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Review

# Tailored lanthanide-doped upconversion nanoparticles and their promising bioapplication prospects

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ABSTRACT

Lanthanide-doped upconversion nanoparticles (UCNPs) which could show unique upconversion photoluminescence (UCPL) have attracted considerable attention due to their excellent chemical and optical characteristics. Compared with down-shifting luminescence, UCPL shows its bright future in the bioapplication where sequential absorption of multiple low-energy photons (such as near-infrared (NIR) excitation) by the ladder-like energy levels of the lanthanide ions ($Ln^{3+}$) leads to the production of higher energy photons (such as ultraviolet, visible light). UCPL shows a variety of advantages such as large anti-Stokes shifts, sharp emissions, long luminescence lifetimes, and high resistance to photobleaching. Furthermore, NIR irradiation has lower photo damage effect, a large penetration depth in tissues, and at the same time, it can avoid the auto-fluorescence interference of biological sample and light scattering phenomenon, which can reduce the background light and improve the signal-to-noise ratio. Thus, UCNPs have emerged as more appropriate nanomaterials for bioapplications. To date, many scientists have focused on the research of the bioapplications of UCNPs, including bioimaging, drug release, and therapies after the special surface modification. In this critical review, recent advances regarding the mechanism, synthesis, modification, and promising bioapplications of UCNPs are reviewed. In particular, the studies related to sensing and bioimaging (UCPL, MR, CT, PET and SPECT), drug release, and therapies (photothermal therapy, photodynamic therapy, and radiotherapy) are presented in detail. For specific bioapplication, tailored UCNPs can be designed and synthesized according to the different synthesis and modification methods as summarized in this review. Finally, we discuss the prospects and challenges of UCNPs in the biomedical and biotechnological fields.



**Contents**



*Abbreviations:* UCNPs, upconversion nanoparticles; UCPL, upconversion photoluminescence; NIR, near-infrared; $Ln^{3+}$, lanthanide ions; QDs, quantum dots; CDs, carbon dots; CW, continuous-wavelength; EG, ethylene glycol; QY, quantum yield; CT, X-ray computed tomography; MR, magnetic resonance; PET, positron emission tomography; SPECT, positron emission computed tomography; PTT, photothermal therapy; PDT, photodynamic therapy; RT, radiotherapy; ESA, excited state absorption; ETU, energy transfer upconversion; CSU, cooperative sensitization upconversion; CR, cross relaxation; PA, photon avalanche; OA, oleic acid; OM, oleylamine; ODE, 1-octadecene; β-hCG, human chorionic gonadotropin; PEG, polyethylene glycol; CTAB, cetyltrimethylammonium bromide; $SiO_2$, silica; $mSiO_2$, mesoporous silica; TEOS, tetraethyl orthosilicate; SERS, surface-enhanced Raman scattering; $C_{18}$TMS, n-octadecyltrimethoxysilane; IBU, ibuprofen; PEI, polyetherimide; HCl, hydrochloric acid; bFGF, basic fibroblast growth factors; FRET, Förster resonance energy transfer; FA, folic acid; —COOH, carboxyl group; —$NH_2$, amino group; PAA, poly(acrylic acid); $C_{18}$PMH-PEG, poly(maleic anhydride-alt-1-octadecene)-poly(ethylene glycol)methyl ethers; PEG-b-PCL, poly(ethylene glycol)-block-poly(caprolactone); PEG-b-PLA, poly((ethylene glycol)-block-lactic acid); 6AA, 6-aminohexanoic acid; EDC, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; NHS, N-Hydroxysuccinimide; NRD, Nile red derivative; GSH, glutathione; $MnO_2$, manganese dioxide; BTB, bromothymol blue; GO, graphene oxide; azo, azobenzene; α-TOS, alpha-tocopheryl succinate; DOX, doxorubicin; $^1O_2$, singlet oxygen; ROS, reactive oxygen species; RB, rose bengal; $TiO_2$, titanium dioxide; PpIX, protoporphyrin IX; Ce6, chlorin e6; ZnPc, Zn(II)-phthalocyanine; HA, hypocrellin A; CDDP, cisplatin; ATP, Adenosine Triphosphate; PMO, periodic mesoporous organosilica.

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## 1. Introduction

Up to now, lanthanide ions ($Ln^{3+}$) doped luminescent materials *via* intra-4*f* or 4*f*-5*d* transitions have drawn rather consistent interest due to their outstanding features, such as excellent photostabilities, sharp-band emissions, long luminescence lifetimes as well as large anti-Stokes shifts [1,2]. In particular, $Ln^{3+}$-doped upconversion nanoparticles (UCNPs) have received considerable attention due to their special anti-Stokes photoluminescent properties compared with traditional down-shifting luminescent materials, since Auzel et al. systematically proposed and summed up the mechanism of upconversion materials [3]. Upconversion photoluminescence (UCPL) is a non-linear process where sequential absorption of two or more low-energy photons (such as near-infrared (NIR) light leads to the production of higher energy photons (such as ultraviolet, visible, and NIR light). It is attributed to the intra-4*f* or 4*f*-5*d* transitions in the ladder-like, abundant and unique energy levels of the $Ln^{3+}$ [4,5]. So far, although a series of luminescent materials, including fluorescent proteins [6,7], organic dyes [8], metal complex [9], semiconductor quantum dots (QDs) [10], and carbon dots (CDs) [11,12] have been developed for luminescent contrast agents and bioapplications, UCNPs have emerged as more appropriate nanomaterials for bioapplications. In addition, it is available and enforceable that tailored UCNPs can be designed and synthesized for specific bioapplication according to the following aspects.

First, the process of upconversion photoluminescence being carried out by low-power NIR continuous-wavelength (CW) laser (e.g., 808 nm or 980 nm) exhibits several advantages, such as deep penetration of living organisms [13,14], weak autofluorescence [15,16], minimal photobleaching [17,18], and low toxicity [19,20], suitable for deep tissue optical imaging or light-responsive drug release and therapies. In addition, NIR light proposes minimized photo-damage to living organisms compared with UV and visible light. Generally, UCNPs are composed of three parts: inorganic host matrix, sensitizer ions, and activator ions which could also be referred to luminescent centers. $Ln^{3+}$ ions embedded in a suitable inorganic matrix, such as $NaYF_4$ [21–24], $NaYbF_4$ [18], $NaGdF_4$/$BaGdF_5$ [25,26], $NaLuF_4$ [27,28], $Y_2O_3$/$Gd_2O_3$ [29,30], $Bi_2O_3$ [31], and $LnF_3$ [32,33], etc., are able to emit distinctive and characteristic upconversion photoluminescence. Among these matrixes, $NaYF_4$ is one of the most popular and ideal host materials due to its excellent properties including high tolerance, low phonon energy, high transparency, and outstanding chemical and thermal stability [34,35]. The desired sensitizers possess relatively large photo absorption cross-sections and appropriate energy levels to match the corresponding activators. To date, a number of researches have demonstrated that $Yb^{3+}$ is an efficient sensitizer with high two-photon absorption cross sections (976 nm, $^2F_{7/2} \rightarrow {}^2F_{5/2}$), which is co-doped with activator (e.g., $Er^{3+}$, $Tm^{3+}$ or $Ho^{3+}$) in the host lattice for the energy transfer from $Yb^{3+}$ to activators under the excitation of 980 nm [36,37]. Recently, some groups focused on a new route to construct the $Nd^{3+}$-sensitized UCNPs with the energy transfer process [$^4F_{3/2}$ ($Nd^{3+}$) → $^2F_{5/2}$ ($Yb^{3+}$) → activators] under the excitation of 808 nm [38–43]. In this way, the energy transfer efficiency under the excitation of 808 nm is similar with that of 980 nm, however, the 808 nm excitation shows minimized heating effect to biological tissues [44,45], since 808 nm band with lower water absorbance is expected (Fig. 1) [39]. Generally, $Er^{3+}$, $Tm^{3+}$, and $Ho^{3+}$ ions holding ladder-like arrangement energy levels, are frequently used as activators to generate UCPL emission under NIR excitation [46].