# Ferromagnetic hybrid nanoparticles for guided magnetic hyperthermia

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## Introduction

Among various therapeutic methods there is a continuous increase of an interest about MRI-guided the magnetic fluid hyperthermia (MFH). The method is based on an deposition of stable and nontoxic suspensions of the magnetic nanoparticles inside the tumor followed by a short-time exposure to a high frequency electromagnetic field. The dissipation of energy connected with magnetic losses results in a local heating by the active particles and consequently to the destruction of the cancer cells. Due to distinct magnetic properties, the particles can be used as a cellular label - an internal contrast agent for MRI.

Two kinds of magnetic heating and consequently of the materials should be distinguished. Superparamagnetic particles, where heating is effectuated by rotation of the particles magnetic moments and ferro- or ferrimagnetic particles, where heating is due to hysteresis losses. Successful use of the latter type requires maintenance of the magnitude of magnetization for small particles as high as possible and adjustment of the coercivity to a reasonable value assuring sufficient heating efficiency but not too high for practical medical heating application. The aim of our study was to prepare ferromagnetic perovskite particles of suitable size, characterize them and test them on rat mesenchymal stem cells.

## Materials

Manganese perovskite nanoparticles, $La_{0.75}Sr_{0.25}MnO_3$ (LSMO), of the size in the range of 30-49 nm were synthesized via sol-gel technique employing citric acid and ethylene glycol. The particles were coated by $Si0_2$ to minimize their toxicity and adverse effects on cells.

Particle suspensions were subjected to several physical tests, i.e., relaxometry, magnetometry, calorimetry, transmission electron microscopy.

Particles in cell culture: The particles (at different concentrations) were added into the culture medium with rat mesenchymal stem cells and incubated for 48 hours. Then the nanoparticles were washed out and cell viability was evaluated. Cell suspensions were subjected to relaxometry measurements, evaluated relaxivities correspond to contrast enhancement in MRI and enable to estimate amount of the particles inside the cells. Feridex® was used as a label in a control cell sample.

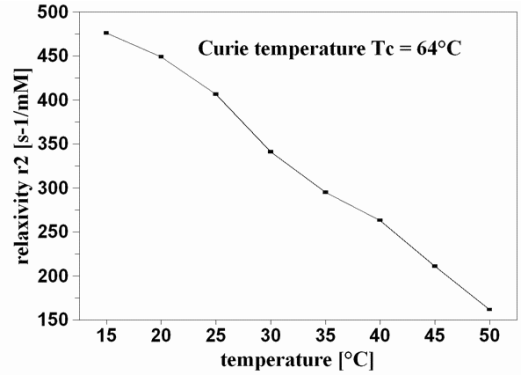


Fig. 1: T2-relaxivity of a water suspension of LSMO nanoparticles at different temperatures

## Results

Relaxometry (at 0.5 T) revealed very strong r2 relaxivity dependence on temperature (see Fig. 1). At 37°C relaxivity of LSMO particles reaches approx. relaxivity two times higher than Feridex. During calorimetric measurements, temperature stabilizes at $T_{max}$ approx. 10°C -15°C lower than Curie temperature $T_c$ (see Fig. 2).

Cell viability is still somewhat lower in the presence of perovskite nanoparticles compared to standard superparamagnetic iron oxide label (Feridex®), $SiO_2$ coating substantially improved survival rate, however, cell viability at concentrations around 0.1 mM (concentration of Mn ions) in the media varied between 70% to 80%, whereas Feridex® labeled cells reached 94% and unlabeled control cells 97%.

Although estimated amount of manganese inside the cells is relatively low (0.24 pg Mn/cell) compared to amount of iron in case of Feridex® loaded cells (14.6 pg Fe/cell), due to high $T_2$ relaxivity of the perovskite nanoparticles the cells labeled by the perovskites provide even better contrast than Feridex® labeled ones. $T_2$ relaxation rate of perovskite loaded cells was 18.1 $s^{-1}$/million of cells compared to Feridex-loaded cells revealing $T_2$ relaxation rate 17.3 $s^{-1}$/million of cells.

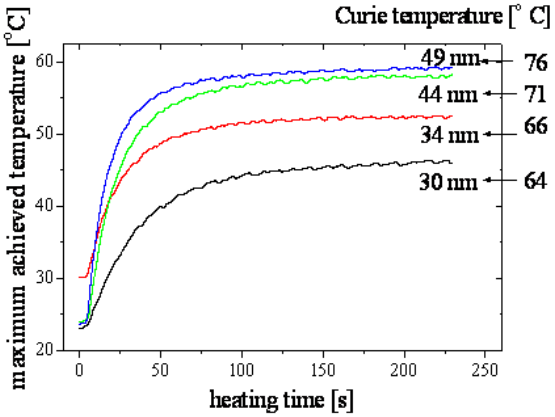


Fig. 2: Temperature reached during heating of nanoparticles with different Curie temperature

## Discussion/Conclusion

We have synthesized and tested ferromagnetic manganese perovskite particles as a cell label which can provide superb MR contrast and, as the material is ferromagnetic, it can be heated by an external alternating magnetic field. Thus the particles can be used for guided thermoablation, with labeled stem cells used as carriers. Moreover, due to its low Curie temperature, thermoablation is self-controlled: the material becomes paramagnetic at temperature above Curie temperature and energy absorption decreases with temperature nearing $T_c$. In fact, the actual maximal reached temperature lies 10-15°C below $T_c$. However, it is necessary to further improve the coating procedure to ensure higher cell viability in the presence of LSMO nanoparticles.

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