In vivo Characterization of the Pharmacokinetics of Perfluorocarbon Nanoparticles in a Mouse Model using ^{19}F MRS

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Introduction: Magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) show potential as tools for non-invasive in vivo study of the pharmacokinetics of drugs tagged with appropriate contrast agents [1]. In clinical use, perfluorocarbon (PFC) nanoparticles can be chemically modified for targeted drug delivery and can carry large payloads of therapeutic agents. Fluorine in PFC nanoparticles provides a ^{19}F signal for MRI and MRS that is distinct from the in vivo background. MRI and MRS thus may be able to track the location and quantity of functionalized PFC nanoparticles in vivo [2]. The objective of this study is to use ^{19}F MRS to characterize the pharmacokinetics of nanoparticles containing perfluoro-15-crown-5 ether (crown ether) in the mouse after intravenous injection to demonstrate proof of concept for MRI/MRS pharmacokinetics assessment.

Methods: MR experiments were performed on a Varian 4.7T MR system. A custom-built 4-turn solenoid coil was used to obtain MR spectra from the tail of adult C57/BL6 mice (n=5) anesthetized with ketamine/xylazine. 20mol% crown ether nanoparticles were administered intravenously through a jugular vein catheter at dose of 1 mL/kg body weight. Following injection of the nanoparticles, MR spectra were obtained from the tail every 5 to 10 minutes for up to 4 hours. Mouse body temperature was maintained at 37°C and heart rate was monitored with an MR-compatible small animal monitoring and gating system (SA instruments, NY). Spectra were analyzed using NUTS NMR data processing software (Acorn NMR Inc., CA). ^{19}F signal intensity was used as a relative measure of crown ether concentration in the blood. To represent PFC clearance with a two-compartment model, signal intensity data were fitted as a function of time to bi-exponential curves with the use of an iterative algorithm (Levenberg-Marquardt).

Another mouse was used for quantitative comparison of in vivo and in vitro measurement of ^{19}F signal intensity. Four 50μL blood samples were acquired at different time points during the course of in vivo MRS. 500 μL of saline was injected subcutaneously to replenish fluid loss after each blood sampling. The in vivo ^{19}F signal intensity trend was fitted to a bi-exponential curve as described above. MR signal intensities from the four isolated blood samples were compared to in vivo signal intensities predicted by the fitted curve.

Results: In five trials, the observed decay of in vivo ^{19}F signal intensity was fitted to a two-compartment model (figure 1). Median residual half-life of crown ether nanoparticles was 8.23 minutes. Assuming sampling from a gamma distribution, residual half-life exhibited a 90% confidence interval of [.08 to 50.67] minutes. Mean terminal half-life was 181.3±40.7 minutes. Assuming sampling from a t distribution with 4 degrees of freedom, terminal half-life exhibited a 90% confidence interval of [142.5 to 220.0] minutes.

In vivo ^{19}F signal intensity was plotted alongside ^{19}F intensity in blood samples acquired from the same mouse (figure 2). Comparing blood intensity data to in vivo intensities predicted by a fitted bi-exponential curve, we obtain a correlation coefficient (Pearsonian r value) of .9895. This relationship illustrates the correspondence between in vivo ^{19}F signal intensity and crown ether concentration in the blood.

Conclusions: ^{19}F MRS successfully tracked the relative concentration of PFCs in mice following injection of PFC-core nanoparticles. We suggest that the use of ^{19}F signal intensity as a measure of concentration will permit non-invasive characterization of the pharmacokinetics of drug-bearing PFC nanoparticles in vivo.

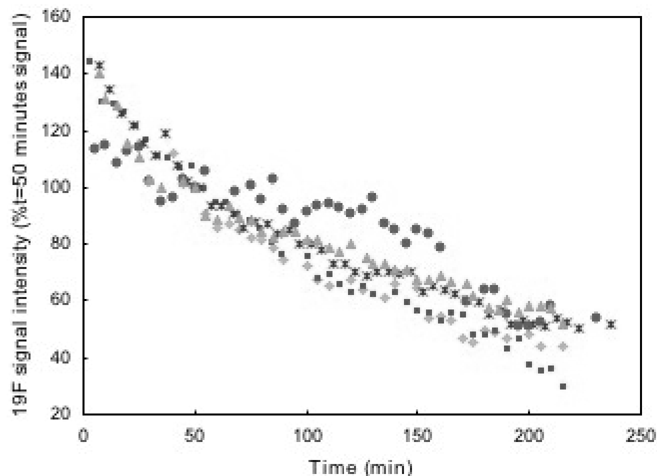

Fig. 1. In vivo ^{19}F signal intensity as a function of time after injection of PFC nanoparticles in five mice. Intensity is normalized to the t=50 min value in each trial.

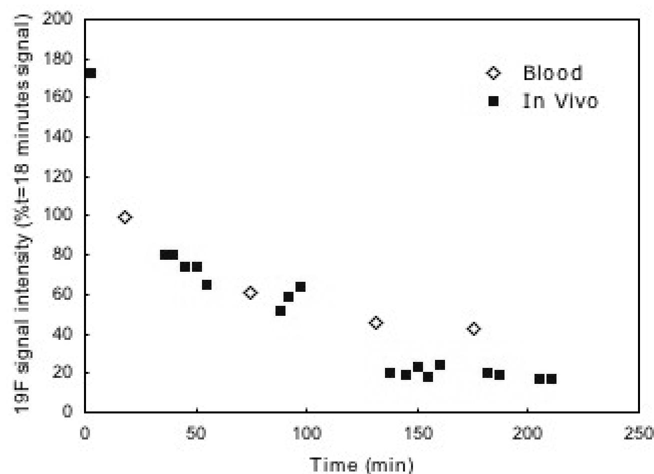

Fig. 2. In vivo ^{19}F signal intensity and ^{19}F signal intensity in extracted blood as a function of time after injection of PFC nanoparticles. For blood data, intensity is normalized to the t=18 min value. For in vivo data, intensity is normalized to a t=18 min value predicted by a bi-exponential fit to the given data.

References:

1. Griffiths JR, Glickson JD, Adv Drug Deliv Rev 2000;41;75-89
2. Winter PM et. al., Curr Cardiol Rep 2006;8(1);65-69