

A Multimodal Nanoparticle Platform Made from an Attractive Combination of Rare Earth Elements (Nd^{3+} , Ce^{3+} and Gd^{3+})

Introduction

Early diagnosis is important to maximise treatment outcomes and to personalise treatment according to the individual variability and medical characteristics of each patient. Imaging techniques provide comprehensive anatomical, physiological and functional information for disease detection and treatment response monitoring. The most commonly used diagnostic imaging methods in medicine today are magnetic resonance imaging (MRI), X-ray computed tomography (CT), positron emission tomography (PET), single photon emission tomography (SPECT), optical fluorescence imaging (FLI) and photoacoustic imaging (PAI). There are differences in the diagnostic information obtained due to their detection methods, spatial and temporal resolution, sensitivity and probe type. These differences create inconvenience to analyse and diagnose the disease. Therefore, in order to predict and treat diseases more comprehensively and accurately, it is imperative to develop a simple and efficient multifunctional nanomaterial that can integrate multiple imaging modalities for detection.

Results

To investigate the structure of the CaF_2 : Ce, Gd, Nd NPs, as shown in Figure 1, we used XRD to demonstrate that the structure of the synthesised NPs is consistent with fluorite-type CaF_2 . In addition, the TEM results visualised that the NPs had homogeneous morphology with a small particle size (15–20 nm). Assessing whether the NPs induce cytotoxicity is a prerequisite for determining whether the NPs can be used for biological applications. Therefore, we selected 4T1 breast cancer cells as a model and investigated the effect of CaF_2 : Ce, Gd, Nd NPs on the survival rate of 4T1 cells using MTS assay. As shown in Figure 2, 4T1 cells were cultured for 24 h, 48 h and 72 h in the presence of different concentrations of CaF_2 : Ce, Gd, Nd NPs. The results show that low concentrations of NPs (< 250 $\mu\text{g}/\text{ml}$) were not significantly toxic to 4T1 cells.

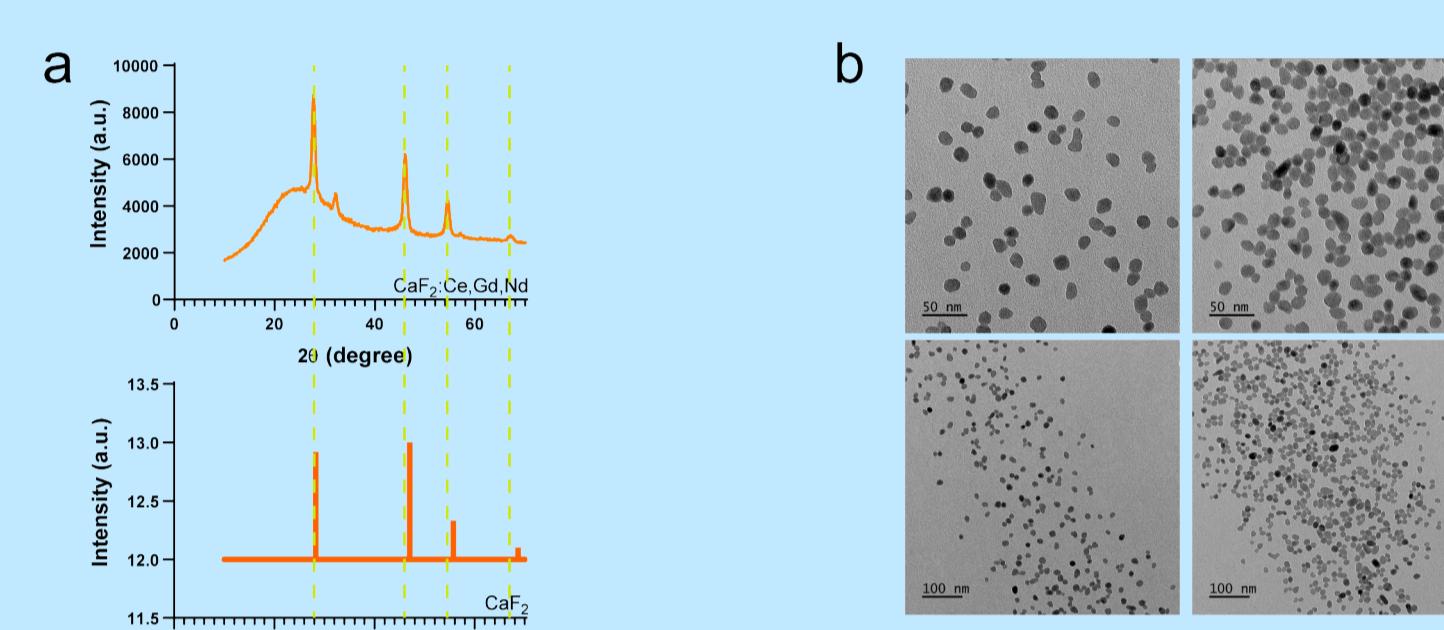


Figure 1 Morphology of CaF_2 : Ce, Gd, Nd NPs. (a) XRD images of CaF_2 : Ce, Gd, Nd NPs and CaF_2 ; (b) TEM images of CaF_2 : Ce, Gd, Nd NPs.

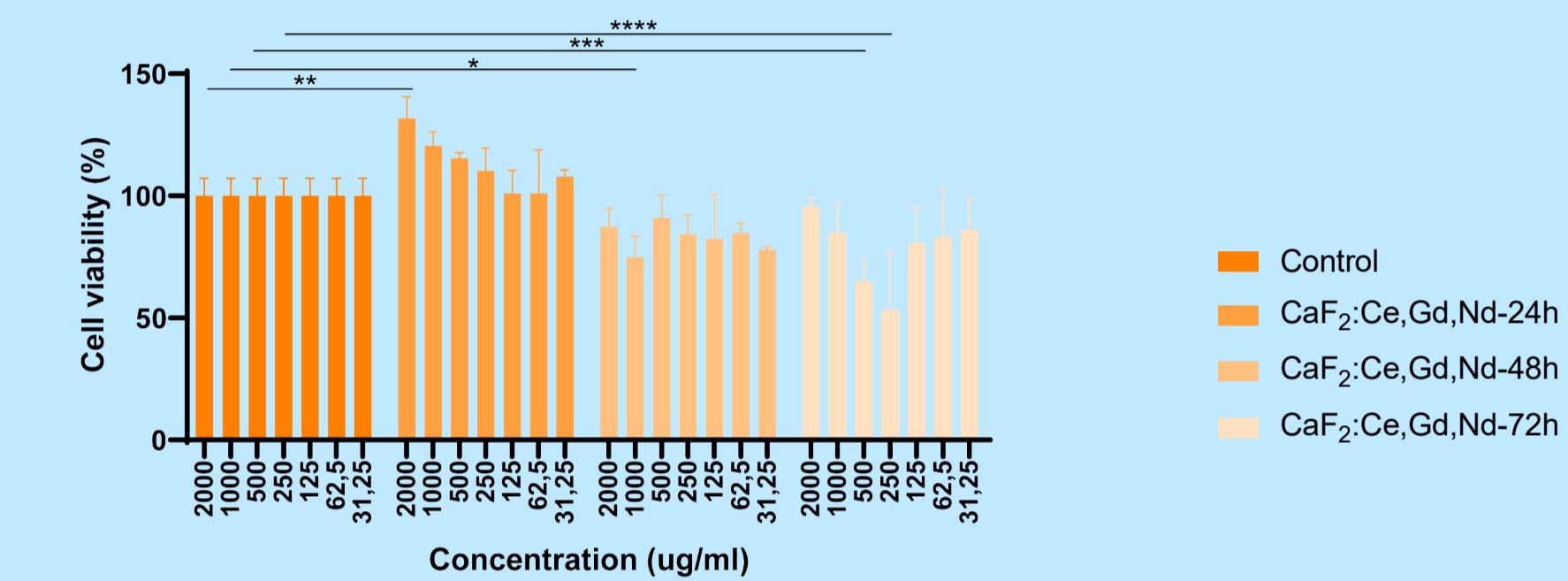
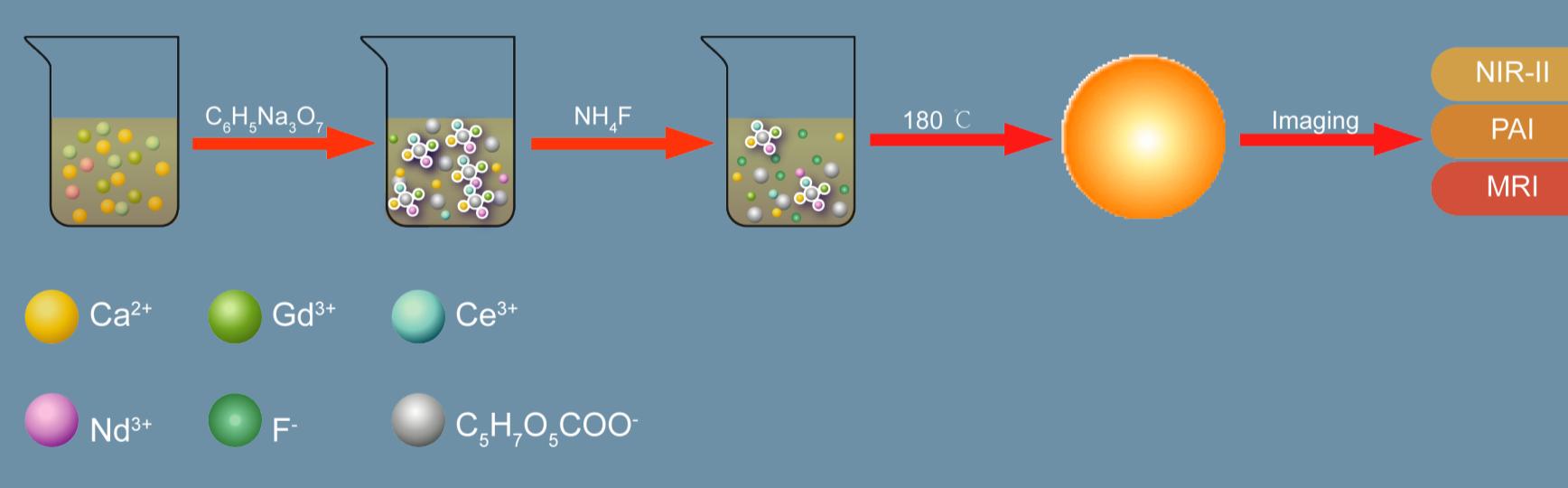


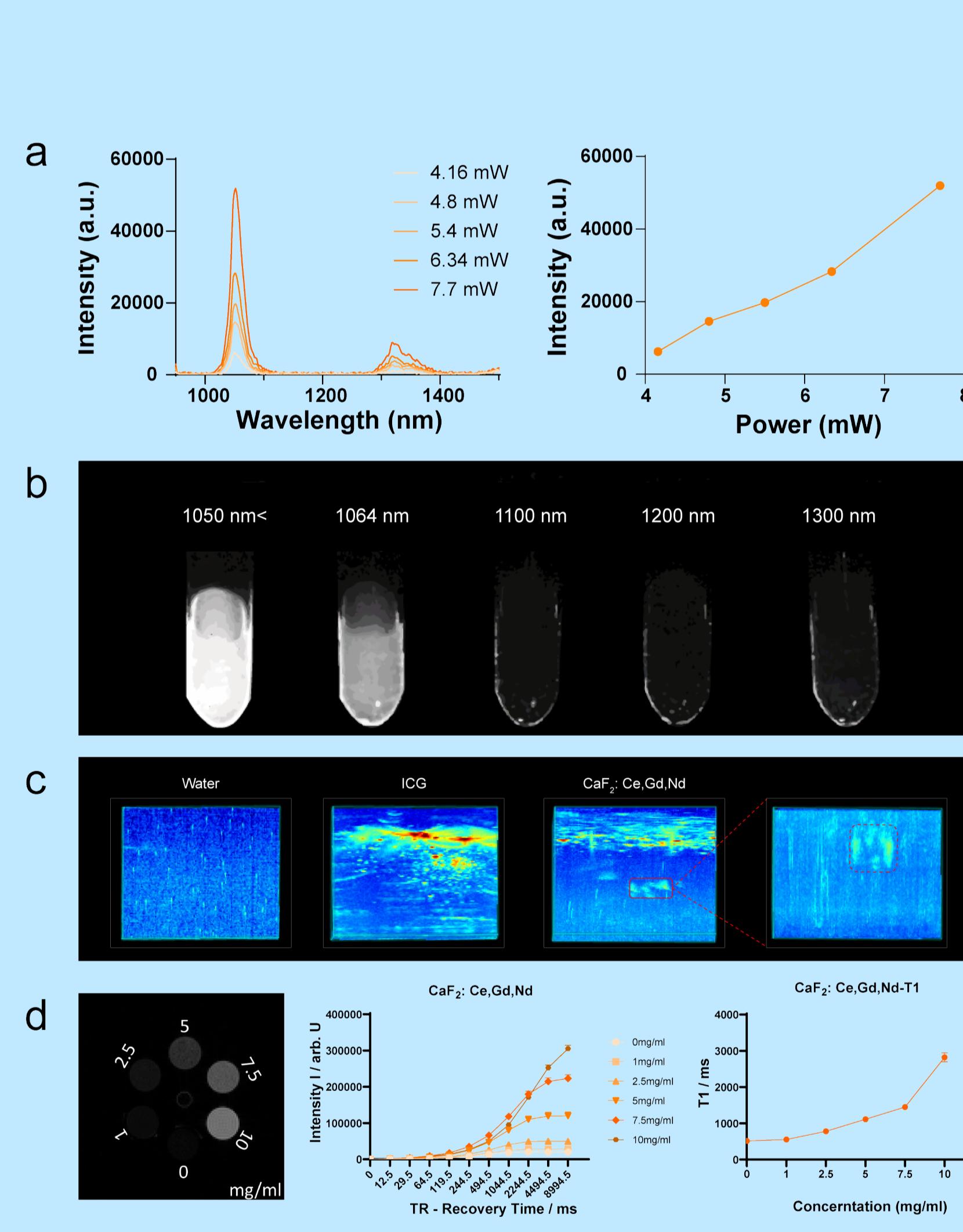
Figure 2 Cell viability of 4T1 cells incubated with CaF_2 : Ce, Gd, Nd NPs at different concentrations (0–2 mg/ml) for 24 h, 48 h and 72 h. All data shown the mean values \pm SD from three independent experiments (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$).

Method

As previously reported [1], we synthesized CaF_2 : Ce, Gd, Nd NPs by a simple hydrothermal method (Scheme 1). Briefly, a certain proportion (Ca^{2+} : Ce^{3+} : Gd^{3+} : Nd^{3+} = 0.68: 0.15: 0.02: 0.02) of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{GdCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ was dissolved in 7 ml water, stirred for 10 minutes (min) to make it fully mixed. Then, sodium citrate solution was added dropwise to the solution and stirred for 30 min, followed by addition of NH_4F solution and stirring for another 30 min. The final solution was transferred to a 50 ml Teflon bottle (Baoshishan, China) held in a stainless steel autoclave, and put in an oven (Heraeus, Germany) maintained at 180 °C for 10 hours (h). Finally, the obtained sample was centrifuged at 5000 rpm for 20 min and washed three times with water and ethanol (99%), then dried in a freeze dryer (Martin Christ).



Scheme 1 Synthesis process and application of CaF_2 : Ce, Gd, Nd NPs.



To test whether the imaging performance of CaF_2 : Ce, Gd, Nd NPs meets our expectations, the luminescence properties of the NPs were examined. It was found that the NPs showed a strong NIR-II signal under low 808 nm laser excitation power (Figure 3a, b). Subsequently, we tested the NPs for suitability as PAI probe. To this end, the NPs were injected into agarose gels and found that under 808 nm laser excitation, the NPs showed high-contrast PA signals, providing assurance for their *in vivo* PA imaging (Figure 3c). Finally, due to the paramagnetic Gd^{3+} doping, we found that the NPs displayed bright T1-weighted images (Figure 3d), leading to the possibility of efficient MR imaging.

Conclusion

In summary, we doped Ce^{3+} , Gd^{3+} , and Nd^{3+} into CaF_2 crystals through a simple hydrothermal process, resulting in novel NPs suitable for multi-modal imaging. The synthesized NPs were highly pure and showed good biocompatibility. CaF_2 : Ce, Gd, Nd NPs themselves exhibit dual modes, because Ce^{3+} and Nd^{3+} dopants contribute to NIR-II and PAI, and the presence of Gd^{3+} shows a high-contrast T1-enhancing effect for MRI. Therefore, CaF_2 : Ce, Gd, Nd NPs may be an informative NIR-II/PAI/MRI multimodal probe for clinical diagnosis. This research also laid the foundation for the use of CaF_2 : Ce, Gd, Nd NPs for biological imaging of cells and deep tissues.

References

- [1] Pedroni, M., Piccinelli, F., Passuello, T., et al. (2013). Water (H_2O and D_2O) dispersible NIR-to-NIR upconverting $\text{Yb}^{3+}/\text{Tm}^{3+}$ doped MF_2 ($\text{M}=\text{Ca}, \text{Sr}$) colloids: influence of the host crystal. *Crystal growth & design*, 13(11), 4906–4913.

Acknowledgments

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