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A Theragnostic Approach for Alzheimer's Disease Focused on Phosphorylated Tau

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Abstract : Introduction: Alzheimer's disease (AD) and other tauopathies are primary causes of dementia, causing progressive cognitive deterioration that entails serious repercussions for the patients' performance of daily tasks. Currently, there is no effective approach for the early diagnosis and treatment of AD and tauopathies. This study suggests a theragnostic approach based on the importance of phosphorylated tau protein (p-Tau) in the early pathophysiological processes of AD. We have developed a novel theragnostic monoclonal antibody (mAb) to provide both diagnostic and therapeutic effects. Methods/Results: We have developed a p-Tau mAb, which was doped with deferoxamine for radiolabeling with Zirconium-89 (89Zr) for PET imaging, as well as fluorescence dies for immunofluorescence assays. The p-Tau mAb was evaluated in vitro for toxicity by MTT assay, LDH activity, propidium iodide/Annexin V assay, caspase-3, and mitochondrial membrane potential (MMP) assay in both mouse endothelial cell line (bEnd.3) and cortical primary neurons cell cultures. Importantly, non-toxic effects (up to concentrations of p-Tau mAb greater than 100 ug/mL) were detected. In vivo experiments in the tauopathy model mice (PS19) show that the 89Zr-pTau-mAb and 89Zr-Fragments-pTau-mAb are stable in circulation for up to 10 days without toxic effects. However, only less than 0.2% reached the brain, so further strategies have to be designed for crossing the Brain-Blood-Barrier (BBB). Moreover, an intraparenchymal treatment strategy was carried out. The PS19 mice were operated to implement osmotic pumps (Alzet 1004) at two different times, at 4 and 7 months, to stimulate the controlled release for one month each of the B6 antibody or the IgG1 control antibody. We demonstrated that B6-treated mice maintained their motor and memory abilities significantly compared with IgG1 treatment. In addition, we observed a significant reduction in p-Tau deposits in the brain. Conclusions /Discussion: A theragnostic pTau-mAb was developed. Moreover, we demonstrated that our p-Tau mAb recognizes very-early pathology forms of p-Tau by non-invasive techniques, such as PET. In addition, p-Tau mAb has non-toxic effects, both in vitro and in vivo. Although the p-Tau mAb is stable in circulation, only 0.2% achieve the brain. However, direct intraventricular treatment significantly reduces cognitive impairment in Alzheimer's animal models, as well as the accumulation of toxic p-Tau species.

Keywords : alzheimer's disease, theragnosis, tau, PET, immunotherapy, tauopathies
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