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Surface Engineering of Lanthanide Nanoparticles for Oncotherapy

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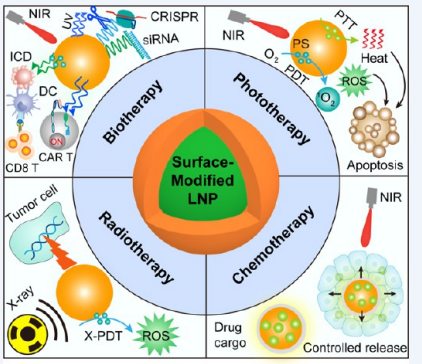
CONSPECTUS: Surface-modified lanthanide nanoparticles have been widely developed as an emerging class of therapeutics for cancer treatment because they exhibit several unique properties. First, lanthanide nanoparticles exhibit a variety of diagnostic capabilities suitable for various image-guided therapies. Second, a large number of therapeutic molecules can be accommodated on the surface of lanthanide nanoparticles, which can simultaneously achieve combined cancer therapy. Third, multivalent targeting ligands on lanthanide nanoparticles can be easily modified to achieve high affinity and specificity for target cells. Last but not least, lanthanide nanoparticles can be engineered for spatially and temporally controlled tumor therapy, which is critical for developing precise and personalized tumor therapy. Surface-modified lanthanide-doped nanoparticles are widely used in cancer phototherapy. This is due to their unique optical properties, including large anti-Stokes shifts, long-lasting luminescence, high photostability, and the capacity for near-infrared or X-ray excitation. Upon near-infrared irradiation, these nanoparticles can emit ultraviolet to visible light, which activates photosensitizers and photothermal agents to destroy tumor cells. Surface modification with special ligands that respond to tumor microenvironment changes, such as acidic pH, hypoxia, or redox reactions, can turn lanthanide nanoparticles into a smart nanoplatform for light-guided tumor chemotherapy and gene therapy. Surface-engineered lanthanide nanoparticles can include antigens that elicit tumor-specific immune responses, as well as immune activators that boost immunity, allowing distant and metastatic tumors to be eradicated. The design of ligands and surface chemistry is crucial for improving cancer therapy without causing side effects. In this Account, we classify surface-modified lanthanide nanoparticles for tumor therapy into four main domains: phototherapy, radiotherapy, chemotherapy, and biotherapy. We begin by introducing fundamental bioapplications and then discuss recent developments in tumor phototherapy (photodynamic therapy and photothermal therapy), radiotherapy, chemotherapy, and biotherapy (gene therapy and immunotherapy). We also assess the viability of a variety of strategies for eliminating tumor cells through innovative pathways. Finally, future opportunities and challenges for the development of more efficient lanthanide nanoprobes are discussed.



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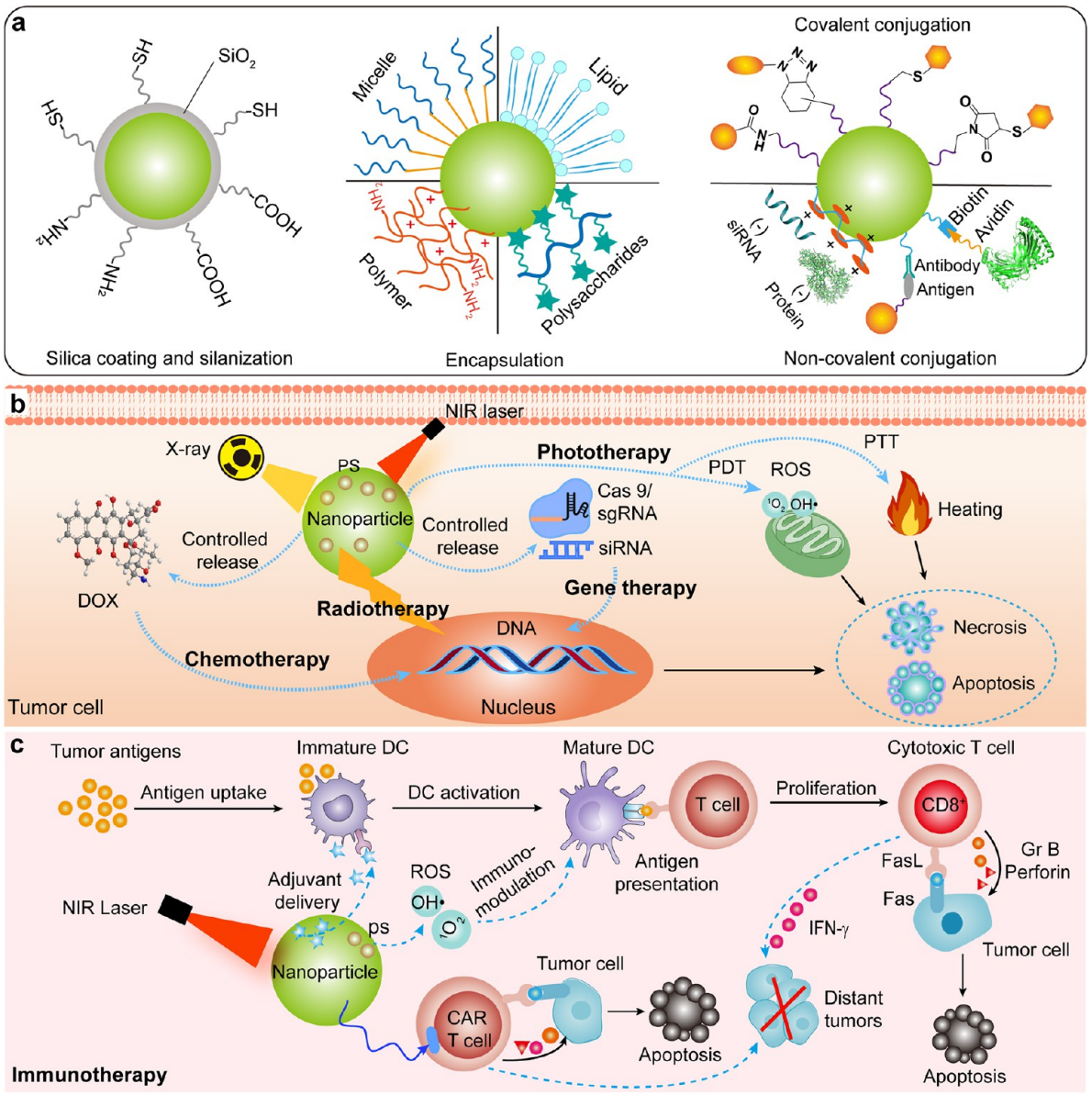

Figure 1. Surface-modified lanthanide nanoparticles for oncotherapy. (a) Main strategies toward surface modification of lanthanide nanoparticles. (b) Main mechanisms of surface-engineered lanthanide nanoparticles for tumor phototherapy, chemotherapy, radiotherapy, and gene therapy. (c) Main mechanisms of surface-engineered lanthanide nanoparticles for tumor immunotherapy. PS, photosensitizer; Gr B, granzyme B; ROS, reactive oxygen species; DC, dendritic cell.

upconversion nanoparticle-based photodynamic therapy, inducing a potent abscopal effect without immune checkpoints.

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1. INTRODUCTION

Cancer is one of the leading causes of death globally. It is estimated that 19.3 million new cancer cases and nearly 10.0 million cancer deaths occurred worldwide in 2020.[5] Current cancer therapies mainly include surgery, chemotherapy, radiotherapy, and immunotherapy, but they all face some challenges. For instance, surgery cannot completely remove all tumor cells in the human body, especially metastases. Chemotherapy and radiotherapy have adverse effects on normal tissues due to their low specificity. The low response rate and high cost limit the clinical applications of immunotherapy.[6] To overcome these challenges, a variety of nanomaterials such as carbon nanotubes, metallic nanoparticles, quantum dots, polymers, micelles, hydrogels, and dendrimers have been used as therapeutics to improve treatment efficacy while reducing side effects.[7] Among these nanomaterials, lanthanide-doped nanoparticles (LNPs) exhibit narrow emission bands, nonphotobleaching, nonblinking, high chemical stability, and multiband emission, making them ideal nanoprobes for bioimaging and oncotherapy.[8] In addition, LNPs can be excited with NIR light that penetrates deep into tissue with little damage to normal tissue. This opens

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the door for NIR-dependent delivery of drugs, genes, and proteins with low phototoxicity and high therapeutic efficacy. Moreover, it is easy to modify the nanoparticle surface with dyes, molecules, targeting ligands, or functional moieties to meet the stringent requirements for specific oncotherapy.

Despite the fact that nanoparticle properties are largely determined by their shape and size, surface ligands (post-nanoparticle synthesis) play a crucial role in regulating solubility, colloidal stability, and targeting ability, as well as encoding nanoparticle functionality.[9] It is possible to apply small organic compounds capable of complexing with active components (e.g., trisodium citrate and oleic acid) as surface ligands, dense or mesoporous silica (SiO_2) with multiple functional groups (e.g., $-NH_2$, $-COOH$, $-SH$), large polymers with tunable polarity (e.g., polyethylene glycols, poly(ethylenimine), or polyvinylpyrrolidone), or other functional biomolecules (such as oligonucleotides, peptides, proteins, vitamins, or polysaccharides).[9,10] It is also possible to provide multiple functionalities by nanoparticle surface modification, such as targeting and cargo delivery. Surface modification strategies typically include physical encapsulation (e.g., self-assembly, coprecipitation, hydrothermal, and solvothermal techniques), silica coating and silanization (e.g., dense or mesoporous silica coating), covalent conjugation (e.g., carbodiimide chemistry, Michael addition, click chemistry), and noncovalent conjugation (e.g., electrostatic conjugation, meta-affinity coordination, biotin–avidin interaction; Figure 1a). Due to the complex tumor microenvironment, proper surface modification is important to maintaining colloidal stability, regulating interactions with biomolecules, and developing effective nanoprobes for oncotherapy.

In this Account, we focus on recent advances in LNP-based nanoplatforms for tumor therapy through multiple pathways. With various surface-modified LNPs, photodynamic therapy and photothermal therapy can induce necrosis or apoptosis in tumor cells by producing reactive oxygen species (ROS) and heat. In tumor cells, radiotherapy, chemotherapy, and gene therapy can lead to DNA damage (or DNA repair), which results in necrosis or apoptosis. Immunotherapy initiated by surface-engineered LNPs can evoke strong proliferation of antigen-specific cytotoxic $CD8^+$ T cells or activate light-switchable chimeric antigen receptor (CAR) T cells to produce perforin, granzymes, or interferon gamma, leading to local and distant tumor cell death (Figure 1b and c).

2. PHOTOTHERAPY OF TUMORS

2.1. Photodynamic Therapy

Photodynamic therapy (PDT) kills tumor cells by generating toxic reactive oxygen species (ROS).[11] Typical PDT consists of three essential components: a photosensitizer, light, and oxygen. With appropriate light irradiation, a type-I photosensitizer produces hydroxyl radicals ($^{\bullet}OH$) via electron transfer to H_2O_2 or H_2O, while a type-II photosensitizer generates active singlet oxygen ($^1O_2$) via energy transfer to O_2. These produced hydroxyl radicals and singlet oxygen constitute ROS that could directly kill tumor cells. The therapeutic efficacy of current PDT is mainly limited by the shallow tissue penetration of excitation, the low ROS productivity of photosensitizers, and the scarce oxygen sources.

2.1.1. Light Source. A rational design of LNPs improves NIR harvesting and photon upconversion to ultraviolet and visible light, facilitating the ROS production of covalently conjugated photosensitizers. NIR excitation allows deep-tissue photodynamic therapy compared with conventional visible light excitation. Enhanced therapeutic effect by deep-tissue PDT has been demonstrated by administering chlorin e6 (Ce6)-modified $NaYF_4$:Yb/Er nanoparticles to tumors covered with 8-mm-thick pork tissue.[12] Other deep-tissue PDT studies have reported Yb/Er-doped nanoparticles loaded with various photosensitizers, such as rose bengal or TiO_2.[13,14] However, such Yb-based nanoparticles inevitably lead to overheating in healthy tissues due to strong water absorption under 980 nm irradiation. To minimize thermal absorption, Nd^{3+}-sensitized nanoparticles can be exploited under 808 nm excitation. Using a $NaGdF_4$:Yb/Er@$NaGdF_4$:Yb/Nd core–shell design, the rate of increase in *in vivo* temperature was 7-fold lower under 808 nm irradiation than under 980 nm irradiation.[15]

2.1.2. Photosensitizer. With the advent of photosensitizers, LNP-enabled photodynamic therapy is developing rapidly. An important strategy for improving ROS generation is simultaneous encapsulation or conjugation of two types of photosensitizers on nanoparticle surfaces, which results in higher therapeutic efficacy. For example, $NaYF_4$:Yb/Er/Nd@$NaYF_4$:Yb/Nd nanoparticles modified with amphiphilic polyethylene glycol polymers ($DSPE\text{-}PEG_{2000}$) were conjugated with two photosensitizers (Ce6 and rose bengal) to enable synergistic PDT.[16] However, overloading of the photosensitizer may cause luminescence quenching and thus lower PDT performance. Aggregation-induced emission luminogens (AIEgens) are characterized by enhanced fluorescence in the aggregated state, which ideally overcomes the concentration quenching effect associated with conventional photosensitizers.[17] A multifunctional platform comprising $NaYF_4$:Yb/Er nanoparticles and AIEgene malononitrile molecules showed an efficient inhibitory effect on the growth of both early (60 mm^3) and late (240 mm^3) tumors.[18] Construction of heterostructures from LNPs and metal–organic frameworks (MOFs) is another strategy to improve ROS production by improving photosensitizer loading capacity while preventing self-quenching. LNPs conjugated with various MOFs, such as zirconium metalloporphyrin-based PCN-222 and PCN-224, and zeolitic imidazolate-based ZIF-8 and ZIF-90, showed potent inhibition of tumor growth and prolonged the survival of tumor-bearing mice.[19−22]

Improving photosensitization by lanthanide-triplet excitation fusion, based on coupling of lanthanide nanoparticles and organic photosensitizers, is an alternative strategy to generate more ROS for improved PDT. In 2021, Zheng et al. developed a facile lanthanide-triplet sensitization using nanoconjugates of LNPs and organic photosensitizers to efficiently generate ROS at ultralow NIR irradiance.[23] They found that lanthanide-triplet sensitization enables over 100-fold higher generation of ROS than conventional upconversion nanoparticle-based photosensitization. When irradiated at ultralow-power (80 mW/cm^2, 808 nm), this nanoprobe significantly inhibited SKOV3 tumor growth *in vivo*, even under 4 mm pork (Figure 2a).

Surface functionalization of PDT nanoprobes based on LNPs can enhance therapeutic efficacy by targeting mitochondria, as mitochondrial dysfunction in cancer cells can disrupt energy supply and evoke apoptosis. For example, Nd^{3+}-sensitized upconversion nanoprobes containing triphenylphosphine, a mitochondria-targeting molecule, induced approximately 2-fold more apoptosis in tumor cells than nontargeting nanoprobes (Figure 2b).[20] In 2018, Zhang et al. developed $NaYF_4$:Yb/Tm nanoprobes containing graphene quantum dots as the

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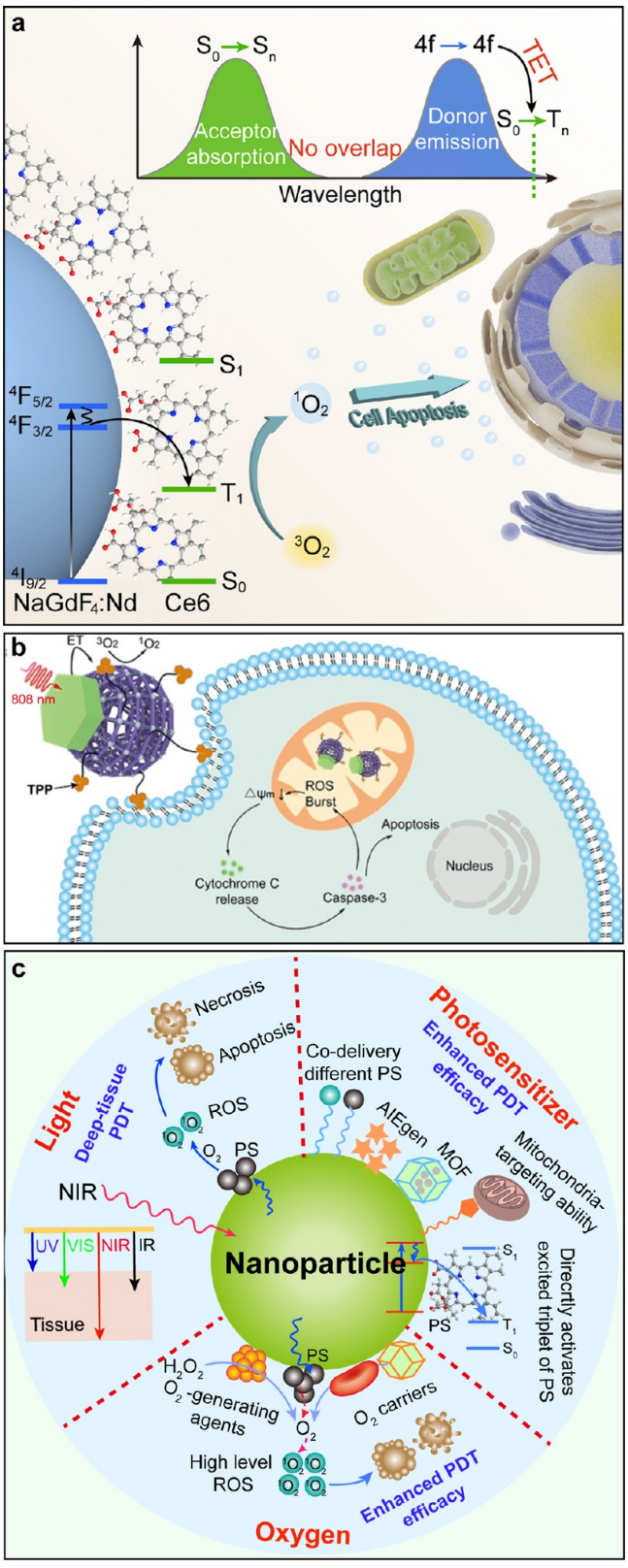

Figure 2. Surface engineering of lanthanide nanoparticles for photodynamic therapy. (a) Scheme of direct lanthanide-triplet energy transfer-based photodynamic therapy. (b) Schematic of mitochondria-coupled upconversion nanoparticle@MOF for enhanced PDT upon 808 nm irradiation. (c) Main strategies used to enhance therapeutic efficacy. PS, photosensitizer; AIEgen, aggregation-induced emission luminogen; MOF, metal−organic framework. Adapted with permission from ref 23, copyright 2021 Elsevier; and ref 20, copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA, respectively.

Figure 2. continued

photosensitizer and tetramethylrhodamine-5-isothiocyanate as the mitochondria-targeting ligand.[24] These nanoprobes induced approximately 2-fold higher apoptosis in 4T1 tumors than the control, which was attributed to direct interactions between the generated $^1O_2$ and mitochondria.

2.1.3. Oxygen. To improve PDT efficacy, there are two main strategies to overcome the hypoxia conditions in tumor tissue. First, surface modified lanthanide nanoparticles can codeliver photosensitizers and O_2-generating agents such as MnO_2, Au_2O_3, catalase, or ferric iron (Fe^{3+}), which can quickly convert hydrogen peroxide into water and oxygen in the tumor microenvironment. The produced oxygen can be activated into ROS by codelivered photosensitizers.[25,26] In 2020, Liang et al. designed a mitochondria-targeting nanoprobe for PDT, which consists of $NaYF_4$:Yb/Er@$NaGdF_4$ nanoparticles, chlorin e6, catalase, and generation-4 polyamidomine dendrimer.[25] Under NIR irradiation, the catalase loaded nanoprobe could produce obvious oxygen bubbles, generate more ROS, and lead to 3-fold apoptosis of 4T1 tumor cells *in vitro*. In addition, surface-engineered LNPs could emerge as oxygen carriers such as red blood cells, perfluorocarbon, and metal−organic frameworks to deliver exogenous O_2 directly to tumor sites.[27,28] In 2017, Wang et al. developed red blood cell microcarriers that deliver O_2 to hypoxic sites by cofunctionalizing nanoparticles on the surface of red blood cells with hypoxia probes and rose bengal.[27] When activated at 980 nm, the hypoxia probe induces around a 12%−35% increase in vascular saturated O_2 within tumors. Microcarrier-based PDT induced 60% of U87MG tumor cell apoptosis *in vitro* and exhibited effective solid tumor eradication *in vivo*. In 2020, He et al. developed multifunctional nanoprobes for biocatalytic cascade-guided PDT by combining ultrasmall Au nanoparticles and metal−organic-framework-coated upconversion nanoparticles.[21] In their work, the nanoprobe could convert H_2O_2 into O_2 to continuously generate $^1O_2$ upon NIR laser irradiation, which showed a synergistic antitumor effect *in vitro* and *in vivo*.

Currently, the main strategies to improve therapeutic efficacy focus on the three key components of PDT, namely, light, photosensitizer, and oxygen (Figure 2c). Despite great progress, LNP-based PDT still faces several challenges: (i) the low quantum yield of upconversion; (ii) the low efficiency of Förster resonance energy transfer between the photosensitizer and the nanoparticle; (iii) the complex procedures to prepare the designed nano complexes; (iv) the low therapeutic efficacy in treating large tumors; (v) the inability to eradicate distant metastatic lesions.

2.2. Photothermal Therapy

Photothermal therapy (PTT) relies on the energy conversion of optical energy into heat, with effective therapeutic temperatures in the range of 41−45 °C or even higher. In addition to the direct killing effect on cancer cells, the high temperature also induces denaturation of cellular proteins, such as enzyme inactivation, physical alteration of chromatin, and inhibition of DNA synthesis and repair, which ultimately leads to cancer cell death.[29] Lanthanide nanoparticles can be surface modified with photothermal agents to realize efficient photothermal therapy (Figure 3a). Gold or silver nanoparticles, used as photothermal

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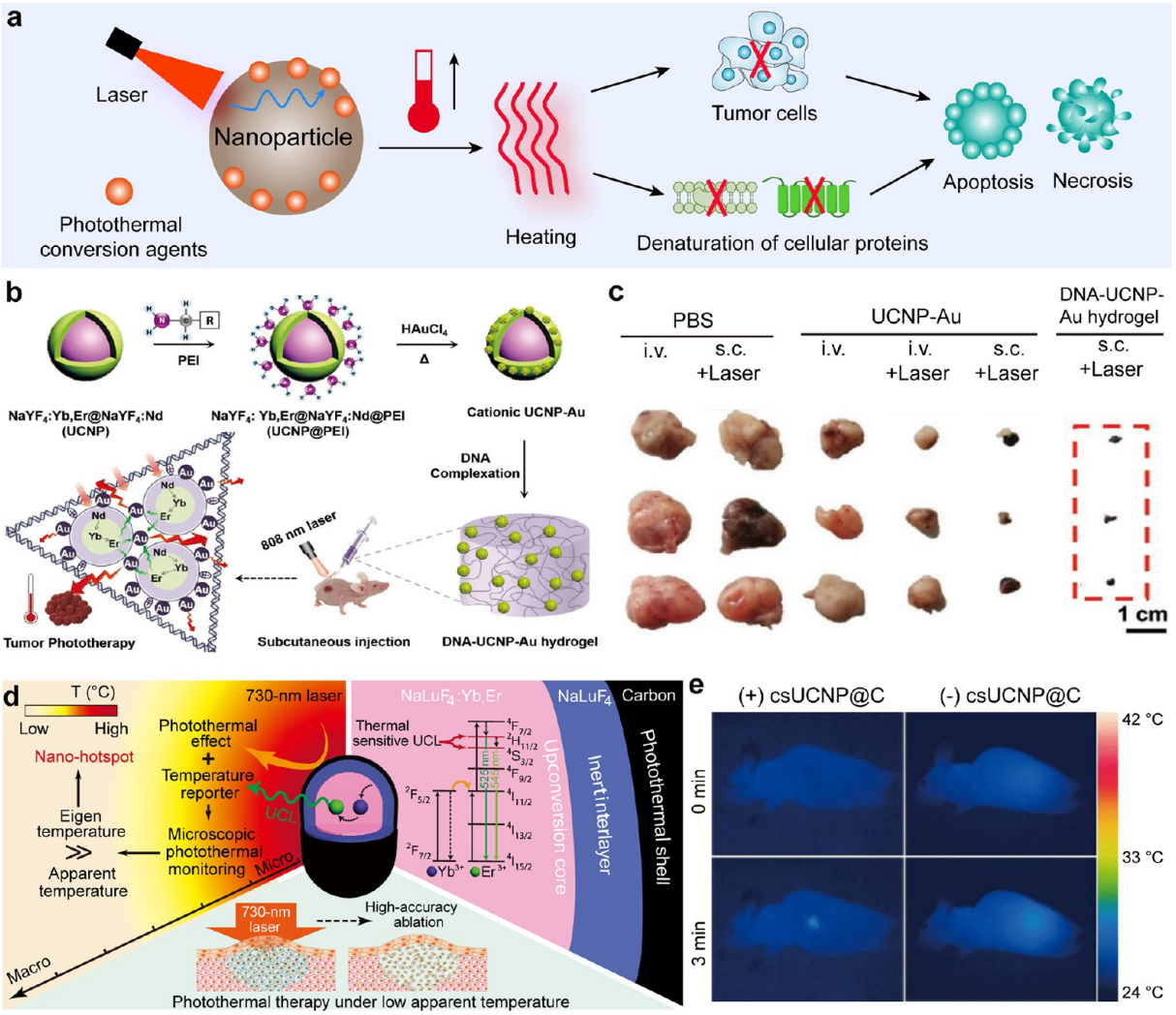

Figure 3. Surfaced engineering of lanthanide nanoparticles for tumor photothermal therapy (PTT). (a) Main mechanisms of lanthanide nanoparticle-based PTT. (b) Schematic synthesis of injectable DNA-inorganic hybrid hydrogels (DNA-UCNP-Au) for PTT. (c) Photographs of isolated tumors from mice treated with upconversion nanotherapeutics. (d) Schematic of the working mechanism of the upconversion nanocomplex for accurate PTT at mild temperatures. (e) Thermal images of nude mice with (left) or without (right) csUCNP@C-labeled Hela tumor cells under 730 nm excitation (0.3 W/cm^2). Adapted with permission from ref 30, copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA; and ref 34, copyright 2016, Nature Publishing Group, respectively.

agents, are often coupled with lanthanide nanoparticles for effective PTT due to their surface plasmon resonance and strong extinction coefficient. For example, Liu et al. developed an injectable DNA-inorganic hybrid hydrogel for PTT by electrostatic complexation of DNA and $NaYF_4$:Yb/Er@$NaYF_4$:Nd nanoparticle-Au nanoconjugates.[30] This hydrogel showed a high photothermal efficiency (42.7%) and eradicated tumors and inhibited tumor recurrence when irradiated at 808 nm (Figure 3b and c). Other photothermal agents such as CuS, Bi_2Se_3, polydopamine, or graphene-based nanoparticles have also been studied as photothermal agents in combination with lanthanide nanoparticles due to their excellent capacity for NIR conversion.[31] In 2018, Zhang et al. reported that the nanocomplex, formed by $NaYF_4$:Er nanoparticles encapsulated with CuS-tethered hyaluronic acid, enables tumor depth imaging and PTT.[31] Upon 808 nm irradiation, the nanoprobes eliminated tumors on day 14 after irradiation, which was ascribed to the high temperature (60 °C) at tumor sites. A similar photothermal ablation of tumor cells was observed in CuS/Ag or CuS-based nanocomposites under 808 nm irradiation.[32,33]

The temperature-sensitive optical feature of lanthanide nanoparticles makes them attractive for monitoring temperature changes in tumor sites during PTT, thereby minimizing damage to adjacent normal tissues. Temperature-feedback nanocomposites based on carbon-coated $NaLuF_4$:Yb:Er@$NaLuF_4$ nanoparticles were developed for real-time PTT monitoring.[34] Upon 730 nm irradiation, these nanocomposites produced sufficient heating to kill tumor cells while avoiding heat dissipation to normal tissues through real-time monitoring of microscopic temperature during therapy (Figure 3d and e). This study provides an efficient lanthanide nanoparticle-based PTT strategy with high spatial resolution and accuracy. Similar to PDT, LNP-based PTT showed little effect on distant metastatic tumors, which need to be combined with other treatments such as immunotherapy.

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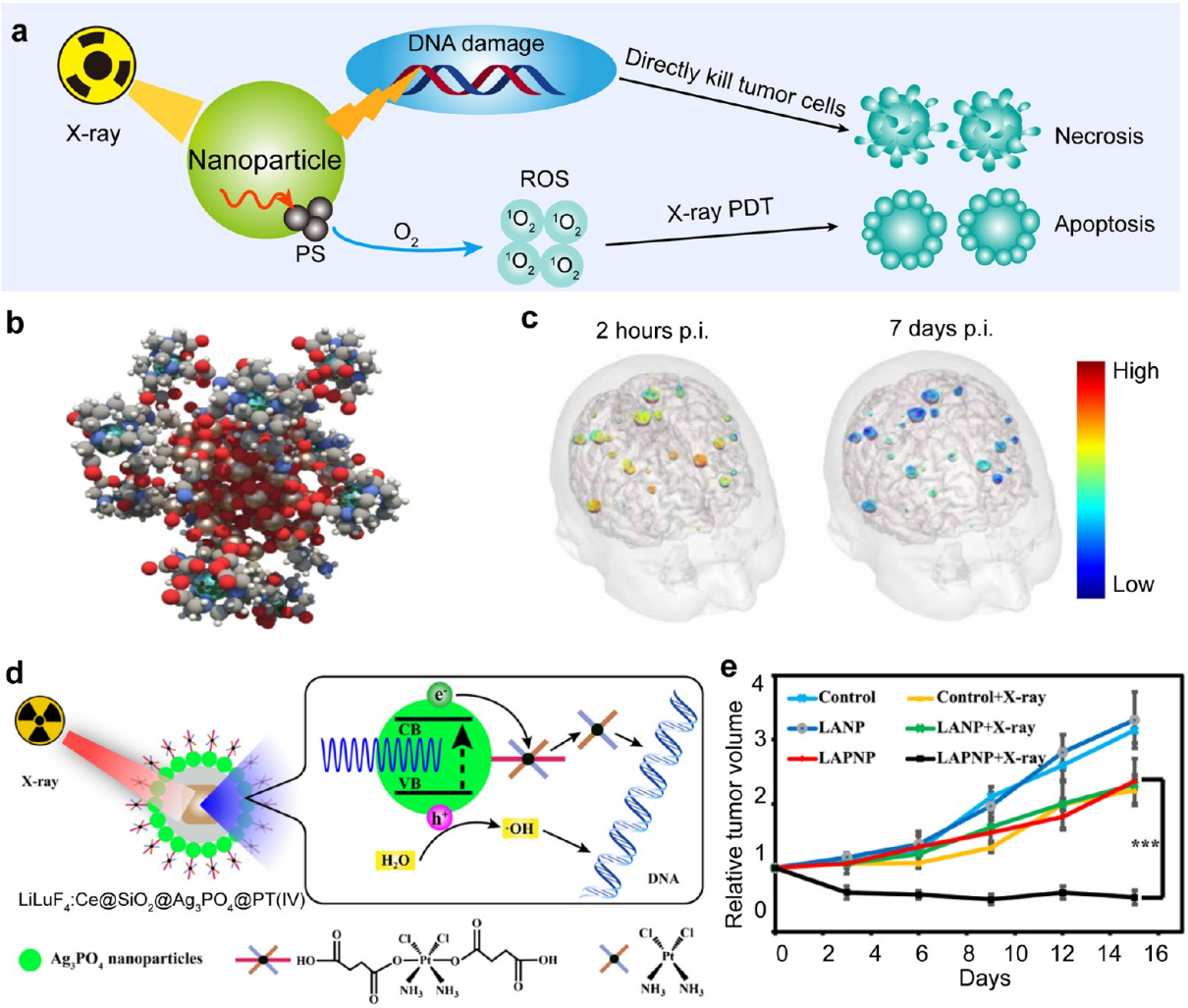

Figure 4. Surface engineering of lanthanide nanoparticles for tumor radiotherapy. (a) Main mechanism of lanthanide nanoparticle-mediated radiotherapy. PS, photosensitizer. (b) Schematic of a Gd-based nanocomplex (AGulX; Si, pearl gray; O, red; C, gray; N, blue; Gd, metallic blue; and H, white). (c) 3D visualization of patients' brains superimposed with color-encoded MRI signal enhancements (SE) in the metastases 2 h after injection and 7 days after injection of AGulX nanoparticles (100 mg/kg body weight). (d) Schematic mechanism of X-ray-induced tumor photodynamic therapy using a $LiLuF_4$:Ce@SiO_2@Ag_3PO_4@Pt(IV) nanocomplex. (e) Volumetric changes of Hela tumors in mice treated with six different nanoformulations. Adapted with permission from ref 38, copyright 2020 American Association for the Advancement of Science; and ref 44, copyright 2018 American Chemical Society, respectively.

3. TUMOR RADIOTHERAPY

Lanthanide ions exhibit strong X-ray absorption and scattering due to their high atomic number between 57 and 71, high *K*-edge energy, and large X-ray mass attenuation coefficient. Lanthanide nanoparticles can therefore be used as efficient radiosensitizers for radiotherapy (Figure 4a). Of all lanthanide ions, the Gd^{3+} ion is most commonly used in tumor radiotherapy. For example, diethylenetriaminepentaacetic acid-functionalized ultrasmall Gd^{3+}-doped nanoparticles (sub-5 nm) consisting of a gadolinium oxide core and a polysiloxane shell have been used as radiosensitizers for U87 tumor cell therapy *in vitro* under X-ray irradiation of 2−8 Gy.[35] This was the first time that Gd^{3+}-based nanoparticles were shown to damage tumor cell DNA upon X-ray irradiation. In 2016, tetraacetic acid-modified gadolinium-polysiloxane nanoparticles (~3 nm) under the name AGuIX (activation and guidance of irradiation by X-ray) were used as radiosensitizers for MRI-guided *in vivo* radiotherapy and showed inhibition of glioma and brain melanoma metastases in mice.[36,37] These promising preclinical results promoted a phase-I clinical trial with a single i.v. injection of these Gd^{3+}-based nanoparticles, conducted in 15 patients with various brain metastases. Interestingly, the phase-I clinical trial showed that these nanoparticles are safe and feasible for patients.[38,39] In addition, these nanoparticles acted specifically on brain metastases and remained in the tumor for up to 7 days (Figure 4b and c). The therapeutic efficacy is being evaluated in a phase-II clinical trial.

Apart from directly killing tumor cells, photosensitizer-conjugated lanthanide nanoparticles can be used for X-ray-mediated photodynamic therapy. Upon X-ray irradiation, the nanoparticle luminescence activates the photosensitizer to produce ROS and kill tumor cells (Figure 4a). For example, Chen and co-workers have demonstrated X-ray-mediated PDT for tumor therapy by coupling photosensitizers (tretrakis(o-aminophenyl)porphyrin, meso-tetra(4-carboxyphenyl)-porphine, or protoporphyrin IX) with scintillators or persistent luminescent nanoparticles (BaFBr:Eu^{2+}/Mn^{2+}, LaF_3:Tb^{3+}, or LaF_3:Ce^{3+}).[40−42] Under X-ray irradiation, these nanocomposites can produce a large amount of ROSs to inhibit tumor

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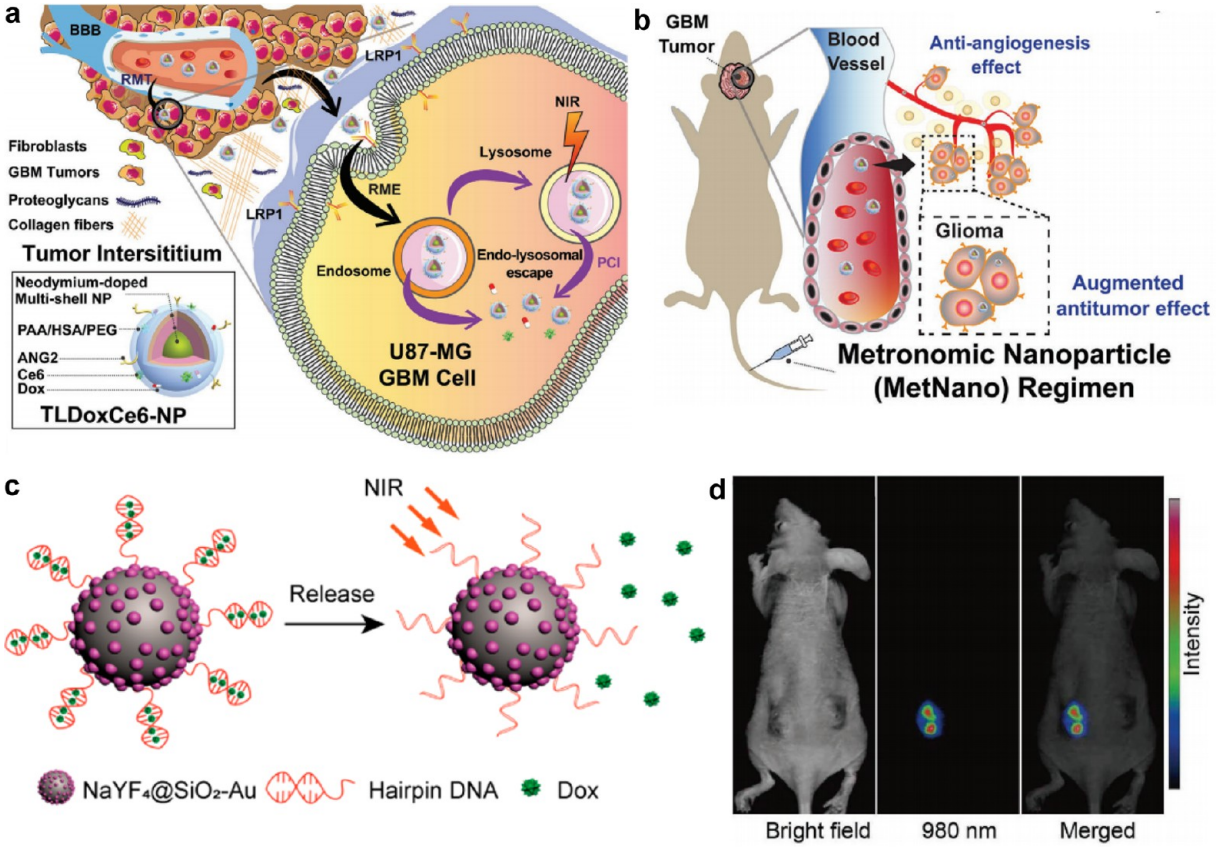

Figure 5. Surface engineering of lanthanide nanoparticles for tumor chemotherapy. (a) Design of TLDoxCe6-NP nanoprobes and their trafficking route after intravenous injection. (b) Mechanism of antitumor effects mediated by metronomic nanoparticles (MetNano), including antiangiogenesis effect on tumor endothelial cells and augmented antitumor effect on gliomas. (c) Design of Dox drug release from hpDNA-loaded $NaYF_4$@SiO_2−Au nanoplatform, triggered by heat generated during upconversion emission. (d) Upconversion luminescence imaging of mice treated with the hpDNA-loaded nanoplatform upon 980 nm irradiation. Adapted with permission from ref 1, copyright 2022 Wiley-VCH Verlag GmbH & Co. KGaA; ref 51, copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA.

growth without phototoxicity. Lutetium (Lu), with the largest atomic number (71) among lanthanides, has the largest *K*-edge energy and X-ray coefficient, making Lu^{3+}-based nanoparticles particularly suitable for X-ray-mediated PDT.[43] In 2018, Wang et al. developed a multilayer core−shell strategy using LuF_4:Ce@SiO_2@Ag_3PO_4@Pt to improve therapeutic efficacy.[44] Upon X-ray irradiation, $LiLuF_4$:Ce nanoscintillators emitted light from 305 to 325 nm, which can activate Ag_3PO_4 to produce hydroxyl radicals and kill tumor cells. Moreover, the introduction of a cisplatin prodrug Pt(IV) into this nanoplatform not only improves the yield of hydroxyl radicals but also directly damages cancer cell DNA upon activation (Figure 4d and e). Despite great achievements, few surface-engineered lanthanide nanoparticles are translated to the clinic for tumor radiotherapy, especially for metastases. An important aspect of future surface engineering will be to improve radio sensitization and achieve rapid renal elimination in order to minimize toxicity after intravenous injection and to avoid long-term retention.

4. TUMOR CHEMOTHERAPY

Chemotherapy is an effective cure for cancer because it is easy and convenient to perform. However, chemotherapy usually induces severe side effects due to the nonspecific distribution of chemical agents. Conjugation of active targeting ligands on nanoparticle surfaces is a promising strategy to improve tumor recognition and delivery efficacy. Recently, various targeting ligands, such as folic acid, arginine−glycine−asparagine peptide, and aptamers, showed potent enhancement of chemical agent uptake by tumor cells, including doxorubicin, phenanthriplatin-(IV), or paclitaxel.[45] Using image-guided tracking and monitoring, these chemical drug-loaded lanthanide nanoprobes achieved much more efficient inhibition of tumor growths than pristine drugs. In 2022, our group developed angiopoietin 2 (ANG2) peptide-modified Yb/Er-based upconversion nanoparticles coloaded with chlorin e6 and doxorubicin (DOX) for metronomic chemotherapy of orthotopic glioblastomas, which showed a 3.5-fold increase in antitumor efficacy compared with standard chemotherapy.[1] This study provided direct evidence for i.v. injection of ANG2-modified nanoprobes, which could cross the blood−brain barrier and be endocytosed into lysosomes of transplanted glioblastomas (Figure 5a and b). This metronomic delivery-based therapy not only showed a direct killing effect on glioblastomas but also inhibited angiogenesis of the tumor microenvironment.

Internal stimuli in the tumor microenvironment, such as low pH, altered redox potential, and hyperthermia, can also be used to target chemical therapy with lanthanide nanoparticles to improve therapeutic efficacy. For instance, $NaYF_4$:Yb/Tm upconversion nanoparticles and the chemical drug DOX were coencapsulated by a pH/photosensitive copolymer to form a dual-sensitive nanoplatform for controlled release of DOX.[46] The nanoplatform was proved to release DOX by low pH and NIR irradiation, showing a 5-fold higher cytotoxic effect on HeLa cells compared with free DOX. The use of a triple-

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stimulus (pH, glutathione, and H_2O_2) nanoplatform comprising mesoporous silica-embedded $NaYF_4$:Yb/Er nanoparticles, DOX, and diselenide (Se−Se)-linked bovine serum albumin and myoglobin proteins to release DOX has been shown to inhibit tumor growth with negligible damage to normal tissues.[47]

Multidrug resistance (MDR) is another major limitation to cancer chemotherapy. Surface-engineered lanthanide nanoparticles represent a promising strategy to overcoming resistance to achieve enhanced chemotherapy or synergistic antitumor effects. For example, Yao et al. developed an azobenzene liposome nanostructure encapsulated with $NaYF_4$:Yb/Tm@$NaGdF_4$ nanoparticles and doxorubicin for effective tumor chemotherapy through NIR-trigger drug delivery.[48] Under 908 nm irradiation, the nanostructure emits UV−visible light and induces rotation-inversion movement, overcoming multidrug resistance in MCF-7/ADR tumors. Moreover, Li et al. designed magnesium silica-coated $NaYF_4$:Yb/Tm@$NaYF_4$ nanocrystals loaded with the precursor to NO (*N*,*N*′-di*sec*-butyl-*N*,*N*′-dinitroso-1,4-phenylenediamine, BNN6) and doxorubicin (DOX) to reverse multidrug resistance in tumor chemotherapy.[49] When irradiated at 980 nm, the released NO from BNN6 down-regulated drug efflux-related P-glycoprotein and ATP-binding cassette transporters, thereby increasing Dox accumulation in the nuclei of MDR tumor cells. This upconverting nanosystem provides a synergistic effect (gas therapy and chemotherapy) to inhibit MDR tumor growth.

Through surface coating with light-responsive nanomaterials, lanthanide nanoparticles also can be constructed to precisely target the release of chemical drugs at tumor sites. For instance, Xiang et al. developed a UV-responsive diblock copolymer to encapsulate $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles and DOX for controlled drug release at tumor sites.[50] On irradiation at 980 nm, UV light emitted from lanthanide nanoparticles can cleave the copolymer to precisely control DOX release. Additionally, the heat transferred from lanthanide nanoparticles can also modulate the release of chemically loaded drugs. Our group has developed hairpin DNA-functionalized $NaYF_4$:Yb/Tm nanoparticle-Au nanoconjugates loaded with DOX for site-specific tumor therapy.[51] When irradiated at 980 nm, the hairpin DNA enables imaging and precise control of DOX release through photothermal upconversion (Figure 5c and d). Despite promising results, LNP-based chemotherapy is still limited due to complex procedures and small production scales.

5. TUMOR BIOTHERAPY

5.1. Gene Therapy

Surface-engineered LNPs can also be used as nanocarriers for gene therapy, including delivery of small interfering RNA (siRNA), microRNA, aptamer-based DNA, and clustered regularly interspaced short palindromic repeats (CRISPR; Figure 6a). With stimulus-responsive nanomaterials, LNPs can release loaded genes at target sites by controlling either the endogenous tumor microenvironment or exogenous photonic/vibrational energies.

5.1.1. Small Interfering RNA. Cancer gene therapy with small interfering RNA (siRNA) involves targeting gene expression using exogenous RNAs, but its cytoplasmic delivery is a concern. LNP-mediated delivery offers advantages over conventional siRNA delivery in that gene silencing can be precisely, spatiotemporally, and remotely controlled. For example, $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles based on photoresponsive nanocapsules have been applied to remotely

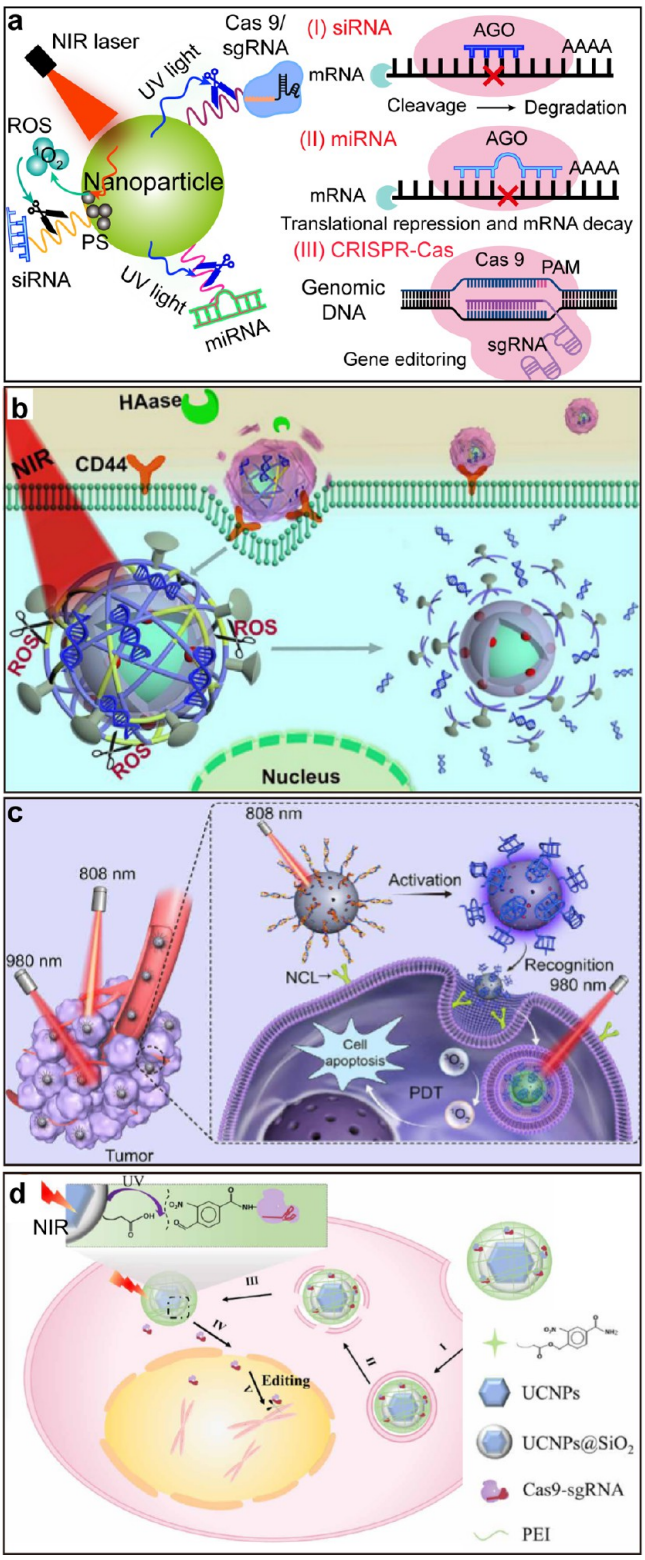

Figure 6. Surface engineering of lanthanide nanoparticles for gene therapy. (a) Proposed mechanisms of lanthanide nanoparticle-based gene therapy using siRNA, miRNA, and CRISPR-Cas9/sgRNA. PS, photosensitizer; AGO, argonaute protein; PAM, protospacer adjacent motif. (b) Schematic of NIR-induced intracellular siRNA release from upconversion nanoparticle-based nanoprobes. (c) Schematic of orthogonal regulation of upconversion-aptamer nanodevices for programmed tumor recognition and therapy. (d) Schematic of NIR-controlled gene editing using an upconversion nanoparticle-Cas9/CRISPR nanocomplex. Adapted with permission from ref 54, copyright

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Figure 6. continued

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release polo-like kinase-1 (PLK1) siRNA, leading to a 2-fold improvement in gene silencing efficiency.[52] In another study, an efficient photoresponsive nanoplatform was achieved by encapsulating $NaYF_4$:Yb/Tm nanoparticles and PLK1 siRNA using charge-variable conjugated polyelectrolyte brushes.[53] Upon 980 nm irradiation, the cationic side chain of brushes turned into a zwitterionic chain, leading to an 80% release of siRNA from the nanoplatform. In addition to photoresponsive linkers, linkers sensitive to singlet oxygen such as diselenide can also be used for controlled release of therapeutic siRNA. For instance, rose-bengal-coated $NaYF_4$:Yb/Er@$NaYF_4$:Yb/Nd nanoparticles were encapsulated in diselenide-linked poly(ethylenimine) and PLK1 siRNA for tumor gene therapy.[54] In response to 980 nm irradiation, the ROS generated from the activated rose bengal promoted the release of PLK1 siRNA into the cytosol, inhibiting PLK1 gene expression (Figure 6b). NIR-triggered rapid release of siRNA enhanced gene silencing efficiency, resulting in substantial suppression in HepG2 tumor growth.

5.1.2. Aptamer-Tethered DNA, microRNA, and Plasmid DNA. Aptamer-tethered DNA, microRNA, and plasmid DNA can also be delivered in a controlled manner to target sites for precise tumor therapy through photon upconversion. In 2020, Zhang et al. reported a photoresponsive nanoplatform comprising $NaYF_4$:Yb/Tm/Gd@$NaYF_4$:Nd/Yb nanoparticles, photocaged DNA nanocombs, a photozipper-protected hairpin, and miRNA-locked photosensitizer pyropheophorbide-a′ for NIR-amplified photodynamic therapy.[55] UV emission could trigger microRNA-responsive cascade hybridization under 808 nm irradiation and activate locked photosensitizers to generate ROS under emitted blue light, thereby cutting off the photozipper. This nanoplatform induced 66.4% apoptosis in HepG2 cells *in vitro* and almost completely eradicated tumors *in vivo* after 808 nm irradiation. In a recent study, core−shell upconversion nanoparticles conjugated with UV-activatable aptamers and rose bengal photosensitizers were used to create an orthogonally regulatable DNA nanodevice for spatiotemporal precision tumor therapy through orthogonal NIR regulation (Figure 6c).[56] In the presence of 808 and 980 nm light, orthogonal upconversion emissions in the UV and green regions can activate aptamer modules and photosensitizers, respectively, leading to spatiotemporally controlled target reorganization. The nanodevice exhibited 77.8% tumor eradication when irradiated with two lasers sequentially, compared to 51.2% with one 980 nm laser alone.

5.1.3. CRISPR. CRISPR-associated protein 9 (CRISPR/Cas9) is a potent technology for gene editing in tumor gene therapy.

On-demand gene delivery based on lanthanide nanoparticles can overcome the limitations of conventional CRISPR/Cas9 techniques in terms of tumor-targeting ability, cellular uptake capability, and off-target effect. Through a UV-cleavable linker, the Cas9 protein was conjugated to silica-coated $NaYF_4$:Yb/Tm nanoparticles and further loaded with PLK1-targeting sgRNA

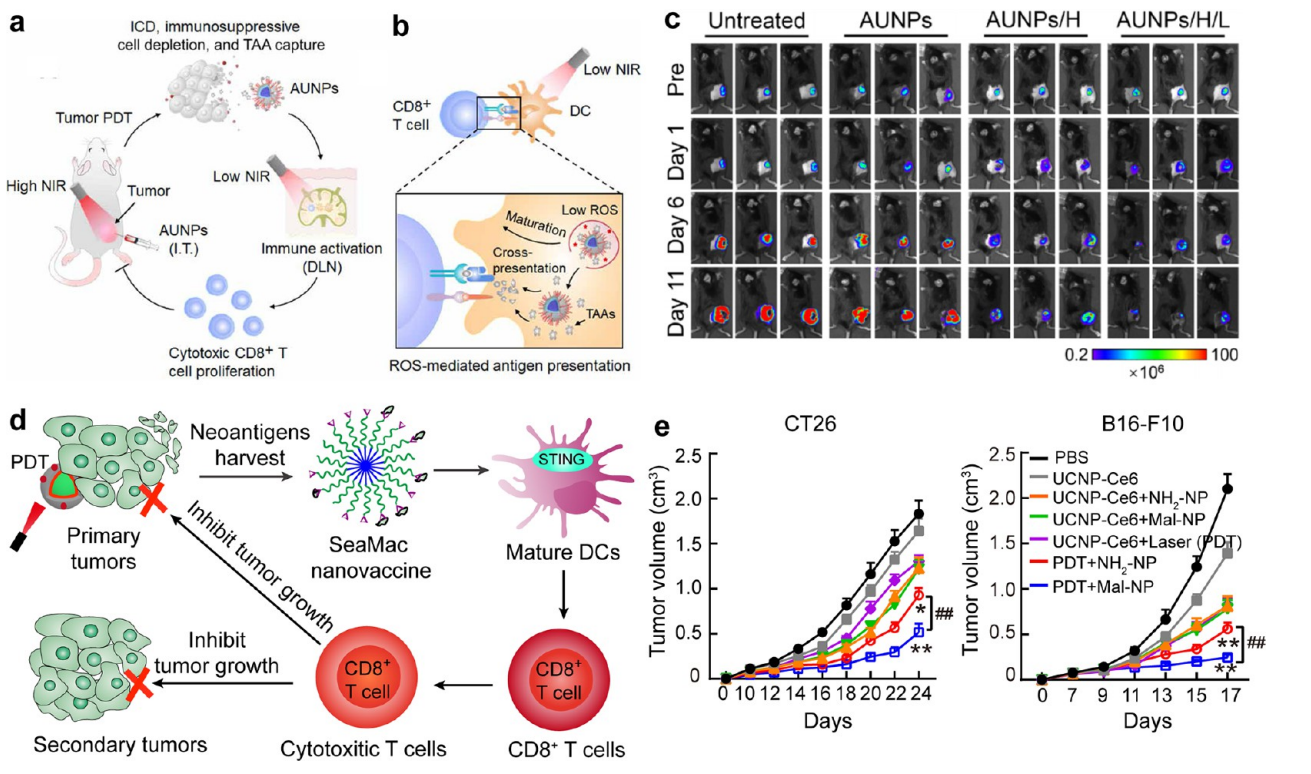

Figure 7. Surface engineering of lanthanide nanoparticles for tumor immunotherapy. (a) Schematic of dual-model ROS-driven tumor immunotherapy based on AUNP nanoprobes. (b) Mechanism of low dose NIR-activated DC maturation in tumor-draining lymph nodes. (c) Bioluminescence images of mice with a B16F10 tumor after different treatments. (d) Schematic of SeaMac nanovaccine-mediated tumor immunotherapy. (e) Tumor growth curves of mice treated with PDT and SeaMac nanoparticles in CT26 (left) and B16−F10 (right) tumor models. Adapted with permission from ref 2, copyright 2020 American Association for the Advancement of Science; and ref 3, copyright 2021 Wiley-VCH Verlag GmbH & Co. KGaA, respectively.

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and poly(ethylenimine).[57] The upconverted UV light from the nanocomplex cleaved the linker and released Cas9/PLK1-sgRNA into the cytosol, inhibiting the proliferation of A549 tumor cells *in vitro* and *in vivo* (Figure 6d). In 2020, Wu et al. developed another NIR-responsive CRISPR delivery nanovector using UV-emitting $NaYF_4$:Yb/Tm nanoparticles encapsulated in a UV-responsive charge-reversal polymer to load Cas9/PLK1-sgRNA plasmid DNA.[58] This technique is highly efficient and site-specific for *in vivo* gene editing with CRISPR/Cas9. Gene payload determines the level of the gene expression after cellular uptake, thus it plays an important role in gene therapy. However, the therapeutic efficacy of LNP-based carriers is limited due to a constraint on the payload.

5.2. Immunotherapy

Immunotherapy activates the patient's own immune system to fight tumors, especially recurrent and metastatic tumors. Compared with conventional cancer treatments, immunotherapy shows long-term antitumor effects with minimal damage to healthy cells. Clinical cancer immunotherapy mainly includes cancer vaccines, adaptive T-cell therapy (mainly chimeric antigen receptor (CAR)-modified T cells), and immunomodulation by blocking suppressive immune checkpoints. Although cancer immunotherapy can modestly improve overall survival rates in most patients, it faces several challenges, including low immune response, immune tolerance, a suppressive microenvironment, and unaffordable treatment costs. Antigens and immune activators can be taken up by immune cells through LNP-based nanocarriers to enhance antitumor immunity. Additionally, LNPs can be used in phototherapy, radiotherapy, and chemotherapy to kill tumor cells and release tumor-associated antigens, initiating antitumor immunity.

5.2.1. Tumor Antigen-Based Immunotherapy. Immune activators, known as adjuvants, can induce maturation and activation of dendritic cells and affect the strength of an antigen-specific immune response. Lanthanide nanoparticles have been applied to deliver immune activators through encapsulation or conjugation strategies to boost immunotherapeutic efficacy. In 2017, Xu et al. developed an upconversion nanoplatform by coating $NaYF_4$:Yb/Er nanoparticles with a layer of an amphiphilic polymer and then loading them with Ce6 photosensitizers and toll-like receptor 7 agonists R837.[59] Upon 980 nm laser irradiation, nanoplatform-mediated PDT could release tumor-associated antigens. These antigens, in combination with loaded R837, evoked strong antitumor immunity. In 2020, an AIEgen-upconversion nanoparticle-based nanoplatform was developed by coupling AIEgens as photosensitizers with silica-coated $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles for the development of solid tumor immunotherapy through dual-model ROS activation.[2] Upon high-power NIR irradiation, the nanoplatform produced high-dose ROS to kill tumor cells and release tumor-associated antigens. The sequential low-power NIR irradiations on tumor-draining lymph nodes could significantly activate cytotoxic $CD8^+$ T cells and prevent both local tumor and distant tumor growth (Figure 7a–c). This dual NIR irradiation-mediated combinational tumor therapy provides an effective strategy to prevent tumor recurrence and metastasis.

In addition, LNPs themselves can also act as an adjuvant to boost antitumor responses. In 2022, our team developed a series of lanthanide-based cGAMP surrogates by reacting lanthanide precursors with adenosine monophosphate/guanosine monophosphate solutions to activate the stimulator of interferon genes (STING).[60] Based on dynamic docking analysis, these LNPs recognize and bind to the active sites of mouse and human STING proteins, thereby stimulating the type-I interferon (IFN) response in both mouse macrophages and human monocytes. Additionally, europium-based coordination nanoparticles could boost both humoral and cellular immune responses associated with the STING-activating pathway, as demonstrated by the increased antibody titers (180-fold) and inhibited tumor growth as well as prolonged survival of tumor-bearing mice.

LNP-based phototherapy can also initiate antitumor immunity by releasing tumor-associated antigens. In 2019, our group developed polydopamine-encapsulated $NaGdF_4$:Yb/Er nanoparticles with surface-loaded photosensitizer Ce6 for PDT and PTT.[61] After irradiation at 980 nm, the released antigens from synergistic phototherapy induced dendritic cell maturation, which subsequently activated cytotoxic T lymphocytes and memory T cells, inhibiting tumor metastasis and relapse. In another example, Wang et al. developed a nanoplatform by encapsulating $NaYF_4$:Yb/Er@$NaYF_4$:Nd nanoparticles, indocyanine green, and rose bengal dyes into a diblock polymer DSPE-PEG-maleimide.[62] This nanoplatform promoted strong antitumor immunity because maleimide groups captured and retained tumor-associated antigens in the tumor.

In addition to phototherapy, LNP-based radiotherapy or chemotherapy can elicit antitumor immunity, to fight tumor metastasis and recurrence. In 2020, Qin et al. reported that polyvinylpyrrolidone-coated mesoporous $NaBiOF_4$:Yb/Er nanoparticles loaded with doxorubicin can induce immunogenic death of tumor cells and reverse pro-tumorigenic tumor-associated macrophages (type M2) to antitumor macrophages (type M1), thereby enhancing the antitumor immune response.[63] This enhanced immune response showed potent inhibition of tumor migration, invasion, and colony formation. In 2021, Li et al. developed a new type of cancer nanovaccine that integrated X-ray-activated $NaLuF_4$:Gd/Tb@$NaLuF_4$ nanoparticles with a photoresponsive CO release mechanism for synergistic gas production and immunotherapy.[64] After low-dose X-ray irradiation, CO release from the nanovaccine could reach tissue depths of 5 cm, induce immunogenic cell death, and reverse the immune-suppressive tumor microenvironment, inhibiting the growth of both local and distant tumors. Despite great success, immunotherapy with tumor-associated antigens is still limited by lower avidity interactions due to tumor heterogeneity.

Neoantigens derived from nonsynonymous mutations with strong immunogenicity can evoke potent tumor-specific immunity. Therefore, neoantigen-based immunotherapy is considered a promising personalized therapy with clinical benefits for patients. In 2021, our group developed a personalized nanovaccine based on self-adjuvanted, polymeric nanoparticles (Mal-PEG_{5000}-$PC7A_{45}$) that can collect neoantigens released from $NaYF_4$:Yb:Er@$NaYF_4$ nanoparticle-mediated PDT *in vivo* and activate the STING pathway.[3] These polymeric nanoparticles harvested neoantigens via the Michael reaction between thiol and maleimide groups, and developed nanovaccines *in situ*. They also activated cytotoxic $CD8^+$ T cells by maturing dendritic cells via the STING pathway (Figure 7d). The activated $CD8^+$ T cells significantly inhibited tumor growth in both CT26 and B16–F10 tumor models (Figure 7e).

5.2.2. Chimeric Antigen Receptor (CAR) T-Cell-Based Immunotherapy. CAR T-cell-based immunotherapy has

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shown great potential for cancer treatment. However, safety concerns remain, such as cytokine release syndrome and "on-target, off-tumor toxicity" resulting from the lack of precise control over the dose, location, and timing of T-cell activity. The unique properties of LNPs allow them to overcome these limitations, such as precise and spatiotemporal control over on-demand activity stimulated by long-wavelength light. For example, in 2021, Nguyen et al. developed an NIR light-tunable nano-optogenetic platform based on $NaYbF_4$:Tm@$NaYF_4$ nanoparticles coupled with the designed light-switchable CAR (LiCAR) T cells for precise spatiotemporal control of LiCAR T cell-based tumor therapy.[65] In this study, silica-coated LNPs were used as miniature light transducers to activate LiCAR T cells after stimulation with NIR light. This demonstrated T-cell-mediated cytotoxicity against both hematological malignancies and solid tumors with tailored dose and duration, as well as a reduction in side effects.

While LNP-mediated immunotherapy has demonstrated a great deal of success in inhibiting tumor recurrence and metastasis, it is mainly based on a few tumor-associated antigens, which can result in a low immune response due to tumor heterogeneity. A future focus of surface engineering research should be on developing neoantigen- or CAR T-cell-personalized immunotherapy using LNPs. Additionally, the long-term immune response, intricate mechanisms, and chronic toxicity of the personalized therapy must be carefully examined.

6. OTHER TREATMENTS

Surface-modified LNPs have been used in other tumor treatments, such as metal ion-mediated tumor ferroptosis, tumor chemo-dynamic therapy, glucose metabolism-mediated tumor apoptosis, and chlorine radical stress-mediated tumor apoptosis. According to a recent study, Fe^{3+}-gallic acid-conjugated $NaGdF_4$:Yb/Tm/Ca@$NaGdF_4$ nanocomplexes were effective in treating human colorectal tumors *in vivo* by ferroptosis and photothermal ablation due to the acidic pH-triggered release of Fe^{3+} in the tumor microenvironment (Figure 8a).[66] In 2021, Chen et al. developed a NIR-controlled proton supplier for tumor chemo-dynamic therapy by coating photoacid-coupled $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles onto an iron-based metal−organic framework (MIL-88B).[67] In their study, the nanoprobe released a high level of H^+ transients from the loaded photoacids in tumor cells when irradiated at 980 nm. The enhanced H^+ transients caused cofilin inaction, resulting in a lower invasion ability of tumor cells. Meanwhile, they could also enhance the iron-mediated Fenton reaction, thereby increasing cytotoxicity to tumor cells.

Reprogrammed glucose metabolism is an inhibitory factor for cancer cell proliferation. Therefore, targeted blocking of glucose uptake can be an effective strategy to combat tumors. In 2021, our group designed an integrated molecular deactivator (iMD) based on $NaYF_4$:Yb/Er@$NaYF_4$ nanoparticles, modified with a thin layer of reduced molybdenum oxide (MoO_{3-x}) nanosheets, glucose phosphate, eosin, and protamine, to inhibit tumor growth by blocking glucose metabolism (Figure 8b).[4] By suppressing the formation of aspartate, these nanoprobes inhibited tumor growth *in vivo* by specifically deactivating various types of glucose transporters on tumor cell membranes in response to irradiation at 980 nm.

Like reactive oxygen species, the chlorine radical ($Cl^•$) can directly induce cellular damage by interfering with DNA replication/transcription or causing one-electron oxidation with the DNA skeleton due to its high reactivity toward certain

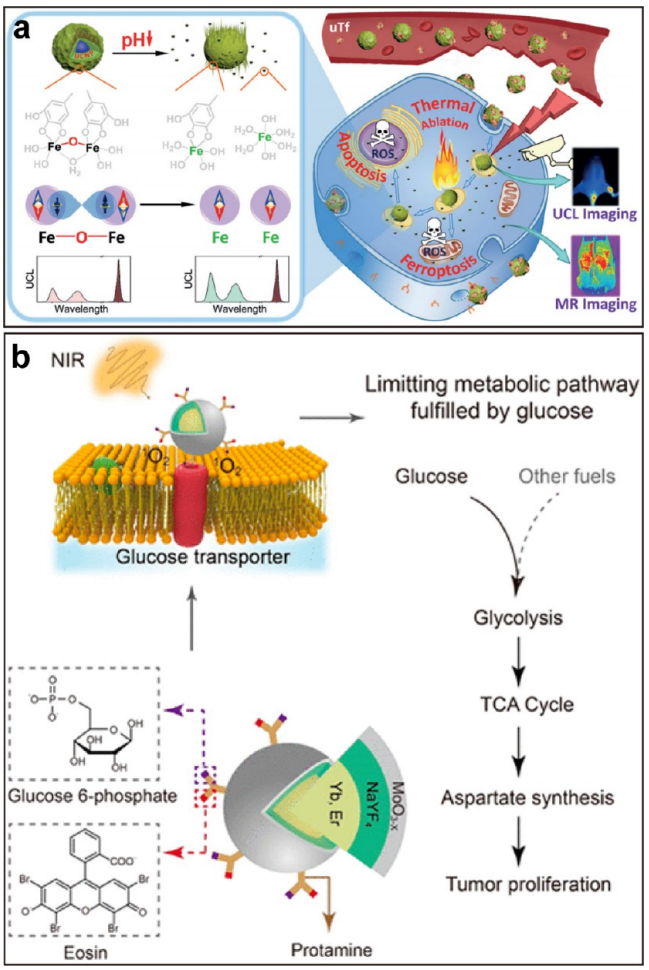

Figure 8. Surface engineering of lanthanide nanoparticles for tumor therapy. (a) Schematic of UCNP@GA-Fe^{III} nanoprobes for MRI and their therapeutic effects by photothermal therapy and ferroptosis. (b) Working mechanism of the upconversion nanoparticle-based integrated molecular deactivator (iMD) to inhibit tumor cell growth by suppressing the synthesis of aspartate. Adapted with permission from ref 66, copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA; and ref 4, copyright 2021 American Chemical Society, respectively.

electron-rich substances, such as nucleophilic atoms or functional groups in biomolecules. Therefore, the chlorine radical has great potential for effective tumor killing. In 2021, Song et al. developed a core-shell structured chlorine radical nanogenerator, consisting of SiO_2-coated $NaYF_4$:Yb/Tm@$NaYF_4$ nanoparticles as the core and Ag^0/AgCl heterodots as the shell.[68] From Ag^0/AgCl heterodots, chlorine radicals were generated via the UV−visible emission of LNPs, showing a great ability to oxidize and attack biomolecules in cancer cells. However, it is necessary to investigate their precise mechanisms and systemic cytotoxicity *in vivo* for their clinical application.

7. CONCLUSION AND OUTLOOK

In recent years, promising applications of surface-engineered LNPs in oncotherapy have been observed, especially in phototherapy and combination therapy. Through surface modification, LNP-based smart nanoplatforms show great advantages in spatially and temporally controlled tumor therapy while reducing side effects. Despite the promising progress, there are still some concerns that need to be resolved to promote the upcoming translational clinical applications.

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First, the upconversion efficiency of surface-modified LNPs in hydrophilic environments is still not satisfactory for bioapplications due to multiphoton nonradiative transitions. Luminescence-based therapeutic efficiency can be enhanced by increasing nanoprobe brightness. To obtain brighter lanthanide nanoprobes, especially surface-engineered LNPs in aqueous solutions, further effort is needed. It should also be investigated and understood how lanthanide ions or drugs/genes leak from the cargo at undesirable sites. This leakage not only reduces therapeutic efficiency but also induces toxic effects, as it can disrupt metabolism and excretion behavior. The development of more biocompatible protection and colloidal stability is considered a promising strategy to promote the clinical applications of LNP-based theranostics. Moreover, surface-engineered LNPs with high absorption in the NIR-II region (1000−1700 nm) should be further investigated as they represent a promising nanoplatform for phototherapy due to deeper penetration and less overheating. Surface stimulus-responsive lanthanide nanotheranostics should be precisely matched to tumor-linked stimuli in the tumor microenvironment. In general, externally responsive nanoprobes have low sensitivity, stability, and accuracy, which lowers their therapeutic efficacy.

The overall limited understanding of the nanotoxicology of lanthanide nanoparticles is one of the major obstacles to the clinical translation of these nanoparticles. *In vitro* and *in vivo* biosafety studies of lanthanide nanoparticles with different surface ligand modifications are rather limited. Most studies to date have evaluated only one dosage or type of surface-modified LNPs within a relatively short time frame.[69−71] These studies have shown that most LNPs would accumulate in the reticuloendothelial system (RES) such as the liver and spleen after systematic injection. Only ultrasmall lanthanide nanoparticles (PEG-coated, size <10 nm) would have a long retention time in the blood and would be excreted for the body of mice via kidneys.[72] Surface modifications can affect LNP biodistribution after systemic administration, such as enhancement of LNPs in targeting tumor sites, but the nanoparticle size is considered to be a key factor for biodistribution and excretion. The clinical application of LNPs is very limited by the fact that their long-term toxicity, biodistribution, and clearance have not been adequately investigated. Thus, there is a need for more systematic and comprehensive studies on the toxicity of surface-engineered LNPs, such as excretion, metabolism, pharmacokinetics, and pharmacodynamics. Additionally, LNPs have not been evaluated for safety in large animals, which could provide better clinical information.

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Notes

The authors declare no competing financial interest.

Biographies

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