Fluorine-19 based MR imaging tracer 19FIT for drug dilvery research.

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Introduction: Fluorine-19 is a promising reporter for drug delivery research because of its high NMR sensitivity, 100% natural abundance and minimal background interference from human body. However, MR imaging of most fluorinated compounds suffers from low signal intensity caused by low quantity, long T_1, and multiple chemical shifts, and low hydrophilicity causes long retention time which might increase the toxicity. To address these issues, we present a ^{19}F based multifunctional drug delivery vehicle ^{19}Fluorine Imaging Tracer (^{19}FIT). Our ^{19}FIT contains 27 ^{19}F nuclei in each molecule with identical chemical shift [1]. Its relatively short T_1 (253.3±25.0 ms in solution and ~370 ms in vivo at 3 T) of our compound allows for increased signal averages in unit scan time and its short retention time reduce the toxicity risk.

Methods: Phantom and animal studies were performed on a Siemens 3T Trio clinical MRI system (Siemens Medical Solution, Erlangen, Germany). A home built double tuned saddle coil was used to detect ^{1}H and ^{19}F signals at 123.22 MHz and 115.94 MHz, respectively. Four 16-week old male BALB/C white mice were used in the animal study. Two mice received 400 µl 150 mM ^{19}FIT (2.2 mmol/kg ^{19}FIT concentration, 60 mmol/kg ^{19}F concentration) and two mice received 200 µl saline and 200 µl 150 mM ^{19}FIT (1.1 mmol/kg ^{19}FIT concentration, 30 mmol/kg ^{19}F concentration) through the tail vein. ^{1}H images were acquired by 3D FLASH pulse sequence with 0.4×0.4×0.4 mm^3 spatial resolution, 100×50 mm^2 FOV, 7.73 ms TR, 2.74 ms TE, 25º flip angle, 150 Hz/pixel bandwidth, 2 averages and 1 min 11 sec imaging time; ^{19}F images were obtained at the same location by a GRE pulse sequence with 1.5×1.5×3.0 mm^3 spatial resolution, 192×96 mm^2 FOV, 400 ms TR, 2.98 ms TE, 90º flip angle, 260 Hz/pixel bandwidth, 16 averages and 5 min 9 sec imaging time. To assess the total fluorine amount of ^{19}F, whole body spectra were acquired using FID pulse sequence with 8 averages, 100 kHz bandwidth, 0.15 ms TE and 1600 ms TR. *In-vivo* T_1 of ^{19}FIT was also measured using series of whole body FID signals with various recovery times of 200, 400, 800, 1600, 3200 ms. Animals were monitored over a month period after the experiment.

Results and Discussions: T_1 values of ^{19}FIT was obtained from both phantom experiment and animal experiment, T_1 of ^{19}FIT solution in vial was 253.3±25.0 ms and in vivo T_1 of ^{19}FIT from one mouse with 1.1 mmol/kg ^{19}FIT was 393.1±48.0 ms, 368.2±5.9 ms, 420.9±83.8 ms and 314.3±52.8 ms for time 0, 4 hours, 8 hours and 24 hours after the injection. The prolonged T_1 of ^{19}FIT in vivo is possibly caused by the altered molecular rotational motion of the compound *in-vivo*. ^{19}F MR images are overlaid onto the proton MRI at various time points in Fig. 1, for a mouse that received 2.2 mmol/kg ^{19}FIT. These overlaid images clearly demonstrate the distribution and clearance process in different organs such as heart, liver and bladder.

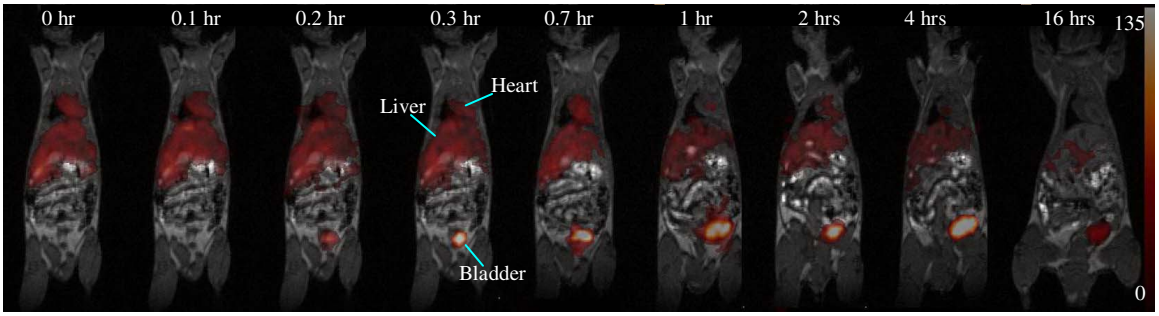

Figure 1. ^{19}F images overlaid on the ^{1}H MRI at various time points for a mouse received 2.2 mmol/kg ^{19}FIT.

After the 16-hour time point, one more fluorine image was taken on 40-hour time point, the fluorine signal was on the noise level and not able to be detected. Plots in Fig. 2 demonstrate the clearance patterns of ^{19}F NMR in two mice (2.2 mmol/kg and 1.1 mmol/kg ^{19}FIT) over time. After two days, signals dropped down to 1/10 for both mice; six days later residual signals were 1/26 and 1/20 of the original amount for 2.2 mmol/kg and 1.1 mmol/kg respectively. The total detectable ^{19}F compounds were 0.085 mmol/kg and 0.055 mmol/kg for initial dosages of 2.2 mmol/kg and 1.1 mmol/kg, respectively. The plots indicate that the signal intensities of both dosages clearly follow a double exponential decay functions. Data was fitted to a double exponential decay function. Decay constants for the mouse with 2.2 mmol/kg ^{19}FIT were 1148.7 and 6996.1 min. and those for the mouse with 1.1 mmol/kg ^{19}FIT were 1053.5 and 17722.8 min.

No death or dramatic reduction in body weight was observed within 4 weeks after the injection of ^{19}FIT, which indicates our ^{19}FIT has no prominent toxic effects over a month.

Perfluoro-15-*crown-5-ether* was used as the comparison. With a dosage of ^{19}F nuclei equivalent to 400 µl 150 mM ^{19}FIT or 2.2 mmol/kg, ^{19}F signal was on the noise level on the images because of the long *in-vivo* T_1 of 1.15 s; with three times higher dosage, during first several hours after the injection, most of the signal was founded in the liver area and no obvious signal intensity change was observed.

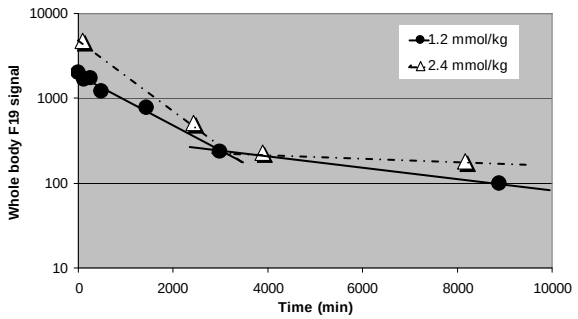

Figure 2. Plot of whole body fluorine signal versus time for 2 mice received 2.2 mmol/kg and 1.1 mmol/kg ^{19}FIT separately.

Conclusion: ^{19}F based drug delivery vehicle ^{19}FIT combined with ^{19}F MR imaging facility on 3T clinical MR scanner has been investigated. The advantages of ^{19}FIT over other fluorine compounds, such as high and singlet fluorine signal, short T_1 and short *in vivo* retention time, make ^{19}FIT to be a perfect ^{19}F based reporter molecule for drug delivery research.

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Reference: [1] Z.X. Jiang, Y.B. Yu. *Tetrahedron.* 2007, 63, 3982–3988.