PTT. The authors highlighted, however, the importance of using small particles (5–6 nm) to allow an easier clearance from the body [136].

In fact, the toxicity of inorganic nanoparticles has long been a concern in regards to their use in biomedical applications [137–139]. In a thorough systematic *in vivo* study, Ali and collaborators designed a series of gold nanorods with various sizes and surface modifications. The authors used PTT to evaluate the killing mechanisms triggered by each system and their long-term toxicity. The particles decorated with polyethylene glycol (PEG) accumulated in the spleen and liver of BALB/c mice from the first to the last day of a 15-month period of evaluation. No signs of organ histopathological abnormalities were detected [140].

Organic materials with photothermal properties have been developed as an alternative to the use of inorganic particles, including indocyanine green and a variety of light-responsive polymers [112,141–143]. The ability to produce heat upon light excitation is obtained by conjugating electron donor and acceptor moieties to biocompatible polymeric chains [144]. Sun and collaborators evaluated the photothermal properties of a donor-acceptor polymeric nanoparticle containing thiophene-fused benzodifurandione-based oligo(*p*-phenylenevinylene) (TBDOPV) as an acceptor segment and 2,2-bithiophene (DT) as the donor moiety.

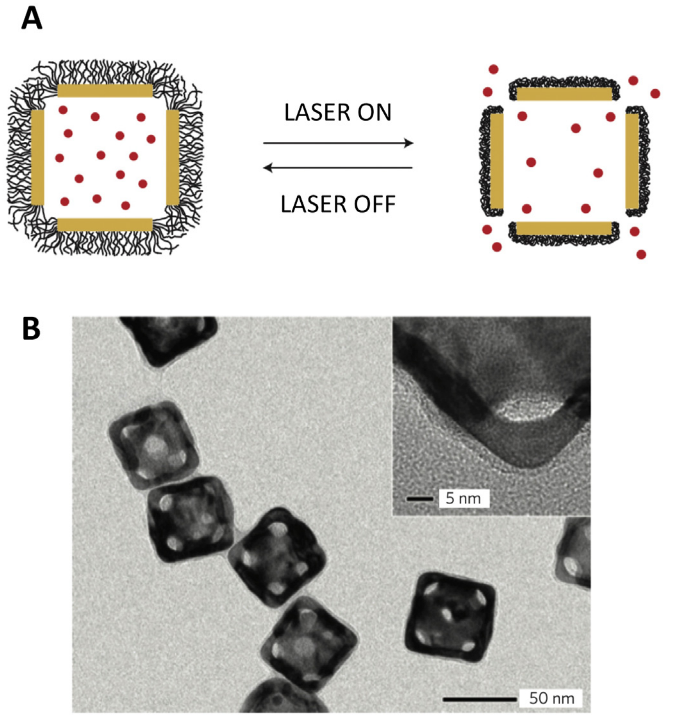

Fig. 6. Schematic illustration and characterization of gold nanocages. (A) A side view of the Au nanocage is used for the illustration. On exposure to a NIR laser, the light is absorbed by the nanocage and converted into heat, triggering the smart polymer to collapse and release the pre-loaded effector. When the laser is turned off, the polymeric chains relax back to the extended conformation and terminate the release. (B) TEM images of Au nanocages at 39 °C. The inset shows a magnified TEM image of the corner of such a nanocage. Adapted with permission from Ref. [135].

PTT triggered by exposure to NIR light in the second optical window (λ_{EX} 1064 nm) caused complete tumor regression in an animal model of cervical adenocarcinoma (HeLa) after 10 days of treatment by intravenous or intratumoral administration of nanoparticles [145].

PTT agents have also enhanced the outcome of cancer treatment with traditional chemotherapeutics. Li and collaborators recently used cell membrane capsules (CMC) originating from mammalian cells as nanocarriers for indocyanine green (ICG) and doxorubicin. The surface of these particles was decorated with folate to improve uptake by cervix adenocarcinoma (HeLa) cells. The targeted combination therapy showed enhanced *in vivo* tumor growth inhibition (above 95%) and the highest survival rate compared to non-targeted or single therapies [146]. In addition to heat generation, Shirata and collaborators detected production of ROS in a mouse model of hepatocellular carcinoma (HuH-7) treated with ICG and NIR light (λ_{EX} 823 nm) [147].

Wang and collaborators optimized the combination effect of paclitaxel and ICG by decorating the surface of lipoprotein-like nanoparticles (HDLs) with iRGD [148]. iRGD is a cyclic peptide with high affinity for alpha V integrins expressed in some cancer cell lines. Once cleaved in the tumor microenvironment, its subunits trigger deep tissue penetration due to affinity for Neuropilin-1, a protein overexpressed in the tumor neovasculature [149]. HDLs co-loaded with paclitaxel and ICG slowed down tumor growth in an animal model of human lung carcinoma (A549). Exposure to NIR light (λ_{EX} 808 nm) intensified the effect and caused tumor regression. The inclusion of iRGD peptide was responsible for 100% survival rate in comparison to 40% after treatment with non-decorated particles [148].

In a different approach, Meng and collaborators designed a thermosensitive polymer able to form nanocapsules. A photothermal component (copper sulfide) and a chemotherapeutic agent (doxorubicin) were encapsulated in the core of the particles. The heat generated by copper sulfide upon NIR-light excitation controlled the release of doxorubicin, promoting a switchable and localized therapy. The increase in temperature played an active role in tumor growth and liver metastasis inhibition [150].

5.3. Upconversion

Despite showing poor tissue penetration and causing phototoxic side effects, UV light has higher energy than NIR and is, therefore, a more potent activator of photosensitizers. A class of drug delivery systems called upconversion nanoparticles (UCNPs) was especially designed to combine the benefits of both ends of the light spectrum. UCNPs convert NIR into UV or visible light *in situ*, overcoming the drawbacks related to the direct use of short wavelengths [151,152]. The process through which upconversion, also known as anti-Stokes emission, occurs was first described by François Auzel in the 1960's [153]. It utilizes the sequential absorption of two or more photons of low-energy excitation to produce a high-energy emission photon. This phenomenon can be accomplished by different mechanisms, including state absorption, energy transfer upconversion, and photon avalanche [151–154].

UCNPs are prepared using lanthanide ions as dopants added to a host lattice. Lanthanides, known as the “rare earth elements”, are comprised of 15 metals with unique optical and luminescent properties, such as photobleaching stability, long lifespan, sharp emission bandwidths and multiple emission bands [155–157]. Most studies use ytterbium (Yb^{3+}) as a device sensitizer and erbium (Er^{3+}) or thulium (Tm^{3+}) as activators of upconversion. The emission of NIR light at 980 nm is absorbed by Yb^{3+}, which activates UV/Vis light irradiation by Tm^{3+} (λ_{EM} 300 to 650 nm) and Er^{3+} (λ_{EM} 410 to 670 nm) [158–160].

Mironova and collaborators developed sodium yttrium fluoride (NaYF$_4$) nanoparticles containing the pair Yb^{3+}/Tm^{3+} targeted towards epidermal growth factor receptors overexpressed in cancer cells. The system killed 90% of breast cancer cells (SK-BR-3) *in vitro* as a result of oxidative stress triggered by UV emission. The upconversion therapy also improved growth inhibition in a murine Lewis lung carcinoma model in comparison to a control unable to generate UV light (Fig. 7) [159].

In a more elaborated approach, Yu and collaborators covered NaYF$_4$:Yb,Er,Tm particles with a titanium dioxide (TiO$_2$) shell, followed by conjugation to a photosensitizer (Chlorin e6) and a cell-penetrating peptide (TATp). Upon NIR excitation at 980 nm, UV/Vis light was emitted and absorbed by the TiO$_2$/Ce6 layer. The consequent production of ROS caused extensive DNA double-strand breaks in breast cancer (MCF7) cells. Both drug-sensitive and resistant animal models showed complete tumor growth inhibition and no signs of toxicity [160].

Recently, upconversion has also been used as a tool to optimize immunotherapy, one of the most promising approaches for cancer treatment [161–165]. Xu and collaborators developed polymer-coated UCNPs co-loading Ce6 and imiquimod, an immune adjuvant. Upconversion of NIR signals into UV irradiation induced the localized production of ROS in tumor-bearing mice and generated tumor-associated antigens. As a result, an immune response was stimulated and intensified by the presence of imiquimod [166].

Depending on the light-responsive materials used to design a drug carrier, it is possible to combine PDT by upconversion and PTT in order to take advantage of both oxidative stress and heat generation upon light irradiation [167–170]. Tsai and collaborators prepared PEGylated UCNPs loaded with a photothermal agent (IR-780) and a photodynamic sensitizer (mTHPC). The emission of NIR light at 808 nm activated IR-780 and induced hyperthermia, while a second laser at 980 nm stimulated the UCNPs to generate visible light (λ_{EM} 660 nm) and activate mTHPC. In this case, upconversion allowed the use of a photosensitizer activated only by visible light in deep regions of the brain. The targeted therapy prolonged the survival of mice bearing orthotopic brain tumors in comparison to single treatments with PDT and PTT [171]. Similarly, Wang and collaborators covered UCNPs

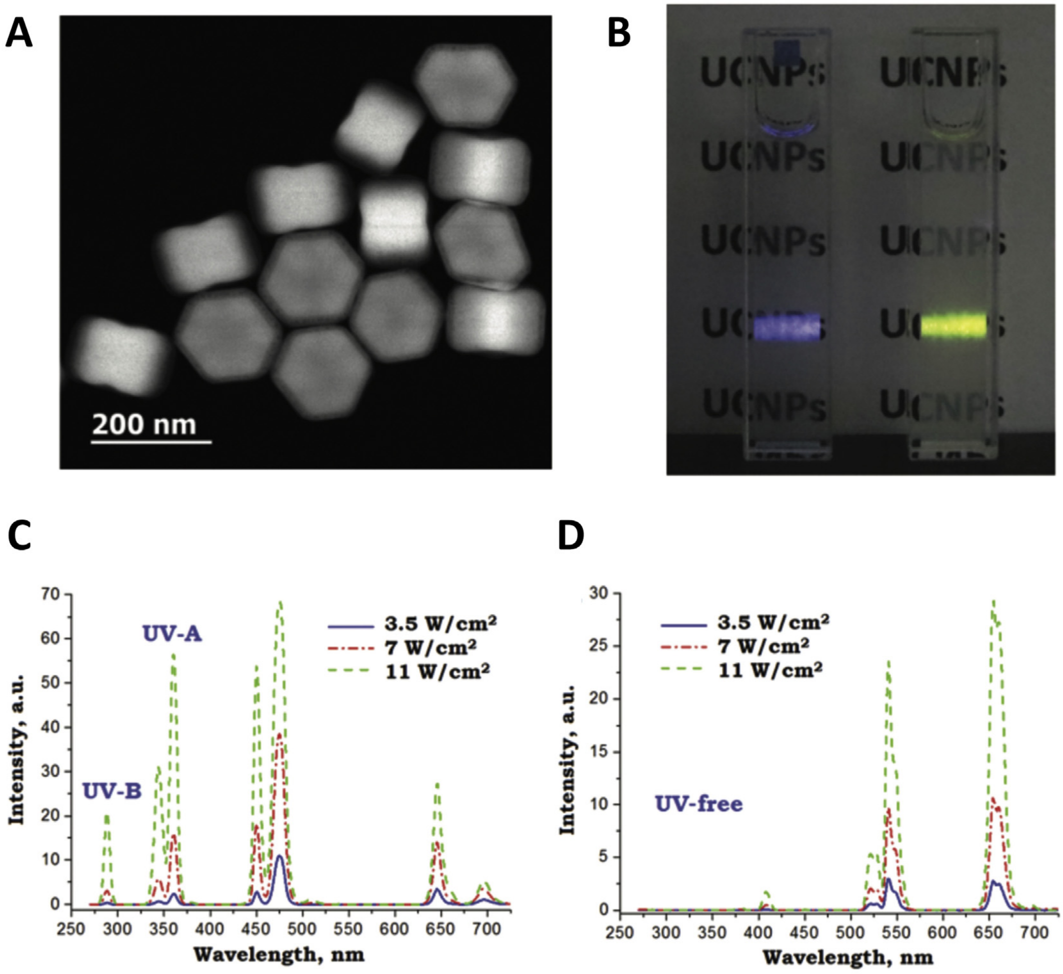

Fig. 7. Characterization of upconversion nanoparticles. (A) High-angle annular dark-field scanning TEM image of UCNPs nanoparticles. (B) Coated UCNPs in phosphate buffer. The left cuvette was filled with UV-emitting particles (β-NaYF4:Yb3+,Tm3+/NaYF4) and the right cuvette was filled with UV-free particles (β-NaYF4:Yb3+,Er3+/NaYF4). Excitation by 975 nm laser light demonstrate uniform UV/blue and green emission, respectively. (C) Spectra of the UV-emitting UCNPs and (D) UV-free UCNPs in phosphate buffer irradiated with 975 nm laser light. Spectra are shown under excitation with the intensities of 3.5, 7 and 11 W/cm^2. Adapted with permission from Ref. [159].

with a mesoporous silica layer, in which doxorubicin, copper sulfide and zinc phthalocyanine were incorporated. Upon NIR irradiation with a single laser at 980 nm, those components acted like a chemotherapeutic drug, photothermal agent and photodynamic sensitizer, respectively. This single platform completely inhibited tumor growth in a murine hepatocellular carcinoma model and enabled multimodal real-time imaging [172].

6. Conclusions

Over several decades, the development of drug delivery systems has expanded the possibilities for using light as a tool to optimize cancer therapy. Carriers that respond to excitation with NIR light have led the most recent efforts on the design of a localized treatment for a variety of tumor types. Although the energy of UV light is potent enough to cause more extreme damage to a targeted tissue, the side effects of acute and chronic exposure to short wavelength light continue to be a safety issue for clinical translation. New delivery technologies have emerged that combine the effect of low- and high-penetration light on localized cancer therapy. The use of photosensitizers that can be excited by an external source of NIR to generate UV light *in situ* has been the main approach of the latest studies on imaging-guided phototherapy. Also, the versatility of carrier types has opened up possibilities of testing the most diverse materials for drug delivery, from rare chemical elements, such as yttrium, to organic polymers. Phototherapy continues to show great potential for combination with immuno- and gene therapies that advance the development of personalized medicines.

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Declarations of interest

None.

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