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Functionalization of Lithium Niobate Nanoparticles with Lanthanide Chelates for Multimodal Imaging Applications

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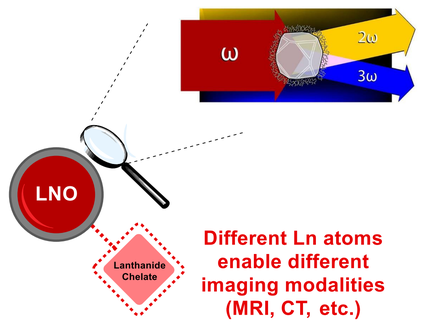
BACKGROUND & AIMS

Cancer is among the leading causes of death worldwide, and as knowledge of the disease continues to grow there is an increasing interest towards **precision medicine**. [1] More specifically, the design of **targeted nanoprobes** combining specific **diagnostic and treatment modalities** offer the perspective of improved therapeutic efficiency and reduced side effects. Nanoscale systems integrating **multiple imaging modalities** allow for precise diagnosis, which could detect malignancies at an early stage of their development and thus increase the success rate of therapeutic interventions.

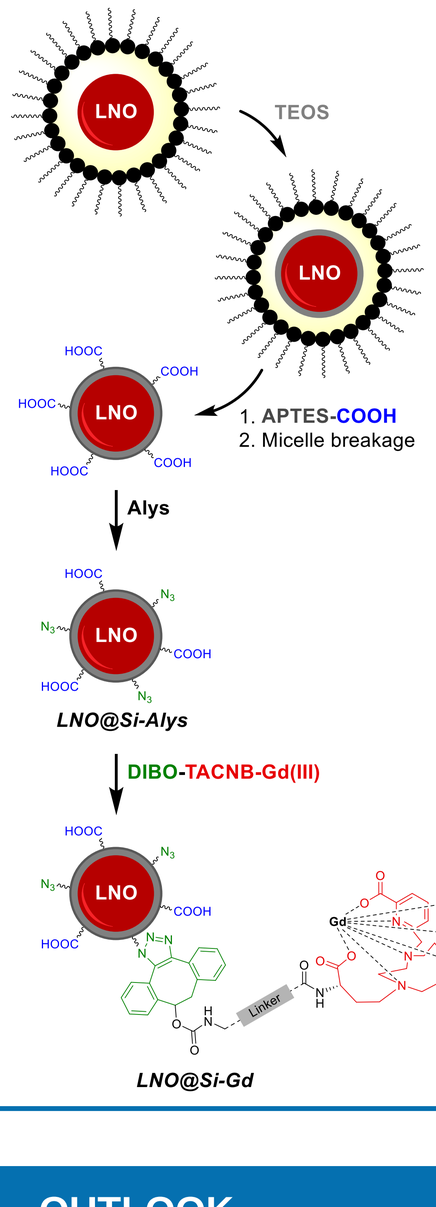
PROJECT GOAL

Develop a multimodal imaging probe based on **harmonic nanoparticle (HNP) materials**.

- HNP crystalline core enables **optical imaging** via generation of **harmonic signals upon laser excitation** (NIR range achievable). [2]
- Functionalization with a lanthanide chelate to achieve imaging modalities more adapted for the **acquisition of anatomical pictures** (such as **MRI** or **CT**). [3]

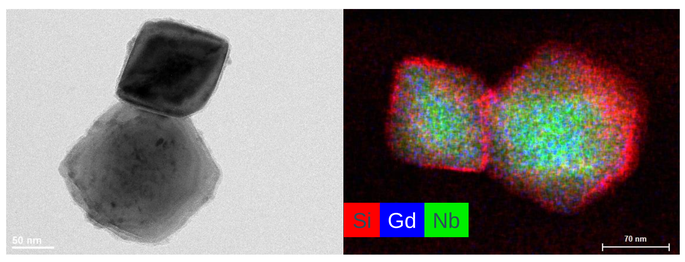


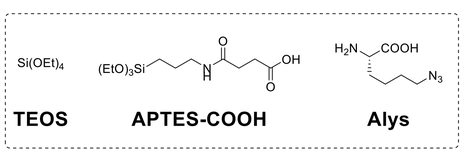
FUNCTIONALIZATION STRATEGY



The HNPs consisting of lithium niobate ($LiNbO_3$, LNO) were first **coated in a silica shell using a water-in-oil microemulsion approach** to improve their biocompatibility and introduce carboxylic acid functional groups at their surface. An **unnatural amino acid** (azido-lysine, Alys), was then coupled to the coated LNOs to further introduce **azide moieties**. The presence of both azide and carboxylic functionalities allows for **potential orthogonal multifunctionalization** of the HNPs. The functionalization with a **copper-free clickable Gd(III) chelate** gave rise to monodispersed ***LNO@Si-Gd*** HNPs in PBS (DLS diameter = 207 nm, PdI = 0.07).

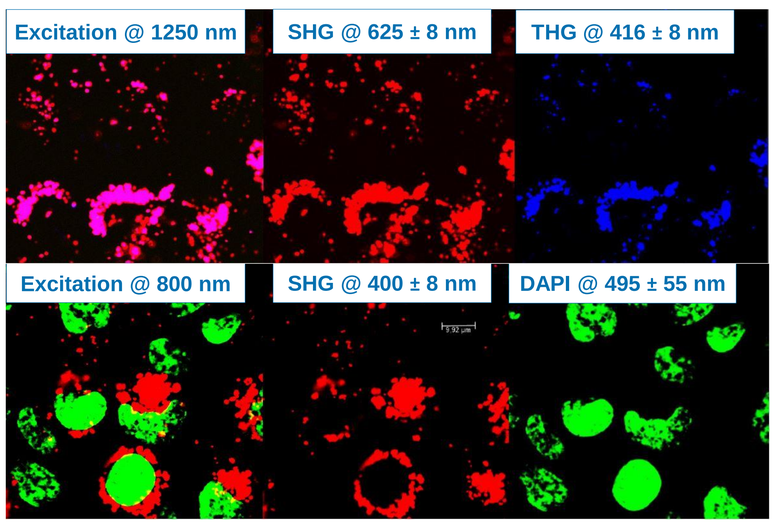
STEM & EDX of *LNO@Si-Gd*





IMAGING RESULTS

Multiphoton microscopy *in vitro*

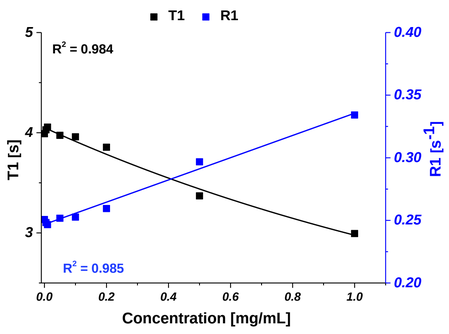


Simultaneous observation of the SHG (second harmonic) and THG (third harmonic) signals, showing the **multi-order response of the LNO core**.

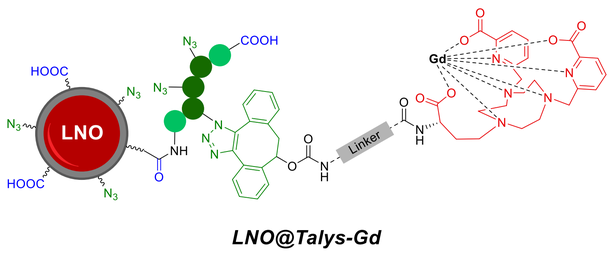
Colocalization of the SHG and DAPI signals demonstrates the **efficient cytoplasmic internalization of *LNO@Si-Gd***.

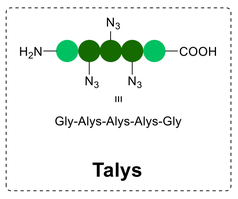
Relaxation time measurement

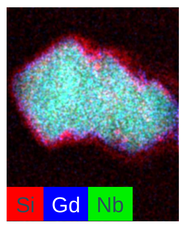
Preliminary MRI evaluation of ***LNO@Si-Gd*** was performed. The T1 relaxation time was measured on a phantom using a 9.4 T NMR spectrometer. A concentration-dependent decrease in the T1 relaxation time was observed, corresponding to an increase in R1 relaxation rate. In order to reach higher signal increase similar to what we previously reported on a similar system, **optimization of the functionalization steps is now necessary to achieve higher Gd grafting**. [4]



OUTLOOK







To increase the Gd(III) density and improve the measured MRI signal, a new strategy is currently under investigation. The LNO HNPs were surface-modified with a **short peptide containing three Alys units** (Talys). This system gave rise to a higher Gd(III) grafting at the surface, as observed by STEM/EDX analyses. In addition to the MRI properties evaluation of ***LNO@Talys-Gd***, the preparation of a CT scan probe based on Yb will be investigated.

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[1] Chen, H., Zhang, W., Zhu, G., Xie, J., & Chen, X. (2017). Rethinking cancer nanotheranostics. Nature Reviews Materials, 2(7), 1-18.; **[2]** Riporto, J., Urbain, M., Mugnier, Y., Multian, V., Riporto, F., Bredillet, K., Beauquis, S., Galez, C., Monnier, V., Chevolot, Y. and Gayvoronsky, V. (2019). Second harmonic spectroscopy of ZnO, BiFeO 3 and LiNbO 3 nanocrystals. Optical Materials Express, 9(4), pp.1955-1966.; **[3]** Kim, J.; Chhour, P.; Hsu, J.; Litt, H. I.; Ferrari, V. A.; Popovtzer, R.; Cormode, D. P., (2017) Use of Nanoparticle Contrast Agents for Cell Tracking with Computed Tomography. Bioconjugate Chem., 28, 1581−1597.; **[4]** De Matos, R., Gheata, A., Campargue, G., Vuilleumier, J., Nicolle, L., Pierzchala, K., Jelescu, I., Lucarini, F., Gautschi, I., Riporto, F. and Le Dantec, R., (2022). Gd3+-Functionalized Lithium Niobate Nanoparticles for Dual Multiphoton and Magnetic Resonance Bioimaging. ACS Applied Nano Materials, 5(2), pp.2912-2922.

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