EGFR MAb-bioconjugated superparamagnetic iron oxide nanoparticles as a specific MRI contrast agent for detection of brain glioma in vivo

Ketao Mu[1], Yuanyuan Qin[1], Yan Zhang[1], He Wang[2], and Wenzhen Zhu[1]

[1]*Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China,* [2]*MR Rresearch China,GE Healthcare, Shang hai, Shang hai, China*

Introduction: Despite considerable interest in noninvasive diagnosis of brain glioma with MRI *in vivo*, high sensitivity and specificity for glioma diagnosis to define the tumor anatomy for surgical section, chemotherapy and radiation therapy need to further research[1].Superparamagnetic iron oxide nanoparticle (SPIONPs) delivery system has become a model system in which to study the target molecule-specific biodistribution, rapid exertion and undesired side-effects using *in vivo* small animal MRI. As a cellular transmembrane receptor, EGFR regulates important cellular processes and is linked to a poor prognosis in various human cancers[2]. Although EGFR offers a useful new tool as a brain glioma biomarker, its monoclonal antibody has not been widely used or translated for use in medical imaging. In this study, we developed a potentially valuable new targeted nanocarrier based on SPIO delivery system, EGFRmAb-bioconjugated nanoparticles—EGFRmAb-SPIONPs. Magnetic targeting is a promising strategy for developing the diagnosis of brain glioma. The purpose of this study was to elucidate strategies for further improvement of this promising approach.

Methodand Materials: EGFRmAb-SPIONs were preparated and characterizated. The preferential accumulation of the EGFRmAb-SPIONPs within gliomas and subsequent magnetic resonance imaging (MRI) contrast enhancement were demonstrated in vitro in C6 cells and in vivo in tumors of rat model.MRI scanning was performed using a 3.0T MRI scanner (Signa HDxt GEMR) and a research coil insert designed specifically for imaging rats was used to MRI.

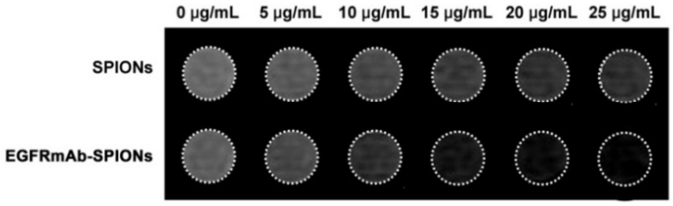

Fig. 1 In vitro T2WI MRI of C6 cells; Upper row: C6 cells with SPIONPs; Lower row: C6 cells with EGFRmAb-SPIONPs.

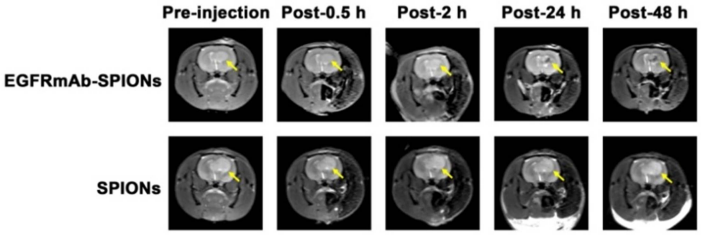

Fig. 2 In vivo MR images of rats' brain bearing C6 gliomas . Upper row: MRI after administration of SPIONPs; Lower row: MRI after administration of EGFRmAb-SPIONPs.

Results: The average particle size of about 10.21 nm, hydrodynamic diameter of about 161.5 nm, saturation magnetization of 55 emu/g Fe and T2 relaxivity of 92.73 $S^{-1}mM^{-1}$ of the EGFRmAb- SPIONs suggested its applicability for MRI.MR T2WI of iron uptake in C6 cells treated with the nanoparticles (EGFRmAb-SPIONPs and SPIONPs) of various iron concentrations were shown in Fig. 1. This result demonstrated that, EGFRmAb-SPIONPs could efficiently and specifically label the C6 cells compared to SPIONPs. Using a rat model of C6 glioma, EGFRmAb-SPIONs provided a better picture or more sensitivity to depict brain glioma on MR images than that of SPIONs. Significantly enhanced T2-weighted images of brain glioma were documented in vivo with EGFRmAb-SPIONs until 48h after injection(Fig. 2). Histochemical analysis of the tumor tissue shown in Fig. 3.The results from cytotoxicity, histopathology and blood toxicity assays suggested that the EGFRmAb-SPIONPs had good biocompatibility and exhibited no toxicity.

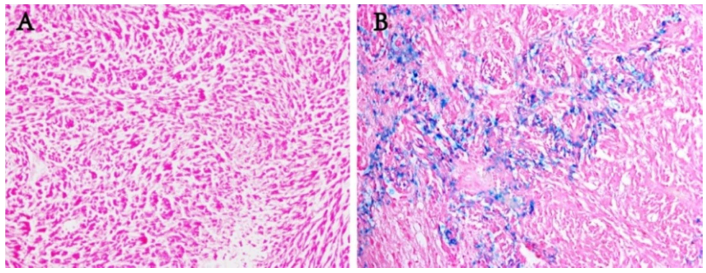

Fig.3 Rats were sacrificed after 48 h of injection of nanoparticles. (A): sections were stained with Prussian blue with SPIONPs (400×); (B): with EGFRmAb-SPIONPs (400×).

Discussion and Conclusions:we showed the following main findings: first, EGFRmAb-SPIONPs is suitable for use as negative MRI contrast agent, specially T2WI; secondly EGFRmAb-SPIONPs could be specifically and efficiently uptaken by C6 glioma cells, and selectively improve the detection of tumor by MRI; thirdly EGFRmAb-SPIONPs could produce the remarkable contrast change of brain glioma in vivo following intra-carotid administration of EGFRmAb-SPIONPs; and fourthly EGFRmAb-SPIONPs had good biocompatibility and exhibited no toxicity, which was very important for the clinical application. Thus, as prolonged retention in tumors, relatively safer toxicity profile and strong T2-relaxation on MR images—an attractive property for their real-time, in vivo monitoring, EGFR MAb-SPIONPs may allow for earlier cancer detection, assessment of the recurrent tumor after tumor resection and postoperative radiotherapy.

Reference:[1] Johnson L, et al. Applications of nanotechnology in cancer. Discovery medicine. 2010;9(47):374-9.

[2] Sun C,et al. In vivo MRI detection of gliomas by chlorotoxin-conjugated superparamagnetic nanoprobes. Small. 2008;4(3):372-9.