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# A $NaYbF_4$: $Tm^{3+}$ nanoprobe for CT and NIR-to-NIR fluorescent bimodal imaging

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ABSTRACT

Early diagnosis that combines the high-resolutional CT and sensitive NIR-fluorescence bioimaging could provide more accurate information for cancerous tissues, which, however, remain a big challenge. Here we report a simple bimodal imaging platform based on PEGylated $NaYbF_4$: $Tm^{3+}$ nanopaticles (NPs) of less than 20 nm in diameter for both CT and NIR-fluorescence bioimaging. The as-designed nanoprobes showed excellent *in vitro* and *in vivo* performances in the dual-bioimaging, very low cytotoxicity and no detectable tissue damge in one month. Remarkably, the $Yb^{3+}$ in the lattice of $NaYbF_4$: $Tm^{3+}$ NPs functions not only as a promising CT contrast medium due to its high X-ray absorption coefficiency, but also an excellent sensitizer contributing to the strong NIR-fluorescent emissions for its large NIR absorption cross-section. In addition, these NPs could be easily excreted mainly *via* feces without detectable remnant in the animal bodies.



## 1. Introduction

X-ray computed tomography (CT), an efficient non-invasive clinical diagnosis technique, could give high-resolution 3D structure details of tissues based on their differential X-ray absorption features. However, CT imaging could not offer clear images of the cancerous lesions and their surrounding soft tissues due to the low density differences between them. Therefore, the CT contrast media (CM) become necessary to distinguish cancerous lesions from their surroundings. The clinically used CT CM is based on the molecule iodinated compounds, not because of their high-performance in X-ray absorption, but their low toxicity and cost. Therefore, large doses of iodinated CM must be applied to get clear images of soft tissues, which would unfortunately cause very short circulation time *in vivo* (within a few minutes) by rapid clearance *via* kidney [1]. These drawbacks limit their applications for targeted tumor diagnostic imaging in CT modality and cause potential renal toxicity because of their rapid kidney's accumulation [2]. Over the past few years, nanoparticles (NPs) as alternative CM have cast new light on long-time circulation and targeted CT imaging due to their unique size effects and interactions with biomolecules both on the cell surfaces and inside cells [3–11]. In addition to many developed iodinated polymeric NPs, such as liposomes, micelles and dendrimers, heavy metal based NPs have emerged recently as new CT CM due to their excellent performance in X-ray attenuation and good biocompatibility [12–15]. Among them, Au NPs are the most investigated candidates for contrast-enhanced *in vivo* CT imaging because of their low toxicity and high X-ray absorption coefficiency [15,16]. Recently, Weissleder's group has developed an efficient CT contrast medium based on $Bi_2S_3$ NPs, which shows much better performance than iodine based CM [14]. Later, Lu's group has developed a new method to produce ultra-small $Bi_2S_3$ nanodots for CT imaging [17]. However, these CM can only be used for contrast-enhanced CT imaging, and multifunctional nano-particulate platforms as contrast agents for more imaging modalities are urgently required to combine the merits of each imaging modality.

Despite the advantages in anatomical delineation, the CT imaging is not sensitive to cells and could not provide cell-level information. Comparatively, fluorescent imaging possesses unique advantages in the sensitivity and cellular level imaging. Once the cellular-sensitive fluorescent imaging is combined with high-resolution CT technology, more accurate information for cancerous tissues could be anticipated. Especially in cancer surgery,

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