Multi-Modality PET-MR Perfluorocarbon Nanoparticle Contrast Agent for Ligand-Targeted Quantitative Imaging

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Introduction. The combination of positron emission tomography and magnetic resonance imaging offers a major breakthrough in detecting, characterizing and monitoring disease. This work introduces a novel contrast agent, detected by both modalities, which employs a self-inserting chelator with linker peptide derived from melittin (a host defense peptide in honeybee venom). Based on a lipid-encapsulated perfluorocarbon (PFC) nanoparticle (NP) [1], which has previously been modified for SPECT imaging [2,3], the proposed ^{64}Cu-labeled molecular imaging agent can be sensitively detected and localized with whole-body PET, directing the focal acquisition of high resolution, high specificity MR imaging. The liquid perfluorocarbon core can be imaged directly with ^{19}F MRI, independent of gadolinium or iron for paramagnetic effects. The objective of this work is to synthesize the peptide linker to chelate ^{64}Cu, label PFC NP and demonstrate the first quantitative imaging of the multi-modality PET-MR agent in vitro.

Methods. Based on previously-published methods [1], lipid-encapsulated perfluoro-15-crown-5-ether nanoparticle emulsion was prepared (devoid of Gd). Peptide-chelator construct was prepared combining the macrocyclic chelator CB-TE2A [4] to the D1-7 segment of the melitin-derived peptide linker [5]. The peptide-chelate (2.4μg) was incubated with 2.5mCi ^{64}Cu for 20min at 95°C and then purified. For self-inserting into the outer lipid membrane of the NP, the ^{64}Cu-labeled peptide was combined with a 100μL aliquot of NP for 30min at 4°C then washed, lightly centrifuged, and resuspended multiple times. The radiolabeled aliquot of NP was reintroduced to the original volume of PFC emulsion resulting in a hot:cold ratio of approximately 1:10. A phantom comprising five 1ml-vials (8mm diameter) was constructed with further dilutions of the PET-MR agent such that a constant amount of ^{64}Cu was in each vial, but the NP concentration (and therefore [^{19}F]) varied 10-fold (*ca*., 6nM – 60nM NP). PET images were acquired with an Inveon small animal PET/CT, and MR images were acquired on a clinical 3T scanner equipped for simultaneous ^{1}H/^{19}F imaging [6] using 3D gradient echo techniques (TR/TE=12/6ms, matrix=64^2, voxel=2x2x2mm^3, 64 averages, scan time=2min).

Results and Discussion. The multi-modality PET-MR agent was successfully created and ^{64}Cu-labeling was achieved. Due to the self-insertion properties of the melittin-derived peptide-chelate, labeling was performed by combining the two already-prepared components. Initial imaging results confirm labeling with strong signal on both PET and MRI (see Fig. 1). The consistent PET signal across vials reflects the constant amount of ^{64}Cu as expected. The ^{1}H MRI, primarily detecting the water in the emulsion, also gives constant signal across vials as expected. The ^{19}F signature from the liquid PFC core of the NP was imaged having SNR that varied monotonically from 50±8 to 826±87 for the lowest to highest concentrations, respectively (see Fig. 2).

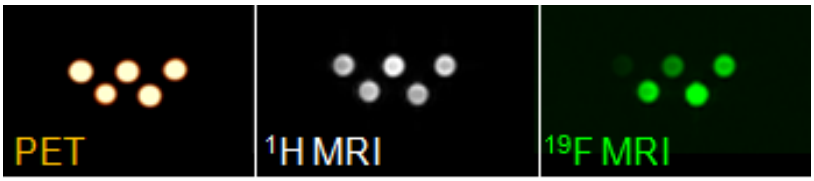

Fig. 1. *In vitro* images of multi-modality PET-MR agent. Phantom consists of 5 vials with constant ^{64}Cu activity, but varying fluorine concentration [^{19}F] (increasing from top left vial to bottom right vial). Cross-sectional PET images (Left) show consistent high signal. Simultaneously acquired proton (Mid) and ^{19}F (Right) MRI acquired in 2min, show constant signal intensity on ^{1}H MRI as expected and increasing signal with increasing [^{19}F] on ^{19}F MRI.

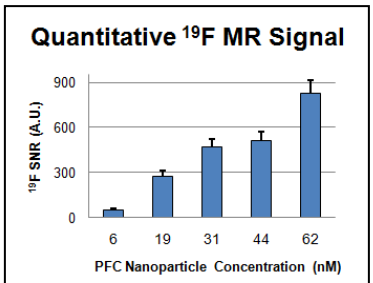

Fig. 2. Signal to noise analysis from ^{19}F MRI of PET-MR agent in vials with varying [^{19}F]. As ^{19}F concentration increases, SNR increases accordingly.

Conclusion. A new multi-modality PET-MR agent was developed wherein efficient radio-labeling can be easily achieved at the time of imaging by combining the two previously-prepared components: a lipid-encapsulated PFC NP and a self-inserting ^{64}Cu-labeled chelate-peptide linker derived from melittin. Using the ^{19}F readout from the NP, quantitative MR imaging is achieved without the need for paramagnetic metals.

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