Overview

Photoactivated drug delivery and bioimaging

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Among the various types of diseases, cancer remains one of the most leading causes of mortality that people are always suffering from and fighting with. So far, the effective cancer treatment demands accurate medical diagnosis, precise surgery, expensive medicine administration, which leads to a significant burden on patients, their families, and the whole national healthcare system around the world. In order to increase the therapeutic efficiency and minimize side effects in cancer treatment, various kinds of stimuli-responsive drug delivery systems and bioimaging platforms have been extensively developed within the past decades. Among them, the strategy of photoactivated approach has attracted considerable research interest because light enables the precise control, in a highly spatial and temporal manner, the release of drug molecules as well as the activation of bioimaging agents. In general, several appropriate photoresponsive systems, which are normally sensitive to ultraviolet (UV) or visible light irradiation to undergo the multiple reaction pathways such as photocleavage and photoisomerization strategy etc. have been mainly involved in the light activated cancer therapies. Considering the potential issues of poor tissue penetration and high photoctotoxicity of short wavelength light, the recently emerged therapies based on long-wavelength irradiation, e.g., near-infrared (NIR) light (700–1000 nm), have displayed distinct advantages in biomedical applications. The light irradiation at NIR window indicates minimized photodamage, deep penetration, and low autofluorescence in living cells and tissues, which are of clinical importance in the desired diagnosis and therapy. In this review article, we introduce the recent advances in light-activated drug release and biological imaging mainly for anticancer treatment. Various types of strategies such as photocage, photo-induced isomerization, optical upconversion, and photothermal release by which different wavelength ranges of light can play the important roles in the controlled therapeutic or imaging agents delivery, and activation will be systemically discussed. In addition, the challenges and future perspectives for photo-based cancer theranostics will be also summarized.

How to cite this article:
WIREs Nanomed Nanobiotechnol 2016. doi: 10.1002/wnan.1408

INTRODUCTION

Cancer remains one of the extremely complex diseases that challenge the people's lives in all age groups around the world.[1] Currently, several standard approaches for cancer therapy have been well developed which include surgery, chemotherapies, and radiotherapies.[2,3] Although surgery is the preferred treatment method for many cancers, it remains a big challenge to unambiguously distinguish between normal and cancer tissues during surgery, so as to achieve complete removal of cancer tissues and

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Conflict of interest: The authors have declared no conflicts of interest for this article.

to minimize recurrences. Alternative treatments including traditional chemotherapy and radiotherapy have been proved effective, both the methods, however, are also severely limited by their systematic toxicity and lack of tumor selectivity, which may result in the damage to both cancerous and healthy tissues.[4] Moreover, toward the processes of targeted chemotherapy and radiotherapy, another major issue is their inabilities to specially deliver the sufficient amount of therapeutic reagents into the disease sites.[5] Therefore, the rationales for the design of 'smart' tumor environment responsive systems that can improve the capability of therapeutic molecules to reach their designated cell targets will be of significance in clinical practice.

So far, numerous stimuli-responsive platforms toward cancer therapy and relevant bioimaging have been extensively investigated both *in vitro* and *in vivo* over the past few decades.[3,6,7] With the latest advances of various stimuli-responsive carriers, the controllable delivery and release of sufficient therapeutic or imaging reagents at the targeted tumor areas have been made highly possible.[8] Currently, a variety of carrier systems with their sensitive activities to respond to internal stimulus conditions such as pH, temperature, enzyme, and redox reactions, or external stimuli including heat and light, have been well-demonstrated.[9,10] Among these different stimulation approaches, light has attracted much more attention and has been substantially studied within the latest decades. Typically, as an external physical stimulus, light can be easily localized at the targeted site in a highly spatial and temporal precision upon the irradiation at a specific wavelength.[11] Besides unique advantages of light irradiations to spatiotemporally direct the theranostic reagents into targeted areas *in vitro* and *in vivo*, the photomediated tumor therapy strategies have also been found noninvasive and they may thus demonstrate minimal toxicity to normal tissue. Moreover, thanks to the rapid development of nanotechnologies, a variety of nanomaterials-based photoactive carriers including nanospheres, nanocapsules, micelles/liposomes, and polymers are also gaining enormous interests recently, mainly owing to their promising ability to penetrate the tumor fenestrated endothelium through the enhanced permeabilization and retention (EPR) effect,[12] and more significantly, due to their spatiotemporal precision or photothermal transduction capability to specially direct the theranostic reagents to the tumor lesion upon light irradiations.[13,14]

In general, the successful photoactivated cancer therapy and imaging is mainly governed by the applied light source and the selected reaction systems that are light responsive. So far, the commonly used exposure wavelengths for cancer therapy and imaging usually rely on the light ranged from ultraviolet (UV) (<400 nm), visible (400–700 nm) as well as long wavelength NIR region (700–1000 nm).[15–17] As for the light responsive reaction systems, they will mostly involve in small organic photosensitive molecules or multifunctional nanomaterials with unique optical properties. In this review, we will briefly summarize the various strategies toward the targeted cancer therapy and related imaging *in vitro* and *in vivo*. The overview of the discussions will be organized with three sections, mainly according to the natures of different light sources with the wavelength ranged from UV, visible to NIR window. Moreover, their unique advantages, *in vitro* and *in vivo* biomedical applications, potential technical limitations, and future perspectives will also be introduced in details on the basis of the samples reported within the past few years.

PHOTOACTIVATED DRUG DELIVERY AND BIOIMAGING ON THE BASIS OF UV LIGHT (<400 nm)

So far, the commonly used light sources in photoinduced chemotherapy mainly include the light energy at UV or short wavelength range, which are mainly attributed to the reason that most of the existing photolabile or photoactivatable systems are sensitive to the irradiation within this wavelength range. In this section, the commonly established UV or relevant short-wavelength light induced anticancer therapy, and imaging will be first summarized. As the examples, two methods on the basis of photoactivation of caged molecules and the controlled drug delivery through the photoactivated structural isomerization will be introduced.

UV Light–Mediated Photoactivation of Therapeutic Molecules through the Photocaged Approach

The first notable strategy toward the photoactivated therapy is the photolysis of 'photocaged' molecules, in which a beam of light (usually at short-wavelength UV window) will be utilized to activate a photocleavable functional group that blocks the activities of therapeutic molecules, thus achieving the controlled delivery or release of these molecules in living systems. In line with this direction, several photocaged systems based on chemical groups such as *o*-nitrobenzyl,[18,19] pyrenylmethyl ester,[20]

coumarinyl ester[21,22] etc. have been established for spatiotemporally regulating biomolecule activities, real-time monitoring cell trafficking, and controlled release of therapeutic molecules *in vitro* and *in vivo*.[23] Additionally, such chemically photocaged approach has also been documented for rational design of photoactivable bioluminescent probes for the remote control of optical imaging in living subjects.[24] For instance, Xing et al. presented a series of stable and novel photo-releasable firefly D-luciferin molecules to real-time image luciferase reporter *in vitro* and *in vivo* (as shown in Figure 1). Typically, the bioactivity of D-luciferin was initially deactivated because the 6-hydroxy group in luciferin structure has been masked by the different nitrobenzene caged groups. UV illumination (e.g., at 365 nm) of these photocaged molecules led to the rapid release of caged moiety and recovered the activity of D-luciferin, which thus conferred significant bioluminescence imaging in living mice. Similarly, Lu et al. demonstrated an effective method for stabilizing the substrate strand of a DNAzymes in 2014.[25] In this design, a 2′-*o*-nitrobenzyl adenosine (terms as photocaged adenosine) was used in the place of normal adenosine at the cleavage site. The substrate strand was functionalized with a fluorophore at the 5′ end and a quencher at the 3′ end. This caged DNAzymes was stable in buffer and human serum solutions. However, upon the UV light irradiation, followed by the addition of Zn^{2+} ions, the caged group would be cleaved and the enhanced fluorescence intensity was observed, clearly indicating the recovery of the DNAzymes. Furthermore, this strategy could also been expended to other DNAzymes strands to effectively sense different types of metal ions in living systems.

Besides the promising usage in bioimaging, this UV light-controlled photocaged strategy has also been extensively investigated for the controlled delivery of specific anticancer reagents including doxorubicin (Dox), paclitaxel (Taxol), and camptothecin (CPT) etc. In 2012, Dcona et al. developed an efficient method to deliver Dox into esophageal adenocarcinoma cells through the concept of photocaged permeability.[26] In order to prevent the nonspecific diffusion of Dox molecules into cell structures, the EDANS fluorophore (5-((2-aminoethyl) amino) naphthalene-1-sulfonic acid), known as sulfonic acid to hinder cellular entry, was applied to conjugate with Dox through a light-cleavable nitroveratryl linker. When the Dox–EDANS conjugate was incubated with cells in the dark condition, very low fluorescence intensity was observed in living cells. However, upon treatment with UV illumination at 365 nm, the cell samples were found to exhibit significant Dox fluorescence in the nucleus, clearly demonstrating the promising drug activities to inhibit tumor cells. In addition to small organic molecule-based drug delivery, this photocaged strategy can also be proposed to functionalize the nanostructures toward light-mediated drug delivery. For example, Yeh et al. recently designed a photocaged nanoconjugate through attaching the 2-nitrobenzylamine (NBA) caged folate molecule onto the Au nanopaticle (Au NPs) surface[27] (Figure 2). This nanoconjugate showed high-binding activity to KB cells under light exposure. Moreover, in order to achieve light-controlled drug release, such photocaged folate moiety was further conjugated with a biodegradable PLGA@lipid nanocarrier, which has been encapsulated with the anticancer Taxol drug molecules. Under UV irradiation

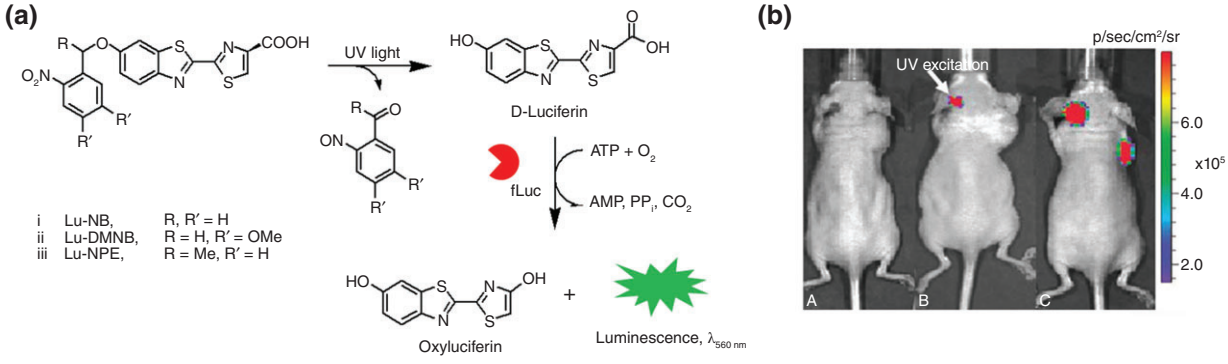

FIGURE 1 | UV light-triggered the release of D-luciferin for real-time bioluminescence imaging. (a) Schematic illustration of the UV-induced release of D-luciferin from the nitrobenzene caged D-luciferin derivatives. (b) In vivo bioluminescence imaging of C6-fLuc tumor-bearing mice after injection with A: compound iii without UV irradiation; B: compound iii with UV irradiation; C: D-luciferin only. (Reprinted with permission from Ref 24. Copyright 2009 the Royal Society of Chemistry).

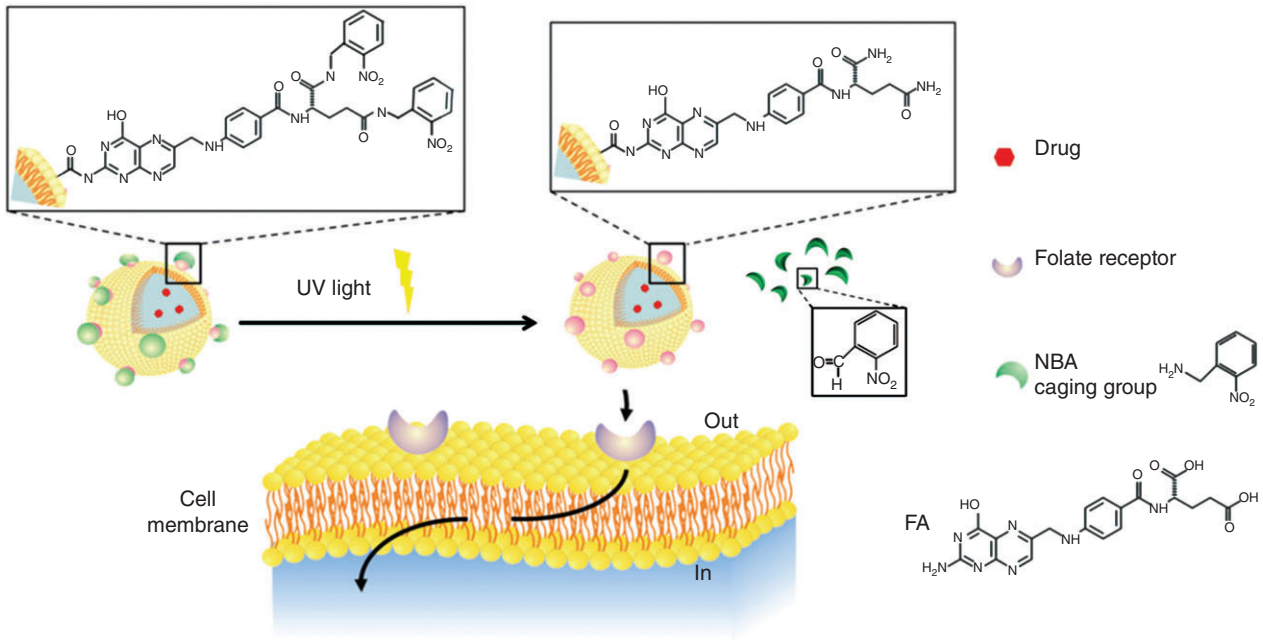

FIGURE 2 | Schematic illustration of process for the photocaged folate nanoconjugates activated by ultraviolet irradiation to remove the caging groups, and then to target cancer cells. (Reprinted with permission from Ref 27. Copyright 2012 John Wiley & Sons, Inc)

(using a Hg lamp), the as-synthesized caged folate/PLAG@lipid nanocarriers indicated highly effective damage to KB tumor cells. As a control, the similar experiments were also conducted by incubation of KB cells with caged folate/PLAG@lipid nanocarriers but no UV light irradiation. The high cell viability was still observed which clearly revealed that the controlled release of Taxol molecules was mainly triggered by UV light illumination. Normally, the successful therapeutic localization and controlled drug delivery to specific biological targets are resort to the effective integration of unique nanocarriers with druggable payload molecules. Except for the conventional nanomaterials used for the light-controlled biomedical applications, the photoactive platforms based on intrinsic biodegradable molecules (e.g., DNA, proteins etc.) have also been utilized. For example, Tan et al. have recently demonstrated a novel self-immolative DNA-based nanostructure to specifically regulate the release of anticancer drug molecules.[28] As proof of concept, the hydrophobic CPT anticancer drug molecules were first coupled with DNA through the photolabile 2-nitrobenzyl ether moiety to form the amphiphilic DNA–CPT conjugate, which can further self-assemble into micelle structures in aqueous solution. Upon UV irradiation, the 2-nitrobenzyl group could be photocleaved, as a consequence, the micellar nanostructures could be rapidly degraded and therefore release the free CPT drug accordingly.

UV Light-Triggered Photoisomerzation for the Controlled Photoactivation of Drug Delivery

Different from the irreversible photorelease in the photocaged strategy, another mostly applied design for the controlled drug delivery has also been well developed, which predominantly consists of a reversible photoisomerization chemical group to link with the carrier system. Upon UV exposure, these photosensitive moieties could undergo reversible *cis–trans* light-switches and resulted in the conformational exchanges between inactive and active states, and thus controlled the drug release from the carriers. So far, several photoisomerization molecules including azobenzene,[29–31] spiropyran,[32,33] and dithienylethene[34,35] have been studied for the UV light-triggered drug delivery and imaging. Recently, Yuan et al. have designed a light-manipulated delivery cargo on the basis of DNA functionalized mesoporous silica nanoparticles (MSNs).[36] Basically, two different DNA strands were applied in their system: (1) one single-strand DNA labeled with a quencher (called arm-DNA) was first conjugated to isocyanato-MSNs surface through its amino group at the 3′ end and (2) a complementary DNA structure was separately modified by azobenzene group (called azo-DNA) and a fluorophore. Upon mixing of two strands of DNA, the double strand DNA was then immobilized on the surface of MSNs so as to cap the

guest Dox molecules within the nanopores. The living cell experiments demonstrated that the azo-DNA modified MSN nanocarriers exhibited good biocompatibility and the anticancer Dox molecules could be released upon UV light irradiation to change the conformation of azobenzene group. Moreover, besides Dox drug molecules, such unique UV light-responsive nanodevice also allowed to incorporate many other therapeutic guest molecules and can be applied in a wide range of desired applications.

Another well-known photochromic molecule, spiropyran, which can respond to light irradiation has also been well established for the purpose of the photo-triggered delivery.[37] For instance, in 2012, Daniel et al. demonstrated a novel nanocarrier through direct precipitation of spiropyran moiety with hydrophobic alkyl chains, which could further self-assemble into nanoparticles (SP NPs) in aqueous solution.[38] In order to improve the NPs stability and loading efficiency, the DSPE–PEG complex, (1, 2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-carboxy (polyethylene glycol)-5000), was then added to form hybrid SP/lipid-PEG NPs. Upon UV light irradiation, the maximum absorption of the prepared nanoparticles was found to shift from 350 to 551 nm. Meanwhile, the average size of NPs was reduced from 143.2 ± 2.1 to 47.1 ± 1.3 nm, suggesting that the NPs were sensitive to UV light illumination. Additionally, such promising light responsive NPs could also encapsulate drug molecules (e.g., paclitaxel and doxorubicin etc.) and fluorescent probes (e.g., rhodamine B, coumarin 6 etc.), and could therefore provide the photo-triggered drug diffusion and fluorescence imaging in different diseases states including cancer.

PHOTOACTIVATED DRUG DELIVERY AND BIOIMAGING ON THE BASIS OF VISIBLE LIGHT (400–700 nm)

Currently, considerable attentions have been paid to the development of light-controlled therapeutic systems mainly owing to the appealing advantages of light activation including spatiotemporal precision, easy manipulation, and long history application as a therapy. So far, UV light excitation remains the most commonly used strategy for the photo-induced therapeutic reagents and imaging probe release *in vitro* and *in vivo*.[39] Although its initial success in principle, the widely accepted disadvantages, which UV light has poor capability of tissue penetration and it often inflicts potential biological damage,[40] may greatly limit its further applications in biomedical fields.[41,42] In terms of these technical barriers, the longer wavelength light exposure at visible range, which can cause less damage to tissue as compared with UV light,[43–46] may serve as an alternative option and has been proposed recently for the light-activated drug delivery.

Visible Light-Induced Biological Agents Release through the Photoactive Small Molecule Moieties

By right, a variety of photoresponsive organic moieties that include but are not limited, vitamin B_{12} derivatives,[17,47,48] ruthenium complexes,[49,50] and trithiocarbonates[43] have been reported for visible light-triggered release. Recently, Lawrence's group reported a series of vitamin B_{12} derivatives for tunable visible light-controlled drug activation and fluorescence imaging in living cells[17] (as shown in Figure 3(a)). Since the cobalt–alkyl (Co-C) bond in vitamin B_{12} is quite weak (cleavage energy < 30 kcal mol^{-1}), all the wavelengths light could be absorbed by the corrin ring (e.g., 330–580 nm) and they could easily proceed the photocleavage reactions. Therefore, upon appending different fluorophores to the corrin ring structure, the corresponding wavelength light will be used to separate the Co-appended ligand from vitamin B_{12} derivatives. With this information in hand, in 2012, the same group designed another unique TAMRA-appended cobalamin conjugate (named as Cob-4), which was found to be selectively photolyzed at three different wavelengths (e.g., 360, 440, and 560 nm).[51] In this Cob-4 probe structure, cobalamin could act as a quencher to deactivate the fluorescence from TAMRA. The other two light-responsive components, termed as NB-1 and coum-3 (TAMRA/rhodamine fluorophore linked with QSY7 quencher through nitrobenzyl group/amino coumarin, to respond 360 and 440 nm light irradiation, respectively), were used as profluorescent reporters for comparing their response to different wavelength light irradiation (Figure 3(b)). Interestingly, in the coexistence of other two components, only Cob-4 could be photolyzed by the light exposure at 560 nm (visible light region), whereas coum-3 and NB-1 components could experience photolysis only at a short-wavelength light illumination, e.g., 360 and 440 nm, respectively. The designed Cob-4 conjugate showed effective cellular permeability and could be applied for the fluorescence imaging analysis in living HeLa cells upon response to visible light excitation (Figure 3(c)). Moreover, through the binding of long-

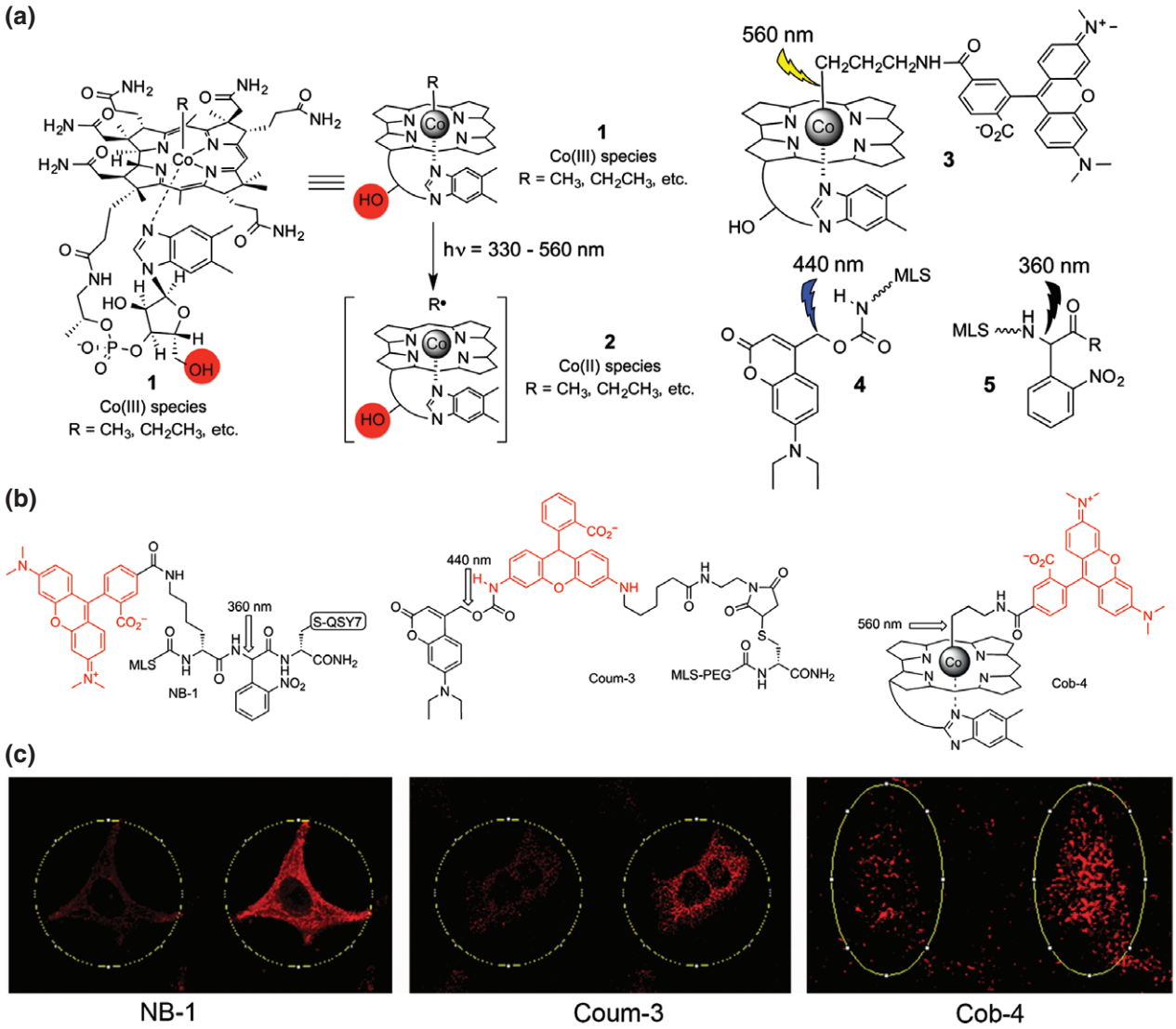

FIGURE 3 | (a) Visible light-responsive cobalt complexes moieties and their applications. (Reprinted with permission from Ref 17. Copyright 2015 American Chemical Society). (b) Chemical structures of the photoresponsive compounds, where TAMRA (red) in NB-1 (360 nm), Rhodamine 110 (red) in coum-3 (440 nm), TAMRA (red) in Cob-4 (560 nm). (c) NB-1, Coum-3, and Cob-4 incubated with HeLa cells before (left) and after (right) photolysis at 355, 440, and 559 nm, respectively. (Reprinted with permission from Ref 51. Copyright 2012 John Wiley & Sons, Inc)

wavelength fluorophores, such as atto725 and Alexa700, to the corrin ring, the specific light-responsive wavelength can be further tuned to red and even to NIR region. Such long-wavelength light-controlled vitamin B_{12} derivatives can thus guarantee broad applications toward real-time fluorescence imaging of enzyme activity, screening of inhibitor molecules, and monitoring relative biological pathways *in vitro* and *in vivo*.[51] Moreover, it is also worthy to notify that such visible light-activated process has been also investigated in photodynamic therapy (PDT) study, one particular anticancer treatment involving in the usage of photosensitizers (PS) to generate reactive oxygen species (ROS) upon light exposure at a suitable wavelength. These ROS demonstrates effective cytotoxicty and would be able to destroy tumor cell structures, and thus achieve the targeted cell death *in vitro* and *in vivo*.[52,53] So far, some PS molecules have been found to respond to visible light irradiation and have already been applied for visible light-activated PDT. By taking the ruthenium complexes as example, Tassiele et al. recently synthesized a new type of trinuclear complexes (e.g., $[Ru(pc)(pz)_2\{Ru(bpy)_2(NO)\}_2]$ $(PF_6)_6$ etc.) and investigated their photoactive biological properties in B16F10 living cells.[54] Upon visible light

irradiation at 660 nm, nitric oxide could be released from the as-prepared nitrosyl ruthenium complexes which indicated promising PDT activity in B16F10 cells.

Visible Light-Induced Biological Agents Release through the Photoresponsive Nanocarriers

Besides light-controlled release based on small organic molecules, different types of functionalized nanostructures have also been developed for visible light-triggered drug delivery in the past decades. Lin's group first reported a visible light-induced release strategy by using MSNs.[49] In this typical study, the cargo dye molecules, sulforhodamine 101 (Sr101) was firstly loaded into the mesoporous of MSN and was then subsequently trapped inside with the complex of $Ru(bpy)_2(PPh_3)$. The formed coordination bonds between Ru(II) and mercaptopropyl moieties from silica surface would prevent the diffusion of Sr101 dye molecules into solution. Under visible light irradiation at 455 nm, the Ru-S bond could be cleaved and another new Ru-O linkage with water molecules was formed concurrently, which therefore removed the entrapped moieties, and as such, resulted in the effective release of cargo Sr101 molecules. Apart from the MSN nanostructures, other types of nanoplatforms, e.g., TiO_2 nanotube have also been established for the visible light-controlled drug delivery. For instance, as proof-of-concept, Xu et al. designed a hydrophilic TiO_2 nanotube-based platform for the storage of drug ampicillin molecules by using the hydrophobic AuNPs as the caps on the surface.[55] In this rational design, the AuNPs could also act as photocatalyst, which can generate active radical species, e.g., $O^{\cdot}_2$ or $OH^{\cdot}$, under visible light illumination to cleave the linkage group between AuNPs and TiO_2 nanotube. So the payload molecules inside the TiO_2 nanotube could diffuse into the surroundings and exhibited the promising drug activity. Moreover, Au NPs alone have also been proposed for visible light-induced drug release mostly owing to their unique exothermic properties after light adsorption.[56] For example, Luo et al. have fabricated a 'smart' light-responsive drug delivery by using DNA-coated Au NPs.[57] In this design, the hairpin DNA (hpDNA) was first covalently conjugated onto the surface of Au NPs. The anticancer drug Dox was then chosen to reversibly intercalate into the adjacent base pairs located in hpDNA structures. When irradiated with visible light (e.g., at 532 nm, corresponding to the plasmonic resonance wavelength of Au NPs), the generated heat from Au NPs would lead to the rapid release of Dox molecules from the nanocarriers.

PHOTOACTIVATED DRUG DELIVERY AND BIOIMAGING USING NIR LIGHT (700 nm–1000 nm)

The photoactivated delivery strategies could enhance therapeutic quality by preventing nontargeted effect through the spatial and temporal precision of light irradiation. Currently, the light irradiations at UV (<400 nm) and visible (400 ~ 700 nm) wavelengths are the most commonly excitation sources for the photo-controlled therapy and imaging *in vitro* and *in vivo*. It is well established that the lights with short wavelength may bear enough energy to induce disruption of chemical structures by either breaking a covalent bond or causing *cis–trans* isomerization. But just like the coins having two sides, despite their promising photoactivation applications, these short-wavelength light illuminations also displayed limited tissue penetrating capability, high autofluorescence background, and potential phototoxicity, especially for the light exposure within UV region. Therefore, the development of more reliable alternatives that enable a high depth tissue penetration and more precise control of photoactivation reaction as well as minimum cellular damage will be of clinical importance. Fortunately, one emerging option to match such demanding request is to utilize illumination light at NIR window (700 ~ 1000 nm).[58] As shown in Figure 4, the major light absorbers in living systems including water, lipids, and some intrinsic proteins such as hemoglobin (Hb) and oxyhemoglobin (HbO_2), usually demonstrate minimum light absorption in NIR range.[59,60] The light excitation at NIR window may exhibit unique advantages toward deep tissue penetration, low fluorescence background, and limited photo damage, which could thus greatly benefit photoactivated delivery in living systems. So far, a variety of strategies have been suggested for targeted cancer therapies and imaging on the basis of NIR light-mediated platforms. One commonly established strategy of using NIR light in biomedicine is to utilize photosensitive nanoplatforms, which can convert long-wavelength NIR light irradiation into UV or visible emissions and thus spatiotemporally trigger the release of payload reagents into living systems.[61,62] Such unique NIR light-mediated process has been well proved inside the living subjects that usually may involve in the usage of new types of functional materials, e.g., upconversion nanoparticles (UCNPs) etc.[63,64] Interestingly, besides the NIR light-

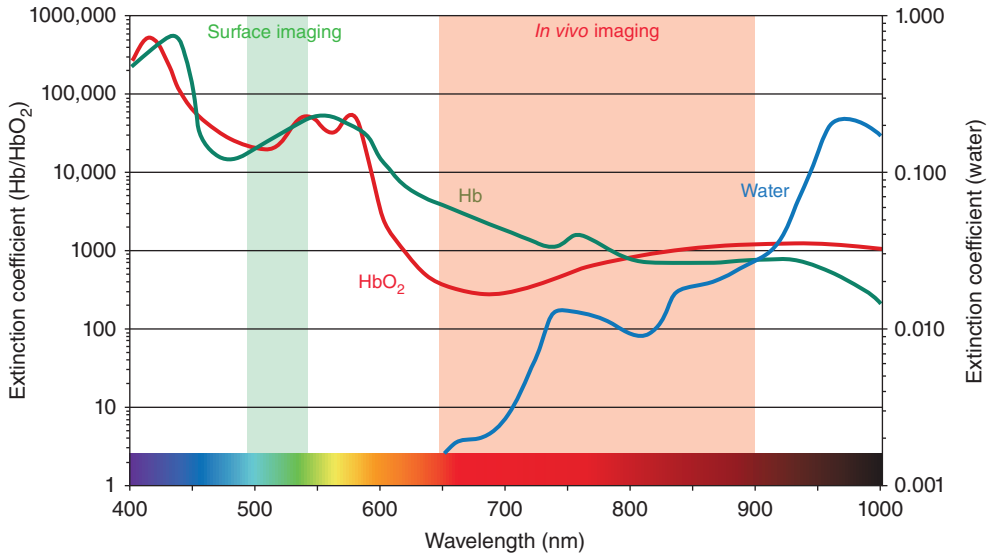

FIGURE 4 | Extinction coefficient value of water, hemoglobin, and oxyhemoglobin. Light absorption of these major absorbers can be avoided by using short-wavelength light. (Reprinted with permission from Ref 60. Copyright 2010 American Chemical Society)

photoactivation process to control the release therapeutic molecules or imaging probes, such upconversion particle system has been also found useful for PDT, in which the NIR light-responsive UCNPs can conjugate with PS reagents. Upon NIR light illumination, the PS molecules from UCNPs activated by the upconverted emissions will be able to produce ROS species, which therefore realize the targeted therapeutic effects *in vitro* and *in vivo*.[4] Another more commonly applied strategy for NIR light-activated therapeutic delivery is mainly based on the concept of photothermal effect. For example, some photoresponsive nanostructures demonstrate unique capabilities to transfer NIR light energy to heat. The localized temperature increase caused by the light-transduced heat effect would trigger the drug release from the nanostrucutres to the tumor sites, and thus achieve the targeted cancer therapy accordingly.[58]

NIR-Triggered Therapeutic Agents Release Based on the Upconverted Emissions at UV or Visible Window

UCNPs are rare earth lanthanide-doped nanoparticles, which can serve as phototherapeutic platforms for the controlled delivery of drugs and imaging probes when triggered by NIR light (usually at 980 nm). Typically, UCNPs have unique optical upconversion properties because they can convert low energy NIR light irradiation into high energy UV or visible light.[65,66] Such impressive function has been realized through the nonlinear multiphoton processes.[67,68] Moreover, the NIR light responsive UCNPs could be easily functionalized with therapeutic reagents or biomolecules on the surface,[69] which can therefore greatly benefit the photoactivated cancer treatment in living subjects. To this direction, as one pioneering study, in 2010, Branda et al. firstly reported the functionalized $NaYF_4$:Tm/Yb UCNPs with 3′,5′-di(carboxymethoxy) benzoin acetate conjugated on the surface.[70] When exposed with NIR light at 980 nm, one of the converted emissions at 290 nm would photocleave the conjugated molecule to produce 5, 7-di(carboxymethoxy)-2-phenyl-benzo[*b*]furan. Despite impressive in principle, however, this strategy was only carried out in organic CH_3CN solution which could be hardly applied in biomedical applications. Subsequently, the same group further developed polymer-conjugated UCNPs with photocleavable *o*-nitrobenzyl moieties in particle structures.[71,72] Under 980 nm laser irradiation, the *o*-nitrobenzyl groups will be cleaved by the upconverted emission at 350 nm, which resulted in the disruption of the polymer micelles and initiated the release of the encapsulated payloads into aqueous solution.

These successful pioneering investigations provided the great possibility for NIR light-induced drug delivery and bioimaging in living cells and *in vivo*.[73] In 2011, Xing et al. developed a novel NIR light-triggered UCNPs nanoplatform for the remote control D-luciferin delivery.[74] In their design, the silica-coated UCNPs were selected with the surface covalently linked by *o*-nitrobenzyl photocaged D-luciferin. Upon long-wavelength NIR irradiation at 980 nm, the converted emission at 365 nm cleaved the photocaged group and induced the release of

D-luciferin, which resulted in the significant bioluminescence enhancement upon the reaction with the firefly luciferase (fLuc) reporter enzyme *in vitro* and in living animals. Based on the similar strategy, recently they also developed *o*-nitrobenzyl photocaged UCNPs systems toward the NIR light-controlled anticancer drugs release and activation of siRNA to knock down enhanced green fluorescent protein (EGFP) expression for intracellular imaging studies.[75,76] Besides this *o*-nitrobenzyl photocage moiety, azobenzene functional groups have also been applied for NIR-induced anticancer drug delivery. For example, Shi et al. reported a mesoporous silica-coated UCNPs (UCNP@mSiO_2) nanocarrier which was functionalized with azobenzene (azo) group and the anticancer drug Dox was loaded into UCNP@m-SiO_2 structure.[77] Under 980-nm laser excitation, the generated UV emission (at 350 nm) induced the *trans–cis* photoisomerization of the azo groups and thus led to the release of Dox molecules. The promising fluorescence imaging and drug activity in HeLa cells indicated that the dosage of the drug release can be well controlled by NIR light exposure.

Apart from the light-induced chemical reactions for photoactivated drug release, the upconverted UV emissions from UCNPs have been also employed as effective triggers to directly activate transition metal-based antitumor drugs. For example, around the same time, Lin's and Xing s groups have independently developed the novel NIR light-activated anticancer drug delivery platforms by integrating a specific antitumor Pt(IV) prodrug with 980-nm lanthanide-doped UCNPs.[78,79] In Lin's design, the novel photoactive Pt(IV) prodrug, *trans*, *trans*, *trans*-[$Pt(N_3)_2(NH_3)(py)(O_2CCH_2CH_2CO_2H)$] was conjugated with core-shell $NaYF_4$:Yb/Tm@$NaGdF_4$/Yb-UCNPs complex. Such prodrug UCNPs nanomedical system could not only exhibit higher *in vivo* anticancer efficacy upon 980-nm laser irradiation. Moreover, it could also supply a new way to carry out tri-modality imaging of cancer development and therapy in living system (Figure 5). While, in Xing's system,[78] the unique nanoplatform was based on the silica-coated UCNPs (UCNPs@SiO_2) that served as nanocarriers to combine with Pt(IV) complex (*trans*, *trans*, *trans*-[$Pt(N_3)_2(OH)(O_2CCH_2CH_2CO_2H)(py)_2$]) through the covalent bonding. Meanwhile, another apoptosis imaging peptide probe, consisting of a fluorescence donor (Cy5) and a quencher (Qsy21), was further anchored to the same UCNPs platforms. After light exposure at 980 nm, the upconverted UV emission locally activated the Pt(IV) prodrug and efficiently induced cell cytotoxicity in cancer cells. More importantly, the activated apoptosis enzyme cleaved the peptide and thus recovered fluorescence signal in the treated cancer cells. This prodrug UCNPs platform provided a new approach for the controlled activation of the Pt(IV) at the localized disease area. Moreover, it could also be employed simultaneously as tumor markers for real-time imaging and earlier evaluation of anticancer treatment efficiency.

Besides the photoactivation processes based on the upconverted emissions to trigger anticancer drug delivery, the similar pathway through the visible emissions converted from NIR light responsive UCNPs have been also proposed to contribute the anticancer therapy, especially for PDT application. Recently, Zhang et al., for the first time, demonstrated one UCNPs-based anticancer treatment by combination of PS reagent, merocyanine 540 (MC540) with silica-coated $NaYF_4$:Yb/Er UCNPs. The particles were further modified with antibody to enhance their tumor uptake and therapeutic effect.[80] After 45 min of 980-nm laser irradiation, this UCNPs platform exhibited primary PDT effects on MCF-7/AZ cancer cells. More recently, Zhang's group reported a core-shell silica-coated UCNPs nanospheres by incorporating two types of PS molecules, Zinc phthalocynanie (ZnPc), and MC540, into one single particle platform. Upon the surface coating with tumor affinity ligand, folic acid, and followed by 980-nm laser illumination, the significant tumor regression was easily observed *in vitro* and in living mice.[81] Although various UCNPs-silica or polymer nanocomposites have been broadly constructed toward *in vitro* and *in vivo* NIR-triggered PDT,[82,83] the lower capacity of PS loading and local hypoxia in tumor environments remained the unfavorable barriers to influence the treatment efficacy of PDT. To this end, Chen's group very recently proposed a strategy to construct a novel rattle structure with a cavity between UCNPs surface and organosilica shell.[84] Such rattle and aromatic framework would accommodate more PS molecules, and meanwhile, shorten the distance between UCNPs and PS which therefore greatly facilitated energy transfer and improved the PDT therapeutic effect. In addition, based on the concept that some bioreductive prodrugs activated only at low-oxygen conditions have been identified to be highly cytotoxic under hypoxia in tumors, Shi et al. recently demonstrated a double silica-shelled Gd^{3+}-coated UCNPs structure capable of codelivering PS reagents (e.g., silicon phthalocyanine dihydroxide, SPCD) and a bioreductive prodrug, tirapazamine (TPZ).[85] Upon 980-nm laser exposure, a synergetic *in vivo* cancer therapy could be first achieved under normal oxygen environment, then immediately followed by the induced

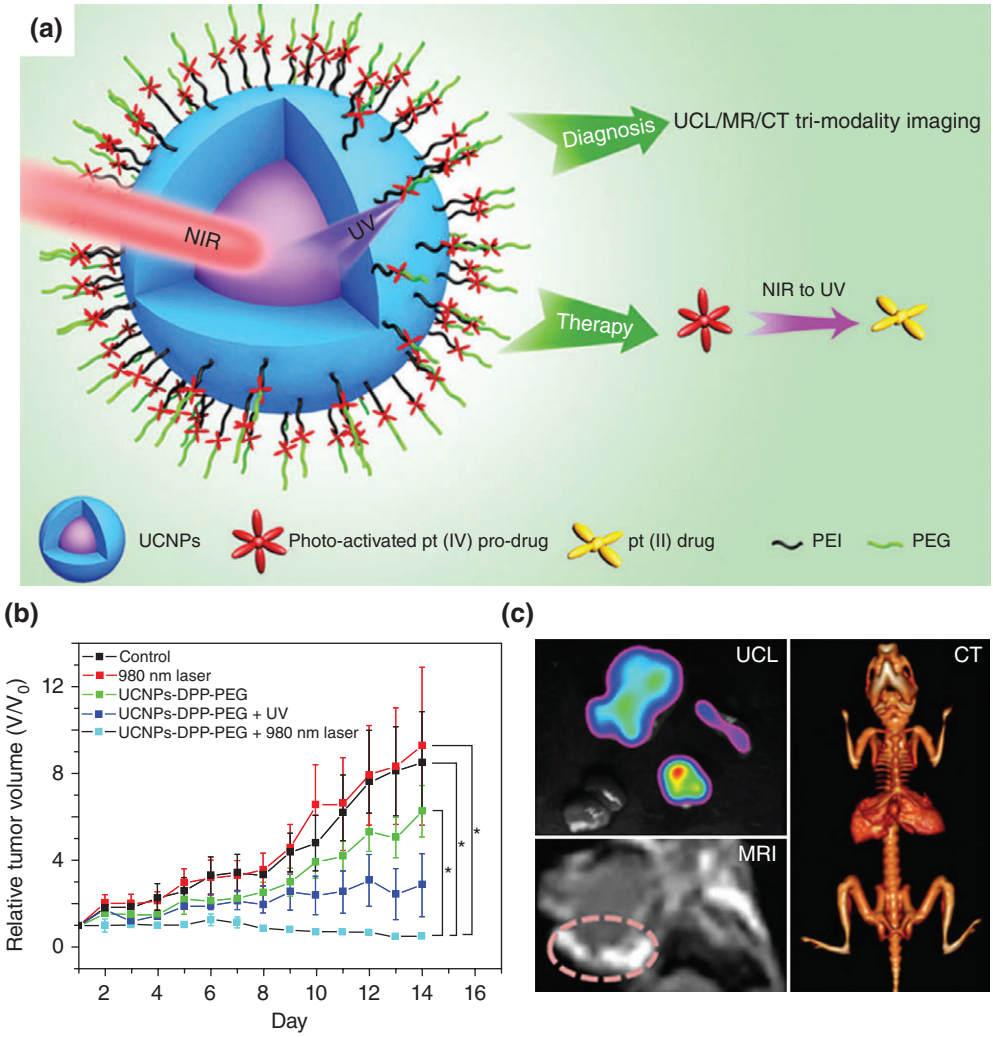

FIGURE 5 | (a) Near-infrared (NIR) light-activated platinum prodrug for cancer therapy and multimodality imaging. (b) The tumor growth curves of different groups after treatment. (c) *In vivo* upconversion luminescence (UCL)/Magnetic Resonance (MR)/computed tomography (CT) trimodality imaging of a tumor bearing Balb/c mouse after injected with the UCNPs at the tumor site. (Reprinted with permission from Ref 79. Copyright 2013 American Chemical Society)

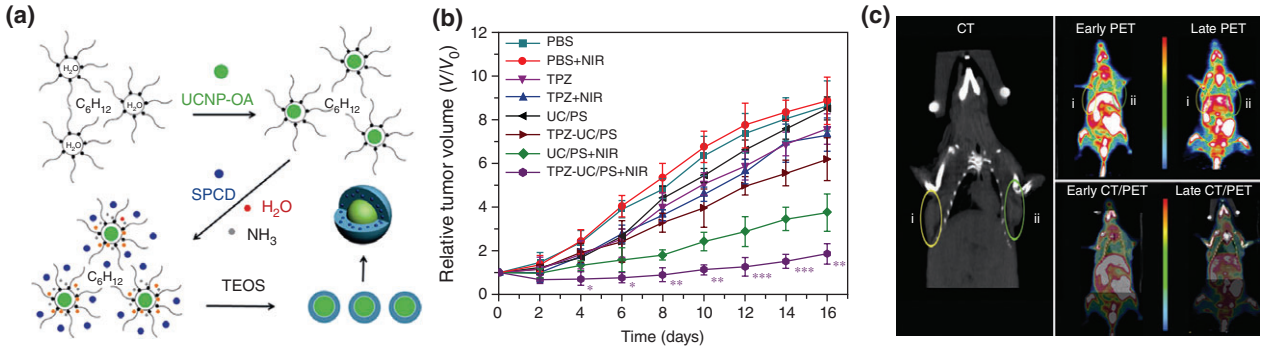

FIGURE 6 | (a) Upconversion nanoparticles (UCNPs) for NIR light (980 nm)-induced photodynamic therapy. (b) The tumor growth curves of different groups after *in vivo* treatment. (c) Computed tomography (CT), positron emission tomography (PET), and CT/PET imaging of HeLa cell-bearing tumors pretreated with photosensitizers-loaded-UCNPs after intravenous injection of ^{18}F-labeled MISO. (A) tumor with near-infrared (NIR) light (980 nm) irradiation and (B) tumor without any further treatment. (Reprinted with permission from Ref 85. Copyright 2015 John Wiley & Sons, Inc)

cytotoxicty of activated TPZ when oxygen is depleted during the PDT process done by UCNPs (Figure 6). Moreover, together with the NIR light-mediated therapy, such unique UCNPs platform also provided the possibility for multimodal computed tomography (CT) and positron emission tomography (PET) imaging for the tumor status.

So far, most successful UCNPs-based PDT progress mainly relies on the NIR light irradiation at 980 nm, at which, however, the water absorption is significant and the inevitable heat effect is very hard to bypass.[86] Therefore, great efforts have been intensively made to adjust the excitation range of UCNPs to a shorter wavelength to meet the medical spectral window (i.e., ~700–900 nm).[87] Very recently, Nd^{3+}-doped upconversion processes based on a new excitation wavelength around 808 nm have been investigated to minimize this unfavorable photothermal effect.[59,88] By taking this promising advantage, Xing et al. very recently presented a unique tumor environment responsive UCNPs platform with the surface modified by enzyme sensitive peptide[89] (Figure 7). Upon tumor-specific enzyme reactions, the cleaved peptides would induce the covalent cross linking of neighboring particles that triggered the accumulation of UCNPs at tumor site. When upon 808-nm laser irradiation, such enzyme-triggered UCNPs cross linking resulted in the enhanced upconversion emission and subsequently amplified ROS generation, which thus greatly improved PDT treatment and multimodality cancer imaging including optical and photoacoustic (PA) imaging *in vitro* and in living subjects.

NIR Light-Triggered Thermal Effect to Control the Release of Therapeutic Agents

Currently, there are various NIR light-absorbing nanomaterials that have been explored for

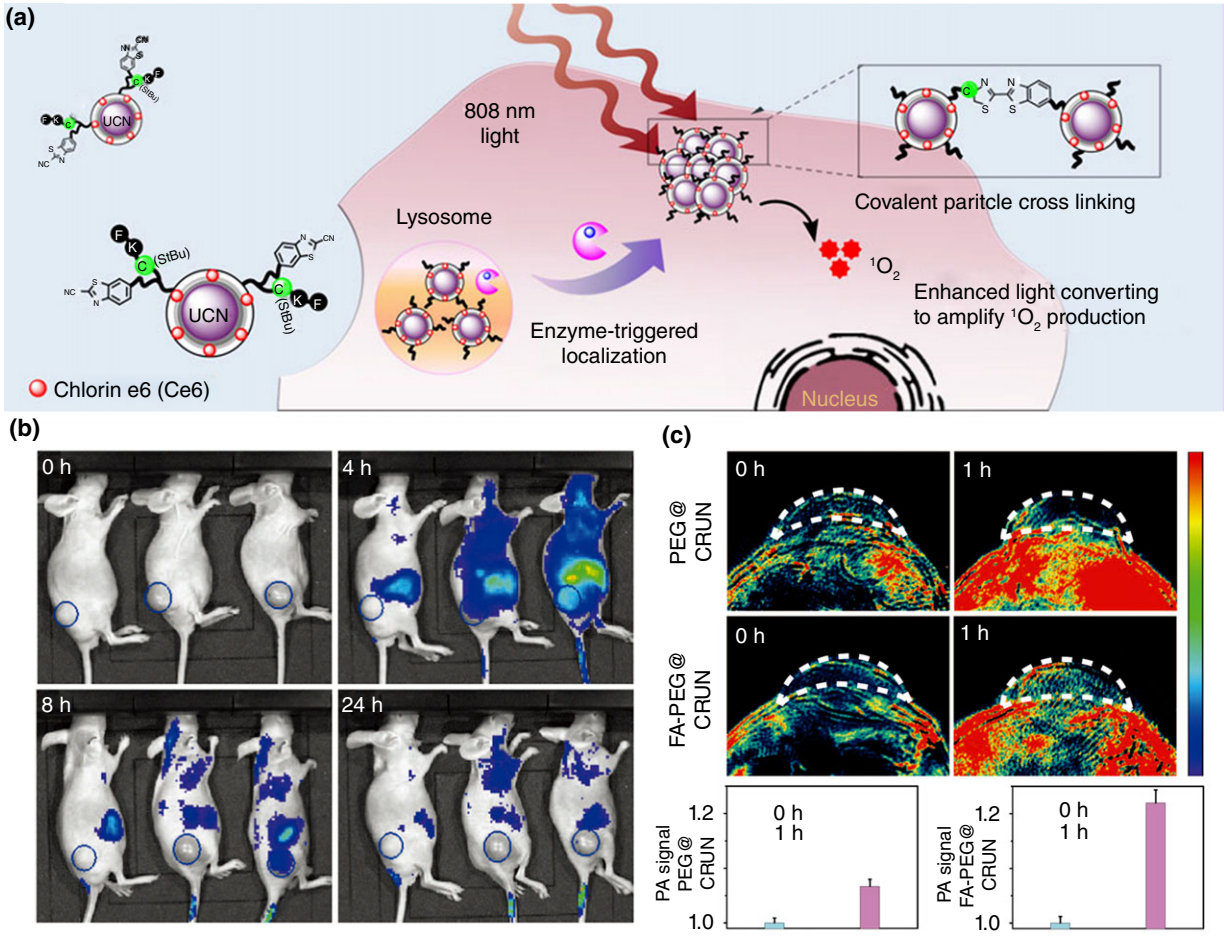

FIGURE 7 | (a) Nd^{3+}-doped upconversion nanoparticles for 808 nm light-triggered bioimaging and PDT therapy. (b) *In vivo* fluorescence imaging of tumor-bearing mice (blue circle) at different time (0, 4, 8, and 24 h) after treated with Saline, PEG@CRUN, FA-PEG@CRUN (from left to right). (c) Photoacoustic imaging in the tumor site at two different time intervals (0 and 1 h) after intravenous injection with PEG@CRUN (top) and FA-PEG@CRUN (middle), the bottom is the photoacoustic imaging signals. (Reprinted with permission from Ref 89. Copyright 2016 Nature Publishing Group)

NIR-induced photothermal cancer therapy (PTT).[4,90] Apart from the studies exploited for direct cancer treatment through the light-induced thermal effect, the generated heat from the NIR light-absorbing nanomaterials has also been proposed to remotely control the release of therapeutic reagents.[91,92] Basically, under NIR light irradiation, the nanostructures which have strong light absorption capacity in the NIR regions could absorb photo energy, and which can subsequently convert it into thermal energy.[93,94] Such generated heat can cause localized temperature increase in the surroundings, which will induce the rapid release of the drug molecules from nanoplatforms.[95,96] So far, various interesting drug delivery systems based on NIR light absorbing nanomaterials have been demonstrated. Taking the commonly studied gold-related nanostructures (e.g., gold nanorods, assembly gold nanoparticles, and gold nanocages) as example, these nanostructures demonstrated intrinsic capability to absorb NIR light and can usually produce photothermal conversion in high efficiency.[97] More importantly, these gold-based nanomaterials can be easily modified with thermosensitive polymers,[98,99] liposomes,[100–102] mesoporous silica shells,[103–105] and even biological samples such as red blood cells etc.[106] For example, In 2009, Xia's group fabricated a type of poly(N-isopropylacrylamide) (pNIPAAm) smart polymer functionalized Au nanocages for the purpose of NIR light-controlled anticancer drug delivery[107] (Figure 8). The as-prepared Au nanocages could efficiently convert the NIR light irradiation (Ti:sapphire laser) into thermal effect, resulting in the collapse of pNIPAAm polymer chains. As a consequence, the pores on the nanocage are opened and thereby release the loaded drug molecules into surroundings.

Moreover, apart from the gold-related nanostructures for NIR light-triggered drug release, a variety of nanostructures, including CuS nanoparticles,[108,109] MoS_2,[110] carbon-based nanomaterials,[111,112] and some hybrid nanostructures or nanocomposites (e.g., Au-Ag NPs,[113] Fe_3O_4-Au NPs,[114] FeCo/graphitic

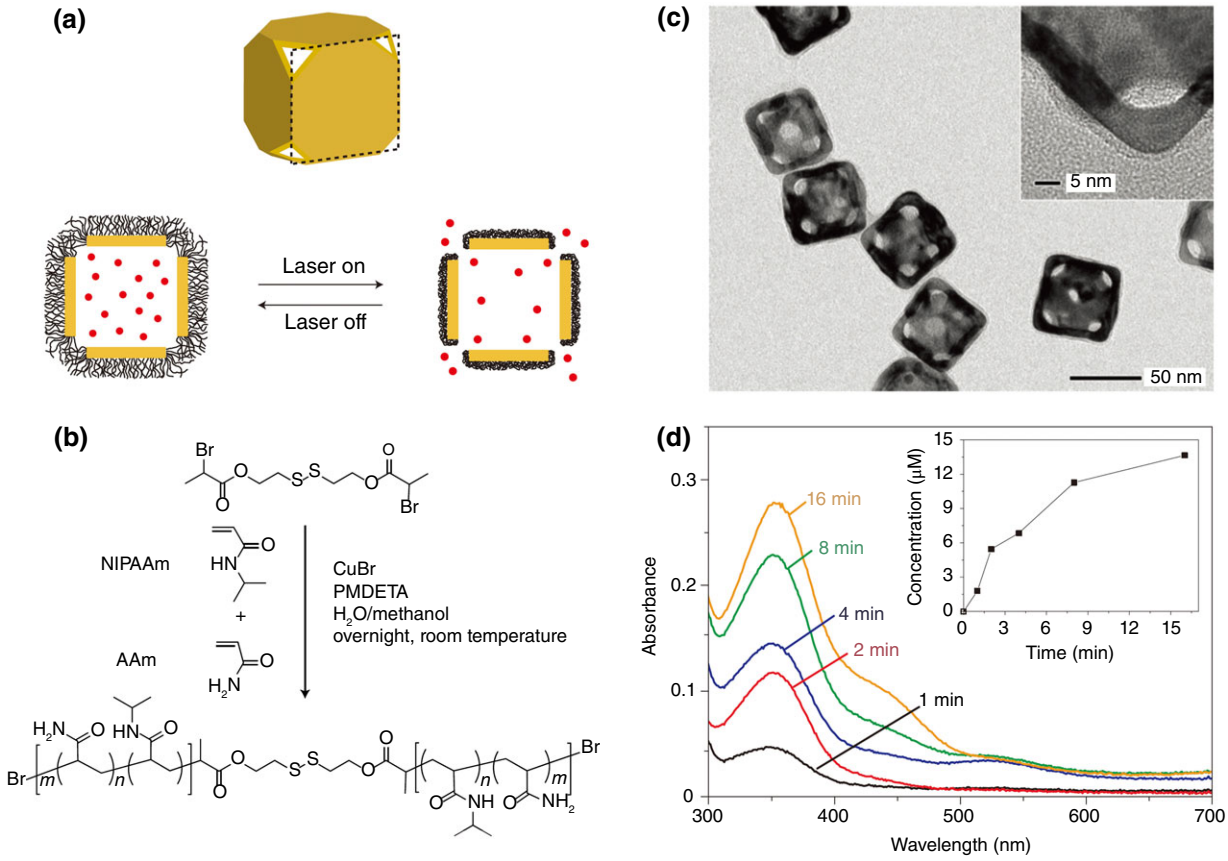

FIGURE 8 | (a) Application of gold nanocages for NIR light-induced photothermal therapy. (b) The synthesis process of the smart polymer pNIPAAm. (c) Transmission electron microscopy (TEM) images of Au nanocages with the surface covered by polymer. (d) Near-infrared (NIR)-light controlled release of the payload from the Au nanocages covered by polymer, the NIR laser irradiated for 1, 2, 4, 8, 16 min, at the power density of 10 $mWcm^{-2}$. (Reprinted with permission from Ref 107. Copyright 2009 Nature Publishing Group)

nanocrystals,[115] and UCNPs-Au composite nanomaterials),[116] also demonstrated their promising photothermal properties for NIR light controlled drug delivery. For instance, Yang et al. presented a new type of assembled Gd_2O_3:Yb/Er mesoporous silica UCNPs composites, which could demonstrate 2D hexagonal (MCM-41-Gd) and 3D cubical (MCM-48-Gd) network structures, respectively.[96] The gold NPs with a diameter of 5 nm were conjugated to the surface of MCM-41-Gd or MCM-48-Gd to form the hybrid nanomaterials. In order to test the performance in cancer therapy, the antitumor drug Dox was loaded to the hybrids through electrostatic interactions. After 980-nm NIR irradiation, such hybrid gold UCNPs nanocrystals could absorb the upconverted green emission (around 550 nm) and then converted it into heat, which therefore promoted the drug Dox release from the Au-UCNPs hybrid composites.

CONCLUSIONS

Currently, various types of theranostic delivery systems, capable of encapsulating drug or imaging molecules, and incorporating stimulus-responsive components, have been extensively developed in disease therapy, particularly in cancer treatment, so as to improve target specificity, treatment efficacy, and to reduce the toxic side effects usually occurred in the conventional medical processing modalities. Among them, the photoactivated therapies have been well established to control drug delivery and biomedical imaging, which shows great potential in clinical practice. In contrast to the classical modalities, this novel technique resorts to a noninvasive external stimulus, light irradiation, which is versatile, easy to manipulate, and importantly, precise control can be easily achieved in a highly spatial and temporal resolution. To date, different strategies including photocage, light-triggered photoisomerization, optical upconversion, and photothermal switching effect have been proposed to activate the therapeutic or imaging agents through light exposure at a broad wavelength range from UV to visible or even NIR windows. In general, the short-wavelength light (i.e., UV or visible light) possess higher energy to easily break a 'photocaged' covalent bond or induce a *cis–trans* conformational change, thus triggering the release and delivery of therapeutic or imaging molecules. However, the usage of UV or visible light still has some disadvantages, such as potential photodamage to normal tissues, high background, and limited penetration depth, which may largely restrict their further clinical applications. The emerging photoactivated technologies based on NIR light irradiation could overcome these technical obstacles, and thus enable great possibilities to remote control the desired theranostic effectiveness. Long-wavelength NIR light is generally less harmful and has better tissue penetration. It usually carries insufficient energy to initialize chemical bond broken, and normally it works with the assistance of robust nanoplatforms, such as UCNPs and gold nanomaterials. So far, NIR light-mediated photoactivation have been successfully proved for the controlled anticancer drug release and relevant imaging *in vitro* and in living subjects.

Although numerous studies have been widely conducted, the photo-based cancer diagnosis and therapy are, in fact, at its immature stage because most of the examined platforms are mainly investigated in laboratories. There are many challenges that still need to be fully addressed before further clinical applications of light-induced cancer therapies. First of all, as most of the demonstrated photo-triggered systems are usually based on functional nanomaterials or polymer structures etc., the photo-to-photo or photo-to-thermal conversion efficiency of the most currently reported nanoplatforms remains limited. For that reason, high power light resources are necessary to obtain the desired treatment or imaging effect *in vitro* and *in vivo*. One solution is to develop new types of high-performance nanostructures with intrinsically excellent optical properties or higher photo-to-photo or photo-to-thermal conversion capacity. Meanwhile, since the long-term safety of these nanomaterials in living subjects will be a potential technical hindrance for the practical applications, particular attention should be also paid to the development of biocompatible and biodegradable nanomaterials with desired photosensitive properties. Moreover, besides the concern of safety, the other major issue in light-triggered anticancer phototherapy and imaging would be the limited photo penetration, as it is known that most cancer lesions are usually deeply buried in the solid tissues or in the organisms, where external light irradiation can hardly reach. In this regard, it would be greatly beneficial if new types of photolabile or photosensitive molecules can be designed and synthesized that are capable of responding to NIR light irradiations directly for efficient NIR light-mediated bioimaging or therapy. In line with the efforts to make NIR light responsive molecules and functional nanomaterials with promising optical properties, one of the necessary solutions, which may bring great opportunities to facilitate the photoactivated cancer therapy and imaging, could be the involvement of new optical transmission devices or optics fibers to effectively

direct light irradiations into the tumors located deeply inside the body. Furthermore, such optical devices would be also beneficial for precision medicine in real-time tracking the therapeutic reagents and meanwhile, monitoring the disease surroundings during the phototherapy period.

While continuous efforts that are required in the design and synthesis of new materials and light devices for improved light-triggered therapy and imaging, the development of new irradiation approaches may also provide alternative options in the photoactivated biomedical applications. For instance, since the discovery of X-radiation (e.g., X-ray) in the late 19th century, several radiation or nuclear imaging modalities including CT, single-photon emission computed tomography (SPECT) and PET etc. have been widely applied in clinics for personalized identification and diagnosis of many vital diseases.[117] Significant benefits in safe and precise examination, and importantly, almost limitless penetration capacity when compared to conventional optical imaging techniques allow them to serve as robust modalities for radiotherapy or nuclear imaging investigations in extensive clinical practice.[118,119] More recently, an emerging hybrid modality through the process of Cerenkov radiation, an intrinsic physical phenomenon where optical photons can be emitted when a charged particle travel faster than the speed of light for the medium, has attracted much attention in cancer research and nuclear medicine. For example, Cheng et al. demonstrated a novel radioisotope ^{131}I labeled quantum dots (QDs) for *in vitro* and *in vivo* optical imaging, in which the radionuclide radiation was used as an internal photo source to illuminate the photoactive QDs.[120] Upon the combination of radionuclide elements with new optical nanomaterials or photoactivated molecules, such unique radiation process would provide promising opportunities to bridge the nuclear imaging technique with the traditional optical imaging modality, and would be thus greatly beneficial for the new generation of photo-triggered cancer therapy and imaging in near future.[121]

Moreover, a systematic understanding of human organism responding to different wavelength light irritation as well as relevant oncology pathway is essential which can provide important insights in the new design, fabrication, noninvasively monitoring therapeutic consequence of photoactivated platforms *in vitro* and in living systems. So far, the auspicious beginning at current stage ambitiously prefigures a bright future for the anticancer treatment. The cancer research is growing so rapidly and also broadening and diversifying; the future perspective of photo-controlled anticancer theranostics definitely demands more collaborative efforts at the interfaces of interdisciplinary subjects including cancer biology, materials engineering, chemistry, radiology, and photophysics—in the aspect of design, fabrication, and implementation. With all the innovations in these different research fields, the effective photoactivation strategies will continuously be developed, which further inspires more efforts toward personalized cancer treatment and diagnosis in the future healthcare.

ACKNOWLEDGMENTS

This work was partially supported by Start-Up Grant (SUG), Tier 1 (RG 64/10), (RG 11/13), and (RG 35/15) awarded in Nanyang Technological University, Singapore; the National Natural Science Foundation of China (grant no. 21405108 and 11304214), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), China.

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