# Magnetosomes, a new class of highly sensitive superparamagnetic contrast agents for MR molecular imaging

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## Background

Superparamagnetic iron-oxide particles, which were introduced as MR contrast agents shortly after the use of gadolinium chelates [1], currently appear to be the preferred material to perform molecular imaging due to their high relaxivity properties. In this study we present a new class of superparamagnetic nanoparticles, naturally produced by magnetotactic bacteria, and which regroup different characteristics of interest for biomedical applications: a perfectly crystalline and regular nanocrystal of magnetite (Figure 1), surrounded by a natural lipid bilayer ensuring their solubilization and a possible functionalization of the surface with biological functions for cellular or molecular targeting. Here, as a preliminary study, we demonstrate the high sensitivity of magnetosomes both *in vitro* and *in vivo* as well as the interest to use them at very high magnetic field.

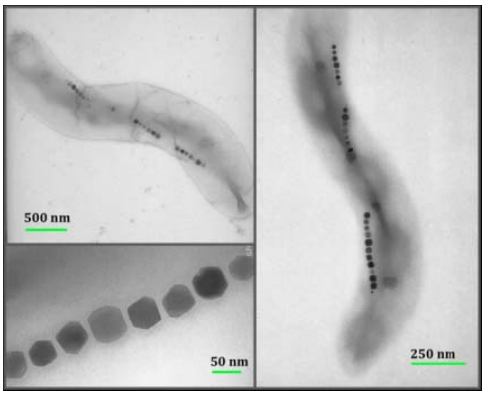


**Figure 1:** Transmission electron microcraph of *M. magneticum* AMB-1 showing the chain of magnetosomes inside the cell

## Materials & Methods

Wild-type AMB-1 bacteria were grown in Komeili's medium supplemented with 0.2 g/l soy bean peptone and 0.1 g/l yeast extract. Static cultures were grown in hermetically sealed Schott bottles containing 80 ml of growth medium with a 30 ml headspace; cultures were flushed with a nitrogen/air mixture at 2% $O_2$ for 10 min after inoculation and grown at 28°C. Bacteria were then centrifugated and magnetosomes nanoparticles were extracted using a permanent magnet. For *in vitro* assays, magnetosomes were re-suspended at different concentrations (from 0.15 to 3µM) in an agar matrix. MR imaging was performed at 7T for *in vitro* assays and at 17.2T for *in vivo* study on preclinical Bruker scanners. A $T_2$ mapping sequence (MSME, TR = 3000ms, 64 TE from 8.3ms to 530ms, $T_{acq}$ = 8.5min) was acquired to measure the transverse relaxivity $r_2$ of magnetosomes. *In vivo* experiments were carried out on "nude" mice. Anatomical $T_2$ weighted (RARE, $TE_{eff}$/TR = 22/3000ms, resolution = 150x150x375µm$^3$, $T_{acq}$ = 16.5min) and $T_2^*$ weighted (FLASH, TE/TR = 8/670ms, resolution = 75x75x150µm$^3$, $T_{acq}$ = 18min) images were acquired prior and after IV injection of 200µL of magnetosomes (dose: 20µmol$_{Fe}$/kg).

## Results

Transverse relaxivity of magnetosomes was measured to 680mM$^{-1}$.s$^{-1}$ (Figure 2), a value relatively higher than $r_2$ relaxivities of commonly used iron nanoparticles (Endorem®: $r_2$~150mM$^{-1}$.s$^{-1}$ and Sinerem®: $r_2$ ~ 100mM$^{-1}$.s$^{-1}$). The gain observed with magnetosomes is probably due to the high regularity of magnetite nano-crystals produced by AMB-1 bacteria. *In vitro* sensitivity at 7T of this contrast agent was estimated to 150nM in term of iron content. Figure 3a- represents the overlay of $T_{2w}^*$ volume on anatomical $T_{2w}$ images of the mouse. After intravenous injection of magnetosomes, an overall $T_2^*$ decrease is observed in the whole brain (Figure 3-b) due to magnetosomes circulating in the vascular compartment. Large blood vessels are also highlighted by the contrast agent (red arrows on Figure 3-a). To confirm this result, we developed a dedicated automatic procedure to specifically detect vascular hypo-intense signals. As shown by Figure 3-c, injection of magnetosomes significantly enhances the number of large blood vessels detected.

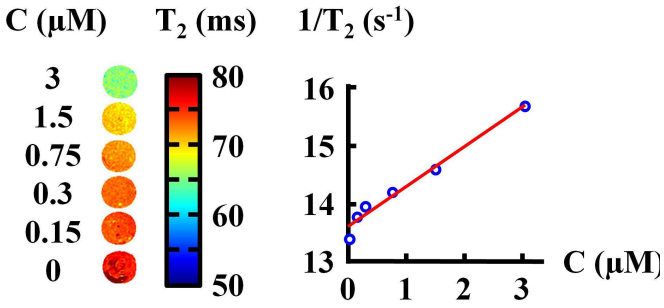


**Figure 2:** Measure of transverse relaxivity $r_2$ of magnetosomes nanoparticles

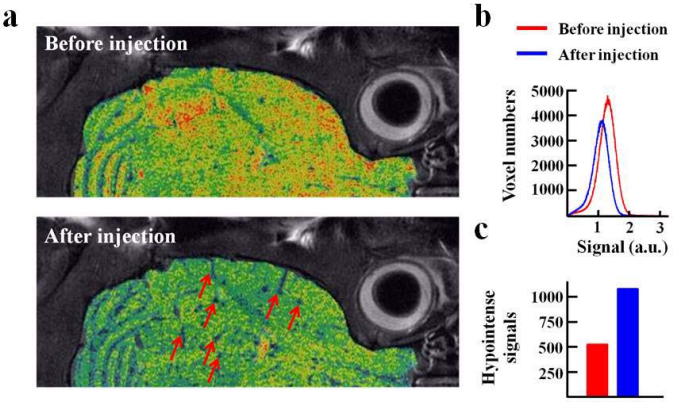


**Figure 3:** a- $T_2^*$ weighted images of the mouse brain acquired before and after IV injection of magnetosomes. b- Signal distribution in the whole brain. c- Number of blood vessels detected.

## Conclusion

In conclusion, our preliminary results demonstrated that the use of microorganisms naturally producing lipid-coated magnetite crystals provides a new class of highly sensitive MR contrast agents. MRI data at ultra-high field confirm that these contrast agents exhibit higher relaxivity properties than superparamagnetic iron oxide nanoparticles chemically produced. The *in vivo* detection of magnetosomes in the mouse brain is therefore obtained after IV injection of a significantly lower dose (20µmol$_{Fe}$/kg) than the one commonly used in rodent studies (200-1000µmol$_{Fe}$/kg). Moreover our group has already shown that genetic manipulation of magnetosomes offers the possibility to insert peptides in its membrane [2] that could be used to target specific biomarkers involved in various pathologies. In conjunction with ultra-high field MR imaging, such functionalized contrast agents should provide enough sensitivity and specificity for MR molecular imaging studies.

## References

[1] Mendonca Dias, et al., MRM, 1986
[2] Ginet et al, Plos One., 2011