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Enhanced brain retention time of MPI tracer via antibody conjugation

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Abstract

Hyperthermia guided by Magnetic Particle Imaging (MPI) is an emerging technique for targeted thermal therapies, including blood–brain barrier opening and localized tumor ablation. However, this technique works best for locally injected magnetic nanoparticles, but faces limitations with intravenous administration. Floating with circulation, the tracers often traverse the target region too quickly, succumbing to heat loss by blood cooling, thus failing to achieve sufficient localized thermal doses. This limitation reduces the efficacy of MPI-guided hyperthermia for precision applications in sensitive tissues such as the brain. Here, we propose a strategy to immobilize the magnetic nanoparticles at the brain capillary level via antibody conjugation specific to the vascular endothelium allowing future localized heating experiments. We present initial experimental proof showing the feasibility of this approach by increasing retention times of particles in the brain evidenced by extended local blood half-life.

I. Introduction

Magnetic Particle Imaging (MPI)-guided hyperthermia enables focused and remote controllable heating of arbitrary targets [1]. This approach requires administration of magnetic nanoparticles (MNPs) to be present at the location of choice. However, systemic, intravenous delivery often reduces heating efficiency compared to local injections, as MNPs in blood usually transit target regions only briefly. Improving access to highly perfused tissues such as the brain could facilitate targeted, non-invasive therapies of these tissues as well. To enhance MNP retention and targeting, particles were conjugated with antibodies that bind specific biological sites [2]. In this study, we investigate how an endothelium-specific antibody (anti-CD31) conjugated to a standard MPI tracer (synomag-D70, Micromod Partikeltechnologie GmbH, Rostock, Germany) affects MPI signal characteristics in the brain *in vivo*.

II. Methods and materials

Magnetic particle spectroscopy (MPS) data was acquired using a 10 µL sample of the MNP suspension (standard synomag-D70 and CD31 conjugated synomag-D70, 10 mg(Fe)/mL), with a 25.25 kHz excitation frequency for 10 s at 37 °C (MPS3, Bruker BioSpin GmbH & Co. KG, Ettlingen, Germany).

Prior to in vivo experiments, a 3D system matrix (SM) was recorded using a 27 mm^3 cuboid sample of the standard synomag-D70 with the following parameters: FOV = 31 × 31 × 17 mm^3, pixel size = 1 mm, A = 14 mT in x-, y- and z-direction G = 2 T/m, 3 orthogonal Tx/Rx coils.

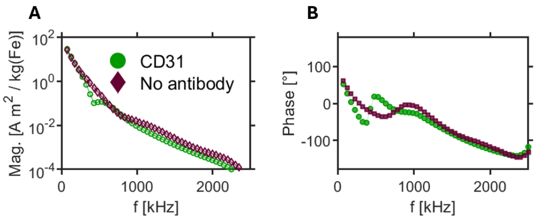

Figure 1: MPS results of antibody conjugated MNPs and the corresponding control.

According to proven and accepted procedures, two Sprague Dawley rats (female, 290 g ±25 g) were isoflurane anesthetized and transferred into a commercial MPI scanner (MPI 25/20 FF, Bruker BioSpin MRI GmbH, Ettlingen, Germany). Anesthesia was maintained throughout the subsequent experiment while vital signs were monitored. MNP administration was performed through the catheterized tail vein. MPI images were acquired during infusion with the head positioned at the FOV center. MNPs were auto-infused at 15 mL/min (total 2.3 mL per animal, 10 mg(Fe)/mL). To reduce rapid clearance (i.e. to saturate the liver uptake), both animals first received 1.5 mL of standard synomag-D70, followed by 800 µL of either antibody-conjugated or standard synomag-D70. *In vivo* MPI images were acquired with a temporal resolution of approximately 2 s and reconstructed using the following parameters: regularization: $\lambda = 0.01$, numbers of iteration: 3, 0.625 MHz bandwidth and an SNR threshold of 4.

III. Results and discussion

The antibody-conjugated samples exhibited similar MPS results, with an iron-weighted third harmonic magnitude (A3*) of 28 $Am^2/kg(Fe)$ compared to 25 $Am^2/kg(Fe)$ for the control (Figure 1A), indicating no signal loss during antibody conjugation at low frequencies. However, the antibody-conjugated MNPs showed a notable decrease around 500 kHz which was absent in the control. At approximately the same frequency, sharp changes in phase values were observed, which were also not present in the control sample (Figure 1B). This indicates particle-particle interactions.

MNP infusion protocols resulted in high-signal brain images (see Figure 2A,B), demonstrating successful MPI brain image acquisition in both experiments. The sum of the raw MPI signals over the course of the experiments are shown in Figure 2C,D. Following the final MNP infusion, exponential decay fitting revealed that the antibody-conjugated MNPs exhibited a longer circulation half-life compared to the unconjugated control (114 min vs. 63 min, Figure 2D).

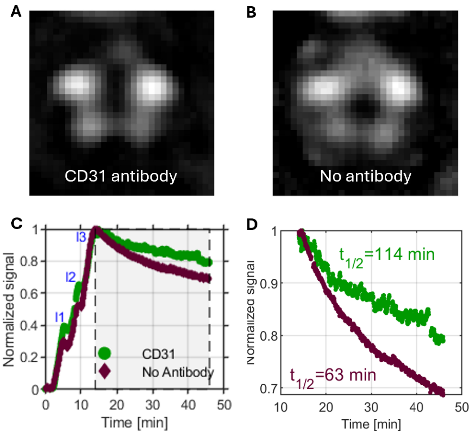

Figure 2: Central MPI brain image slices of CD31-conjugated (A) and standard synomag-D70 (B). Sum of raw MPI signal over the duration of experiment (C, D). For technical reasons, the MNPs were injected in 3 subsequent infusions (I1-I3, C).

IV. Conclusion

The MPS results showed minor differences between antibody-conjugated MNPs and the control. However, the longer half-life of antibody-conjugated MNPs proves improved retention in the brain. This is further supported by the noisier decay signal of the antibody-conjugated MNPs (Figure 2C), showing a 2.4-fold higher standard deviation. This may result from the conjugated MPNs' binding kinetics. Overall, these findings provide an initial foundation for developing more effective target selective, MPI-guided hyperthermia approaches in the brain.

Acknowledgments

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Author's statement

OB and JF are employees of Bruker BioSpin. The research related to animal use complies with all the relevant national regulations and institutional policies and has been approved by the authors' institutional review board under permit G20/150.

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