

Proceedings Article

# Dendronized iron oxide: SUPERSPIO20 as MPI tracer and magnetic hyperthermia agent

D. Felder-Flesch<sup>a,b,\*</sup> · L. Streit<sup>b</sup> · S. Jakimoska<sup>b</sup> · I. Blanchard<sup>c</sup> · S. Valable<sup>c</sup> · G. Cotin<sup>b</sup>

<sup>a</sup>Institute of Physics and Chemistry of Materials IPCMS UMR CNRS UNISTRA 7504, Strasbourg, France

<sup>b</sup>SUPERBRANCHE, Strasbourg, France

<sup>c</sup>Université de Caen Normandie, CNRS, Normandie Université, ISTCT UMR6030, GIP Cyceron, 14000 Caen, France

\*Corresponding author, email: [Delphine.felder@ipcms.unistra.fr](mailto:Delphine.felder@ipcms.unistra.fr)

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## Abstract

The rise of MPI technology has led to the growing development of equipment requiring the use of an optimized magnetic tracer for increased sensitivity and resolution. In addition, MPI technology paves the way for truly targeted tumor treatment using the field free point approach for focused magnetic hyperthermia. The need for a theranostic tracer is therefore essential for further preclinical and clinical development. Among the many methods of synthesizing nanoparticles, thermal decomposition is the method of choice for perfect control of the size, distribution, shape and composition of nanoparticles. Mastery of this method has led to the development of SuperSpio20, a dendronized iron oxide nanoparticle whose 20 nm iron oxide core has a first-order MPI signal and optimized heat release for focused mild hyperthermia. The controlled dendronized coating maintains a hydrodynamic diameter of less than 35 nm, allowing intravenous injection. This design also allows the labelling of therapeutic cells without the need for a transfection agent for the development of MPI-tracked cell therapies.

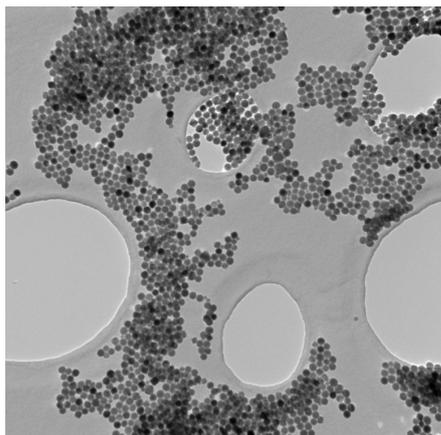
## I. Introduction

Currently the emergence of focalized magnetic hyperthermia (FMH) equipment that allow the application of the alternative magnetic field on a chosen and small volume of space paves the way for MPI/FMH theranostic combination. This combination requires a tracer efficient in both imaging and therapy [1], while being intravenously injectable and specific to certain type of cells such as cancer cells.

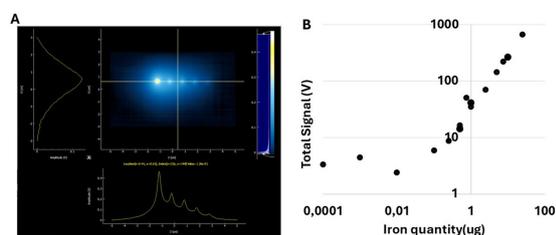
## II. Methods and materials

SUPERSPIO20 was synthesized through a thermal decomposition process and functionalized with a dendritic shell as previously described [2] by performing a direct

ligand exchange. MPI measurements were performed on a MOMENTUM CT (Magnetic Insight, Cyceron imaging platform, Caen France) imager. For CT acquisition, a Scan-2D Xray FOV = 10×5cm, resolution: 0.07×0.07mm was used. For CT acquisition, High Sensitivity/High resolution mode was used with the following parameters: 2D MPI projection imaging with a FOV=10×6 cm, resolution: 0.25×0.25 mm, multichannel RF excitation Z and X, gradient scanning in Y (5.7 T/m). MH was measured on a HYPER module (340 kHz and 16 mT) from Magnetic Insight, USA. In vivo: Healthy SCID mice (i.e. non tumor bearing) were used in accordance with the current European directive (2010/63/EU); user facility #G14118001 (CYCERON, Université de Caen Normandie), authorization from the regional animal ethics committee (C2EA-54 CENOMEXA) and project authorization (APAFIS n° 55164) issued by the French Ministry of Higher Educa-



**Figure 1:** Transmission Electron Microscope (TEM) images of SUPERSPIO20 a spherical nanoparticle of 20 nm iron oxide core.



**Figure 2:** MPI calibration curve of SUPERSPIO20. Increasing concentrations of SUPERSPIO20 were deposited on a phantom (A) and MPI signal was expressed as a function of iron quantity (B).

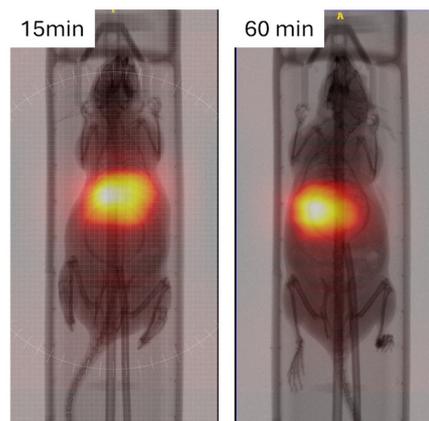
tion, Research and Innovation.

SUPERSPIO were injected intravenously (400  $\mu\text{g}$ ) and whole body 2D CT/MPI (MOMENTUM CT, Cycleron, Caen) images were obtained 15 min and 1 hour later using a similar protocol used for *in vitro* studies. The animal was placed in a prone position under anesthesia (2% isoflurane in Air) and its breathing was monitored using a sensor placed under its abdomen.

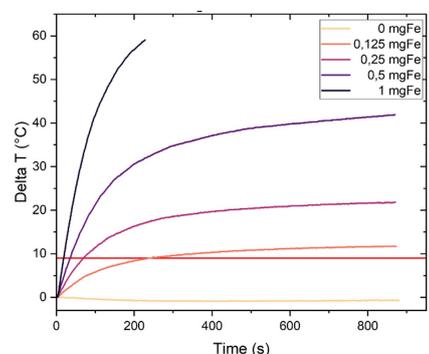
### III. Results and discussion

#### III.I. Nanoparticle characterization

The thermal decomposition synthesis method which consists in the decomposition of an iron precursor at high temperature allows fine control over the size, distribution, shape, composition and crystallinity. Figure 1 shows the transmission electron microscopy (TEM) images of SUPERSPIO20, a spherical 20 nm core iron oxide with a narrow size distribution and high crystallinity. The colloidal stability of dendronized SUPERSPIO20 was investigated by Dynamic Light Scattering (DLS) under different physiologically relevant media conditions and



**Figure 3:** In vivo detection of SUPERSPIO with MPI. Representative images of MPI signal merged with the CT images in mice taken 15 min and 60 min after IV injection of 400  $\mu\text{g}$  of SUPERSPIO20.



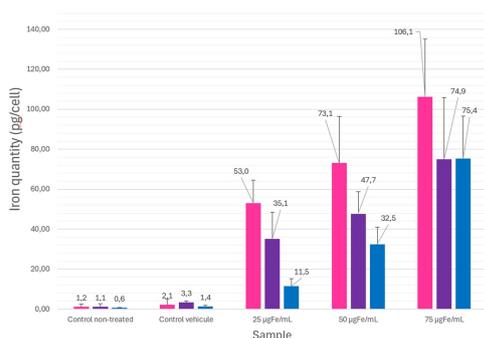
**Figure 4:** Delta of temperature for different masses of iron obtained at 340 kHz and 16 mT.

a monomodal distribution with a mean hydrodynamic size of 35 nm was obtained (data not shown). In general, dendronized SUPERSPIO were stable over an acceptable period of time (up to few days) and displayed a mean hydrodynamic diameter smaller than 50 nm whatever the molecule architecture or dendron generation. [3]

#### III.II. MPI measurements and first in vivo results

SUPERSPIO20 presents a high signal in MPI with a limit of detection (LOD) at 100 ng in water (Figure 2). The linearity of the signal as a function of the amount of SUPERSPIO20 indicates good quantification of the nanoparticles.

Comparison to VivoTrax (Ferucarbotran) was achieved. Data was acquired by imaging a 1mL point source of each of the samples. The relaxometer scan mode was used to evaluate and analyze the particle's properties. SUPERSPIO20 showed a very high signal efficiency with close to five times the signal per mass of iron



**Figure 5:** Determination of iron content (pg) per cell (ferrozine assay) after 24 hours of co-incubation of hMSCs from three donors with increasing amounts of SUPERSPIO20.

compared to VivoTrax, the outlier being a formulation at  $0.5\text{mg mL}^{-1}$  of iron. The imaging resolution was also 10% better (data not shown).

After intravenous injection in healthy mice, SUPERSPIO20 induced a high MPI signal, mostly located within the liver at 15 min which kept constant at 1 hour (Figure 3).

### III.III. Hyperthermia measurements

Temperature increase was measured for different amounts of SUPERSPIO20 in suspension at 340 kHz and 16 mT. For all tested doses, the  $+9^{\circ}\text{C}$  increase necessary to reach  $46^{\circ}\text{C}$  *in vivo* was observed in 300 s or less (Figure 4).

### III.IV. Cell internalization studies

Studies on the internalization of SUPERSPIO20 in primary macrophages from patients and in human mesenchymal stem cells (hMSCs) were conducted. In primary macrophages, we observed good internalization of SuperSPIO20 (up to  $300\text{ pgFe/cell}$ ) but with differences between donors. For hMSCs (Figure 5), the labelling rate also varies greatly from one patient to another, but with the possibility of achieving high labelling rates (close

to  $80\text{ pgFe/cell}$ ) without the use of a transfection agent. No toxicity (data not shown) was detected for any of the SUPERSPIO20 doses tested in these studies.

## IV. Conclusion

These results show that intravenously injected dendronized Superspio<sup>®</sup> are very promising as MPI/FMH theranostic agent at low injected dose and through a cell-based delivery approach. SUPERSPIO20 is a unique formulation thanks to its dendronized coating ensuring a low hydrodynamic diameter, combined with a 20 nm monodisperse core showing both dual-imaging (MRI and MPI) and therapeutic function (MH). No other formulation shows such combined theranostic properties in such a small nanoparticle.

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## Author's statement

Conflict of interest: L.S, S.J and G.C are employees of Superbranche.

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