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DOI

[10.2174/1381612825666190708202403](https://doi.org/10.2174/1381612825666190708202403)

Publication date

2019

Document Version

Final published version

Published in

Current pharmaceutical design

License

Article 25fa Dutch Copyright Act

[Link to publication](#)

Citation for published version (APA):

Ding, Y., Hong, X., Liu, Y., & Zhang, H. (2019). Recent Advances in Magnetic Upconversion Nanocomposites for Bioapplications. *Current pharmaceutical design*, 25(17), 2007-2015. <https://doi.org/10.2174/1381612825666190708202403>

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REVIEW ARTICLE

Recent Advances in Magnetic Upconversion Nanocomposites for Bioapplications

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ARTICLE HISTORY

Received: April 24, 2019
Accepted: June 19, 2019

DOI:

10.2174/1381612825666190708202403

Abstract: The combination of magnetism and upconversion luminescent property into one single nanostructure is fascinating for biological fields, such as multimodal bioimaging, targeted drug delivery, and imaging-guided therapy. In this review, we will provide the state-of-the-art advances on magnetic upconversion nanocomposites towards their bioapplications. Their structure design, synthesis methods, surface engineering and applications in bioimaging, drug delivery, therapy as well as biodetection will be covered.

Keywords: Magnetic optical nanocomposite, upconversion luminescence, structure design, synthesis, surface modification, bioimaging, drug delivery, therapy.

1. INTRODUCTION

Magnetic optical nanocomposites integrating magnetic and optical properties may have a significant potential for bioapplications, *e.g.*, magnetic separation, magnetic resonance imaging (MRI), magnetic hyperthermia, optical bioimaging and optical labeling [1-9]. The magnetic component of the nanocomposite is usually superparamagnetic iron oxide-based nanoparticles, whereas the optical part is diverse from organic dyes, quantum dots (QDs) to lanthanide doped nanoparticles [10-18]. Especially, lanthanide-doped upconversion nanoparticles (UCNPs) have attracted considerable attention ascribed to their unique luminescent properties, such as large anti-Stokes shift, narrow emission bandwidths, tunable emission wavelengths, and absence of photobleaching and photoblinking [19-22]. Importantly, the near-infrared (NIR) excitation light has a deeper tissue penetration depth than ultraviolet (UV) and visible light necessary for the excitation of organic dyes, QDs, *etc.* [23-27]. Thus, magnetic upconversion nanocomposites are regarded as one of the ideal nanoplatforms for background-free bioimaging, magnetic targeted drug delivery, imaging-guided phototherapy, *etc.*

Despite the robust application potential of the nanocomposites and the continuous growth of research interest, relevant reviews are scarce. The one published 5 years ago covered synthesis and bioapplications in multimodal imaging and magnetic targeted drug delivery [9]. In recent years the synthesis strategy has improved and application has expanded to photothermal and photo/sono-dynamic therapy, biodetection, *etc.* It is therefore very demanding to update the latest advance in this field.

This review will update relevant progress on the design principle, synthesis, surface engineering and bioapplications of magnetic upconversion nanocomposites.

2. RATIONAL DESIGN OF MAGNETIC UPCONVERSION NANOCOMPOSITES

In order to be used in biological fields, the magnetic upconversion nanocomposites must have sufficient upconversion luminescence (UCL), strong magnetism, proper size and good biocompatibility. These requirements can be fulfilled by rational structure design, developed synthesis techniques and surface engineering.

2.1. Design Principle

The combination of UCL and magnetism provides intriguing dual-functionalities, however, the interplay of these functional components has to be considered. The emission quenching effect of magnetic nanoparticles (MNPs) has been widely recognized for fluorescent dyes and QDs [1, 28-30]. Although the quenching effect of MNPs to UCL was found to be much weaker than Au, and a layer of MNPs could act as a buffer to alleviate gold-induced UCL quenching [31], the reduction of UCL intensities in the presence of MNPs has also been frequently identified [32-38]. The quenching effect is generally attributed to the broad absorption of the MNPs (extending from UV to NIR region), which can attenuate both the excitation and emission light of the upconversion component. Accordingly, the shorter wavelength emission (*e.g.*, green emission) is quenched more seriously than the longer wavelength emission (*e.g.*, red emission) [32, 36]. Besides, the close proximity of the MNPs and the UCNPs in magnetic upconversion nanocomposites is also widely regarded as a major reason for UCL quenching. As far as the quenching mechanism is concerned, nonradiative energy transfer (ET) has been taken into consideration although not distinctly pointed out in most cases [39]. The ET efficiency depends on both the spectral overlap between the absorption of the acceptor and the emission of the donor as well as the donor-acceptor distance. It becomes much less efficient when the donor-acceptor distance is enlarged, which is often used as the basis for suppressing UCL quenching in most cases. In magnetic upconversion nanocomposite systems, reabsorption and nonradiative ET are very likely to coexist, similar to our previously reported ET nanoplatforms composed of NaYF₄: Yb, Er@NaYF₄ UCNPs and a photosensitizing molecule

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rose bengal [40]. Challenor *et al.* [36] found that the thermal effect of Fe_3O_4 nanoparticles also had a significant impact on the UCL properties of solid-state NaYF_4 : Yb, Er nanoparticles, however, this phenomenon was rarely noticed by other groups. It is probably due to the different measurement conditions, such as the power density of the excitation light and the concentration of the samples.

Fig. (1). Typical structures of magnetic upconversion nanocomposites.

Until now, various structures have been designed for constructing magnetic upconversion nanocomposites. Fig. 1 provides the schematic structures of some typical ones. The first one is a typical core-shell structure with one component inside and the other component outside. The second one is the coencapsulation structure with both the magnetic and upconversion components wrapped within SiO_2 , polymer, *etc.* The third one is the Janus structure with two non-centrosymmetric hemistruces comprising the two components separately. The last one is a spacer inserted structure with the two components separated by, typically, SiO_2 . In the core-shell structure, either the magnetic or the upconversion component can be wrapped inside. However, it is preferred to coat the magnetic core with upconversion shell for the sake of UCL. In the coencapsulation structure, the magnetic and upconversion components are wrapped together. Although it is difficult to determine whether the two components are distributed uniformly or the upconversion component is in direct contact with the magnetic component, the UCL was found to be quenched significantly [35]. In the Janus structure, the magnetic and upconversion components are incorporated into two separate hemistruces, thus improving UCL by reducing light attenuation and ET efficiency. Spacer inserted structure is the most popular for the alleviation of UCL quenching. The lengthened distance between the upconversion and magnetic components facilitates the decrease in the reabsorption rate and especially ET efficiency.

As iron oxide-based MNPs can always reduce the upconversion luminescence to some extent, alternatives have also been reported recently. Chen *et al.* [41] introduced a 4-carboxyl-tetramethylpiperidine 1-oxyl (TEMPO) nitroxide radical as a contrast agent for MRI. The TEMPO radical was doped into silica, and coated onto NaYF_4 : Yb, Er@ NaYF_4 UCNPs to construct multifunctional nanoprobes for UCL/MRI dual-modal imaging. Although the UCL intensity decreased by ~65% after transferring NaYF_4 : Yb, Er@ NaYF_4 UCNPs from cyclohexane to water, which can be ascribed to H_2O solvent effect, the UCNPs@TEMPO@ SiO_2 nanocomposites exhibited similar UCL intensity compared with UCNPs@ SiO_2 . It indicates negligible quenching effect of the TEMPO radicals to UCL. Nanoscale Fe-MIL-101- NH_2 metal-organic framework (MOF) was also incorporated with NaYF_4 : Yb, Er UCNPs by Li *et al.* [42] to construct core-shell structured nanoprobes for UCL/MRI bimodal bioimaging.

Apart from efficient UCL, strong magnetism of the nanocomposites is also preferred. As the incorporation of nonmagnetic components, such as NaYF_4 -based UCNPs and SiO_2 , would reduce the magnetism significantly, magnetic nanoparticle clusters consisting of numerous MNPs were introduced to prepare magnetic upconversion nanocomposites [43-47]. The resultant nanocomposites generally possess higher magnetism (saturation magnetization $M_s > 10$ emu/g), however, the size of the nanocomposites increased dramatically (generally, larger than 200 nm). It might induce unsatisfactory colloidal stability, reticuloendothelial system clearance, *etc.* [48-51]. Zeng *et al.* [52] synthesized core-shell Fe_3O_4 @ NaYF_4 : Yb, Er nanocomposites with oleylamine (OM) capped Fe_3O_4 nanoparticles (~10 nm) acting as the seeds. The obtained Fe_3O_4 @ NaYF_4 : Yb, Er nanocomposites exhibited an average size of ~50 nm and M_s of 16.6 emu/g. However, further modification of the OM capped nanocomposites with biocompatible molecules, *e.g.* polyethylene glycol (PEG), is a prerequisite for broad bioapplications. Recently, we have designed and fabricated water-dispersible multimagnetic beads-embedded Fe_3O_4 @ NaYF_4 : Yb, Er nanocomposites [53]. The average size of the nanocomposites is ~33.8 nm, much smaller than those with magnetic nanoparticle clusters as the core. Simultaneously, the M_s of the nanocomposites is ~17.8 emu/g, higher than those following single magnetic nanoparticle embedded approach. The nanocomposites exhibited a great potential in magnetic field-assisted sensitive UCL bioimaging.

2.2. Synthesis

The magnetic upconversion nanocomposites can be synthesized by multiple methods, such as seed-mediated growth, amorphous layer-intermediated synthesis, co-encapsulation, ligand coupling, electrospinning, *etc.*

Seed-mediated growth method involves the growth of one component with its reaction precursors on the surface of the other pre-formed component [32, 48, 52, 54-61]. Xia and coworkers [32] obtained NaYF_4 : Yb, Tm@ Fe_3O_4 nanocomposites by thermolysis of $\text{Fe}(\text{acac})_3$ in the presence of oleic acid (OA) capped NaYF_4 : Yb, Tm seeds. The ~30 nm core-shell structured nanocomposites exhibited excellent water dispersibility after being modified with dopamine hydrochloride. By using OM capped Fe_3O_4 nanoparticles as the seeds, Fe_3O_4 @ NaYF_4 : Yb, Er nanocomposites with an ultra-small size of 14.5 nm were prepared via thermal decomposition of lanthanide trifluoroacetates [58]. Luo and coworkers [61] synthesized Fe_3O_4 @ Mn^{2+} -doped NaYF_4 @ Mn^{2+} -doped NaYF_4 : Yb, Er core-inert shell-active shell structured nanocomposites with OA capped Fe_3O_4 nanoparticles as the seeds. The shell was formed by the hydrothermal reaction of MnCl_2 , lanthanide nitrates and NaF in the presence of OA and appropriate solvents. Mn^{2+} doping was found to play an important role in the formation of the core-shell structure by inducing hexagonal to cubic phase transformation of NaYF_4 , which improved the lattice match degree of NaYF_4 with Fe_3O_4 . Chen *et al.* [48] transferred OA capped Fe_3O_4 nanoparticles to water phase by breaking the double bond of OA with NaIO_4 to produce carboxyl group, and deposited the precursor of upconversion nanophosphor ($\text{Gd}_2\text{O}(\text{CO}_3)_2\text{H}_2\text{O}$: Yb, Er/Tm) on the surface of Fe_3O_4 by precipitating lanthanide ions with urea. Then, negatively charged sodium alginate and positively charged polyethyleneimine (PEI) were alternatively adsorbed on the surface by electrostatic interaction to prevent aggregation during the conversion of $\text{Gd}_2\text{O}(\text{CO}_3)_2\text{H}_2\text{O}$: Yb, Er/Tm to NaGdF_4 : Yb, Er/Tm in the autoclave. The amine groups in PEI can also be used for further functionalization with PEG diacid. Except for the generally produced core-shell structured magnetic upconversion nanocomposites, dumbbell-like MnFe_2O_4 - NaYF_4 : Yb, Er Janus nanoparticles have also been fabricated recently by Wu *et al.* [60]. MnFe_2O_4 nanoparticles with a diameter of 11 nm were firstly prepared to act as the seeds, and then epitaxial growth of Yb, Er doped NaYF_4 with trifluoroacetate lanthanide precursors produced MnFe_2O_4 - NaYF_4 : Yb, Er nanocomposites. The dumbbell structure is a little bigger

(13.1±1.4 nm) than the MnFe_2O_4 core. Seed-mediated growth method is simple, straightforward and advantageous for producing nanocomposites with relatively small size, however, the lattice mismatching between the upconversion component and magnetic component brings about difficulties for the epitaxial growth process and undesired defects in the interface.

Amorphous layer-intermediated synthesis can alleviate the negative effects resulting from crystal mismatch between two components. An amorphous layer, such as SiO_2 and polymer, is introduced as the buffer to mediate the growth of the second component [44, 53, 62, 63]. SiO_2 is used most frequently due to its excellent water dispersibility, good biocompatibility, facile surface modification, favorable optical transparency, mature silanization chemistry, *etc.* [64-67] Zhu and coworkers [43] firstly coated citrate groups-capped Fe_3O_4 cores (~180 nm) with SiO_2 (thickness: ~35 nm) by Stöber method, and then precipitated a lanthanide carbonate layer ($\text{Lu, Yb, Er/Tm(OH)CO}_3$) on the surface with lanthanide chlorides and urea. After the calcination process and treatment with HF and NaF, $\text{Fe}_3\text{O}_4@\text{NaLuF}_4$: Yb, Er/Tm nanocomposites with an average size of ~330 nm were obtained. Gai *et al.* [68] prepared nonporous silica coated Fe_3O_4 ($\text{Fe}_3\text{O}_4@\text{nSiO}_2$) with Stöber method first, followed by mesoporous silica layer (average pore size: 2.2 nm) using cetyltrimethylammonium bromide (CTAB) as the organic template. Finally, NaYF_4 : Yb, Er nanocrystals were deposited on the surface of the CTAB-removed bilayer silica coated Fe_3O_4 ($\text{Fe}_3\text{O}_4@\text{nSiO}_2@\text{mSiO}_2$) using lanthanide chlorides, NaF, *etc.* Zhang and coworkers [62] transferred oleate-capped Fe_3O_4 nanocrystals (~20 nm) to water phase by SiO_2 coating by reverse microemulsion. The $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanospheres were then coated with Y/Yb, Er(OH) CO_3 , and underwent thermal treatment and ion exchange in the presence of HF and NaF. $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{NaYF}_4$: Yb, Er nanorattles with a diameter of ~115±20 nm were obtained. They are composed of a magnetic core (~20±10 nm), a silica middle layer (~10±5 nm), an intervening hollow space, and a NaYF_4 : Yb, Er shell (~20±5 nm). Zhang *et al.* [44] synthesized $\text{Fe}_3\text{O}_4@\text{LaF}_3$: Yb, Er nanocomposites with polyacrylic acid (PAA) modified Fe_3O_4 nanoparticle clusters as the core. The uncoordinated carboxyl groups of PAA not only rendered Fe_3O_4 nanoparticle clusters water dispersibility, but also anchored rare earth ions through coordination interaction. LaF_3 : Yb, Er shell was thus formed on the surface of Fe_3O_4 following co-precipitation reaction. The size of the nanocomposites could be controlled from 190 nm to 220 nm depending on the reaction time and the amount of the shell precursors. Branched PEI, a well-known polyelectrolyte with high coordinating capacity with various nanomaterials, was used to transfer OA capped Fe_3O_4 nanoparticles to polar ethylene glycol by ligand exchange and direct the growth of Yb, Er codoped NaYF_4 [53]. By carefully adjusting the relative amount of Fe_3O_4 nanoparticles, $\text{Fe}_3\text{O}_4@\text{NaYF}_4$: Yb, Er nanocomposites with multiple magnetic beads embedded were obtained.

Co-encapsulation method was also used to construct magnetic upconversion nanocomposites. Different from the seed-mediated growth approach, this method is not restricted by the crystal mismatch between these functional components. Until now, organic polymer and inorganic oxides (*e.g.*, SiO_2 and TiO_2) have been explored to encapsulate preformed MNPs and UCNPs [35, 46, 69-73]. A typical example of polymer encapsulation was presented by Xu *et al.* [69], who encapsulated hydrophobic UCNPs and MNPs with an amphiphilic block polymer, poly (styrene-block-allyl alcohol) ($\text{PS}_{16}\text{-}b\text{-PAA}_{10}$), by a microemulsion method. Fluorescent dye and an antitumor drug can be co-loaded within the nanocomposites for additional functionalities. Recently, Yu *et al.* [70] encapsulated NaYF_4 : Yb, Er UCNPs, Fe_3O_4 functionalized zirconium bis-(monohydrogen orthophosphate) monohydrate ($\alpha\text{-ZrP}$) and gentamicin sulfate (GS) with chitosan (CHI). The Fe_3O_4 nanoparticles and GS were intercalated into the interlayer of $\alpha\text{-ZrP}$, while the NaYF_4 : Yb, Er UCNPs were adsorbed on the surface of $\alpha\text{-ZrP}$. The

encapsulation with CHI not only improved the stability and biocompatibility of the layered multifunctional nanosystems, but also prolonged the drug release time. Inorganic encapsulation of MNPs and UCNPs was firstly explored by Liu *et al.* [73] with SiO_2 , where magnetic upconversion nanocomposites with NaYF_4 : Yb, Er UCNPs (~10 nm) and Fe_3O_4 nanoparticles (~16 nm) encapsulated in SiO_2 were obtained by using a simple reverse-microemulsion method. Recently, TiO_2 encapsulation was developed to construct magnetic upconversion nanocomposites [46, 71]. For example, Shen *et al.* [71] synthesized dual-core-shell ($\text{Fe}_3\text{O}_4\text{-NaYF}_4$: Yb, Er) $@\text{TiO}_2$ multifunctional nanocomposites. Trisodium citrate modified Fe_3O_4 nanoparticles (~150 nm) were firstly assembled with PEI modified NaYF_4 : Yb, Er UCNPs (~50 nm) by electrostatic attraction, and then TiO_2 was coated by the sol-gel process of hydrolysis and condensation of tetrabutyl titanate (TBOT). The TiO_2 shell not only encapsulated the MNPs and UCNPs to form stable magnetic upconversion nanocomposites, but also acted as a sonosensitizer for sonodynamic therapy of deeply located tumor.

Ligand coupling strategy incorporates MNPs and UCNPs through coordination, electrostatic attraction, covalent interaction, *etc.* [34, 45, 74-76] Surface ligands served as the bridges to link MNPs and UCNPs, eliminating the requirement of lattice matching of the two components. Shen *et al.* [77] synthesized NaYF_4 : Yb, Er/ Fe_3O_4 hetero-NPs using coordination-based coupling method. 1,10-decanedicarboxylic acid (DDA) or 11-mercaptoundecanoic acid (MUA) firstly inserted into the OA ligand on the surface of as-prepared NaYF_4 : Yb, Er UCNPs by ligand exchange. Then the overhanging coordinative groups of DDA or MUA on UCNPs captured Fe_3O_4 nanoparticles by multivalent binding-like coordination interaction. Multiple Fe_3O_4 nanoparticles were anchored onto the surface of NaYF_4 : Yb, Er UCNPs. Cheng *et al.* [31] adsorbed dopamine (DA) modified MNPs (~5 nm) onto the surface of PAA modified NaYF_4 : Yb, Er UCNPs (~160 nm) by electrostatic interaction, and then coated the UCNP-MNP complex by a thin gold shell. The multifunctional nanocomposites can be used for multimodal imaging, therapies, cell isolation and detection [18, 31, 78, 79]. Zhao *et al.* [45] coupled amino-modified $\text{Fe}_3\text{O}_4@\text{SiO}_2$ and carboxyl-modified NaYF_4 : Yb, Er by covalent interaction under the assistance of crosslinking agents N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) and N-hydroxy-succinimide (NHS). After further modification with MnO_2 nanosheets, the nanocomposites could act as bioimaging agents and magnetic targeted drug carriers.

Electrospinning is a versatile and straightforward technique to construct one-dimensional micro-/nanostructures. It has been used by Dong's group to prepare magnetic upconversion multifunctional nanofibers and nanoribbons with various structures in the past few years [80-83]. $\text{Fe}_3\text{O}_4/\text{NaYF}_4$: Yb, Er/polyvinylpyrrolidone (PVP) composite nanofibers were obtained when mixing Fe_3O_4 nanoparticles and NaYF_4 : Yb, Er UCNPs together with PVP to prepare the electrospinning solution [80]. To improve UCL, nanostructures with UCNPs isolated from Fe_3O_4 nanoparticles were also developed. By using an electrospinning setup equipped with a homemade coaxial dual-spinneret, core-shell nanofibers with $\text{Fe}_3\text{O}_4/\text{PVP}$ as the core and NaYF_4 : Yb, Er/PVP as the shell were fabricated, where the electrospinning solutions containing Fe_3O_4 or NaYF_4 : Yb, Er were prepared separately and injected into coaxial inner and outer plastic syringes, respectively [80]. When the electrospinning solutions containing Fe_3O_4 or NaYF_4 : Yb, Er were loaded into two separate syringes, and ejected from specially designed spinnerets simultaneously, Janus nanofibers and nanoribbons with Fe_3O_4 and NaYF_4 : Yb, Er distributed in two half sides were obtained [81, 82]. Recently, quadrifunctional [polyaniline (PANI)/ Fe_3O_4 /polyacrylonitrile (PAN)]/ $[\text{Bi}_2\text{WO}_6\text{:Yb, Er/PAN}]$ bilayered composite fibrous membrane with electricity-magnetism at one layer and UCL-photo-catalysis at the other layer were prepared [83]. It was realized

by using a layer-by-layer electrospinning process, *i.e.*, ejecting one electrospinning solution after the other one was completely consumed. The electrospinning method is simple, however, the large size of the obtained one-dimensional nanocomposites has hindered their practical applications in biomedical fields.

Due to the extraordinary physical and chemical properties of graphene, Yan *et al.* [84] fabricated a new class of multifunctional nanocomposites by incorporating brittle Fe_3O_4 nanocrystals (~200 nm) and NaYF_4 : Yb, Er UCNP (s) (~50 nm) within graphene oxide (GO) matrix. The nacre-like structured nanocomposites were obtained by co-assembly of positively charged nanocrystals with negatively charged GO nanosheets and subsequent vacuum filtration. The ~23 μm -thick graphene nanocomposite films exhibited favorable UCL and magnetism as well as enhanced mechanical properties. By adsorbing Fe^{3+} in $\text{Fe}(\text{acac})_3$ and Zn^{2+} in $\text{Zn}(\text{acac})_2$ onto negatively charged GO nanosheets by an electrostatic force after the hydrothermal process, $\text{GO@ZnFe}_2\text{O}_4$ was prepared [85]. Nitrosonium tetrafluoroborate (NOBF_4) modified NaGdF_4 : Yb, Tm UCNP (s) were further anchored by physical adsorption. Ultrasmall ZnFe_2O_4 nanoparticles (3-5 nm) and monodisperse UCNP (s) (less than 10 nm) were found to be loaded successfully on GO nanosheets.

Recently, Engel *et al.* [17] developed a modular system for constructing stimuli-responsive multifunctional nanoparticle aggregates using supramolecular host-guest chemistry. UCNP (s), MNPs and Au nanoparticles were firstly modified with β -cyclodextrin (β -CD, the host), and then divalent guest molecule, arylazopyrazole (E-AAP), was used to interconnect these nanoparticles by entering the immobilized β -CD to form aggregates. After (NIR converted-) UV light irradiation, E-AAP can be isomerized to Z-AAP, which does not fit into β -CD cavities. The nanoparticles were thus redispersed. Reversibly, the Z-isomer of AAP can be converted to E-isomer under green light irradiation, which renders dynamic and reversible self-assembly of these nanoparticles. The size, shape and properties of the multifunctional nanoparticle aggregates can be adjusted by varying the nanoparticle ratio, the AAP linker concentration, the irradiation time of green light, *etc.*

In order to provide guidance for researchers to choose suitable synthesis method of magnetic upconversion nanocomposites towards their bioapplications, we have summarized some important features, *e.g.*, size, Ms and dispersibility, of magnetic upconversion nanocomposites obtained by various methods in the literature. UCL intensity is not listed due to its dependency on specific measurement conditions.

2.3. Surface Engineering

In order to apply the magnetic upconversion nanocomposites in biological and biomedical fields, good aqueous dispersibility and biocompatibility are always required. To this end, surface modification with SiO_2 , poly(allylamine) (PAAm), ozone, and particularly, poly(ethylene glycol) (PEG) and its derivatives, have been adopted. SiO_2 can not only act as a buffer or a glue to incorporate IONPs with UCNP (s), but also render magnetic upconversion nanocomposites biocompatible and easily functionalized with various biomolecules [87]. PAAm was used by Wu *et al.* [60] to endow OM capped MnFe_2O_4 - NaYF_4 : Yb, Er Janus nanoparticles with hydrophilicity by ligand exchange, and the amino group of PAAm was further used for covalent conjugation with folic acid (FA). Shen *et al.* [77] used ligand ozonolysis treatment to transfer hydrophobic NaYF_4 : Yb, Er@ Fe_3O_4 nanocomposites to water phase by producing carboxyl groups from broken double bonds of OA ligands. As a popular class of polymer in biological applications, PEG and its numerous derivatives have not only been widely applied to improve the solubility and biocompatibility of the hydrophilic magnetic upconversion nanocomposites [34, 42, 75, 85], but also been designed to transfer the hydrophobic magnetic upconversion nanocomposites to water phase [52, 57, 59, 61]. For example, Cui *et al.*

[57] prepared OM capped $\text{Co}_{0.16}\text{Fe}_{2.84}\text{O}_4$ @ NaYF_4 : Yb, Tm and Fe_3O_4 @ NaYF_4 : Yb, Er nanocomposites by a two-step thermolysis method, and then transferred them to water phase by ligand exchange with bisphosphonate polyethylene glycol conjugates (BP-PEG). The PEGylation could stabilize the nanocomposites against aggregation in aqueous solution and also affect the circulation time and reticuloendothelial clearance of the nanocomposites.

3. BIOAPPLICATIONS OF MAGNETIC UPCONVERSION NANOCOMPOSITES

Compared with organic dyes and QDs, lanthanide-doped UCNP (s) are particularly attractive in bioimaging due to the resistance of photobleaching and background autofluorescence interference and the deep tissue penetration depth of the NIR excitation light [88, 89]. The incorporation of MNPs brings in additional functionalities, *e.g.*, MRI and magnetic targeted drug delivery. Some new therapeutic techniques, such as photodynamic therapy (PDT) and photothermal therapy (PTT), have also been explored with magnetic upconversion nanocomposites. With the multifunctional nanocomposites as luminescent tags, biodetection can also be realized. Importantly, these applications can be combined into one single nanopatform, for example, imaging-guided drug delivery and therapies. In this section, we will review the applications of magnetic upconversion nanocomposites in bioimaging, drug delivery, therapies and biodetection. To get an insight of researchers' interest in these bioapplications of magnetic upconversion nanocomposites, we scanned over 60 publications on magnetic upconversion nanocomposites from 2004 to estimate the proportions of these applications (Fig. 2). It can be seen clearly that bioimaging gets the most attention, drug delivery and therapies hold similar percentages, while biodetection is paid relatively less attention than the others.

Fig. (2). The proportion of different bioapplications of magnetic upconversion nanocomposites from literature published since 2004.

3.1. Bioimaging

Bioimaging is the most popular application of magnetic upconversion nanocomposites due to the intriguing UCL properties and MRI capability [32, 42-44, 48, 57]. Chen *et al.* [48] incubated MCF-7 breast cancer cells with PEGylated Fe_3O_4 @ NaGdF_4 : Yb, Er nanocomposites, and observed bright UCL under 980 nm excitation. When they injected Fe_3O_4 @ NaGdF_4 : Yb, Tm nanocomposites into the chicken breast at 1 cm depth, background-free deep tissue UCL imaging was realized. The nanocomposites could also act as T_1 - and T_2 -weighted MRI contrast agents due to the presence of Fe_3O_4 core and NaGdF_4 shell. Xia *et al.* [32] injected NaYF_4 : Yb, Tm@ Fe_3O_4 nanocomposites into the right forepaw of a nude mouse, and realized T_2 -weighted MRI and NIR-to-NIR UCL dual-modal imaging of the lymphatic system *in vivo*. MRI, UCL and computed tomography (CT) tri-modal imaging of tumor-bearing mice have also been achieved by using multifunctional nanocomposites composed of Fe_3O_4 and Yb, Er/Tm doped NaLuF_4 [43]. With

Table 1. The properties of magnetic upconversion nanocomposites prepared with various methods according to the literature.

Synthesis Method	Material	Size/nm	Ms/emu·g ⁻¹	Water Dispersibility	Refs.
Seed-mediated synthesis	Fe ₃ O ₄ @NaGdF ₄ :Yb, Er@NaGdF ₄ : Yb, Er	~32	1.1	No	[56]
Seed-mediated synthesis	Fe ₃ O ₄ @NaYF ₄ : Yb, Er	~50	16.60	No	[52]
Seed-mediated synthesis	Fe ₃ O ₄ @NaYF ₄ : Yb, Er/Tm	65/68	7.0	Yes	[48]
Seed-mediated synthesis	Fe ₃ O ₄ @NaYF ₄ : Yb, Er	~14.5	8.45	No	[58]
Seed-mediated synthesis	Fe ₃ O ₄ @NaYF ₄ : Yb, Er, Mn ²⁺	24-36	6.2	No	[59]
Seed-mediated synthesis	Fe ₃ O ₄ @NaYF ₄ : Mn ²⁺ @NaYF ₄ : Yb, Er, Mn ²⁺	~20	3.85	No	[61]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @nSiO ₂ @mSiO ₂ @NaYF ₄ : Yb, Er/Tm	~80	38.0	Yes	[68]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @SiO ₂ @Y ₂ O ₃ :Yb, Er	75.63±3.77	7.22	Yes	[39]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @SiO ₂ @NaLuF ₄ : Yb, Er/Tm	~330	15	Yes	[43]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @SiO ₂ @NaYF ₄ : Yb, Er	~115±20	1.28	Yes	[62]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @PAA@LaF ₃ : Yb, Er	190-220	20-29	Yes	[44]
Amorphous layer-intermediated synthesis	Fe ₃ O ₄ @PEI@NaYF ₄ : Yb, Er	~33.8	17.8	Yes	[53]
Co-encapsulation method	Fe ₃ O ₄ -NaYF ₄ : Yb, Er@SiO ₂	~ 60	1.64	Yes	[73]
Co-encapsulation method	NaYF ₄ :Yb, Er/Tm-Fe ₃ O ₄ @SiO ₂	~150	5.6	Yes	[86]
Co-encapsulation method	Fe ₃ O ₄ -NaYF ₄ : Yb, Tm@TiO ₂	~310	12.23	-	[46]
Co-encapsulation method	NaYF ₄ : Yb, Er-IONP@PS _{16-b} -PAA ₁₀	~250	~40	Yes	[69]
Co-encapsulation method	NaYF ₄ : Yb, Er-α-ZrP/Fe ₃ O ₄ /GS@CHI	~1700×625 (diameter×thickness)	2.1	Yes	[70]
Ligand coupling strategy	NaYF ₄ : Yb, Er@Fe ₃ O ₄	~250/140	9.25/7.05	No	[77]
Ligand coupling strategy	NaYF ₄ : Yb, Er@SiO ₂ @Fe ₃ O ₄	100-150	2.85	Yes	[74]
Ligand coupling strategy	NaYF ₄ : Yb, Er@Fe ₃ O ₄	~170	~45	Yes	[31]
Ligand coupling strategy	NaGdF ₄ : Yb, Tm@NaGdF ₄ : Yb@ ZnFe ₂ O ₄	~100	~1.4	Yes	[8]
Ligand coupling strategy	NaYF ₄ : Yb, Er@mSiO ₂ @Fe ₃ O ₄	~70-100	~2.7	Yes	[34]
Electrospinning	[Fe ₃ O ₄ /PVP]@[NaYF ₄ : Yb, Er/PVP] nanofiber	~260 (diameter)	~30	No	[80]
Electrospinning	[Fe ₃ O ₄ /PMMA]@[NaYF ₄ : Yb, Er/PMMA] nanoribbon	~10000×1000 (width×thickness)	~30	No	[82]

¹⁸F-labeled Fe₃O₄@NaYF₄:Yb, Tm or Co_{0.16}Fe_{2.84}O₄@NaYF₄: Yb, Er providing magnetic, upconversion luminescent and radionuclide capabilities, MRI, UCL and positron emission tomography (PET) tri-modal imaging was realized by Cui *et al.* [57] Single photon emission computed tomography (SPECT) could also be incorporated by introducing ⁶⁴Cu or ^{99m}Tc.

3.2. Drug Delivery

Magnetic upconversion nanocomposites are promising for drug delivery due to their magnetic manipulation capacity [45, 63, 68-71,

90]. Gai *et al.* [68] loaded ibuprofen (IBU) into mesoporous Fe₃O₄@nSiO₂@mSiO₂@NaYF₄: Yb, Er/Tm nanocomposites, and studied the IBU release process in simulated body fluid (SBF). It was found that amino modification of the nanocomposites could delay the release of IBU markedly, and the UCL intensity increased with the increasingly released amount of the drug. Zhao *et al.* [45] loaded Congo red, a model anionic drug, onto MnO₂ nanosheet-modified Fe₃O₄@SiO₂@NaYF₄: Yb, Er by electrostatic interaction. The MnO₂ nanosheets served as not only drug carriers, but also UCL quenchers. The drug can be released by glutathione (GSH)

induced reduction reaction of MnO_2 . Simultaneously, increased UCL intensity can be used for monitoring GSH levels. Peng *et al.* [90] loaded etoposide (VP16) on glycine-functionalized $\text{Fe}_3\text{O}_4@\text{TiO}_2$: Yb, Er nanocomposites through hydrogen bonding. The release of the drug could be triggered by microwave induced local heating. The drug loading and release mechanisms were also studied by using microcalorimetry. *In vivo* studies with magnetic upconversion nanocomposites as drug carriers have also been explored by several groups [34, 62, 71]. Zhang *et al.* [62] loaded anti-tumor drug doxorubicin (DOX) into the interior hollow space of $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{NaYF}_4$: Yb, Er nanorattles by using the mesoporous shell as the gateway to the loading cavity. After injecting the DOX-loaded nanorattles to the tail veins of tumor-bearing nude mice, magnetic targeting enhanced accumulation of the nanocarrier in tumors was demonstrated by stronger UCL compared with nontargeted cases (enhanced permeability and retention (EPR) effect induced accumulation). Accordingly, the enhanced therapeutic efficacy was observed for targeted delivered nanocarriers after pH-sensitive DOX release in the cancerous tissues. With hyaluronic acid (HA) modified $\text{Fe}_3\text{O}_4\text{-NaYF}_4$: Yb, Er@ TiO_2 nanocomposites as drug carriers for DOX, synergetic chemotherapy and sonodynamic therapy (sonosensitizer: TiO_2) effect was also observed in tumor-bearing mice by Shen *et al.* [71]

3.3. Therapies

Rather than just drug carriers, the magnetic upconversion nanocomposites can also contribute to therapy directly. For instance, it is popular to use the NIR-excitable upconversion component as UV-vis source to trigger PDT or PTT efficacy. Until now, therapy has held a large proportion in the applications of magnetic upconversion nanocomposites, and multiple therapeutic modalities have been explored, such as PDT, PTT, stem cell therapy, and Fenton reaction induced therapy [8, 31, 72, 75, 79, 91]. Zeng *et al.* [91] loaded FA-functionalized $\text{Fe}_3\text{O}_4@\text{NaYF}_4$: Yb, Er with photosensitizer (tetrasulfonic phthalocyanine aluminium), and realized FA-targeted MRI and visualized PDT with tumor-bearing nude mice under NIR irradiation. UCL, MRI, photoacoustic tomography (PAT) multimodal imaging-guided photothermal ablation of the tumor were also demonstrated with HA and Prussian blue nanoparticles decorated NaYF_4 : Yb, Er@ $\text{SiO}_2@\text{Fe}_3\text{O}_4$ nanocomposites [75]. Both magnetic field and HA contributed to the targeting process of the multifunctional nanocomposites to the tumor. Cheng *et al.* [79] labeled mouse mesenchymal stem cells (mMSCs) with PEGylated NaYF_4 : Yb, Er@ $\text{Fe}_3\text{O}_4@\text{Au}$ nanocomposites, and then tracked the labeled mMSCs by UCL and MRI after injecting them into wound-bearing mice with a magnet placed nearby the wound site. Remarkable stem cell therapeutic efficacy was observed in the wound site resulting from magnetically induced translocation of the labeled stem cells. Bi *et al.* [8] used platinum (IV) prodrugs (Pt(IV)) as a bridge for coupling NaGdF_4 : Yb, Tm@ NaGdF_4 : Yb UCNPs and ZnFe_2O_4 MNPs. Multimodal imaging (UCL, CT, MRI and PAT) guided synergetic therapy (chemotherapy, PDT and Fenton reaction) was demonstrated. The reduction of the Pt(IV) prodrugs to high virulent Pt(II) by glutathione after entering the cancer cells could reduce the side effects of cisplatin such as cytotoxicity and drug resistance.

3.4. Biodetection

The application of magnetic upconversion nanocomposites in biodetection has also been explored in the past few years [18, 92, 93]. The unique UCL properties under NIR excitation endow the biodetection with high sensitivity, and the magnetism facilitates the separation and purification processes greatly. Zhang *et al.* [92] incorporated UCNPs and MNPs into polystyrene microspheres, and then modified the multifunctional microspheres with rabbit-anti-mouse antibodies for sandwich-structured immunoassay. The coded signal of UCNPs can only be excited under NIR excitation, while the reporter signal of fluorescein labeling rabbit-anti-mouse antibodies can only be excited with blue light. It avoids optical interfer-

ence between the coded and reporter signals, in stark contrast with microspheres encoded with QDs or organic dyes. This unique advantage allowed for detection of mouse IgG with the detection limit of 0.01 ng/mL. Benefiting from tunable and narrow emission bands of UCNPs, double-antibody sandwich immunoassay was also realized.

Wang *et al.* [18] developed a sensitive and convenient method for simultaneous isolation and detection of circulating tumor cells (CTCs) by using multifunctional magnetic upconversion nanocomposites. Anti-EpCAM antibody-functionalized NaYF_4 : Yb, Er@ $\text{Fe}_3\text{O}_4@\text{Au}$ nanocomposites were used to specifically recognize the tumor cells in the sample solution flowing through a microfluidic device containing silicon nanowire (SiNW) arrays. The cancer cells were then captured by a magnet placed right below the microfluidic chamber. The magnetic field induced capture of CTCs on microfluidic SiNW array not only exhibited high capture efficiency (~90%), but also allowed for the convenient release of the captured CTCs for further analysis and re-culturing. Due to the autofluorescence-free nature of UCL imaging, highly sensitive detection of small numbers of CTCs could be achieved. This detection technique was also used for real clinical samples, and obtained consistent results with clinical outcomes for lung cancer patients.

CONCLUSION

This review has discussed the design principle of magnetic upconversion nanocomposites, and updated their recent advances in the synthesis, surface modification and bioapplications. Despite the great progress over the past decade, some key issues remain to be addressed. For example, the exact effect mechanism of MNPs on UCL should be clarified so as to provide guidance for enhancing the UCL intensity efficiently. It is still challenging to prepare monodisperse magnetic upconversion nanocomposites with efficient UCL, strong magnetism, readily controllable size and excellent aqueous dispersibility. On top of that, the uniformity of relevant properties of every nanocomposite deserves more attention and study.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was supported by the Netherlands Organization for Scientific Research in the framework of the Fund New Chemical Innovation under grant nr. 731.015.206, EU H2020-MSCA-ITN-ETN Action program, ISPIC, under grant nr. 675743, EU H2020-MSCA-RISE Action program, CANCER, under grant nr. 777682, the National Natural Science Foundation of China (Grant No. 11604043), Thirteenth Five-Year Science and Technology Research Project of Education Department of Jilin Province (No. JJKH20170910KJ), Open Project of Key Laboratory for UV-Emitting Materials and Technology of Ministry of Education (130028853), China Postdoctoral Science Foundation (No. 2017M611294), and the 111 project (No. B13013).

REFERENCES

- [1] Corr SA, Rakovich YP, Gun'ko YK. Multifunctional magnetic-fluorescent nanocomposites for biomedical applications. *Nanoscale Res Lett* 2008; 3: 87-104. [<http://dx.doi.org/10.1007/s11671-008-9122-8>]
- [2] Veisheh O, Sun C, Gunn J, *et al.* Optical and MRI multifunctional nanoprobe for targeting gliomas. *Nano Lett* 2005; 5(6): 1003-8.

- [http://dx.doi.org/10.1021/nl0502569] [PMID: 15943433]
- [3] Sahoo Y, Goodarzi A, Swihart MT, *et al.* Aqueous ferrofluid of magnetite nanoparticles: Fluorescence labeling and magnetophoretic control. *J Phys Chem B* 2005; 109(9): 3879-85. [http://dx.doi.org/10.1021/jp045402y] [PMID: 16851439]
- [4] Pittet MJ, Swirski FK, Reynolds F, Josephson L, Weissleder R. Labeling of immune cells for in vivo imaging using magnetofluorescent nanoparticles. *Nat Protoc* 2006; 1(1): 73-9. [http://dx.doi.org/10.1038/nprot.2006.11] [PMID: 17406214]
- [5] Quarta A, Di Corato R, Manna L, *et al.* Multifunctional nanostructures based on inorganic nanoparticles and oligothiophenes and their exploitation for cellular studies. *J Am Chem Soc* 2008; 130(32): 10545-55. [http://dx.doi.org/10.1021/ja800102v] [PMID: 18627147]
- [6] Yao X, Niu X, Ma K, *et al.* Graphene quantum dots-capped magnetic mesoporous silica nanoparticles as a multifunctional platform for controlled drug delivery, magnetic hyperthermia, and photothermal therapy. *Small* 2017; 13(2): 1602225. [http://dx.doi.org/10.1002/smll.201602225] [PMID: 27735129]
- [7] Zhu T, Ma X, Chen R, *et al.* Using fluorescently-labeled magnetic nanocomposites as a dual contrast agent for optical and magnetic resonance imaging. *Biomater Sci* 2017; 5(6): 1090-100. [http://dx.doi.org/10.1039/C7BM00031F] [PMID: 28425537]
- [8] Bi H, Dai Y, Yang P, *et al.* Glutathione mediated size-tunable UCNPs-Pt(IV)-ZnFe₂O₄ nanocomposite for multiple bioimaging guided synergetic therapy. *Small* 2018; 14(13): 1703809. [http://dx.doi.org/10.1002/smll.201703809]
- [9] Li X, Zhao D, Zhang F. Multifunctional upconversion-magnetic hybrid nanostructured materials: synthesis and bioapplications. *Theranostics* 2013; 3(5): 292-305. [http://dx.doi.org/10.7150/thno.5289] [PMID: 23650477]
- [10] Bigall NC, Parak WJ, Dorfs D. Fluorescent, magnetic and plasmonic-hybrid multifunctional colloidal nano objects. *Nano Today* 2012; 7(4): 282-96. [http://dx.doi.org/10.1016/j.nantod.2012.06.007]
- [11] Lee JE, Lee N, Kim H, *et al.* Uniform mesoporous dye-doped silica nanoparticles decorated with multiple magnetite nanocrystals for simultaneous enhanced magnetic resonance imaging, fluorescence imaging, and drug delivery. *J Am Chem Soc* 2010; 132(2): 552-7. [http://dx.doi.org/10.1021/ja905793q] [PMID: 20017538]
- [12] Wang D, He J, Rosenzweig N, Rosenzweig Z. Superparamagnetic Fe₂O₃ beads-CdSe/ZnS quantum dots core-shell nanocomposite particles for cell separation. *Nano Lett* 2004; 4(3): 409-13. [http://dx.doi.org/10.1021/nl035010n]
- [13] Ma Q, Nakane Y, Mori Y, *et al.* Multilayered, core/shell nanoprobe based on magnetic ferric oxide particles and quantum dots for multimodality imaging of breast cancer tumors. *Biomaterials* 2012; 33(33): 8486-94. [http://dx.doi.org/10.1016/j.biomaterials.2012.07.051] [PMID: 22906608]
- [14] Bertorelle F, Wilhelm C, Roger J, Gazeau F, Ménager C, Cabuil V. Fluorescence-modified superparamagnetic nanoparticles: intracellular uptake and use in cellular imaging. *Langmuir* 2006; 22(12): 5385-91. [http://dx.doi.org/10.1021/la052710u] [PMID: 16732667]
- [15] Zhang M, Shi S, Meng J, *et al.* Preparation and characterization of near-infrared luminescent bifunctional core/shell nanocomposites. *J Phys Chem C* 2008; 112(8): 2825-30. [http://dx.doi.org/10.1021/jp076079c]
- [16] Zhang Y, Pan S, Teng X, Luo Y, Li G. Bifunctional magnetic-luminescent nanocomposites: Y₂O₃/Tb nanorods on the surface of iron oxide/silica core-shell nanostructures. *J Phys Chem C* 2008; 112(26): 9623-6. [http://dx.doi.org/10.1021/jp8015326]
- [17] Engel S, Möller N, Stricker L, Peterlechner M, Ravoo BJ. A modular system for the design of stimuli-responsive multifunctional nanoparticle aggregates by use of host-guest chemistry. *Small* 2018; 14(16): e1704287. [http://dx.doi.org/10.1002/smll.201704287] [PMID: 29573341]
- [18] Wang C, Ye M, Cheng L, *et al.* Simultaneous isolation and detection of circulating tumor cells with a microfluidic silicon-nanowire-array integrated with magnetic upconversion nanoprobe. *Biomaterials* 2015; 54: 55-62. [http://dx.doi.org/10.1016/j.biomaterials.2015.03.004] [PMID: 25907039]
- [19] Zhou B, Shi B, Jin D, Liu X. Controlling upconversion nanocrystals for emerging applications. *Nat Nanotechnol* 2015; 10(11): 924-36. [http://dx.doi.org/10.1038/nnano.2015.251] [PMID: 26530022]
- [20] Gnach A, Bednarkiewicz A. Lanthanide-doped up-converting nanoparticles: merits and challenges. *Nano Today* 2012; 7(6): 532-63. [http://dx.doi.org/10.1016/j.nantod.2012.10.006]
- [21] Mader HS, Kele P, Saleh SM, Wolfbeis OS. Upconverting luminescent nanoparticles for use in bioconjugation and bioimaging. *Curr Opin Chem Biol* 2010; 14(5): 582-96. [http://dx.doi.org/10.1016/j.cbpa.2010.08.014] [PMID: 20829098]
- [22] Park YI, Lee KT, Suh YD, Hyeon T. Upconverting nanoparticles: a versatile platform for wide-field two-photon microscopy and multimodal in vivo imaging. *Chem Soc Rev* 2015; 44(6): 1302-17. [http://dx.doi.org/10.1039/C4CS00173G] [PMID: 25042637]
- [23] Li F, Du Y, Liu J, *et al.* Responsive assembly of upconversion nanoparticles for pH-activated and near-infrared-triggered photodynamic therapy of deep tumors. *Adv Mater* 2018; 30(35): e1802808. [http://dx.doi.org/10.1002/adma.201802808] [PMID: 29999559]
- [24] Chen S, Weitemier AZ, Zeng X, *et al.* Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics. *Science* 2018; 359(6376): 679-84. [http://dx.doi.org/10.1126/science.aag1144] [PMID: 29439241]
- [25] Jayakumar MKG, Idris NM, Zhang Y. Remote activation of biomolecules in deep tissues using near-infrared-to-UV upconversion nanotransducers. *Proc Natl Acad Sci USA* 2012; 109(22): 8483-8. [http://dx.doi.org/10.1073/pnas.1114551109] [PMID: 22582171]
- [26] Wang C, Tao H, Cheng L, Liu Z. Near-infrared light induced in vivo photodynamic therapy of cancer based on upconversion nanoparticles. *Biomaterials* 2011; 32(26): 6145-54. [http://dx.doi.org/10.1016/j.biomaterials.2011.05.007] [PMID: 21616529]
- [27] Idris NM, Gnanasammandhan MK, Zhang J, Ho PC, Mahendran R, Zhang Y. In vivo photodynamic therapy using upconversion nanoparticles as remote-controlled nanotransducers. *Nat Med* 2012; 18(10): 1580-5. [http://dx.doi.org/10.1038/nm.2933] [PMID: 22983397]
- [28] Roychowdhury A, Pati SP, Kumar S, Das D. Effects of magnetite nanoparticles on optical properties of zinc sulfide in fluorescent-magnetic Fe₃O₄/ZnS nanocomposites. *Powder Technol* 2014; 254: 583-90. [http://dx.doi.org/10.1016/j.powtec.2014.01.076]
- [29] Hong X, Li J, Wang M, *et al.* Fabrication of magnetic luminescent nanocomposites by a layer-by-layer self-assembly approach. *Chem Mater* 2004; 16(21): 4022-7. [http://dx.doi.org/10.1021/cm049422o]
- [30] Mandal SK, Lequeux N, Rotenberg B, *et al.* Encapsulation of magnetic and fluorescent nanoparticles in emulsion droplets. *Langmuir* 2005; 21(9): 4175-9. [http://dx.doi.org/10.1021/la047025m] [PMID: 15835991]
- [31] Cheng L, Yang K, Li Y, *et al.* Facile preparation of multifunctional upconversion nanoprobe for multimodal imaging and dual-targeted photothermal therapy. *Angew Chem Int Ed Engl* 2011; 50(32): 7385-90. [http://dx.doi.org/10.1002/anie.201101447] [PMID: 21714049]
- [32] Xia A, Gao Y, Zhou J, *et al.* Core-shell NaYF₄:Yb³⁺,Tm³⁺@FexOy nanocrystals for dual-modality T₂-enhanced magnetic resonance and NIR-to-NIR upconversion luminescent imaging of small-animal lymphatic node. *Biomaterials* 2011; 32(29): 7200-8. [http://dx.doi.org/10.1016/j.biomaterials.2011.05.094] [PMID: 21742376]
- [33] Shrivastava N, Rocha U, Muraca D, *et al.* Magnetic upconverting fluorescent NaGdF₄:Ln³⁺ and iron-oxide@NaGdF₄:Ln³⁺ nanoparticles. *AIP Adv* 2018; 8: 056710. [http://dx.doi.org/10.1063/1.5007748]
- [34] Liu B, Li C, Ma P, *et al.* Multifunctional NaYF₄:Yb,Er@mSiO₂@Fe₃O₄-PEG nanoparticles for UCL/MR bioimaging and magnetically targeted drug delivery. *Nanoscale* 2015; 7(5): 1839-48. [http://dx.doi.org/10.1039/C4NR05342G] [PMID: 25521795]
- [35] Challenor M, Gong P, Lorensen D, *et al.* The influence of NaYF₄:Yb,Er size/phase on the multimodality of co-encapsulated magnetic photon-upconverting polymeric nanoparticles. *Dalton Trans* 2014; 43(44): 16780-7.

- [36] Challenor M, Gong P, Lorensen D, *et al.* Iron oxide-induced thermal effects on solid-state upconversion emissions in NaYF₄:Yb,Er nanocrystals. *ACS Appl Mater Interfaces* 2013; 5(16): 7875-80. [http://dx.doi.org/10.1021/am401837h] [PMID: 23855820]
- [37] Chen F, Zhang S, Bu W, *et al.* A "neck-formation" strategy for an antikenning magnetic/upconversion fluorescent bimodal cancer probe. *Chem Eur J* 2010; 16(37): 11254-60. [http://dx.doi.org/10.1002/chem.201000525] [PMID: 20715197]
- [38] Jing P, Wang Q, Liu B, *et al.* Controlled fabrication of bifunctional Fe₃O₄@SiO₂@Gd₂O₃:Yb,Er nanoparticles and their magnetic, up-conversion luminescent properties. *RSC Advances* 2014; 4: 44575-82. [http://dx.doi.org/10.1039/C4RA06146B]
- [39] Yu X, Shan Y, Li G, Chen K. Synthesis and characterization of bifunctional magnetic-optical Fe₃O₄@SiO₂@Y₂O₃: Yb³⁺, Er³⁺ near-infrared-to-visible up-conversion nanoparticles. *J Mater Chem* 2011; 21: 8104-9. [http://dx.doi.org/10.1039/c1jm10622h]
- [40] Ding Y, Wu F, Zhang Y, *et al.* Interplay between static and dynamic energy transfer in biofunctional upconversion nanoplateforms. *J Phys Chem Lett* 2015; 6(13): 2518-23. [http://dx.doi.org/10.1021/acs.jpclett.5b00999] [PMID: 26266728]
- [41] Chen C, Kang N, Xu T, Wang D, Ren L, Guo X. Core-shell hybrid upconversion nanoparticles carrying stable nitroxide radicals as potential multifunctional nanoprobe for upconversion luminescence and magnetic resonance dual-modality imaging. *Nanoscale* 2015; 7(12): 5249-61. [http://dx.doi.org/10.1039/C4NR07591A] [PMID: 25716884]
- [42] Li Y, Tang J, He L, *et al.* Core-shell upconversion nanoparticle@metal-organic framework nanoprobe for luminescent/magnetic dual-mode targeted imaging. *Adv Mater* 2015; 27(27): 4075-80. [http://dx.doi.org/10.1002/adma.201501779] [PMID: 26053933]
- [43] Zhu X, Zhou J, Chen M, Shi M, Feng W, Li F. Core-shell Fe₃O₄@NaLuF₄:Yb,Er/Tm nanostructure for MRI, CT and upconversion luminescence tri-modality imaging. *Biomaterials* 2012; 33(18): 4618-27. [http://dx.doi.org/10.1016/j.biomaterials.2012.03.007] [PMID: 22444645]
- [44] Zhang L, Wang YS, Yang Y, *et al.* Magnetic/upconversion luminescent mesoparticles of Fe₃O₄@LaF₃:Yb³⁺, Er³⁺ for dual-modal bioimaging. *Chem Commun (Camb)* 2012; 48(91): 11238-40. [http://dx.doi.org/10.1039/c2cc36059d] [PMID: 23059635]
- [45] Zhao P, Zhu Y, Yang X, *et al.* Multifunctional MnO₂ nanosheet-modified Fe₃O₄@SiO₂/NaYF₄:Yb, Er nanocomposites as novel drug carriers. *Dalton Trans* 2014; 43(2): 451-7. [http://dx.doi.org/10.1039/C3DT52066H] [PMID: 24065169]
- [46] Lv Y, Yue L, Li Q, *et al.* Recyclable (Fe₃O₄-NaYF₄:Yb,Tm)@TiO₂ nanocomposites with near-infrared enhanced photocatalytic activity. *Dalton Trans* 2018; 47(5): 1666-73. [http://dx.doi.org/10.1039/C7DT04279E] [PMID: 29327753]
- [47] Liu Z, Sun L, Li F, *et al.* One-pot self-assembly of multifunctional mesoporous nanoprobe with magnetic nanoparticles and hydrophobic upconversion nanocrystals. *J Mater Chem* 2011; 21: 17615-8. [http://dx.doi.org/10.1039/c1jm13871e]
- [48] Chen H, Qi B, Moore T, *et al.* Synthesis of brightly PEGylated luminescent magnetic upconversion nanophosphors for deep tissue and dual MRI imaging. *Small* 2014; 10(1): 160-8. [http://dx.doi.org/10.1002/smll.201300828] [PMID: 23828629]
- [49] Zhang G, Yang Z, Lu W, *et al.* Influence of anchoring ligands and particle size on the colloidal stability and *in vivo* biodistribution of polyethylene glycol-coated gold nanoparticles in tumor-xenografted mice. *Biomaterials* 2009; 30(10): 1928-36. [http://dx.doi.org/10.1016/j.biomaterials.2008.12.038] [PMID: 19131103]
- [50] Duan X, Li Y. Physicochemical characteristics of nanoparticles affect circulation, biodistribution, cellular internalization, and trafficking. *Small* 2013; 9(9-10): 1521-32. [http://dx.doi.org/10.1002/smll.201201390] [PMID: 23019091]
- [51] Jo DH, Kim JH, Lee TG, Kim JH. Size, surface charge, and shape determine therapeutic effects of nanoparticles on brain and retinal diseases. *Nanomedicine (Lond)* 2015; 11(7): 1603-11. [http://dx.doi.org/10.1016/j.nano.2015.04.015] [PMID: 25989200]
- [52] Zeng LY, Xiang LC, Ren WZ, *et al.* Multifunctional photosensitizer-conjugated core-shell Fe₃O₄@NaYF₄:Yb/Er nanocomplexes and their applications in T₂-weighted magnetic resonance/upconversion luminescence imaging and photodynamic therapy of cancer cells. *RSC Advances* 2013; 3: 13915-25. [http://dx.doi.org/10.1039/c3ra41916a]
- [53] Ding Y, Hong X, Zou P, *et al.* Magnetic upconversion luminescent nanocomposites with small size and strong super-paramagnetism: polyelectrolyte-mediated multimagnetic-beads embedding. *ACS Appl Nano Mater* 2018; 1(1): 145-51. [http://dx.doi.org/10.1021/acsnm.7b00059]
- [54] Chamé KF, Ojeda MM, González FG, Rentería VMT, Ojeda MLM, Velásquez CO. Green and red upconversion luminescence in multifunctional Ag@Fe₃O₄@Gd₂O₃:Er³⁺ composites. *J Alloys Compd* 2018; 744: 683-90. [http://dx.doi.org/10.1016/j.jallcom.2018.02.038]
- [55] Campos-Goncalves I, Costa BFO, Santos RF, Durães L. Superparamagnetic core-shell nanocomplexes doped with Yb³⁺/Er³⁺/Ho³⁺ rare-earths for upconversion fluorescence. *Mater Des* 2017; 130: 263-74. [http://dx.doi.org/10.1016/j.matdes.2017.05.064]
- [56] Zhong C, Yang P, Li X, *et al.* Monodisperse bifunctional Fe₃O₄@NaGdF₄:Yb/Er@NaGdF₄:Yb/Er core-shell nanoparticles. *RSC Advances* 2012; 2: 3194-7. [http://dx.doi.org/10.1039/c2ra20070h]
- [57] Cui X, Mathe D, Kovács N, *et al.* Synthesis, characterization, and application of core shell Co_{0.16}Fe_{2.84}O₄@NaYF₄(Yb, Er) and Fe₃O₄@NaYF₄(Yb, Tm) nanoparticle as trimodal (MRI, PET/SPECT, and optical) imaging agents. *Bioconjug Chem* 2016; 27(2): 319-28. [http://dx.doi.org/10.1021/acs.bioconjchem.5b00338] [PMID: 26172432]
- [58] Cheng Q, Guo H, Li Y, Liu S, Sui J, Cai W. A facile one-pot method to synthesize ultrasmall core-shell superparamagnetic and upconversion nanoparticles. *J Colloid Interface Sci* 2016; 475: 1-7. [http://dx.doi.org/10.1016/j.jcis.2016.04.040] [PMID: 27135942]
- [59] Qin Z, Du S, Luo Y, *et al.* Hydrothermal synthesis of superparamagnetic and red luminescent bifunctional Fe₃O₄@Mn²⁺-doped NaYF₄:Yb/Er core@shell monodisperse nanoparticles and their subsequent ligand exchange in water. *Appl Surf Sci* 2016; 378: 174-80. [http://dx.doi.org/10.1016/j.apsusc.2016.03.219]
- [60] Wu Q, Lin Y, Wo F, *et al.* Novel magnetic-luminescent janus nanoparticles for cell labeling and tumor photothermal therapy. *Small* 2017; 13(39): 1701129. [http://dx.doi.org/10.1002/smll.201701129] [PMID: 28834345]
- [61] Luo Y, Zhang W, Liao Z, *et al.* Role of Mn²⁺ doping in the preparation of core-shell structured Fe₃O₄@upconversion nanoparticles and their applications in T₁/T₂-weighted magnetic resonance imaging, upconversion luminescent imaging and near-infrared activated photodynamic therapy. *Nanomaterials (Basel)* 2018; 8(7): 466. [http://dx.doi.org/10.3390/nano8070466] [PMID: 29949933]
- [62] Zhang F, Braun GB, Pallaoro A, *et al.* Mesoporous multifunctional upconversion luminescent and magnetic "nanorattle" materials for targeted chemotherapy. *Nano Lett* 2012; 12(1): 61-7. [http://dx.doi.org/10.1021/nl202949y] [PMID: 22133237]
- [63] Huang S, Chen Y, Liu B, *et al.* Synthesis of magnetic and upconversion nanocapsules as multifunctional drug delivery system. *J Solid State Chem* 2015; 229: 322-9. [http://dx.doi.org/10.1016/j.jssc.2015.06.024]
- [64] Barbe C, Bartlett J, Kong LG, *et al.* Silica particles: a novel drug-delivery system. *Adv Mater* 2004; 16(21): 1959-66. [http://dx.doi.org/10.1002/adma.200400771]
- [65] Ding Y, Chu X, Hong X, Zou P, Liu Y. The infrared fingerprint signals of silica nanoparticles and its application in immunoassay. *Appl Phys Lett* 2012; 100: 013701. [http://dx.doi.org/10.1063/1.3673549]
- [66] Abdul Jalil R, Zhang Y. Biocompatibility of silica coated NaYF₄ upconversion fluorescent nanocrystals. *Biomaterials* 2008; 29(30): 4122-8. [http://dx.doi.org/10.1016/j.biomaterials.2008.07.012] [PMID: 18675453]
- [67] Zhang W, Liu M, Liu A, Zhai G. Advances in functionalized mesoporous silica nanoparticles for tumor targeted drug delivery and theranostics. *Curr Pharm Des* 2017; 23(23): 3367-82.

- [http://dx.doi.org/10.2174/1381612822666161025153619] [PMID: 27784244]
- [68] Gai S, Yang P, Li C, *et al.* Synthesis of magnetic, up-conversion luminescent, and mesoporous core-shell-structured nanocomposites as drug carriers. *Adv Funct Mater* 2010; 20(7): 1166-72. [http://dx.doi.org/10.1002/adfm.200902274]
- [69] Xu H, Cheng L, Wang C, Ma X, Li Y, Liu Z. Polymer encapsulated upconversion nanoparticle/iron oxide nanocomposites for multimodal imaging and magnetic targeted drug delivery. *Biomaterials* 2011; 32(35): 9364-73. [http://dx.doi.org/10.1016/j.biomaterials.2011.08.053] [PMID: 21880364]
- [70] Yu S, Gao X, Jing H, Zhang R, Gao X, Su H. Fabrication and characterization of novel magnetic/luminescent multifunctional nanocomposites for controlled drug release. *CrystEngComm* 2014; 16: 6645-53. [http://dx.doi.org/10.1039/c4ce00582a]
- [71] Shen S, Guo X, Wu L, *et al.* Dual-core@shell-structured Fe₃O₄-NaYF₄@TiO₂ nanocomposites as a magnetic targeting drug carrier for bioimaging and combined chemo-sonodynamic therapy. *J Mater Chem B Mater Biol Med* 2014; 2: 5775-84. [http://dx.doi.org/10.1039/C4TB00841C]
- [72] Du B, Han S, Zhao F, *et al.* A smart upconversion-based light-triggered polymer for synergetic chemo-photodynamic therapy and dual-modal MR/UCL imaging. *Nanomed - Nanotechnol* 2016; 12: 2071-80. [http://dx.doi.org/10.1039/B715402J] [PMID: 18478693]
- [74] Mi C, Zhang J, Gao H, *et al.* Multifunctional nanocomposites of superparamagnetic (Fe₃O₄) and NIR-responsive rare earth-doped up-conversion fluorescent (NaYF₄: Yb,Er) nanoparticles and their applications in biolabeling and fluorescent imaging of cancer cells. *Nanoscale* 2010; 2(7): 1141-8. [http://dx.doi.org/10.1039/c0nr00102c] [PMID: 20648340]
- [75] Du B, Cao X, Zhao F, *et al.* Multimodal imaging-guided, dual-targeted photothermal therapy for cancer. *J Mater Chem B Mater Biol Med* 2016; 4: 2038-50. [http://dx.doi.org/10.1039/C6TB00215C]
- [76] Li N, Zhao Y, Cheng C, Yang Y, Yuan H, Carlini R. Preparation of core-shell magnetic nano-upconversion materials and its targeting effect. *Mater Lett* 2018; 227: 44-6. [http://dx.doi.org/10.1016/j.matlet.2018.05.003]
- [77] Shen J, Sun LD, Zhang YW, Yan CH. Superparamagnetic and upconversion emitting Fe₃O₄/NaYF₄:Yb,Er hetero-nanoparticles via a crosslinker anchoring strategy. *Chem Commun (Camb)* 2010; 46(31): 5731-3. [http://dx.doi.org/10.1039/c0cc00814a] [PMID: 20585692]
- [78] Cheng L, Yang K, Li Y, *et al.* Multifunctional nanoparticles for upconversion luminescence/MR multimodal imaging and magnetically targeted photothermal therapy. *Biomaterials* 2012; 33(7): 2215-22. [http://dx.doi.org/10.1016/j.biomaterials.2011.11.069] [PMID: 22169825]
- [79] Cheng L, Wang C, Ma X, *et al.* Multifunctional upconversion nanoparticles for dual-modal imaging-guided stem cell therapy under remote magnetic control. *Adv Funct Mater* 2013; 23: 272-80. [http://dx.doi.org/10.1002/adfm.201201733]
- [80] Ma Q, Wang J, Dong X, Yu W, Liu G. Electrospinning fabrication and characterization of magnetic-upconversion fluorescent bifunctional core-shell nanofibers. *J Nanopart Res* 2014; 16: 2239. [http://dx.doi.org/10.1007/s11051-013-2239-4]
- [81] Xi X, Ma Q, Dong X, Wang J, Yu W, Liu G. Flexible Janus nanofiber to help achieve simultaneous enhanced magnetism-upconversion luminescence bifunction. *IEEE Trans Nanotechnol* 2015; 14: 243-9. [http://dx.doi.org/10.1109/TNANO.2014.2385085]
- [82] Ma Q, Wang J, Dong X, Yu W, Liu G. Magnetic-upconversion luminescent bifunctional flexible coaxial nanoribbon and Janus nanoribbon: one-pot electrospinning preparation, structure and enhanced upconversion luminescent characteristics. *Chem Eng J* 2015; 260: 222-30. [http://dx.doi.org/10.1016/j.cej.2014.09.033]
- [83] Li J, Ma Q, Dong X, *et al.* Novel electrospun bilayered composite fibrous membrane endowed with tunable and simultaneous quadrifunctionality of electricity-magnetism at one layer and upconversion luminescence-photocatalysis at the other layer. *RSC Advances* 2016; 6: 96084-92. [http://dx.doi.org/10.1039/C6RA20591G]
- [84] Yan L, Chang YN, Yin W, *et al.* Enhanced multifunctional properties of graphene nanocomposites with nacre-like structures. *Adv Eng Mater* 2015; 17: 523-31. [http://dx.doi.org/10.1002/adem.201400237]
- [85] Bi H, He F, Dai Y, *et al.* Quad-model imaging-guided high-efficiency phototherapy based on upconversion nanoparticles and ZnFe₂O₄ integrated graphene oxide. *Inorg Chem* 2018; 57(16): 9988-98. [http://dx.doi.org/10.1021/acs.inorgchem.8b01159] [PMID: 30070830]
- [86] Hu D, Chen M, Gao Y, Li F, Wu L. A facile method to synthesize superparamagnetic and up-conversion luminescent NaYF₄: Yb, Er/Tm@SiO₂@Fe₃O₄ nanocomposite particles and their bioapplication. *J Mater Chem* 2011; 21: 11276-82. [http://dx.doi.org/10.1039/c1jm11172h]
- [87] Lu H, Yi G, Zhao S, Chen D, Guo LH, Cheng J. Synthesis and characterization of multi-functional nanoparticles possessing magnetic, up-conversion fluorescence and bio-affinity properties. *J Mater Chem* 2004; 14: 1336-41. [http://dx.doi.org/10.1039/b315103d]
- [88] Zhou J, Liu Z, Li F. Upconversion nanophosphors for small-animal imaging. *Chem Soc Rev* 2012; 41(3): 1323-49. [http://dx.doi.org/10.1039/C1CS15187H] [PMID: 22008740]
- [89] Chen G, Shen J, Ohulchanskyy TY, *et al.* (α-NaYbF₄:Tm³⁺)/CaF₂ core/shell nanoparticles with efficient near-infrared to near-infrared upconversion for high-contrast deep tissue bioimaging. *ACS Nano* 2012; 6(9): 8280-7. [http://dx.doi.org/10.1021/nn302972r] [PMID: 22928629]
- [90] Peng H, Cui B, Zhao W, Wang Y, Chang Z, Wang Y. Glycine-functionalized Fe₃O₄@TiO₂:Er³⁺,Yb³⁺ nanocarrier for microwave-triggered controllable drug release and study on mechanism of loading/release process using microcalorimetry. *Expert Opin Drug Deliv* 2015; 12(9): 1397-409. [http://dx.doi.org/10.1517/17425247.2015.1031652] [PMID: 25824126]
- [91] Zeng L, Luo L, Pan Y, Luo S, Lu G, Wu A. In vivo targeted magnetic resonance imaging and visualized photodynamic therapy in deep-tissue cancers using folic acid-functionalized superparamagnetic-upconversion nanocomposites. *Nanoscale* 2015; 7(19): 8946-54. [http://dx.doi.org/10.1039/C5NR01932J] [PMID: 25920333]
- [92] Zhang Y, Dong C, Su L, *et al.* Multifunctional microspheres encoded with upconverting nanocrystals and magnetic nanoparticles for rapid separation and immunoassays. *ACS Appl Mater Interfaces* 2016; 8(1): 745-53. [http://dx.doi.org/10.1021/acsami.5b09913] [PMID: 26653130]
- [93] Tang Y, Liu H, Gao J, *et al.* Upconversion particle@Fe₃O₄@molecularly imprinted polymer with controllable shell thickness as high-performance fluorescent probe for sensing quinolones. *Talanta* 2018; 181: 95-103. [http://dx.doi.org/10.1016/j.talanta.2018.01.006] [PMID: 29426547]