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Core–shell Fe_3O_4@$NaLuF_4$:Yb,Er/Tm nanostructure for MRI, CT and upconversion luminescence tri-modality imaging

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A B S T R A C T

Core–shell Fe_3O_4@$NaLuF_4$:Yb,Er/Tm nanostructure (MUCNP) with multifunctional properties has been developed using a step-wise synthetic method. The successful fabrication of MUCNP has been confirmed by transmission electron microscopy, powder X-ray diffraction, energy-dispersive X-ray analysis and X-ray photoelectron spectroscopy. The MUCNP exhibits superparamagnetic property with saturation magnetization of 15 emu g^{-1}, and T_2-enhanced magnetic resonance (MR) effect with an r_2 value of 21.63 s^{-1} mM^{-1} at 0.5 T, resulting from the Fe_3O_4 cores. Moreover, the $NaLuF_4$-based MUCNP provides excellent X-ray attenuation and upconversion luminescence (UCL) emission under excitation at 980 nm. *In vivo* MR, computed tomography (CT) and UCL images of tumor-bearing mice show that the MUCNP can be successfully used in multimodal imaging. *In vitro* tests reveal that the MUCNP is non-cytotoxic. These results suggest that the developed MUCNP could be served as an MR, CT and UCL probe for tri-modality imaging.

1. Introduction

Recent years have witnessed the rapid pace of research and development of rare earth upconversion nanophosphors (RE-UCNPs) as potential bioimaging agents because of their distinct optical and chemical properties, such as sharp emission lines, long lifetimes, superior photostability and non-photoblinking [1–33]. The upconversion luminescence (UCL) process involves the conversion of low-energy light in the near-infrared (NIR) region to higher energy visible light through multiple photon absorption or energy transfer [1–8]. This special photoluminescence mechanism excludes both conventional luminescent materials (such as QDs and organic dyes) and endogenous fluorescent substances. As a result, RE-UCNPs for photoluminescence bioimaging exhibit many advantages, such as the use of non-invasive NIR radiation and the absence of autofluorescence of biological tissues [11,12]. In particular, Yb^{3+} and Tm^{3+} co-doped RE-UCNPs show intense UCL emission at 800 nm under continuous-wave excitation at 980 nm, and are therefore ideal candidates for high contrast whole-body small-animal imaging [10,12,17–28]. For example, we have recently reported that the detection limit for the UCL imaging of a whole-body mouse is only 50 cells [28].

Usually, photoluminescent imaging has one shortcoming of the low penetration depth of the excitation and emission light, which can be solved by magnetic resonance imaging (MRI) [34,35] and X-ray computed tomography (CT). To combine the merits of these imaging modalities, multimodal imaging based on RE-UCNPs has been developed. For example, by introducing Gd^{3+} in the host matrix or on the nanoparticle surface, magnetic-luminescent RE-UCNPs have successfully been fabricated for dual-modal imaging of T_1-enhanced MRI and UCL imaging [36–39]. CT gives high spatial resolution and 3D tomography information about deep anatomic structures due to the high penetration of X-rays, whilst MRI provides comparable resolution but with far better contrast. Considering the different spatial resolution, imaging penetration depth, and areas of application of these different imaging modalities, a combination of CT, MRI and luminescence imaging using a sole probe is urgently required.

Owing to their large magnetic moment, superparamagnetic Fe_3O_4 nanoparticles have been combined with RE-UCNPs together for fabricating magnetic operation, T_2-enhanced MR imaging and UCL imaging [40]. For example, Liu et al. developed multifunctional nanoparticles, $NaYF_4$:Yb,Er@Fe_3O_4@Au, which combined optical and magnetic properties useful for multimodality imaging [41]. Recently, our group reported an imaging agent with

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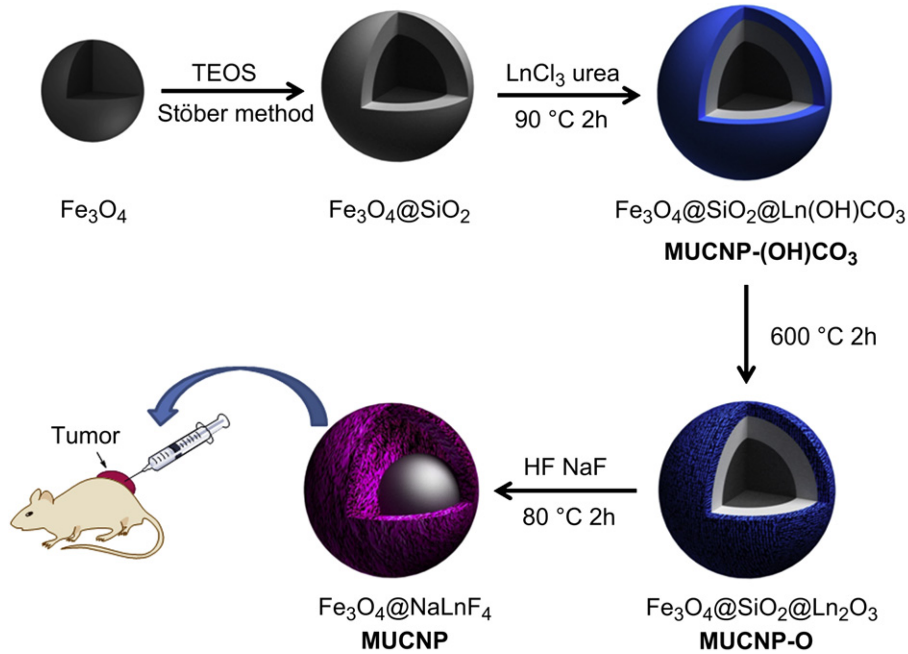

Scheme 1. Schematic representation of the synthetic routine of the multifunctional Fe_3O_4@$NaLuF_4$:Yb,Er/Tm nanoparticle (MUCNP). Ln stands for lanthanide elements (Lu:Yb:Er = 78:20:2 or Lu:Yb:Tm = 79:20:1).

$NaYF_4$:Yb,Tm@Fe_xO_y core–shell nanostructure for T_2 MRI and UCL bimodal lymphatic imaging [42]. It should be noted that the intensity of UCL emission will be weaker in the presence of the Fe_3O_4-shielding, because both excitation and emission light are absorbed by the Fe_3O_4 shell. Therefore, it is expected that a different core–shell nanostructure with Fe_3O_4 nanoparticles as core and RE-UCNPs as shell might show excellent upconversion luminescent and magnetic properties.

$NaLuF_4$ may be an ideal building block for multimodal bioimaging probes since RE-UCNPs based on the $NaLuF_4$ host have high UCL quantum yield [10,28]. Furthermore, owing to the large atomic number and high X-ray absorption coefficient of lutetium, $NaLuF_4$ can be used as a contrast agent for CT imaging. In this work, core–shell Fe_3O_4@$NaLuF_4$:Yb,Er/Tm nanostructure (MUCNP) with Fe_3O_4 as the core and $NaLuF_4$:Yb,Er/Tm as the shell layer has been designed and synthesized by a step-wise method.

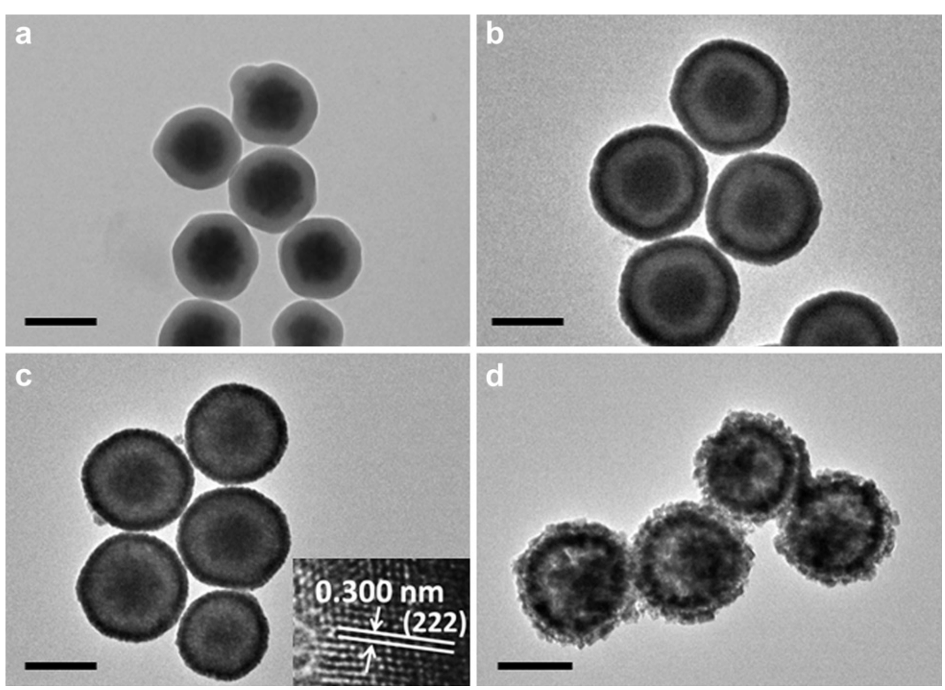

Fig. 1. TEM image of Fe_3O_4@SiO_2 nanoparticle (a), Fe_3O_4@SiO_2@Lu,Yb,Er/Tm(OH)CO_3 nanoparticle (MUCNP-(OH)CO_3) (b), Fe_3O_4@SiO_2@Lu_2O_3:Yb,Er/Tm nanoparticle (MUCNP-O) (c), and Fe_3O_4@$NaLuF_4$:Yb,Er/Tm nanoparticle (MUCNP) (d). HR-TEM image of MUCNP-O (c, inset). The scale bars represent 200 nm (a–d).