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 64Cu-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 19F MRI, independent of gadolinium or iron for paramagnetic effects. The objective of this work is to synthesize the peptide linker to chelate 64Cu, 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 64Cu for 20min at 95°C and then purified. For self-inserting into the outer lipid membrane of the NP, the 64Cu-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 64Cu was in each vial, but the NP concentration (and therefore [19F]) 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 1H/19F imaging [6] using 3D gradient echo techniques (TR/TE=12/6ms, matrix=643, voxel=2x2x2mm3, 64 averages, scan time=2min).

Results and Discussion. The multi-modality PET-MR agent was successfully created and 64Cu-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 64Cu as expected. The 1H MRI, primarily detecting the water in the emulsion, also gives constant signal across vials as expected. The 19F 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). 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 64Cu-labeled chelate-peptide linker derived from melittin. Using the 19F readout from the NP, quantitative MR imaging is achieved without the need for paramagnetic metals.