Protein MRI Contrast Agents (ProCAs) with Unique Capability in Early detection and Molecular Imaging of Varies Types of Cancer

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The major barriers limiting the application of MRI to detect small lesions and metastasis at the early stage and patient selection for targeted therapy based on molecular imaging of disease biomarkers, are due to the lack of desired MRI contrast agents capable of enhancing the contrast between normal liver tissues and tumors with high relaxivity, tumor targeting, high intra-tumoral distribution and no toxicity. To address the critical need, we have developed a novel class of protein-based MRI contrast agents (ProCAs) with significant improvement of both r_1 and $r_2$relaxivities and *in vivo* dose efficiency in mouse models. Several key factors for relaxivitysuch as correlation time, exchangeable water numbers from first coordination shell and secondary/ outer sphere are improved by protein design of Gd^{3+} binding site(s) in stable proteins and protein modification. Our recent studies have shown that the Gd^{3+} binding constant of ProCAs is comparable to DTPA but metal selectivity for Gd^{3+} over physiological metal ions such as $Ca^{2+,}$ Mg^{2+} and Zn^{2+} are >10000 fold than DTPA and there is no detectable cellular and animal toxicity. It enables non-invasive early detection primary liver tumors and metastatic tumors at 0.2 mm from the current threshold of 20 mm or larger. In addition, our developed ProCAs enable the 100 fold increase of detection size of metastatic liver tumors by MRI from the current threshold of 20 mm or larger with high confidence using our established melanoma metastatic mouse model. Furthermore, we have designed several MRI contrast agents that specifically targeting to cancer biomarkers including HER2, EGFR, GRPR, VEGFR, and CXCR4 that expressed on various types of cancers using animal models. These new classes of targeted MRI probes exhibit advantages in crossing the endothelial boundary, tissue distribution, and tumor tissue retention as demonstrated by even distribution of the imaging probe across the entire tumor mass. The capability to spatially and temporally visualize intratumoral distribution as well as quantification of the levels of major disease biomarkers would greatly improve our ability to track the change of the biomarkers during tumor progression, monitor treatment efficacy, aid in patient selection, and further develop novel targeted therapies for clinical application.

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