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Brownian superparamagnetic nanoparticles for cell viability assessment in Magnetic Particle Imaging

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Abstract

Molecular imaging tools can noninvasively track cells *in vivo*. However, no techniques today can rapidly monitor cell therapies to allow for nimble treatment optimization for each patient, the epitome of Personalized Medicine. Magnetic Particle Imaging (MPI) is a new tracer imaging technology that could soon provide MDs unequivocal therapy treatment feedback in just three days. MPI with Brownian superparamagnetic iron oxide nanoparticles shows promise towards noninvasive sensing of cell viability via viscosity changes in apoptotic cells. This unique ability could greatly improve the efficacy of cell therapies by enabling rapid personalization of the treatment.

I. Introduction

There are now over 1,000 cell therapies in clinical trials. Current molecular imaging methods, including MRI with 19F or superparamagnetic iron oxide (SPIO), ultrasound with microbubbles and nuclear medicine with radioisotopes, all have limitations in persistence, sensitivity, resolution or artifacts. No cell tracking tools today can fully and rapidly assess treatment efficacy to allow for nimble treatment optimization for each patient. For example, immunotherapy has become a mainstream treatment of bloodborne cancers (10% of all tumors), but it remains an open challenge for "solid tumors," which account for 90% of tumors [2]. Magnetic Particle Imaging (MPI) is a new imaging method ideal for tracking cells [1, 3–8]. It could soon allow MDs to gauge treatment efficacy directly and rapidly—in just three days. MPI offers ideal micromolar sensitivity; positive, linear and quantitative contrast with 100-fold higher SNR/cell compared to 19F MRI; zero radiation, robust penetration and no artifacts anywhere in the body—including in the lungs and inside bones (Fig. 1).

An outstanding challenge for all cell tracking methods is distinguishing live from apoptotic cells. Cellular viscosity changes when cells undergo apoptosis [9]. While some imaging techniques could potentially discern cell viability through genetic manipulation, they are often not translational.

MPI, in contrast, provides a unique sensing ability that could detect cell viability. MPI scanning requires an 180-degree rotation of the SPIO. This rotation time is slowed by Néelian and Brownian relaxation constants (Fig. 2) [10]. Néelian and Brownian relaxation in MPI is akin to T1 and T2 in MRI. In Néelian relaxation, the SPIO domain flips with no physical rotation, so Néelian SPIOs cannot sense viscosity changes. With Brownian

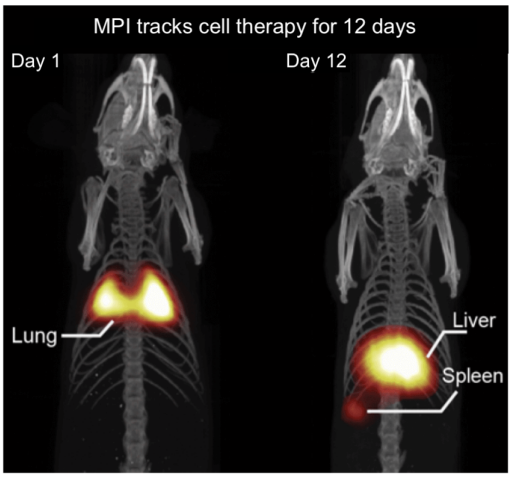

Figure 1: UC Berkeley first-in-animal study of MPI directly monitoring cell therapy quickly in 3 days, allowing time for modifying the therapy. Here, MPI can see 1 million therapeutic cells in lungs (Day 1) and in the liver (Day 12) (Reproduced with permission from Springer Nature) [1].

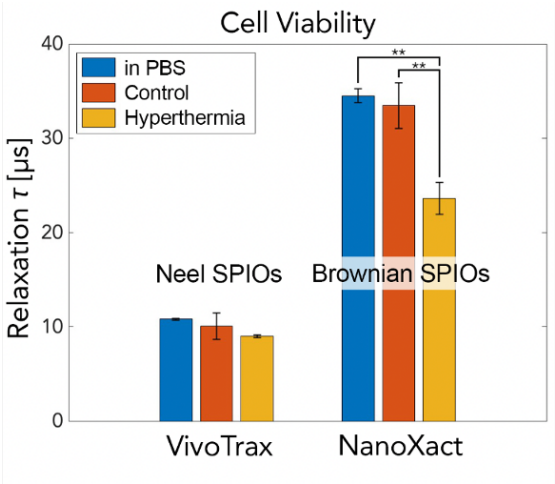

Figure 3: MPI can noninvasively gauge cell viability Cellular viscosity changes when cells undergo apoptosis. MPI viscometry can infer cell death ($p<0.01$) of therapeutic cells. No other imaging modality can provide this unique sensing capability.

relaxation, the entire SPIO aligns with the field, so Brownian relaxation scales linearly with the nanoscale viscosity. Since Néelian and Brownian relaxation occurs in parallel, we observe the faster of the two. Here, we demonstrate for the first time promising data showing that Brownian MPI particles can infer cell death via viscosity sensing.

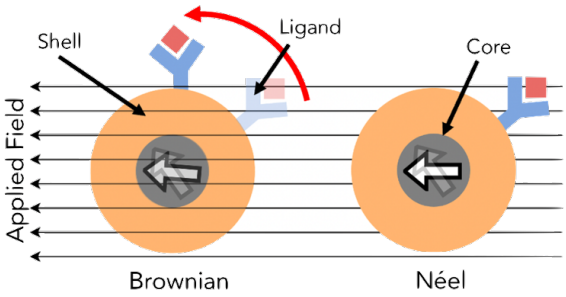

Figure 2: SPIO relaxation mechanisms Brownian relaxation (left) involves the physical rotation of the SPIO, including its shell and any attached ligands, with the applied magnetic field. Néelian relaxation (right) only involves the reorientation of the internal magnetic domain of the SPIO with the applied magnetic field. There is no physical rotation of the SPIO.

II. Methods

We used nanoComposix NanoXact (hydrodynamic diameter 16 nm, PVP coating) and Magnetic Insight VivoTrax (hydrodynamic diameter 4.2, carboxydextran coating) to label LLC1 lung cancer cells. NanoXact was chosen for our Brownian SPIO because we found its relaxation time scales linearly with viscosity [11]. VivoTrax was chosen as our Néelian SPIO as its relaxation time does not vary with viscosity. Due to concentration variations, two flasks of cells were incubated with 100 µL of NanoXact and the other two with 300 µL of VivoTrax. After 24 hours, the cells were harvested and washed with a phosphate buffer. The NanoXact and VivoTrax labeled cells were divided into two groups. One group was incubated at 37°C (control), and the other group was incubated in a hot water bath at 60°C to induce cell death via hyperthermia for 2 hours [12]. Relaxation time constants of both groups of cells were measured using a periodic square-wave pulsed magnetic field of amplitude 10 mT and 1 kHz frequency in the Arbitrary Waveform Relaxometer (AWR) [13]. We integrated and fitted the gradiometric received signals to a rising exponential function to determine the relaxation time constant.

III. Results and Discussion

We observed distinct relaxation mechanisms in the two groups of cells labeled with Brownian (NanoXact) and Néelian (VivoTrax) SPIOs (Fig. 3). As hypothesized, there are statistically significant ($p<0.01$) changes in Brownian relaxation due to viscosity changes in apoptotic cells. There are only minor changes in relaxation time in cells labeled with Néelian SPIOs (VivoTrax). These data show great promise for MPI cell tracking using Brownian SPIOs to monitor therapeutic cell viability.

IV. Conclusion

Nanoscale viscosity is challenging to measure *in vivo*. We have demonstrated that Brownian MPI relaxation is a

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new and unexplored tool for measuring viscosity changes during cell death. No other cell tracking tool (MRI, CT, X-ray or nuclear medicine) offers this unique cell viability sensing ability. In the future, we plan to exploit Brownian relaxation contrast to allow for distinguishing bound SPIOs (which will have restricted rotation) from unbound SPIOs in an imaging format. This remains an open challenge for medical imaging.

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Author's statement

Conflict of interest: Dr. Conolly is a co-founder of a startup company that manufactures and sells preclinical MPI scanners. Part of this work was presented at the world molecular imaging congress.

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