

# MRI Guided Magnetic Nanoparticle Based Drug Delivery for Neurodegenerative Diseases: Preliminary In-vivo and In-vitro Study

Yujuan Zhao<sup>1</sup>, Noah Snyder<sup>1</sup>, Tiejun Zhao<sup>2</sup>, Liza Bruk<sup>1</sup>, James Eles<sup>1</sup>, Xia Li<sup>1</sup>, X. Tracy Cui<sup>1</sup>, and Tamer S. Ibrahim<sup>1</sup>  
<sup>1</sup>University of Pittsburgh, Pittsburgh, Pennsylvania, United States, <sup>2</sup>Siemens Medical Solutions USA, Pittsburgh, Pennsylvania, United States

**Target Audience:** Audiences who are interested in drug delivery research and development for Neurodegenerative Diseases by using MRI technology.

**Purpose:** To develop a new magnetic nanoparticle (MNP) based drug release system and to study the feasibility that MRI fields triggering MNP drug release *in-vitro* and *in-vivo* in the region of central nervous system.

**Introduction:** Neurodegenerative diseases are generally not well-understood with no effective drugs available to treat and prevent these diseases. Oxidative markers and damaged cell components were observed in neurodegenerative patients [1]. Magnetic sensitive silica nano-spheres was used to control drug release [2]. A potent antioxidant compound could be incorporated in magnetic nanoparticle and delivered into central nervous systems (CNS) tissue for lowering oxidative stress related to numerous neurodegenerative diseases. In this study, the feasibility of using MRI fields to trigger the drug loaded MNPs is investigated. *In-vitro* and *in-vivo* results are provided.

## Methods:

**Experiments:** Silica magnetic nanoparticles were synthesized. Fluorescent compound was loaded to represent the drug release. All the experiments were done with a 7T MRI (Germany, Siemens). The effects of high intensity static magnetic fields on the stability of the particles were measured. Echo Planar Imaging (EPI) sequence was used to generate proper gradient field frequency to stimulate the drug release from designed dialysis sample tubes. The release of fluorescein *in-vitro* was measured using spectrum meter. For the pilot study, magnetic nanoparticles loaded with fluorescein were also injected into the brain of a rat. The rat was exposed to the gradient field stimulation and then tissue slices were examined for fluorescein release with brightfield and fluorescence microscopy. Magnetic nanoparticles were also injected into the rat brain without MRI stimulation exposure as the control.

**Results and Discussion:** The synthesized particles were placed inside the 7T MRI for 1 hour to compare with controlled groups. Figure 1 shows that the static field did not increase the drug release from magnetic nanoparticles. MRI scanner room data was used to test the fringe fields. The heated sample (80 °C) was used as a positive control for the release. The EPI sequence was applied with RF amplitude as 0 Voltage to make sure release; if there is any, will only come from the gradient field for the synthesized particles.

The readout is Z gradient field. Figure 2 shows the major frequency of the applied field is ~1.7 kHz and intensity is about 16 mT/m. We have placed the sample at the location (80 cm away from the imaging isocenter) to generate 12 mT gradient field. For the *in-vitro* experiments, two 10 minutes gradient fields' stimulations were applied at time point of 130 and 170 minute.

The release of fluorescein was measured. Figure 3 shows that after samples reached a plateau during the passive release phase with fluorescein diffusion across the dialysis membrane, constituent fluorescein increase was observed indicating MRI triggered release.

In-vivo images are shown in Figure 4. Magnetic nanoparticles (10 μL, 20 mg/mL) were injected 2 mm into the rat brain with 10 mins stimulation done with 1.7 kHz and 12 mT gradient fields. The control was just injected but no stimulation was done. The animal was immediately sacrificed. The brain was removed and flash-frozen. Brain slice in Figure 4 shows clear increase fluorescence in tissue surrounding magnetic nanoparticles.

**Conclusion:** *In-vivo* drug release from silica magnetic nanoparticles via MRI stimulation was demonstrated by observing fluorescein release from silica magnetic nanoparticles injected into the brain of rodents.

**References:** [1]. Gan, L. and J.A. Johnson, *Biochim Biophys Acta*, 2014. [2]. Hu, S.H., et al., *Langmuir*, 2008.

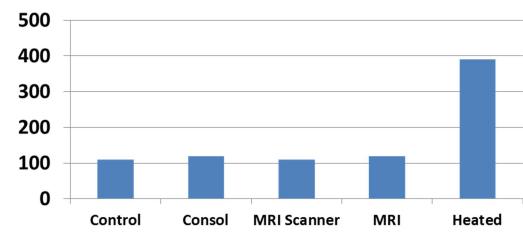


Fig. 1 Stability of MNP in the magnetic static field

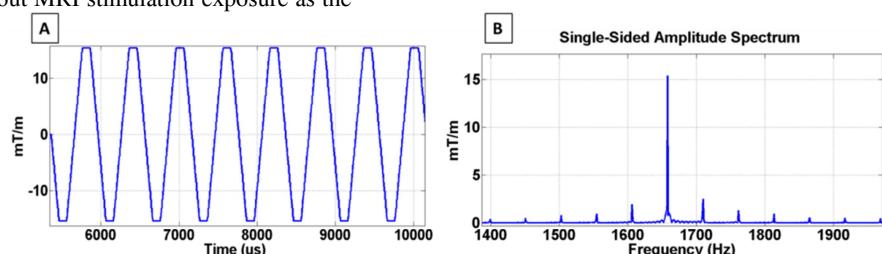


Fig. 2. Gradient fields generated by the applied EPI sequence (a). Fourier transform of the gradient field (b).

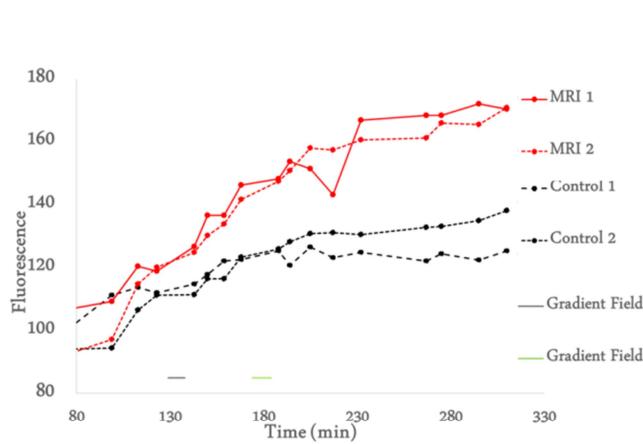
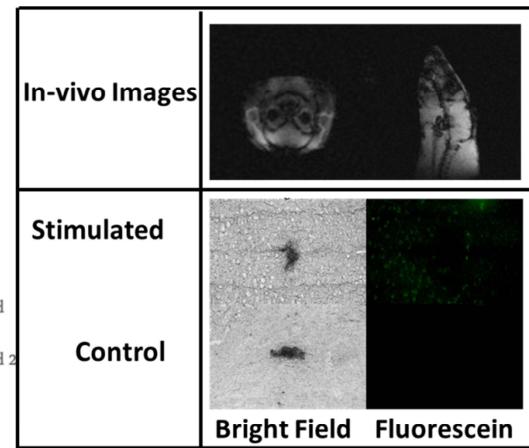


Fig. 3 MRI triggered release from magnetic nanoparticle. Fig. 4 In-vivo MRI triggered fluorescein release



Bright Field      Fluorescein