

Rare Earth Luminescent Materials and the Biomedical Applications

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Abstract: Rare-earth luminescent materials have emerged as the promising materials for biomedical applications. This review systematically summarizes the recent advances in the biomedical applications of rare-earth luminescent materials. And this review provides a systematic overview of the luminescence mechanisms, classification, and the synthesis strategies of rare-earth luminescent materials. To facilitate the technological advancement and practical implementation of rare-earth luminescent materials, this review summarizes and proposes systematic optimization strategies from multiple perspectives, including the improvement of optical properties, enhancement of biocompatibility, and development of scalable synthesis technologies. These efforts are expected to further facilitate their clinical translation in the precision medicine.

Keywords: rare-earth materials; luminescence; bioimaging; drug delivery; tumor therapy

1. Introduction

With the continuous advancement of biomedical technologies, high-performance luminescent materials have demonstrated broad application prospects in disease diagnosis, bioimaging, and precision therapy owing to their unique optical advantages [1–3]. Compared with other luminescent media, rare-earth luminescent materials exhibit optical properties, characterized by narrow emission peaks, long fluorescence lifetimes, pronounced Stokes shifts, and reliable chemical stability. Benefiting from these optical advantages, rare-earth luminescent materials not only enable high-resolution, deep-tissue, and multimodal bioimaging, but also facilitate the detection of tumor microenvironment-associated biomarkers and other biological targets [4,5]. Based on these considerations, as shown in Figure 1, this review summarizes and organizes the classification, luminescence mechanisms, and commonly employed synthesis strategies of rare-earth luminescent materials, while also discussing recent advances in their applications in bioimaging, drug delivery, and cancer therapy.



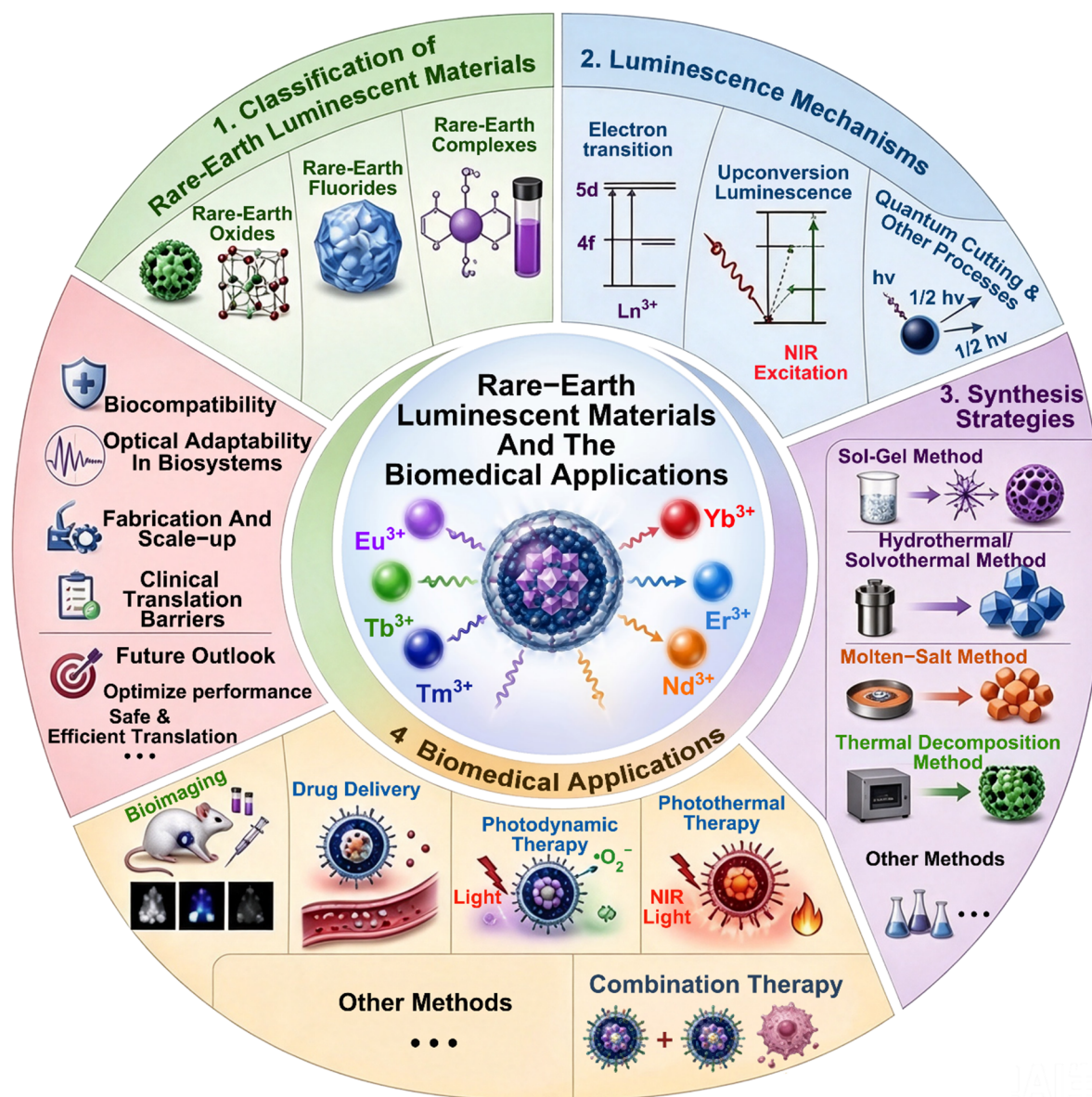


Figure 1. Schematic diagram of rare earth luminescent material classification, luminescence mechanism, and biological applications.

2. Classification, Luminescence Mechanisms, and Synthesis Methods

2.1. Classification

Rare-Earth Fluoride: Fluoride hosts include NaYF_4 and NaGdF_4 , which can effectively suppress nonradiative relaxation pathways and minimize the associated energy loss, serving as the desirable host matrices [6]. By incorporating Yb^{3+} ions as sensitizers and Er^{3+} , Tm^{3+} , or Ho^{3+} ions as activators into rare-earth fluorides, upconversion luminescence ranging from the ultraviolet to visible regions can be achieved under near-infrared excitation [7]. **Rare-Earth Complex:** Rare-earth complex luminescent materials are formed through coordination interactions between rare-earth ions and organic ligands including β -diketones, aromatic carboxylic acids, bipyridines, and macrocyclic ligands [8,9]. For example, Xu et al. developed a series of lanthanide molecular scintillators with full-spectrum tunable luminescence. Relying on ligand triplet excitons, the radioluminescence intensity under X-ray excitation is drastically enhanced. Meanwhile, the emission color can be precisely modulated by varying lanthanide metal centers and organic ligands [9]. **Rare-Earth Oxide:** By doping oxide hosts with rare-earth ions such as Eu^{3+} , Tb^{3+} , and Nd^{3+} as activator centers, multicolor luminescence can be achieved. For instance, Joshua Baggott reported that by doping Ln^{3+} into LiAlSiO_4 , multicolored luminescence can be observed under UV lamp irradiation. Specifically, Sm^{3+} -doped samples emit violet light, Eu^{3+} dopants produce red emission, Tb^{3+} doping yields green luminescence [10].

2.2. Luminescence Mechanisms

Rare-earth ions possess a unique electronic configuration, with a general electronic configuration of $[Xe]4f^{1-14}5d^{0-1}6s^2$. The 4f electrons of rare-earth ions are partially filled and shielded by the outer $5s^25p^6$ electron shells. The distinctive electronic configuration allows efficient absorption of excitation energy and subsequent electronic transitions. Their sharp spectral characteristics, photostability, and wide spectral tunability make rare-earth ions attractive candidates for constructing advanced luminescent materials [11–13]. The luminescence of rare-earth ions originates from electronic transitions between different energy levels within the 4f electron configuration, which are mainly divided into two categories: f-f transitions and f-d transitions [14,15].

Direct excitation of individual rare-earth ions is often restricted by their weak absorption capability and low emission intensity, which ultimately compromises the overall luminescence efficiency. The introduction of sensitizers into the system can effectively overcome these limitations and represents an effective strategy for enhancing the luminescence performance of rare-earth materials. Sensitizers absorb excitation photons and subsequently transfer the acquired energy to rare-earth ions through nonradiative energy-transfer processes, resulting in enhanced luminescence intensity of the emitting centers [16,17]. Sensitization involves energy transfer from sensitizers to luminescent centers through effective energy-level alignment. When the excited-state level of the sensitizer lies above that of the emitting ion with a small energy mismatch, excitation energy can be efficiently transferred to rare-earth ions via nonradiative energy-transfer processes. The rare-earth ions are subsequently populated to higher excited states and generate characteristic emissions through radiative relaxation. In particular, Yb^{3+} has emerged as a representative sensitizer in upconversion luminescent systems owing to its intense near-infrared absorption and simple energy-level configuration.

Upconversion luminescent materials represent a prominent research focus in the field of rare-earth luminescent materials [18–21]. The realization of rare-earth upconversion luminescence mainly relies on several mechanisms, including excited-state absorption (ESA), energy transfer upconversion (ETU), cooperative sensitization upconversion (CSC), cross-relaxation (CR), and photon avalanche (PA) [22]. Among the various upconversion mechanisms mentioned above, energy migration-mediated upconversion (EMU) serves as an important hybrid luminescence strategy and is particularly advantageous for multilayer core-shell nanostructures. Recently, quantum cutting (QC) has gradually attracted increasing research interest. Through multi-step resonant energy transfer and phonon-assisted relaxation processes, QC enables photon splitting [23,24].

2.3. Synthesis

Hydrothermal/Solvothermal Method. Hydrothermal and solvothermal methods are classical strategies for the synthesis of rare-earth luminescent materials. For the preparation of materials via hydrothermal/solvothermal methods, metal salt precursors are first dissolved and thoroughly mixed under stirring. After pH adjustment, the resulting solution is transferred into a sealed autoclave for reaction. Upon completion of the reaction, the system is cooled to room temperature, and the products are collected by filtration, followed by washing and drying to obtain the final samples [25,26]. **Sol-Gel Method.** During a typical sol-gel process, precursor compounds are dissolved in a liquid medium and continuously stirred to achieve a uniform solution. Hydrolysis and polycondensation reactions are then induced under controlled thermal conditions, leading to gel formation. The resulting gel is subsequently dried and subjected to thermal treatment to obtain the final products [27]. **Molten-Salt Method.** The molten salt method shares similarities with the high-temperature solid-state method but involves the incorporation of a molten salt system, typically composed of NaCl and KCl, into the precursor mixture. During the process, the reactants are uniformly dispersed in the molten salt medium, facilitating product formation through a liquid-phase reaction pathway. Compared with the conventional high-temperature solid-state method, the molten-salt method offers several advantages, including a lower reaction temperature, reduced energy consumption [28]. **High-temperature solid-state method.** The high-temperature solid-state method is a classic and industrially mature synthetic technique for the fabrication of rare earth luminescent materials, which is primarily suitable for the preparation of rare earth fluorescent powders and long-afterglow luminescent materials, such as oxides, oxysalts, and fluorides. This solvent-free route adopts solid powders as raw materials. Under high-temperature conditions, atomic diffusion, chemical bond reconstruction, and lattice phase transition occur at the interface of raw materials, thereby promoting crystal nucleation and directional growth and ultimately yielding well-crystallized rare earth luminescent materials [29]. **Thermal Decomposition Method.** The thermal decomposition method is a classical synthetic approach for the preparation of high-quality rare earth luminescent nanomaterials. The process is typically performed under an inert atmosphere, in which rare-earth organic precursors are introduced into high-boiling-point solvents, such as oleic acid. Upon heating to elevated temperatures, the precursors undergo thermal decomposition, resulting in the formation of nanomaterials with

highly uniform particle sizes. This synthetic strategy enables precise control over particle size and morphology through the modulation of reaction parameters, yielding materials with excellent dispersibility and reduced crystal defects. It is particularly suitable for the preparation of rare earth fluoride upconversion luminescent materials such as NaYF₄ and NaGdF₄, and therefore has broad application prospects in fields including bioimaging, and tumor therapy [30,31].

As shown in Table 1, the synthesis strategies described above involve different processing procedures, leading to significant variations in the microstructures and morphologies of the resulting materials. Key parameters, such as particle size and crystallinity, are summarized in the following table. Different synthetic strategies and processing techniques determine the composition and structure of materials. By optimizing the synthetic routes, the particle size and other structural parameters can be precisely regulated. Precise control over the size and structure of materials enables the optimization of their physicochemical properties and luminescence performance, ultimately affecting their applications in biomedical fields. Fundamentally, the preparation process, structural characteristics, and properties of materials are closely interconnected. Within this framework, an appropriate synthesis strategy serves as a critical prerequisite for achieving biomedical applications.

Table 1. Comprehensive comparison of the synthesis methods.

	Particle Size	Crystallinity	Morphology
Hydrothermal/Solvothermal Method	nanometer scale	medium	diverse morphologies
Sol-Gel Method	nanometer scale	low	Powder, film
Molten-Salt Method	nanometer scale	high	lamellar morphology
high-temperature solid-state method	micrometer scale	high	irregular powder
Thermal Decomposition Method	nanometer scale	medium	nanoparticles, nanorods

3. Biomedical Applications

3.1. Bioimaging

Bioimaging technologies are essential techniques in modern biomedical research, disease diagnosis, and intraoperative guidance, enabling the visualization of biological tissues. Rational regulation of core-shell architectures provide an effective strategy to address the trade-off between optical performance and tissue penetration capability. Rational lanthanide doping composition and concentration tailor emission to the near-infrared biological window, minimizing tissue scattering and autofluorescence to improve penetration depth and resolution, while excessive doping induces concentration quenching. Surface modification optimizes particle hydrophilicity and biocompatibility, reduces nonspecific adsorption and background interference, and improves *in vivo* stability. For instance, Wang et al. constructed a multi-layer core-shell upconversion nanotheranostic system PURH (PCpG/UCNP@mSiO₂-RB-HA). By doping rare-earth ions in the multi-layer structure to tune its dual-band near-infrared luminescence performance, they realized *in vivo* fluorescence visual imaging of tumor-targeted accumulation and light-controlled molecular activation (Figure 2) [32]. Comparative analysis of ex vivo organ imaging and quantitative fluorescence statistics, among nPURH, PURH and irradiation groups indicated that the rare-earth nanoprobe modified by combined targeting and light regulation achieved significantly improved radiant efficiency at tumor sites. Meanwhile, some studies have demonstrated that rare-earth luminescent materials can serve as photoresponsive probes for deep-tissue bioimaging [33,34].

Rare-earth NIR-II luminescent nanomaterials reduce tissue photon absorption/scattering and autofluorescence interference to boost imaging depth and resolution. Core-shell NaErF₄ and NaNdF₄ nanocrystals produce efficient steady-state NIR-II emission, enabling high-resolution *in vivo* visualization of mouse vasculature, lymphatic vessels and deep tumors for pinpointing microtumors, thus facilitating early tumor diagnosis and intraoperative precise navigation. For instance, Li et al. constructed down-conversion rare-earth NIR-II nanoprobe RENPs@Lips based on the outstanding NIR-II optical properties of core-shell NaErF₄/NaNdF₄ down-conversion rare-earth nanoparticles. These nanoprobe enable high-contrast *in vivo* fluorescence visual imaging of tumor blood vessels in tumor-bearing mice, as shown in Figure 3 [35]. Intravenous tail vein injection of RENPs@Lips enabled NIR-II fluorescence visualization of tumor blood vessels. The imaging modality clearly distinguished the femoral artery from tumor-specific feeding vessels. Using this imaging system, NIR-II fluorescence-guided simulated intraoperative vascular embolization for osteosarcoma was performed. After clamping, the fluorescence signal in the tumor blood supply area diminished markedly, which directly verified the embolization and occlusion efficacy.

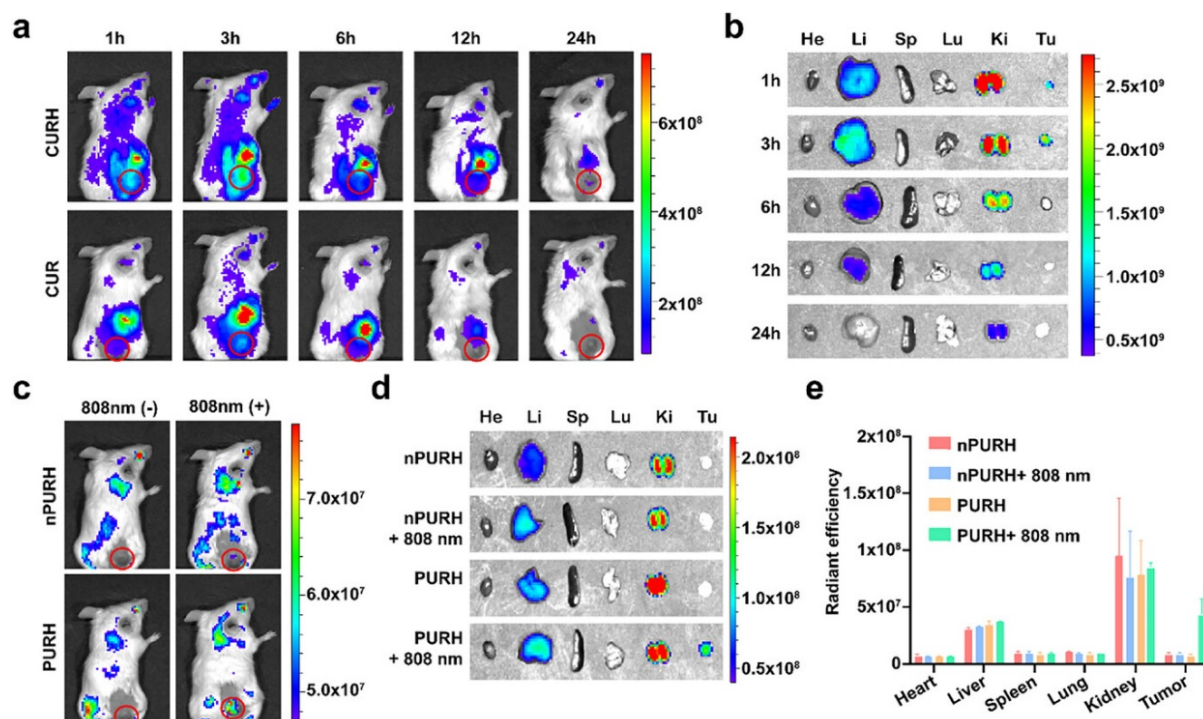


Figure 2. *In vivo* fluorescence imaging and photo-controlled activation of PURH nanosystem. Reproduced with permission [32]. Copyright 2025, Wiley-VCH GmbH.

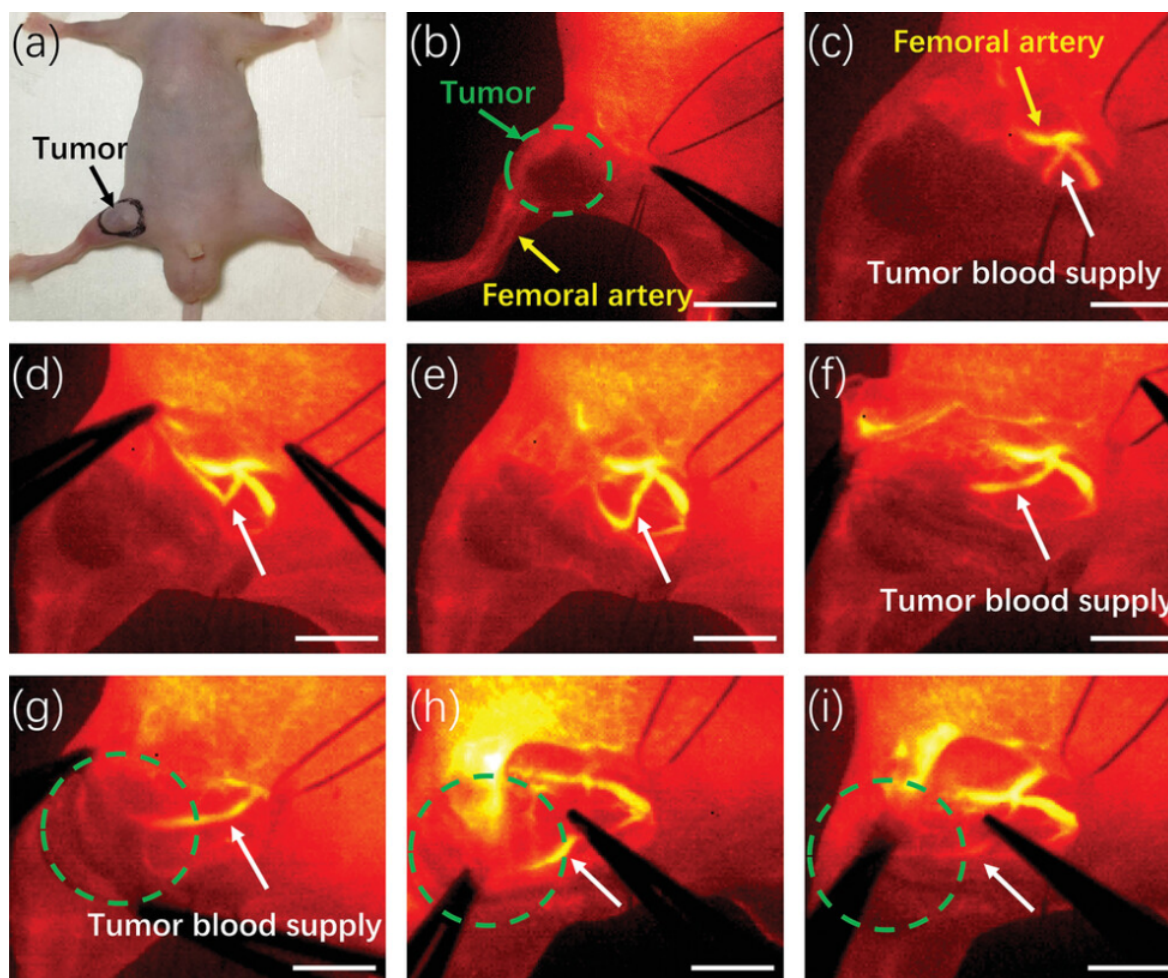


Figure 3. NIR-II image-guided intraoperative surgery. Reproduced with permission [35]. Copyright 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

3.2. Drug Delivery

The primary objective of drug delivery systems is to achieve targeted transport and controlled release of therapeutic agents, thereby increasing drug accumulation at diseased sites, reducing off-target toxicity to healthy tissues, and improving overall therapeutic efficacy [36,37]. Owing to their unique nanostructures, favorable biocompatibility, and tunable optical properties, rare-earth luminescent materials are regarded as promising carriers for drug delivery. They not only enable targeted delivery and controlled release of drugs, but also allow integration with imaging and therapeutic functions to construct a “diagnosis-delivery-therapy” theranostic platform, significantly enhancing the precision and effectiveness of drug delivery. NIR-responsive systems have become the widely used approaches in drug delivery due to the deep-tissue penetration capability. For example, Tam et al. [38] designed a NIR-triggered drug release system based on rare-earth upconversion nanoparticles. A core-shell structure of $\text{LiYbF}_4: \text{Tm}^{3+} @ \text{LiYF}_4$ was employed as the photoconversion core, which converts deeply penetrating and biocompatible 980 nm NIR light into UV emission. This approach enhances therapeutic efficacy while minimizing chemotherapy-induced toxicity. Dubey et al. constructed a theranostic nanocarrier by embedding $\text{CaF}_2: \text{Yb}^{3+}, \text{Er}^{3+}$ upconversion nanoparticles into mesoporous SiO_2 . This system is capable of co-loading hydrophilic doxorubicin (DOX) and hydrophobic curcumin (CUR), with loading efficiencies of 98% and 95%, respectively [39].

3.3. Photodynamic Therapy

Rare-earth upconversion nanoparticles (UCNPs) can transform deeply penetrating near-infrared (NIR) light into high-energy ultraviolet emission. This enables effective excitation of photosensitizers in deep tumor tissues, thereby triggering robust ROS generation for tumor ablation [40,41]. For instance, Ling et al. [42] developed an enzyme-triggered $\text{UCNP}@ \text{SiO}_2\text{-Bodipy}@ \text{FFYp}$ composite nanoplateform and systematically investigated its NIR-excited targeted PDT performance, as illustrated in Figure 4. Within the tumor microenvironment, alkaline phosphatase (ALP) can trigger the *in situ* assembly of UCNPs, thereby enhancing ROS generation under NIR irradiation. *In vivo* studies further demonstrated that this platform effectively suppressed tumor growth upon NIR irradiation.

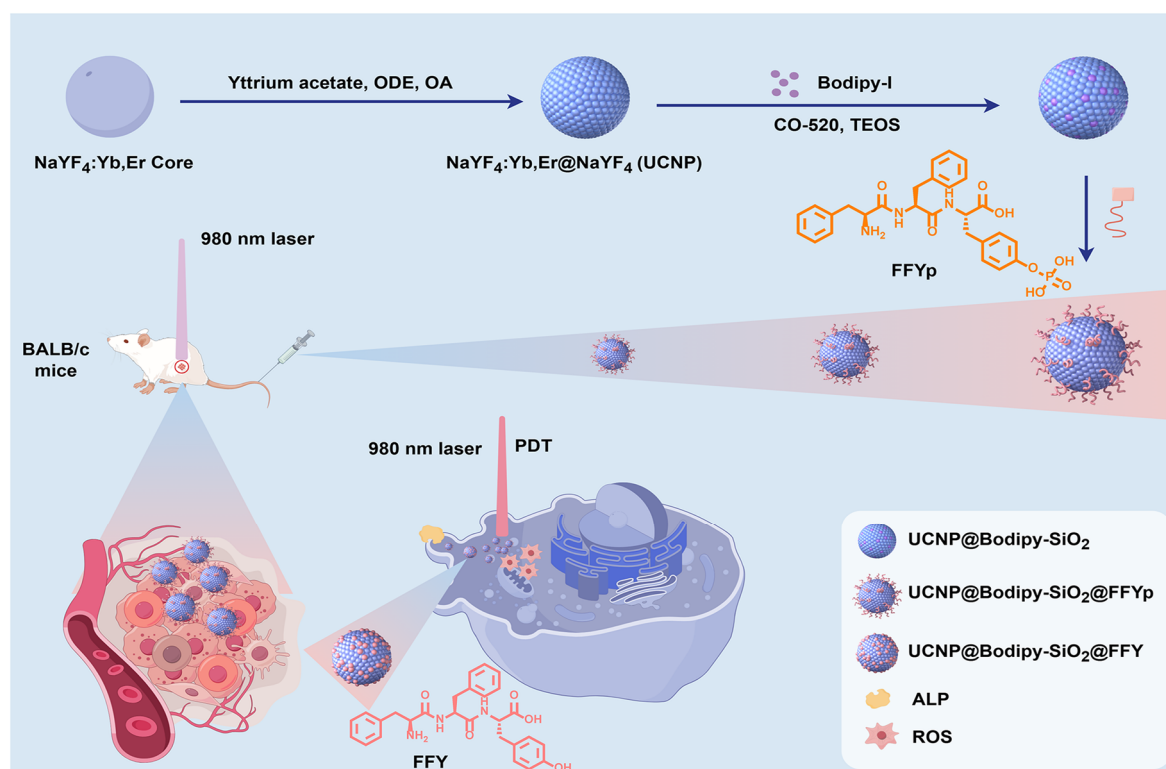


Figure 4. Schematic illustration of the $\text{UCNP}@ \text{SiO}_2\text{-BODIPY}@ \text{FFYp}$ composite nanoplateform for PDT. Reproduced with permission [42]. Copyright 2025, Royal Society of Chemistry.

Additionally, Li et al. designed a mitochondria-targeting nanoplateform denoted $\text{NZ}@ \text{TG}$, as shown in Figure 5 [43]. This nanoplateform employed Nd^{3+} -doped NaGdF_4 nanocrystals as the near-infrared-responsive core, which was integrated with zinc tetracarboxyphthalocyanine (ZnPcC_4) to construct an organic/inorganic hybrid photosensitizing

system. Meanwhile, the mitochondria-targeting ligand glycyrrhetic acid (GA) and the hypoxia-activated prodrug TH302 were co-loaded via DSPE-PEG coating. Upon 808 nm near-infrared irradiation, Nd^{3+} ions absorbed the near-infrared energy and transferred it to ZnPcC_4 through lanthanide–organic molecule interfacial triplet energy transfer, thereby efficiently generating reactive oxygen species (ROS). Mediated by glycyrrhetic acid (GA), the nanoplatform preferentially accumulated in mitochondria, causing substantial local ROS accumulation that disrupted mitochondrial membrane structure, decreased membrane potential, and reduced ATP production, further amplifying intracellular oxidative stress. Simultaneously, during photodynamic therapy, continuous oxygen consumption exacerbates the hypoxic tumor microenvironment, thereby triggering the activation of the hypoxia-responsive prodrug TH302. The activated drug releases DNA cross-linking cytotoxic metabolites, induces DNA damage in tumor cells, and arrests the cell cycle at the G₂/M phase, ultimately achieving efficient tumor suppression.

3.4. Photothermal Therapy

Photothermal therapy (PTT) is an effective tumor treatment strategy that utilizes photothermal agents to convert near-infrared light energy into heat, inducing tumor cell ablation through hyperthermia. To overcome the limited photothermal conversion efficiency and tumor thermal resistance encountered in conventional photothermal therapy, researchers have developed a carbon-based rare-earth upconversion composite nanoplatform, effectively addressing the inherent limitations of single-mode PTT [44].

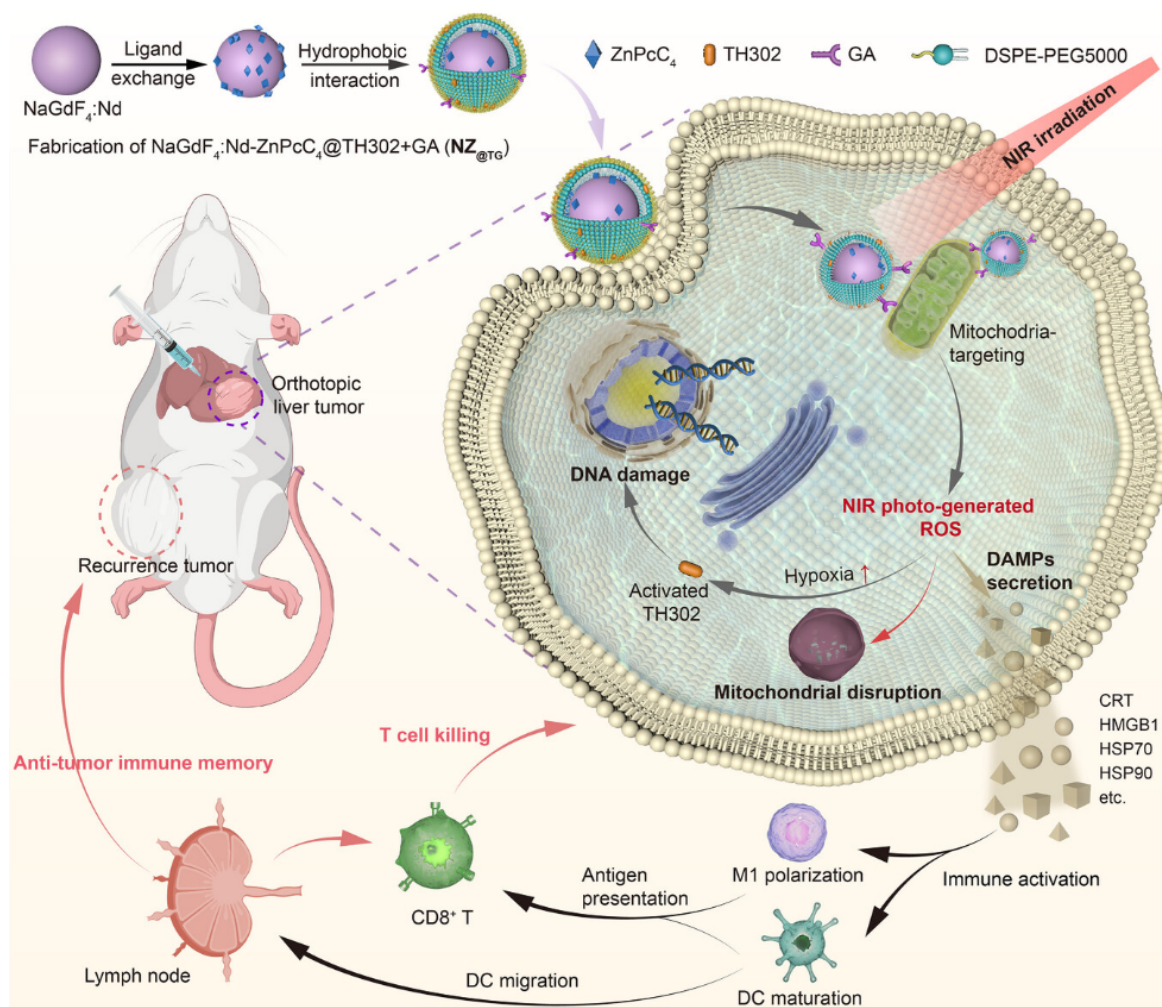


Figure 5. Schematic illustration of nanocomposites for cancer therapy and the underlying antitumor mechanisms triggered by NIR irradiation. Reproduced with permission [43]. Copyright 2025, Wiley-VCH GmbH.

4. Challenges and Future Perspectives

The practical biomedical and industrial translation of these materials remains hindered by limitations in synthesis strategies, fabrication processes, and clinical translation challenges.

4.1. Biocompatibility

Rare-earth-based inorganic nanomaterials possess small particle sizes and high specific surface areas. Unmodified rare-earth nanoparticles can gradually dissolve under acidic microenvironments and release rare-earth ions, which may accumulate in organs such as the liver, spleen, and bones, posing potential risks of cytotoxicity and organ damage [45]. Moreover, most current studies are limited to *in vitro* cytotoxicity assays and short-term *in vivo* animal experiments, while a comprehensive evaluation framework has yet to be established to elucidate the long-term accumulation behavior, metabolic pathways, and potential toxicity. To address these challenges, future studies should establish standardized biosafety evaluation frameworks by integrating cellular assessments, tissue and organ analyses, and long-term *in vivo* tracking experiments to achieve a comprehensive evaluation of the toxicological effects of these materials.

4.2. Fabrication and Scale-Up

Rare-earth luminescent materials are mainly fabricated via traditional approaches, such as hydrothermal methods. Nevertheless, these synthesis strategies still suffer from intrinsic limitations that hinder the practical translation [46,47]. The sol-gel method suffers from a prolonged preparation process and a tendency toward particle aggregation, resulting in significant variations in the morphology and particle size of samples between different batches. Hydrothermal/solvothermal synthesis relies on high-pressure reactors with low yield and poor scalability. High-temperature thermal decomposition methods are costly, requiring expensive precursors and organic solvents, while also involving complicated purification procedures. The molten salt method suffers from poor particle size control and difficult post-processing. To address these bottlenecks, the scalable synthesis strategies are urgently required to reduce solvent consumption, energy expenditure, costs and pollution.

4.3. Clinical Translation Barriers

Current biomedical investigations of rare-earth luminescent materials are mostly limited to *in vitro* and small-animal studies with substantial barriers to clinical translation [48–50]. Divergent material formulations, surface modification schemes and experimental setups across labs result in absent universal benchmarks and application standards. Moreover, scarce pharmacology and long-term biosafety data severely block their clinical transformation [51].

5. Conclusions

A variety of rare-earth material systems and mature synthetic strategies have been well developed to support their diversified biomedical applications, effectively overcoming the inherent performance defects of traditional fluorescent materials. Nevertheless, the clinical translation and industrialization of such materials are still restricted by multiple critical bottlenecks. Current studies generally focus on superficial performance optimization while neglecting systematic biomedical adaptability; the unsatisfactory *in vivo* optical stability, insufficient clinical-grade biocompatibility, and long-term biosafety risks severely limit their practical application. Moreover, existing mechanistic investigations remain fragmented and incomplete, and the unclear interaction mechanisms between materials and biological systems, together with the absence of unified safety evaluation criteria, constitute core obstacles to clinical transformation. In addition, conventional preparation techniques suffer from poor batch stability, low production efficiency and high cost, resulting in a prominent disconnect between laboratory research and large-scale industrial production.

Priority should be given to exploring *in vivo* metabolic and biological interaction mechanisms of rare-earth luminescent materials and establishing standardized, long-term biosafety evaluation systems to fill the gaps in current safety assessment research. Furthermore, interdisciplinary integration is essential to optimize traditional synthesis routes and develop scalable, low-cost and eco-friendly preparation technologies, so as to improve the batch consistency and practical applicability of materials. It is also necessary to precisely optimize material properties for complex physiological microenvironments and expand their multifunctional integrated applications in precise diagnosis and synergistic therapy.

Author Contributions

Y.Q., J.Z., L.C., and L.D.: Drafting of the manuscript; Y.Q., T.J., and L.D.: Critical review & editing of the manuscript. All the authors discussed the results and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

This manuscript is a review article, and no original experimental data were generated.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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