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Trimodal Synergistic Nanocomposites with Cascade Nanozyme Activity: Toward Potentially NIR-responsive Switching Imaging and Therapy

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Abstract: Herein, we designed and synthesized a multifunctional nanocomposite (UCNPs@FMn/ICG, denoted as UMI) that integrates upconversion luminescence imaging with trimodal synergistic therapy. This nanocomposite enables switching between upconversion luminescence imaging and a combined photodynamic (PDT), photothermal (PTT), and chemodynamic therapy (CDT) response simply by altering the excitation wavelength. Under 980 nm irradiation, UMI exhibited intense upconversion emission, demonstrating its potential for applications in near-infrared (NIR)-mediated optical imaging. When excited at 808 nm, UMI generated reactive oxygen species for PDT and produced substantial heat for PTT, highlighting highly efficient dual photodynamic and photothermal functions. The PDT performance of UMI was evaluated by the photocatalytic degradation experiment of 1,3-diphenylisobenzofuran (DPBF). At a concentration of $400\text{ }\mu\text{g}\cdot\text{mL}^{-1}$, UMI rapidly degraded 83.9 % of DPBF within 30 s under 808 nm irradiation ($91.0\text{ mW}\cdot\text{cm}^{-2}$). Simultaneously, it reached a temperature of $43.1\text{ }^{\circ}\text{C}$ within 10 min under $560\text{ mW}\cdot\text{cm}^{-2}$ irradiation, achieving a photothermal conversion efficiency of around 43.3 %. Thus, by synergizing pH-activated enzymatic catalysis and NIR-triggered phototherapeutic effects, UMI emerges as a versatile theranostic nanocomposite, paving the way for precise and efficient multimodal treatment guided by upconversion luminescence imaging.

Keywords: lanthanide; upconversion luminescent nanoparticles; near-infrared excitation; phototherapy

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具有级联纳米酶活性的三模态协同纳米复合材料： 面向潜在的近红外响应切换成像与治疗

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摘要: 设计并合成了一种多功能纳米复合材料(UCNPs@FMn/ICG, 简称 UMI), 该材料有望将上转换发光成像与三模态协同治疗相结合。只需改变激发波长, 该纳米复合材料就能在上转换发光成像与联合的光动力疗法(PDT)、光热疗法(PTT)和化学动力学疗法(CDT)响应之间进行切换。在 980 nm 照射下, UMI 表现出强烈的上

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转换发射,展示了其在近红外光介导的光学成像应用中的潜力;当受到 808 nm 光激发时,UMI 能产生活性氧用于 PDT,并产生大量热量用于 PTT,凸显了其高效的双重光动力和光热治疗潜力。通过 1,3-二苯基异苯并呋喃 (DPBF) 的光催化降解实验评估了 UMI 的 PDT 性能,在 808 nm 激光照射下,UMI ($400\ \mu\text{g}\cdot\text{mL}^{-1}$) 30 s 内迅速降解了 83.9% 的 DPBF;另外,在 808 nm 激光 ($560\ \text{mW}\cdot\text{cm}^{-2}$) 照射下,UMI 水分散液在 10 min 内温度达到 $43.1\ ^\circ\text{C}$,达到约 43.3% 的光热转换效率。因此,通过协同 pH 激活的酶催化作用和近红外光触发的光疗效应,UMI 有望成为一种多功能的诊疗一体化纳米复合材料,为实现上转换发光成像引导下的精准、高效多模式治疗提供了新思路。

关 键 词: 镧系元素;上转换发光纳米颗粒;近红外光激发;光疗

1 Introduction

Cancer remains a global medical challenge and a leading cause of countless fatalities^[1]. Conventional therapeutic strategies, including surgical resection, radiotherapy, and chemotherapy, are widely used for cancer treatment^[2]. However, these methods are limited by a high risk of recurrence and the non-specific toxicity^[3]. In recent years, phototherapy has attracted considerable attention owing to its advantages in precise spatial targeting, minimal invasiveness, tumour specificity, low toxicity, and reduced side effects^[4]. Based on distinct therapeutic mechanisms, phototherapeutic strategies primarily include photo-induced chemotherapy, photoimmunotherapy (PIT), photodynamic therapy (PDT), which generates cytotoxic reactive oxygen species, and photothermal therapy (PTT), which induces localized hyperthermia, among others^[5-8].

Beyond phototherapy, chemodynamic therapy (CDT) has emerged as a novel oncology treatment strategy. Its fundamental principle lies in exploiting specific features of the tumor microenvironment to achieve highly selective and localized therapeutic effects^[9-10]. Malignant cells undergo metabolic reprogramming to sustain their high energy demands, thereby fostering rapid proliferation and creating a tumor microenvironment characterized by an acidic pH and an aberrant redox balance^[11-12]. CDT functions through Fenton or Fenton-like reactions, which catalyze the conversion of endogenous hydrogen peroxide (H_2O_2) into highly cytotoxic hydroxyl radicals ($\cdot\text{OH}$). This mechanism offers significant advantages over conventional therapies by selectively killing cancer cells while minimizing side effects on normal

tissues and reducing the risk of drug resistance^[13-14]. Nonetheless, CDT is limited, as constrained tumor H_2O_2 levels and high glutathione concentrations hinder sustained $\cdot\text{OH}$ production and oxidative damage^[15-18]. Consequently, achieving optimal therapeutic outcomes with a monotherapy remains challenging. To substantially improve treatment efficacy, a synergistic multi-modal strategy that combines complementary therapeutic modalities is essential.

Compared to UV and visible light, near-infrared (NIR) light is more desirable for a variety of bioapplications due to its deeper tissue penetration and reduced photodamage to biological samples^[19-20]. Up-conversion luminescence is an anti-Stokes emission process that occurs through the sequential absorption of two or more low-energy photons *via* the ladder-like energy levels of lanthanide dopants in up-conversion nanoparticles (UCNPs)^[21-23]. Rare-earth-doped UCNPs can convert NIR excitation into UV or visible emission, offering significant advantages including a large anti-Stokes shift (up to several hundred nanometers), excellent photostability, enhanced penetration depth, and the absence of autofluorescence interference from biological specimens. Current research focuses on developing new diagnostic and therapeutic platforms by integrating the optical properties of UCNPs with functional composites capable of drug loading and site-specific activation^[24]. This integration facilitates a synergistic strategy for multimodal therapy^[25]. Conventional nanozymes employed for tumor therapy include iron-based nanozymes, composite nanozymes, and manganese-based nanozymes. The flower-like manganese dioxide (FMn) nanostructure serves as a versatile

scaffold for CDT, exhibiting distinct advantages over traditional iron-based catalysts. FMn possesses pH-responsive multi-enzyme mimetic catalytic properties, including peroxidase (POD), oxidase (OXD), catalase (CAT), and superoxide dismutase (SOD)-like activities, which can enhance the production efficiency of toxic $\cdot\text{OH}$ through multi-enzyme mimetic cascade reactions^[26]. Rare-earth doped UCNPs exhibit unique optical properties such as narrow emission bands, large anti-Stokes shifts, and low light scattering. Their excitation by near-infrared (NIR) light enables real-time optical imaging with superior tissue penetration depth^[27-28], providing a robust platform for the development of imaging-guided therapeutic systems^[29]. Conventional monotherapy suffers from the limitation that the catalytic consumption of hydrogen peroxide by nanozymes cannot be replenished, resulting in low generation efficiency of $\cdot\text{OH}$. By utilizing FMn to develop multi-enzyme mimetic nanostructures and establishing real-time imaging systems to track drug action, we can supplement H_2O_2 levels while increasing scavenging by endogenous antioxidants, thereby effectively enhancing the therapeutic outcome of CDT. Addressing the challenge of limited efficacy associated with single-modality treatments, the introduction of multi-modal therapeutic agents can synergistically improve treatment effectiveness. Indocyanine green (ICG) is a suitable agent for combined PDT and PTT due to its excellent biocompatibility, efficient singlet oxygen ($^1\text{O}_2$) generation, and high photothermal conversion efficiency^[30]. Furthermore, its excitation wavelength lies in the NIR region, which complements the use of UCNPs for deep-tissue excitation and real-time imaging. By leveraging the exceptional upconversion luminescence properties of UCNPs, it is feasible to achieve NIR-mediated optical imaging-guided combination of PTT/PDT/CDT.

In this study, we developed a nanocomposite (UCNPs@FMn/ICG, denoted as UMI) for upconversion luminescence imaging and trimodal synergistic therapy. Preliminary studies indicated that UMI exhibited pH-responsive multi-enzyme mimetic activities, such as POD-, OXD-, CAT-, and SOD-like

behaviors under acidic conditions, which could collectively contribute to elevated reactive oxygen species (ROS) levels. The catalytically generated O_2 and H_2O_2 can further serve as substrates for PDT and CDT, respectively, thereby enhancing the potential efficacy of these combined therapeutic modalities. Simultaneously, the reaction between flower-like MnO_2 (FMn) and H^+ releases Mn^{2+} ions, which may subsequently participate in Fenton-like reactions to potentiate CDT. Under NIR irradiation (980 nm for UCNPs and 808 nm for ICG), the UMI nanocomposite functions as an integrated theranostic platform, enabling concurrent upconversion luminescence imaging, localized hyperthermia generation, and reactive oxygen species production. Furthermore, owing to the relatively large size compared to common biomolecules in living systems, UMI nanocomposite is not rapidly cleared from tumor tissue following endocytosis-mediated internalization. This property facilitates passive targeting and sustained accumulation at the tumor site. Consequently, these characteristics render UMI a promising candidate for image-guided trimodal synergistic therapy (PTT/PDT/CDT).

2 Experiment

2.1 Synthesis of Core-shell Nanoparticles NaYF_4 :20%Yb,2%Er@ NaYF_4 (Denoted as UCNPs)

The synthesis of UCNPs was carried out following previously reported methods^[31], with detailed procedures provided in Section 2 of the Supporting Information.

2.2 Synthesis of UCNPs@FMn (Denoted as UM)

A 4 mL portion of the as-synthesized core-shell UCNPs cyclohexane dispersion was placed in a beaker, followed by the addition of 6 mL oleic acid. The mixture was stirred uncovered at room temperature for at least two days to allow for the complete evaporation of cyclohexane, resulting in a final mixture containing solely oleic acid and UCNPs. Separately, 250 mg of potassium permanganate (KMnO_4) was dissolved in 150 mL of deionized water under ultrasonication to obtain a homogeneous solution, which was then reserved for subsequent use. The prepared

KMnO₄ aqueous solution was then introduced into the mixture containing oleic acid and UCNPs with cyclohexane completely removed. The reaction was conducted under continuous stirring in the dark at room temperature for 3 h.

The resulting product was divided equally among eight centrifuge tubes and collected by centrifugation (9 000 r·min⁻¹, 5 min). Ethanol was added to each tube to a total volume of 30 mL, followed by ultrasonication for at least 15 min to ensure homogeneity. The solids were collected again by centrifugation (9 000 r·min⁻¹, 5 min), and the ethanol wash was repeated once. Subsequently, the precipitate in each tube was resuspended in 30 mL of deionized water and dispersed by sonication for at least 30 min. The solids were isolated by centrifugation (10 000 r·min⁻¹, 5 min), followed by an additional repetition of the water wash step.

Finally, all precipitates obtained from the final washing cycle were combined into a single centrifuge tube. The tube was sealed with perforated plastic film and transferred to a vacuum freeze-dryer for overnight lyophilization.

2.3 Synthesis of Flower-like MnO₂-coated UCNPs@FMn-NH₂ (Denoted as UMN)

Freeze-dried UM (100 mg) was dispersed in toluene (30 mL) by ultrasonication (35 min). AP-TES (600 μL) was added, and the mixture was further sonicated for 5 min before refluxing at 80 °C for 12 h^[32-33]. The resulting product was collected by centrifugation (6 500 r·min⁻¹, 5 min) and thoroughly washed with ethanol (seven cycles) to remove residual toluene, followed by washing with deionized water (three cycles with gradually reduced centrifugation speed). The final precipitate was collected and denoted as UMN.

2.4 Synthesis of Multifunctional Nanocomposite UCNPs@FMn/ICG Loaded with Indocyanine Green (Denoted as UMI)

Indocyanine green (ICG, 15 mg) was introduced into an aqueous dispersion of UMN (15 mL in deionized water). The resulting mixture was stirred continuously at room temperature in the dark for 12 h. The product was collected by centrifugation at

9 500 r·min⁻¹ for 5 min, washed twice with deionized water, and finally dispersed in 12 mL of deionized water to obtain UMI. The concentration of the UMI dispersion was determined gravimetrically. Two 5.00 mL glass vials were dried at 100 °C for 6 h, cooled to room temperature, and weighed. Aliquots of the UMI dispersion (500 μL) were added to each vial, followed by drying at 100 °C for 12 h. After cooling, the vials were reweighed, and the concentration was calculated from the mass difference. The average value from both vials was used to dilute the dispersion to a final concentration of 400 μg·mL⁻¹.

2.5 In vitro Photothermal Performance of UMI Nanocomposite

To evaluate the photothermal performance of UMI, aqueous dispersions of UMI with concentrations of 0, 50.0, 100, 200, 400 μg·mL⁻¹ were prepared, respectively. A volume of 2.00 mL from each dispersion was placed in a standard cuvette and irradiated with an 808 nm laser (power density: 560 mW·cm⁻²) for 10 min. Temperature changes were monitored in real time using a BENETECH thermocouple thermometer (± 0.1 °C) with a probe positioned 1 cm below the liquid surface and outside the laser path. Temperature data were recorded at 10 s intervals. The photothermal conversion efficiency (η) was calculated from the thermodynamic data of the 400 μg·mL⁻¹ aqueous dispersion of UMI under continuous 808 nm irradiation for 600 s using the established thermodynamic model^[34]:

$$\eta = \frac{hS(T_{\max} - T_{\text{surr}}) - Q_{\text{Dis}}}{I(1 - 10^{-A_{808}})}, \quad (1)$$

where S represents the surface area, h denotes the heat transfer coefficient, $T_{\max}$ is the maximum temperature of the system, T_{surr} indicates the ambient temperature, Q_{Dis} represents the heat generated by the absorption of light by the solvent, A_{808} is the absorbance of the material, and I represents the laser power (1.735 W).

2.6 Infrared Thermal Imaging of UMI for in vitro Photothermal Testing

Aqueous UMI dispersions with concentrations of 0, 50.0, 100, 200, 400 μg·mL⁻¹ were prepared, and 2.00 mL of each was transferred to a standard

cuvette. The samples were equilibrated at room temperature to ensure identical initial temperatures before irradiation. Subsequently, each dispersion was irradiated with an 808 nm laser (power density: $560 \text{ mW} \cdot \text{cm}^{-2}$) for 10 min. Simultaneously, infrared thermal images were recorded using an Optris PI infrared thermal imager, and temperature data were extracted from the recorded video at time points of 0, 2, 4, 6, 8, 10 min, respectively.

2.7 *In vitro* Singlet Oxygen ($^1\text{O}_2$) Generation by Multi-effect UMI Nanocomposite

The generation of singlet oxygen ($^1\text{O}_2$) by UMI was assessed using the molecular probe 1,3-diphenylisobenzofuran (DPBF)^[35]. DPBF exhibits a characteristic absorption maximum at around 410 nm, which irreversibly decreases upon reaction with $^1\text{O}_2$. All experiments were conducted under light-protected conditions to prevent unintended photodegradation.

Aqueous dispersions of UMI with concentrations of 0, 50.0, 100, 200, 400 $\mu\text{g} \cdot \text{mL}^{-1}$ (2.00 mL each) were aliquoted into cuvettes, followed by the addition of DPBF solution (150 μL). The samples were irradiated with an 808 nm laser (power density: $91.0 \text{ mW} \cdot \text{cm}^{-2}$) for durations of 0, 5, 10, 15, 20, 25, 30 s, and the real-time absorbance decrease at 410 nm was monitored. The changes in DPBF absorbance at different irradiation durations were recorded synchronously. Through analysis of the data, the $^1\text{O}_2$ generation efficiency of UMI and the efficacy of its photodynamic effect were evaluated.

3 Results and Discussion

3.1 Synthesis and Mechanisms of UMI

Oil-soluble core-shell UCNP (NaYF₄:20%Yb, 2%Er@NaYF₄) were synthesized *via* a thermal coprecipitation method^[31], where the inert NaYF₄ shell suppressed surface quenching and enhanced the up-conversion luminescence of UCNP. Subsequently, using these UCNP as templates, sheet-like MnO₂ was formed *via* a redox reaction between the oleic acid on the UCNP surface and potassium permanganate through a microemulsion process. The MnO₂ nanosheets underwent self-assembly on the surface

of UCNP, forming a flower-like MnO₂ (FMn) coating to yield UCNP@FMn (UM)^[36]. The FMn surface was subsequently functionalized with amino groups through 3-aminopropyltriethoxysilane (APTES) hydrolysis and polycondensation to obtain UCNP@FMn-NH₂ (UMN). Finally, ICG was loaded onto UMN through condensation or nucleophilic substitution reactions with surface amino groups, resulting in the formation of nanocomposite UCNP@FMn/ICG (denoted as UMI), which integrates both ICG and the flower-like MnO₂ components (Fig. 1(a)).

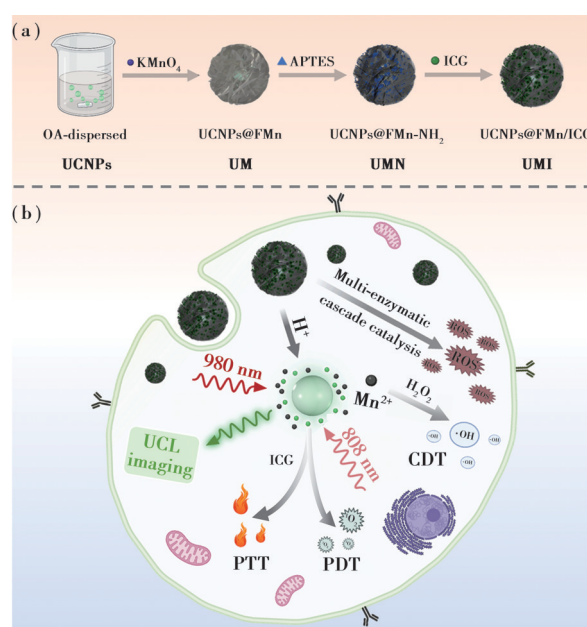


Fig.1 Schematic illustration of (a) the synthesis of UCNP@FMn/ICG (UMI) nanocomposites and (b) the potential applications for intracellular upconversion luminescence imaging, photothermal therapy (PTT), photodynamic therapy (PDT), and chemodynamic therapy (CDT)

In an acidic microenvironment, the FMn component of UMI is designed to react with protons (H^+), releasing Mn^{2+} ions that can catalyze a Fenton reaction to convert endogenous H_2O_2 into hydroxyl radicals ($\cdot\text{OH}$). This mechanism is expected to enable CDT against cancer cells, based on the demonstrated performance of UMI *in vitro*. Under 808 nm NIR laser irradiation, the incorporated ICG molecules generate reactive oxygen species (ROS) while concurrently converting the light energy into localized heat, enabling a combined mechanism of PDT and PTT. The FMn layer in UMI is expected to function as

a multi-enzyme mimetic (POD, OXD, CAT, and SOD-like), thereby enabling a cascade catalytic strategy to significantly enhance ROS generation. Additionally, upon switching to 980 nm NIR irradiation, the UMI exhibits upconversion luminescence, enabling fluorescence imaging, which can support real-time fluorescence guidance during diagnosis and therapy (Fig. 1(b)).

3.2 Characterization

We first characterized the morphology and structure of the UCNPs, UM, and UMI nanocomposite systematically using transmission electron microscopy (TEM). As displayed in Fig. 2(a), the UCNPs ($\text{NaYF}_4: 20\% \text{Yb}, 2\% \text{Er} @ \text{NaYF}_4$) exhibit a typical

hexagonal crystal structure^[37], forming parallelepiped-shaped nanoparticles with an average size of approximately 43 nm. Subsequently, MnO_2 nanosheets were deposited on the UCNPs surface through *in situ* oxidation, forming a flower-like MnO_2 (FMn) layer (Fig. 2(b), Fig. S1). The corresponding TEM image demonstrates the successful fabrication of UCNPs@FMn (UM). As shown in Fig. 2(c), the final UCNPs@FMn/ICG (UMI) nanocomposite exhibits smoother and more rounded edges compared to the well-defined sheet-like morphology of UM (Fig. 2(b)). This morphological transition, resulting from surface organic modification, suggests the successful loading of ICG on the UMI nanocomposite.

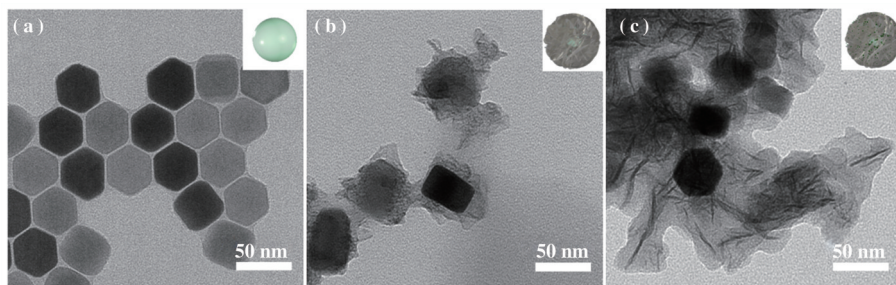


Fig.2 Transmission electron microscope (TEM) images of (a) $\text{NaYF}_4: \text{Yb}, \text{Er} @ \text{NaYF}_4$ (UCNPs), (b) UCNPs@FMn (UM), and (c) UCNPs@FMn/ICG (UMI)

Fourier-transform infrared (FTIR) spectra of UCNPs, UM, UMN, and UMI are shown in Fig. 3(a). In the curve of UM, the broad absorption peak at approximately $3\,400\text{ cm}^{-1}$ corresponds to the O—H stretching vibrations, while peaks at $2\,920\text{ cm}^{-1}$ and $2\,850\text{ cm}^{-1}$ correspond to C—H stretching vibrations of CH_2 and CH_3 groups, respectively, originating from trace amounts of oleic acid or 1-octadecene in the material. Additionally, the band at $1\,640\text{ cm}^{-1}$ is assigned to the C=O stretching vibration of oleic acid^[38-39]. The FTIR spectrum of UM further reveals a distinct peak at 754 cm^{-1} , corresponding to the Mn—O stretching vibration, which suggests the successful formation of the FMn shell^[40-41]. The curve of UMN displays additional characteristic bands: a peak at $1\,090\text{ cm}^{-1}$ attributable to Si—O—Si stretching (with possible contribution from C—N stretching), and the absorption band at $3\,200\text{ cm}^{-1}$ possibly attributed to N—H stretching vibration. These features collectively verify the successful silanization of the surface

with APTES^[42-45]. The spectrum of UMI exhibits characteristic peaks at $1\,230\text{ cm}^{-1}$ corresponding to the S=O stretching vibration, and a peak at 700 cm^{-1} whose assignment to S—N bond absorption is tentative and requires further validation. Nevertheless, these features suggest the successful loading of ICG, achieved *via* condensation or nucleophilic substitution between APTES-derived amino groups and the indole nitrogen of ICG^[46].

To further verify the results drawn from the FT-IR spectra, particularly regarding the successful APTES modification and ICG loading, we characterized the materials using X-ray photoelectron spectroscopy (XPS). The surface composition and chemical states of UMI were further analyzed by XPS (Fig. 3(b)). The XPS spectrum shows six distinct peaks at binding energies of 685, 642, 532, 399, 285, 159 eV, corresponding to the characteristic photoelectron signals of F 1s, Mn 2p, O 1s, N 1s, C 1s, and S 2p, respectively^[47]. These elemental signals provide direct

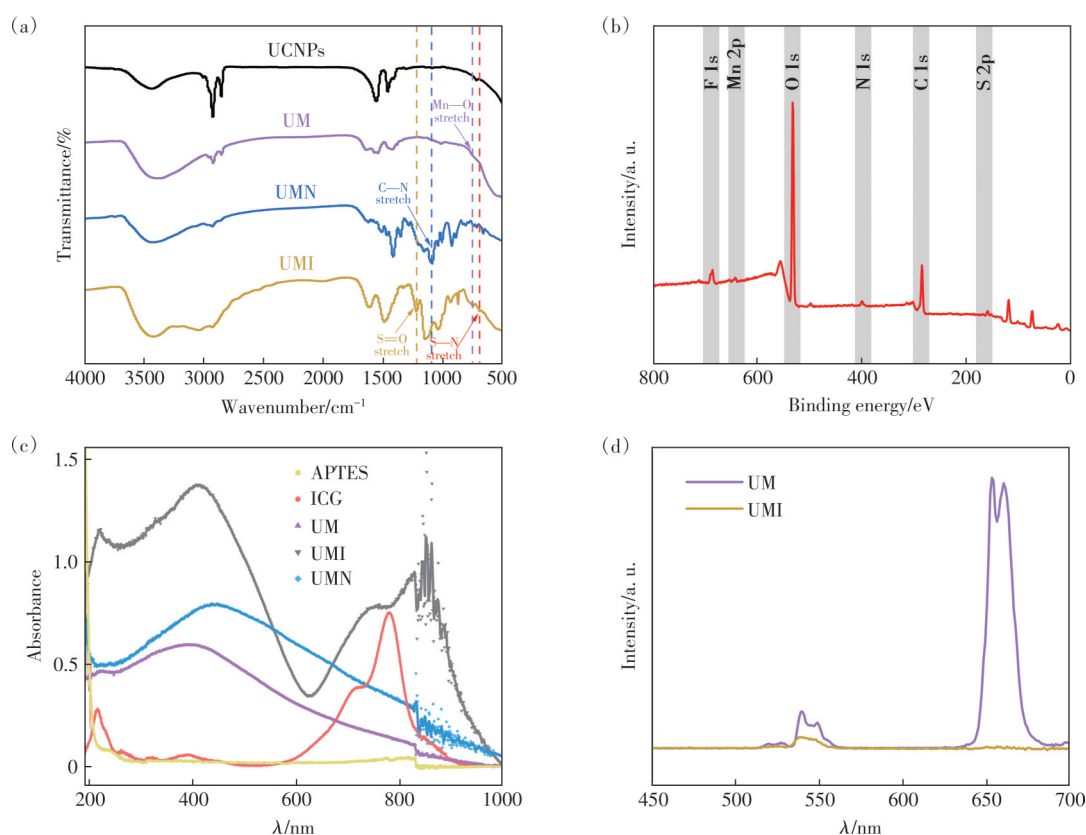


Fig.3 (a) Fourier transform infrared spectra of UCNPs, UM, UMN, and UMI. (b) X-ray photoelectron spectroscopy (XPS) of UMI. (c) UV-Vis-NIR absorption spectra of UM, APTES, UMN, ICG, and UMI. The raw, unsmoothed absorption data are presented by solid dots, while the corresponding smoothed profiles are shown as solid lines in matching colours, respectively. (d) Upconversion emission spectra of UM and UMI (Excitation wavelength: 980 nm)

evidence for the coexistence of all expected components: the F element signal originates from the UCNPs; the Mn and O signals from the flower-like MnO_2 (FMn) shell; the N signal confirms the presence of APTES from the silanization step; and the C and S signals correspond to the loaded ICG molecules. The simultaneous detection of these key elements, each traceable to a specific synthetic step, collectively verifies the successful stepwise construction and final integration of the nanocomposite UMI.

High-resolution X-ray photoelectron spectroscopy (XPS) analysis of UMI nanocomposites provides further verification of its chemical composition and bonding states (Fig. (4)). In the Mn 2p spectrum (Fig. 4(a)), two characteristic peaks at 653.48 eV ($\text{Mn } 2p_{1/2}$) and 641.98 eV ($\text{Mn } 2p_{3/2}$) correspond to Mn(IV) ^[48-49], confirming the successful formation of FMn in UMI (Fig. 4(a)). The C 1s spectrum (Fig. 4(b)) displays two characteristic peaks at 286.9 eV ($\text{C}=\text{N}$) and 285.4 eV ($\text{C}-\text{N}$), attributed primarily

to the organic components of ICG and APTES. Similarly, the N 1s spectrum (Fig. 4(c)) exhibits signals corresponding to $\text{N}=\text{C}$ and $\text{N}-\text{C}$, further supporting the presence of ICG and APTES. Additionally, the S 2p spectrum (Fig. 4(d)) shows a distinct peak at 168.0 eV, assigned to the $-\text{SO}_3\text{H}$ group of ICG. Thus, these high-resolution spectral features consistently verify the successful integration of all functional components and the precise synthesis of the UMI nanocomposite.

The crystal structure and phase composition of the UMI nanocomposite were analyzed by X-ray diffraction (XRD). The XRD patterns (Fig. S2) of pure FMn, UM, and UMI nanocomposites were compared with the reference pattern for hexagonal-phase NaYF_4 (JCPDS: 16-0334)^[50]. In the diffraction pattern of UM, besides the characteristic peaks of NaYF_4 , broadened diffraction peaks are observed at 2θ ranges of 22.5° – 26.8° , 35.3° – 40.1° , and 65.2° – 67.5° , which correspond to the characteristic diffraction of

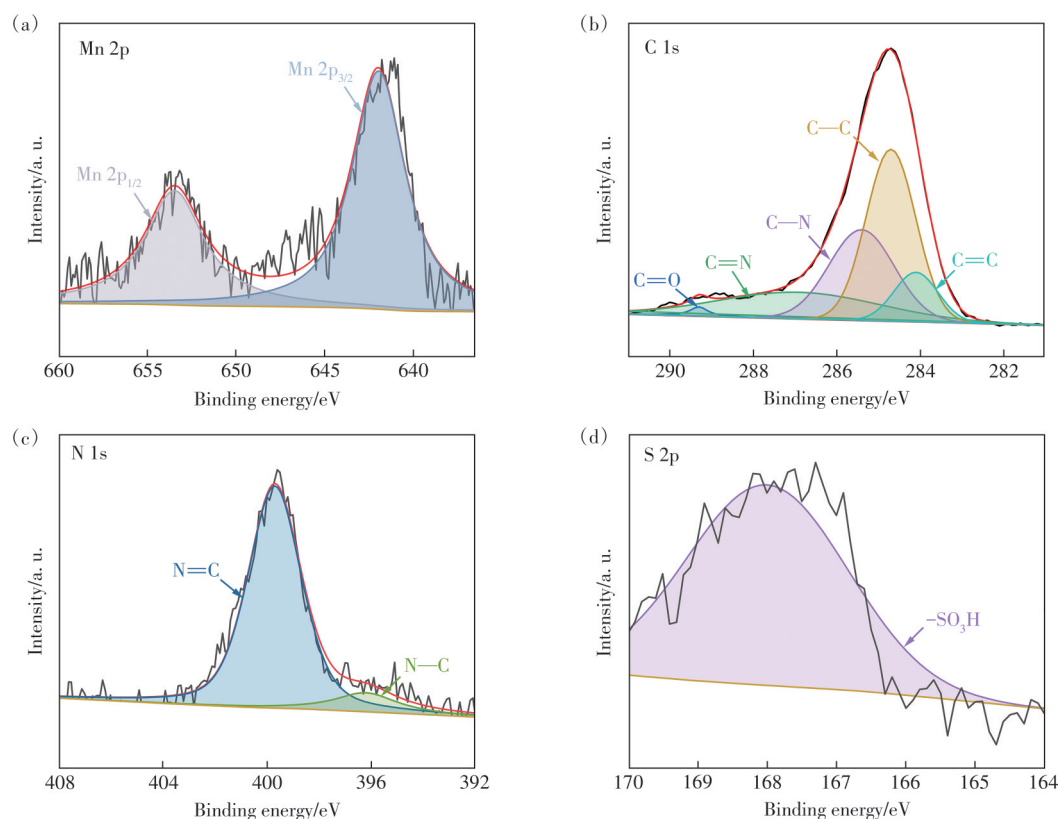


Fig.4 High-resolution X-ray photoelectron spectra (XPS) of UMI nanocomposite. (a) Mn 2p. (b) C 1s. (c) N 1s. (d) S 2p

the FMn layer^[51]. This indicates the successful coating of the FMn layer on the UCNPs surface. Further comparison of the XRD patterns for UM and UMI reveals a significant reduction in the intensity of all diffraction peaks in the ICG-modified UMI, which is attributed to the shielding effect of the coated organic layer. This attenuation of X-ray diffraction signals, together with the characteristic functional groups identified in FTIR analysis, provides complementary evidence for the successful surface modification of the nanocomposite with the organic photosensitizer ICG.

The Ultraviolet-visible-near-infrared (UV-Vis-NIR) absorption spectra of UM, APTES, UMN, ICG, and UMI are shown in Fig. 3(c). The spectrum of UMI not only retains the absorption band of UM near 400 nm but also exhibits a strong absorption band around 800 nm, which is attributed to the loaded ICG photosensitizer^[52]. Notably, this peak displays a bathochromic shift of more than 20 nm relative to the absorption maximum of free ICG (779 nm). This redshift is likely induced by molecular interactions, such as π - π stacking or hydrophobic effects, between

ICG and surrounding components in the nanocomposite, such as residual oleic acid^[53]. Simultaneously, the UMN spectrum retains the characteristic UV absorption feature around 200 nm attributed to APTES, as well as the UV-vis-NIR absorption feature near 400 nm of UM. These spectral characteristics provide conclusive evidence for the successful step-wise construction and final assembly of the UMI nanocomposite.

The upconversion luminescence properties of the nanomaterials were systematically investigated to verify their structural evolution. As shown in Fig. 3(d), upon 980 nm NIR excitation, both UM and UMI exhibit typical upconversion luminescence properties from UCNPs, with Er³⁺ emission peaks at 525 nm, 545 nm, and 654 nm, corresponding to the transitions of $^2\text{H}_{11/2} \rightarrow ^4\text{I}_{15/2}$, $^4\text{S}_{3/2} \rightarrow ^4\text{I}_{15/2}$, and $^4\text{F}_{9/2} \rightarrow ^4\text{I}_{15/2}$, respectively^[54]. Compared with the pristine UC-NPs (Fig. S3), the UM exhibits a marked reduction in overall emission intensity. Notably, the quenching is more pronounced for the green emissions at 525 nm and 545 nm than for the red emission at 654 nm, which is attributed to the strong absorbance of

the FMn shell in the blue-green spectral region (around 425 nm). In the final UMI nanocomposite, the red emission at 654 nm is nearly completely quenched. This is due to the efficient spectral overlap and subsequent energy absorption by the loaded ICG molecules, which possess a strong absorption band precisely in this region. The stepwise quenching of the distinct upconversion bands (first the green emissions by the FMn shell and subsequently the red emission by ICG) serves as direct optical proof of the sequential and successful integration of each functional component within the UMI nanocomposite. The retained upconversion luminescence property endows UMI with the capability for potentially cellular upconversion fluorescence imaging. Meanwhile, the interaction between ICG and the UMN matrix induces a red shift in the ICG absorption peak. This shift enhances the absorption of UMI at 808 nm and distinguishes this absorption from the 980 nm excitation wavelength required for upconversion luminescence of the UCNPs component. As a result, irradiation at 980 nm exclusively activates the UCNPs core for upconversion luminescence imaging, while 808 nm excitation selectively activates ICG for therapeutic purposes. Thus, UMI allows orthogonal switching between imaging and therapeutic functions simply by varying the excitation wavelength.

3.3 Multi-enzyme Mimetic Catalytic Performance of Nanocomposites

Based on previous reports, MnO_2 exhibits multi-enzyme mimetic catalytic properties^[26], which under acidic and H_2O_2 -rich tumor microenvironment (TME) conditions can catalyze H_2O_2 decomposition to generate highly toxic hydroxyl radicals ($\cdot\text{OH}$), thereby enabling chemodynamic therapy (CDT) in the studied material. To evaluate the potential of the nanocomposite for CDT, we first assessed the peroxidase (POD)-like and oxidase (OXD)-like activities of its FMn component using UM. The POD-like activity of UM was evaluated using a TMB- H_2O_2 colorimetric system, taking advantage of the characteristic overexpression of H_2O_2 levels in the tumor microenvironment. In this assay, the FMn layer in the UM catalyzes

the conversion of hydrogen peroxide into highly reactive hydroxyl radicals ($\cdot\text{OH}$), which subsequently oxidize colorless TMB (3,3',5,5'-tetramethylbenzidine) to blue-colored oxidized TMB (ox-TMB)^[55]. Fig. 5(a) displays the catalytic oxidation of TMB by H_2O_2 in the presence of varying concentrations of UM. The intensity of the characteristic ox-TMB absorption peak at 652 nm increases progressively with higher UM concentrations. This concentration-dependent enhancement directly demonstrates the POD-like catalytic function of UM and confirms its ability to generate $\cdot\text{OH}$ radicals in a controllable manner. To evaluate the pH-responsive nature of its catalytic activity, the POD-like behavior of UM was systematically assessed across a range of pH values. As shown in Fig. 5(b), UM exhibits a pronounced pH-dependent activity profile, with significantly enhanced catalytic efficiency under acidic conditions and markedly diminished activity in neutral or alkaline environments. This sharp activity transition aligns with the characteristic acidic tumor microenvironment, suggesting that the POD-like function of UM can be selectively activated within pathological tissues. The enhanced performance at low pH is likely attributable to the optimized surface chemistry and charge state of the FMn layer, which facilitates more efficient H_2O_2 adsorption and Fenton-like reaction kinetics under acidic conditions. This pH-responsive catalytic switch not only confirms the smart design of UM but also underscores its potential for spatially selective therapeutic action, minimizing off-target effects in normal tissues.

The OXD-like activity of UM was further evaluated under a simulated acidic tumor microenvironment (pH 6.5) in the absence of exogenous H_2O_2 . As shown in Fig. 5(c), UM efficiently catalyzed the oxidation of TMB, producing a pronounced absorption peak at 652 nm, characteristic of ox-TMB, confirming its intrinsic OXD-like capability. This catalytic behavior is attributed to the FMn layer in UM, which facilitates the activation of dissolved molecular oxygen (O_2) through a single-electron transfer process, thereby generating superoxide anion radicals ($\text{O}_2^{\cdot-}$) that subsequently oxidize TMB^[26]. Beyond

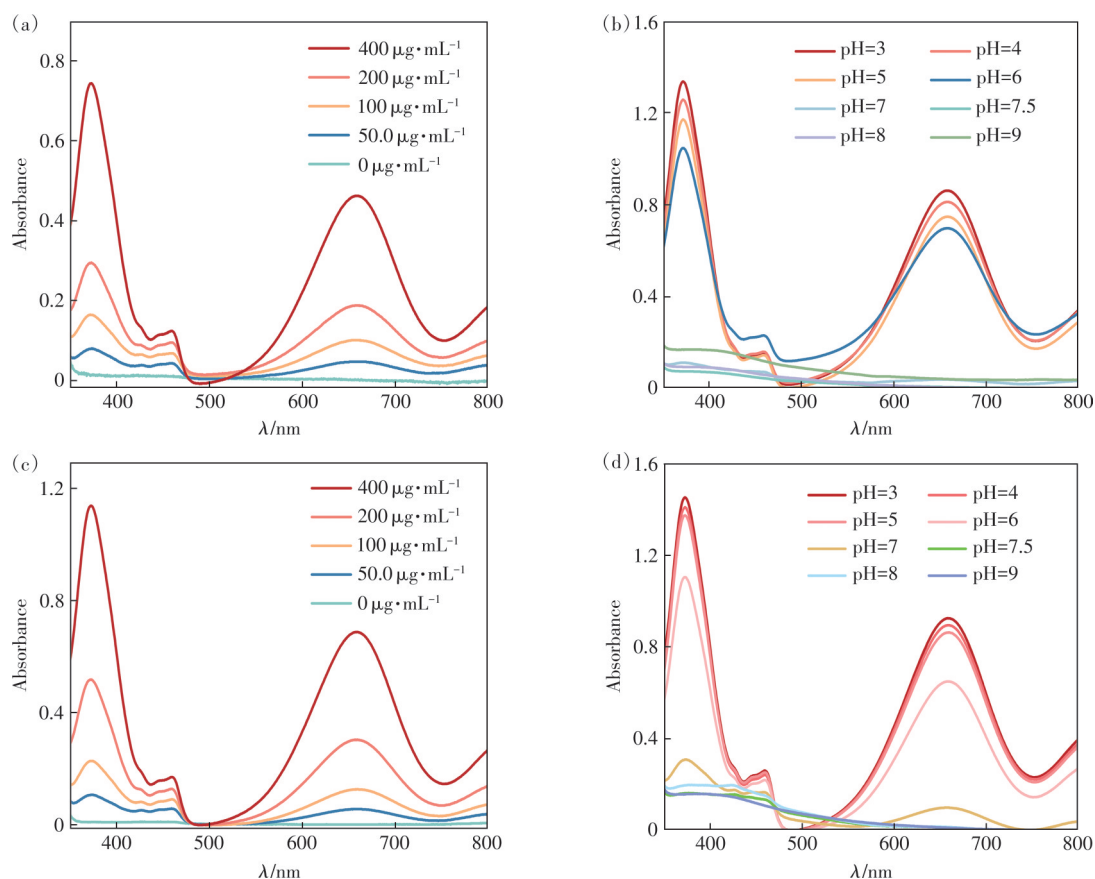


Fig.5 (a) UV-Vis absorption spectra of the TMB- H_2O_2 reaction system under different concentrations of UM ($0\text{--}400\ \mu\text{g}\cdot\text{mL}^{-1}$). (b) UV-Vis absorption spectra of the TMB- H_2O_2 reaction system containing $400\ \mu\text{g}\cdot\text{mL}^{-1}$ of UM at different pH values. (c) UV-Vis absorption spectra of the TMB reaction system under different concentrations of UM. (d) UV-Vis absorption spectra of the TMB reaction system containing UM ($400\ \mu\text{g}\cdot\text{mL}^{-1}$) at different pH values

producing a diagnostic colorimetric signal, the generated O_2^- and its derivative H_2O_2 can directly induce oxidative damage on tumor cells, thereby contributing to the therapeutic efficacy of chemodynamic and related oxidative therapies. Consistent with its POD-like activity, the OXD-like performance of UM exhibits strong pH dependence. Catalytic efficiency increased approximately 4.7-fold as the pH decreased from 7.5 to 5.0 (Fig. 5(d)), whereas only minimal activity was observed under neutral or alkaline conditions.

Although chemodynamic therapy (CDT) does not inherently rely on oxygen, its efficacy, especially for OXD-like reactions that require O_2 as a substrate, can be constrained by the hypoxic tumor microenvironment^[13,56]. Moving beyond the POD-like and OXD-like activities exhibited in the intermediate product UM, we directly utilized the final nanocomposite UMI to investigate its integrated multi-

enzyme mimicking catalytic properties. This approach allows us to assess how the combined catalytic functions of UMI operate under physiologically relevant conditions and whether its structural design effectively addresses the substrate limitations (*e.g.*, O_2 and H_2O_2 availability) posed by the tumor microenvironment, thereby evaluating its potential for a self-enhanced and sustainable ROS-generating therapeutic strategy. As displayed in Fig. S4, qualitative analysis using commercial assay kits revealed that UMI possesses CAT-like activities. The CAT activity data were derived from triplicate parallel measurements of the same sample using a microplate reader. Simultaneously, the SOD-like activity reached a maximum value of 1.53 units, which corresponded to a UMI concentration of $12.3\ \mu\text{g}\cdot\text{mL}^{-1}$ (Tab. S1). The raw data in the table consist of the absorbance readings at 450 nm obtained for each sample using a microplate reader, as required for the commercial

kit assay, along with the corresponding calculated SOD activity values derived therefrom. These properties are attributed to the MnO_2 shell, where CAT-like activity catalyzes H_2O_2 into O_2 , and the SOD-like activity dismutates $\text{O}_2^{\cdot -}$ into O_2 and H_2O_2 . By regenerating the essential substrates (H_2O_2 and O_2) that are consumed during the POD- and OXD-like reactions, these complementary activities establish an autonomous and self-sustaining catalytic cascade. This integrated system effectively mitigates substrate depletion in the tumor microenvironment and synergistically enhances the overall efficacy of CDT.

To further verify that the CAT-like activity of UMI originates from the FMn shell, the evolution of dissolved oxygen was monitored in real time using the intermediate UM. As shown in Fig. S5, for the group of $\text{H}_2\text{O}_2 + \text{UM}$, the addition of UM solution (250 μL , 400 $\mu\text{g} \cdot \text{mL}^{-1}$) to an H_2O_2 solution (5.00 mL, 1.00 $\text{mmol} \cdot \text{L}^{-1}$) induced rapid O_2 generation, reflected by a sharp increase in dissolved oxygen concentration that reached a plateau of 5.10 $\text{mg} \cdot \text{L}^{-1}$ at approximately 200 s. In contrast, the control group ($\text{H}_2\text{O}_2 + \text{H}_2\text{O}$) exhibited no significant change in dissolved oxygen concentration during the same period. This direct comparison clearly demonstrates that the O_2 generation results from the catalytic decomposition of H_2O_2 by the FMn shell, thereby verifying the origin of the CAT-like activity in the nanocomposite.

These results corroborate the CAT assay data obtained for UMI and confirm that the FMn shell effectively catalyzes H_2O_2 decomposition into O_2 . Together with the previously demonstrated POD-, OXD-, and SOD-like activities, these results validate the rational design of a multi-enzyme cascade nanocomposite responsive to the acidic tumor microenvironment. By regenerating essential substrates (O_2 and H_2O_2) and amplifying ROS generation through multi-enzyme-mimetic synergistic cascade catalysis, this integrated nanocomposite establishes a self-sustaining catalytic cycle that significantly enhances the efficacy of CDT.

3.4 *In vitro* Photothermal Performance of UMI

To verify whether the loading of ICG endows

the material with PTT performance, we evaluated the photothermal conversion performance of UMI. The photothermal conversion performance of UMI was evaluated by irradiating its aqueous dispersion with an 808 nm laser and monitoring the temperature evolution over 10 min at varying concentrations (0, 50.0, 100, 200, 400 $\mu\text{g} \cdot \text{mL}^{-1}$). As displayed in Fig. 6(a), the temperature rise exhibits a clear concentration dependence under NIR-irradiation, confirming that UMI possesses a significant and tunable photothermal effect. When irradiated with the 808 nm laser for 10 min, the temperature rose to 43.1 $^{\circ}\text{C}$ at a UMI concentration of 400 $\mu\text{g} \cdot \text{mL}^{-1}$. While lower concentrations of 200, 100, 50.0 $\mu\text{g} \cdot \text{mL}^{-1}$ resulted in temperatures of only around 31.5 $^{\circ}\text{C}$, 26.7 $^{\circ}\text{C}$, and 22.8 $^{\circ}\text{C}$, respectively (Fig. 6(b)). In contrast, the temperature of the blank control group (deionized water) remained constant at 15.6 $^{\circ}\text{C}$ throughout the experiment. Given the strong photothermal response and the attainment of a therapeutically relevant temperature ($>42^{\circ}\text{C}$) at 400 $\mu\text{g} \cdot \text{mL}^{-1}$, this concentration was identified as optimal for effective PTT.

A photothermal conversion efficiency (η) of 43.3% was determined for UMI through quantitative analysis of its heating and cooling profiles (Fig. 6(c), 6(d)) using the standard method described in Section 2.5. The raw UV-Vis-NIR test absorption value at 808 nm for UMI used in the photothermal conversion efficiency (η) formula is shown in Fig. S6. This efficiency, measured under 808 nm irradiation (560 $\text{mW} \cdot \text{cm}^{-2}$) where the dispersion temperature reached 43.1 $^{\circ}\text{C}$ in 10 min before rapidly cooling, exceeds that of numerous reported nanomaterials^[57-63]. Furthermore, infrared thermal imaging was employed to dynamically record the spatio-temporal temperature variation of UMI dispersions at varying concentrations over a 10 min laser irradiation period (Fig. 6(e)). The resulting images display a clear time- and concentration-dependent photothermal profile, which validates the quantitative heating data and intuitively demonstrates the tunability of the photothermal effect.

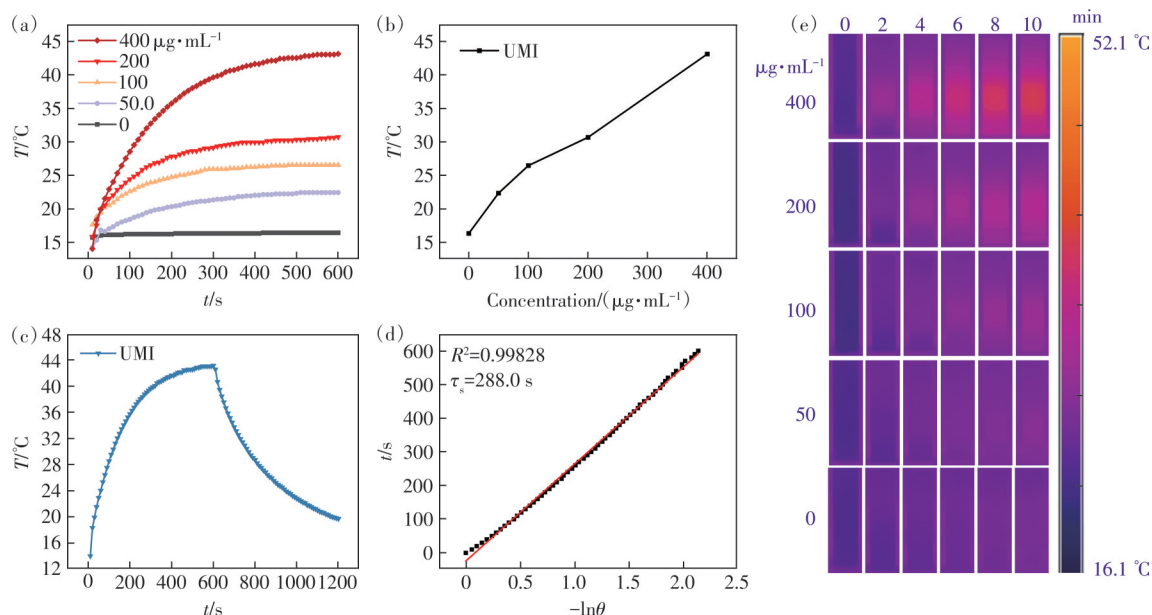


Fig.6 (a) Temperature evolution profiles of UMI aqueous dispersions at different concentrations (0, 50, 100, 200, 400 $\mu\text{g}\cdot\text{mL}^{-1}$) under 808 nm laser irradiation ($560\text{ mW}\cdot\text{cm}^{-2}$) for 10 min. (b) Quantified maximum temperature curves of UMI aqueous dispersions at varying concentrations (0, 50, 100, 200, 400 $\mu\text{g}\cdot\text{mL}^{-1}$) under 808 nm laser irradiation ($560\text{ mW}\cdot\text{cm}^{-2}$) for 10 min. (c) Temperature response curve of UMI aqueous dispersion (400 $\mu\text{g}\cdot\text{mL}^{-1}$) during 10 min of continuous 808 nm laser irradiation ($560\text{ mW}\cdot\text{cm}^{-2}$) and the subsequent cooling phase after laser shutoff. (d) Cooling time *versus* negative natural logarithm of temperature ($-\ln\theta$) for the UMI aqueous dispersion system (400 $\mu\text{g}\cdot\text{mL}^{-1}$), with a thermal relaxation time $\tau_s = 288.0\text{ s}$. (e) Infrared thermal images of UMI aqueous dispersions at different concentrations under 808 nm laser irradiation ($560\text{ mW}\cdot\text{cm}^{-2}$) (control group: deionized water, 0 $\mu\text{g}\cdot\text{mL}^{-1}$)

3.5 *In vitro* PDT Performance of UMI

The PDT performance of UMI was evaluated by monitoring singlet oxygen ($^1\text{O}_2$) generation using 1, 3-diphenylisobenzofuran (DPBF) as a chemical probe^[64]. This detection method is based on the specific decrease in the characteristic DPBF absorption at 410 nm upon reaction with $^1\text{O}_2$. When DPBF was

introduced into aqueous dispersions of UMI at various concentrations (0, 50, 100, 200, 400 $\mu\text{g}\cdot\text{mL}^{-1}$) and irradiated with an 808 nm laser, a time-dependent reduction in the absorbance at 410 nm was observed over a 30 s period (Fig. 7(a)). These results confirm that the loaded ICG within UMI can be effectively activated by 808 nm irradiation to generate

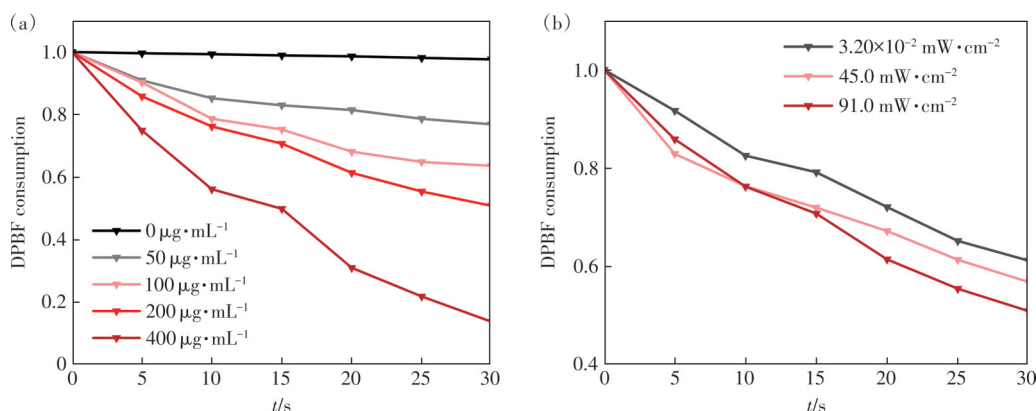


Fig.7 (a) Degradation curves of DPBF co-incubated with UMI aqueous dispersions at different concentrations (0, 50, 100, 200, 400 $\mu\text{g}\cdot\text{mL}^{-1}$) under 808 nm laser irradiation ($91.0\text{ mW}\cdot\text{cm}^{-2}$). (b) Degradation curves of DPBF co-incubated with UMI aqueous dispersion (200 $\mu\text{g}\cdot\text{mL}^{-1}$) under 808 nm laser irradiation at different power densities (3.20×10^{-2} , 45.0, 91.0 $\text{mW}\cdot\text{cm}^{-2}$) for 30 s. The corresponding UV-Vis spectra in Fig.7 are provided in the Supporting Information (Fig. S7–S12)

ROS, thereby enabling effective PDT. Quantitatively, at a UMI concentration of $400\ \mu\text{g}\cdot\text{mL}^{-1}$, approximately 83.9% of the DPBF probe was degraded within 30 s of irradiation. This rapid and near-complete probe degradation indicates exceptionally high $^1\text{O}_2$ yield and PDT efficiency, which surpasses that of many previously reported nanomaterials under comparable conditions^[57, 60, 65-68]. The outstanding performance can be attributed to the UMI-optimized nanostructure, which enables efficient light harvesting *via* ICG to generate ROS and integrates with multi-enzyme-mimetic synergetic cascade catalysis, thus maximizing the production of ROS for remarkable therapeutic effects.

The influence of laser power density on ROS generation was further investigated at 3.20×10^{-2} , 45.0, 91.0 $\text{mW}\cdot\text{cm}^{-2}$ using a fixed UMI concentration of $200\ \mu\text{g}\cdot\text{mL}^{-1}$ (Fig. 7(b)). The results reveal a clear positive correlation between power density and ROS yield. Over the 30 s irradiation period, the DPBF degradation efficiency increased in a time-dependent, stepwise manner with higher power densities. Even at a relatively low concentration ($200\ \mu\text{g}\cdot\text{mL}^{-1}$), the DPBF degradation efficiency rose from 38.9% to 49.2% as the power density was elevated, indicating a power-dependent enhancement of ROS generation. This trend is attributed to the increased photon flux, which drives more efficient activation of the photosensitizer ICG, consistent with the light-dose dependence typical of PDT mechanisms. Collectively, these results confirm that UMI exhibits efficient and tunable photodynamic performance under 808 nm excitation, achieving substantial ROS generation within short irradiation times even at relatively low concentrations. The superior PDT performance can be attributed to the following synergistic mechanisms. The FMn layer catalyzes the decomposition of hydrogen peroxide to generate hydroxyl radicals and oxygen, and the *in-situ* generated oxygen subsequently serves as a substrate for ICG to produce singlet oxygen ($^1\text{O}_2$) during PDT process upon 808 nm excitation. Moreover, FMn possesses multi-enzyme-mimetic cascade catalytic activity, which continuously regenerates hydrogen peroxide, a substrate required

for enhancing CDT and synergistically potentiating PDT. In other words, the combination of FMn and ICG synergistically enhances the individual therapeutic effects of each component. In summary, upon 980 nm irradiation UMI enables exclusive activation of the UCNP core for imaging, while under 808 nm irradiation it selectively activates ICG for PDT and PTT, synergistically enhancing therapeutic efficacy in conjunction with the intrinsic CDT performance of FMn. By simply switching between 980 nm and 808 nm excitation, selective switching between imaging and therapy can be achieved. This robust *in vitro* performance provides a strong foundation for its potential application in cellular-level PDT studies.

4 Conclusion

In summary, we have successfully developed a multifunctional nanocomposite, UCNP@FMn/ICG (UMI). It integrates a multi-enzyme mimetic FMn shell and NIR-responsive ICG photosensitizer into a single nanoplateform, promising synergistic effects and tumor-selective therapy guided by upconversion luminescence imaging. In addition, FMn exhibits pH-responsive multi-enzyme mimetic activities *in vitro* (including peroxidase-, oxidase-, catalase-, and superoxide dismutase-like behaviors). These combined activities lead to a synergistic cascade catalytic effect, demonstrating the potential to enhance CDT efficacy, pending validation in cellular or *in vivo* models.

Under 980 nm excitation, UMI exhibits excellent upconversion luminescence suitable for potential real-time imaging. When irradiated at 808 nm, the loaded ICG generates $^1\text{O}_2$ for photodynamic therapy (PDT), while simultaneously converting light into heat for photothermal therapy (PTT). At a concentration of $400\ \mu\text{g}\cdot\text{mL}^{-1}$, UMI degraded 83.9% of DPBF within 30 s and achieved a photothermal conversion efficiency of 43.3%. The individual PDT and PTT performances surpass those of many existing PDT/PTT nanomaterials. Therefore, UMI represents an acid-responsive, NIR-activatable theranostic platform that combines upconversion imaging with trimodal therapy (PDT/PTT/CDT). While challenges such as long-term biosafety and colloidal stability

require to be addressed further, this work demonstrates a promising strategy for targeted and image-guided cancer treatment.

Supplementary Information and Response Letter are available for this paper at: <http://cjl.lightpublishing.cn/thesisDetails#10.3724/CJL.20260113>

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