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Smart Nanostructures for Cargo Delivery: Uncaging and Activating by Light

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Abstract

Nanotechnology has begun to play a remarkable role in various fields of science and technology. In biomedical applications, nanoparticles have opened new horizons, especially for biosensing, targeted delivery of therapeutics, and so forth. Among drug delivery systems (DDSs), smart

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nanocarriers that respond to specific stimuli in their environment represent a growing field. Nanoplatforms that can be activated by an external application of light can be used for a wide variety of photoactivated therapies, especially light-triggered DDSs, relying on photoisomerization, photo-cross-linking/un-cross-linking, photoreduction, and so forth. In addition, light activation has potential in photodynamic therapy, photothermal therapy, radiotherapy, protected delivery of bioactive moieties, anticancer drug delivery systems, and theranostics (i.e., real-time monitoring and tracking combined with a therapeutic action to different diseases sites and organs). Combinations of these approaches can lead to enhanced and synergistic therapies, employing light as a trigger or for activation. Nonlinear light absorption mechanisms such as two-photon absorption and photon upconversion have been employed in the design of light-responsive DDSs. The integration of a light stimulus into dual/multiresponsive nanocarriers can provide spatiotemporal controlled delivery and release of therapeutic agents, targeted and controlled nanosystems, combined delivery of two or more agents, their on-demand release under specific conditions, and so forth. Overall, light-activated nanomedicines and DDSs are expected to provide more effective therapies against serious diseases such as cancers, inflammation, infections, and cardiovascular disease with reduced side effects and will open new doors toward the treatment of patients worldwide.

1. INTRODUCTION

The nanotechnology revolution has led to a remarkable array of applications in high-tech sciences and technologies,[1–4] particularly in biotechnology and biomedicine.[5,6] These advances have been incorporated into diagnosis and biosensing approaches for targeted and controlled delivery of therapeutic agents and treatment of serious diseases, such as cancers, inflammation, infections, and cardiovascular diseases.[7–14]

Nanotechnology is a new flexible branch of bioscience, allowing development of exciting methods for delivery of therapeutic agents into targeted cells and tissues using safe, efficient, and trackable routes. Nanomedicine has provided novel and unique systems to accommodate combinations of imaging probes (fluorescence and photoacoustic) with specific targeting ligands and attached therapeutic payloads in a compact unit.[15]

In drug delivery systems (DDSs), nanoparticles (NPs) play a key role and have opened new horizons to obtain ever more efficient and high-performance nanocarriers through which targeted and selective delivery of therapeutic agents is achievable.[16,17] In DDSs, various basic materials can be incorporated in the design of nanocarriers such as albumin,[18] nanocarbons (e.g., carbon nanotubes (CNT), reduced graphene oxide (reduced GO), and fluorescent carbon NPs),[19–21] virus and bacteriophage-based NPs,[22,23] stimuli-responsive polymer moieties,[24–29] metal NPs,[30] and semiconductor NPs.[31]

In this regard, designing nanosystems possessing multiple functionalities with versatile abilities is becoming a focus. Smart materials capable of responding to various stimuli are considered to be an important category of advanced materials; such materials can be employed in biomedical applications and nanomedicine, particularly in the design of nanocarriers for drug delivery approaches, giving rise to the development of so-called smart stimuli-responsive DDSs.[25,32,33]

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Nanosystems that can respond to specific stimuli arising from an internal source such as pH alterations, redox activities, enzymatic reactions, overexpression of biomolecules (e.g., adenosine triphosphate, glutathione)[33] or alternatively that can respond to external triggers such as thermal energy, ultrasound waves, light irradiation, mechanical forces, and electromagnetic fields[27,32] have provided many avenues toward precise and controlled delivery and release of therapeutic agents.

Among the external stimuli mentioned above, light has attracted special attention due to its ease of production, noninvasive nature, controllable intensity, and spatially confined application for finely controlled durations. Thus, light has been utilized in an abundance of applications for intelligent targeted delivery systems that can provide good control of the treatment process and allow transport and release of drugs at disease sites.[11,12,25]

Light responsiveness can be either reversible or irreversible depending on the nature of the substrates that absorb the light. Photocleavable polymers (e.g., containing *o*-nitrobenzyl[34] and coumarin[35]) undergo an irreversible reaction in which photons transform sensitive unstable bonds to more polar and stable states, whereas photochromic molecules show reversible reactions such as double bond rotation, photo-oxidation, and photoinduced cleavage; then, after removing the applied light, they undergo reisomerization[36] or reformation. Furthermore, different wavelengths of light can be applied to induce light responsiveness: ultraviolet (UV) light with 100–400 nm wavelength, visible light (400–750), and near-infrared (NIR) with 750–2000 nm. Longer wavelength photons contain lower amounts of energy but have much better penetration depths into living tissue due to decreased absorption of tissue chromophores and less scattering. On the other hand, although UV light possesses higher energy per photon, it is considered hazardous for clinical application due to its ability to damage biomolecules (nucleic acids, proteins, and lipids) and high absorption and scattering in tissues.[37] Light with visible wavelengths is mainly used for shallow applications in skin and mucosa, whereas NIR is used to interact with carriers at greater depths in tissue. The problem of NIR photons having too low an energy to carry out many photochemical reactions could be solved by taking advantage of mechanisms such as two photon absorption or upconversion.[38–43]

Different mechanisms have been suggested to be employed for light-activated drug delivery/release systems including bond-cleavage, isomerization, cross-linking, electrostatic assembly/disassembly, reduction, oxidation, photocaging/uncaging, as well as nonlinear photoconversion mechanisms such as two-photon absorption and upconversion photoexcitation. In addition, light sources can be used for nanomedicine-related therapies such as photodynamic therapy (PDT), photothermal therapy (PTT), and radiotherapy. Most important light-activated mechanisms are illustrated in Figure 1.

In this review, we will discuss various mechanisms pertaining to light-mediated activation of nanovehicles to release therapeutic agents in targeted delivery systems. This will followed by coverage of the integration of light into dual/multiresponsive DDSs and application of light stimuli in some aspects of phototherapy such as PTT, PDT, radiotherapy, and so forth. Challenges and discussion regarding the biological effects and nanotoxicity of light-activated nanomaterials, the efficiencies and effectiveness of different photoactivated

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mechanisms and nanoplatforms, as well as their synthesis methods are taken into consideration.

2. CHROMOPHORES: A NEED FOR PHOTOABSORBERS

Although nanocarriers can have many types of structure, the most important requirement for light activation is that they need to have specific chromophore molecules in their structure to harvest the light. Chromophores can be photosensitizers, photactive chemical groups, or as one of the main components can be employed in various photoinduced mechanisms related to DDSs.

When photoactive chromophores absorb a photon, they undergo photochemical changes such as photoisomerization (i.e., a conformational alteration in a double bond restricted in rotation), which can lead to hydrophilic/hydrophobic transitions in the photoactivatable structures inducing alterations in dipole moment, in size and shape, or the occurrence of reversible cis–trans isomerization, e.g., in azobenzene and its derivatives,[26,44] bond cleavage, e.g., in coumarin, reversible photo-cross-linking, photo-oxidation,[45] photodimerization of cinnamoyl groups, or generation of ionic charges and zwitterionic species for other chromophores.[26] Such changes can be used for disruption and dissociation of polymeric NPs or even for changing the lower critical solution temperature (LCST) transition.[26]

In the following sections, the main drug release mechanisms including photocleavage/photodegradation-based mechanisms, photoisomerization, photoreduction, photo-cross-linking, photoelectrostatic assembly, and photothermal absorption will be discussed. Afterward, two multiphoton processes including two-photon absorption and upconversion as important nonlinear photoabsorption mechanisms will be discussed.

3. MISCELLANEOUS PHOTOTRIGGERED DRUG RELEASE MECHANISMS

3.1. Drug Release via Photochemical Bond Cleavage/Photodegradation

In a recent study, Kohman et al. developed photolabile DNA nanocage structures as an approach to trigger release of cargos (especially bioactive molecules). A different range of molecular sizes from small molecules to macromolecules such as proteins, which generally have amino-groups, has been suggested to be encapsulated via photocleavable cross-linkages between an *o*-nitrobenzyl (o-NB) motif and DNA nanocages. Here, exposure to light irradiation induced cleavage of the linker and uncaging, allowing diffusion of the cargo molecules away from the protective cavity (Figure 2a).[46] In a novel strategy, Fan et al. used X-ray radiation, which penetrates extremely well through living tissue, to achieve an on-demand/dose-controlled release from upconversion NPs (UCNPs, see below), i.e., poly-ethylene glycol (PEG)-modified NO-releasing theranostic UCNPs based on *S*-nitrosothiol-grafted mesoporous silica (MSN). Besides simultaneous upconversion luminescent-based imaging, exposure to X-ray irradiation caused cleavage of S–N bonds of *S*-nitrosothiol and hence release of the nitric oxide (NO).[47]

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3.1.1. Photoinduced Switch in Hydrophobicity for Drug Release—Hydrophobic–hydrophilic switching of self-assembled NPs can induce drug release. In a recent study, an amphiphilic self-assembled polymeric NP that contained a photosensitive chromophore [7-(didodecylamino)coumarin-4-yl] methyl methacrylate was synthesized. Upon absorption of 800 nm NIR light, a two-photon process triggered photocleavage of the photoactive chromophore resulting in a drastic change in the structure of the photoresponsive polymer NP through hydrophobic/hydrophilic switching, followed by photodegradation of the NP (Figure 2b).[48]

Photoactivated self-assembled Janus micromotors have been also reported,[49,50] which showed potential as DDSs. Cao et al.[50] prepared Janus composite nanosheets containing photosensitive spiropyran-incorporated poly(3-sulfopropyl methacrylate) polymer brushes on one side. Structural transformation of the closed hydrophobic spiropyran into open hydrophilic zwitterionic merocyanine moieties due to photocleavage of C–O using UV and visible light could induce a hydrophobic-to-hydrophilic transition in poly(3-sulfopropyl methacrylate).

Furthermore, photoinduced hydrophobic to hydrophilic transition of hydrophobic molecules such as 2-diazo-1,2-naphthoqui-none (DNQ) molecules can occur via the Wolf rearrangement reaction. DNQ is a hydrophobic photolabile chromophore that can transform into the hydrophilic 3-indenecarboxylic acid (3-IC) molecule via a UV (1-photon)/NIR (2-photon)-induced Wolf rearrangement reaction. This can lead to destabilization/dissociation of some nanocarriers such as amphiphilic micelles, thus inducing release of the encapsulated cargos.[42,51–54]

3.1.2. Drug Release via Cleavage and Uncaging of Photolabile Protecting Groups—Photolabile protecting groups or so-called photoactivatable cages that are able to be unlocked or destroyed by exposure to light (i.e., photolabile uncaging) can be employed as nanocarrier structures. By exploiting photolabile protecting groups, the desired molecules are masked and protected via covalent chemical bonds, and when exposed to light, photocleavage of these bonds (i.e., photolysis) can be induced. Thus, the protected and inactive molecules/compounds, which have high activity when free, become unprotected and uncaged leading to their activation, followed by their delivery and release at the desired biological site such as via binding to cell receptors or specific intracellular release (Figure 3a).[32,35,53,55,56] A wide-variety of photo-uncaging compounds have been reported based on *o*-nitrobenzyl, *o*-nitro-phenethyl, indoline, quinoline, amino-coumarin, perylene, nitrophenyl, nitrophenyl-propyloxy compounds, ruthenium photocages, nitrodibenzofuran (NDBF), boron-dipyrromethene derivatives, and so forth.[35,53,55–58] Nanocarriers including gold (Au) NPs,[59] micelles,[60] liposomes,[61] and peptide-based nanocarriers[35] have been reported to demonstrate photocaging/uncaging behavior. Various cargos such as thiols,[35] platinum(II) complexes,[57] diphospho-myo-inositol pentakisphosphates ($InsP_7$),[62] cyclooxygenase-2 enzyme inhibitors,[63] copper complexes,[58] and anticancer drugs/prodrugs (e.g., camptothecin, coumarin, 5-fluorouracil, doxorubicin (DOX))[43,59,60,64] have been shown to be protected and carried by the photocaging nanocarriers. The light irradiation has ranged from NIR,[63,65,66] to UV[58] to visible light,[55,67] and using mechanisms such as two photon excitation,[63,68,69] upconversion by UCNPs,[64] or simple one photon excitation[70] can

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be employed to induce uncaging of the photolabile protecting groups. Photolabile protecting groups can provide advantages including high cleavage efficiency, avoidance of side reactions,[35] accurate spatial and temporal controlled of drug release,[71] deeper tissue penetration,[56] dual/multiresponsive behavior, tunable drug release rate, and photosensitive cytotoxicity.[60] Mahmoodi et al.[35] exploited NDBF groups as photolabile cages for protecting and masking thiols against photoisomerization by photolysis in a cysteine-containing peptide nanocarrier. Either 365 nm (one-photon) or an 800 nm (two-photon) irradiation could be used to unmask and deprotect the thiol groups. UV irradiation of human ovarian carcinoma (SKOV3) cells incubated with an NDBF cage-equipped farnesylated peptide led to photolysis and uncaging of the caged peptide, its intracellular activation, and migration from the Golgi apparatus/cytosol to the cellular plasma membrane as a result of enzymatic palmitoylation (Figure 3b). Caging structures have been based upon degradation of structures by photo-generated acids. For instance, UV-activated photoacid generation could trigger removal of hydroxyl groups and controllable deprotection of acetal-modified dextran (Ac-Dex) particles. These then became soluble in water, thus releasing their cargos.[72]

3.1.3. Photo-oxidation Disruption/Cleavage-Based Drug Release—In this approach, irradiation of nontoxic dyes (photosensitizers) using correct wavelength light can be used for the generation of reactive oxygen species (ROS) via the photodynamic effect. These photosensitizers often have tetrapyrrole structures (e.g., phthalocyanines, porphyrins) or are dyes, such as phenothiazinium, boron-dipyrromethene (BODIPY), and squaraine, or can even be natural products (e.g., curcumin, hypericin, riboflavin).[10,73] This photodynamic mechanism can be used for inducing disruption of a nanocarrier membrane such as photo-oxidizable lipids, which leads to leakage of the encapsulated cargos and their subsequent release.[36] Figure 3c is a schematic of a photoinduced ROS production mechanism.[74]

NIR irradiation is a desirable factor in the design of photo-oxidation-triggered drug release. Recently, a poly(methacrylic acid)-based nanogel equipped with diselenide crosslinker and the ROS-generating indocyanine green dye was reported to demonstrate light-responsive drug release. Here, photocleavage of the diselenide linker was obtained through utilizing ROS generation under NIR irradiation. The nanogels then underwent disassembly (Figure 3d).[75]

In photo-uncaging mechanisms, generation of photoinduced ROS can be used to induce drug release by oxidative degradation of the carrier. In a recent study, a modular design was used for caging ligands where a low-energy red/near-IR light was used for efficient uncaging of metal ions. Here, the exposure to red/near-IR irradiation induced excitation of the photosensitizer modules (as an integral part of the cage structure). The generated singlet oxygen then cleaved the dithioethenyl moiety. It is worth noting that, in singlet oxygen-induced photocleavage, linker cleavage can be obtained through reaction of the singlet oxygen with an electron-rich alkene inside the structure.[76]

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3.2. Drug Release via Switchable Chemical Bonds (Photoisomerization)

Photoisomerization of chemical bonds leading to cargo release can be achieved using various approaches. It is known that light can isomerize many photolabile organic molecules. In photoinduced isomerization, light is first used to isomerize the molecules, but after the light is switched off (in a reversible manner), the molecules revert to their initial conformation with the lowest energy state releasing energy as longer wavelength light or heat.[53] In one study, a short (532 nm, 5 min) laser irradiation of sub-100 nm nanoparticles formed by cross-linking of Au NPs by dithiol-PEG resulted in a temperature increase (up to 62.5 °C), and conformational changes in the cross-linked PEGs leading to opening of the interparticle gaps between Au NPs and subsequent drug release (Figure 4a).[77]

In some cases, photoisomerization of the photoswitchable chromophore (for example, acting as the capping agent or “valve” in MSNs) via cis–trans isomerization can directly induce liberation of the encapsulated cargo.[78] For instance, a study based on red-shifting the responsive wavelength of the photosensitive chromophore reported advantages in comparison with upconversion and two-photon absorption such as much lower light intensity required and improved simplicity of the system. Here, β-cyclodextrin (β-CD) acting as the supramolecular valve capping agent and tetra-*ortho*-methoxy-substituted azobenzene (mAzo) as the red light-sensitive/absorber moiety were used in the MSNs. After the cis–trans isomerization of mAzo under red-light followed by the formation of a strong host–guest complex between trans mAzo and β-CD, the dissociation of the complex occurred resulting in cargo release (Figure 4b).[79]

3.3. Photo-Cross-Linking-Induced Shrinkage of Polymeric NPs for Drug Release

Polymers can undergo cross-linking through various approaches,[80,81] particularly in response to light irradiation (e.g., UV light).[81,82] Photochemically activated cross-linking of polymers can be employed in light-triggered drug release nanosystems. Polymerizable double bonds inserted into a polymeric bilayer, either with or without the presence of a radical initiator, can undergo photo-cross-linking and photopolymerization reactions that induce the bilayer to shrink, therefore creating pathways or pores for cargo release.[36] In a study, a photochemically reversible aliphatic polyamide-based polymer was synthesized with photosensitivity (under UV light irradiation) and thermosensitivity (under heating) after functionalization with cinnamoyl. Photochemical cross-linking of the polymer solutions was achieved with 364 nm light and de-cross-linking occurred with 254 nm (Figure 4c).[82] Photo-cross-linking can induce a decrease in the NP size[83] that can be exploited as for cargo release from a nanocarrier.[36] In one study, Shi et al.[84] synthesized 100 nm hydrophilic PEG-grafted poly(4-cinnamic acid)-*co*-poly(3,4-cinnamic acid) self-assembled NPs, which were photo-cross-linked via UV irradiation with a decrease in NP size (Figure 4d). This system was suggested to be useful for controlled drug release.

3.4. Photothermally Triggered Drug Release

In the photoinduced thermo-release process, absorption of an external photon is followed by a light-to-heat energy conversion. The generated heat can be used to trigger cargo release from heat-sensitive nanovehicles.[85]

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Noble metal NPs can be used as the photothermal converting agent due to their excellent optoelectronic features. In case of noble metal NPs such as Au, silver (Ag), platinum (Pt), and palladium NPs,[86] absorption of photons over a range of wavelengths (e.g., NIR or visible) causes electrons within the metal nanostructure to undergo photoexcitation; then, the electrons release their energy by exchanging with the surrounding environment in the form of localized heat production.[36] This is an example of localized surface plasmon resonance (LSPR) (i.e., electrons with free resonant oscillation in the conduction band of metal NPs under an applied external electromagnetic field, which results in dipole oscillations).[87,88] The photothermal activity of various metal NPs with a high (plasmonic) absorption mostly in the NIR region of the spectrum has been employed for DDS applications, such as Au nanoshells,[30] Au nanorods,[89] Au–Ag–Au nanorods,[90] Au nanocages,[91] Au nanospheres, Au nanoclusters,[92] and Au hollow nanocrystals.[93] Photothermally activated release has also been reported with nanocarbons (e.g., reduced GO,[20] single-walled carbon nanotubes (SWCNTs),[94] fluorescent carbon NPs,[95] etc.). Other studies have used transition-metal dichalcogenides (e.g., MoS_2 nanosheets,[96] WS_2 nanosheets[97]), semiconductor NPs (e.g., CuTe, $Cu_{1.75}S$[31,98]), and hybrid NPs (e.g., Au nanocage-CNT).[99] For semiconductor NPs, enhanced plasmonic absorption under a wide range of NIR irradiation conditions leads to an improved photothermal effect with high in vivo stability and biocompatibility, which have all been indicated as some of their advantages.[31] Figure 5a shows a schematic of photothermally triggered drug release from copper-sulfide ($Cu_{1.75}S$)-equipped polymeric NPs.[31]

Light irradiation with power densities in the region of 1.5 W/cm^2[92] or even as low as 0.6 and 0.2 W/cm^2[20,99] can be applied to maintain the viability of tissues and cells. Photothermal therapy (of cancerous cells/tissues or bacteria), imaging and sensing, and enhanced chemotherapy are new horizons that have been suggested to be enabled by photothermally triggered DDSs.[19,100,101]

3.5. Photoreduction-Triggered Drug/Prodrug Release

Photoinduced reduction of inactive nontoxic prodrugs (e.g., metal complex prodrugs) to active toxic forms accompanied by release of the activated prodrug under various photoirradiations such as UV[102] and NIR[103,104] can be exploited for controlled cargo delivery to biological sites with reducing potentials, such as tumors. Selective production of Pt(II) species from Pt(IV) complexes under light irradiation is an interesting approach. In one study, conjugation of a photoactivatable metal complex prodrug (e.g., Pt(IV)) to a cancer-targeted RGD-containing peptide was reported to photoactivate the Pt(IV) complexes into cytotoxic Pt(II) species and allow their direct release into the tumor environment under visible light irradiation.[105] In another DDS, photoactivatable Pt(IV)–azide prodrug-loaded micellar NPs were reported to release active Pt(II) species under UVA light, which was suggested to be a robust drug release platform (Figure 5b).[102]

3.6. Photoinduced Electrostatic Assembly/Disassembly for Drug Release

Electrostatic interactions can be utilized for construction of nanocarriers through organized assembly of adjacent NPs or molecules. The charged building blocks play the main role in this mechanism, and they can form ordered self-assemblies.[106,107] Self-assembly of

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nanoparticles can be achieved using various external stimuli such as temperature,[108] pH,[109] and the presence of biomolecules[110,111] and magnetic fields.[112] In self-assembled structures, a high level of order and intermolecular specific interactions are required.[106]

Therefore, self-assembly of colloidal nanoparticles using non-equilibrium driving forces can lead to highly organized structures[113] and can pave the way for reversible self-assembly and disassembly of structures. Zhang et al.[114] synthesized spiropyran-functionalized SiO_2–Pt Janus micromotor particles that exhibited dynamically reversible self-assembly behavior in the presence of hydrogen peroxide, *N*,*N*-dimethylformamide (DMF), and H_2O all caused by electrostatic attractions and π–π stacking between merocyanine molecules induced by light irradiation (Figure 6a). Here, irradiation of UV light (365 nm) triggered self-assembly of these “Janus micromotors”, whereas 520 nm green light irradiation led to fast disassembly into “mono-motors” (Figure 6b).

Chen et al.[115] studied reversible self-assembly/disassembly of Au NPs decorated with hydrophilic PEG and hydrophobic photoresponsive polymethacrylate-containing spiropyran units. Employing photosensitive spiropyran units, visible light irradiation weakened the intermolecular interactions followed by the Au NPs becoming individual particles, whereas UV irradiation induced the Au NPs to self-assemble into oligomers by π–π stacking and electrostatic attractions. Cardenas-Daw et al.[116] showed that light stimulation could trigger ground-state hydrogen bonding via short-lived intermolecular excited-state proton transfer that resulted in a nanoscale H-bonded supra-molecular rearrangement.

Self-assembled nanosystems can be used for controlled drug delivery and release,[117] such as colloidal nanoparticles.[49,118] Li et al.[118] synthesized nanoscale “colloidosome” capsules via electrostatic self-assembly of oppositely charged organosilica NPs for controlled release of small molecules and macromolecules. Irradiation with 365 nm light induced reversal of the surface charge on the positively charged NPs, followed by disruption of the electrostatic interactions between the now all positively charged NPs that disassembled the colloidosomes and led to release of the cargos (Figure 6c and d). A novel mechanism was suggested that could have prospective application in controlled drug delivery by Kundu et al.[119] Here, nonphotoresponsive NPs were reversibly self-assembled within a photoswitchable medium by modulating the interparticle interactions. Protonated merocyanine (MCH^+)-containing medium modulated the assembly of Au NPs. Blue light irradiation increased the acidity of the medium, leading to weakening of hydrogen bonding and disassembly of the NPs. However, in the dark or ambient conditions, the NPs spontaneously reassembled (Figure 6e and f).

3.7. Two-Photon Absorption for Photoexcited Drug Release

Two-photon absorption could be an advantageous approach for deep tissue penetration. Two-photon absorption relies on two long wavelength photons arriving simultaneously and exciting the molecule possessing a high two-photon cross-section to a state with twice the energy of a single photon. Because of the necessity for a very high photon density to ensure simultaneous absorption, extremely high peak power levels are required that can only be provided by pulsed lasers with femtosecond peak durations. These lasers are often titanium-sapphire emitting around 800 nm. In one approach, two-photons are simultaneously

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absorbed by a specific fluorophore molecule, and the emitted fluorescence activates a photosensitizer (e.g., azobenzene). Both of these are bound covalently to a nanomaterial or doped in it, and this photochemical reaction eventually induces drug release. Here, the photosensitizer is isomerized after the absorption of two-photon NIR irradiation by the fluorophore, which can then carry out Forster resonance energy transfer (FRET) (Figure 7a).[68,120,121] Alternatively, two-photon activation can lead to drug release through phototriggered bond cleavage; for instance, two-photon sensitive photolabile protecting groups can be used for controlled intra-cellular drug release via photochemical cleavage (Figure 7b).[68] In another study, Croissant et al. designed disulfide-nanogated MSNs incorporating covalently bound two-photon absorbing electron donors. Two-photon-reductive cleavage of the disulfide nanogates activated cargo release.[122] Two-photon can also allow simultaneous imaging and drug release.[123] Recently, a two-photon-sensitive photothermal-conjugated brush polymer-incorporated nanocarrier with DNQ moieties was reported to transition to a hydrophobic form under two-photon NIR irradiation, producing photothermally regulated disassembly and fast release of the cargo.[124]

3.8. Upconversion Mechanism for Photoexcited Drug Release

In the photon upconversion mechanism, NIR light is converted to UV or visible light, which occurs at half the wavelength, which then can sensitize photoactive moieties via photoreactions (Figure 8a). In this mechanism, two basic requirements are needed, including an excitation intensity exceeding a specified threshold and the presence of an appropriate photoactive compound as an absorber of the upconverted emitted light. Upconversion avoids overheating problems and photodamage to tissues and cells while still providing deep penetration into tissues, high detection sensitivity, low autofluorescence, and high signal-to-noise ratio.[126–129] Upconversion mostly relies on lanthanide metal ions (e.g., La^{3+}, Tm^{3+}, Er^{3+}, Ho^{3+}) doped into NPs.[128,130–134] Differing from two-photon absorption that requires both photons to arrive simultaneously, upconversion relies on the NP having “virtual” excited states at half the energy of the full excited state, such that two long wavelength photons (delivered by a continuous-wave laser) can be sequentially absorbed. NIR light intensities as low as 0.35 W cm^{-2} have been reported.[135] The photosensitive moieties can be located in various nanocarriers through different methods, including encapsulation or deposition inside core–shell or self-assembled amphiphilic structures, in the pores of mesoporous NPs, covalent or noncovalent binding, or even direct surface attachment.[41]

Upconversion of luminescence can induce photoisomerization or photodegradation of chemical bonds, inducing cargo release. In the case of photodegradation, upconversion NPs (UCNPs) convert NIR irradiation to UV/vis light, and the upconverted emitted light is absorbed by a photosensitizer that then undergoes photocleavage through a photoreaction. This nonlinear process results in liberation of the cargo.[135] In a recent study, NIR-triggered sub-80 nm core–shell–shell NPs were synthesized with an upconversion emission core, a photosensitive compound incorporated in the middle silica shell, and β-CD acting as the gatekeeper of the drug-loaded MSN in the outer-most shell. Under irradiation with 980 nm NIR light, both 540 nm green light and 660 nm red light were produced from the upconversion mechanism; the green light was designed for cell-imaging and the red light for dissociation of the β-CD capping agents and release of the cargos. Red light was also used

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for the generation of singlet oxygen via PDT for eradication of cancer cells (Figure 8b).[136] In other studies, the exploitation of an upconversion mechanism to induce photocleavage reactions with subsequent disassembly of the nanocarriers has also been reported.[135,137] Upconversion can also be used for photoisomerization-triggered drug release. Liu et al. synthesized NIR-triggered upconversion NPs coated with azobenzene-modified MSN (Figure 8c). Here, under NIR irradiation, simultaneous UV and visible emission occurred from the upconversion NP, which then were both absorbed by the photoactive azobenzene agents located in the pores of the MSN, leading to a reversible trans–cis isomerization. Subsequently, consecutive rotation-inversion movements of azobenzene moieties caused cargo release.[138] Interestingly, in another study, it was shown that sometimes NIR-induced heating through 1-photon absorption by azobenzene molecules rather than the expected upconversion mechanism was responsible for the drug release, because upconversion NPs did not produce enough photons to photoisomerize azobenzene molecules.[139]

4. LIGHT ACTIVATION AS A COMPONENT OF DUAL/MULTIRESPONSIVE SMART DELIVERY VEHICLES

Although light is an external stimulus that can be applied directly to the DDS to release cargo with good spatiotemporal control, light possesses some limitations in its specificity. Moreover, all light-activated systems suffer from the problem of limited light penetration into tissue. UV irradiation can only be applied to very superficial parts of the body, such as the skin, mucosa, and eyes. On the other hand, a light stimulus would be more effective if the targeted (diseased) tissues could be distinguished from the healthy ones. Therefore, internal stimuli and microenvironmental elements characteristic of diseased tissue (including enzymes, pH, temperature, and redox status) could be combined with light activation to enhance the efficiency of targeted delivery and minimize unwanted side-effects in the surrounding tissues.[140]

Employing enzyme activation is a promising approach in dual-responsive systems. One of the basic concepts is the linkage of a specific enzyme-sensitive motif to the surface of the light-responsive carrier, which is taken up into the desired cell. Expression of site-specific enzymes would then release the cargo inside the cell, which is then activated by light.[141]

Small pH changes alter the microenvironmental protonation state and can change the tertiary structure of functional groups (mainly in the peripheral amino acids of the nanocarrier scaffold), leading to their swelling or shrinking, and production of fenestrations or pores in the carrier releasing the cargo.[142] Using this strategy, Feng et al.[143] encapsulated azobenzene (as the photosensitive core) with poly(acrylic acid) (PAA). The degree of ionization of the PAA carboxylic acids determined the final diameter of the nanoparticle due to pH-dependent swelling and azobenzene-induced cargo release under UV irradiation. Moreover, azobenzene was able to conserve the microscopic structure of supramolecular amphiphilic materials. In a recent study, a combination of azobenzene with pH-responsive water-soluble pillar[6]arenes was used to form a host–guest interaction, producing supramolecular micelles or vesicles that efficiently released the loaded drug (mitoxantrone) into cancer cells.[144] Not only was the cytotoxicity of the drug reduced in healthy tissues, but

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the drug itself was protected from UV irradiation, and delivery of the drug led to induction of apoptosis in tumor cells. Altering the photoresponsive core using other suitable materials and their derivatives could be used in multistimuli-responsive nanocarriers. For example, spiropyran photosensitive moieties (which can isomerize under light irradiation switching from UV to visible), when encapsulated with dimethyllaminoethyl groups, can form self-assembled micelles in which light irradiation leads to changes in the hydrophobic properties and structural configuration. Similar self-assembled nanoparticles can respond to fluctuations in heat and proton concentrations as well.[145]

Integration of pH sensitivity into the light-responsive carrier can be achieved via titratable amine groups, Schiff bases, and hydrazide bonds that can be incorporated into a connecting linker chain. Suitable functional groups like chitosan may facilitate pH sensitivity.[146] The interaction of the loaded drug with components of the carrier can also impart pH responsiveness to the carrier. Wang et al.[147] showed that the functional groups of DOX can bind to the amine and carboxyl groups of porous carbon nanocapsules, generating pH sensitivity, whereas the basic carbon structure of the carrier would absorb NIR energy and generate heat to release the drug. Another strategy to induce simultaneous pH and light responsiveness is the use of a pH-sensitive gate keeper on the surface of mesoporous silica nanoparticles that encapsulate a loaded cargo attached inside the carrier through light-sensitive linkers like nitroveratryl moieties.[148] In such a system, the capping molecules are detached only in an acidic environment, and the loaded cargo is released only after photoactivated cleavage of its anchor.

A platform consisting of a thermosensitive liposome surrounding Au NPs that could be activated with NIR light and further equipped with pH-sensitive moieties was synthesized to improve drug release, which could be used in deeper parts of the body. Once the platform was illuminated with NIR, the Au NPs generated heat resulting in drug release. The results indicated good intracellular uptake and effective drug release in the cytosol after activation of the carrier by light.[149]

Because the intracellular concentration of reducing agents is significantly higher than that in the extracellular space, introduction of redox responsiveness into a carrier could be a promising strategy for intracellular delivery of drugs.[140] This redox responsiveness can be accomplished through two mechanisms: (a) gate-keeping in which a redox-sensitive degradable linker is used to cap the porous carrier and (b) disassembly of NPs such as polymerosomes, hydrogels, and polymeric micelles. Both strategies can lead to drug release into desired tissues and cells.[150] The combination of light and redox responsiveness was demonstrated by Huang et al.[151] who modified poly(ether imide) polymers with a nitrobenzyl photo-trigger derivative to generate a self-assembled micelle containing photosensitive amphiphilic polymers. They then used dithiodipropionic acid as a “stabilizer belt” around the carrier to protect it from photodegradation and also equipped it with a disulfide-based reduction trigger. The loaded cargo was only released in the presence of both light and redox stimuli (i.e., it functioned as an “AND” logic gate). Cross-linking of polymeric carriers with appropriate linkers can not only increase the stability of the carrier but also impart the desired stimuli responsiveness and improve the efficiency of targeted delivery. Among the strategies for cross-linking, photoinitiation is desirable due to its well-

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controlled initiation at room temperature, its possible reversibility, and effectiveness.[152] In this regard, disulfide bonds[153] and nitrobenzyl methyl esters[154] can be introduced into the principle chain and into copolymers to provide UV responsiveness. Shao et al.[155] conjugated coumarin moieties with a polylysine moiety in a self-assembled telodendrimer polymer through disulfide bonding. Exposure to UV irradiation reversibly induced cross-linking and micelle formation without any change in drug release efficiency. The disulfide bond showed high sensitivity to reducing conditions that could be used for cargo release in tumors. Kim et al. employed a functionalized, reduced GO as nanocarrier, taking advantage of the simultaneous proton sponge effect and NIR-activated photothermal-facilitated endosomal disruption. Endosomal escape and cytosolic delivery was obtained followed by glutathione-triggered release of DOX.[156] To combat multi-drug resistance of tumors, Yu et al. developed dual-responsive 30 nm sized micellar NPs, which facilitated a long blood circulation half-life and passive targeting. Here, NIR light irradiation triggered good tumor penetration and cytosolic release via tunable hyperthermia; moreover, weakly acidic conditions ($pH \leq 6.2$) induced dissociation of the micelles and led to DOX release.[157]

Light can be also a promising component in triple stimuli-responsive nanosystems. Park et al.[158] generated a triple-responsive polymeric micelle to promote targeted drug delivery. They first cross-linked pluronic acid with phenyl boronic acid via disulfide bonds (Plu-SS-BA) and then added lactose-modified chitosan (Chitlac) through an interaction between the phenyl boronic acid groups and lactose groups. Finally, they attached the photoresponsive moiety (conjugated spiropiran) onto the prepared micelles. Chen et al.[159] synthesized a triple-responsive amphiphilic copolymer containing spiropyran as a pH and photosensitive moiety, and poly(*N*-isopropylacrylamide-*co*-acrylamide (PNIPAAm) as a temperature-sensitive moiety. This nanosystem could self-assemble into micelles in which spiropyran and PNIPAAm formed the core and the shell, respectively. Panels a and b in Figure 9 show the triple-stimuli responsiveness of such a nanocarrier.[159] Elsewhere light/thermal/pH triple-stimuli-responsive DDSs have also been reported.[160]

5. APPLICATIONS OF LIGHT AS A THERAPEUTIC IN CANCER NANOMEDICINE

Although surgery, chemotherapy, and radiotherapy are currently being used as primary methods of treating cancer, limited accessibility of the tumor, damaging side effects, limited selectivity, and a high death toll on healthy cells are just some of the challenges these approaches are facing.[161–164] The use of NPs for imaging and drug delivery to cancer cells and tumors has opened new doors to improve the efficiency of delivery by enhancing the carrier circulation in the blood, encouraging its accumulation in the targeted area, and controlled release of the drug.

Light-responsive nanocarriers have gained significant attention for use in drug and gene delivery in different areas of biomedicine.[165,166] The high surface areas of these platforms allow researchers to incorporate both targeting components and a higher payload and design complex structures with multistage treatment capabilities. The result of these advantages has encouraged extensive use of nanomaterials in light-activated cancer therapy such as

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photochemotherapy, PTT, and PDT. The impressive results from light-responsive nanomaterials in cancer therapy have encouraged further investigation by combining imaging and therapy (theranostics) or by exploring other candidates to be delivered alongside the drug payload (codelivery).

5.1. Targeted and Controlled Release for Photo-chemotherapy

Light-stimuli responsive nanomaterials have been widely used for carrying anticancer drugs into targeted cells and releasing the chemical with controlled dosage and improved uptake. For instance, Strong et al.[167] synthesized a DOX-loaded PNIPAAm hydrogel-coated Au-silica nanoshell nanocarrier. At ambient temperature, the hydrogel coating was in a swollen state, which allowed it to hold a large quantity of water and drug. Once in targeted cells, NIR light was used to increase the temperature of Au-silica nanoshell, which led to a change in the hydrogel state followed by expulsion of a large quantity of water release of the drug into the cells. Thus, an NIR-triggered increase in drug release up to 3-fold was obtained.[167]

In another study, Wang et al. designed a folic acid (FA)-modified paclitaxel-loaded polyethylenimine-functionalized porous titanium dioxide NP for increased loading capacity, controlled release, and targeting of cancer cells. The use of FA increased the cellular uptake of loaded NPs due to receptor-mediated endocytosis. By UV light exposure, free radicals cleaved the polyethylenimine from the NP surface, resulting in drug release into the cytoplasm; the cell viability of KB (human nasopharyngeal carcinoma cells) decreased to less than 10% and less than 55% for A549 (human lung carcinoma cells). One of the main advantages of this platform was effective blocking of channels by polyethylenimine, leading to a longer circulation time. This design also allowed for precise control over release of the drug by changing the UV irradiation time.[168]

A similar finding was reported where DOX-loaded MSNs equipped with mAzo and β-CD were designed for controlled drug release. In this porous platform, a host–guest interaction between β-CD and mAzo acted as a valve to close the pores. The supramolecular structure formed by β-CD and mAzo could open when illuminated with red-light, leading to DOX release, and suggested the possibility of controlled drug release even in relatively deep parts of the body.[79] Elsewhere, reversible morphology transitions of supramolecular-branched copolymer self-assemblies via switching between UV and visible light irradiation followed by cis–trans isomerization of the Azo moieties and host–guest interactions of Azo and β-CD led to controlled release of DOX molecules.[169]

Recently, upconversion silica NPs modified with *ortho*-nitrobenzylalcohol-derived functional groups were investigated by Alonso-Cristobal et al.;[170] here, the functional groups were loaded with covalently bonded DOX. When the platform was exposed to NIR light, UV light was emitted, degrading the linkers and resulting in release of DOX molecules. The synthesized platform showed good controlled release and effective delivery, causing a decrease in cell viability.

Photocages have shown potential in targeted anticancer drug delivery for cancer chemotherapy. Caged anticancer camptothecin prodrug was reported to be effectively delivered to folate receptor-expressing tumor cells (e.g., A549 cells) by FA-incorporated

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SCL micelles. This system inhibited premature drug leakage in physiological conditions, and dual pH/glutathione-responsive disassembly was shown with subsequent drug release in mildly acidic/reducing conditions, and concurrent NIR irradiation induced photoactivated cytotoxicity up to 9.7-fold.[60]

5.2. Photothermal Therapy (PTT)

The principle behind the PTT approach is the fact that NPs are capable of efficiently transforming absorbed light into localized heat, causing hyperthermia in the local environment surrounding the NPs.[171,172] When used as a sole therapy, this method can provide good results, but the simplicity of this approach has encouraged researchers to use it in combination with other approaches for reducing cancer cell viability.[161,166] Strong et al. reported a combination of PTT for drug delivery in which an increase in drug uptake and enhancement of controlled release were observed.[167] In another study, two different anticancer drugs (DOX and irinotecan) were loaded onto GO nanostructures that were stabilized with poloxamer 188 with a dual structure. Here, photochemotherapy and PTT were combined together to increase the overall efficacy. NIR irradiation was used to trigger release and increase the temperature, resulting in activation of the intrinsic apoptosis pathway (Figure 10). The best cell killing was obtained by employing GO loaded with both drugs, and the effectiveness of PTT was confirmed where a further decrease in cell viability was observed.[173] Elsewhere, a DOX-loaded targeting peptide-functionalized graphene nanosheet coated with mesoporous silica showed synergistic targeted therapy of glioma mediated by PTT and sustained drug release.[174] A 740 nm NIR-triggered coumarin-based fluorescent iron oxide nanoparticle for mitochondrial targeting was shown to cause an enhanced hyperthermia effect and cytotoxicity against cancer cells.[175]

Different nanaomaterials have been used in PTT, and among them, Au nanostructures such as Au-silica nanoshells or Au nanorods have been most widely used due to their high light to heat conversion and simultaneous capability to be used for imaging.[161,167,176] AgNPs, carbon nanotubes, graphene and GO, copper sulfide, and palladium are some other nanomaterials that have been used as nanocarriers for PTT treatments.[177–180]

Recently, PTT has been equipped with radioisotope labeling to provide concurrent radiotracing and photothermal ablation of tumor. Riedinger et al. incorporated ^{64}Cu in CuS nanocrystals for this application, which was suggested to be useful for clinical application.[181]

5.3. Photodynamic Therapy (PDT)

Unlike PTT, the basic mechanism of the PDT process is more complex and requires photosensitizer moieties in addition to a light source. In this approach, light excites the photosensitzer to a long-lived triplet state that can interact with molecular oxygen to produce reactive oxygen species (ROS), including free hydroxyl radicals and singlet oxygen. These short-lived reactive species attack their immediate surroundings, leading to the death of all living cells that have taken up the photosensitizer. Although this method is very effective for eliminating tumor cells, it has limitations such as targeting capability (selectivity for cancer cells) and low penetration depth, and some photosensitizers have poor water solubility.

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Similar to PTT, PDT is also used in combination with other techniques to improve its performance and reduce side effects.[165,182] For instance, Au nanorods have been used with various photosensitizers to improve the treatment efficiency.[183,184] More examples of PDT nanocarriers can be found in reviews published by Kim, Song, and Shanmugam.[85,161,185,186] In recent works by Hamblin et al., photoactivated DNA damage by ROS generation from AgNPs for lung cancer treatment[187] and free radicals generated by PDT using a functionalized fullerene against sarcoma[11] have been reported. To address the depth limitation of PDT, Tang et al. used X-rays for activation of a photosensitizer with the goal of treating tumors located deep inside the body. A mesoporous LaF_3:Tb scintillation NP was synthesized to carry Rose Bengal as the photosensitizer. These NPs exhibited good absorption of ionizing radiation and a high luminescence efficiency. The results showed a good FRET efficiency (85%), and the proposed approach also benefited from a well-defined structure, a simple drug loading approach, good water solubility, and ultracolloidal stability.[188] Xiang et al. reported one of the first platforms for cancer cell lysosome-specific cogeneration of NO and singlet oxygen upon NIR light illumination with a high targeting ability and controlled release. Here, 4 nm nanocarriers were synthesized using carbon-doped TiO_2 NPs that could photogenerate ROS, loaded with FA groups for cancer targeting, and incorporating ruthenium nitrosyl to also generate NO. They demonstrated that this nanoplatform was capable of targeting tumor cells, accumulating in lysosomes, along with on-demand release of NO and ROS upon NIR exposure. This setup could also be used for imaging and tracking using blue fluorescence emission.[189] Elsewhere, NO-releasing vehicles based on QD-doped TiO_2 incorporating a photosensitizer was also tested for ROS generation and PDT.[190] Another way of overcoming the penetration depth limitations of light used for PDT is to completely do away with an external light source. For example, in one study, the in situ-emitted bioluminescence from luminol was absorbed by a photosensitizer via bioluminescence resonance energy transfer (BRET) resulting in excitation of the photosensitizer and generation of ROS that could eradicate cancer cells.[191]

5.4. Combined PTT/PDT

Chu et al. used a combination of PDT and PTT triggered with LSPR. They used the photosensitizer (sulfonated aluminum phthalocyanines (AlPcS)) loaded onto Au nanoring carriers. Once the nanocarrier was subjected to LSPR excitation around 1064 nm for only a few femtoseconds, the heat generated in the Au nanoring caused hyperthermia, and the AlPcS produced singlet oxygen through two-photon absorption resulting in cancer cell death. However, the area that could be treated was too limited in size due to uneven distribution of the laser radiation.[192] Electrostatically formed nanocarriers can be used for cancer therapy. In Song et al.'s study, DOX-loaded nanoassemblies based on J-aggregate of an organic NIR dye, IR825, were employed as a controlled and safe drug delivery system for combined cancer targeted chemotherapy and PTT. Here, enhanced NIR absorbance at 915 nm, high photostability, prolonged blood circulation, high passive tumor accumulation, and enhanced antitumor activity were demonstrated.[193] Table 1 shows some of the recently published studies on the combination of PTT and PDT.

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5.5. Theranostics

Light-responsive NPs have been widely used in theranostics (where a combination of diagnosis and therapy is required), as light is a particularly effective modality for imaging applications. For instance, Yang et al. synthesized theranostic micelles for near-infrared fluorescence (NIRF) imaging and PTT, where the carrier generated stable NIRF signals with negligible noise, and at the same PTT, caused severe damage to cancer cells.[197] CNT is another interesting material used in theranostics. Liu et al. used an MSN shell and a single-walled CNT core structure for combined PTT and chemotherapy while at the same time allowing for dual-modality imaging. The structure was further modified with PEG to improve the solubility and stability. The platform loaded with DOX showed high sensitivity to light stimuli. Because of the presence of the metallic shell around the single-walled CNT and the strong NIR absorbance, the structure offered good contrast for both photoacoustic (PA) and magnetic resonance imaging (MRI) applications, confirming the accumulation of nanocarriers into tumors in mice.[198]

Imaging combined with PDT was investigated by Li et al. They developed an upconversion nanomaterial consisting of PEG-functionalized Yb^{3+} and Er^{3+} codoped with Gd_2O_3, and loaded with two photosensitizers. This was tested for bimodal magnetic resonance and fluorescence imaging and NIR light-triggered PDT. There was negligible cytotoxicity caused by the nanocarrier and effective NIR killing of HeLa cancer cells. Furthermore, this upconversion nanoplatform was capable of offering visible emission caused by NIR light excitation, magnetic relaxivity characteristics, and antitumor effects, which made it a perfect candidate for theranostics applications.[199] Additional recent examples of combinations of PDT/PTT are presented in Table 2.

5.6. Drug/Gene Delivery (Codelivery)

Another interesting application for light-responsive nanomaterials is the simultaneous delivery of drugs and genes. For instance, Han et al. developed a complex structure that utilized codelivery by using both pH responsivity and short- and long-term light irradiation to trigger each step of the process. The synthesized carrier was composed of protoporphyrin IX (PpIX) (as photosensitizer) and plasmid DNA both trapped inside a pH-sensitive chimeric peptide carrier. At physiological pH and in the presence of matrix metalloproteinase-2, the hydrolysis of a peptide Pro-Leu-Gly-Val-Arg-NH_2 (PLGVR) sequence and exfoliation of PEG resulted in uptake of carrier by tumor cells (rich in matrix metalloproteinase-2). This uptake was followed by two-step light irradiation: (1) short-term illumination for endosomal escape due to the proton-sponge effect of H_8 and the photochemical internalization PCI effect of PpIX aimed at improving plasmid DNA expression, and (2) long-term irradiation to activate the phototoxicity of PpIX. It was concluded that the dual step light therapy could address the bottlenecks of synergistic treatment such as endosomal escape, interference between antitumor drug toxicities, cell bioactivity, and gene transfection (Figure 11a).[209] Yin et al.[210] explored the use of light-triggered Au nanorod platforms loaded with DOX and small interfering RNA (siRNA) for pancreatic adenocarcinoma treatment. Gene silencing efficiency of 80%, 75% inhibition of proliferation, and 90% cancer growth inhibition were reported. Figure 11b shows that no significant increase in tumor size was observed for the combination of DOX+siRNA+NIR

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over the course of 25 days, whereas the other six control groups showed tumor progression. Yuan et al.[211] reported a light-triggered platform for combined delivery of photosensitizer and oligonucleotides (e.g., siRNA, antisense, single-stranded antisense oligonucleotides (SSOs), and microRNA (miRNA) antagomirs) for maximizing treatment efficiency. Chlorin e6 was conjugated with an oligonucleotide directed against the Bcl-x gene, where the combination of spatial and temporal effects led to cell viability reduction to less than 30%.

5.7. Light-Responsive Cargo-Protected Delivery for Cancer Therapy

Light stimuli can be employed in protected delivery systems for anticancer drugs. Yang et al. developed a method for increasing the selectivity and targeting capability of the nanocarrier used for PTT or photochemotherapy. In this design, a DNA sequence was used to hybridize and mask a sgc8 aptamer attached to the surface of two different carriers: Au nanorods and single-walled CNT. The exposure of the nanocarrier to NIR resulted in localized heat generation on the surface. The temperature rise dehybridized the double-stranded DNA and released the aptamer, which could recognize specific cancer cells. Human leukemic lymphoblast cells (CCRF-CEM cells) were exposed to DOX-loaded single-walled CNTs conjugated to the DNA-hybridized aptamer. The results demonstrated that the caged aptamer was inactive without the presence of NIR and caused no damage to cells. Unlike the caged aptamer, the platform with free aptamers showed high toxicity both with and without NIR. Overall, the caged aptamer combined with NIR showed maximum cancer cell killing due to its enhanced targeting and combination of drug release and hyperthermia.[212] Figure 11c shows this experimental design.

5.8. Light-Responsive Cancer Radiotherapy

In a nanomedicine-modified approach employing ionizing radiation, X-ray irradiation can be absorbed by NPs, e.g., Au NPs, selenium semiconductor NPs, and so forth, which act as radio-sensitizing agents, inducing ROS generation that leads to cytotoxicity and eradication of tumor cells.[213–215] The use of various NPs can enhance radiotherapy-mediated killing of cancer cells.[216] In a study by Fan et al.,[217] a UCNP core/porous silica shell theranostic nanosystem was designed for simultaneous chemotherapy and high-energy X-ray radiotherapy including cisplatin (CDDP) as a radio-sensitizer along with dual modality imaging by magnetic resonance/luminescence (Figure 12a). The CDDP-loaded nanocarriers showed more effectiveness compared to that of free CDDP and synergistic chemo-radiotherapy treatment. Elsewhere, gamma-irradiation radiotherapy enhanced by super-paramagnetic NPs has also been shown.[218] Using combined radiotherapy and PTT has also shown more effective results and synergistic effects as an antitumor therapy.[219] Hyperthermia can reduce the dose required for radiotherapy.[220] MR imaging and radiotherapy can also be used together to obtain image-guided radiotherapy of cancer.[221]

6. OTHER APPLICATIONS OF LIGHT IN DDSs

In this section, we cover some additional examples of new advances in light stimuli-responsive nanocarriers. Chiang et al. explored the idea of expanding the application of PTT (normally used as a cancer treatment) as an approach to treat infection. A combination of PTT and light-triggered antibiotic release system was investigated. This platform contains a

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poly(lactic-*co*-glycolic acid) (PLGA) shell and an aqueous core including vancomycin and polypyrrole NPs. Light irradiation resulted in heat generation by polypyrrole, which had two effects: (i) activating the PLGA molecular switch leading to vancomycin release (ii) and tissue hyperthermia. They found an increase in bacterial cytotoxicity.[222]

Protected delivery of biomolecules has been the aim of several studies. Wang et al. developed a bovine serum albumin (BSA)-loaded light-responsive hydrogel for protein delivery in deep tissues based on a gel-to-sol transition caused by red light irradiation. A supramolecular complex consisting of mAzo and β-CD was used in which methoxy groups were incorporated to tailor the wavelength required to isomerize the azo moieties by shifting to red-light. Red-light isomerization and blue-light/photothermal-induced disassembly and reassembly of the mAzo/β-CD complexes (Figure 12b) provided on-demand and controlled protein release (Figure 12c).[223]

Photocages have been suggested as novel NIR-cleavable linkers to release small molecules from biomacromolecules, for example, to release a drug from an antibody conjugate. A cyanine dye-drug conjugate was reported where drug release occurred under 690 nm light irradiation.[224] Cyanine fluorophores have also been suggested for delivery of small biomolecules, where low-intensity 690 nm NIR irradiation activated the release of caged molecules.[225] Controlling enzyme activity may be possible via two-photon caging/uncaging in the NIR range. For instance, the action of cyclooxygenase-2 enzyme inhibitors could be suppressed via coupling to photocages, which could be activated via two-photon 800 nm radiation. This approach could be exploited for specific target recognition via incorporation of peptide targeting vectors.[63] Elsewhere, controlled release of an inhibitory neurotransmitter was achieved using a modular design to construct photocages containing an electron-rich two-photon absorbing dye and an electron acceptor. Irradiation with 340–420 nm light led to quenching of the dye fluorescence by electron transfer and finally to bond-cleavage and cargo release.[68] The delivery and spatiotemporally controlled release of carbon monoxide into cells by the chemically stable and nontoxic photoresponsive “carbon monoxide-releasing molecules” has been explored. These carbon monoxide-releasing molecules were formed from transition-metal-free photolabile constructs based on BODIPY chromophores (COR-BDPs) and were described as a novel visible/NIR (up to 730 nm)-activatable nanosystem.[71] In other applications, photocages have also been suggested for overcoming problems with photoisomerization and enhancing control of the protection/deprotection of thiol groups, e.g., using NDBF photocages.[35] Photocage-based systems can provide advantages such as biocompatible chromophores and red-shifted absorption;[55] two-photon cages can be designed to have enhanced two-photon absorption cross-sections, good water solubility, and low toxicity. They can be used for physiological processes such as Ca^{2+} signaling with good spatiotemporal control.[69,226]

Electrostatic host–guest interactions can also be employed to achieve controlled drug release. For example, a photocontrolled nanosystem for the dynamic capture and release of DNA or proteins was developed with a self-assembled ternary structure composed of amphiphilic cyclodextrin (α-CD) vehicles. Azobenzene groups were noncovalently linked to the cyclodextrin via host–guest complexation, and then linking agents were bound to DNA and proteins that formed links to the vehicles through multivalent electrostatic attraction.

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Cis–trans photoisomerization of the azobenzenes induced switching from multivalent binding sites to a low-affinity monovalent binding site, leading to dissociation of the complex.[227] Song et al.[228] synthesized Au NPs electrostatically cross-linked to a DNA hydrogel (Dgel). Laser irradiation induced local heating that led to DNA denaturation and melting, leading to disassembly of the Au NPs and release of the loaded cargo (Figure 13a). NIR-triggered photothermal release systems can provide light-encoded logic gate operations with spatiotemporal-controlled release. In another study, Shi et al. prepared Au nanocage@smart polymer shells that exhibited LSPR and were combined with a “prodrug” activation process that acted as an “AND”, an “OR”, or an “INHIBIT” logic gate under different conditions and provided logically controlled drug release under different NIR irradiation conditions (Figure 12b).[229]

PDT is effective for inactivation/eradication of various micro-organisms such as Gram-positive/negative bacteria, viruses, parasites, and fungi so it can be exploited for treatment of viral lesions and dermatological, bacterial, dental, and gastric infections.[74] Recently, Hamblin’s research group reported that PDT could effectively be used to treat oral candidiasis in a mouse model.[230] UVA-excited TiO_2 NPs have been used to kill Gram-positive/negative bacteria and fungi,[231] and fullerene-based PDT has been used for both antimicrobial and anticancer therapies,[232] blue-light inactivation of Gram-negative pathogens in bio-films,[233] and even for activation of cell proliferation in skin.[234] A PDT approach has also been reported for treatment of rheumatoid arthritis.[235]

Intracellular barriers can be overcome by exploitation of light-triggered gene delivery. Wang et al. reported endosomal/lysosomal escape and cytosolic gene delivery using NIR photo-thermally generated gases that induced rupture of endosomes/lysosomes.[236] In a similar effort to increase delivery into the cytosol, a two-step light irradiation working via PDT disrupted endosomes by oxidizing the membrane. This “photochemical internalization” led to the delivery of therapeutic macromolecules into the cytoplasm.[237]

7. CHALLENGES, PERSPECTIVES, AND CRITICAL REMARKS

In this section, we attempt to address some important questions regarding light-activated DDSs and nanostructures. For instance, what are the important features of various nanomaterials used in DDSs and light-activated platforms? How do nanomaterials, particularly light-activated ones, behave in biological environments, and do they cause toxicity/damage? What are the nanotoxicity mechanisms, what synthesis methods of photoactivated nanomaterials are available, and which light-activated strategy should be chosen according to the required/desired application regarding the efficiency of light-activated mechanisms?

Nanomaterials

One important issue is exploring the pros and cons of different NPs that could be applied in light-activated platforms. These NPs can be made from various materials with specific features, such as quantum dots (QDs) with fluorescent emission, AuNPs with theranostic capabilities, MSNs, polymeric NPs, UCNPs (lanthanide-doped NPs, e.g., Ln^{3+}-doped

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$NaYF_4$), organosilica NPs, carbon nanomaterials (e.g., GOs, CNTs, carbon nanodots), and prodrugs (metal (e.g., Pt) complexes).[32]

Among metal NPs, AuNPs are both nontoxic and biocompatible, and their features such as good photothermal conversion, high light absorption efficiency, and shape can be desirably tuned. Furthermore, they can be used for both therapy and diagnostics.[166,238–240] As a DDS, AuNPs can be variously functionalized to provide targeting ability and eliminate the probable toxic side effects. Moreover, they are able to deliver a wide variety of cargos such as proteins and nucleic acids.[241,242] MSNs are biocompatible and thermally stable with a high loading capacity due to their high surface area and porous structure. The properties of these NPs including porosity, pore diameter, and topography are also tunable. Furthermore, they provide controlled drug release. The unique structure of MSN allows the incorporation of different targeting and imaging agents as well as smart moieties as stimulus-responsive gatekeepers.[243,244] Polymeric NPs provide a wide range of carrier forms including dendrimers, micelles (hydrophobic core/hydrophilic shell NPs), and nanogels (as hydrophilic cross-linked polymeric networks) and are capable of different surface functionalization. Biodegradable polymers are promising nanocarriers due to their outstanding biological and environmentally friendly properties and negligible toxicity, general preparation methods, and enhanced therapeutic efficiency. They can be exploited to design miscellaneous nanocarriers[245] or can even be used as coatings (e.g., PEG) on other NPs due to their physiological properties, e.g., reducing immunogenicity and antigenicity and enhancing NP stability in the bloodstream.[246] Photoactivated polymeric nanocarriers have also shown advantages for enhanced gene transcription efficiencies.[247]

Prodrug complexes offer improvements in solubility, lipophilicity, oral absorption, active transport of biomolecules (e.g., nucleoside analogues), and membrane permeability. They are beneficial for antibody/gene-direct enzyme prodrug therapy.[248,249]

CNTs are innately multimodal platforms. In addition, they can be further functionalized with diverse functional groups as therapeutics, imaging, or targeting ligands[250] with facile surface modifications;[251] however, they have certain shortcomings such as their possible toxicity (which can be noticeably decreased by modification and functionalization) and poor solubility in aqueous solutions (can be solved by stabilizing agents).[251] QDs benefit from unique optoelectronic properties and small size.[252] Unlike heavy metal QDs with some known toxicity, the newly emerged QDs have been reported as promising agents for drug delivery and imaging, which have shown potentials for enhancing the stability, biodistribution, circulation time, targeted delivery, and metabolism process of drugs.[253]

Magnetic NPs are biocompatible with facile and low cost synthesis methods, where through their controlled synthesis, decreased toxicity and immunogenicity and enhanced stability are available. These NPs can provide localized hyperthermia, magnetic field-guided targeting and diagnosis, cell tracking, and drug/gene delivery.[254]

Nanogels have demonstrated larger cargo encapsulation compared to those of liposomes and micelles but are inappropriate for hydrophobic drugs. They can be simply synthesized using amphiphilic block copolymers that are combined, and consequently, the oppositely charged

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chains self-assemble. In addition, here, the exploitation of chemical cross-linking hinders disassembly of the hydrophilic chains in aqueous conditions.[255]

NP Biostability and Interplay with Biological Environments

The interplay between various NPs and a variety of biological milieus, addressing their biostability, biodistribution, toxicity, and so forth have been widely covered in the literature. Generally, DDSs inside the body are prone to fast clearance and often do not have a long enough circulation time. They may be metabolized into toxic agents, leading to a reduction in their activity. Polymeric NPs have shown enhanced biodistribution and pharmacokinetics of therapeutics, reduced multiple drug resistance, less reticuloendothelial clearance,[256] and minimal damage to cells and tissues.[257]

Nonbiodegradable polymers show limited clearance in biological conditions, so their optimization in future investigations is necessary.[53] Regarding biodegradable polymers, their good drug encapsulation and facile modification as well as biocompatibility, control over biodistribution, and degradation kinetics are remarkable advantages.[258] Organic conductive polymers such as polypyrroles (as a PTT agent) have shown high stability and biocompatibility, although with low cytotoxicity even with long-term biological exposure.[259]

The high stability and photostability of UCNPs in physiological sites along with insignificant cytotoxicity have been reported.[260] Furthermore, NIR-activated UCNPs have been reported as targeted highly active antitumor cytotoxic prodrugs.[128] Polymer coating on UCNPs can provide high efficiency gene transfection and reduced cytotoxicity.[261]

The interplay of fullerenes with biological environments such as their biodistribution, accumulation, metabolism, adsorption, and excretion are correlated with their administration route and dosage.[262] AgNPs are reported to accumulate in different organs via inhalation or subcutaneous injection and cross the blood brain barrier (BBB).[264]

The biodegradability and safety issues of several chromophores including *o*-nitrobenzyl and azobenzene-derived compounds (azobenzenes are considered toxic by the FDA) are not yet assured. Hence, more investigations to find biocompatible chromophores should be undertaken.[36,128]

Lipid-based NPs have highly dynamic behavior in biological environments when interacting with biomolecules and cells.[265] Their chemical, physical, and biological stability have also been investigated,[266,267] and no consistent results have been reported regarding the general stability of liposomes.[267] Stealth liposomes have been shown to possess particular stability in the bloodstream.[263]

Organic dyes as bioreagents have been reported with properties such as metabolic and chemical degradability.[260] The photodegradation of some chromophores such as *o*-nitrobenzyl esters might generate undesirable products due to the UV-absorbing feature.[268] Inorganic PTT agents such as Prussian blue NPs have indicated high photothermal stability.[259] Several organic dyes such as ICG are FDA-approved for clinical uses. Such small molecules could be simply removed by the clearance system; thus, they are highly beneficial for biomedical applications.[269]

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Inorganic NPs are nonbiodegradable with higher stability, which imposes restrictions in the case of increasing long-term retention inside the body where they may remain for longer periods of time, possibly causing long-term toxicity. Importantly, their in vivo behavior and pharmacokinetics should be understood well.[259]

Nanocarbon NPs have shown higher photothermal stability, e.g., in comparison with AuNPs.[259] GO-based carriers have demonstrated high gene transfection efficiency and concomitant gene therapy/PTT.[269] CNTs are known to efficiently cross biological barriers, e.g., cellular membranes,[250] and modulate biomolecular functions and biological processes, e.g., gene silencing, cell functions and activities.[270]

Moreover, some QDs are intrinsically toxic and chemically instable with an inappropriate lifetime.[260] The stabilizers of QDs have a major role in their biodistribution and clearance.[271]

Nonetheless, many of the agents and molecules utilized in the light-activated nanoplatforms still need to be investigated in depth to better understand their in vivo behavior and correlated side effects. Moreover, developing novel organic NPs and chromophores could eliminate the demand for inorganic photoactive nanomaterials.

Nanotoxicity Mechanisms and Correlated Side Effects

The nanotoxicity of nanomaterials is a critical determining factor for their future biological and biomedical uses. The behavior of NPs in biological milieus is the outcome of their physiochemical features such as shape, size, stability, chemistry, reactivity, and so forth. Although the exact mechanisms of toxicity of NPs are not completely understood, they have often been related to oxidative stress generation and transcription of pro-inflammatory genes.[272,273] Moreover, another toxicity-related concern is accumulation/absorption of NPs, especially non/slowly biodegradable NPs onto the surface of tissues, cells, and biomolecules (e.g., enzymes and proteins) that might interfere with biological processes and disrupt the internal regulatory mechanisms of the body.[274] The toxicity results of QDs have been somewhat inconsistent, but mostly, toxicity has been ascribed to the core nanocrystal material, and the size of the QDs and some other factors such as dose and the presence of capping materials and functional coatings may play a role.[275] Again, reports on the nanotoxicity of CNTs have been somewhat conflicting and have ranged from those showing high toxicity to those showing only insignificant toxicity. CNT toxicity depends on various factors such as NP kinetics, cellular uptake, geometry, size, chemistry, surface functionalization, aggregation, administration route, purity, cellular uptake, and so forth. The toxicity of CNTs might cause side effects including damage to the cell envelope, interference with transmembrane electron transfer, oxidization of cellular components, the production of dissolved heavy metal ions that can lead to ROS production, induction of inflammation and fibrosis, biopersistence, and possible carcinogenic effects (CNT inhalation could produce malignant mesothelioma).[251,264,276]

No consistent reports exist for the nanotoxicity of graphene-based nanostructures, but possible cytotoxicity and genotoxicity have been suggested; nevertheless, functionalized graphene nanomaterials have been suggested to have less toxicity. The dosage and

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concentration of graphene nanomaterials play the principal role in toxicity evaluation, but other factors such as administration route, geometry, surface chemistry, functionalization, aggregation, corona effect, impurities, and so forth have been suggested to play a role. The possible toxicity mechanisms for graphene-based nanomaterials have been reported to be interference in intracellular metabolic pathways, ROS generation, damage to cell membranes, physical destruction, autophagy, apoptosis, necrosis, inflammatory responses, and DNA damage.[275,277,278] Regarding fullerenes, adverse effects such as inflammation after inhalation of high-doses have been found, whereas oral administration leads to insignificant toxicity. Toxicity after long-term administration has been investigated[262] as well as production of oxidative stress in some cases.[279] Polymeric nanomaterials are generally regarded to have no toxicity or immunological or pro-inflammatory effects and do not induce neutrophil activation. For example, poly(D,L-lactide-*co*-glycolide) is a polymer with negligible toxicity, which only generates bio-compatible metabolites.[264] Chitosan is a natural biocompatible polymer with very low if any toxicity. However, some significant cytotoxicity was reported when applied as a coating for stabilizing PLGA.[280] In addition, in vitro toxicity evaluation of polymeric NPs may differ from in vivo evaluation, as Voigt et al. reported some in vitro dose-dependent cell death but found no evidence of toxicity in vivo.[281] Lipid-based NPs have shown very low cytotoxicity, although some conflicting results necessitate further studies to better understand their biodistribution, tolerability, effect of administration routes, and pharmacokinetics before they can conclusively be considered to be nontoxic. Carrying out more in vivo investigations regarding all classes of NPs is indispensable.[275] Interestingly, cationic liposomes have shown genotoxicity even at noncytotoxic concentrations. The toxicity of cationic liposomes is due to the presence of the cationic head groups and might be dose dependent. They have been reported to induce inflammatory responses, oxidative stress, and DNA damage.[282] The toxicity of iron oxide NPs has been associated with ROS generation, DNA damage, and lipid peroxidation. Iron oxide NPs can accumulate in many organs of the body and can cross the BBB. They may induce reduced cell viability and inflammation and could disturb the blood clotting system. Titanium oxide NPs (although chemically inert) can have harmful effects such as DNA damage, genotoxicity, lung inflammation, and toxic effects on organs and lipid homeostasis.[264] Several studies have considered AuNPs to be nontoxic with negligible effects on cellular functions. However, the toxicity of AuNPs can be influenced by their surface functionalization, NP size, administration dose, cationic side chains, a variety of applied stabilizers, and so forth.[264,275] Regarding AgNPs, side-effects such as dose-dependent reduced cell viability, oxidative stress production, lactate dehydrogenase (LDH) leakage, and DNA adduct generation have been found.[264]

Light-Activated Mechanisms and Their Efficiencies

To decide which particular photoactivation mechanism is suitable for any specific DDS, the various advantages and drawbacks should be taken into account. Generally, light-activated nanoplatforms are capable of only being activated when light irradiation is delivered into a specific spatially targeted tissue, which is a promising strategy for diminishing collateral damage to surrounding tissues. However, various light wavelengths differ markedly in their interplay with biological environments and tissues. In this section, we address some

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examples of light-activated mechanisms, highlighting their efficiencies, benefits, and drawbacks.

UV light has a higher average photon energy leading to nonspecific reactivity, and its low tissue penetration imposes more risk of damage toward superficial tissues. Visible light has less adverse effects, and NIR light has the least danger, which together with its deeper penetration has been suggested to be the most advantageous wavelength range.[53,258]

UV light consists of high-energy photons that are directly absorbed by most biological molecules, leading to short tissue penetration depth and increasing the likelihood of off-target damaging photochemical reactions.[53] Using UV light for excitation of conventional bioreporters such as QDs and organic dyes increases the risk of damage to cells and tissues.[260] It has been suggested that micro/nanoplatforms that can be activated with continuous wave UV lasers, unlike conventional broad-band UV light, have less risk of damage to surrounding tissues and to therapeutic cargos.[32] Elsewhere, the UV activation of chromophores such as *o*-nitrobenzyl moieties has been compared to that of two-photon excitation, but the two-photon absorption cross section is low.[256]

One photon-activated photochemical reactions (e.g., photo-cleavage, photoisomerization, and photorearrangement) have high efficiency and a fast response rate. The development of chromophores that have one-photon absorption peaks at longer-wavelengths into the NIR region (by developing new candidates or modifying existing chromophores) is essential. In this regard, the development of NIR/visible light-absorbing chromophores is preferred due to the drawbacks of UV excitation and the difficulties associated with nonlinear multiphoton excitation. Furthermore, the number of long-wavelength light-responsive materials activated with one-photon irradiation is considerably higher than easily accessible UV-activated counterparts. However, long-wavelength-activated nanoplatforms possess several shortcomings such as innate toxicity, being expensive, intricate fabrication methods, and interferences by ambient short wavelength visible light, which should be resolved for future applications.[53]

Visible light displays biological tissue absorption and scattering coefficients that are intermediate between UV and NIR light; thus, it is not as efficient a light source as NIR. However, focused laser light has been reported to have enhanced efficiency compared to that of noncoherent light from LEDs, e.g., in PTT therapy.[259]

NIR-activated nanoplatforms are biologically useful because of the minimal absorption of NIR by tissues/cells (thus lessening any chance of tissue phototoxicity) and increasing the chance of light absorption by chromophore-incorporated DDS.[283] NIR-activated organic dyes incorporated in micelles have been reported to mediate safe and efficient PTT. Inorganic nanomaterials such as MoS_2 have displayed highly efficient NIR absorbance and an improved extinction coefficient compared to those of AuNPs and GO and have been extensively exploited for PTT.[259] Accurately controlled drug release in physiological conditions is achievable via NIR photothermally activated nanocarriers.[284]

Although NIR light is less harmful to tissues and cells than UV and visible light, to overcome the low energy per photon and high scattering by tissues, the use of organic

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chromophores with high two-photon absorption ability has been suggested. Moreover, UCNPs can also convert NIR radiation to short wavelength visible/UV providing a localized UV treatment.[32] UCNPs have been reported to mediate efficient PDT application.[128] Using UCNPs also can lead to deeper penetration and improved imaging resolution in tissue.[260]

Instead of using UV (that requires one photon absorption) to activate photocleavable groups (such as coumarin derivatives) many works have used NIR irradiation and a two-photon excitation process.[268] Using two-photon NIR absorption has advantages such as excellent 3D spatial resolution with less scattering loss, inhibition of premature release of cargo, much deeper tissue penetration, and less oxidative stress-induced cytotoxicity.[32] Nonetheless, NIR absorption of chromophores through two-photon excitation is usually not efficient, and is cumbersome and difficult. The introduction of high two-photon absorption cross sections presents a difficult synthetic challenge to organic chemists. Highly conjugated systems with strong-electron donating and accepting groups encourage electron charge separation and two-photon absorption. Because two-photon absorption depends on the square of the intensity, the easiest way to produce sufficiently high intensities is with a very short pulse of light. Femtosecond pulsed lasers (such as Ti:Sapph) are effective but expensive. Recently, chromophores with an enhanced two-photon cross section such as [7-(diethylamino) coumarin-4-yl]methyl esters have been employed.[268]

Modification of photocaged chromophores to have red-shifted absorbance bands is a novel strategy to increase the efficiency of light activation. In this regard, modified photoactivated materials such as tricyanofuran and photocages (e.g., DANP and BODIPY) have been reported. Azobenzene chromophores with red-shifted absorbance bands have been reported with biomedical applications. However, modified chromophores may suffer reductions in quantum efficiency, as has been found for an *o*-nitrobenzyl-activated photocage.[53]

Photon upconversion by UCNPs requires much lower NIR intensities to induce emission of a shorter wavelength photon than conventional two-photon absorption (TPA). This is because the two photons are absorbed sequentially via a “virtual excited state” rather than simultaneously in TPA.[268] Typically, UCNPs are excited by less expensive CW lasers than by femtosecond lasers.[32,268] However, there is still room for the efficiency of lanthanide upconcversion to be further enhanced. One solution may be to optimize the lattice structure of the UCNPs.[128] NIR-activated UCNPs can be used for inhibition of tumor growth and provide deep tissue penetration.[285] Recently, limited in vivo application of UCNP nanomaterials using 980 nm light excitation has been reported. The use of other wavelengths to activate UCNPs (e.g., 808 nm) could lead to less heating and tissue damage compared to activation with 980 nm that hits a distinct water peak in tissue.[128]

The two multiphoton nonlinear processes, i.e., upconversion luminescence and two-photon absorption, are not yet efficient enough; thus, stronger and more focused lasers are needed, restricting their in vivo application. In addition, new efficient solutions must be developed to overcome problems with NIR light in tissue, such as scattering and beam defocusing. Moreover, the high efficiency of one-photon downconversion of long-wavelength light may hinder the two mechanisms.[53]

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NIR light has been widely employed for in vivo imaging of physiological structures, biomolecular processes, and metabolic reactions.[263] NIR-activated Au-caged nanostructures have shown strong plasmon resonance coupling for theranostic applications. NIR activation along with biomolecular (e.g., aptamer) targeting of metal NPs can be advantageous for highly sensitive detection of cancer cells at lower concentrations as well as mediating localized hyperthermia.[286]

Photoactivated thermal NPs can utilize low power densities producing no damage to healthy tissues compared to that with laser beams alone and can eradicate larger volumes of cancer tissue (both light-treated and -shielded).[32] Using various AuNPs, e.g., nanocages, nanoshells, nanorods, and so forth, as potential candidates can lead to efficient PTT because of their tunable LSPR and their strong optical extinction in the NIR region and also in the visible spectrum (e.g., Au nanorods). Red-shifted AuNPs induced by designed aggregation have shown enhanced NIR-triggered PTT.[259] The plasmonic effects of AuNPs have shown capabilities in the design of concurrent theranostic PTT/PBT nanoplatforms.[269] PTT agents such as Prussian blue can provide high efficiency and fast response.[259] Nanomaterials such as CNTs, graphene, AuNPs, CuS NPs, and Pd NPs have all been reported to provide suitable NIR-to-heat conversion for DDSs. PTT agents routinely become more efficient when modified to be NIR activated.[287] Structural and surface modification of NPs, for example, modification of CuS NPs to form nanoflowers[259] or coupling of $Cu_{2-x}Se$ to the surface of CNTs (to overcome the low molar extinction coefficients of CNTs),[288] can increase the photothermal conversion efficiency and reduce the incident laser power density. Some conventional photosensitizers such as porphyrins have shown superior PDT capability (>75% $^1O_2$ generation).[259] Combined PTT and PDT can lead to synergistic photo/cytotoxicity, but on the other hand, may lead to oxidative stress generation, self-destruction, poor solubility, and less target selectivity. When intracellular delivery of intact biomolecules to the nucleus or ribosomes is required after they have been taken up by endocytosis, a new photochemical delivery mechanism is described.[32] The idea is that the biomolecule is combined with a photosensitizer that localizes to the endosomal membrane, and light delivery breaks apart the endosomes, releasing the biomolecule before it can be degraded by lysosomal enzymes. New research has shown efficient simultaneous fluorescent imaging and PTT using a unique platform (i.e., high quantum yield and high photothermal conversion).[269]

In addition to the aforementioned issues, some other different approaches can be found mentioned in the literature. Interestingly, CNTs have shown near-infrared photoluminescence via a one photon-activated upconversion mechanism.[289] A photoreduction (as opposed to the more usual photo-oxidation) mechanism has been shown to be advantageous for cancerous tumors.[32] Some organic chromophores exhibiting features such as “photoblinking”, leading to a low signal-to-noise ratio using time-resolved imaging, have been reported.[260] Coumarin, DNQ, and *o*-nitrobenzyl derivatives are regarded as chromophores with simultaneous UV/NIR sensitivity, which can be notably advantageous in light-activated therapies.[256] Linear/dendritic self-immolating polymers incorporating multiple pendant or single terminating photosensitizers (e.g., *o*-nitro-benzyl or coumarin derivatives) have been proposed as polymeric nanocarriers with high photoactivation efficiency.[256] The family of photocages containing coumarin can be activated via a

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photosolvolysis mechanism. This involves providing access to nucleophilic (e.g., water-rich) microenvironments during photoactivation of coumarin-mediated light-responsive nanomaterials so that a more efficient photocleavage reaction can occur.[53] Modified BODIPY chromophores have shown good efficiency for absorption of green light to improve their relatively low quantum yield for photouncaging.[55] The uncaging efficiency of some photocages such as amino-1,4-benzoquinone can be limited in polar solvents, and undesirable side-reactions between the photocage and photocleaved product can occur.[53] QDs have shown a penetration depth of 200 μm.[271] Superior quantum yield, exceptional photostability with sharp emissions, broad range of excitation spectra, tunable fluorescent emission, and brighter photoluminescence have made them promising for theranostic applications. QDs can also be considered as direct photoactivated ROS generators (PDT agents), albeit with relatively low efficiency. Despite that, their high photostability allowing prolonged photoactivation could lead to an overall effective PDT protocol.[260,269]

Nanocarbon materials such as CNTs can exhibit a broad absorption spectrum extending all the way from UV to NIR combined with a high mass extinction coefficient at NIR (e.g., CNTs and GO).[259] Nanohybrids of different photo-activating nanomaterials such as QD/photosensitizer and UCNP/photosensitizer hybrids have shown advantages as combinations, including deeper tissue penetration, higher ROS generation, better PDT efficiency, and allowance of image-guided PDT.[269]

Synthesis Methods

The synthesis of various NPs employed in light-activated platforms and their postsynthesis stability can be a critical issue. Here, the synthesis of some related nanomaterials used in the fabrication of light-activated DDSs are discussed.

Regarding the synthesis of biodegradable polymers (e.g., PLGA and poly(lactic acid)), a variety of techniques have been developed.[258] Because many properties of polymeric NPs such as their size, shape, morphology, charge, and so forth affect their behavior in biological environments, these parameters must be carefully considered when designing the synthesis process.[258]

UCNP-based DDSs are usually synthesized using methods such as sol–gel, hydrothermal-assisted template method, polymer grafting, self-assembly, electrospinning,[128] and onestep ligand exchange.[260] Controlled synthesis of UCNPs is also achievable so that their lifetime, size, shape, and luminescent emission properties can be tuned.[260]

UCNPs with high stability in aqueous solutions can be obtained via techniques such as the one-step ligand exchange method (to eliminate the alteration of interface charge equilibration),[260] localized photoexcited polymerization of a polymeric shell surrounding UCNPs,[290] or via a method where cross-linking moieties are used together with amphiphilic groups to improve the stability in water and physiological conditions with varying pH values.[291] Colloidal stability of UCNPs can also be achieved via surface modifications such as PEGylation.[260]

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UCNPs are known to have an overall hydrophobic character.[290] Using hydrophobic ligands required in the synthesis can lead to their aggregation in aqueous solutions, which can then be overcome by using methods such as layer-by-layer assembly, ligand exchange, silica coating, removal of capping-ligands, and polymer encapsulation.[260] Nevertheless, some of these chemical modifications of UCNPs can result in poor stability, reduced reproducibility, and low yield.[260] Suitable surface modification of UCNPs can also lead to the facile conjugation of biomolecules and ligands while maintaining their aqueous stability.[292]

Synthesis of QDs can be finely tuned according to their desired properties. In the synthesis of QDs, the role of stabilizing ligands in QD formation as well as providing colloidal stability has been highlighted.[271] Stability of QDs is a challenging issue as their photo-oxidation[293] and photothermal[294] destruction have been reported. However, in recent studies, some strategies have been suggested to improve their photostability[293] and photo-thermal stability[294] and enhance their stability through the control of precursor stoichiometry.[295] Interestingly, bovine serum albumin (BSA), a well-known biocompatible material, has been reported to be among various stabilizers of QDs.[296] Improvements in the synthesis of QDs, such as synthesis in the aqueous phase,[296] large-scale synthesis,[297] green synthesis,[298] and a new facile synthesis[299] have been reported. In the future, improved synthesis methods of novel nanocarbons, e.g., extended fullerene derivatives, may lead to a wide range of activating wavelengths and enhanced light penetration into tissues.[259]

Self-assembled polymeric NPs are among the most frequently-used candidates for light-activated DDSs, which can be synthesized via a range of methods such as layer-by-layer (LBL) self-assembly and aqueous dispersion polymerization.[259] Photores-Photoresponsive block copolymer micelles can be fabricated using methods including radical polymerization techniques such as ATRP and reversible addition–fragmentation chain transfer polymerization (RAFT) with facilitated synthesis and functionalization or other methods such as “click chemistry” (allowing accurate positioning of light-responsive moieties in specific sites of the polymeric NP, e.g., DNQ-cored micelles and *o*-nitrobenzyl-functionalized micelles) and ring-opening metathesis polymerization.[268,300] Electrostatic interactions can lead to the tailored arrangement of adjoining charged building blocks, e.g., NPs or molecules, to produce light-activated electrostatically self-assembled particles.[115,301,302] Lastly, PTT agents can be synthesized by relatively simple methods; for example, Prussian blue uses simple solution chemistry in aqueous solutions, and AuNPs use seed-mediated shell growth or sacrificial galvanic replacement.[259] The facile synthesis of some photocages such as DANP and “acceptor Stenhouse adducts” has been reported in the literature.[53]

8. CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we have covered various applications of light in NP-based biomedical approaches, particularly concentrating on photoactivated DDSs. The main mechanisms responsible for triggered release of therapeutic agents via photoactivation include photocleavage, photoisomerization, photo-cross-linking, photoreduction, and photoinduced thermal triggers. In addition, several nonlinear photon absorption pathways involved in

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triggered drug release, including photon upconversion and two-photon absorption, have been discussed.

The application of light irradiation in various delivery systems was covered. The use of light in cancer therapy includes PTT, PDT, protected delivery, radiotherapy, light-controlled anti-cancer drug release, and their possible combinations. Many intriguing combinations of different stimuli are possible that can provide synergistic antitumor effects as well as functioning as cancer theranostics. These nanosystems may in the future be able to prevent cancer metastasis and overcome multidrug resistance (MDR). Moreover the theranostic approach allows real-time monitoring and tracking of cancer cells and tumors. Furthermore, in the present perspective, the nanotoxicity and interplay of nanomaterials with biological environments as critical issues were covered, and the efficiency and effectiveness of different light-activated nanomaterials as well as the synthesis methods were discussed.

Integration of light into dual/multistimuli-responsive DDSs can lead to promising nanosystems that provide major improvements in the transport and release of therapeutics or may even allow the design of DDSs that can carry out “logic steps” to be used in a biocomputing system. It is becoming possible to design platforms that can transport several therapeutic agents simultaneously, e.g., the codelivery of genes and drugs. Engineering multifunctional nanocarriers with smart release features using innovative nanoplatforms (e.g., UCNPs, chemiluminescent-based NPs, etc.) that simultaneously possess other functions such as diagnosis, targeting, and multidrug delivery are concepts expected to provide new opportunities. It is becoming possible to design nanosystems that are activated as a result of chemical reactions occurring inside the body. NPs may be able to provide their own light using chemiluminescence or bioluminescence reactions, thereby eliminating the need for an external light source. UCNPs can lessen the problem of NIR irradiation causing excessive hyperthermia that can potentially damage tissues.

Some biological barriers are extremely difficult to overcome, such as the heterogeneity of biological targets, the presence of desmoplasia (tough collagen structures located within tumors), and the elevated interstitial pressure that is typical of tumors with disturbed vasculature. These factors can all limit the efficacy of DDSs. By improving the ability of light-activated DDSs to reach and accumulate in target cells and disease sites, the efficiency of localized light irradiation can be improved. Nevertheless, despite all of the aforementioned issues, there is still a need to design simpler nanoplatforms that can be constructed using methods that are economical in both time and money. These considerations are particularly important when clinical translation of these nanomedicines is envisaged.

Despite the tremendous capabilities of light-activated DDSs, many important challenges still remain to be overcome before translational and clinical use can be widely adopted. Abundant safety concerns still exist regarding potential toxicity of nanomaterials (nanotoxicology). Moreover, light itself is not completely harmless. UV light is widely perceived as being potentially damaging, although in reality UV damage to cells is rapidly repaired, and long-term repetition of UV irradiation of tissues is required to cause cancer via UV-induced mutagenesis. NIR irradiation does have the potential to cause thermal damage,

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and in many light-activated nanomedicines, photothermal effects are the primary mechanism of action. The use of biocompatible and biodegradable materials that also possess the desired stability during circulation in the bloodstream as well as appropriate clearance from blood are also important to achieve clinical approval of light-activated nanosystems. Integration with already FDA-approved platforms such as liposomes and albumin NPs could be used to move toward solutions to the above-mentioned issues. Penetration limits of light, especially UV and visible light in body tissues is still a major challenge, and exploitation of NIR due to its low absorbance and scattering has opened new doors toward light-enhanced therapies like PTT and PDT (e.g., using UCNPs). Therefore, the development of light-activated agents working in the NIR window is highly preferred. However, NIR irradiation itself has a penetration limit of approximately 1 cm, which makes it hard to reach diseased sites located in the deeper parts of the body.

It is known that long-wavelength light-activation of photosensitizers and triggered release of bioactive agents is beneficial in healthcare and biomedical applications. Some examples are destruction of cancers or infections, tissue engineering, regenerative medicine, and exploration of biological processes. PDT and PTT are good examples of exploitation of long wavelength light-based therapies, where high efficiency and improved results are obtainable. Nevertheless, for the clinical and translational applications of light-activated nanomaterials and successful bench-to-bedside transition, further studies regarding safety, facile inexpensive synthesis methods, much higher efficiency, and lower side-effects are urgently required.

Designing appropriate medical devices capable of locally delivering/triggering light-activated nanoplatforms by transporting light inside the body (e.g., via optical fibers, endoscopy, etc.), as well as real-time tracking of the phototherapeutic agents and monitoring the progress of the treatment, could provide many benefits. Image-guided light-activated therapies, especially for cancer treatment, could lead to advances such as imaging the diseased site before starting the therapy, better localization of the therapy at the diseased site, improved spatiotemporal control, and imaging of the diseased site after treatment.

We believe that, in the coming years, many innovative breakthroughs and discoveries will continue to be brought to fruition in the dynamic and fast-moving field of light-activated nanoplatforms and DDSs.

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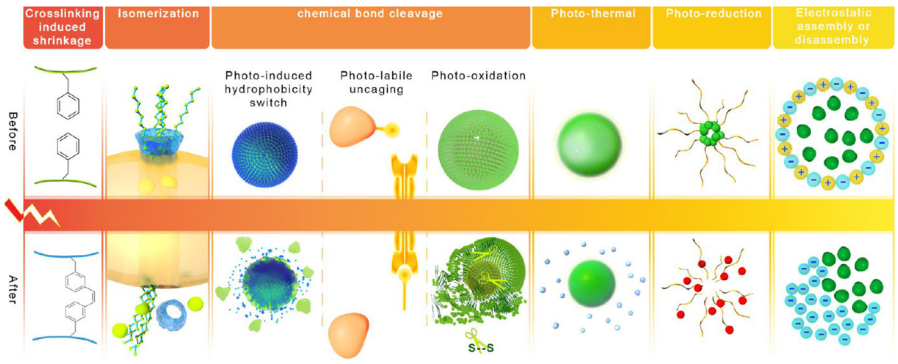

Figure 1.

Light-activated mechanisms used for DDSs, including photoshrinking, photoisomerization, photobond cleavage, photothermal, photoreduction, as well as electrostatic assembly/disassembly.

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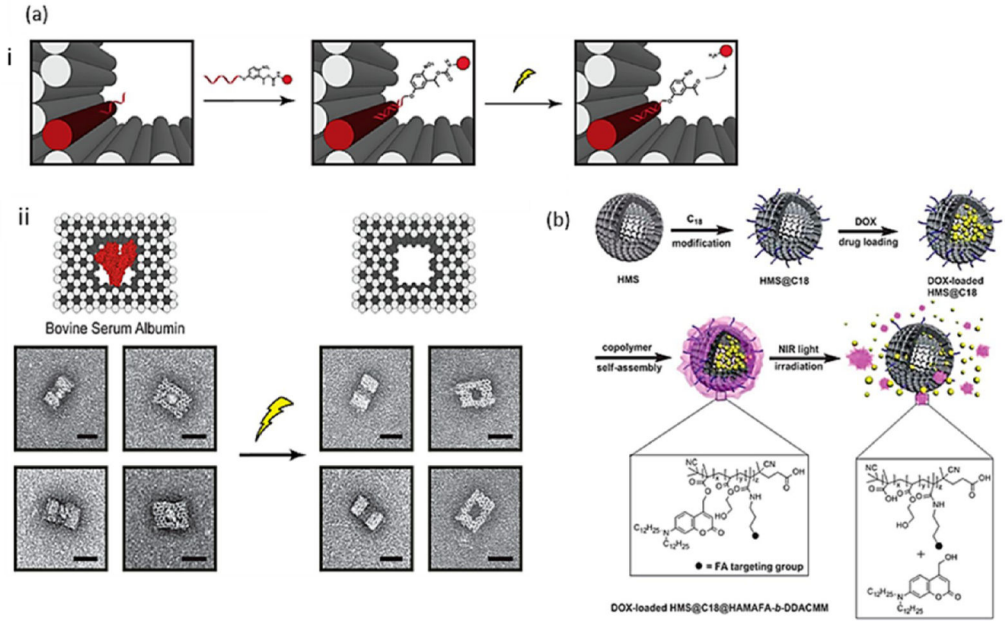

Figure 2.

(a) Photocleavable DDSs: (i) encapsulation of the cargo, photocleavage reaction, and subsequent cargo release; (ii) light-triggered release of proteins (bovine serum albumin) from nanocages. Reprinted with permission from ref 46; copyright 2016, American Chemical Society. (b) Schematic indicating synthesis of a nanocarrier comprised of HMS@C18@HAMAFA-*b*-[7-(didodecylamino)coumarin-4-yl] methyl methacrylate and its application for delivery and controlled release of cargos using degradation upon NIR light exposure. Reprinted from ref 48; copyright 2013, The Royal Society of Chemistry.

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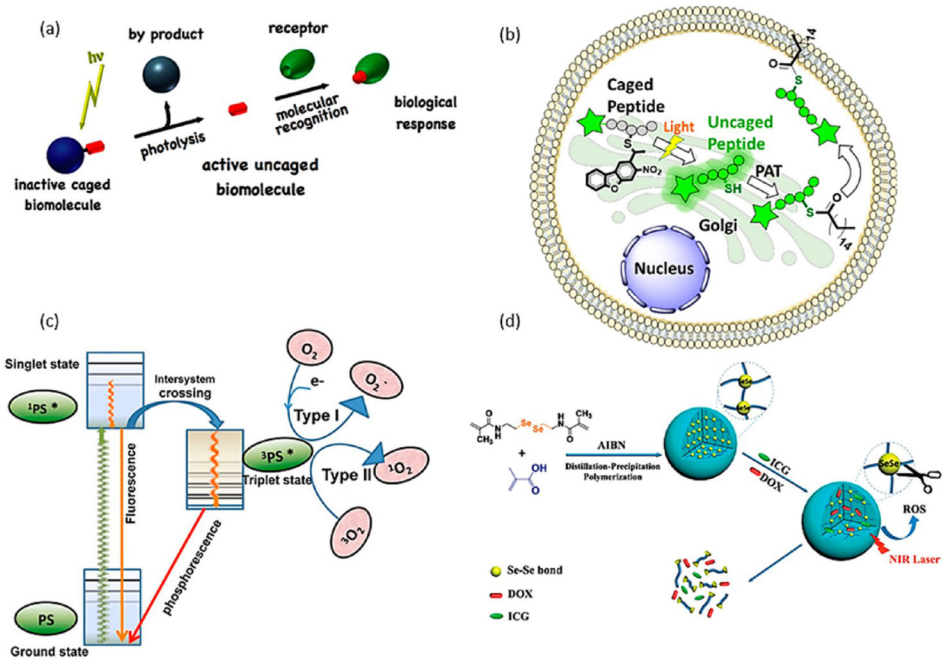

Figure 3.

(a) The principle of uncaging photolabile protecting groups through exposure to light, followed by release of the caged and protected compound. Reprinted from ref 56 (open access). (b) Intracellular uncaging and deprotecting of an NDBF-caged thiol group-incorporated peptide due to UV irradiaton followed by migration of the liberated peptide from the Golgi/cytosol to the cellular plamsa membrane as a result of enzymatic palmitoylation. Reprinted with permission from 35; copyright 2016, American Chemical Society. (c) Mechanism of the photodynamic effect: a photosensitizing dye or molecule in ground-state absorbs a photon and then excites to a singlet state, and fluorescence emission occurs due to an energy loss; intersystem crossing can then lead to a long-lived triplet state that can induce photochemical reactions or lose energy via phosphorescence. This photochemistry can trigger local generation of ROS (e.g., singlet oxygen, superoxide radicals, or hydroxyl radicals). Reprinted with permission from ref 74; copyright 2011, John Wiley and Sons. (d) Synthesis of diselenide-cross-linked nanogels and their biodegradable behavior as well as NIR-induced ROS-triggered nanogel degradation and controlled release of the cargos. Reprinted with permission from ref 75; copyright 2015, John Wiley and Sons.

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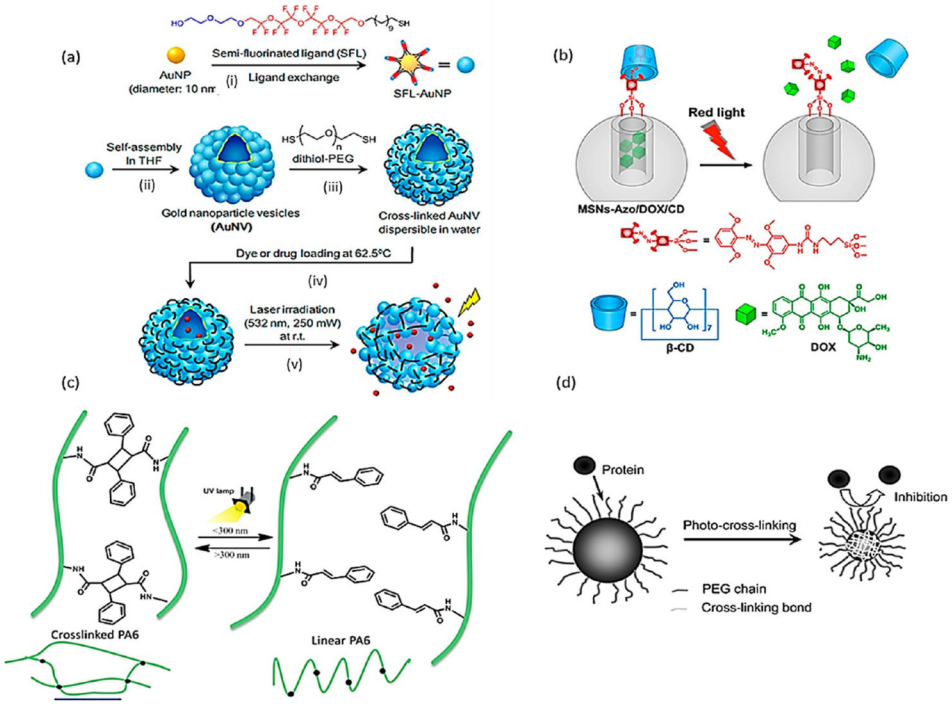

Figure 4.

(a) Fabrication process of cross-linked nanovehicles from cargo molecule-loaded Au nanovehicles for light-sensitive cargo release, including AuNP surface modification with semifluorinated ligands, then forming self-assembled and cross-linked nanovehicles. Reprinted with permission from ref 77; copyright 2013, American Chemical Society. (b) Red-light-triggered DDS using mAzo/β–CD supramolecular valve-modified MSNs. Reprinted with permission from ref 79; copyright 2016, American Chemical Society. (c) Effect of 254 nm irradiation on gel-to-sol transition of Polyamide 6 bearing pendant cinnamoyl moieties in hexafluoroisopropanol milieu. Reprinted with permission from ref 82; copyright 2014, American Chemical Society. (d) Photo-cross-linking of cinnamate moieties under 280 nm UV irradiation leading to a size decrease in the NP. Reprinted with permission from ref 84; copyright 2009, American Chemical Society.

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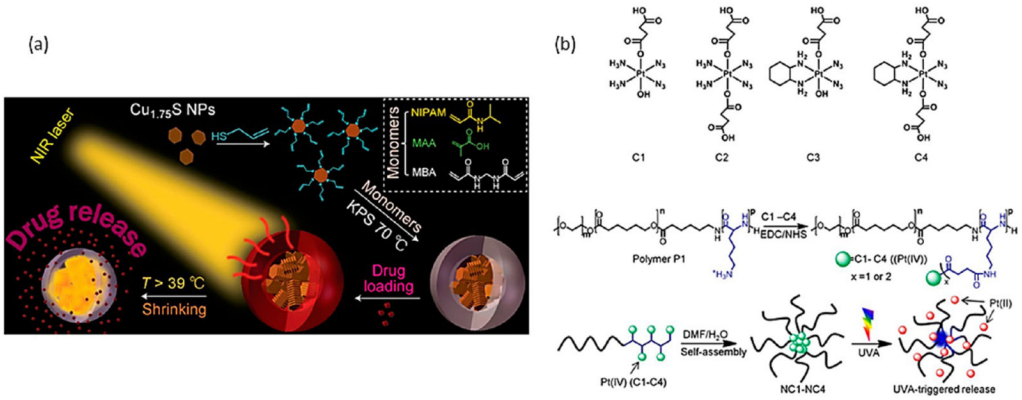

Figure 5.

(a) Photoinduced thermosensitive Cu 1.75 S@p(*N*-isopropylacrylamide (NIPAAm)) methylacrylic acid nanocomposites. Reprinted with permission from ref 31; copyright 2015, Springer. (b) Chemical structure of light-responsive Pt(IV) prodrugs C1–C4 (top), fabrication and self-assembly of micellar NPs NC1–NC4, and their UVA irradiation-triggered cargo (Pt(II)) release (bottom). Reprinted with permission from ref 102; copyright 2014, Elsevier.

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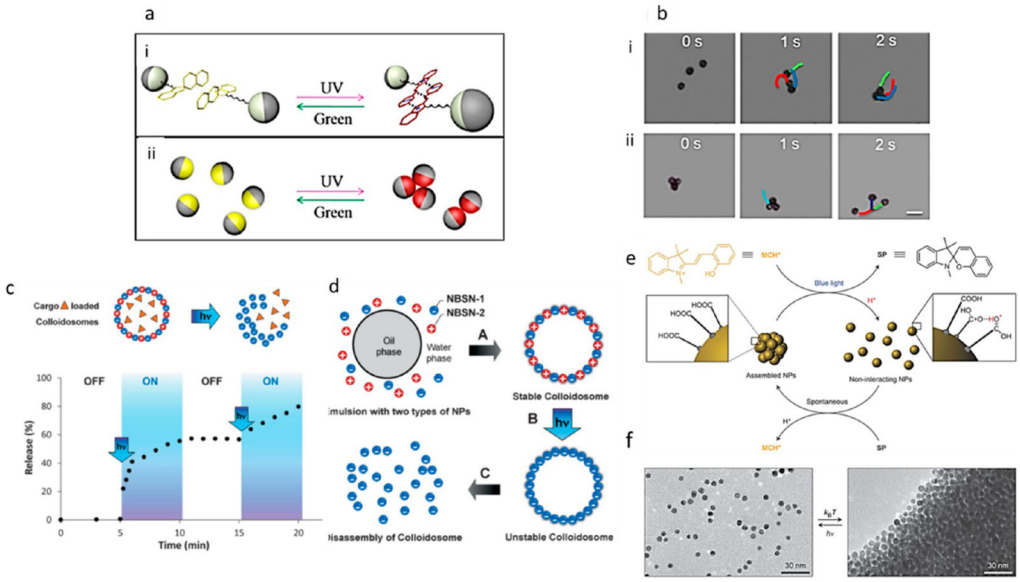

Figure 6.

(a) Light-triggered autonomous self-assembly/disassembly (i), and mechanism of spiropyran-functionalized Janus motors using UV and green light irradiation (ii). (b) Time lapse images of the dynamic self-assembly (i) and disassembly (ii). Reprinted with permission from ref 114; copyright 2015, American Chemical Society. (c) Schematic of cargo release profile from the colloidosomes induced by 365 nm laser irradiation with a 5 min on/off cycle. (d) Schematic of formation of the stable colloidosome vehicles via self-assembly of oppositely charged NPs (NBSN-1 and NBSN-2) in an oil/water emulsion and their disassembly by light irradiation (365 nm laser for 10 min). Reprinted with permission from ref 118; copyright 2015, John Wiley and Sons. (e) Light-induced self-assembly of nonphotoresponsive NPs functionalized with COOH-terminated ligands within a protonated merocyanine (MCH^+)-containing photoswitchable medium. (f) Transmission electron microscopy images showing reversible dispersion/disassembly (left) and aggregation/assembly (right) of Au NPs. Reprinted with permission from ref 119; copyright 2015, Nature Publishing Group.

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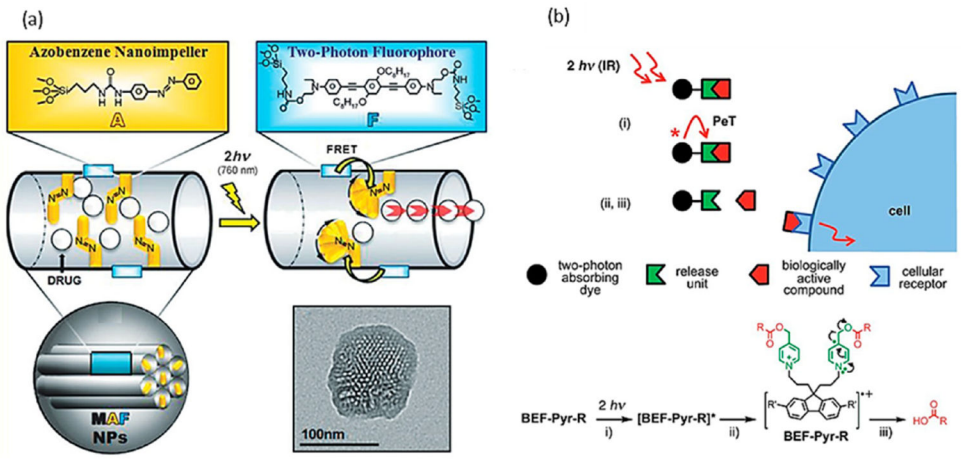

Figure 7.

(a) MSNs incorporating azobenzene moieties “A” and two photon fluorophores “F”, forming so-called MAF nanoimpellers, and a 760 nm two-photon irradiation-triggered drug molecule release from them via FRET and photoisomerization of azobenzenes. Reprinted with permission from ref 125; copyright 2013, John Wiley and Sons. (b) Two-photon excited photocleavage and uncaging of photolabile protecting groups: (i) two-photon excitation, (ii) dye donates an electron to the release unit, (iii) this unit undergoes a photochemical reaction ending in cargo release. Reprinted from ref 68; copyright 2015, permission from The Royal Society of Chemistry.

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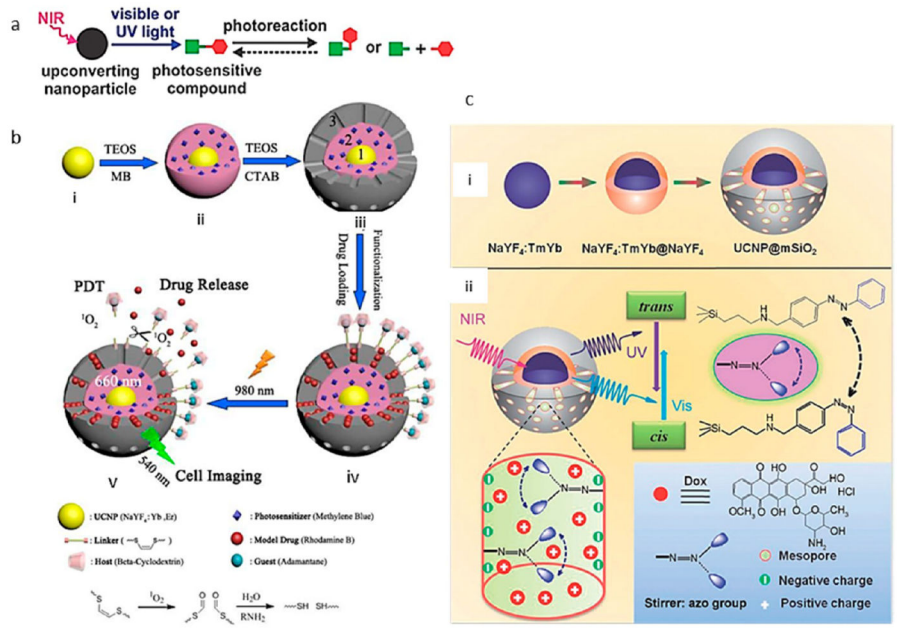

Figure 8.

(a) Photoreactions of photolabile compounds triggered by conversion of NIR to UV/vis via UCNPs, (b) synthesis of NIR-responsive multifunctional core–shell–shell UCNPs for theranostics of cancers.[135] Copyright 2015, permission from The Royal Society of Chemistry. (b) (i) UCNP core, (ii) core–shell structure of UCNP@SiO_2 methylene blue, (iii) core–shell–shell structure of UCNP@SiO_2 (methylene blue)@mSiO_2 NP, (iv) surface modification of the cargo-loaded NPs with linker β-CD, (v) NIR-triggered release of cargos (i.e., rhodamine B), cell imaging, and PDT in which $^1O_2$ generation is induced and causes cleavage of $^1O_2$-sensitive linkers followed by dissociation of β-CD gatekeepers. Reprinted with permission from ref 136; copyright 2016, American Chemical Society. (c) (i) Fabrication process of mesoporous silica-coated UCNPs and (ii) NIR-activated release of DOX employing UCNPs and trans–cis photoisomerization of azobenzene moieties incorporated in the pores of the mesoporous silica layer. Reprinted with permission from ref 138; copyright 2013, John Wiley and Sons.

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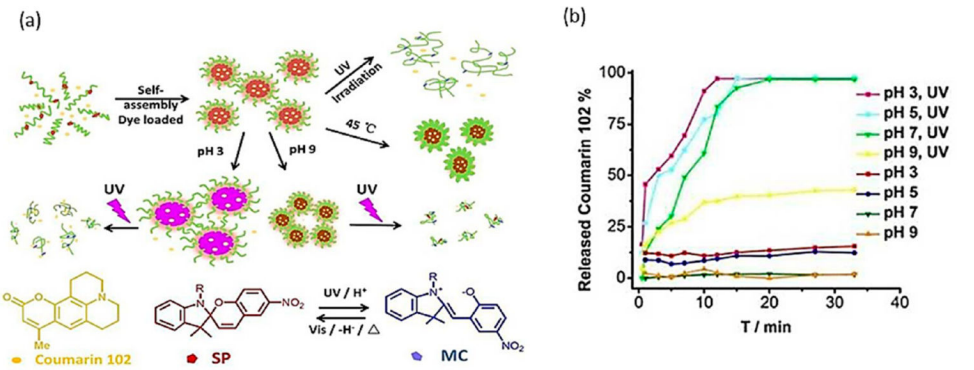

Figure 9.

(a) Scheme of the preparation and (b) release profile of coumarin 102. Under UV irradiation, dissociation of the self-assembled micelles occurred, and an acidic milieu induced swelling of the micelles with both conditions leading to drug release. The combination of pH and light stimuli gave a substantial boost to the release rate compared to that of a single pH or light trigger. In alkaline milieu or above the lower critical solution temperature (LCST), NPs shrunk with insignificant release. Reproduced from ref 159; copyright 2015, permission from The Royal Society of Chemistry.

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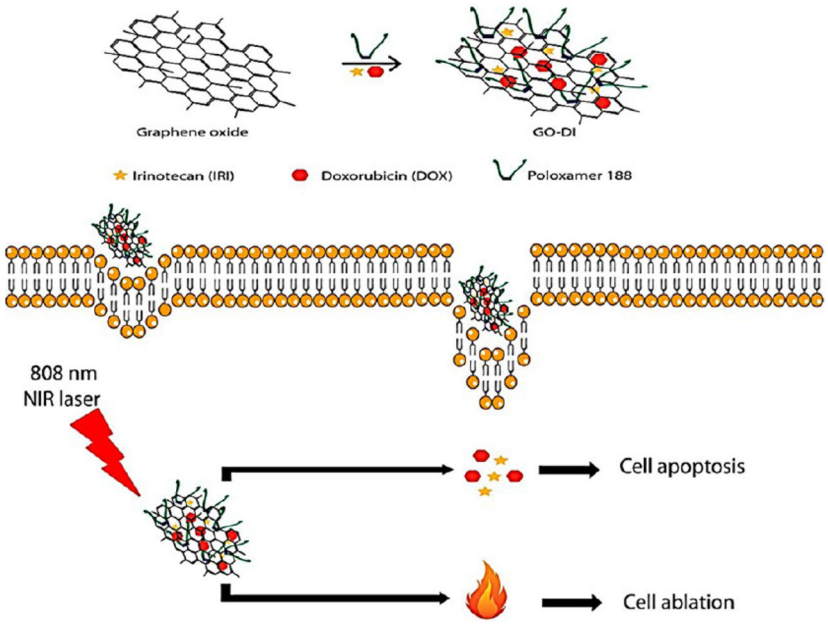

Figure 10.

Schematic illustrating the anticancer activity of DOX and irinotecan coloaded GO under NIR laser irradiation. Reprinted with permission from ref 173; copyright 2015, American Chemical Society.

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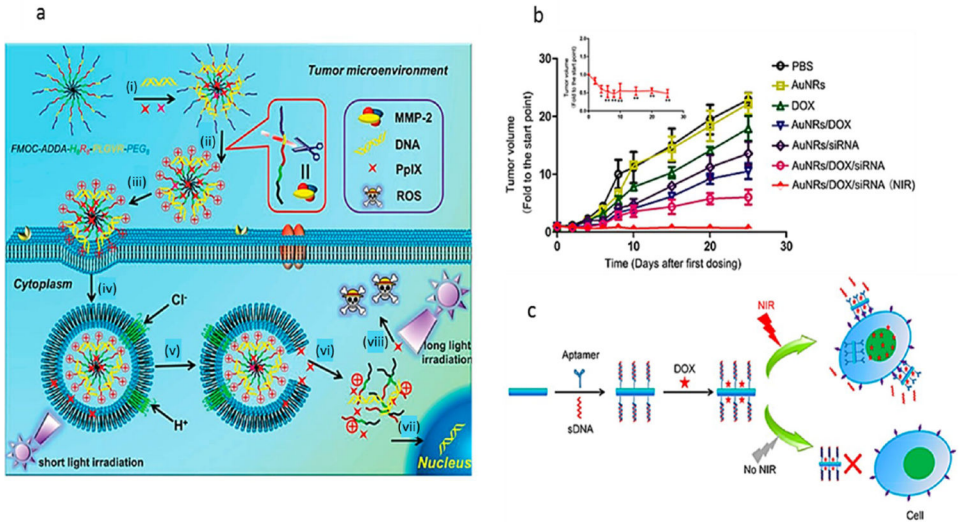

Figure 11.

(a) Nanocarrier comprised of DNA and PpIX-trapped pH-responsive chimeric peptide: (i) PpIX and DNA encapsulation, (ii) matrix metalloproteinase-2 enzyme-induced detachment of PEG, (iii) nanocarrier endocytosis facilitated by electrostatic interaction, (iv) endosome formation together with acidification, (v) “proton sponge” effect and photochemical internalization (PCI) effect-induced endosomal escape, (vi) cytoplasmic diffusion;, (vii) translocation into nucleus followed by gene expression, and (viii) long-term photoirradiation-triggered phototoxicity. Reprinted with permission from ref 209; copyright 2015, John Wiley and Sons. (b) Antitumor activity (i.e., tumor volume versus time curve) in a Panc-1 xenograft animal model under 665 nm light irradiation. Au nanorods/DOX/siRNA with NIR irradiation indicates the strongest inhibition. Reproduced from ref 210 (open access). (c) Schematic of NIR-activated single-stranded DNA (ssDNA)-caged aptamer-conjugated nanocarrier. Reprinted with permission from ref 212; copyright 2015, Springer.

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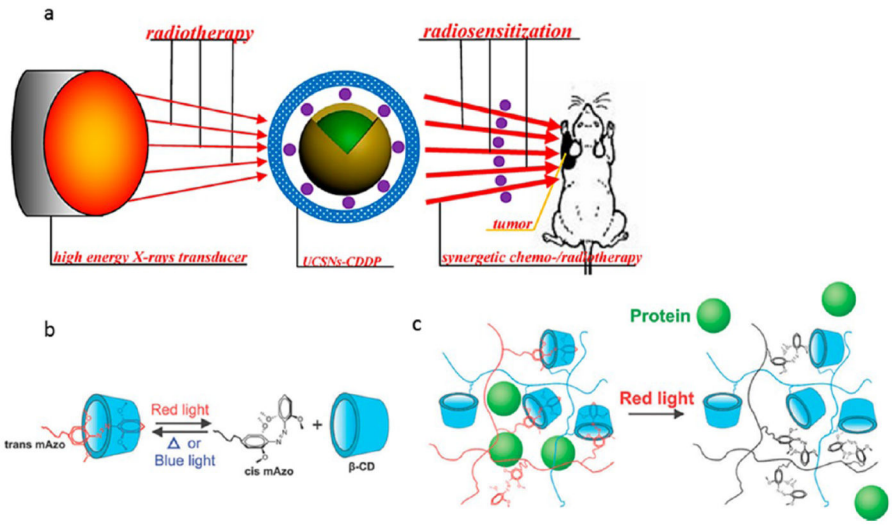

Figure 12.

(a) Radiosensitization by a UCNP core/porous silica shell nanoplatform with CDDP as a radio-sensitizer. Reprinted with permission from ref 217; copyright 2013, American Chemical Society. (b) Red-light triggered disassembly of the mAzo/β-CD complexes due to cis–trans isomerization, and their blue light/photothermal-triggered reassembly (left), followed by (c) red-light-induced protein release (right). Reprinted from ref 223; copyright 2015, permission from The Royal Society of Chemistry.

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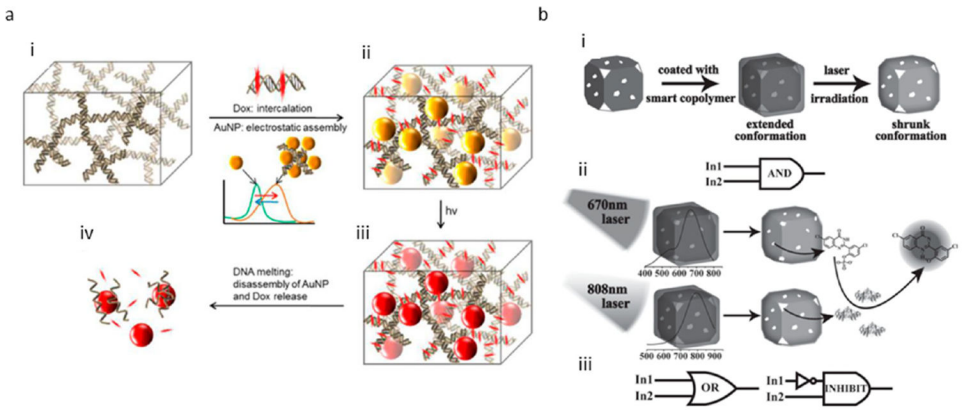

Figure 13.

(a) (i) Dgel, (ii) Dox (red dots)- and AuNP (yellow balls)-incorporated Dgel, (iii) photothermal heating (AuNPs become heated (red balls)), and (iv) heat-triggered denaturation of AuNP-Dgel inducing release of DOX. AuNP assembly and disassembly represented as a shift in absorption peak in the curve. Reproduced from ref 228; copyright 2015, permission from The Royal Society of Chemistry. (b) (i) Light-responsive AuNC copolymer and (ii, iii) its logic-gate function through NIR irradiation encoding. Reprinted with permission from ref 229; copyright 2014, John Wiley and Sons.

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Table 1

Recent Reports Regarding Combination of PDT and PTT for Cancer Therapy

nanomaterial	model drug loaded	therapeutic methods	diagnostic strategies	animal and cancer model	structure/mechanism	result	ref
gold nanoshell (GNS)	doxorubicin	PTT, chemo	optical imaging	Bel-7402 cells and nude mice with Bel-7402 tumors	GNS@ polymeric nanovesicle NIR energy converted to heat, which penetrate into cancer cells, causing rupture of the Au layer and finally triggering release of DOX inside the tumor	polymeric vehicle with compact Au layer was able to precisely release drug at the tumor site, which effectively penetrates into tumor tissue	30
Cu_xS	doxorubicin	PTT, chemo	upconversion luminescence	L929 and HeLa cells and female mouse with H22 cells	Y2O3:Yb/Er-NH_2-FA-Cu_xS FA conjugated on the surface of hollow nanospheres makes the nanocomposite recognize the targeted cancer cells	it was found that the nanosphere composite could trigger drug release under pH alteration and NIR radiation	194
self-assembled polymer	*cis*-aconitic anhydride-modified doxorubicin (CAD)	PDT, chemo	confocal imaging	A549 lung cancer cells and mice	pH sensitive nanocarrier releases CAD and Chlorin e6 photosensitizer into tumor and an NIR laser triggers the PDT	significant increase in cellular uptake and improved phototoxicity after NIR exposure	195
polymer (2-nitroimidazole coated with PVA)	enhanced DOX	PDT, chemo	confocal imaging	HeLa cells and HeLa tumor-bearing mice	core–shell structure/single oxygen release triggered by light radiation causing a localized hypoxic environment, which leads to release of DOX	an effective strategy that utilizes the combination of light-activated ROS and hypoxia modality; reduced cell viability of HeLa cells to <35% due to the PDT and chemo combination	196

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Table 2

Summary of Recently Published Reports on PDT and Theranostics with PDT and PTT

light-activated therapeutic mode	nanomaterial	biological system	laser (nm)	diagnostic strategies	result/advantage	ref
PDT	β-$SnWO_4$	in vitro: HeLa; in vivo: 4T1 breast-adenocarcinoma mouse cell line (BALB/c)	465	fluorescence microscope	good stability and high biocompatibility; significant toxicity under blue light irradiation; capable of creating equal effect to that of conventional chemotherapeutic doxorubicin with fewer side effects	200
PDT	core–shell Na-FY_4:Yb,Er,Tm@ TiO_2–Chlorin e6-TAT	in vitro: doxorubicin-resistant human breast cancer cells (MCF-7/Dox); in vivo: mice treated with MCF-7 and MCF-7/DOX	980	confocal laser scanning micros-copy	successful production of cytotoxic effects by DNA double strand breakage using dual-photosensitizer design against multidrug-resistant cancer cells; platform loaded with TAT to identify and locate the photosensitizer inside the nucleus	201
PDT	UCNPs@ TiO_2-TPP (triphenylphosphine)	in vitro: MCF-7; in vivo: xenograft mouse model (treated with MCF-7)	980	confocal fluorescence imaging	TPP is added for targeting mitochondria; ROS generated from light exposure of TiO_2 is localized in mitochondria; Domino effect caused by PDT through mitochondria-mediated intrinsic apoptotic pathway; activation of an inner membrane anion channel; opening of mitochondrial permeability transition pores; release of cytochrome *c* to cytoplasm inducing apoptosis	202
theranostics with PTT and PDT	gold nanostar (GNS)	in vivo: mice with xenograft tumors	980	surface-enhanced Raman scattering (SERS), computed tomography (CT) and two-photon luminescence (TPL) imaging	GNS probe (30 nm) can penetrate deeper into tumor and enhance tumor uptake at high injection dose; GNS shows significantly higher photon to heat conversion efficiency than that of the Au nanoshells (commonly used PTT agent) due to plasmonic effect	203
theranostics with PTT/PDT	iron oxide deposited GO (GO-IONP-PEG)	in vitro: 4T1 murine breast cancer cell line; in vivo: BALB/c mice	808	diffusion-weighted (DW)-MRI	DW-MRI as an early prognosis tool for PTT, suggesting that there is correlation between tumor growth suppression and changes in ADC value less than 48 h after PTT, which is	204

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light-activated therapeutic mode	nanomaterial	biological system	laser (nm)	diagnostic strategies	result/advantage	ref
					important for PTT treatment efficacy	
theranostics with PTT/PDT	hybrid of GO/Au (Go/Au) complex (GA) NP	in vitro: SCC7 cells (tumor and normal organs); in vivo: athymic nude mice with SCC7	808	optical and photoacoustic (PA) imaging	hybrid GA nanocomposites conjugated to MMP14 (CP)-activatable significantly enhances photoconversion efficiency and improves the PTT effect compared to those with Au or GO alone	205
theranostics with PTT/PDT	Mn-IR825@PDA-PEG	in vitro: HeLa (human cervical cancer cells), A549 (human alveolar basal epithelial cells), and 4T1 (murine breast cancer cells); in vivo: injected 4T1 into Balb/c mice	808	MRI	self-assembled PTT and MRI agents building a carrier-free high loading platform; rapid renal excretion (reducing long-term toxic effect); efficient passive tumor homing and PTT ablation	206
theranostics with PTT/PDT	Chlorin e6@Au nanoclusters-PEG_{2K} -FA	in vitro: MGC-803; Iin vivo: MGC-803 tumor-bearing nude mice	wide range	fluorescence microscope	improved cellular uptake and effective PDT therapy result; improved penetration into tumors and retention behavior of tumor; capable of maintaining stealth and renal clearance from reticuloendothelial system	207
theranostics with PTT/PDT	core–shell UCNPs@ TiO_2	in vitro: HeLa; in vivo: HeLa cells injected in mouse	980	MRI CT	better penetration due to the use of NIR instead of UV light; platform can act as a biocompatible photosensitizer to successfully generate ROS upon NIR radiation causing cell death; capable of MR and CT imaging	208