Magnetic Particle Imaging for the Imaging and Treatment of Stroke

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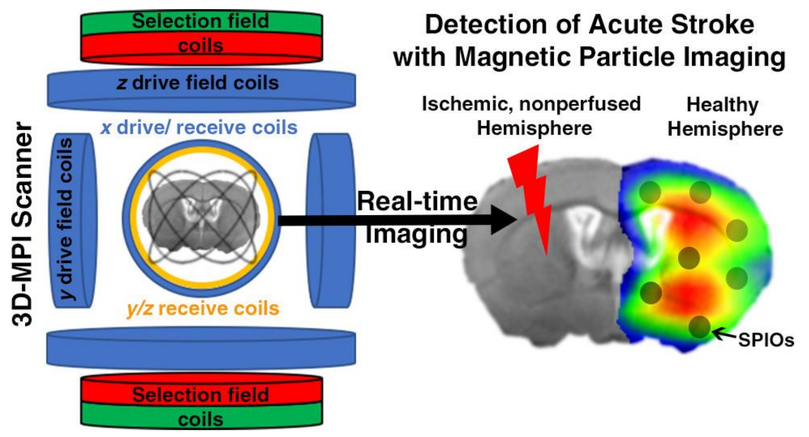
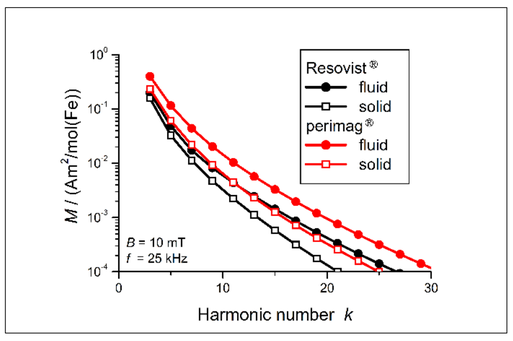
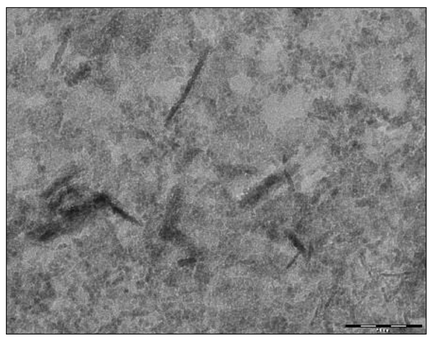
Introduction:

Ischemic stroke is a devastating disease and a leading cause of disability and death worldwide. Thrombolysis of cerebral blood clots with recombinant tissue-type plasminogen activator (rt-PA) is the only evidence-based medical treatment for stroke. Despite 20 years of experience with rt-PA, fifty percent of treated patients remain disabled for life. A narrow therapeutic time window, insufficient thrombolysis rates, serious side effects of this therapy, and time-consuming imaging techniques decrease the efficacy of stroke treatment. Our project aims to develop a new dual approach by combining therapy and monitoring of stroke patients with Magnetic Particle Imaging (MPI). This new imaging technique enables the rapid assessment of cerebral perfusion (Real-time MPI)[1,2], as well as the steering of magnetic nanoparticles by magnetic fields (Force-MPI)[3].

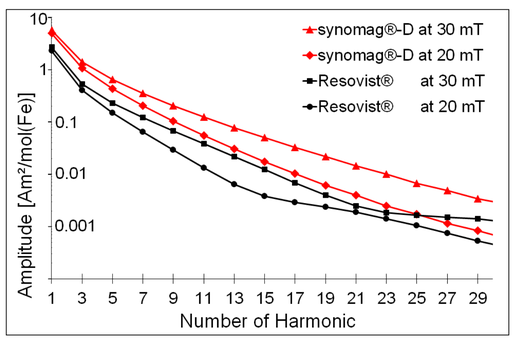


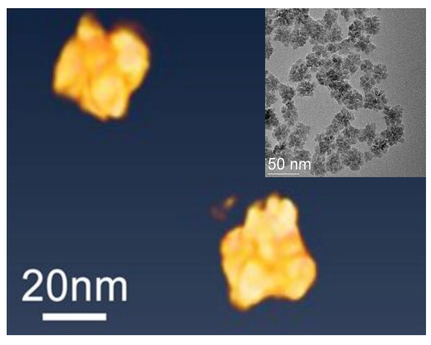
perimag® and synomag® as tracers for MPI:





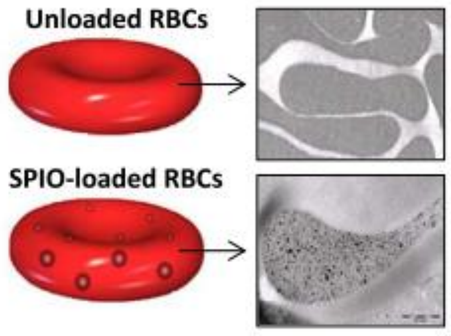
Magnetic particle spectra (MPS) of suspended and immobilized perimag® and Resovist® (left)[4], TEM image of perimag® particles (scale: 50 nm) (right)



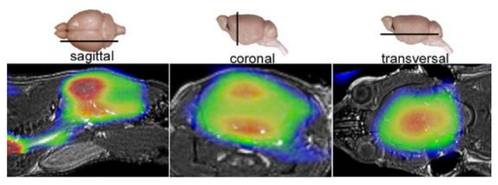


MPS of 50 nm synomag®-D at 20 and 30 mT, amplitude of odd harmonics scaled to the amount of iron compared to Resovist® (left)[5], TEM tomography image of synomag®-D with a closer look at two particles viewed parallel to the electron beam direction[6] (L.J. Zeng, Chalmers University of Technology, Göteborg)

Encapsulation of MPI tracers in red blood cells (RBCs) for prolonged imaging:

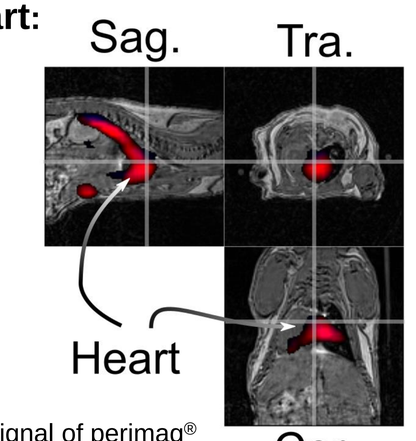


Tracer particles were encapsulated in RBCs to reduce the amount of injected tracers and to minimize possible side effects (TEM, scale bar: 500 nm).



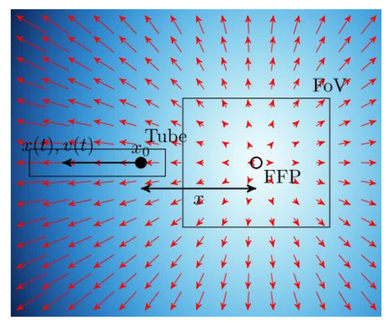
MPI signal of Tracer-RBCs two days after injection (MPI-MRI overlay). Imaging could be performed for at least 48 h in healthy mice.

In vivo measurement of perimag® flowing into the heart:

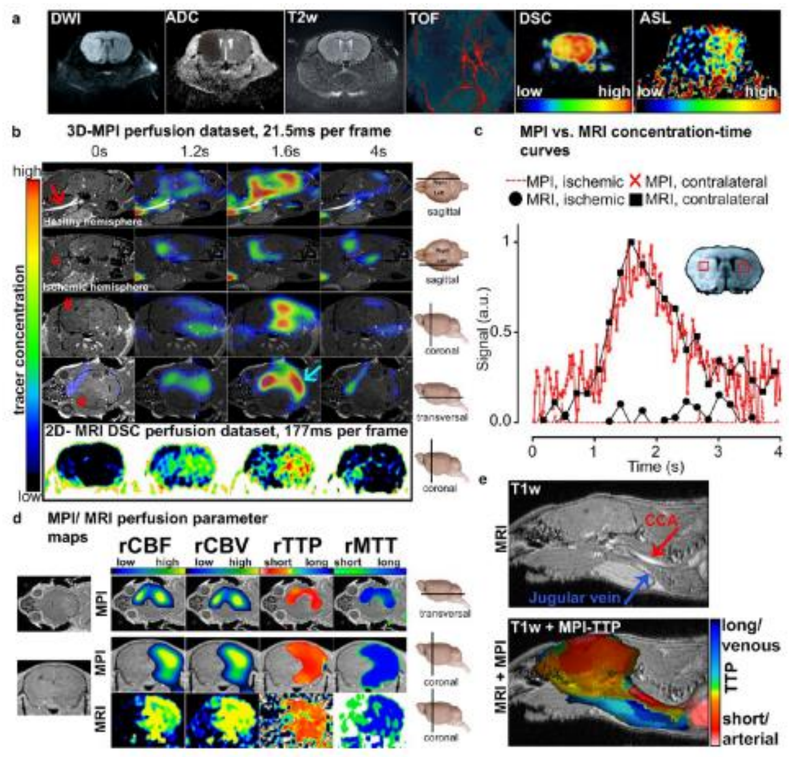


MPI signal of perimag® (red) in the heart of a mouse

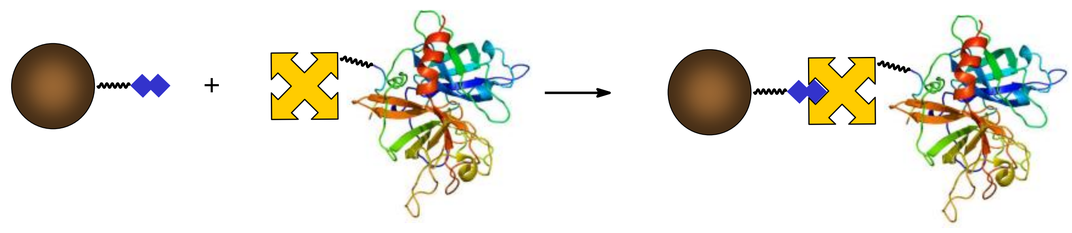
Switch between Imaging and Force MPI:



MPI stroke imaging:



Conjugation of rt-Pa to perimag® for thrombolysis of cerebral blood clots



Biotinylated tracer particle

Streptavidin modified recombinant tissue-type plasminogen activator (rt-PA)

rt-PA conjugated MPI tracer

MPI detects reduced cerebral perfusion comparable to MRI after induction of stroke[2]:

(a) Ischemic stroke in the left hemisphere was assessed with different MRI sequences
(b) Contrast agent bolus passing through the brain in slices of the automatically fused 3D MPI/MRI data at several time points. The ischemic hemisphere could be easily detected in MPI (red hash mark).
(c) MRI and MPI signals were plotted over time for certain selected regions of interests (filled black circles, MRI signal of ischemic hemisphere; filled black squares, MRI signal healthy hemisphere; red dotted line, MPI signal of ischemic hemisphere; red crosses, MPI signal of healthy hemisphere).
(d) Calculated perfusion parameter maps of the MPI and MRI curves showed a similar reduction of the relative cerebral blood flow (rCBF) and volume (rCBV) or a delay in the relative time to peak (rTTP) and rel. mean transit time (rMTT).
(e) Overlaying the MPI with the TTP parameter map enabled the differentiation of arterial and venous vessels.

References:

1. Ludewig, P., et al., Magnetic Particle Imaging in a mouse model of acute ischemic stroke. Proceedings of International Workshop on Magnetic Particle Imaging (IWMPI), 2016.
2. Ludewig, P., et al., Magnetic Particle Imaging for Real-Time Perfusion Imaging in Acute Stroke. ACS nano, 2017. 11(10): p. 10480-10488.
3. Nothnagel, N., et al., Steering of Magnetic Devices with a Magnetic Particle Imaging System. IEEE Trans Biomed Eng, 2016. 63(11): p. 2286-2293.
4. Eberbeck, D., et al., Multicore magnetic nanoparticles for magnetic particle imaging. IEEE Trans Magn, 2013. **49**(1): 269-274.
5. Grüttner, C., et al., synomag® Nanoflower Particles: A new tracer for MPI, Proceedings of International Workshop on Magnetic Particle Imaging (IWMPI), 2018: p. 17.
6. Bender, P., et al., Relating Magnetic Properties and High Hyperthermia Performance of Iron Oxide Nanoflowers. J. Phys. Chem. C, 2018. **122**(5): p. 3068-3077.

MAGneTISe Project: **MAGne**tic Particle Imaging for the **T**reatment and **I**maging of **S**trok**e** (EuroNanoMED III, Joint Transnational Call)