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# *In vivo* monitoring of tumor response to chemotherapy by PET/NIRF imaging of cell death using a novel phosphatidylserine-targeted molecular probe

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## Abstract

Phosphatidylserine (PS) exposure is one of the most prominent and ubiquitous fingerprints of dying cells, making it an attractive biomarker for molecular imaging. Synthetic bis-zinc(II)-dipicolylamine (Zn-DPA) derivatives have high selectivity for biological membranes enriched with PS. Our study aims to apply PET/NIRF imaging with a novel DPA-containing probe ($^{18}$F-MTTI-170) to visualize and evaluate cell death induced by Paclitaxel in a U87MG tumor xenograft model. *In vitro* toxicity of Paclitaxel to U87MG cells was determined by a colorimetric assay. The response of U87MG cells to Paclitaxel treatment was determined by flow cytometry, fluorescence staining, and cell uptake study. Established U87MG tumors in nude mice were daily treated with a combination of All-Trans Retinoic Acid (ATRC) (1.5 µg/kg) and Paclitaxel (45 µg/kg). Longitudinal PET imaging was performed with $^{18}$F-MTTI-170 before treatment and at day 3, 6, and 9 after treatment. NIRF imaging was carried out with $^{19}$F-MTTI-170 before treatment and at day 4, 7, and 11 after treatment. Our data demonstrated that U87MG human glioma cells are sensitive to Paclitaxel treatment. After being treated with Paclitaxel for 15 h, U87MG cells were stained with PSVue643 (Cy5-Zn-DPA). The strong red fluorescence signal was identified in the cytosol of the treated cells but not on the untreated cells. Besides, the fluorescent signal was effectively blocked by co-incubation with excess amount of unlabeled Zn-DPA. For cell uptake study, about 1.5% of $^{18}$F-MTTI-170 uptake in Paclitaxel-treated U87MG cells was determined after 1 hr incubation, which is significantly higher than 0.69% and 0.39% observed for $^{18}$F-FP-DPA (single modality compound) and $^{18}$F-FP-Dye (negative control), suggesting that the Zn-DPA moiety is indeed the component binding to PS, and the cell uptake of $^{18}$F-MTTI-170 is significantly higher than that of $^{18}$F-FP-DPA. Daily treatment with ATRC and Paclitaxel effectively inhibited the growth of U87MG tumors by inducing cell death. The cell death was clearly visualized by $^{18}$F-MTTI-170 PET. The tumor uptake, which was observed at day 9 after treatment, was significantly higher than that in the untreated tumors with a ratio of 6.70. The NIRF imaging results are consistent with the findings by PET. In conclusion, PET/NIRF imaging with MTTI-170 is sensitive enough to allow visualization of Paclitaxel induced cell death in U87MG tumor xenograft model. Fully quantitative imaging of tumor response to therapy with MTTI-170 offers the potential to provide early assessment of cancer treatment efficacy leading to individually tailored therapeutic plans with improved outcomes.

## Biography

Koon Yan Pak is a co-founder, President & CEO of Molecular Targeting Technologies, Inc. He was formerly employed by Centocor, a top-tier Biopharmaceutical Company, in the Research and Development Department. During his tenure with Centocor, he was instrumental in developing Centocor's technetium-99m imaging products. Dr. Pak is the former President of the Chinese American Society of Nuclear Medicine and the former Vice-Chair of Global Monte Jade Science and Technology Association. He is also the co-founder and former Chairman of the Chinese Entrepreneur Association. Dr. Pak holds numerous patents in the diagnostic imaging and therapy field and has published over 50 articles covering the use of antibodies for cancer and cardiovascular disease. Dr. Pak's recent awards include the State University of New York Honor Roll of Alumni, Ben Franklin Emerging Business Award and the Asian Chamber of Commerce for the Outstanding Asian American Business Award.