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Advanced Near-Infrared Light-Responsive Nanomaterials as Therapeutic Platforms for Cancer Therapy

Yi-Hsin Chien, Kok Ken Chan, Tommy Anderson, Kien Voon Kong, Beng Koon Ng, and Ken-Tye Yong*

Cancer is one of the leading causes of death in the world. Even though there has been huge progress in the field of cancer drugs and therapies, the treatment outcome is still bleak for most cancer patients. Nanotechnology has offered a revolutionizing approach for cancer therapeutics. By using nano-sized particles as delivery systems, drugs or other therapeutic biomolecules is transported efficiently to the target sites. Moreover, these particles are designed to carry out more than one cancer treatment simultaneously. In recent years, near-infrared (NIR) light-responsive nanomaterials have gained much attention owing to the fact that NIR light has a greater penetration depth, minimal phototoxicity, lower autofluorescence, and reduced light scattering. Among the available NIR light-responsive nanomaterials, gold nanorods, upconversion nanoparticles, carbon dots, and transition metal dichalcogenide as well as metal oxides, black phosphorus, and polymeric nanomaterials have become attractive options owing to their excellent optical properties, ease of synthesis and modification, outstanding photodynamic and photothermal conversion properties, and most importantly, favorable toxicity level and biocompatibility which are prerequisites for biological applications. In this review, the outstanding properties, synthesis, and surface functionalization of the aforementioned NIR light-responsive nanomaterials are introduced in detail. Recent advances of these nanomaterials for various cancer treatment modalities are summarized to highlight their versatility and potential in cancer theranostics. Finally, a perspective on the future research direction for these nanomaterials and their translation for clinical settings is proposed.

1. Introduction

Cancer is one of the major threats to human survival. Cancers start as localized diseases but grow uncontrollably to the extent that cancer cells migrate to other tissues and organs. This migration is a critical process in cancer development known as metastasis. Traditional cancer therapies such as surgery, chemotherapy,^[1] and radiotherapy (RT)^[2] currently used in clinical treatments have some disadvantages, including toxic side effects,^[3] drug resistance,^[4] and decrease in immune function. Moreover, these therapies suffer from a lack of selectivity, killing not only cancer cells but also normal ones. In addition, the lack of specific targeting in those therapies leads to insufficient drug concentrations at tumor sites. Hence, to improve this inefficiency, various types of alternative cancer treatments have been developed based on nanotechnology. Nanotechnology is a multidisciplinary field bridging material science, biology, chemistry, engineering, and medicine. In particular, nanomedicines featuring biocompatible nanocomposites for targeted and marker-assisted drug delivery are revolutionizing cancer theranostics, rendering it one of the most promising solutions for cancer treatment.^[5]

Generally, therapeutic biomolecules can be targeted to a specific site using ligand-functionalized nanocarriers. For instance, nanocarriers such as liposomes,^[6] polymer wrapped nanoparticles,^[7] and core-shell nanostructures^[8] are widely developed as drug delivery systems (DDS) for cancer treatment. In these targeting strategies, nanocarriers have the capability to increase intracellular drug concentrations in cancer cells while minimizing toxicity to normal cells, simultaneously increasing anticancer effects and reducing systemic toxicity. These nanomaterials can be developed based on their unique physical, optical, magnetic, and radiative properties.^[9] Among them, nanoparticles with good optical properties have emerged as a useful tool in biomedical applications such as bioanalytical science, bioimaging, and imaging-guided therapy.^[10] To date, different types of luminescent nanomaterials with high quantum yields, such as inorganic quantum dots,^[11] noble metal nanoparticles (gold, silver, and platinum),^[12] lanthanide-doped nanophosphors,^[13] and organic dyes^[14] have been applied in biomedical applications.

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In particular, near-infrared (NIR) light-responsive luminescent nanomaterials have become attractive options for next-generation cancer treatments. The preference for NIR light in cancer therapy can be explained by the propagation of NIR light through tissues and its corresponding signal-to-background ratio (SBR). Generally, the excitation photons need to travel through tissues before being able to reach and interact with the functionalized nanomaterials. The light will experience absorption of photons caused by oxyhemoglobin, deoxyhemoglobin, melanin, fat, and water in tissues with the absolute absorption determined by the concentrations of each constituent. NIR light (650–900 nm) experiences minimal absorption in tissues and possesses deeper penetration depth.^[15] For instance, a study carried out by Henderson et al. found that 810 nm NIR light can penetrate through 2.5–3 cm of the human hand which is biologically beneficial for light-triggered cancer therapies. Besides, excitation light intensity can also be attenuated by light scattering due to the microscopic structures in biological tissues.^[16] Thus, using NIR light which has minimal absorbance coefficient will indirectly reduce the scattering effect. In addition, after absorbing excitation light, there is a chance that fluorescence will be emitted from the tissues, known as autofluorescence which can generate sufficiently strong background signals. This can severely limit the SBR and interfere with the emission of the targeted nanomaterials. Also, the use of short wavelength light such as in the UV region can cause DNA damages. Thus, the employment of NIR light in cancer therapy allows the light to penetrate tissue or skin to reach deep regions in the body where injected optically sensitive nanoparticles accumulate, without suffering from absorption, scattering, and autofluorescence while minimizing phototoxicity to the treatment target.

NIR light can be used in light-triggered photothermal therapy (PTT), offering a minimally invasive cancer treatment. Generally, cell death induced by PTT can be attributed to necrosis and apoptosis.^[17] Cell death due to necrosis is identifiable by the loss of plasma membrane integrity and subsequent release of intracellular components which includes damage-associated molecular patterns into the extracellular milieu. This abnormal process occurs when cell temperature rises above 50 °C and it can trigger inflammatory and immunogenic effects.^[18] On the other hand, cell death by apoptosis can be observed at temperature above 40 °C, where the integrity of the cell membrane is maintained and “eat-me” signals such as phosphatidylserine, is expressed to identify the cell for phagocytosis.^[19] Photodynamic therapy (PDT) is another cancer therapy that can exploit the deep penetration properties of NIR light. Typically, there are two nontoxic components that are used synergistically to induce cell death in an oxygen-dependent manner.^[20] The first component is a light-sensitive component known as photosensitizer (PS). The second component is the administration of light of a specific wavelength that activates the PS. Subsequently, the PS will transfer the photon energy to molecular oxygen, generating cytotoxic reactive oxygen species (ROS). As different PSs can be excited by light of specific wavelengths, careful selection of NIR light-responsive nanomaterials is required to allow the transfer of photon energy to the PS through fluorescence resonance energy transfer (FRET). Furthermore, cancer therapy can be localized to a specific location by irradiating NIR light at the target site, minimizing the adverse side effects of cancer therapy.

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In this review, we discuss the properties, synthesis, and surface modification of a range of NIR light-responsive nanomaterials such as gold nanorods (Au NRs), lanthanide-doped upconversion nanoparticles (UCNPs),^[21] carbon dots (CDs), transition metal dichalcogenides (TMDCs), as well as other notable nanomaterials such as metal oxides, black phosphorus (BP), and polymeric nanomaterials, that have been gaining extensive interest in cancer theranostic applications (**Scheme 1**). Recent theranostic applications of the nanomaterials such as PTT, PDT, DDS, gene-delivery, bioimaging, multi-modal therapy systems, and NIR-triggered drug release system are critically reviewed and summarized. This review aims to provide an overview of the current progress and insight into the future works of these NIR light-responsive nanomaterials for cancer theranostics.

2. Gold Nanorods

2.1. Local Surface Plasmonic Resonance and Synthesis

Gold (Au) nanostructure is a type of noble metal nanomaterial with dimensions of 100 nm or even smaller. Size effect in Au

Scheme 1. Illustration of NIR light-responsive nanomaterials as cancer therapeutic platform.

nanostructures produce properties different from their bulk materials in terms of electronic, optical, surface-area-to-volume ratio, and surface catalytic properties. As the free electrons are confined within a small-sized nanoparticle, they induce surface plasmon oscillations of electrons in the conduction band. Based on Mie theory, surface plasmon resonance (SPR) displays a unique optical phenomenon associated with collective oscillations between an electromagnetic wave and free electron of metal, where resonant photons are confined into nanoscale as shown in Figure 1A.^[22] These nanoparticles can enhance

the electromagnetic field around the surface of the particles, which decay gradually over a distance comparable to the particle size.^[23] The shape of Au nanostructures is a critical factor in controlling their physical and chemical properties. Among the different shapes, the nonspherical Au nanostructures exhibit anisotropic optical and electronic properties due to their unique aspect ratios. Specifically, Au NRs have been applied in many important applications such as nanomedicine, bio-imaging, colorimetric sensors, and therapeutic platforms. The unique optical properties of Au NRs are attributed to the anisotropic rod shape that induces two plasmon modes on two axes, namely the transverse local surface plasmon resonance (LSPR) mode and the longitudinal LSPR mode. As shown in Figure 1B, the UV-vis spectrum shows the transverse band at around 500 nm when they are irradiated with high-energy visible electromagnetic waves polarized along the transverse direction. The longitudinal band in Au NRs with an aspect ratio of 4 oscillates in resonance toward the low-energy NIR wavelength at 800 nm. In general, the longitudinal wavelength can be synthetically tuned from visible to NIR regions by modulating the aspect ratio of Au NRs. In general, there are two methods to synthesize Au NRs, namely the bottom-up and top-down approaches. Bottom-up methods include wet-chemical,^[24] sonochemical,^[25] photochemical reduction techniques,^[26] and electrochemical,^[27] while in the top-down methods, Au NRs with various aspect ratios are generated by different physical lithography and Au deposition processes.

The most common synthesis method is the seed-mediated Au NRs growth developed by Murphy et al.^[24] and El-Sayed et al.^[28] Typically, Au seeds (≈ 1.5 nm) were prepared from reducing chloroauric acid (HAuCl_4) with sodium borohydride (NaBH_4) in cetyltrimethylammonium bromide (CTAB) solution. Next, the growth solution is obtained by reducing Au^{3+} ions into Au^+ ions by using ascorbic acid (AA) in CTAB solution. A small amount of prepared Au seeds solution is then added to the growth solution and thereafter, the Au^+ complex ions are reduced to form Au

A: Nanospheres

B: Nanorods

Figure 1. Schematic illustration of the interaction of polarized light and A) gold nanospheres and B) nanorods to form the electronic coherent surface plasmon resonance (SPR) oscillation. Reproduced with permission. Copyright 2009,^[22b] Wiley-VCH.

NRs. Ag^+ ion is a key factor in producing Au NRs with high yield and tunable aspect ratios. Although the underlying mechanisms are not fully understood, Ag^+ ions play a critical role in improving the morphology and yield of Au NRs, probably due to the fact that Ag^+ ions are bonded to the higher-energy lattice plane {100} facets of Au nanocrystal. This slows the growth speed of these facets, leading to Au atoms to deposit mainly on the {110} facets, resulting in growth in the longitudinal direction to form rod-shaped nanostructures.^[29] To date, the seed-mediated growth method to prepare Au NRs have been reported to have achieved yield as high as 99%. The high yield is attained not only by the addition of Ag^+ ions, but also by adjusting factors such as pH of the growth solution, temperature, and amount of reducing agents. Despite the success, CTAB which is a commonly used surfactant in the synthesis of Au NRs has the potential to induce cytotoxicity. Recently, some studies have demonstrated the use of aromatic additives^[30] or polyphenolic compounds^[31] in the seed-mediated growth of Au NRs with uniform morphology and high yield.

Functionalization of Au NRs is a critical process for biological applications. Typically, CTAB-capped Au NRs are modified with biocomposite agents or inorganic species such as organic molecules, liposomes, SiO_2 shells, polymers, and biopolymers. Thiol functional groups are widely used to react with gold surfaces via Au–S metal bonds.^[32] In the past decades, there is an increasing number of literature in developing ligand-exchange procedures using thiol-based and customized-thiol ligands. For instance, Wijaya and coworkers demonstrated a round-trip phase transfer process wherein CTAB-capped Au NRs were first transferred into a dodecanethiol (DDT) solution, and the Au NRs-DDT were then extracted into aqueous phase using mercapto-carboxylic acids (MCA), $\text{HS}-(\text{CH}_2)_n-\text{COOH}$ ($n = 5, 10, \text{ and } 15$) as the capping ligand.^[33] Ligand-exchanged NRs (NR-MCA) could be further conjugated with thiolated poly(ethylene glycol), PEG_{MW} ($\text{MW} = 356, 5000, \text{ and } 1000$). The NR-MCA and NR- PEG_{MW} were found to be monodisperse in physiological buffers and maintained the characteristics of Au NRs. Polyethylene glycol thiolate (PEG-SH) is a type of PEG well known for its biocompatibility. Yamashita and coworkers presented the synthesis of Au NRs coated with PEG-linked Diels–Alder cycloadduct via Au–S bonding.^[34] In addition, Dreaden and coworkers reported macrolide-functionalized Au NRs which were specifically delivered to tumor-associated macrophage (TAM) cells. Antibodies and macrolides were linked by click chemistry to thiol-PEG chain followed by conjugation onto Au NRs surface to induce TAM-dependent cytotoxicity toward breast cancer cells in co-culture.^[35] Synthetic polymers can be designed to be end-functionalized with specific purposes which are then directly coated on Au NRs surface through ligand exchange. Hotchkiss and coworkers fabricated three types of polymers, namely PDMAEMA (poly(2-(dimethylamino) ethyl methacrylate), PAA (poly(acrylic acid)), and polystyrene by fragmentation chain transfer polymerization (RAFT) for functionalization onto Au NRs.^[36] The procedure consists of a two-step process: 1) seed-mediated Au NRs synthesis and 2) polymer preparation through RAFT process to enable covalent attachment of the polymers (PDMAEMA, PAA, and hydrophobic polystyrene) to Au NRs surface using either NaBH_4 or lithium aluminum hydride (LiAlH_4). SiO_2 core–shell system has also been proven to be capable of removing CTAB and modifying the surface of Au NRs. Huang and coworkers designed and pre-

pared multifunctional GNR- SiO_2 -FA for diagnosis and therapy of gastric cancer MGC803 cells.^[37] In their study, silica was used to replace CTAB molecule by the classic Stöber method to reduce cytotoxicity and improve biocompatibility.

2.2. Biomedical Applications of Au NRs

Over the past decade, Au NRs have attracted much attention in biomedicine applications such as bioimaging,^[38] PTT,^[39] PDT,^[40] surface-enhanced Raman spectroscopy (SERS),^[41] DDS,^[42] and diagnostic platforms.^[43] The contributing factors for their wide use are their LSPR optical properties, flexible surface modification, and high biocompatibility. LSPR with strong anisotropic plasmon coupling by electron oscillation along different surface directions is contributed by nonradiative relaxations through phonon–phonon and electron–phonon coupling. These mechanisms induce the generation of localized heat and photon energy that can be transferred to the surroundings or ligands for enhanced photoluminescence (PL) and hyperthermia upon NIR light irradiation. In the following section, we summarized some of the cancer theranostic applications of Au NRs such as bioimaging, PTT, DDS, and PDT.

2.2.1. Bioimaging

The LSPR properties of Au NRs are determined by size, shape, aspect ratio, and surrounding environment.^[44] The plasmonic coupling effects of Au NRs are due to the interaction with surface-modified groups or neighbouring nanoparticles at nanoscale distances which provides an interesting optical phenomena for plasmonic devices and fundamental optical explorations.^[45] This optical property can be used for biological imaging such as two-photon-enhanced luminescence (TPL),^[46] dark-field mode microscopy (DFM),^[47] optical coherence tomography (OCT),^[48] photoacoustic tomography (PAT),^[49] and X-ray computed tomography (CT).^[50] DFM is a fundamental technique which utilized Au NRs owing to their extinction band from stronger light scattering and absorption at the NIR region.^[51] Colorful dark-field images can be obtained during cellular imaging, single-molecule imaging, and real-time chemical reaction. For instance, by using dark-field imaging, Zhang et al. observed a morphological change from rod-shaped $\rightarrow$ fusiform $\rightarrow$ spherical during the chemical etching of Au NRs.^[52] The colors of the scattered light changed from bright red $\rightarrow$ yellow $\rightarrow$ green. Their results demonstrated that the chemical reshaping of Au NRs can be used to monitor the coupling reaction and to prepare fusiform nanostructures. Huang et al. prepared Au NRs conjugated with monoclonal anti-epidermal growth factor receptor (anti-EGFR) antibodies which were then incubated with a nonmalignant epithelial cells (HaCat) and two malignant oral epithelial cells (HOC 313 clone 8 and HSC 3).^[53] The anti-EGFR antibody-conjugated Au NRs displayed more distinctive dark-field images within malignant cells than nonmalignant ones, owing to the overexpressed EGFR on cytoplasmic membrane of malignant cell surface.

As a result of the overlap of longitudinal LSPR with TPL excitation bands, Au NRs possess resonance-enhanced emission, which is beneficial for in vitro and in vivo TPL bioimaging. TPL imaging has relatively deeper light penetration depth, lower

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background fluorescence, and higher 3D spatial resolution. For instance, Wang et al. reported plasmon resonant TPL of single Au NR by two-photon excitation laser-scanning microscopy.^[54] The in vivo emission of the TPL from a single Au NR was nearly 60 times brighter than TPL from a single rhodamine molecule by using mouse ear blood vessels as a study model. In another scattering-based imaging, OCT uses a short coherence light source to obtain micrometer resolution and 3D cellular images by measuring the differences in absorption-scattering profiles of the media. Oldenburg et al. prepared Au NRs as imaging agents for spectroscopic optical coherence tomography (SOCT).^[55] The absorption profile of Au NRs exhibited a high contrast within the tumor site of human breast invasive ductal carcinoma. In a separate study, Jung et al. demonstrated in vivo bioimaging of Au NRs uptaken in sentinel lymph node (SLN) of mice to achieve high-resolution 3D images by OCT-based imaging.^[48]

2.2.2. Photothermal Therapy/Drug Delivery System/Gene Delivery

Au NRs have been widely used for plasmonic PTT for cancer treatment because of their unique optical properties and low toxicities.^[56] Upon light irradiation, Au NRs can convert photon energy into thermal energy, resulting in a temperature increase of more than 20 °C in the surrounding environment.^[57] Important factors to consider when comparing PTT efficiency of Au NRs of different shapes and sizes are the absorbance coefficient and absorbance efficiency per Au NR. Mackey et al. evaluated the PTT efficiency of Au NRs of three different sizes through theoretical calculations and experiments to optimize the size of Au NRs.^[58] Interestingly, there were three different contributions of absorbance to the total extinction in Au NRs of different diameters (38 × 11 nm, 28 × 8 nm, and 17 × 5 nm) based on discrete dipole approximation (DDA). The theoretical results revealed that the electromagnetic field around the surface of Au NRs and the ratio of the absorbance/scattering increased as the Au NRs size decreased. According to simulation results, Au NRs with a dimension of 28 × 8 nm were found to generate heat in the most efficient manner when operating in plasmonic resonance. To confirm their theoretical results, 28 × 8 nm Au NRs were incubated with human oral squamous cell carcinoma (HSC-3) for 2 h before exposure to NIR radiation. Two hours after NIR radiation treatment, viability of cells treated with 28 × 8 nm Au NRs and 2 min of 808 nm laser irradiation was found to be lower than 20%, which was more effective than 17 (30%) and 38 nm (100%) Au NRs with the same treatment condition. The novel tumor-targeting strategy is highly efficient to enhance precise recognition of cancer cells and cell uptake through blood circulation. Shanmugam and his team designed a folic acid (FA)-modified Au NRs vehicle carrying anticancer drug doxorubicin (DOX) and platinum (IV) (Pt (IV)) for targeted delivery.^[59] First, Au NRs with an aspect ratio of 4 and LSPR band at 808 nm were prepared. Then, DOX molecules were bound into hybridized double-stranded DNA through the interaction of DOX and C–G base pairs of the DNA duplex. Another prodrug, Pt (IV) were conjugated with 5' amine functional group of complementary cDNA. Lastly, the Au NR nanocomposites were conjugated with FA to specifically target folate receptors overexpressed on the cell membrane. These FA-targeted Au

NRs carrying DOX and Pt(IV) were used as a photothermal contrast agent and DDS to demonstrate the combination of chemotherapy and hyperthermia therapy in vitro and in vivo with NIR light as the trigger for the release of cargo.

In some literature, scientists have illustrated tumor-targeting methods with external stimuli such as thermo-responsive polymers, pH-responsive polymers, and magnetic field trigger for enhancement of therapeutic efficacy. For instance, Zhang and coworkers developed a thermo- and pH-responsive polymer shell, poly(*N*-isopropylacrylamide-co-acrylic acid) (PNIPAM), mesoporous silica-coated Au NRs (AuNR@mSiO₂) as a multi-functional theranostic nanoplatform with NIR light as a trigger (Figure 2A,B).^[60] These core-shell nanocomposites (abbreviated as Nanocom) with an average diameter of ≈280 nm were dispersed in phosphate buffered saline (PBS) solution (pH = 7.4) with a negative zeta potential of −18.5 mV. The absorbance peaks in every formation steps of Nanocom-Dox are shown in Figure 2D, where the longitudinal SPR peak at 760 nm remained after polymer coating and DOX loading. The transmission electron microscopy (TEM) images of polymer-coated AuNR@mSiO₂ and AuNR@mSiO₂ with monodisperse morphology are shown in Figure 2C. In photothermal tumor ablation experiments, mice bearing murine 4T1 tumor (≈40 mm³) were injected with different treatments of PBS, DOX, Nanocom, and Nanocom-Dox, followed by NIR laser irradiation. After 5 min of irradiation by 760 nm laser (500 mW), the temperature increased by only ≈7 °C in PBS group, while it reached 65 °C in the group treated with 70 μg mL^{−1} of Nanocom-Dox (Figure 2E). The combinational effect of chemotherapy and PTT was demonstrated using two nanocomposites (Nanocom and Nanocom-DOX) which were intravenously injected into mice bearing 4T1 cells tumor followed by 808 nm laser treatment with different power densities for 10 min. One significant finding from the in vivo experiment is shown in Figure 2F, revealing the combined effect of hyperthermia and chemotherapy of Nanocom-DOX which inhibited tumor growth for the whole experimental duration.

Studies on cell-mediated delivery have gained much attention in recent years because cell-mediated delivery can cross impermeable biological barriers and arrive at critical areas in the body that drugs and nanomaterials cannot easily access.^[61] In a study by Li et al., they discovered that 7 nm Au NRs (designated as sAuNRs) were more efficient for cell uptake than 14 nm Au NRs (designated as bAuNRs) in cell-mediated PTT applications.^[62] In their cell uptake experiments, the BSA-coated sAuNRs and bAuNRs were utilized in real-time fluorescence imaging and flow cytometry analysis with RAW 264.7 macrophages and hepatic stellate cells (HSCs) as the cell models. Their results showed that macrophages had 52.5% and HSCs had 22.5% cell uptake of sAuNRs. In a separate experiment, the cell uptake of bAuNRs in macrophages achieved 35.3% uptake while HSCs only reached 14.0%. The sAuNRs-laden macrophages were used in intratumoral treatment with NIR irradiation which achieved tumor suppression by almost 95%. No tumor recurrence was observed during 14 days post-treatment.

In general, gene therapy requires an efficient protection of nucleic acid from degradation by nucleases. This is typically achieved by loading genetic materials such as plasmid DNA (pDNA) and small interfering RNA (siRNA) into nanocarriers. pDNA and siRNA are negatively charged molecules owing

Figure 2. The strategies illustrating A) nanocomposite synthesis process and B) targeted thermo/chemotherapy using this nanocomposite with NIR laser irradiation. The characterization of the Nanocom and NIR-triggered drug release profiles: C) TEM image of Nanocom and AuNR@SiO₂ (inset), D) the absorbance spectra of Au NRs, Au@SiO₂, Nanocom, and Nanocom-Dox; E) the temperature gradually increased and plateaued after 5 min of irradiation by constant laser power (760 nm, 500 mW, 16 W cm⁻²) with different particle concentrations. F) In vivo antitumor activities were evaluated by measuring the tumor volume for groups injected with PBS, Dox, Nanocom, and Nanocom-Dox (with or without laser irradiation) through the tail vein. Reproduced with permission.^[60] Copyright 2014, American Chemical Society.

to their phosphate backbone. Therefore, nanocarriers with positively charged surface can be conjugated with pDNA and siRNA through simple electrostatic forces. Genetic materials can also be covalently conjugated onto nanocarriers by chemical processes, where the release of genetic materials can be triggered by external (e.g., light, temperature)^[63] or internal (e.g., enzyme, glutathione [GSH], or pH value)^[64] sources. Thermo-responsive polymers are often used to regulate the release of drug/gene molecules from nanocarrier systems. Shen and coworkers prepared PEI-Au NRs using a layer-by-layer (LBL) assembly method

using polystyrene sulfate and polyethyleneimine (PEI) as delivery vehicles with high biocompatibility and low immunotoxicity.^[65] siRNA specific to pyruvate kinase M2 (PKM2) was used for gene silencing to counteract cancer cell proliferation. PEI-siRNA Au NRs protect siRNA from degradation and facilitate endosomal escape, both of which are prerequisites for successful gene silencing. In combination with the photothermal activity upon NIR irradiation, their nano-sized system showed dual functions of reducing tumor proliferation by both gene silencing and thermal therapy. The synergistic strategies of complementary

gene/chemo/photothermal/photodynamic therapy were widely applied in several reports. Chen and coworkers reported yet another example of the combinational gene/chemo/photothermal therapy by rattle-structured rough nanocapsules (Au@HSN-PGEA, AHPs).^[66] The nanocapsules were prepared by Au NRs (core) and polycationic mesoporous silica shell, exploiting the advantages of its surface roughness, NIR responsiveness, and light-triggered release ability for a trimodal cancer therapy (gene/chemo/photothermal). Sorafenib (SF, a hydrophobic antiproliferative and antiangiogenic drug) and antioncogene p53 were co-delivered using AHPs to demonstrate its application in light-triggered trimodal therapy and gene transfection in vivo.

2.2.3. Photodynamic Therapy

Photosensitizers such as chlorin e6 (Ce6)^[67] and methylene blue (MB),^[68] aminolevulinic acid (ALA),^[69] silicon phthalocyanine (Pc4), m-tetrahydroxyphenylchlorin (mTHPC),^[70] indocyanine green (ICG),^[71] and mono-L-aspartyl chlorin e6 (NPe6), has the ability to generate singlet oxygen species. Ce6 is the most commonly used PS molecule due to its rapid removal from the body and high singlet oxygen generation efficiency, with absorption peaks around 410 and 665 nm. However, there are some drawbacks associated with PS molecules such as poor water solubility and hydrophobic properties, which can be overcome by using nanocarrier systems, polymer modifications, and protein and peptide conjugations. Laser sources with precise emission wavelength are used to induce cytotoxic singlet oxygen generation based on appropriate absorbance of PS and nanomaterials. Although many PSs have shown their ability to inhibit the growth of cancer cells, there is still limited tumor selectivity, which can be improved by effective targeting strategies such as modifications with antibodies and aptamer. For instance, Wang et al. designed a targeted cancer therapy with switchable aptamer-based PS-AuNR platform to greatly enhance specific targeting and multimodal therapy for leukemia.^[72] The DNA sequence was chosen with cultured precursor T cell (acute lymphoblastic leukemia, ALL) line named CCRF-CEM as model target cells, a B-cell line from human Burkitt's lymphoma (Ramos) as the negative control, and Sgc8 as the aptamer-targeting agent, which has high affinity for human protein tyrosine kinase-7 (PTK7). Then, the as-prepared Ce6-labeled short DNA sequences were hybridized with the Sgc8 aptamer onto the Au NRs surface where complementary sequence A₁₅ was chosen as a reporter. In PTT-only treatment, the cell viability decreased to $\approx 63\%$ ($p < 0.001$) after being treated with Sgc8-NR/A₁₅ nanocomposites and 10 min of 750 nm laser irradiation, resulting in a temperature increase to 55 °C. When incubated with Ce6-labeled A₁₅/Sgc8-NRs followed by NIR irradiation to perform combinational PTT and PDT multimodal therapy, the cell viability dropped intensely to below 32% ($p < 0.05$). Tumor hypoxia condition limits the therapeutic effect of PDT owing to poor oxygen supply in tumor site or tumor vascular systems. To increase the oxygen sources in the hypoxic microenvironment of tumors, Zhang et al. designed smart NIR light/H₂O₂-triggered and O₂-evolving nanocomposites to overcome the hypoxic tumor tissue by self-sufficient O₂ generation.^[68] These smart theranostic nanocomposites (NCs)

(Figure 3A) were composed of phenyl mesoporous silica (APMs)-coated AuNRs core-shell nanostructure. APMs were filled up with [Eu(THA)₃(phen)] to activate MB, a typical PS with high quantum yield, by FRET effect and coated with catalase enzyme to improve the water solubility of MB. The APMEC@MB composite exhibited high stability during systemic circulation. Subsequently, tumor-targeted peptide (cRGD) was conjugated onto the surface of APMEC@MB to obtain APMECR@MB NCs. In this synergistic PDT and PTT process, the APMECR@MB NCs system contained catalase enzyme that could catalyze H₂O₂ into O₂. Since the malignant cancerous cells contained a high amount of H₂O₂ in the tumor site, the APMECR@MB NCs could produce a high quantity of ROS by converting the energy of 808 nm into 613 nm (visible region) to excite the MB molecules ($\lambda_{\text{ex}} = 613$ nm), enabling PDT treatment on hypoxic tumors. Besides, APMECR@MB NCs could be used as an efficient photothermal agent for PTT owing to LSPR peak of Au NRs. The confocal images of PC-3 cancer cells treated with APMECR@MB, APMECs@MB, and free MB are shown in Figure 3B while the cell viabilities after being incubated with free MB, APMECs, APMEs@MB, APMECs@MB, and APMECR@MB with 808 nm laser irradiation are shown in Figure 3C. The viability of PC-3 cells treated with APMECR@MB and NIR light irradiation decreased dramatically, clearly revealing the high inhibition efficiency of hypoxic tumor cells by NIR-triggered synergistic PTT and PDT. In a separate study, Choi et al. employed GSH-sensitive linkages to cross-link folic acid (FA) and AuNRs to achieve controllable disulfide bond release with high redox sensitivity.^[73] As GSH concentration is much higher in cancer cells than in normal cells,^[74] disulfide bonds can be cleaved faster in the reducing environment inside cancer cells. Based on this concept, the Au NRs composites with an aspect ratio of 3.84 induced significant hyperthermia effects and enhanced singlet oxygen generation to produce strong cell toxicity in MCF7 and A549 cell lines. As the MCF7 cells have higher amounts of overexpressed FA reporters than A549 cells, it resulted in lower cell viability as confirmed by in vitro experiment. Overall, the FA-PEG-P(Asp)-DHLA-AuNR100-SS-Ce6 nanocomposites with 5 min of 880 nm laser (200 mW cm⁻²) irradiation and subsequent 670 nm laser irradiation (0.1 mW cm⁻²) managed to achieve over 70% cell death.

3. Upconversion Nanoparticles

3.1. Luminescent Properties and Synthesis

Most conventional contrast agents exhibit luminescent emission with a Stokes shift, where they are excited by photons with high energy and subsequently emit photons of lower energy and longer wavelength.^[75] Conversely, the emission of upconverting nanoparticles (UCNPs) is based on an anti-Stokes process that converts low-energy photons such as NIR light into higher-energy photons in the ultraviolet (UV), visible, or NIR range.^[75b,76] The photon upconversion is related to real energy states with long lifetime in the f- and d-orbitals of lanthanide ions with more than one metastable level.^[77] The upconversion photoluminescence (UCPL) emits from the electronic transitions of 4f-4f orbital with concomitant wave functions localized within lanthanide ions.^[78] For instance, lanthanide-doped UCNPs

Figure 3. A) Scheme illustrating the assembly strategies of APMECR@MB NCs and the synergistic PDT/PTT mechanism of their treatment. B) Confocal images of PC-3 cells treated with APMECR@MB, APMER@MB, and free MB with calcein AM (green, live cells) and propidium iodide (red, dead cells) after 808 nm laser exposure for 5 min at 37 °C. C) In vitro toxicity evaluation of PC-3 cells treated with APMECR@MB, APMER@MB, or free MB, and 808 nm laser exposure for 5 min at 37 °C. Reproduced with permission.^[68] Copyright 2016, Royal Society of Chemistry.

Table 1. Cancer therapy applications of gold nanorods.

Precursor	Synthesis method	Treatment type	Injected dose	Laser wavelength [nm]	Power density [W cm ⁻²]	Irradiation time [min]	Therapy efficiency [%]	Ref.
HAuCl ₄ CTAB NaBH ₄ AgNO ₃	Seed-mediated growth	PTT/DDS	200 ppm	808	3	10	—	[59]
HAuCl ₄ CTAB NaBH ₄ 3-(Methacryloxy)propyl triethoxysilane	Seed-mediated growth/hydrothermal	PTT/DDS	9.5 mg	760	16	20	—	[60]
HAuCl ₄ CTAB NaBH ₄ AgNO ₃ NaOL	One-pot seedless technique	PTT	100 μm	808	1.0	5	64.2	[62]
HAuCl ₄ CTAB NaBH ₄ TEOS	One-pot approach	Gene therapy/DDS/PTT	100 μg mL ⁻¹	808	2	5	≈88	[66]

(Ln-UCNPs) can be defined as particles with trivalent lanthanide ions, and their emission properties are contributed by elements such as scandium(V) and yttrium(Y) from IIIB lanthanide series in the periodic table. Most studies of Ln-UCNPs were based on guest–host system by employing sodium yttrium fluoride (NaYF₄) as an efficient UC host and Yb³⁺ ions as guest sensitizers which collect and transfer energy to co-doped ions

such as Er³⁺, Ho³⁺, or Tm³⁺ to emit green, red, and blue lights, respectively, upon 980 nm laser irradiation (Figure 4).^[79]

Development of simple synthesis strategies to obtain high-quality Ln-UCNPs with well-controlled crystallinity, shape, composition, and size is a critical factor to enable tuning of their optical and chemical properties, which determines their applicability in various fields. In the past decade, many reports

Figure 4. The electron diagram of commonly used sensitizers (Er^{3+} and Tm^{3+}) and activators (Yb^{3+}). Reproduced with permission.^[79a] Copyright 2009, Royal Society of Chemistry.

Figure 5. A diagram of surface modification methods used to alter the surface chemistry of UCNP. Reproduced with permission.^[100] Copyright 2018, Royal Society of Chemistry.

have described the synthesis methods of Ln-UCNPs by thermal decomposition,^[80] hydro/solvothermal synthesis,^[81] Ostwald-ripening method,^[40] sol-gel processing,^[82] coprecipitation method,^[33,83] and ionic liquid-based synthesis.^[84] Among them, wet-chemistry approaches such as hydrothermal/solvothermal and thermal decomposition methods were widely applied in preparations of UCNPs with small size (<100 nm) and monodispersity for bioimaging and nanomedicine applications. For instance, in a typical process in hydrothermal synthesis, UCNPs were prepared from lanthanide compounds, fluoride

salts, oleic acid (OA), and 1-octadecene (ODE). The reaction was performed in a sealed autoclave or heating mantle at temperatures between 160 and 300 °C. The UCNPs were mainly synthesized in high-boiling organic solvents (i.e., OA, ODE) which resulted in controllable crystal growth on the hydrophobic nanoparticles surface. Normally, surface modification is required to form hydrophilic surfaces on these UCNPs before employing them in bioanalytical applications.^[85] In order to transform the hydrophobic UCNPs into water-soluble UCNPs, a few surface modification strategies are employed (**Figure 5**), such as ligand

exchange,^[86] LBL assembly,^[87] ligand removal,^[88] and core-shell nanostructure in particular surface silanization.^[89] Ligand oxidation technique utilizes the oxidation of carbon-carbon double bonds in the ligand by Lemieux-von Rudloff reagent to generate carboxyl functional groups. Chen et al. reported a method to encage the OA-stabilized hydrophobic NaYF₄:Yb/Er UCNP into carboxyl-based UCNP with water-dispersible properties using Lemieux-von Rudloff reagent (MnO₄⁻/IO₄⁻). However, its applicability to a limited number of ligands with unsaturated carbon-carbon bonds is a major drawback.^[90] Ligand exchange is another method to transfer hydrophilic ligands onto the surface of hydrophobic UCNP to obtain water-dispersible nanoparticles suitable for further bioconjugation. A class of hydrophilic ligands such as PAA,^[91] trisodium citrate,^[92] 3-mercaptopropionic acid (3-MPA),^[92] tetramethylammonium hydroxide (TMAH),^[93] PEG-phosphate,^[94] and PEI^[95] have all been used to cap UCNP. Most of LBL assembly procedures involve decorating the surface of UCNP using polymers, hydrophilic molecules, or amphiphilic polymers.^[96] Li et al. reported multiple LBL depositions of a positively charged polymer, poly(allylamine hydrochloride) (PAH), and a negatively charged polymer, poly(styrene sulfonate) (PSS), onto the surface of negatively charged UCNP to generate PAH/PSS/PAH UCNP nanocomposites.^[97] They successfully modified NaYF₄:Yb/Er nanoparticles with stable amine-rich shells. Advantages of LBL assembly include simplicity, well-controlled thickness, universality, high stability, and biocompatibility. However, LBL method is only applicable to hydrophilic nanocrystals. Silica coating is a common method to modify UCNP and is an essential process for further surface functionalization. There are two methods utilized in coating silica shell onto UCNP surface based on the formation of capping ligands. The first is Stöber method that is used to coat silica on hydrophilic or hydrophobic UCNP. The other method is based on sol-gel chemistry in a reverse micelle nanocarrier to introduce silica coating onto UCNP with hydrophobic capping ligands. Coating silica shells on UCNP surface can improve their stability in various buffers to facilitate facile functionalization with functional groups (-NH₂, -COOH, or -SH).^[89b,89c,98] Although silica shell coating provides many advantages such as controllable pore size, biocompatibility, and chemical stability for biomedical applications, there are still several limitations and drawbacks. Silica coating is unable to maintain dispersible and stable UCNP because of the large hydrodynamic radius. Besides, silica-coated UCNP have a propensity to aggregate and precipitate within a few hours to several months, and therefore exhibits poor stability and lower UC emission intensity in aqueous and buffer solutions.^[7a,99]

3.2. Biomedical Applications of UCNP

UCNP are attractive nanomaterials that demonstrate unique optical behavior which permits deep-tissue excitation, high resolution, low autofluorescence, and diversified excitation wavelength.^[21c,101] Thus, UCNP present a promising new generation of imaging contrast agents for bioimaging of cells, organ, and tissue. In this section, we discussed a few topics of UCNP-based cancer therapeutic applications including bioimaging, DDS, PTT, and PDT.

3.2.1. Bioimaging

In previous studies, conventional fluorophores, organic dyes, and quantum dots were found to be less suitable for bioimaging because of photobleaching, autofluorescence, and excitation wavelength in UV to visible region, which has limited light penetration depth. To overcome these drawbacks, the anti-Stokes characteristic of UCNP can be exploited for UCPL imaging using excitation in NIR spectral range, which falls within the important “optical transparency window (NIR-I, 700–1000 nm)” and “second biological window (NIR-II, 1000–1700 nm).” NIR light within these spectral ranges experience reduced scattering and are capable of penetrating deeper into the tissue. As such, the use of NIR-excited UCNP may further improve the signal-to-noise ratio of various imaging techniques.

Nonfunctionalized UCNP have been used to image a variety of cell lines such as HeLa cells, breast cancer cells, KB cells, HepG2 cells, and Panc-1 cells through cellular endocytosis. Du et al. demonstrated that the Ho³⁺-activated NaYbF₄ UCNP displayed bright green UC emission (${}^5F_4, {}^5S_2 \rightarrow {}^5I_8$) and red UC emission (${}^5F_5 \rightarrow {}^5I_8$) due to the transitions of Ho³⁺ ions (Figure 6A).^[102] As shown in Figure 6B, green and red UC emissions were observed in HeLa cells, demonstrating that the HeLa cells could be labeled by the UCNP for live cell imaging. Interestingly, Chen et al. reported that multicolor NaLuF₄ UCNP, which were co- or tri-doped with Yb³⁺/Er³⁺/Tm³⁺, were able to be utilized as fluorescent probes for imaging of living onion epidermal cell.^[103] By comparing conventional slice imaging and fluorescent images of UCNP-incubated living onion obtained using confocal fluorescence microscope equipped with 980 nm NIR diode laser, the latter images clearly showed the onion cell microstructures in vivo while conventional imaging has no detectable optical signals.

In an in vivo study, Alkahtani et al. utilized water-soluble Y₂O₃:Er, Yb UCNP (40–50 nm diameter) as efficient UCPL contrast agents to image the special geometry in fire ants.^[104] Y₂O₃:Er,Yb UCNP were fed to fire ants and the UCPL and scattering results were scanned by a 2D galvanoscanner at a scan rate of 100 Hz over 5 mm × 5 mm area, which were recorded using a photon counter (Hamamatsu photon counter model number, H7155-21). The UCPL spectrum with high signal-to-noise ratio displayed strong green UCPL signal based on radiative transitions of erbium ions under 980 nm diode laser (8 kW cm⁻²) using their homemade optical setup. The UCPL emission spectrum of different ants displayed slight variations despite the same particles being fed to them. These variations were contributed to the nanoparticles' temperature sensitivity, as the UCNP could be used for optical temperature sensing. The temperature can be recorded by measuring the ratio of 520 and 550 nm emission peaks of erbium-doped UCNP and using Boltzmann distribution on the biological sample.^[105] After using the UCNP for high-contrast imaging, the authors applied 3D X-ray imaging to confirm that the UCNP were actually inside the body of the fire ants.

Recently, dye-sensitized UCNP have been proposed and explored for optical bioimaging because of their ability to enhance the emission intensity by more than 10³–10⁴ times. This was attributed to the higher absorption cross-section in dyes compared to lanthanide ions.^[106] Many researchers have invested

Figure 6. A) The UC emission spectrum of the Ho^{3+} -activated NaYbF_4 UCNPs upon 980 nm laser excitation at room temperature (inset: TEM image and illustration of the energy level diagram of $\text{NaYbF}_4:\text{Ho}^{3+}$ UCNPs). B) In vitro images of HeLa cells incubated with $\text{NaYbF}_4:\text{Ho}^{3+}$ UCNPs with 980 nm laser irradiation: a) DIC image; b) TIRF image (green channel, 540 ± 40 nm); c) TIRF images (red channel, 650 ± 10 nm); d) merged images of (a-c); e) green; f) red; g) merged images with $100\times$ objective lens, and h) 3D image of UCNPs in live HeLa cell. Reproduced with permission.^[102] Copyright 2017, Elsevier.

Figure 7. A) A schematic illustration of amphiphilic polymer coating of Cy7-CS:Nd core-shell UCNPs to disperse them in aqueous solution (top). Multicolor UCPL from water-dispersed Cy7-sensitized ($\text{NaYF}_4:\text{Yb}^{3+}/\text{X}^{3+}$)@ $\text{NaYF}_4:\text{Yb}^{3+}/\text{Nd}^{3+}$ ($\text{X} = \text{Er}, \text{Tm}, \text{and Ho}$) UCNPs were exemplified (down). B) UCPL images in living HeLa cells incubated with phosphatidylcholine coated, Cy7-CS:Nd core-shell UCNPs. C) UCPL lymphatic imaging at 30 min post-injection of phosphatidylcholine coated, Cy7-CS:Nd core-shell UCNPs. All the emission spectra were obtained by 800 nm excitation. Reproduced with permission.^[109] Copyright 2016, Royal Society of Chemistry.

huge amounts of resources to develop dye-sensitized UCNPs with high quantum yield and efficient UCPL.^[107] Hydrophobic dye-sensitized UCNPs can be converted into hydrophilic phase by coating them with amphiphilic polymers or silica shells. For example, Wu et al. reported that IR-806-sensitized core-shell ($\text{NaYF}_4:\text{Yb}^{3+}/\text{Er}^{3+}$)@ $\text{NaYF}_4:\text{Yb}^{3+}$ UCNPs were encapsulated in water-soluble Pluronic F127 polymer.^[108] These dye-sensitized UCNPs were injected into the fmice model for optogenetic analysis. Similarly, the first application of dye-sensitized UCNPs for lymphatic imaging was reported by Zou's group in 2016.^[109] The as-prepared $\text{NaYF}_4:\text{Yb}, \text{Nd}, \text{Er} @ \text{NaYF}_4:\text{Nd}$ (abbreviated as CS:Nd) core-shell UCNPs were attached with NIR light-responsive cyanine dye derivative (abbreviated as Cy7) on the UCNPs surface. As shown in **Figure 7A**, these Cy7-CS:Nd core-shell UCNPs were loaded into a polymer (amphiphilic phosphatidylcholine) and exhibited UCPL in solution (photograph in **Figure 7A**). Importantly, the UCPL intensity was enhanced approximately 17 times because of the strong overlapping of absorbance spectrum between Cy7 and Nd^{3+} ions, resulting in energy transfer from Cy7 to Nd^{3+} ions. In addition, Cy7-based UCNPs have been applied for HeLa cellular and lymphatic imaging (**Figure 7B,C**) under 808 nm laser irradiation.

3.2.2. Drug/Gene Delivery System

Generally, UCNP-mediated DDS can be categorized into two directions: 1) NIR-triggered photocleavage of molecular moieties or drug and 2) polymer/silica-coated nanocarrier. Photochemical reactions can be activated by UV photons, which can trigger the release of drugs from DDS in living systems via effective photoactivation or photocleavage of organic bonds. However, UV light is often associated with high phototoxicity and limited tissue penetration, limiting its application in light-triggered therapy. Thus, UCNPs can act as a powerful platform to convert NIR irradiation into UV or visible emission that drive photochemical reactions for precise drug release at tumor site with minimal phototoxicity and greater light penetration.^[21a,110] Some groups have reported the use of photocaged molecules such as D-luciferin, nitric oxide,^[111] 5-fluorouracil (5-FU),^[112] and 2-nitrobenzylamine hydrochloride (NBA)^[13,113] in providing spatially and temporally controlled "on-command" drug delivery. Recently, Kang et al. reported UCNPs@mSiO₂ nanocomposites which were modified with photocleavable linker and Arg-Gly-Asp (RGD) peptide with molecular cap via cyclodextrin-adamantine host-guest complexation.^[114] Calcium regulators were loaded

Figure 8. A) Schematic illustration of the a) NIR-regulated upconversion-based PDD and b) the photolysis of the prodrug under upconversion emission from the YSUCNPs. B) TEM image of YSUCNPs; C) The photo-regulated release of chlorambucil (drug) from YSUCNP-ACCh and YSLnNP-ACCh (similar yolk-shell nanoparticle consisting of the $\text{NaYF}_4:\text{Yb}/\text{NaLuF}_4$ yolk without the Tm^{3+} activator) in PBS solution (pH = 7.5) controlled by a 980 nm laser irradiation at 570 mW cm^{-2} . D) The KB cells viability with different conditions (YSUCNP + hv; YSLnNP-ACCh + hv; YSUCNP-ACCh, and YSUCNP-ACCh + hv). hv: continuous-wave irradiation at 980 nm. E) Survival rate of mice intratumorally injected with 0.04 mL of 10 mg mL^{-1} YSUCNP-ACCh (purple line), YSLnNP-ACCh (green line), and 0.04 mL saline (blue line) on the 1st day and 9th day with daily irradiation of 980 nm laser (50 mW cm^{-2}) for 20 min for 16 days. Reproduced with permission.^[115] Copyright 2014, Royal Society of Chemistry.

into UCNP@mSiO₂ nanocomposite, and intracellular release of the calcium regulators was controlled by UV light emitted from UCNP@mSiO₂ nanocomposites under NIR light irradiation. Their findings proposed that these UCNP@mSiO₂ nanocomposites can be used to control macrophage phenotypes such as classically activated pro-inflammatory phenotypes (M1) or alternatively activated anti-inflammatory and pro-healing (M2), which could provide a potential treatment of inflammatory diseases.

In another study, Chien et al. designed and developed caged-UCNP nanocomposites for bioimaging and targeted drug release via uncaging process upon NIR light illumination.^[13] The caged-PEGylated UCNP@mSiO₂ UCNP nanocomposites comprised of PEGylated UCNP@mSiO₂ and folic acid (FA) linked via an amide bond between amine group from FA and carboxylate group from PEG. Then, photocaged molecule (NBA) was used as an FA mask through covalent amide bond formation. In addition, anticancer drug DOX was thiolated on the surface of PEGylated UCNP@mSiO₂ through disulfide bonds, which could be cleaved by lysosomal enzymes within the tumor cells to release DOX. In this design, the emitted UV light from UCNP@mSiO₂ upon 980 nm laser irradiation uncaged a photolabile group and permitted folate-conjugated UCNP@mSiO₂ to target and subsequently release DOX inside cancer cells. This work presented the novel approach of using photocaged molecules to cover the tumor-homing agent (i.e., folic acid) to prevent undesirable targeting of normal cells during circulation. Their results confirmed the concept that photocaged UCNP@mSiO₂ could act as a

nanoplatfrom to reduce adverse side effects and to improve selective targeting. In 2014, Zhao's group reported a different concept of phototrigger-controlled drug-release devices (PDDs) in tumor tissues of living animal.^[115] Their NIR-regulated PDDs were composed of yolk-shell-structured nanocage UCNP@mSiO₂ (YSUCNP, $\text{NaYF}_4:\text{Tm}^{3+}, \text{Yb}^{3+}/\text{NaLuF}_4$), mesoporous silica shells, 7-aminocoumarin derivative (as ACCh) which served as the cage, and anticancer drug chlorambucil which were loaded into the yolk-shell nanostructure (Figure 8A). The TEM image of yolk-shell-structured nanocage is shown in Figure 8B. The drug release on/off process was driven by 980 nm diode laser irradiation (Figure 8C). In their in vitro studies, significant KB cell death was observed in the group treated with YSUCNP-ACCh + hv, showing 50% cell viability because the drug was efficiently uncaged and released into the KB cells (Figure 8D). In addition, YSUCNP-ACCh was intratumorally injected into tumor-bearing mice on the first day and ninth day with 980 nm irradiation (50 mW cm^{-2}) for 20 min each day for 16 days of observation. In vivo results showed that the survival rate of mice with malignant S180 murine tumor model after YSUCNP-ACCh treatment was dramatically prolonged.

In the second method, anticancer drug or molecules were loaded into pores of mesoporous silica shells or polymer shells to exploit the huge surface area and large pore volume which can contain drugs or other molecules for chemotherapy purposes. Yang et al. first demonstrated the multifunctional core-shell-shell UCNP@mSiO₂ constructed by $\text{NaGdF}_4:\text{Yb}$,

Figure 9. A) Schematic illustrating the synthesis process of multifunctional core-shell UCNP@PAA nanocomposites and UCPL imaging and anticancer therapy (inset: TEM image of UCNP@PAA). B) The fluorescence spectrum and insert photographs of core-shell UCNP@PAA in cyclohexane solution exposed to a 980 nm laser (top) and 808 nm laser (bottom) (1: Er@Y@Nd, 2: Er@Y@Nd@Y, 3: Er@Y@Nd@Y@Er). C) Fluorescence microscopy images of MCF-7 cells treated with UCNP@PAA at 10 min, 3 h, and 6 h at 37 °C under 808 nm irradiation. (All scale bars are 20 μ m.) D) In vitro cytotoxicity of free DOX, UCNP@PAA-DOX, and UCNP@PAA in MCF-7 cells after 48 h of incubation. E) The tumor volume inhibition of mice after treatment with saline solution (control), pure DOX, UCNP@mSiO₂-DOX, and UCNP@PAA-DOX. Reproduced with permission.^[118] Copyright 2015, Wiley-VCH.

Er@NaGdF₄:Yb@NaNdF₄:Yb, followed by conjugation with CuS nanoparticles and simultaneous loading of anticancer drug DOX into the mesoporous silica holes.^[116] Their results showed that the CuS nanoparticles could induce photothermal effect upon NIR laser irradiation. Meanwhile, DOX molecules were gradually released due to the increase in temperature, resulting in a synergistic therapeutic effect by PTT/chemotherapies. In contrast, some literature described that mesoporous silica shell coating on UCNP exhibited lower capacity of drug loading and more rapid drug release than stimuli-responsive drug release systems, especially pH-responsive and thermo-responsive polymers.^[117] For instance, Liu et al. reported the 808 nm excited PAA-coated UCNP nanostructures (Er@Y@Nd@Y@PAAUCNPs, **Figure 9A**) which were constructed by LBL approach.^[118] The optimized Er@Y@Nd@Y UCNP displayed UCPL intensity 12.8 times higher than Er@Y@Nd UCNP upon 808 nm excitation, as described in **Figure 9B**. Moreover, Er@Y@Nd@Y@PAA UCNP could perform as a pH-responsive nanocarrier with a higher loading capacity of DOX compared to UCNP@mSiO₂, as indicated by in vitro and in vivo experiments. In vitro cytotoxicity results by MTT assay (**Figure 9D**) and fluorescence microscopy images of MCF-7 cells (**Figure 9C**) were evaluated in three treatment groups of free DOX, DOX-loaded UCNP@PAA, and UCNP@PAA on MCF-7 cells. The results displayed comparable cytotoxicities between free DOX and DOX-loaded UCNP@PAA at the same DOX concentration, which indicated that the

UCNP@PAA was a pharmacologically active drug nanocarrier. The results of UCNP@PAA showed no cytotoxicity in vitro. In the in vivo studies, mice models were divided into four treatment groups, namely saline solution (as control), DOX only, UCNP@mSiO₂-DOX, and UCNP@PAA-DOX. UCNP@PAA-DOX exhibited better therapeutic efficacy by inhibiting 89% of the tumor while UCNP@mSiO₂-DOX and DOX-treated groups only managed to inhibit 75% and 70% of the tumors, respectively (**Figure 9E**).

Effective and specific delivery of therapeutic genetic materials into cells have been extensively studied in recent years, with materials such as polymeric lipids, peptides, and viral vectors become commonly used as gene transfection agents.^[119] The approach of using functionalized UCNP in gene therapy have drawn much attention owing to their unique optical and chemical properties. For instance, Jayakumar et al. presented a remote-controlled gene expression using photocaged DNA/siRNA molecules encapsulated into mesoporous silica-coated UCNP.^[120] The silica coating of UCNP increased the capacity of DNA/siRNA loading and delivery. NIR-to-UV UCNP could be used to trigger the release of caged nucleic acids in solution, in cells, and deep tissues. In a study to mimic deep-tissue activation, cells transfected with UCNP-containing photocaged green fluorescent protein (GFP) plasmids were subsequently loaded in a PDMS device and then transplanted into mice. NIR irradiation activated the cells in the PDMS device

Figure 10. A) Schematic illustration of the synthesis and modification process, UCPL/magnetic resonance imaging (MRI), intracellular chemotherapy, and PTT using UCNPs@Au-DOX nanocomposites. B) The UCPL spectra of cit-UCNPs, cit-UCNPs@Au, and UCNPs@Au-DOX in water ($400 \mu\text{g mL}^{-1}$) under excitation of 980 nm laser (1.5 W cm^{-2}) (the inset is a TEM image of cit-UCNPs@Au). C) The Infrared thermal images of the different concentrations of UCNPs@Au-DOX nanocomposites under 808 nm laser irradiation (1.5 W cm^{-2}) (time points: 0, 1, 2, 3, 4, 5, 6, 7, and 8 min). D) The cytotoxicity assays of HeLa cells incubated with various concentrations of free DOX, cit-UCNPs@Au, and UCNPs@Au-DOX with and without 808 nm laser irradiation (1.5 W cm^{-2} , 8 min of break after every 8 min of irradiation for 3 times) (control group: HeLa cells were cultured in medium solution). Reproduced with permission.^[125] Copyright 2017, Royal Society of Chemistry.

under the skin, and release of pDNA or siRNA subsequently induced specific gene expression or downregulation for therapeutics. In another study, Wang et al. prepared LBL multi-layered polymer-coated UCNPs loaded with Ce6 and siRNA to target the Plk1 oncogene.^[121] Toxicity to cancer cells was $\approx 35\%$ after sole Plk1 gene silencing and higher ($\approx 50\%$) after sole PDT therapy. On the other hand, the combination of NIR-triggered PDT and gene therapy enhanced the tumor-specific toxicity to $\approx 80\%$.

3.2.3. Photothermal Therapy

Lanthanide-doped nanoparticles such as NaYF₄ with high concentrations of Nd³⁺ can induce local temperature increase upon 532 nm laser irradiation, with the potential for PTT application.^[122] However, visible light presented the drawback of phototoxicity and limited penetration depth. While UCNPs have the ability to absorb NIR light and subsequently emit visible light, these particles cannot be used by themselves for PTT since they lack the capability to produce thermal effect. This can be solved by using NIR light-responsive UCNPs modified with silica shells and coupled with plasmonic nanomaterials such as metallic nanoparticles/nanoshells, inorganic semiconductors,

and enzymes. For instance, Ai et al. reported that the enzyme-triggered covalently cross-linked UCNPs exhibited an enhanced upconverted light emission under 808 nm illumination.^[123] Furthermore, multifunctional UCNPs can be easily coupled to plasmonic nanoparticles that have high extinction coefficient and possess PTT capability. Recently, He et al. reported silica-coated UCNPs conjugated with gold nanoparticles (AuNPs) and gold nanostars (AuNSs) onto the UCNPs surface.^[124] Zinc phthalocyanine (ZnPc), a type of PS was loaded into the silica shells of the Au-UCNP clusters to obtain highly emissive agents for both in vitro imaging and simultaneous PTT and PDT. The results of their studies showed that ZnPc loaded AuNS-UCNP clusters could simultaneously induce PTT and PDT to effectively increase cell death by over 20% than either modality alone.

Another study was reported by Wei et al. in 2017, in which they synthesized cit-UCNPs@Au NPs (cit: citrate) by using a typical solvothermal method to produce the UCNPs (NaYF₄:Yb,Er@NaGdF₄) followed by in situ growth of Au NPs on the surface of the UCNPs.^[125] As shown in **Figure 10A**, their successful strategy demonstrated chemotherapy and PTT using a new chemotherapy prodrug, SH-PEG-DOX, and intracellular imaging by UCPL and magnetic resonance imaging (MRI). Figure 10B displayed the UCPL signals of cit-UCNPs, cit-UCNPs@Au, and UCNPs@Au-DOX in water ($400 \mu\text{g mL}^{-1}$)

Figure 11. A) Schematic illustration of the penetration depth of light with different wavelengths in a tissue model. Reproduced with permission.^[128] Copyright 2014, Chemical Society Reviews. B) Synthesis process of SUCNPs@mSiO₂ and its mechanism in PDT. C) Tumor growth curves in mice groups treated with PBS, SUCNPs, ZnPC+MC540 UCNPs@mSiO₂, ZnPC+MC540 SUCNPs@mSiO₂. Reproduced with permission.^[129] Copyright 2015, Royal Society of Chemistry.

under excitation of 980 nm laser, and a TEM image of cit-UCNPs@Au. To evaluate the photothermal performance of UCNPs@Au-DOX, infrared thermal images were recorded every minute for 8 min for different concentrations of UCNPs@Au-DOX under continuous irradiation with an 808 nm laser (1.5 W cm⁻²). As shown in Figure 10C, the temperature increased in a concentration-dependent manner, as can be observed with reference to the temperature bar ranging from 11.8 to 95.7 °C. The in vitro PTT/chemotherapy results were shown in Figure 10D, where various concentrations of free DOX, cit-UCNPs@Au, and UCNPs@Au-DOX were incubated with HeLa cells with and without 808 nm laser irradiation for 3 × 8 min, with 8 min break in between irradiations. Obvious cell death and excellent synergistic effect of chemotherapy and PTT were achieved as indicated in reduced viabilities of cells treated with cit-UCNP@Au (18.6%) and UCNPs@Au-DOX (3%) with 808 nm laser irradiation. Another material, nanographene oxide (NGO), with single layer or multilayer of sp²-bonded carbon atom has been used as an effective PTT agent.^[126] For example, Li et al. proposed NGO-coated UCNPs (NaLuF₄:Er³⁺, Yb³⁺) nanocomposites that act as an NIR imaging diagnosis and therapy nanoplatform with great material stability and a high photothermal conversion efficiency under 808 nm laser (2.0 W cm⁻²).^[127] In this work, the photothermal conversion efficiency of UCNPs@NGO was ≈40%, which was higher than the efficiency of NGO alone (≈35%). Furthermore, the results also displayed that the UCPL spectra from both UCNPs@OA and UCNPs@NGO in water exhibited three intense characteristic emission bands at 520, 540, and 653 nm, respectively, which were utilized for in vivo UCPL imaging of white mouse under excitation of 980 nm.

3.2.4. Photodynamic Therapy

The penetration depth of light with different wavelengths in a tissue model is shown in Figure 11A. It shows that visible light has poor penetration depth and the high energy associated with visible light may damage healthy cells during phototherapy.^[128] To date, most studies have focused on combinations of PSs and UCNPs to develop NIR-triggered PDT nanoplatforms, since UCNPs are able to emit high-energy photons in UV to visible region under NIR excitation. Two kinds of PSs (ZnPC and MC540) were loaded into mesoporous silica-encapsulated UCNPs (β-NaYF₄:Yb³⁺, Er³⁺) as reported by Gao et al.^[129] Interestingly, they used a stem-cell-membrane-coated UCNPs (SUCNPs@mSiO₂) to mimic mesenchymal stem cell, resulting in longer blood circulation time, improved tumor-targeting capacity, and increased antitumor efficacy. In Figure 11B, the two-step process was illustrated: i) the stem cell-membrane vesicles were derived from mesenchymal stem cells and ii) the stem cell-membrane vesicles were conjugated with dual-PS-loaded UCNPs@mSiO₂. The generation of cytotoxic ROS was induced by NIR light which activated the PSs in SUCNPs@mSiO₂. Furthermore, the SUCNPs@mSiO₂ displayed two emission peaks in green (≈540 nm) and red (≈660 nm) wavelengths to excite MC540 and ZnPC, respectively, for PDT treatment. The in vivo results showed obvious tumor growth inhibition efficacy of approximately 66% in the dual-PS-loaded SUCNPs@mSiO₂ group relative to the PBS-injected group (Figure 11C). The stem cell-membrane coating rendered not only good tumor-targeting functionalities of stem cells but also prolonged blood circulation time with immune escape capability. Besides, other materials such as

Figure 12. A) Schematic illustration of the PDT, PTT and chemotherapy of UCNP@ZrO₂-Ce6/DOX/PCM multifunctional nanocomposites under 808 nm NIR laser excitation. B) TEM image of UCNP@ZrO₂-Ce6/DOX/PCM. C) UV-vis absorption spectra of UCNP@ZrO₂-Ce6/DOX/PCM under 808 nm laser irradiation, and the UV-vis absorption spectra of Ce6 molecules. D) In vitro heating curves of UCNP@ZrO₂-Ce6/DOX/PCM with different times (saline solution as the control) under NIR irradiation (power density: 0.5 W cm⁻² for 4 min). E) In vitro anticancer efficiency of different types of as-synthesized samples with or without 808 nm laser irradiation. Reproduced with permission.^[133] Copyright 2017, Elsevier.

ZnO or TiO₂ were used as PSs for PDT treatment, because of their good biocompatibility, high reactivity, water solubility, and long circulation time in the body.^[130] For instance, ZnO nanoparticles generated ROS upon UV light irradiation which caused cell membrane destruction, resulting in the efflux of cytoplasm and subsequent cell death. When TiO₂ nanoparticles were used as PSs, radicals were generated via redox reactions of O₂ or H₂O at the TiO₂ surface under visible or UV light irradiation.^[21b,131] Tong et al. reported core-shell UCNP@mSiO₂/TiO₂ nanocomposites with UCNP as core structures and mesoporous silica coating as shell structures, with continuous assembly TiO₂ nanoparticles inside the pores of mSiO₂.^[132] Moreover, they developed a NIR light-photocontrolled UCNP@mSiO₂/TiO₂ nanoplatform with o-nitrobenzyl derivative linker (TC linker) and anticancer drug DOX for synergistic bioimaging, chemotherapy, and PDT purposes. Upon 980 nm irradiation, ROS were generated from TiO₂ by upconverted UV excitation which also induced the TC linker to undergo photodecomposition, releasing DOX in the process.

Some efforts are aimed at developing novel treatment strategies using nanoparticles capable of multimodal imaging and theranostics with triggered release. Feng et al. reported a novel theranostic system for remote-controlled drug release, multimodal biomedical imaging (UCPL, MRI, and CT), and syner-

gistic cancer therapy (chemotherapy/PTT/PDT).^[133] Core-shell-structured UCNP (β-NaGdF₄:Yb/Er@β-NaGdF₄:Yb/Nd) were used as UCPL, MRI, and CT imaging agents (Figure 12A). In the synthesis process, hollow and mesoporous ZrO₂ nanocarriers with large surface area and pore size were used to encapsulate the UCNP@SiO₂ surface by a sol-gel method. The resultant nanocomplex is shown in Figure 12B. In addition, these ZrO₂ nanoparticles with excellent biocompatibility also presented good CT imaging capability. The UCPL spectrum of UCNP@ZrO₂-Ce6/DOX/PCM nanoparticles is shown in Figure 12C. To impart therapeutic capability to the nanocomplex, Ce6 (PS) and DOX were loaded into the UCNP@ZrO₂ nanocarrier. Subsequently, tetradecanol as phase-change material (PCM) with a melting point of 40 °C was used to cover the channels of ZrO₂ (Figure 12D). These multifunctional UCNP@ZrO₂-Ce6/DOX/PCM nanocomposites formed a thermal-responsive nanosystem capable of releasing DOX and generating ROS under NIR light irradiation. Under 808 nm laser excitation, the PCM molecules dissolved as temperature of the medium increased to 47.2 °C, which led to the release of DOX and ZrO₂ for chemotherapy and PDT, respectively. The viability of cells treated with UCNP@ZrO₂-Ce6/DOX/PCM and 808 nm NIR laser excitation was found to be as low as 14.8%, as shown in Figure 12E.

Table 2. Cancer therapy applications of upconversion nanoparticles.

Precursor	Synthesis method	Treatment type	Injected dose	Laser wavelength [nm]	Power density [W cm ⁻²]	Irradiation time (min)	Therapy efficiency [%]	Ref.
RECl ₃ (RE ³⁺ = Y ³⁺ , Yb ³⁺ , Nd ³⁺ , Er ³⁺) OA, ODE	Thermal decomposition	Ex vivo imaging	2 mg mL ⁻¹	808	3.5	–	–	[109]
YCl ₃ , YbCl ₃ , TmCl ₃ , NH ₄ F, OA, ODE	Thermal decomposition	DDS	100 ppm	980	1.8	60	–	[13]
YCl ₃ , YbCl ₃ , ErCl ₃ , OA, ODE	Solvothermal method	PTT/PDT	70 μg mL ⁻¹	980	0.05	20	80	[115]
YCl ₃ , YbCl ₃ , ErCl ₃ , OA, ODE	Thermal decomposition	PTT/PDT	4.0 mg kg ⁻¹	808	51	–	89	[118]
NaGdF ₄ (Gd:Yb:Er = 78%:20%:2%) PAA, PEG	Thermal decomposition	PDT/gene therapy	0.5 mg mL ⁻¹	980	0.5	20	≈80	[121]
RE(CH ₃ CO ₂) ₃ (RE = Y, Yb, Er, and Nd), NH ₄ F, NaOH, OA, ODE	Thermal decomposition	PDT	30 mg mL ⁻¹	808	0.4	45 (5 min per session)	–	[123]
NaYF ₄ :Yb,Er@NaGd citrate, OA, ODE	Solvothermal methods	PTT/DDS	200 μg mL ⁻¹	808	1.5	10	97	[125]
LuCl ₃ , YbCl ₃ , ErCl ₃ , OA, ODE, NH ₄ F, NaOH	Thermal decomposition	PTT	0.5 mg mL ⁻¹	808	1	5	≈100	[127]

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4. Carbon Dots

4.1. Luminescence Properties and Synthesis

Carbon dots (CDs) are defined as carbon nanoparticles with dimensions less than 10 nm. They are composed of amorphous or crystalline core predominantly of sp² carbons with lattice spacing similar to graphitic or turbostratic carbon.^[134] Typically, CDs have strong absorption in short wavelength region of 230–340 nm with a tail extending to the visible region. The first absorption peak located around 230–280 nm is attributed to π – π^* transition of the C=C bonds and the second peak around 300–340 nm is associated with n– π^* transition of the C=O surface group. However, CDs that possess absorption in longer wavelengths are highly desirable for phototherapies. Hence, many studies have explored the modulation of their absorption spectra to cover a wider range of wavelengths by surface functionalization or heteroatom doping. For instance, Sarkar and coworkers initiated a theoretical study using 1 nm nitrogen-doped CDs as a model to study the effect of various nitrogen centers on the absorption spectrum of the CDs. Their study revealed that graphitic nitrogen exhibited a pronounced electron-doping effect that changed the electronic energy levels of CDs, leading to red-shifting of their absorption spectrum.^[135] In line with this study, Martindale further confirmed that absorption in 300–800 nm was 20 times higher in graphitic nitrogen-doped CDs compared to other CDs.^[136] The strong absorption in the visible–NIR range is vital for phototherapy applications.

Excitation-dependent PL is one of the most intriguing features of CDs as diverse emissions can be obtained from a single type of CD by varying the excitation wavelength. However, the mechanism underlying this property remains unclear. Particle size differences, shapes, precursors, and synthesis methods have been reported as contributing factors to the excitation-dependent behavior. Among these, size variation and the different functional moieties that exist on the surface of CDs are the more widely accepted factors.^[138] Though this optical property is highly ben-

eficial for multicolor imaging applications, emission intensities were found to reduce as the emission red-shifted, causing the quantum yield at longer wavelength emission to suffer. This setback drove many groups to derive CDs with comparable quantum yields throughout the emission spectrum. An outstanding work in preparing multicolor CDs with comparable emission intensities at different wavelengths was carried out by Pan and coworkers (**Figure 13**).^[137] The group prepared multicolor CDs via microwave-assisted pyrolysis of citric acid in formamide solution. Formamide played a crucial role in the formation of multicolor CDs, unlike the blue-color-emitting CDs prepared without formamide. From the emission spectra, it was seen that there were three dominating peaks at 466, 555, and 637 nm. The broad absorption peak, especially in the visible light region, signified the existence of numerous electronic absorption transitions.

CDs have also been found to exhibit UCPL. Generally, multiphoton absorption is the key contributing factor to this optical phenomenon. This process involves absorption of two or more photons usually coming from a femtosecond NIR laser source, followed by electronic transitions from HOMO to LUMO. The emitted light has a shorter wavelength and higher energy as compared to the excitation wavelength.^[139] Despite the many advantages of UCPL such as deeper penetration depth, lower photobleaching, minimal phototoxicity, and lesser tissue autofluorescence, there have been controversial opinions about the origin of the UCPL in CDs. A report by Wen and coworkers suggested that the UCPL observed in CDs did not originate from the upconversion process, but rather from downconversion PL excited by the leaking component from the second order diffraction light $\frac{\lambda}{2}$ which coexisted with the selected first order excitation wavelength, λ .^[140] This component could be eliminated by adding a long-pass filter at the excitation pathway and the UCPL was no longer observed. Hence, extra precaution is needed when analyzing the UCPL in CDs.

Many methods have been employed to modulate PL emission of CDs to cover the whole visible and NIR region, such as careful selection of precursors, control of synthesis processes

Figure 13. S) Schematic illustrating the synthesis of multicolor emission CDs. B) PL spectra of CDs under different excitation wavelengths. C) UV-vis absorption spectrum of CDs. D) Photographs of PL emission recorded from 330 nm to 600 nm in 30 nm increments. Reproduced with permission.^[137] Copyright 2015, Wiley-VCH.

and parameters, surface modifications, and heteroatom dopings. For instance, Jiang et al. investigated preparation of CDs that emitted blue, green, and red PL by using various kinds of phenylenediamines precursors.^[142] o-Phenylenediamines, m-phenylenediamines, and p-phenylenediamines were subjected to solvothermal treatment at 180 °C for 12 h to produce green-, blue-, and red-emitting CDs, respectively, under a single UV excitation wavelength. It was found that the various carbon precursors resulted in different particle sizes and nitrogen contents, which was believed to be responsible for the difference in PL emissions. The resultant CDs possessed PL quantum yield (QY) as high as 26.1% in ethanol solution and exhibited UCPL under excitation by 800 nm femtosecond laser. In another report, Yuan et al. reported a solvothermal synthesis route to prepare multicolor carbon quantum dots (CQDs).^[141] By varying the precursors, synthesis duration, and solvents, CQDs with different particle sizes were produced (Figure 14). The increasing size of CQDs corresponded to red-shifts in PL emissions and first excitonic absorption wavelengths, which indicated that the bandgap transition of the CQDs originated from quantum confinement effect.

In contrast with PL emissions of semiconductor QDs which depend on quantum confinement effect corresponding to the particle sizes, PL emissions of CDs have been reported to be associated with the surface functional groups.^[134] Hence, surface modification is another route to achieve multicolor and long wavelength emissions in CDs. Nie and coworkers reported preparation of excitation-independent blue-emitting CDs and excitation-dependent multicolor fluorescent CDs by refluxing chloroform and diethylamine for different time durations.^[143]

Detailed studies were carried out to investigate the surface states and it was found that surface moieties such as C=O and C=N were found on multicolor CDs, which could introduce a lot of structural configurations and new energy levels, resulting in many electronic transition possibilities. This study allowed the emission of CDs to be tuned to cover the whole visible spectrum. Zhang and coworkers developed a different approach in controlling the surface properties to obtain CDs with different emission spectra.^[144] In their report, PEG₄₀₀ was first heated up in a round-bottom flask at 150 °C for 12 h until a faint yellow solution was formed. Blue fluorescent CDs (B-fCDs) were obtained by subjecting the faint yellow solution to dialysis. The faint yellow solution was added with PEG₁₀₀₀ and heated up for another 6 h at 150 °C until a golden yellow solution was obtained. Green fluorescent CDs could be obtained by dialyzing this golden yellow solution. To obtain CDs with longer emission wavelength, 2,2'-(ethylene-dioxy)-bis(ethylamine) was added to the golden yellow solution and heated up for another 1–1.5 h at 150 °C, until the color of the solution changed into brown. The resultant solution was dialyzed and purified by silica gel column chromatography, producing orange fluorescent CDs. It was believed that the step-by-step surface passivation had an impact on the C–N bonds which could modify the electronic structure of CDs by generating low-energy bandgaps, therefore modulating their emission properties.

Similar to surface modification, many groups have reported the influence of heteroatoms doping on PL properties of CDs. In a work by Yang and coworkers, it was reported that doping with nitrogen, sulfur, and selenium was able to influence the optical

Figure 14. A) Schematic preparation of multicolor CQDs from citric acid under different solvents and synthesis durations. B) Photographs of multicolor CQDs under white light (left) and 365 nm UV light excitation (right). Reproduced with permission.^[141] Copyright 2016, Wiley-VCH.

properties of CDs.^[145] Carbon nanoparticles from Chinese ink as carbon precursors were first oxidized and cut to produce oxidized CQDs which had an emission peak at 482 nm. These CQDs were further reduced and doped with either nitrogen, sulfur, or selenium using a one-step hydrothermal method. The group found that nitrogen-doped CQDs experienced blue-shift (428 nm) of their PL emission while sulfur- (539 nm) and selenium- (563 nm) doped CQDs experienced red-shift of their PL emissions. The effect of heteroatoms on PL emission was explained by the electronegativity of heteroatoms. Sulfur and selenium have low electronegativity, thus when they were doped in CQDs, they could serve as electron donors which resulted in red-shift of the PL emissions. In contrast, the PL emission blue-shifted upon doping with nitrogen. Apart from PL, doping of heteroatoms enables tuning of absorption properties to become more responsive toward long wavelength excitation. For instance, Geng and coworkers prepared nitrogen and oxygen co-doped CDs that had a broad range of absorption from visible light to NIR.^[146] The group attributed the strong absorption in NIR range to oxygen- and nitrogen-containing moieties at edges of the CDs. Graphitic nitrogen atoms tended to inject excess electrons into the unoccupied π^* orbitals and significantly reduced the HOMO–LUMO gap and the energies of the corresponding optical transitions, leading to a red-shift of the absorption spectrum. Likewise, oxygen-containing functional groups also reduced the energy levels and caused the red-shift of the absorption spectrum. The high absorption in NIR range allowed the CDs to serve as a good PTT agent with a conversion efficiency of 38.3% at low power density (0.8 W cm^{-2}).

Besides tuning and modifying the optical properties of CDs, doping with metal heteroatoms such as gadolinium, copper, and gold, can render CDs with new capabilities. For instance, Zhao

and coworkers prepared a novel gadolinium and ytterbium co-doped CDs through a facile one-step hydrothermal process.^[147] The resultant CDs not only possessed outstanding optical properties, but also a high longitudinal relaxivity and excellent X-ray absorption performance which allowed the CDs to be employed as a multimodal probe for MRI and CT imaging of xenografted tumor model with enhanced contrast.

4.2. Biomedical Applications of CDs

4.2.1. Bioimaging

Owing to its fascinating optical properties, including tunable absorption and PL spectrum and excellent photostability, many groups have employed CDs as fluorescent labels for long wavelength, multicolor, and/or multimodal imaging. Lu and coworkers developed NIR-emitting polymer CDs, which at the same time also displayed UCPL capabilities (**Figure 15**).^[148] Dopamine and o-phenylenediamine were selected as carbon precursors due to their molecular structures which favored the generation of large conjugated sp^2 structure. By optimizing the hydrothermal temperature, the precursors underwent a dehydration process to form intertwined polymer chains with benzene rings and heterocycles in the backbones. The cross-linked polymer chains were the dominant structure which contributed to emission in NIR wavelength. The excitation-independent CDs emitted strong deep-red and NIR luminescence centered at 710 nm with a shoulder peak at 665 nm and a high PL QY of 26.28% using 540 nm excitation. The CDs also exhibited UCPL properties under NIR femtosecond pulsed laser excitation. Similar to the one-photon PL, this UCPL also exhibited a peak emission at 660 nm and

Figure 15. Schematic diagram of the preparation and applications of CDs. Reproduced with permission.^[148] Copyright 2017, Wiley-VCH.

shoulder peak at 701 nm under 800 nm pulsed laser excitation. The group later employed these outstanding properties for bioimaging of nude mouse. CDs were subcutaneously injected into the back of a nude mouse. As a result, bright fluorescence with excellent signal-to-noise ratio at excitation and emission wavelengths of 540 and 600 nm, respectively, could be observed. The carbon nanodots were also employed for light-emitting diode applications.

In Parvin's work, the group employed dual-emission CDs for in vitro and in vivo imaging of living tissues.^[149] CDs were prepared by hydrothermal synthesis of a solution consisting of ethylene diamine, phosphoric and citric acids under ambient pressure, and the resultant CDs had emissions in green (QY = 30%) and red (QY = 78%) wavelengths under different excitation wavelengths, indicating their excitation-dependent PL. Standard toxicity assay confirmed that the CDs posed no significant toxicity threat to macrophage cells at concentrations up to 1 mg mL⁻¹. In vivo studies further confirmed that these CDs can be used as a fluorescent agent to label tumor cells in nude mice. Interestingly, the CDs also exhibited photoacoustic (PA) signals under NIR light irradiation which can be used for PA imaging. PA images taken at different time intervals indicated relatively constant PA signals from CDs which had accumulated in the tumor region, even after extended circulation in blood, implying the stability of these CDs. Histological examination further confirmed that the observed fluorescence and PA signals originated from the CDs that had accumulated in the tumor.

Several studies have reported multiple imaging modalities using CDs doped or functionalized with heteroatoms. Shi et al. chelated Gd³⁺ ions on the surface of cyclic DTPA dianhydride-functionalized CQDs through carbodiimide chemistry.^[150] The doped CQDs contained 8.06% w/w Gd³⁺ with an enhanced longitudinal relaxivity of 56.72 mM⁻¹ s⁻¹. The high longitudinal relaxivity is vital for a stronger signal-to-noise ratio and would provide enhanced imaging efficacy. In another report, Yu and coworkers developed a one-step hydrothermal approach to prepare Gd-doped CDs for dual-mode fluorescence and MRI.^[151] The as-prepared CDs exhibited strong blue PL with a high PL

QY of 69.86% and were able to be used as a fluorescent label. The Gd-doped CDs had a comparatively higher longitudinal relaxivity (14.33 mM⁻¹ s⁻¹) than commercially available Magnevist (4.5 mM⁻¹ s⁻¹). It is worth noting that in both cases, Gd ions were functionalized onto the exterior of CDs. Hence, fluorescence properties of the CDs were not perturbed.

Du and coworkers developed gadolinium-doped CDs (Gd-doped CDs) for MRI-guided radiotherapy of tumors.^[152] Gd-doped CDs were first prepared through a one-step hydrothermal synthesis route with an average dimension of ≈ 18 nm and had a significantly higher relaxivity of 6.45 mM⁻¹ s⁻¹ compared to commercially available contrast agent Magnevist (4.05 mM⁻¹ s⁻¹). The CDs also had a relatively long circulation time of ≈ 6 h which allowed efficient passive tumor targeting through the leaky vasculature of solid tumors. This was further validated by using subcutaneous liver cancer models in mice. Accumulation of the Gd-doped CDs in subcutaneous tumor region led to the region being brighter than surrounding healthy tissues with relative signal enhancement reaching 1.93 and 1.74 when evaluated using coronal and transverse scanning, respectively. Their work also demonstrated that with the combination of radiotherapy, Gd-doped CDs had a remarkable effect in inhibiting the growth of solid tumors.

While most CD-based imaging is based on conventional routes of excitation and collecting their fluorescence emission, other innovative imaging strategies have been employed. For instance, Yang and coworkers employed a FRET-based, oxygen-sensitive system for tumor imaging.^[153] Carboxyl-functionalized ruthenium (II) complex with red emission and oxygen-level-dependent intensity were conjugated through simple EDC/NHS coupling with CDs which displayed UCPL under NIR light. Subsequently, PEGylation was carried out to induce aggregation of the resultant polymeric probe. The emission of the resultant CD-Ru-mPEG probe was oxygen sensitive and could be used to image tumor, which is hypoxic in nature. In vivo imaging was carried out on a mouse model with the right leg being ligatured to block arterial cruralis circulation and thus creating a hypoxic condition. After being administered with the complex to both legs, PL was observed only from the right leg with gradual intensity

Figure 16. Schematic diagram of the delivery mechanism of CDs nanocomplex: 1) negatively charged CDs nanocomplex can afford a longer circulation period, 2) accumulation of CDs nanocomplex to tumor site through EPR effect, 3) CDs nanocomplex response to the extracellular pH and the surface charge being converted, 4) high uptake by the cancerous cells, 5) endosomal escape made easy by “proton sponge” effect and controlled cisplatin release from cisplatin (IV) as a result of reductive environment of cytosol, 6) cisplatin binding with DNA to induce cytotoxicity. Reproduced with permission.^[154] Copyright 2016, American Chemical Society.

enhancement over time, while the left leg exhibited negligible luminescence. To further demonstrate the capability for tumor imaging, nude mice bearing subcutaneous HeLa tumors were intravenously injected with the CD-Ru-mPEG probe and it was found that luminescence was able to be observed in the tumor region. Their results showed that the CD-Ru-mPEG were able to reach the tumor tissues through the circulatory system and could be effectively used as an innovative alternative for tumor imaging.

4.2.2. Chemotherapy and Gene Therapy

Apart from the excellent optical properties, low toxicity, and facile preparation procedures, ease of functionalization and modification to the surface properties of CDs give them an edge over other commonly used nanomaterials to serve as a platform for delivery of therapeutic molecules. In an outstanding work by Feng and coworkers, the group utilized a pH-responsive charge conversion approach to enhance the release of cisplatin (IV) from CDs which served as nanocarriers (**Figure 16**).^[154] It is commonly known that regular physiological pH is around 7.4, while at the tumor site the pH decreases to 6.8, as a result of improved glycolysis and plasma membrane proton-pump activity of cancer cells. The CDs were first covalently bonded with cisplatin (IV) by electrostatic interaction followed by conjugation with PEG-(PAH/DMMA). PEG-(PAH/DMMA) is an anionic polymer with dimethyl maleic acid which can experience charge conversion to a cationic polymer in the mildly acidic tumor environment. This led to strong electrostatic repulsion and release of positive CDs-Pt (IV). The CDs-Pt (IV) had a high affinity toward the negatively charged phospholipid bilayer of cancer cell membrane, which gave rise to improved uptake and effective activation of cisplatin (IV) in the reductive cytosol. In vitro and in vivo studies confirmed that this charge-convertible system had a superior therapeutic performance under acidic extracellular microenvironment

as compared to normal physiological condition or noncharged-convertible nanocarriers.

In another report, Feng et al. developed a CDs-based anticancer DDS that was responsive to tumor extracellular microenvironment for superior drug delivery.^[155] The system consisted of CDs as nanocarriers, cisplatin (IV) as drugs, and RGD peptide as targeting ligand which was further functionalized by monomethoxy polyethylene glycol (mPEG) through pH-responsive benzoic-imine bond. When the CDs-RGD-Pt(IV)-PEG were in the vicinity of tumor cells, the slight acidic extracellular pH would hydrolyze the benzoic-imine bond, exposing the RGD peptide. RGD peptide is a targeting ligand which can enhance the uptake of nanocarrier by cancer cells through RGD-integrin $\alpha_v\beta_3$ interaction. After uptake, cisplatin(IV) was reduced to cisplatin in the reductive cytosol of cancer cells, thus inducing cytotoxicity and killing the cancer cells. This system was able to provide an effective tumor extracellular microenvironment-triggered targeted drug delivery for highly efficacious cancer treatment.

RNA interference (RNAi) is a relatively new treatment modality where mRNA is sequence-specifically cleaved and degraded by siRNA, resulting in silencing of gene expression.^[157] This treatment mode is beneficial as siRNA can be designed based on a target mRNA sequence, thus can be used to silence many different genes. However, naked siRNA is extremely hydrophilic, has a high molecular weight, and is anionic in nature, making it hard to penetrate the phospholipid bilayer of the cell membrane.^[158] Naked siRNA is also known to have a short half-life as a result of degradation caused by the nucleases in plasma. Hence, it is vital to have nanocarriers that are biologically safe and have large loading capacities to deliver siRNA to the targeted region. CDs have also been reported to be an effective siRNA delivery system. Kim and coworkers developed highly fluorescent poly(ethyleneimine) (PEI)-passivated CDs as fluorescent labels and nanocarriers for siRNA delivery for GFP gene silencing (**Figure 17**).^[156] The CDs were synthesized by using a one-step microwave pyrolysis with

Figure 17. Schematic illustration and application of CD-PEI-mediated siRNA delivery and bioimaging. Reproduced with permission.^[156] Copyright 2017, Springer.

citric acid and PEI as precursors. PEI played several roles as surface passivation, enhancement of fluorescence, siRNA loading capacity, and cellular uptake. The CD-PEIs were first complexed with siRNA through electrostatic interactions by simply mixing in buffer solution. Their results clearly showed that siRNAs complexed with CD-PEIs were protected from ribonuclease degradation, suggesting better stability as compared to naked siRNAs. In their *in vitro* studies, HeLa cells were used as model cells and the GFP expression levels in cells treated with siRNA-CD-PEI exhibited highest gene silencing as compared to other treatment groups. The therapeutic efficacy was also evaluated *in vivo* in tumor-bearing xenografted mice model. The tumor growth in mice treated with siRNA-CD-PEI was inhibited, implying that the proposed system had remarkable gene silencing efficacy.

4.2.3. Photothermal Therapy

Although most of the reported CDs that exhibited PTT features have absorption in the NIR region, their absorption peaks are generally not located in the first NIR window.^[159] This finding speculated that a superior photothermal conversion efficiency can be accomplished by adjusting the absorption peak to longer wavelength region. In a recent work by Permatasuri and coworkers,^[160] the group developed CDs with peak absorption centered at 650 nm with an excellent photothermal conversion efficiency of 54.3%. By optimizing the molar ratio of carbon precursors (citric acid and urea), reaction temperature, and duration, the as-prepared CDs possessed up to 70.9% pyrrolic-N on their surface, which contributed to the absorption peak in NIR region. Higher absorption coefficient was also observed with increasing pyrrolic-N concentration which inherited plentiful of delocalized electrons, ensuing in delocalized electron waves spread-

ing through the surface of CDs which in turn enabled penetration of electrons in between forbidden electronic transitions.

Zheng and coworkers developed a facile strategy to prepare CDs from hydrophobic cyanine dye and PEG800 in ethanol via solvothermal synthesis process.^[161] Cyanine dyes are known to have good photothermal property.^[162] The as-synthesized CyCDs exhibited excellent hydrophilicity and absorption from 600 to 900 nm. The CyCDs displayed favorable photothermal conversion efficiency of 38.7%, capable of increasing CyCDs solution temperature up to 37 °C under 2 W cm⁻², 808 nm laser irradiation. This was due to the intrinsic property of CyCDs, which were composed of intrinsic cyanine dyes, serving as a nanoscale formulation for PTT. The photothermal properties of CyCDs were verified by *in vitro* and *in vivo* studies. CT26 cells served as the model cell line and after 5 min of 808 nm laser irradiation, most of the cancer cells were dead, which suggested that CyCDs could serve as a good PTT agent. *In vivo* studies were carried out in CT26-tumor-bearing BALB/c mice. The mice were intravenously injected with CyCDs and over time, fluorescence signal at the tumor site increased, indicating the accumulation of CyCDs at the cancer site. The fluorescence signals were able to be detected at the tumor region even at 240 h post-injection, which could be attributed to the EPR effect. After four times of NIR light treatment at 2-day intervals, the mice were sacrificed and most of the tumors were found to be eliminated. It was concluded that the tumor inhibitory rate was as high as 91%.

In another report, Lan et al. developed NIR emissive CDs with PTT capabilities for simultaneous fluorescence imaging and PTT (Figure 18).^[163] The sulfur and selenium co-doped CDs were prepared by a one-step hydrothermal synthesis route with polythiophene and diphenyl diselenide as precursors. The S, Se co-doped CDs were excitation independent and had emission peaks at 731 and 820 nm under 460 nm excitation. The group explained that the NIR emission of the S, Se co-doped CDs may have emerged due to bandgap opening caused by doping of Se, which is a heavy

Figure 18. Schematic illustration for the preparation of NIR emissive CDs. Reproduced with permission.^[163] Copyright 2017, Springer.

element, in the graphitic lattices of CDs. The NIR emission of S, Se co-doped CDs was highly favorable for both in vitro and in vivo imaging. Interestingly, the S, Se co-doped CDs also exhibited PL under 880 nm femtosecond pulsed laser. The fluorescence intensity increased with escalating laser power. The two-photon absorption was measured to be 30045 GM by using fluorescein as a reference. In addition, the CDs exhibited photothermal properties under 635 nm light irradiation with a calculated efficiency of $\approx 58.2\%$, capable of increasing the temperature of aqueous CDs solution of different concentrations by 22–30 °C. In vitro and in vivo studies further showed that besides good photothermal effect, the as-prepared CDs also displayed low cytotoxicity. When 4T1 murine breast-cancer-bearing mice were injected with CDs and subjected to 10 min of 880 nm laser light, the temperature increased and reached ≈ 52 °C after 6 min of irradiation. The tumor growth was inhibited, indicating that the CDs had the capability to kill cancer cells by the high temperature generated during the laser exposure.

4.2.4. Photodynamic Therapy

As compared with chemotherapy and PTT, PDT features better efficiency with lesser adverse effects, minimal phototoxicity, and less invasiveness. In an interesting work by Yang and coworkers,^[164] the group utilized magnesium and nitrogen co-doped CDs with a high PL QY of 84.6% as the carriers for water-insoluble PS Ce6. In this FRET-based system, the CDs served as donors while Ce6 acted as the acceptors. The CDs were first passivated with 1,2-ethanediamine (EDA) which also acted as the linker between CDs and Ce6. EDA also served to reduce the gap between the donor and the acceptor, thus improving the FRET efficiency. This FRET system had an enhanced fluorescence property where CDs would transfer more energy to Ce6, resulting in much stronger PL emission. In vitro studies showed that the CDs-Ce6 induced excellent PDT effect as approximately 50% of the CDs-Ce6-transfected cancer cells were killed with just 30 s of laser exposure, which was much more effective than the control group treated with Ce6 only.

In another report, Li and coworkers developed CDs that have PDT capability without the need of a PS.^[165] Mono-hydroxyphenyl triphenyl porphyrin (TPP) which is a type of PS and chitosan were

used as carbon precursors to derive TPP CDs using a simple one-pot hydrothermal synthesis. The PDT performance of TPP CDs was evaluated by analyzing the ROS production capability using 1,3-diphenyl-isobenzofuran (DPBF). Under 6 mW cm^{-2} , 625 nm light illumination, the absorption of TPP CDs and DPBF mixture at 419 nm were measured and it was found that the absorption decreased by 50% after 28 min of irradiation, indicating that the DPBF was consumed by ROS generated from TPP CDs. The group carried out in vitro studies using human hepatocellular liver cancer (HepG2) cells as a cell model. TPP CDs were found in lysosomes of the HepG2 cells and with 16 mW cm^{-2} , 625 nm illumination for 1 h, most of the cells were dead as confirmed by MTT assay. Furthermore, in vivo studies were carried out on hepatocarcinoma 22 xenograft models in Chinese Kun Ming mice to evaluate the therapeutic effect of TPP CDs. The tumor sizes in mice that were intratumorally administered with TPP CDs and exposed to 60 mW cm^{-2} light were found to have decreased from 100 to 56 mm^3 while the tumor sizes in control groups (treated with saline) have increased to $\approx 800 \text{ mm}^3$. Other treatment groups (treated with TPP or TPP with light irradiation) also exhibited increases in tumor sizes which were smaller than that in the group treated with saline only. The weight of the mice in the four groups indicated that there was no severe complication that aroused from TPP CDs. These results hence validated the therapeutic effect of TPP CDs.

Different from earlier reports, Guo and coworkers employed a novel strategy of heteroatom doping to develop CDs with PDT capability.^[166] In their work, the CDs doped with copper and nitrogen were prepared by a one-step hydrothermal synthesis using EDTA $\cdot$ 2Na and CuCl_2 . The copper atoms were located in the inner region of Cu, N-CDs by N-Cu-N complexation, giving rise to absorption in the NIR region. This endowed Cu, N-CDs with the capability to generate heat and ROS under NIR light illumination. Further characterization confirmed that the Cu, N-CDs could achieve a temperature increase from 25 to 54 °C in 10 min using a 1 W cm^{-2} , 808 nm laser. In addition, the group used DPBF as a chemical trapping agent to evaluate the ROS production by measuring DPBF absorption at 418 nm. The absorption of DPBF decreased in the presence of Cu, N-CDs with 808 nm light irradiation, indicating the generation of oxidative products. Subsequently, the photo-induced properties were evaluated in vitro and in vivo using B16 cells and nude mice bearing B16 cells, respectively. The group found that the synergistic effect of PDT and PTT was able to inhibit the growth of tumor cells. In addition, Cu, N-CDs could also serve as a fluorescence label and infrared thermal imaging agent.

Jia and coworkers developed a different approach to produce a multifunctional nanocomplexes for fluorescence and PA imaging-guided synergistic PDT/PTT therapy for cancer treatment (Figure 19).^[167] CDs served as the fluorescent label and PDT agents while gold nanorods (GNRs) acted as the PA and PTT agents. By incorporating them into a SiO_2 scaffold, the GNR@ SiO_2 -CDs nanocomplex exhibited improved stability in physiological environment while preventing PL quenching of CDs by GNR. The therapeutic efficacy was evaluated using nude mice bearing B16-F0 skin cancer cells. The mice were divided into four treatment groups. The groups were treated with saline (control group), GNR@ SiO_2 -CDs + 635 nm laser irradiation (PDT), GNR@ SiO_2 -CDs + 808 nm laser irradiation (PTT),

Figure 19. A) Schematic illustration of GNR@SiO₂-CDs nanocomplex preparation. B) Schematic illustration of GNR@SiO₂-CDs nanocomplex applications in PA imaging, PTT, and PDT for cancer treatment. Reproduced with permission.^[167] Copyright 2016, Royal Society of Chemistry.

and GNR@SiO₂-CDs + 635 nm + 808 nm laser irradiation (PDT+PTT). The intratumoral temperatures of the four treatment groups were measured using an infrared thermal camera. It was found that the localized tumor temperature of PDT+PTT treatment group quickly increased to 53.9 °C, comparable to the PTT groups (53.5 °C). The PDT treatment group experienced negligible temperature increase. The tumor sizes of different treatment groups were measured every 2 days after different treatments. The mice in the PDT+PTT groups exhibited substantial necrosis and black scab at the tumor sites. The black scab dropped off at day 14 post-treatment, signifying complete ablation of the tumor. The PDT and PTT groups experienced delays in tumor growth, suggesting that the PDT or PTT effect alone was inadequate to eliminate the tumors completely. The tumor in mice in the control group experienced progressive growth during the experimental period. In addition to fluorescence and PA imaging, these collective results indicated the potential of GNR@SiO₂-CDs to serve as a novel synergistic dual-imaging-guided photo-mediated PDT/PTT agent for cancer treatment.

5. Transition Metal Dichalcogenides

5.1. Properties and Synthesis

TMDCs refer to a group of materials with MX₂ structure composed of one transition metal (M) such as molybdenum, tungsten, and titanium, and two chalcogen atoms (X) such as sulfur, selenium, or tellurium. Covalent bonding of these atoms forms a monolayer structure with three-atom thickness, resembling a 2D morphology. TMDCs typically exist in bulk form consisting of many monolayers stacked together by weak Van Der Waals force among the layers. Akin to exfoliation of graphene sheets from

graphite, TMDC nanosheets with interesting properties can be obtained by exfoliating the monolayers from the bulk material.

Depending on its elemental composition, electronic, optical, and chemical properties of a specific TMDC vary accordingly.^[173] The properties of TMDC nanostructures also differ from those of their bulk counterpart. While bulk MoS₂ and WS₂ are indirect bandgap materials, their monolayers possess direct bandgaps of approximately 1.8 and 1.9 eV, respectively.^[174] Attractive properties of TMDC monolayers have led to many applications such as gas sensors,^[175] field effect transistors,^[176] integrated circuits,^[177] and batteries.^[178] Application of TMDCs as theranostic materials generally stem from several desirable properties. First, strong NIR absorption has been reported in TMDC nanomaterials, which facilitates applications such as PTT and photoacoustic imaging.^[179] Transition metal component in TMDCs consisted of elements with high atomic numbers, which enabled effective X-ray absorption. Finally, the 2D structure of exfoliated TMDC nanosheets provides a large surface area for functionalization and attachment of biomolecules. TMDC nanosheets such as MoS₂ and WS₂ were also found to be less toxic than other 2D nanomaterials such as graphene,^[180] which generates further interest in this material.

Interest in bioapplications of TMDCs in recent years has been supported by developments in synthesis and functionalization of water-soluble TMDCs. Exfoliation methods such as mechanical exfoliation^[181] or exfoliation in solvents such as dimethylformamide (DMF)^[182] and water-ethanol mixture^[183] suffered from low production yield and poor solubility in aqueous media, which hindered the adoption of these methods for bioapplications. One efficient exfoliation method of TMDCs is by intercalation, typically by n-butyllithium into bulk TMDCs.^[184] Due to their small size, lithium ions can enter the interlayer space in between TMDC layers and cause aggressive reactions when they come in contact with water, generating hydrogen gas and disrupting

Table 3. In vivo cancer therapy applications of carbon dots.

Precursor	Synthesis method	Treatment type	Injected dose	Laser wavelength [nm]	Power density [W cm ⁻²]	Irradiation time [min]	Photothermal efficiency [%]	Ref.
1,3,6-trinitropyrene, branched polyethylenimine	Hydrothermal	PTT	200 $\mu\text{g mL}^{-1}$	808	0.8	5	38.3	[146]
Cyanine dye, PEG800	Solvothermal	PTT	4 mg per kg body weight	808	1–1.5	5	38.7	[161]
Prussian blue nanoparticles, citric acid, urea	Microwave-assisted carbonization	PTT	20 mg per kg body weight	808	0.8	10	≈ 30	[168]
Polythiophene and diphenyl diselenide	Hydrothermal	PTT	80 μL of 1 mg mL ⁻¹ CDs	880	0.5	10	58.2	[163]
Polythiophene phenylpropionic acid	Hydrothermal	PTT	100 μL of 2 mg mL ⁻¹ CDs	671	2	10	38.5	[159]
Polythiophene benzoic acid	Hydrothermal	PDT/PTT	100 μL of 2 mg mL ⁻¹ CDs	635	2	10	36.2	[169]
Citric acid, nitric acid, ethanolamine	Pyrolysis	PTT	100 μL of 20 mg mL ⁻¹ CDs	808	2	10	3.77	[170]
EDTA, copper chloride	Hydrothermal	PDT/PTT	200 μL of 3 mg mL ⁻¹ CDs	808	1	10	—	[166]
Hypocrella bambusae	Solvothermal	PDT/PTT	200 μL of 2 mg mL ⁻¹ CDs	635	0.8	10	27.6	[171]
o-Phenylenediamine, L-cysteine	Hydrothermal	PTT	2 mg kg ⁻¹	808	1	10	41.3	[172]

the interlayer forces to eventually yield monolayer TMDCs.^[184b] To avoid the use of dangerous organolithium substances, Zheng et al. exfoliated bulk MoS₂ using sodium naphthalenide as intercalant.^[185] However, despite its efficiency, this method is sensitive to oxygenated atmosphere and water, and violent reaction involved have led to other alternatives, such as intercalation in sulfuric acid,^[186] oleum,^[187] and tetrabutylammonium.^[188]

Naked monolayer TMDCs exhibit limited solubility in water. Over time, it aggregates in water and ionic solution such as PBS and biological media,^[184a,189] therefore unready for application in in vitro and in vivo settings. To improve their solubility and biocompatibility, surface modification of TMDC nanosheets is necessary. Chou et al. proposed using sulfur atom of thiol (–SH) groups to bind to defect sites on MoS₂ layers.^[184a] Due to the aggressive reaction in Li-based exfoliation, defect sites are usually present on TMDCs surface.^[190] Thiolated PEG were able to bind onto MoS₂ nanosheets and improved the stability of the MoS₂ in aqueous solution and in various pH as compared to naked MoS₂. Liu et al. later proposed using dithiol moiety, as two sulfur atoms were expected to provide stronger binding onto defect sites.^[191]

In recent years, facile noncovalent functionalizations have been explored with molecules such as bovine serum albumin (BSA),^[192] chitosan,^[187] polyvinylpyrrolidone (PVP),^[179a] and other polymers.^[193] A study by Guan et al. suggested BSA as a more efficient and biocompatible exfoliating agent for MoS₂ and WS₂ as compared to PVP and polyacrylic acid (PAA), due to its larger molecular size and stronger hydrophilic and hydrophobic domain for conjugation.^[193] They proposed that nonpolar disulfide and benzene moieties as important groups in facilitating noncovalent binding by hydrophobic interaction to the surface of TMDCs such as MoS₂ or WS₂, in line with their DFT simulation which suggested stronger binding energies between these moieties to MoS₂. Other efforts have applied mechanical shear forces by grinding in ionic liquids (IL)^[194] or blending in sodium cholate^[195] for large-scale production of TMDC nanosheets.

To achieve TMDCs with controllable dimensions, several bottom-up approaches via hydro/solvothermal or high-

temperature reactions have been proposed. For example, MoS₂ was synthesized by hydro/solvothermal reaction using (NH₄)₂MoS₄ as a precursor in N₂H₄.^[196] Wang et al. proposed a one-step synthesis and functionalization by solvothermal reaction of (NH₄)₂MoS₄ in a solution of PEG-400, which served as the surface group.^[197] Gd-doped WS₂ was synthesized by the mixture of tungsten and gadolinium precursors at high temperature in nitrogen.^[198] While these methods provide a simple synthesis approach with controllable dimensions and shapes, more studies would be necessary to elucidate the mechanism and formation of nanostructures.

5.2. Biomedical Applications of TMDCs

5.2.1. Photothermal Therapy

Applications of TMDCs in PTT are based on their strong absorption in NIR range and efficient photothermal conversion. This photothermal property of MoS₂ was firstly presented by Chou et al.^[199] using exfoliated MoS₂ synthesized by Morrison method.^[184b,190] This synthesis route yielded water-soluble chemically exfoliated MoS₂ (ceMoS₂) nanosheets with absorbance covering a wide range of spectrum, including NIR region. High NIR extinction coefficient at 800 nm was obtained at 29.2 Lg⁻¹ cm⁻¹, comparable to reduced graphene oxide and higher than graphene oxide.^[200] Upon exposure to 0.8 W cm⁻² 800 nm light, the temperature of ceMoS₂ solution increased to over 40 °C. Preliminary demonstration by a 20-min irradiation of 800 nm light onto ceMoS₂-treated HeLa cells achieved significant cell death as the temperature reached 64 °C. In addition, examination by time-domain thermo-transmission (TDTT) suggested a high thermal conductance of ceMoS₂, which is beneficial for PTT applications.

Functionalized WS₂ for PTT was obtained by Cheng et al. by PEGylation of WS₂ using lipoic acid-PEG (**Figure 20A**).^[189] WS₂ nanosheets with a high extinction coefficient of 23.8 Lg⁻¹ cm⁻¹

Figure 20. A) Scheme showing exfoliation and PEGylation of WS₂ nanosheets. B) Photothermal heating of pure water and different concentrations of WS₂-PEG solutions under 0.8 W cm^{-2} 808 nm laser irradiation. C) The relative tumor volumes of 4T1 tumors in mice after various treatments with intratumoral (i.t.) or intravenous (i.v.) injection of WS₂-PEG. D) Infrared thermal images of 4T1 tumor in mice model treated with saline (upper row), or WS₂-PEG (middle row) intratumoral injection, or WS₂-PEG intravenous (i.v.) injection (bottom row) under 808 nm laser irradiation. Reproduced with permission.^[189] Copyright 2013, Wiley-VCH.

at 808 nm and strong photothermal properties were obtained (Figure 20B). PEGylation improved the solubility of WS₂ nanosheets in aqueous media, especially in the presence of salt. These PEGylated WS₂ nanosheets were biocompatible at high concentration, in contrast to nonfunctionalized WS₂. In vitro incubation of 4T1 murine breast cancer cells with 0.1 mg mL^{-1} WS₂-PEG and subsequent irradiation of 0.8 W cm^{-2} 808 nm laser for 5 min were able to destroy the majority of transfected 4T1 cells. In xenografted mice model, the temperature of tumor region with WS₂ administration reached 65°C after 5 min of NIR irradiation and resulted in eradication of tumor (Figure 20C,D).

Wang et al. observed the influence of size and PEGylation on the photothermal property of MoS₂ synthesized from a bottom-up approach.^[197] PEGylated MoS₂ of varying sizes were obtained by altering the concentration and ratio of MoS₂ precursors and PEG. It was observed that smaller PEGylated MoS₂ exhibited superior NIR absorption and photothermal effect, which they attributed to the improved solubility of the nanosheets. In another study, the bottom-up synthesis of MoS₂ yielded nanoflower-like structures.^[201] Irradiation of 2 W cm^{-2} 808 nm light for 5 min was able to increase the temperature of $80 \text{ }\mu\text{g mL}^{-1}$ MoS₂ nanoflowers solution from 26.5 to 73.5°C with a photothermal conver-

sion efficiency of 27.6%. In this work, in vitro PTT using MoS₂ not only induced lower cell viability, but also caused significant destruction of cells by disruption of lysosomal membranes, cytoskeleton integrity, and cell adhesion capability. Cellular damage was also observed in in vivo tumor cells treated with MoS₂ and NIR light irradiation, which demonstrated the capability of the MoS₂ nanoflowers as photothermal agents.

PTT using small TMDC nanodots from MoSe₂ was demonstrated by Yuwen et al.^[202] MoSe₂ nanodots with an average particle size of 2.3 nm were produced via ultrasonication of bulk MoSe₂ with Pluronic F127 as the surfactant. These MoSe₂ nanodots possessed direct bandgap absorption peak around 800 nm, with an extinction coefficient of $17.4 \text{ Lg}^{-1} \text{ cm}^{-1}$ at 808 nm and a photothermal conversion efficiency of 46.5%. MoSe₂ nanodots were biocompatible in vitro at concentrations up to $160 \text{ }\mu\text{g mL}^{-1}$ and exhibited better photostability than ICG. In vitro PTT application of these MoSe₂ nanodots was demonstrated in HeLa cells incubated with $40 \text{ }\mu\text{g mL}^{-1}$ MoSe₂ and treated with 2 W cm^{-2} , 785 nm light irradiation, displaying pronounced effect as cell viability of less than 8% was achieved.

Besides accumulation in the target region, theranostic nanomaterials are also expected to induce no toxicity and avoid

Figure 21. A) Scheme showing preparation of MoS₂-PPEG. B) Photographs of MoS₂-PPEG dispersion in PBS (pH 5.0 and 7.4) after incubation at 37 °C for determined time intervals. UV-vis spectra (left-bottom axis) and 808 nm absorption (right-top axis) of MoS₂-PPEG dispersions in C) pH 5.0 and D) pH 7.4 at different degradation times. E) The temperature of tumor sites in mice treated with PBS and MoS₂-PPEG under 808 nm irradiation. F) Relative tumor volumes of mice under different treatments. Reproduced with permission.^[203] Copyright 2017, American Chemical Society.

prolonged accumulation in the body. One strategy against long-term accumulation is by degradation of nanomaterials into small ions and molecules. In a study by Chen et al., photothermal application of MoS₂ nanosheets with degradable property was reported.^[203] MoS₂-PAA was synthesized by hydrothermal reaction of ammonium molybdate tetrahydrate and PAA, and subsequently functionalized with PEG-amine to produce MoS₂-PPEG (Figure 21A). After 5 min of 1 W cm⁻² 808 nm light irradiation, temperature of 200 μg mL⁻¹ MoS₂-PPEG solution rose from 25.8 to 51.4 °C. They also displayed excellent photostability across several cycles of irradiation. Of particular interest is the fact that MoS₂-PPEG suffered from degradation in aqueous solution over several days, with faster degradation observed at pH 7.4 than pH 5.0 (Figure 21B-D). They concluded that these MoS₂-PPEG followed previously proposed route of degradation to Mo^{VI} ion species such as MoO₄²⁻,^[204] and that OH⁻ played a critical role in the degradation process.^[205] As

shown in Figure 21E,F, NIR irradiation onto intratumorally injected 4T1 tumor revealed that photothermal treatment based on MoS₂-PPEG raised the temperature of tumor site and inhibited tumor growth. Biodistribution studies revealed that MoS₂-PPEG were mainly excreted through the renal pathway, which would be useful in avoiding prolonged accumulation of the nanomaterial.

In another study, degradable TMDCs based on vanadium disulfide were synthesized for PTT and multimodal imaging.^[206] VS₂ nanosheets were obtained by bottom-up synthesis of VCl₄ in sulfur, and sonicated in 1,2-dioleoyl-sn-glycero-3-phosphate (DOPA) to produce VS₂ nanodots, which were subsequently encapsulated in lipid-PEG micelles. These VS₂@lipid-PEG nanodots exhibited high extinction coefficient of 22.6 Lg⁻¹ cm⁻¹ at 808 nm with 31.5% photothermal conversion efficiency. PTT of 4T1 tumor at 24 h post-intravenous injection of VS₂@lipid-PEG nanodots resulted in complete tumor ablation within 2 days

Figure 22. A) Photoacoustic images and B) photoacoustic signals of tumor site in mice before and after intratumoral (i.t.) or intravenous (i.v.) injection with WS₂-PEG solution. Reproduced with permission.^[189] Copyright 2013, Advanced Materials. C) In vivo photoacoustic images of orthotopic brain tumor region before (Pre) and after intravenous injection of S-MoS₂. Ultrasound images (gray) delineated the skin and skull boundaries. PA signal (green) enhancement showed the accumulation and distribution of S-MoS₂ within the brain tumor at deep depth. D) PA maximum amplitude projection (MAP) images of brain tumor region before and after 24-h post intravenous injection of S-MoS₂, showing blood vessels (gray) and brain tumor (green). E) Statistical results of PA signal in the tumor region at different post intravenous S-MoS₂ injection times. Reproduced with permission.^[209] Copyright 2016, Wiley-VCH.

without recurrence in 14 days. The VS₂@lipid-PEG nanodots were also shown to undergo degradation into smaller oxygenated molecules in the presence of oxygen. The small VS₂@lipid-PEG were observed to prefer fecal clearance in vivo, contrary to previously reported renal pathway in degradable MoS₂.^[203]

5.2.2. Photoacoustic Imaging and Photothermal Therapy

Photoacoustic imaging is a novel imaging modality where photons are used as excitation for materials to generate acoustic waves as measured signals to be processed into an image. It has gained much popularity due to advantages such as higher imaging depth, higher spatial resolution, and minimal invasiveness.^[207] Mechanism of PA imaging utilizes photon excitation to generate heat, which in turn induced thermoelastic expansion and acoustic waves.^[207,208] As this process relies on heat generation, nanomaterials with high NIR absorption could induce strong acoustic waves, making them desirable PA contrast

agents. As both PA imaging and PTT similarly rely on NIR absorption properties of nanomaterials, many studies utilized them simultaneously as PA imaging-guided PTT.

In an aforementioned study carried out by Cheng et al., multifunctional WS₂-PEG were used for PA imaging in combination with PTT, demonstrated in mice model.^[189] PA images of 4T1 tumor lesion were taken with 700 nm laser as excitation source. Significant differences were observed in images obtained pre- and post-injection. Whilst PA images of untreated mice only displayed blood vessels surrounding the tumor, mice treated with intratumoral or intravenous injections of WS₂-PEG produced strong signals in tumors. Compared to intratumoral injection, intravenous injection produced more uniform and pronounced features due to the passive accumulation of WS₂-PEG in tumor over time via enhanced permeability and retention (EPR) effect (Figure 22A,B). In addition, their potential in multimodal imaging was also demonstrated by the use of WS₂-PEG as CT imaging contrast agent based on X-ray attenuations by high atomic number tungsten.

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BSA-exfoliated MoS₂ was utilized for noninvasive PA imaging of subcutaneous and orthotopic brain tumor (Figure 22C–E).^[209] In comparison to few-layered MoS₂-BSA (F-MoS₂) and multi-layered MoS₂-BSA (M-MoS₂), single-layer MoS₂-BSA (S-MoS₂) displayed the highest NIR absorption and PA signal with great photostability. It was previously proposed that in addition to NIR absorption, the elasticity of the nanomaterial contributed to the generation of PA signals.^[210] PA signals were measured after adjusting the concentrations of S-MoS₂, F-MoS₂, and M-MoS₂ solutions to be of the same NIR absorbance value. Among them, S-MoS₂ exhibited the strongest PA signal which can be attributed to the higher elasticity of the nanosheets. They observed that BSA functionalization enhanced the transfection of the MoS₂ nanosheets into U87 glioma cells in vitro. Using this cell model, S-MoS₂ was able to penetrate the brain blood barrier with observable PA signal at 1-h post-injection with increasing signal strength over a 24-h period. Successful imaging of tumor at approximately 1.5 mm depth below the skull was achieved. Their results showed that MoS₂-BSA was successfully employed as an effective contrast agent, achieving over 36-fold stronger signal than pre-injection. Tumor measurement from this process also displayed good agreement with MRI imaging of the brain tumor.

Several approaches have been explored to introduce metal nanoparticles or metal dopants onto TMDC nanosheets to enable additional imaging modalities. Liu et al. conjugated MoS₂ nanosheets with iron oxide nanoparticles (IONP) and ⁶⁴Cu to perform multimodal-imaging-guided PTT.^[211] Thiol groups in meso-2,3-dimercaptosuccinic acid (DMSA)-modified IONPs allowed easy binding onto defects in MoS₂ while ⁶⁴Cu were conjugated onto the sulfur atoms based on chelator-free approach. Conjugation of IONPs did not affect NIR absorption of MoS₂, but they acted as paramagnetic agent for T2-weighted MRI imaging.^[212] This MoS₂-based nanocomplex was capable of MRI, positron emission tomography (PET), and PA imaging for accurate distribution of MoS₂ nanosheets as a function of time, prior to PTT on the tumor. Another IONP-functionalized MoS₂ was produced by hydrothermal reaction for one-step synthesis and PEGylation, followed by growth of IONP.^[213] Through this approach, Fe₃O₄ were formed on the surface of MoS₂, producing MoS₂-Fe₃O₄ complex (MSIO). The complex retained strong photothermal property with a photothermal conversion efficiency of 43.93%. Paramagnetic property of this complex was utilized as a magnetic-targeted theranostic nanomaterial. In an in vitro model, transfection of MSIO was conducted with a magnet being applied onto culture dish containing HeLa cells. MSIO nanoparticles were selectively accumulated in cells surrounding the magnet, which suffered from photothermal ablation upon exposure of 808 nm laser, while cells elsewhere remained viable due to no uptake of MSIO. This magnetic targeting strategy served as an active targeting approach against Panc-1 tumor model in mice. PA imaging of MSIO displayed stronger signal in tumor site with a magnetic field applied as compared to passive accumulation. The magnetic-induced accumulation led to superior hyperthermia effect in in vivo model as tumor temperature reached 47 °C, compared to 42 °C without magnetic targeting.

PEGylated WS₂ with different metal dopants was synthesized by Cheng et al. via a bottom-up approach.^[198] Hydrothermal reaction of WCl₆ and MCl_x in oleylamine and 1-octadecene produced

WS₂:Mⁿ⁺ with Mⁿ⁺ ranging from Fe³⁺, Co³⁺, Ni²⁺, Mn²⁺, and Gd³⁺. Formation with Gd³⁺ with increasing ratios of Gd³⁺ to WS₂ reduced Hounsfield units and increased T1 relaxivity. Among the different ratios investigated, WS₂:Gd³⁺-PEG with 70:30 precursor ratio was deemed optimal for simultaneous CT and MRI imaging. In addition, X-ray absorption of WS₂ was employed for radiotherapy of 4T1 cancer cells. This enabled multimodal theranostics by CT, MRI, PA imaging, and photothermal and radiotherapy. By using NIR light with a low power density of 0.5 W cm⁻², mild PTT was applied in combination with radiotherapy using 4 Gy X-ray to induce tumor cell death. This synergistic effect was caused by reduced hypoxia by PTT, which in turn sensitized the tumor region to radiotherapy.^[214]

In recent years, there is an increasing number of studies exploring the use of small TMDC-based quantum dots/nanodots. Ultrasmall WS₂-PEG quantum dots were prepared by exfoliation method for bioimaging and simultaneous PTT and radiotherapy.^[179c] NIR absorption and corresponding photothermal effect increased with decreasing sizes of WS₂-PEG QDs. The photothermal conversion efficiency of 3 nm WS₂-PEG QDs was determined to be 44.3%. WS₂-PEG QDs did not pose any significant toxicity and due to their size, they accumulated in the kidney, followed by rapid clearance within 30 days. As simultaneous photothermal and radiotherapy agent, WS₂-PEG QDs provided improved radiotherapy efficacy with sensitizer enhancement ratio of 1.22, which increased to 1.31 when NIR irradiation was applied. This therapy when applied in in vivo studied yielded a higher efficacy with complete tumor removal in 5 days without any recurrence over the next 17 days. In addition, PA and CT imaging capabilities of the QDs were also demonstrated with visible contrast in tumor 2 h post-injection.

Small MoS₂ nanodots for PTT and PA imaging were synthesized by hydrothermal reaction of ammonium molybdenite in methanol with hydrazine and PVP.^[179a] GSH was subsequently used to replace PVP to form MoS₂-GSH nanodots with smaller hydrodynamic size and excellent colloidal stability in serum. This resulted in small hydrodynamic size of 7.5 nm which aided in fast clearance of the nanodots via renal pathway. The extinction coefficient of MoS₂-GSH nanodots at 808 nm was measured to be 15.7 Lg⁻¹ cm⁻¹, which enabled their use in PA imaging and PTT. PA imaging was applied to observe the accumulation of MoS₂-GSH in the tumor, showing maximum signal 2–4 h post-injection before declining. Based on this result, PTT was carried out using a 1 W cm⁻² laser at 4 h post injection. It was revealed that PA signal measurement was in agreement with inductively coupled plasma atomic emission spectroscopy (ICP-AES) result, as overall MoS₂ levels dropped after 12 h. This was explained by the preferred renal clearance of smaller MoS₂-GSH nanodots which facilitates rapid clearance from the body.

Improvement of NIR absorption of MoS₂ quantum dots was performed by functionalization with polyaniline (PANI) of aniline and 3-aminobenzoic acid(aniline-COOH), and PEG.^[215] The introduction of aniline-COOH into the reaction prevented aggregation of the synthesized MoS₂ quantum dots in PBS, and absorption of polyaniline contribute to increased NIR absorption in MoS₂-PANI,^[216] with a photothermal conversion efficiency of 31.6%. This was demonstrated in in vitro treatment showing superior photothermal effect by MoS₂-PANI as compared to MoS₂

Figure 23. A) Scheme showing synthesis and structure of ReS_2 -PEG nanosheets. B) UV-vis-NIR spectra of ReS_2 nanosheets before and after surface modification. C) The temperature of water and different concentrations of ReS_2 -PEG solution under 0.8 W cm^{-2} 808 nm laser irradiation for 5 min. D) CT images of mice and E) PA images of tumors on mice before and 24 h after intravenous injection of ReS_2 -PEG. F) Relative imaging signals from tumor site in mice before and after intravenous injection of ReS_2 -PEG. G) SPECT images of 4T1-tumor-bearing mice 5 min and 24 h after intravenous injection of $^{99\text{m}}\text{Tc}$ - ReS_2 -PEG. Reproduced with permission.^[219] Copyright 2017, Wiley-VCH.

quantum dots alone. Strong PA signals were recorded, displaying peak contrast of 4T1 tumor in mice at 8 h post-intravenous injection with a signal intensity that was five times higher when compared to pre-injection. As observed in previous studies, the addition of PTT to radiotherapy produced the most effective anticancer approach due to the reduction in hypoxia by increased blood circulation under hyperthermia condition.^[214b]

While MoS_2 and WS_2 have been at the forefront of theranostic TMDCs, several other TMDCs have recently been explored for such applications. Previously described VS_2 @lipid-PEG was demonstrated for multimodal bioimaging.^[206] In addition to PA imaging, VS_2 @lipid-PEG was utilized for MRI imaging due to its paramagnetic properties, and SPECT imaging by chelator-free attachment of $^{99\text{m}}\text{Tc}^{4+}$ ions onto the surface of VS_2 nanosheets. PTT at 24 h post-injection was supported by PA signals of VS_2 , showing the strongest signal at this time point. Motivated by inherent biocompatibility of Ti, TiS_2 was synthesized by high-temperature reactions of Ti precursor and S in oleylamine and octadecene.^[179b,217] Hydrophobic TiS_2 nanosheets with an average diameter of $\approx 100 \text{ nm}$ were functionalized with poly(maleic anhydride-*alt*-1-octadecene)-PEG based on hydrophobic interaction. Its extinction coefficient of $26.8 \text{ Lg}^{-1} \text{ cm}^{-1}$ rendered it as an efficient photothermal and PA agent. PA signals in the tumor were observed from 2 h up to 24 h after injection. PTT with 5-min exposure to 808 nm (0.8 W cm^{-2}) laser caused the temperature to increase to 65°C and induced rapid cancer death, with mice survival for over 60 days. Although preliminary tests displayed no apparent toxicity in vivo, further evaluation would be necessary.

Mao et al. obtained MoSe_2 hybrid nanoparticles composed of MoSe_2 nanosheets and nanodots by hydrothermal synthesis of Na_2MoO_4 and Se with PEG as the surfactant.^[218] MoSe_2 nanodots with 10 nm size were attached on large MoSe_2 nanosheets, and this nanohybrid exhibited 48.46% conversion efficiency. Their biocompatibility was demonstrated for up to $200 \mu\text{g mL}^{-1}$ in vitro and they did not cause toxicity in vivo for up to 50 mg kg^{-1} for 30 days. As a PTT agent, HeLa and HepG2 cells were incubated

with multiple concentration of MoSe_2 nanohybrid and exposed to 8 min of 808 nm light (1 W cm^{-2}), resulting in concentration-dependent toxicity, achieving less than 10% cell viability in both cell lines. PA imaging produced signal enhancement as early as 30-min post injection, and better CT contrast than commercial iopromide-300.

Another recently studied TMDC species, rhenium disulfide (ReS_2) nanosheets were synthesized by a bottom-up approach and functionalized with PEG (Figure 23A).^[219] ReS_2 nanosheets with a lateral size of 10 nm and hydrodynamic size of 25 nm were obtained. Despite its different composition, ReS_2 exhibited NIR absorption and induced high temperature increase under 808 nm light, similar to other TMDCs (Figure 23B,C). High Hounsfield unit of 22 HU Lg^{-1} also suggested their capability for radiotherapy and CT imaging. This was confirmed by two- and fourfold improvements of CT and PA signal, respectively, in the ReS_2 -PEG-injected 4T1 tumor in mice model (Figure 23D–F). Furthermore, they can be conjugated with technetium ($^{99\text{m}}\text{Tc}$) by chelator-free approach for single-photon emission computed tomography (SPECT) imaging (Figure 23G). Combination of mild PTT and radiotherapy using ReS_2 -PEG were performed, hence demonstrating their potential for theranostics.

5.2.3. Photothermal Therapy and Drug/Gene Delivery

Owing to the 2D structure of TMDC nanosheets, they present a large surface area for conjugation with biomolecules and serve as efficient nanocarriers. Loading of drug molecules onto the surface of TMDC would enable simultaneous chemotherapy and PTT. Liu et al. conjugated a series of hydrophobic drugs onto MoS_2 nanosheets (Figure 24A).^[191] Exfoliated MoS_2 was functionalized with lipoic acid-PEG. High NIR absorbance of the MoS_2 with an extinction coefficient of $28.4 \text{ Lg}^{-1} \text{ cm}^{-1}$ at 800 nm excitation enabled PTT application of the nanomaterial.

Figure 24. A) Scheme showing the fabrication process of MoS₂-PEG and subsequent drug loading. B) UV-vis-NIR spectra of MoS₂-PEG/DOX obtained at various drug loading concentrations after removal of excess free drug molecules. C) Tumor volume growth of different groups of mice in various treatments. D) Scheme of combination therapy with MoS₂-PEG/DOX. E) Infrared thermal images of 4T1-tumor-bearing mice recorded by an infrared camera. Reproduced with permission.^[191] Copyright 2014, Wiley-VCH.

Conjugations with a series of cancer drugs such as DOX (Figure 24B), 7-ethyl-10-hydroxycamptothecin(SN38), and photodynamic drug Ce6 via hydrophobic interaction were achieved with high loading ratio of 239%, 39%, and 118%, respectively. This interactions between drugs and TMDCs were confirmed by PL quenching of DOX and Ce6. Combination of chemotherapy and PTT of MoS₂-PEG/DOX were able to enhance anticancer effect in in vitro and in vivo cancer models (Figure 24C-E). Furthermore, the addition of folic acid as targeting moiety into the formulation was demonstrated in vitro to further enhance the specificity of the drug delivery.

Yin et al. demonstrated that the release of drugs from MoS₂ can be triggered by photothermal effect.^[187] Chitosan-functionalized MoS₂ was conjugated with DOX via hydrophobic interaction onto its surface. Upon irradiation with NIR light with different power densities, laser-power-dependent release of DOX from MoS₂-CS-DOX was observed. As shown in Figure 25A, irradiation with 808 nm (0.8 W cm⁻²) light for 10 min induced a significant DOX release of approximately 6% from MoS₂-CS-DOX, as compared to 0.2% in the same time frame without irradiation. This result, therefore, suggested the use of NIR as a controllable trigger for drug release from the nanocomplex in vitro and in vivo, which could regulate their toxicity (Figure 25B-E). Another hydrophobic drug, resveratrol (RV) was conjugated to BSA-exfoliated MoS₂ nanosheets for drug delivery and PTT.^[192] Effi-

cient loading onto BSA-exfoliated MoS₂ nanosheets by hydrophobic interaction was achieved at 180% weight ratio. In agreement with previous DOX model, quick release of RV was also triggered by NIR irradiation onto the nanocomplex. They also proposed that the weakened interaction between RV and MoS₂ was attributed to the thermal effect of MoS₂.^[220]

Another TMDC species, selenide molybdenum has also been engineered into drug delivery and PTT platform.^[221] MoSe₂ synthesized by a hydrothermal reaction was functionalized by dopamine polymerization on its surface. Modification with polydopamine (PDA) not only resulted in improved biocompatibility but also enhanced NIR absorption and photothermal effect of MoSe₂@PDA. Although drug loading capacity of 0.1 mg DOX per milligram MoSe₂@PDA was lower than the aforementioned reports, the use of MoSe₂@PDA-DOX in synergistic photothermal and chemotherapy still resulted in superior efficacy when compared to photothermal or chemotherapy alone.

In a different approach, nanocomposites of WS₂-iron oxides-mesoporous silica (WS₂-IO@MS-PEG) for chemotherapy and PTT were designed by a multi-step approach.^[222] 3-DMSA-modified IONPs easily bound to surface of exfoliated WS₂ due to interactions of thiols in DMSA and defects on the WS₂ surface.^[189] In this formulation, DOX was loaded into mesoporous silica instead of TMDC surface. Nevertheless, photothermal properties of WS₂ were able to accelerate DOX release from

Figure 25. A) The release profile of DOX in PBS buffer (pH 5.00) in the absence and presence of 808 nm irradiation. Cytotoxicity of B) KB and C) Panc-1 cells with different treatments with or without irradiation (power = 1.0 W cm⁻²). D) The growth of tumors after various treatments. E) Photograph of tumors from mice of different treatment groups. Reproduced with permission.^[187] Copyright 2014, American Chemical Society.

the nanocomposite. In vitro demonstration on 4T1 cells using 808 nm irradiation with a low power density of 0.3 W cm⁻² for 20 min showed that this combination therapy was capable of decreasing cell viability to approximately 20%, while no toxic effect was observed in control cells. Similarly, irradiation using 0.55 W cm⁻² for 10 min achieved a more significant anticancer effect in combination therapy as compared to individual therapies. In addition, by conjugating IONPs to WS₂, this nanocomposite was capable of MRI and CT imaging with superior HU than WS₂ alone.^[189] In another study, nanocomposite was designed based on mesoporous silica growth on MoS₂.^[223] DOX loading capacity onto these PEGylated mesoporous silica-MoS₂ (PSMS-PEG) was recorded at 190% w/w of MoS₂. In vitro evaluation in MCF-7, HeLa, HepG2, and HCT-8 cell lines presented approximately 8.5-, 1.4-, 36-, and 12-fold lower IC₅₀ of NIR-induced DOX-PSMS-PEG, respectively, when compared to free DOX.

A smart MoS₂ nanocomplex with PEI and hyaluronic acid (HA) was formulated to achieve targeted delivery against MCF-7-ADR breast cancer, and NIR, pH, and enzyme-responsive release of DOX.^[224] DOX was conjugated onto MoS₂ of 30–50 nm lateral size at 33.6% weight ratio at pH 8. In addition to pH-dependent and photothermal-induced DOX release, hyaluronidase (HAase) in tumor microenvironment was expected to degrade HA, leading to DOX release from MoS₂-PEI-HA. This was indeed shown by 23.2% and 41.6% DOX release after 6 h in the presence of 0.5 mg mL⁻¹ HAase in pH 7.4 and pH 5, respectively. The DOX release was further enhanced to 77.4% by irradiation of 0.6 W cm⁻² 808 nm light. Superior fluorescence signals of NIR-irradiated DOX@MoS₂-PEI-HA compared to DOX@MoS₂-PEI-HA and DOX only were observed in in vitro MCF-7-ADR cells. They found that the use of PTT inhibited the expression of

p-glycoprotein, which increased the sensitivity of MCF-7-ADR cells to chemotherapy. The NIR irradiation improved the anticancer effect from 76% to 96% in MCF-7-ADR tumor in DOX@MoS₂-PEI-HA-treated mice without any tumor relapse. Histology studies also confirmed nuclear damage, shrinkage, and wounds in tumor tissues, while no inflammation was induced in normal organ tissues.

In an in situ administration strategy, MoS₂ nanosheets and DOX were complexed with poly(lactic-co-glycolic acid) (PLGA)-based oleosol to form PLGA/MoS₂/DOX (PMD) oleosol.^[225] Under 808 nm (1 W cm⁻²) light irradiation, the MoS₂ and DOX-filled PMD implant displayed temperature rise of 30.2 °C and induced rapid DOX release from 8.7% to 31.8% in 5 min. In mice model, PMD immediately transformed to solid upon injection, avoiding leakage and enabling effective therapy. PTT using 0.6 W cm⁻² laser led to tumor lesion disappearance over time with no tumor left after 4 weeks, with survival and no relapse in mice in 2 months. This strategy aids in the prevention of MoS₂ accumulation in major organs often seen in intravenous administration. Nevertheless, maintaining biocompatibility and hemocompatibility of PMD requires careful formulation and prevention of *N*-methylpyrrolidone (NMP) from leaking in vivo.

In addition to drug delivery, similar approaches were also applied for delivery of genetic materials. The surface of TMDC nanosheets was functionalized with cationic polymers to render a positively charged surface, prior to electrostatic binding with genetic materials. This has been demonstrated by polyethylenimine (PEI)-coated MoS₂-PEG as a transfection agent of siRNA.^[226] NIR irradiation was utilized by Kim et al. on covalently modified MoS₂-PEI-PEG for delivery of pDNA to HCT 116 and B16F1 cells.^[227] Irradiation of NIR light onto transfected MoS₂ caused

Figure 26. A) Scheme showing sequential plasmid DNA delivery using MoS₂-PEI-PEG nanocomposite by photothermally triggered endosomal escape followed by redox-mediated polymer detachment and DNA release. Luciferase reporter gene expression assay of different polyplexes in the absence and presence of NIR irradiation in B) HCT 116 cells and C) B16F1 cells. D) Confocal laser-scanning microscopic images of HCT116 cells treated with MoS₂-PEI-PEG/DNA polyplexes with and without laser irradiation, and with laser irradiation and DEM treatment. Nuclei were stained with DAPI (blue), MoS₂-PEI-PEG were labeled with FITC (green), endo/lysosomes were stained with LysoTracker (red), and pDNA was labeled with TOTO-3 iodide (red). White arrow and yellow arrow represent endosomal escape of MoS₂-PEI-PEG nanocomposite and intracellular gene release from MoS₂-PEI-PEG carrier, respectively. Reproduced with permission.^[227] Copyright 2015, Wiley-VCH.

hyperthermia-induced endosomal ruptures and release of endosomal contents, including MoS₂-PEI-PEG-pDNA into the cytosol (Figure 26A). This resulted in easier migration and increased activity of pDNA. In contrast, such an effect was not observed in PEI-pDNA only, confirming the beneficial photothermal effect from MoS₂ (Figure 26B,C). Additionally, pDNA release was also contributed by the rapid release of LA-PEI and SH-PEG from MoS₂ in the reducing environment in cells, as evidenced by the suppressed release of pDNA in the nonreducing environment of cells treated with diethyl maleate (DEM) (Figure 26D).

Another study investigated the combination of gene therapy and PTT based on WS₂@PEI quantum dots.^[228] WS₂@PEI quantum dots were conjugated with Survivin-targeting siRNA. Application of PTT in addition with gene therapy led to low cell viability of 13% and 12.4% in BEL-7402 and HeLa cells, respectively, while gene therapy alone resulted in only 60% and 45% cell viability. This combination therapy enhanced Survivin silencing to 71.9% when compared to gene therapy which only managed to achieve 46.2%. In addition to Survivin, downregulation of heat shock protein HSP70 was observed, which were otherwise overexpressed in cells treated with PTT only. As HSP70 is responsible for tolerance against heat and suppression of apoptosis,^[229] the synergistic application of PTT and gene therapy resulted in sensitization of cells toward hyperthermia. These results were also well translated in vivo as Survivin and HSP70 expressions were downregulated and 91% of the tumor was inhibited.

Dendrimer functionalization strategy was proposed to improve gene compaction and versatility of the nanocarrier.^[230] MoS₂ nanoflakes were functionalized with lipoic acid-conjugated generation 5 (G5) poly(amidoamine) (PAMAM) dendrimers for

transfection of Bcl-2 (B-cell lymphoma-2) siRNA into 4T1 cells. Upon functionalization, hydrodynamic size of MoS₂ nanoflakes decreased, which suggested that the functionalization improved colloidal stability of functionalized G5-MoS₂ by preventing aggregation of as-made MoS₂. G5-MoS₂ displayed excellent photothermal property with a photothermal conversion efficiency of 47.8%. siRNA compaction was observed as the size of G5-MoS₂/siRNA shrank upon complexation. G5-MoS₂/siRNA delivered the siRNA efficiently into cells and caused 47.3% knockdown of Bcl-2 gene expression in 4T1 cells. The synergistic photothermal and gene therapy achieved the lowest in vitro cell viability of 21%. In vivo result showed that PTT was more effective than gene therapy in tumor inhibition. Nevertheless, the combination of both resulted in the lowest tumor volume at the end of the treatment period. One-hundred percent of the mice treated with combination therapy survived for 40 days of observation, while 60% of mice treated with PTT survived.

5.2.4. Photothermal and Photodynamic Therapy

Simultaneous photodynamic and photothermal therapies by TMDC nanocomplex were based on a similar approach by conjugation of photosensitizers onto TMDC. BSA-functionalized WS₂ was conjugated with photosensitizer MB by hydrophobic interaction to achieve simultaneous PDT and PTT.^[186] Irradiation with 665 nm light on WS₂-BSA@MB resulted in lower singlet oxygen generation compared to unconjugated MB. As 808 nm light irradiation could trigger the release of lipophilic photosensitizer

Table 4. In vivo cancer therapy applications of transition metal dichalcogenides.

TMDC material	Functionalization	Treatment type	Injected dose	Laser wavelength [nm]	Power density [W cm ⁻²]	Irradiation time [min]	Temperature increase in vivo	Conversion efficiency [%]	Ref.
WS ₂	LA-PEG	PTT	20 mg kg ⁻¹	808	0.8	5	35 °C	—	[189]
MoS ₂	PEG	PTT	200 µg Mo	808	1	5	—	—	[197]
MoS ₂	LA-PEG	PTT	8 µg	808	1	15	—	27.6	[201]
MoS ₂	Polyacrylic acidLA-PEG	PTT	50 µg	808	1	10	Reached 52.1 °C	—	[203]
VS ₂	PEGDOPA	PTT	20 mg kg ⁻¹	808	0.6	5	Reached 58 °C	31.5	[206]
MoS ₂	DMSA-IONPLA-PEG	PTT	6.85 mg kg ⁻¹	808	0.78	5	Reached 51 °C	—	[211]
MoS ₂	Fe ₃ O ₄ PEG	PTT	100 µg	808	1	12	22 °C	43.93	[213]
WS ₂	C ₁₈ PMH-PEGGd ³⁺	PTT/RT	20 mg kg ⁻¹	808	0.54 Gy (RT)	103 (RT)	Reached 47 °C	—	[198]
WS ₂	LA-PEG	PTT/RT	40 µg	808	16 Gy (RT)	10	Reached 45 °C	44.3	[179c]
MoS ₂	Glutathione	PTT	100 µg	808	1	5	Reached 52 °C	—	[179a]
MoS ₂	PolyanilinePEG	PTT/RT	—	808	1.5	5	16.3 °C	31.6	[215]
TiS ₂	C ₁₈ PMH-PEG	PTT	20 mg kg ⁻¹	808	0.8	5	Reached 65 °C	—	[179b]
ReS ₂	C ₁₈ PMH-PEG	PTT/RT	20 mg kg ⁻¹	808	0.6	20	Reached 45 °C	—	[219]
MoS ₂	LA-PEGDOX	PTT/DDS	3.4 mg kg ⁻¹	808	0.56	20	Reached 45 °C	—	[191]
MoS ₂	ChitosanDOX	PTT/DDS	2 mg kg ⁻¹	808	0.9	7	22.5 °C	24.37	[187]
MoS ₂	BSARV	PTT/DDS	2 mg kg ⁻¹	808	1	5	—	—	[192]
MoSe ₂	PolydopamineDOX	PTT/DDS	0.1 mg mL ⁻¹	808	2	5	—	44.5	[221]
WS ₂	IONP, MS, C ₁₈ PMH-PEGDOX	PTT/DDS	8.4 mg mL ⁻¹	808	0.55	10	15 °C	—	[222]
MoS ₂	PEI-HADOXNOTA- ⁶⁴ Cu	PTT/DDS	200 µL	808	0.6	10	—	—	[224]
MoS ₂	PLGA oleosolDOX	PTT/DDS	75 µg MoS ₂	808	0.6	5	Reached 56.5 °C	—	[225]
MoS ₂	Gen 5-PAMAM	PTT/GDS	0.1 mg	808	1.2	5	Reached 60.2 °C	47.8	[230]
MoS ₂	LA-PEGCe6	PTT/PDT	6.85 mg kg ⁻¹	808600 (PDT)	0.455 × 10 ⁻³ (PDT)	20	Reached 44.8 °C	—	[231]
WSe ₂	BSAMB	PTT/PDT	20 µg	808650 (PDT)	1.650.05 (PDT)	510	—	35.07	[233]
MoS ₂	PEIFe ₃ O ₄ ICGPt(IV)	PTT/PDT/DDS	2 mM Mo	808	2.5	10	—	27.7	[234]

MB from WS₂-BSA@MB, when both 808 nm and 665 nm light were used, the MB activity and singlet oxygen generation was restored. This result was elucidated by quenching of MB activity by WS₂-BSA, which were restored upon photothermal-triggered release. As shown in HeLa cell model, NIR irradiation to induce the photothermal process prior to photodynamic excitation was necessary to produce a synergistic effect.

Another PS, Ce6 was adsorbed onto the surface of MoS₂-PEG.^[231] Quenching of fluorescence and singlet oxygen generation was observed in Ce6 conjugated with MoS₂-PEG. Nevertheless, they reported more effective PDT effect by MoS₂-PEG/Ce6 than Ce6 alone. They observed stronger fluorescence in vitro in MoS₂-PEG/Ce6 than Ce6 alone, which they attributed to rapid and efficient uptake of Ce6 with MoS₂-PEG as the nanocarriers. In this work, they also employed mild photothermal effect into the microenvironment of MoS₂-PEG/Ce6-treated 4T1 cells to enhance cellular membrane permeability and improve the cellular uptake of MoS₂-Ce6.^[232] Hence, the combination of PDT and PTT achieved the most effective tumor growth inhibition. A similar effect was seen in tungsten-diselenide-based nanocarriers.^[233] Triggered release of MB by photothermal effect was confirmed by restoration of MB fluorescence and activity in NIR-irradiated cells. However, they observed that singlet oxygen generation in

WSe₂-BSA-MB was inferior to MB alone, due to energy transfer from conjugated MB to WSe₂-BSA. Nevertheless, the synergistic PTT and PDT combination with WSe₂-BSA/MB translated to a superior therapy as compared to PDT using MB alone.

Combination therapy of photothermal, photodynamic, and drug therapy and multimodal imaging was achieved by modification of MoS₂ nanoflower with iron oxide, ICG, and Pt(IV) prodrug.^[234] In this nanocomplex, iron oxide enabled T2 MRI imaging capability, while ICG acted as PS. The use of ICG with 808 nm excitation enabled simultaneous activation of photothermal and photodynamic processes. Conjugation of ICG enhanced the NIR absorption of the nanocomplex which was reflected in stronger signals in photothermal and PA imaging. Evaluation by 1,3 diphenylisobenzofuran (DPBF) as a chemical probe revealed that ICG in the nanocomplex maintained its ability to generate singlet oxygen, and absorption spectra suggested that ICG were also photostable in the MoS₂@Fe₃O₄-ICG nanocomplex (also labelled as Mo@Fe-ICG). The Mo@Fe-ICG was nontoxic even at concentrations as high as 400 µM. Toxic effect against incubated HeLa cells was only observed upon conjugation of Mo@Fe-ICG/Pt with Pt(IV) prodrug, which was further enhanced by irradiation of 808 nm light due to the release of Pt(IV) in addition to PTT and PDT. In vivo studies in mice bearing H22 tumor

Table 5. Synthesis and properties of transition metal dichalcogenides for theranostic applications.

TMDC material	Synthesis method	Modification	Lateral size (l)/thickness (t)/hydrodynamic size (hd)	Extinction coefficient	Theranostic applications	Ref.
MoS ₂	Solvothermal	Glutathione	7.5 nm (hd)	15.7 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT, PA imaging	[179a]
MoS ₂	Exfoliation	Chitosan	80 nm (l) 4–6 nm (t)	–	PTT, drug delivery, CT imaging	[187]
MoS ₂	Exfoliation	–	14.7 nm (hd)	–	PDT, down- and upconversion fluorescence Imaging	[188]
MoS ₂	Exfoliation	LA-PEG	50 nm (l) 2 nm (t)	28.4 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT, drug delivery	[191]
MoS ₂	Exfoliation	BSA	89 nm (l) 5–15 nm (t)	–	PTT, drug delivery	[192]
MoS ₂	Ionic liquid grinding	Chitosan	120 nm (l) 1.4 nm (t)	62.6 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT	[194]
MoS ₂	Solvothermal	PEG	79.2 nm (l) 0.29 nm (t)	–	PTT	[197]
MoS ₂	Exfoliation	–	0.8 μ m (l) 1.6 nm (t)	29.2 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT	[199]
MoS ₂	Solvothermal	LA-PEG	90 nm (l)	–	PTT	[201]
MoS ₂	Hydrothermal	Polyacrylic acid LA-PEG	90 nm (l)	–	PTT	[203]
MoS ₂	Sonication	BSA	181 $\pm$ 3 nm (l) (hd) 10.65 nm (t)	–	PA imaging	[209]
MoS ₂	Exfoliation	DMSA-IONP-PEG-Amine LA-PEG	50–200 nm (l)	–	PTT, PA, MRI, and PET imaging	[211]
MoS ₂	Hydrothermal	Fe ₃ O ₄ PEG	190.1 nm (hd)	–	PTT, PA, and MRI imaging	[213]
MoS ₂	Solvothermal	Polyaniline PEG	21.5 $\pm$ 3.9 nm (hd)	–	PTT, RT, PA, and CT imaging	[215]
MoS ₂	Exfoliation	PEG-amine Mesoporous silica DOX	450 nm (hd)	–	PTT, drug delivery	[223]
MoS ₂	Exfoliation	PEI-HA DOX NOTA- ⁶⁴ Cu	30–50 nm (l) 5–7 nm (t)	–	PTT, drug delivery	[224]
MoS ₂	Solvothermal	PLGA oleosol DOX	100 nm (l)	–	PTT, drug delivery	[225]
MoS ₂	Exfoliation	LA-PEG PEI	90 nm (hd)	–	PTT, gene delivery	[226]
MoS ₂	Exfoliation	LA-PEG SH-PEG	100–150 nm (l) 6–8 nm (t)	–	PTT, gene delivery	[227]
MoS ₂	Hydrothermal	Gen 5 polyamidoamine (PAMAM)	420 nm (hd)	–	PTT, gene delivery	[230]
MoS ₂	Exfoliation	LA-PEG	100 nm (hd)	28.4 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT, PDT, and PA imaging	[231]
MoS ₂	Hydrothermal	PEI Fe ₃ O ₄ ICG Pt(IV)	80 nm (hd)	–	PTT, PDT, PA, MRI imaging	[234]
WS ₂	Exfoliation	LA-PEG	3 $\pm$ 0.18 nm (l)	–	PTT, RT, PA, and CT imaging	[179c]
WS ₂	Exfoliation	BSA	20–100 nm (l) 4–5 nm (t)	21.8 Lg ⁻¹ cm ⁻¹ at 808 nm	PTT, PDT, and CT Imaging	[186]
WS ₂	Exfoliation	LA-PEG	50–100 nm (l) 1.6 nm (t)	23.8 Lg ⁻¹ cm ⁻¹ at 808 nm	PTT, PA, and CT imaging	[189]
WS ₂	High-temperature reaction	Gd ³⁺ C ₁₈ PMH-PEG	90–100 nm (hd)	22.6 Lg ⁻¹ cm ⁻¹ at 808 nm	PTT, RT, photothermal imaging, CT, and MRI imaging	[198]
WS ₂	Exfoliation	IONP mesoporous silica C ₁₈ PMH-PEG Cy5.5 DOX	60 nm (hd)	23.8 Lg ⁻¹ cm ⁻¹ at 800 nm	PTT, drug delivery, MRI, fluorescence imaging	[222]
WS ₂	Exfoliation	LA-PEI	8 nm (hd)	–	PTT, gene delivery, PA, CT imaging	[228]
VS ₂	High-temperature synthesis and sonication	DOPA mPEG-DSPE	35 nm (l)	22.6 Lg ⁻¹ cm ⁻¹ at 808 nm	PTT, PA, MRI, and SPECT imaging	[206]
TiS ₂	High temperature synthesis	C ₁₈ PMH-PEG	100 nm (hd)	26.8 Lg ⁻¹ cm ⁻¹ at 808 nm	PTT, PA imaging	[179b]
ReS ₂	High temperature synthesis	C ₁₈ PMH-PEG	10 nm (l) 0.5 nm (t) 25 nm (hd)	–	PTT, RT, PA, CT, SPECT imaging	[219]
MoSe ₂	Sonication	Pluronic F127	2.32 $\pm$ 0.69 nm (l) 0.7–2.1 (t) 7.2 nm (hd)	17.4 Lg ⁻¹ cm ⁻¹ at 785 nm	PTT	[202]
MoSe ₂	Hydrothermal	PEG-400	10 nm (l)	–	PTT, PA imaging	[218]
MoSe ₂	Hydrothermal	Polydopamine	314 nm (hd)	–	PTT, drug delivery	[221]
WSe ₂	Exfoliation	BSA	210 nm (hd)	–	PTT, PDT	[233]

demonstrated that addition of Pt(IV) in Mo@Fe-ICG/Pt resulted in a slight improvement for the combination therapy.

The potential for PDT using MoS₂ quantum dots as an intrinsic photosensitizer was investigated by Dong et al.^[188] Their work reported photoluminescent MoS₂ QDs synthesized by a top-down approach, which exhibited anti-Stokes emission and singlet oxygen generation capability. UCPL in the MoS₂ QDs produced emission ranging from 525 to 610 nm when excited at 775–900 nm, which was demonstrated successfully for in vitro imaging of HeLa cells. Singlet oxygen generations by MoS₂ QDs and PS protoporphyrin IX (PPIX) were compared under 630 nm irradiation. MoS₂ QDs were found to be more photostable and induced singlet oxygen generation in a more rapid fashion than PPIX. Preliminary in vitro demonstration in HeLa cell using singlet oxygen sensor green (SOSG) indicated greater singlet oxygen presence in MoS₂-treated cells than in untreated cells. However, further studies would be required to clarify the efficacy of this approach.

6. Other NIR Light-Responsive Nanomaterials

6.1. Metal Oxides

Metal oxide nanoparticles encompass a wide range of materials, ranging from iron oxides, molybdenum oxides, cerium oxides, copper oxides, and many others. Metal oxides have found applications in electronic and photocatalytic functions due to their optoelectronic and magnetic properties,^[235] which are also shown to be beneficial in theranostics. Species like iron oxides, gadolinium oxides, and hafnium oxides have been applied in cancer radiotherapy and in imaging modalities such as CT and MRI imaging.^[236] Iron oxides have been approved for clinical use as MRI contrast agent.^[237] On the other hand, some metal oxide species like copper oxides are considered unusable in biological settings, due to their high toxicity in cells.^[238] In general, there are several synthesis approaches of metal oxide species, including coprecipitation method, hydro/solvothermal reaction, sol-gel method, microwave, laser ablation, and template-based synthesis.^[239] Metal oxides from different synthesis methods may also display different shapes, such as spherical versus nanocube iron oxides,^[240] molybdenum oxide nanosheets and nanospheres,^[241] and porous TiO₂.^[242] In particular, an often-used strategy to modify their chemistry and optical properties is the use of a reducing agent, which has also been shown to affect the size and morphology of resulting metal oxides.^[239] In this section, several formulations of NIR light-responsive metal oxides such as iron oxides, molybdenum oxides, and titanium oxides, and their theranostics applications will be discussed.

Among metal oxides, iron oxides have been well studied for a long time with abundant research works in their theranostic applications.^[243] Modifications of iron oxide morphologies allow the engineering of intrinsic magnetic properties into superparamagnetic properties,^[244] which is beneficial for MRI imaging, magnetic hyperthermia, and targeted accumulation by external magnetic field.^[245] In a recent study, Espinosa et al. utilized magnetic and NIR light-responsive properties of iron oxide nanocubes for bimodal thermal therapy against cancer.^[240] Combination of photothermal and magnetic hyperthermia was

applied onto the nanocubes by exposure of NIR light and alternating magnetic fields at 520 kHz to produce a cumulative thermal effect. Dense packing of nanocubes was found in endosomes which inhibited magnetic hyperthermia in cells in vitro.^[246] However, the magnetic hyperthermia effect was recovered by the photothermal effect which restored Brownian motion of the nanocubes. This resulted in a cumulative 15 °C temperature rise in the tumor in vivo, which was consistent in 2 days post-injection. Overall, this strategy may allow a reduction in doses of iron oxides, magnetic field strength, and NIR excitation power to comply with in vivo settings. In another study, superparamagnetic iron oxide (SPION) nanoparticles were functionalized as targeted PTT, NIR fluorescence, and MRI contrast agent.^[247] Functionalizations with DSPE-PEG-amine and heptamethine cyanine dye (MHI-148) produced stable nanoparticles with NIR fluorescence and tumor-targeting capability, which were highly biocompatible in vitro at concentrations up to 1 mg mL⁻¹. As intrinsic MRI signals gradually weakened due to iron degradation, the stable NIR fluorescence provided long-term signal retention for up to 12 days. NIR absorption of MHI-148 in addition to DSPE-SPION contributed to superior PTT efficacy compared to DSPE-SPION only.

Modification of some metal oxide nanomaterials can introduce new optoelectronic properties which enable NIR-based applications. TiO₂ typically exhibited absorption in the UV region, which can be tuned by hydrogenation reaction to produce black titanium dioxides with absorbance in the NIR region.^[248] In 2016, Ou et al. synthesized Magnéli-phase titanium oxide (Ti₈O₁₅) with high NIR absorbance for PTT application. Ti₈O₁₅ with an average size of 200 nm was obtained from TiO₂ via partial reduction of Ti⁴⁺ to Ti³⁺ ions, which introduced a wide absorption band in Ti₈O₁₅ throughout visible and NIR spectrum, coupled by a color change from white to dark blue. Compared to less than 4 °C in TiO₂, a temperature rise of more than 27 °C was achieved in Ti₈O₁₅ upon exposure of 1 W cm⁻² 808 nm light for 5 min. Reduced black titanium was also demonstrated as imaging-guided simultaneous PTT and PDT agent.^[249] They enabled photothermal and PA imaging in vivo with PA signals detectable as early as 5 s after intravenous injection. The radiosensitizing capability of TiO_{2-x} was demonstrated by ROS and hydroxyl generation and was confirmed by 2,7-dichlorofluorescein signals in HeLa cells. TiO_{2-x} treatment with 808 nm (1 W cm⁻²) irradiation ablated the tumor in 2 days. The TiO_{2-x} was also biocompatible at a dose of 10 mg kg⁻¹ Ti for up to 90 days. In another study, black titanium oxide was designed for targeted drug delivery using mesoporous silica coating as DOX loading sites.^[250] Mesoporous silica improved drug loading of the nanocomplex from 0.5% to 5%, and the photothermal effect of TiO₂ contributed to 74.1% drug release in pH 5 in 48 h. Targeted PTT and drug delivery/release by folic-acid-modified NC-FA-DOX contributed to a more effective therapy than treatment by DOX alone. In another study, mesoporous TiO_{2-x} was synthesized by hydrogen reduction of TiO₂ and conjugated with DOX, PDA, and Cy5.5 dye.^[242] Reduction of TiO₂ to TiO_{2-x} caused a fourfold increase in absorbance at 808 nm, which was further enhanced by conjugation with PDA and Cy5.5. NIR fluorescence from Cy5.5 allowed fluorescence imaging in addition to intrinsic PA imaging. The nanocomplex was able to accumulate in tumor 1 h post-injection, and retention after 24 h was confirmed by PA imaging. The formulation

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also assisted in the quick release of DOX as a result of PDA dissociation from TiO_{2-x} in acidic pH and under NIR light. Hence, in vivo therapy was achieved through synergistic PTT and PDT of $\text{DOX@TiO}_{2-x}\text{@PDA-Cy5.5}$ nanocomplex.

A transition-metal-based oxide, tungsten oxide nanoparticles gained their NIR absorbance due to LSPR effect.^[251] Small nonstoichiometric $\text{WO}_{2.9}$ tungsten oxide nanorods which were 13.1 ± 3.6 nm in length and 4.4 ± 1.5 nm in diameter were obtained by a high-temperature reaction.^[252] The application of $\text{WO}_{2.9}$ for PTT under 980 nm irradiation with a low power density (0.35 W cm^{-2}) for 5 min resulted in a temperature increase of 20°C in HeLa tumors in mice models. To facilitate rapid excretion, tungsten oxide nanodots (WO_{3-x}) with 1.1 ± 0.3 nm size were produced with pentaerythritol tetrakis (3-mercaptopropionate)-terminated poly(methacrylic acid) (PTMP-PMAA) ligand.^[253] WO_{3-x} nanodots were composed of W^{5+} and W^{6+} mixture with a ratio of 89:11. They displayed pH- and oxygen-dependent NIR absorption. It was observed that high pH values and oxygen levels gradually reduced their absorption, with the latter due to their oxygen-deficient structure.^[254] They were biocompatible in vitro up to 1 mg mL^{-1} in multiple cell lines and quickly excreted from mice in vivo upon rapid accumulation in RES organs 2 h after injection. The use of WO_{3-x} nanodots for PTT and RT demonstrated 100% survival of mice models for 45 days. Combination of PTT and PDT was attempted by Deng et al. by electrostatic attachment of ICG onto tungsten oxide nanorod bundles to enable simultaneous PTT and PDT.^[255] On the other hand, Qiu et al. utilized intrinsic properties of PVP-decorated $\text{W}_{19}\text{O}_{48}$ for PTT/PDT/RT combination along with CT imaging.^[256] The 1.5 W cm^{-2} 980 nm light and 6 Gy radiation were utilized to induce synergistic effect for tumor removal in 5 days and long-term survival of the mice model without relapse for over 9 months.

Another transition metal oxide, molybdenum oxide (MoO_x) has attracted interest due to their degradable nature. Degradable MoO_x nanosheets were produced by Song et al. via hydrothermal reduction, which were stable in acidic pH but underwent degradation in physiological pH.^[241a] Water-soluble MoO_x -PEG with $37.3 \text{ Lg}^{-1} \text{ cm}^{-1}$ extinction coefficient at 800 nm demonstrated stability in pH 5.4 and lower, but suffered oxidation into MoO_4^{2-} ions at pH 9.4 and above. This, in turn, facilitated rapid excretion through urine and feces in mice model. Due to the slower degradation, superior PA signal retention was discovered in acidic and hypoxic tumor environment compared to normal cells. In vivo PTT of MoO_x was demonstrated using 0.7 W cm^{-2} 808 nm laser for 10 min, resulting in 4T1 tumor ablation, as tumor temperature rose to 55°C . Furthermore, their nanosheet structure enabled loading of SN 38 and Ce6, with 230% and 80% weight loading capacity. In another study, hollow PEGylated MoO_{3-x} nanospheres as DDS was synthesized by a hydrothermal reaction.^[241b] PEG acted as both reducing agent and surfactant to produce Mo with oxidation states from +4 to +6. This PEGylation produced blue PEGylated MoO_3 nanospheres with NIR absorbance band from 700 to 1000 nm with a peak at ≈ 800 nm. Insoluble drug Camptothecin (CPT) were loaded onto hollow pores in the nanospheres for triggered release by 808 nm light. This translated to 95% tumor inhibition by PEG- MoO_3 -CPT in 15 days, which was more effective than PTT with PEG- MoO_3 only.

To exploit deeper penetration of light in second NIR window,^[258] Yin et al. designed biodegradable MoO_x for PTT with excitation in this spectral range.^[257] PEG- MoO_x was obtained via hydrothermal reaction in a water-ethanol mixture at pH 1.2. PEG- MoO_x was responsive to 808 and 1064 nm irradiations with conversion efficiencies of 27.3% and 37.4%, respectively (Figure 27A). Under the same treatment temperature, three times more ROS was generated under 1064 nm excitation as confirmed by higher cell deaths when compared to 808 nm excitation (Figure 27B–D). This was further confirmed in Panc-1 xenografted mice model. Phototherapy was applied using 808 or 1064 nm excitation to achieve tumor temperature of 43°C . It was observed that mice treated with 1064 nm exhibited the smallest tumor size post-treatment, indicating the better synergistic PDT and PTT effect by 1064 nm excitation (Figure 27E). A controllable synthesis of molybdenum oxides from molybdenum sulfides by a solvothermal reaction was proposed to produce MoO_2 , MoO_3 , and MoO_{3-x} .^[259] By increasing the reaction duration, MoO_2 , MoO_{3-x} , and MoO_3 with varying optical properties were obtained. The resultant MoO_2 displayed the strongest NIR absorbance with an efficient photothermal conversion of 61.3%, as temperature as high as 73.5°C was observed in $80 \mu\text{g mL}^{-1}$ solution under 808 nm light (2 W cm^{-2}).

A strategy using degradable MoO_x -PEG in a microgel combination for pH/temperature/photosensitive therapeutic agent was proposed.^[260] Despite high photothermal conversion efficiency of 62.5%, unstable photothermal effect was observed with prolonged incubation, which was attributed to the degradation of MoO_x in nonacidic pH. Hence, a microgel composed of *N*-isopropylacrylamide (NIPAM) which served as a pH-responsive polymer, and methacrylic acid (MAA) to provide acidic environment,^[261] was utilized to form PEGMA- MoO_x /p(NIPAM-co-MAA) complex. This contributed to delayed degradation and a more stable photothermal property of MoO_x in the nanocomplex. Compared to the absorbance of PEGMA- MoO_x which dropped by 95.9% in 8 days, the absorbance of PEGMA- MoO_x /p(NIPAM-co-MAA) only reduced by 46% over 14 days.

In a recent report, manganese oxides in the form of MnO_2 nanosheets, which were sensitive to tumor microenvironment, were synthesized for MRI imaging and PTT.^[262] Soybean phospholipid (SP)-modified MnO_2 -SP nanosheets displayed excellent stability in various media, including PBS, cell culture media, and simulated body fluid. PTT was performed based on intrinsic $5 \text{ Lg}^{-1} \text{ cm}^{-1}$ extinction coefficient at 808 nm with a conversion efficiency of 21.4%. Under reducing environment such as pH 5 and in the presence of GSH, these nanosheets gradually disintegrated to Mn^{2+} ions. The r_1 relaxivity increased from $0.87 \text{ mM}^{-1} \text{ s}^{-1}$ in neutral environment to $5.45 \text{ mM}^{-1} \text{ s}^{-1}$ in pH 5, hence enabled tumor microenvironment-sensitive imaging. Application of MnO_2 -SP nanosheets with 1.5 W cm^{-2} 808 nm light in vivo produced satisfactory tumor removal within 16 days, while the nanosheets themselves were nontoxic at 20 mg kg^{-1} dose in mice for a month of observation period.

Besides these metal oxides, composite metal oxides such as tungsten bronzes have been utilized in theranostics. Cs_xWO_3 nanorods exhibited absorption in 800–1300 nm with a high extinction coefficient of $4.8 \times 10^{10} \text{ M}^{-1} \text{ cm}^{-1}$ at 980 nm, which was attributed to SPR effect.^[263] Thermal therapy in vitro revealed that cellular damage induced lysosomal membrane damage and

Figure 27. A) UV-vis-NIR absorbance spectrum of the PEG-MoO_x nanoparticles aqueous solution. The inset shows the photograph of the PEG-MoO_x aqueous solution. The NIR I and II biological windows are indicated by yellow and blue bars. Comparison of the cell viability of HeLa cells incubated with PEG-MoO_x nanoparticles under 808 nm and 1064 nm laser irradiation at an environmental temperature of B) 37 °C and C) 4 °C. D) Fluorescence images of HeLa cells after co-staining using CA/PI: I) Control + 808 nm, II) Control + 1064 nm laser, III) PEG-MoO_x nanoparticles (50 μg mL⁻¹), IV) PEG-MoO_x nanoparticles (100 μg mL⁻¹), V) PEG-MoO_x nanoparticles (100 μg mL⁻¹) + 808 nm laser (power density: 1.2 W cm⁻², the maximum temperature control at 43 °C), VI) PEG-MoO_x nanoparticles (100 μg mL⁻¹) + 1064 nm laser (power density: 1.0 W cm⁻², the maximum temperature control at 43 °C) (scale bar: 50 μm). E) Tumor weights for each group on the 15th day of observation. Reproduced with permission.^[257] Copyright 2018, Royal Society of Chemistry.

skeleton protein degradation, leading to a combination of necrosis and heat/ROS induced apoptosis. Tian et al. synthesized NIR light-responsive PVP-coated Rb_xWO₃ for PA, CT imaging, and DOX delivery.^[264] The nanorods composed of Rb and W with a ratio of 0.27 were produced by a hydrothermal reaction of Rb₂SO₄ and WO₃ precursors in the presence of PEG and PVP. Rb_xWO₃ produced stronger photothermal response under 980 nm excitation compared to 808 nm excitation. However, significant light attenuation by water at 980 nm wavelength meant that 808 nm excitation had superior photothermal effects in deeper location. This photothermal conversion efficiency was calculated to be 17.8%. DOX was further attached to the nanomaterial at 0.326 mmol g⁻¹ to produce effective therapy by PTT and chemotherapy. Another tungsten bronze species, (NH₄)WO₃ nanocubes possessed absorption which significantly increased at wavelengths of 1000 nm and above.^[265] Photothermal conversion efficiency of 39.4% was recorded using 1064 nm excitation, which was higher than previously mentioned tungsten bronzes. In vivo study based on 4T1 tumor model revealed that in addition to tumor removal, the PTT with (NH₄)WO₃ also contributed to inhibition of lung metastasis. Recently, a pilot study on K_xWO₃ with wide-band absorption was conducted.^[266] K_xWO₃ nanorod with 25.7% photothermal conver-

sion efficiency was nontoxic in vitro even at 1 mg mL⁻¹ concentration. Using 1064 nm (1.5 W cm⁻²) excitation, HeLa tumor on mice was removed within 5 days post-treatment.

Some efforts were aimed at conjugating metal oxides with NIR light-responsive nanomaterials to embed additional theranostic capability. For example, Ding et al. modified biocompatible Mn₃O₄ with PEG and PDA to achieve chemo/PTT in addition to intrinsic MRI capability.^[267] In addition to NIR absorbance, PDA provided π-π stacking sites for DOX loading. As a complex, they achieved superior MRI contrast than commercial Magnevist and served as an efficient chemo/PTT agent, achieving 94.81% tumor growth inhibition in H22 tumor xenografted mice. Jin and coworkers synthesized hollow tantalum oxide (TaO_x) nanoparticles functionalized with PEG, polypyrrole (Ppy), NIRDye800, and DOX as a multifunctional theranostic agent against esophageal cancer.^[268] PPy&DOX@TaO_x-NIRDye800-PEG complex had strong absorption in the NIR region. DOX was loaded onto the nanocomplex at 10.00 ± 1.08% weight ratio for triggered release by 808 nm light excitation. Conjugation of NIRDye800 with tantalum oxides without fluorescence quenching allowed PA imaging and NIR fluorescence under 830 nm excitation, in addition to intrinsic CT

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imaging capability. Using PPy&DOX@TaO_x-NIRDye800-PEG for PTT/chemotherapy against KYSE30 tumor xenografted mice model, they found that while PTT alone was successful in eradicating tumor, relapse and liver metastasis occurred in mice, which were not observed in the PTT/DOX-treated group. Finally, aerosol administrated treatment of the nanoparticles against esophageal cancer was proven successful, as confirmed by accumulation within the tumor and gastrointestinal tract.

6.2. Black Phosphorus

Research on 2D nanomaterials began back in 2004 when Novoselov and coworkers first exfoliated graphene sheets from graphite using a micromechanical cleavage procedure.^[269] Since then, there has been an increasing number of 2D nanomaterials such as TMDCs with well-studied properties that can be exploited for cancer theranostic applications. As one of the latest additions of 2D nanomaterials, black phosphorus (BP) has been found to exhibit many novel properties such as ease of fabrication, relatively high drug loading capability, and excellent photothermal conversion efficiency. Atomically thin BP has a layer-dependent direct bandgap that can be tuned from 0.3 eV in bulk materials to 2 eV in monolayered BP, which enables the absorption spectra of BP to cover a wide range of spectrum from ultraviolet to infrared wavelengths.

The structure of BP is made up of corrugated planes of phosphorus atoms which are held by strong intralayer P–P bonds and weak interlayer van der Waals forces. By breaking these weak interactions using commonly used exfoliation techniques such as solvothermal and liquid ultrasonication, bulk BP can be exfoliated into thin BP nanosheets or quantum dots. Shao and coworkers first dispersed bulk BP powder in *N*-methyl-2-pyrrolidone and then ultrasonicated them for 4 h using a power of 1200 W, followed by overnight sonication in an ice bath using a power of 300 W.^[270] The resultant dispersion was purified by centrifugation. Although this preparation method is simple, the use of high power ultrasonication is dangerous and extra precautions should be taken when experiments are being carried out.

Besides facile preparation procedures and excellent photothermal conversion efficiency, another superior property of BP QDs is their outstanding biocompatibility since phosphorus is a benign element that makes up to ≈1% of human body weight as one of the components of human bones. Besides, the release of P_xO_y with no toxic intermediates also contributes to the low toxicity of BP.^[271] These favorable characteristics have led to the employment of BP QDs and nanosheets in various treatment modes of cancer therapy. Sun and coworkers prepared BP QDs with a lateral size of about 2.6 nm that exhibited superior NIR photothermal efficiency of 28.4% with a large extinction coefficient of 14.8 Ig⁻¹ cm⁻¹ at 808 nm excitation.^[272] The temperature of low concentration BP QDs solution increased by 31.5 °C after only 10 min of NIR light irradiation. The photothermal properties were further verified in vitro using C6 and MCF7 cancer cells as the cell models. BP QDs were found to exhibit no dark toxicity even at high concentration of 200 ppm. On the other hand, when irradiated with 808 nm (1 W cm⁻²) laser, the cell viabilities of both cell models were reduced to less than 10%.

Zhao et al. designed a NIR imaging-guided PTT using dye-modified BP nanosheets.^[273] Covalent conjugation of Nile Blue dye to BPs not only enhanced the stability of the BPs but also allowed NIR emissions from the complex, forming a novel synergistic PTT and NIR imaging capabilities. As a result, these BPs were successfully used in in vivo experiments. Nude mice bearing MCF7 breast tumors were injected with 100 μL of 100 mg mL⁻¹ BPs through the tail vein followed by NIR irradiation 1-h post injection. The tumor temperature increased by 23.5 °C as compared to the control group which only experienced a temperature increase of 11.5 °C. No obvious side effect was found and the tumor was completely cured within 16 days.

BP has also been reported to be used as a PDT agent. However, most of the current PDT agents and PS faced a similar bottleneck. Intrinsic oxygen starvation in hypoxic solid tumor would result in the failure of PS to generate a sufficiently large amount of ROS. In addition, the fast depletion of oxygen by PDT agents further aggravates the situation, resulting in low PDT efficiency. Liu and coworkers designed dual-triggered oxygen-supported BP nanosheets which served both as a PS and nanocarrier.^[274] BP was conjugated with DNA duplex of 5'-Cy5-aptamer-heme/3-heme-labeled oligonucleotides which could passivate peroxidase activity. After recognition of aptamer target, the quenched fluorescence was restored by cellular adenosine triphosphate. This subsequently triggered the catalytic function toward excessive intracellular hydrogen peroxide and generated sufficient oxygen to sustain the PDT of BP nanosheets. This dual-triggered self-sustained system not only exerted tumor microenvironment for enhanced PDT but also suppressed hypoxia-associated therapy resistance.

Recent reports have found that BP nanosheets have high reactivity with oxygen and water and can degrade in aqueous media resulting in poorer phototherapy efficiency. Shao and coworkers loaded BP QDs into PLGA by an emulsion technique to produce biodegradable BPQDs/PLGA nanospheres.^[270] BP QDs were isolated from oxygen and water by the hydrophobic PLGA, leading to enhanced photothermal stability and lower degradation rate. In vivo experiments showed that BPQDs/PLGA had excellent PTT efficiency and inhibited tumor growth efficiently. After performing their therapeutic function, biodegradable PLGAs would degrade, which allowed the release and subsequent degradation of BP QDs into nontoxic phosphate and phosphonate, thus enabling safe clearance from the body. This therapeutic strategy which combined biocompatibility and biodegradability with excellent PTT has an immense potential for future clinical studies.

Yang and coworkers developed a novel nanocomposite formulation consisting of IONPs and Au nanoparticles on black phosphorus sheets.^[275] The IONPs served as an MRI contrast agent while Au nanoparticles acted as a plasmonic photothermal agent. By exploiting the properties of the different materials, the group investigated the therapeutic capability of these nanocomposites in vitro and in vivo. They found that the nanocomposites were able to inhibit tumor growth, owing to the synergistic PTT and PDT using a low-power 650 nm NIR laser. The suppression of tumor growth was able to be visualized with the help of MRI. In addition, a complete blood count assessment and serum biochemistry assay were carried out to investigate the potential toxicity of the nanocomposites. The blood count, liver function, and kidney function markers such as platelets, alanine aminotransferase,

and white blood cells were found to be within the normal reference ranges, indicating that no obvious toxicity was caused by the nanocomposites.

6.3. Polymeric Nanomaterials

In the past two decades, various types of polymeric nanomaterials such as micelles, vesicles, and micro/nanogels have been explored to deliver therapeutic cargoes for cancer treatments.^[276] However, these polymeric nanomaterials lack on-demand drug release at target sites. Smart responsive polymeric nanomaterials have gained huge popularity as a means to deliver drugs, gene/siRNA, and proteins efficiently to the target site. A smart responsive system typically consist of polymeric nanoparticles and various internal or external stimuli, such as enzymes,^[276a,277] sugars,^[278] pH,^[279] redox reaction,^[280] temperature,^[281] and light.^[282] In particular, optical excitation for light-responsive nanomaterials can be spatially and temporally controlled from outside of the biological system. Light-responsive polymers are typically synthesized by self-assembly method from amphiphilic block copolymers. Dissociation and disruption of polymeric micelles can be demonstrated through photoisomerization,^[276a,283] photo-rearrangement,^[284] photo-cleavage,^[285] and energy conversion. For instance, the behavior of the polymers can be modified by alteration into different isomer structures through photoisomerization using UV or NIR light excitation. Common photoisomerization molecules such as azobenzene (AZO), spiropyran (SP), and dithienylethene (DTE), have been used to form functionalized polymeric micelles. The use of AZO molecules is based on the reversible *trans-cis* photoisomerization of their nitrogen–nitrogen double bond ($N=N$). AZO and its derivatives can transform from planar *trans* form to nonplanar *cis* form under 340–380 nm light irradiation. On the other hand, the process can be reversed when they are irradiated by 420–490 nm light or moved into the dark. Based on this concept, Wang et al. designed an ionomer with a self-assembled double hydrophilic block copolymer of PEG and PAA with a cationic AZO-based surfactant and pyrene sulfonic acid dye.^[286] After being irradiated by 360 nm light for 300 s, the AZO underwent photoisomerization and subsequently released the dye, as confirmed by an increase in fluorescence of the solution. In contrast, the fluorescence was slightly quenched when the solution was subjected to visible light (≈ 440 nm) irradiation for 900 s, indicating that the dye has been re-encapsulated into the polymers. In another study, Xiao et al. presented a cellular-uptake-shielding platform, namely “plug and play” (PnP), by loading DOX in the AZO-based PAA template.^[287] The PnP template demonstrated light-responsive remote-controlled drug release at target sites. Trans-AZO could strongly interact with α -cyclodextrin (α -CD), while such interaction was hindered due to the mismatch between α -CD with *cis*-AZO under UV light irradiation. In other words, the release processes were driven by the photoswitchable host–guest interactions between α -CD and AZO moieties. The PnP template (200 mg L^{-1}) was incubated with HeLa cells for *in vitro* studies. The cell viability was about 90% in dark condition, but decreased to 42% after 20 min of UV irradiation, indicating that α -CD-DOX have been released from

Figure 28. Illustration of the breathing process of A) a jellyfish and B) vesicle by highly reversible green fluorescence quenching and recovery. C) Schematic demonstration of the amphiphilic diblock copolymer poly(ethylene glycol)-block-poly(dimethylamino-azobenzene) (PEG-b-PDMA-AZO) and the vesicle structure. Reproduced with permission.^[288] Copyright 2012, Wiley-VCH.

the PnP template. The combination of light with other stimuli are widely used in applications with AZO-containing photoisomerization systems. Dong et al. designed a pH-responsive polymeric vesicle with on–off switchable fluorescence mimicking the breathing and light-emitting behavior of jellyfish (Figure 28A).^[288] In this study, the polymeric vesicles were synthesized via aqueous self-assembly of amphiphilic diblock copolymers with dimethylamino-azobenzenes (DMA-AZOs) fluorescent chromophores to form amphiphilic diblock copolymer poly(ethylene glycol)-block-poly(dimethylamino-azobenzene) (PEG-b-PDMA-AZO) (Figure 28C). The PEG-b-PDMA-AZO could expand and shrink reversibly under different pH values through variation of their wall thickness. The result is shown in

Figure 28B, as the fluorescence was strong in the shrinking state and quenched in the expanding state, similar to the breathing behavior of jellyfish.

In a photo-rearrangement procedure, a typical photo-trigger group such as hydrophobic 2-diazo-1,2-naphthoquinone (DNQ) molecules can be changed into hydrophilic 3-indenecarboxylic acid (3-IC) molecule ($pK_a = 4.5$) through UV-triggered Wolff-rearrangement reaction. Notably, Urdabayev and Popik reported that DNQ molecules could also experience Wolff-rearrangement through two-photon absorption of low-energy NIR light.^[284b] Recently, more studies focused on fabrication of NIR light-responsive DNQ-containing polymers and their development in nanomedicine applications. Liu et al. prepared NIR light-sensitive polymeric micelle (Dex-DNQ) by modification of hydrophilic dextran (Dex) and hydrophobic DNQ molecules for enhanced intracellular delivery of DOX.^[289] Under NIR laser irradiation, the encapsulated DOX was released into cancer cells upon the dissociation of these biocompatible Dex-DNQ micelles by Wolff rearrangement reaction. As the aforementioned DNQ-containing micelles lacked highly efficient tumor-targeting properties, nanomaterials exhibiting both NIR sensitivity and active targeting can be designed to enhance the intratumoral uptake and delivery. Based on this motivation, Sun et al. presented a new strategy that combined sugar-triggered targeting molecules and light-responsive groups.^[290] The sugar-targeted nanocarriers were prepared by DNQ-decorated poly(amidoamine)-blockpoly(3-caprolactone) amphiphiles by self-assembly into spherical micelles (less than 200 nm in size), in which the propargyl focal point could be easily click conjugated with the desired sugar-targeting groups (glucose, Glu; lactose, Lac) to produce Glu/Lac-D3-PCL-DNQ. The micelles suffered from sensitivity to 365 and 808 nm light irradiation, with the latter due to two-photon absorption. This can be observed by a decrease in absorbance and a change in morphology. Based on these properties, DOX could be controllably released by changing the duration of light irradiation. Thus, the drug delivery performance of DOX-loaded-Glu/Lac-D3-PCL-DNQ nanocarriers in in vitro studies showed that the DOX release was higher with increasing duration of light irradiation.

7. Conclusion and Outlook

Conventional cancer therapy such as chemotherapy and radiotherapy suffer from issues like inefficient and nonspecific drug delivery, which lead to ineffective and costly therapies with toxic side effects in patients. In recent decades, nanomaterials have been proposed as a potential solution by engineering them into theranostic agents to solve these shortcomings. Moreover, tunable optical properties of nanomaterials may be beneficial for multimodal imaging and therapy. This is especially true in the NIR range, which is the transparent optical window of biological tissues. As highlighted in this review, studies in recent years have investigated the use of NIR light-responsive nanomaterials such as gold nanorods, UCNPs, carbon dots, and TMDCs as well as metal oxides, black phosphorus and polymeric nanomaterials in theranostic applications. In general, strong NIR absorption and photothermal conversion allow the use of these nanomaterials as UCPL and photoacoustic imaging, photothermal, and even as

PDT contrast agents. Intrinsic properties in these nanomaterials can facilitate additional theranostic modalities by MRI, CT imaging, and radiotherapy. Complexation of these nanomaterials with chemotherapy drugs, genes, or PSs enables synergistic anticancer effects by the combination of NIR light-based therapy and NIR light-triggered controllable drug release.

We have critically discussed the status of Au NRs on their unique optical properties, surface modification, and NIR light-triggered bioapplications. Seed-mediated synthesis of Au NRs enables tuning of their aspect ratios by controlling several key factors including the amount of Ag ions, temperature, and pH value. This, in turn, also allows for facile tuning of their LSPR band from visible to NIR range and enhance scattering coefficient and long-term photostability. Such properties have been shown to be advantageous for the application of Au NRs in bioimaging modalities such as DFS, OCT, TPL, and X-ray computed tomography. Under NIR light excitation, this LSPR enables Au NRs to convert incident photons into localized heat for hyperthermia effect. As previously described, particle size plays an important role in affecting LSPR profile of Au NRs as well as their cellular uptakes. Optimization of these properties has to be achieved for efficient NIR light-responsive applications. Surface modification strategies using NIR-active polymers and other nanomaterials such as mesoporous silica may further improve their properties and multifunctional capabilities.

Practical therapeutic applications of UCNPs requires a full understanding of their optical properties, morphology, surface chemistry as well as the potential to introduce multiple treatment capabilities for a more effective therapy. However, the low QY of UCNPs is a major setback for its practical use in cancer theranostics. The low QY of less than 1% requires a relatively high intensity of NIR light to effectively trigger photoresponsive treatments, which could exceed the maximum allowable limits of exposure and induce significant photodamage. Host lattice manipulation, surface passivation, surface plasmon coupling, and photonic crystal engineering are among the many techniques employed to develop UCNPs with high QY. Besides, most of the current UCNP-based treatment systems are responsive to 980 nm NIR light excitation which is a major drawback due to the fact that it overlaps with absorbance spectrum of water, resulting in overheating and tissue damage. The shift of absorbance to a shorter wavelength is highly desirable. The incapability of UCNPs to degrade into biologically benign components is another safety concern which requires careful design of UCNP-based systems. New methodology can be developed to produce sub-10 nm or even smaller UCNPs that are beneficial for efficient clearance. The surface properties can also be controlled to ensure effective uptake and prolonged in vivo stability.

The tunability of optical properties is an important feature of CDs which facilitate their widespread use in biological applications. Specifically, their PL can be tuned to produce long wavelength or multicolor emissions, while absorption of CDs can be tweaked to respond to NIR light irradiation. These can be done through careful selection of carbon precursors and solvents in combination with optimization of experimental conditions, such as pH and temperature, as well as synthesis route, which is influential to the absorption and emission peaks of the resultant CDs. Post-synthesis surface modification is another commonly used route to control the emission properties of CDs. Functional

Table 6. Summary of synthesis, advantages, challenges, and future works of NIR light-responsive nanomaterials.

Nanomaterials	Synthesis	Advantages	Challenges	Future Works
Gold nanorods	<ul style="list-style-type: none"> Seed mediated Hydrothermal Wet-chemical Sonochemical Photochemical reduction technique Electrochemical Physical lithography 	<ul style="list-style-type: none"> Tunable absorption Photostability Easy surface modification Strong scattering and absorption cross-sections 	<ul style="list-style-type: none"> Limited media tolerance Costly synthesis 	<ul style="list-style-type: none"> Preventing nanoparticles aggregation Improving solubility in plasma
<ul style="list-style-type: none"> Upconversion Nanoparticles 	<ul style="list-style-type: none"> Thermal decomposition Coprecipitation synthesis Hydro/solvothermal synthesis Hydrothermal coprecipitation Emulsion method Sonochemical synthesis 	<ul style="list-style-type: none"> Tunable absorption and fluorescence Upconversion properties Low autofluorescence Low phototoxicity 	<ul style="list-style-type: none"> Hydrophobic surfactant Low absorption cross-section Low stability 	<ul style="list-style-type: none"> Improving the low absorption intensity Exploration PL and PL QY with multiple dopants Improving the UCNPs stability
Carbon dots	<ul style="list-style-type: none"> Laser ablation Arc discharge Electrochemical Chemical oxidation Hydrothermal Thermal oxidation Reverse micelles Supported templates 	<ul style="list-style-type: none"> Tunable absorption and fluorescence Flexible synthesis route and precursors 	<ul style="list-style-type: none"> Low PLQY at high wavelength Lack of understanding of the effect of precursors on the properties of carbon dots Controversial PL mechanism 	<ul style="list-style-type: none"> Controlling the composition of carbon dots Improving the PL QY at long wavelengths Understanding the PL mechanism
Transition metal dichalcogenides	<ul style="list-style-type: none"> Exfoliation Hydro/solvothermal reaction High-temperature reaction 	<ul style="list-style-type: none"> High NIR absorption Strong radiation absorption by transition metals Large surface area of the 2D structure Wide variety of TMDC compositions and structures 	<ul style="list-style-type: none"> Limited functionalization strategies Lack of systematic studies among many TMDC species 	<ul style="list-style-type: none"> Exploring functionalization chemistry of TMDCs Designing biocompatible/degradable nanoparticles Investigating the properties and applicability of various TMDC compositions

groups that exist on the surface of CDs can be affected by post-synthesis functionalization/oxidation/reduction process. Doping with heteroatoms can be a useful strategy to control the emission maxima and improve the PL QY of the as-prepared CDs, as the presence of heteroatoms may introduce new energy levels or change the existing energy bandgap. Doping with heteroatoms that are low in electronegativity can result in the red-shift of the emission spectrum. Also, doping CDs with heteroatoms can improve their absorbance at longer wavelengths. Likewise, doping with certain heavy metal elements such as gadolinium can endow CDs with new functionalities such as MRI imaging. A balance between the factors mentioned above needs to be achieved in order to obtain CDs with optimized properties and functionalities.

The wide assortment of TMDC compositions provides a range of nanomaterials with varying properties. In general, they share a strong NIR absorption property which has been useful not only for PTT but also PA imaging. Intrinsic properties of transition metals such as X-ray absorption also enable additional applications such as CT imaging and radiotherapy. Compared to other nanomaterials, the 2D structure of TMDC nanosheets provides large surface areas which are beneficial for surface functionalization and drug/gene loading with high capacity. The synthesis and functionalization of TMDCs play important roles in determining

their morphology, optical properties, and biocompatibility. Some reports have even described the degradable property of TMDC nanomaterials. As such, there is a need for systematic studies on how these properties may be influenced by these factors. Furthermore, current functionalization chemistry for TMDCs is still limited and investigation of new facile functionalization strategies would be beneficial. Presently, many works in this area are based on MoS₂ and WS₂, while studies on other TMDC species such as TiS₂ and VS₂ have just emerged. Hence, further studies on other TMDC species may unveil more information on their properties and applicability.

In addition, other nanomaterials such as metal oxides, black phosphorus, and polymeric nanomaterials have been utilized in NIR light-responsive applications. Despite their potential, they face several challenges which have to be resolved before their translation into clinical applications. For instance, metal oxide species of varying compositions and properties have been synthesized through different approaches, which lead to complexity in the control and optimization of their properties. Black phosphorus currently also face some barriers for their application, in the form of high sensitivity to ambient atmosphere. Future works in understanding the formation mechanism as well as functionalization and modification of these nanomaterials to preserve their unique properties are necessary.

Overall, numerous studies have demonstrated the potential applications of these NIR light-responsive nanomaterials, especially in in vivo tumor xenografted mice models. Despite these encouraging results, there are still many obstacles before these nanomaterials can be translated into clinical settings. Currently, there is a limited number of clinical studies of these nanomaterials, let alone in NIR-based applications against cancer. NIR light-responsive gold nanostructures have shown the most progress in clinical stage. AuroShell, a type of gold nanoshells used for PTT, has been undergoing a pilot clinical study (ClinicalTrials.gov Identifier: NCT00848042). Trials have also been conducted on silica-gold-nanoparticles-based PTT against arteriosclerosis^[291] and gold-nanorod-based PTT against canine neoplasia.^[292] The use of functionalized gold nanoparticles (CYT-6091) for chemotherapy have also passed phase 1 clinical trial.^[293] Various IONPs have been approved by FDA as MRI contrast agents, and clinical studies for their use in magnetic hyperthermia are ongoing.^[237] Another metal oxide, hafnium oxide is studied as radiation-excited therapy agent (ClinicalTrials.gov Identifier: NCT01946867). The reason behind the slow clinical translation might be due to the novelty of NIR-based theranostics using the nanomaterials and the incomplete understanding of the nanomaterials.

Further studies to optimize the formulation and biological safety of these nanomaterials are necessary. For instance, studies on the pharmacokinetics of carbon dots and TMDCs are still being investigated in animal models.^[294] As such, accelerating clinical translation would necessitate advances in several key areas. Firstly, there is a need for reliable synthesis to produce homogeneous nanomaterials with controllable and consistent properties. As numerous studies described previously, NIR properties and biocompatibilities of these nanomaterials rely heavily not only on their compositions but also their morphologies and synthesis approaches. Moreover, the particle size is an important factor that needs to be taken into consideration during the design of the nanomaterials. It has been reported that nanoparticles with sizes larger than 20 nm are known to be able to circulate in the body for a week or longer before being excreted by the urinary system.^[295] This is to ensure that the nanoparticles have sufficient time to be delivered to the target location and interact with other biocomponents. Further research should also be carried out to improve their colloidal and optical stability in a biological environment. Although these NIR light-responsive nanomaterials are considered nontoxic, there are still concerns over the long-term stability and pharmacokinetics of these nanomaterials when applied for in vivo cancer therapeutics. For instance, UCNPs are generally considered chemically safe, but the aggregation of UCNPs in cells and tissues, decomposition of UCNPs releasing lanthanide ions, and in vivo interactions between UCNPs with other substances are still major toxicity concerns. There is also a need to understand how the nanomaterials are excreted from various organs and the time duration needed. The decomposition of these nanomaterials and any potential secondary toxicity effects should be well understood before proceeding to subsequent clinical studies.

Prior to clinical trials, it is imperative to realize optimized properties of the nanomaterials to provide significant benefits in terms of efficacy and minimal side effects in the human model. Achieving this would require studies to carefully examine phar-

macokinetics and therapeutic strategies, including the use of NIR irradiations as a part of the theranostic schemes. Most biocompatibility and toxicity studies are initially carried out in vitro before proceeding to animal studies. However, conventional in vitro models where cells are cultured in multi-well plates lack the complexity of actual biological tissues, which may not be sufficient to evaluate the intricate interactions of nanomaterials with physiological barriers. This limitation can be overcome with the recent development of tumor-on-a chip which can mimic the transport of nanomaterials to the tumor model in an in vitro setting and take into account key factors such as interstitial flow, cell binding, and effects of particle sizes on accumulation and diffusion of the nanomaterials. Then, careful design and use of preclinical models such as in vivo mice models are necessary.^[296] Although many different animal models have been used for various therapeutic modes, one well-recognized setback is the difference in therapeutic efficacies between preclinical studies and the outcome of clinical trials. Development of tumor models mimicking realistic condition such as tumor metastases will be invaluable for future studies, which may contribute to more consistent and consequential results. In summary, there are still many challenges that need to be addressed for the successful clinical translation of these nanomaterials. Nevertheless, we believe that current work on these NIR light-responsive nanomaterials will continue to provide breakthrough innovations for cancer therapy.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

black phosphorus, carbon dots, gold nanorods, metal oxide, NIR light-responsive nanomaterials, polymeric nanomaterials, transition metal dichalcogenide, upconversion nanoparticles

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