# 99mTc-MIBI and PET Tracers Uptake by MDR Tumor

# III. 7. $^{99m}$Tc-MIBI and PET Tracers Uptake by MDR Tumor

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## Introduction

Cellular accumulation of $^{99m}$Tc-methoxy isobutyl isonitrile (MIBI) has been shown to correlate with the level of P-glycoprotein (P-gp) expression[1]. P-gp is an energy-dependent membrane transporter protein that is responsible for the development of multi-drug resistance (MDR) of tumors to a broad spectrum of cytotoxic drugs. It has been shown that $^{99m}$Tc MIBI is a Pgp transport substrate. Evaluation of Pgp function using $^{99m}$Tc MIBI may open a new possibility for the prediction of efficacy of cancer chemotherapy.

Recently, positron emission tomography (PET) imaging of tumor using tracers of metabolic substrate, especially $^{18}$Ffluorodeoxyglucose (FDG), has demonstrated excellent clinical usefulness in oncology. FDG uptake by tumor representing elevated glucose metabolism of malignant cell is correlated to the grade of malignancy, to the growth rate, and to the cell density. Other PET tracers for tumor imaging $^{11}$C-methionine (Met), $^{11}$Cthymidine (Thd) representing amino acid metabolism and nucleic acid metabolism respectively, have been more correlated to the proliferation of cancer cells. However, correlation of these metabolic tracers and the P-gp function has never been studied. In this study, FDG, Met, Thd and MIBI uptake were compared with the MDR tumor and the control tumor.

## Materials and methods

Mouse leukemia cell P388 and vincristine-resistant subline P388VCR are kindly gifted from Japanese Foundation for Cancer Research. P388VCR is well known muti-drug-resistant subline[2]. Six-week old female CDF1 mice were implanted by subcutaneous injection with 0.1ml suspension of $10^7$ P388 cells in the right thigh regions and P388VCR cells in the left thigh. These cell lines are used for tumor innoculation as ascites after i.p injection of fresh recovered frozen stocks. Tracer experiments were performed 9 days after tumors transplantation following 8 hr of fasting. A dose of 28 μCi of $^{18}$Ffluorodeoxyglucose (FDG), 76 μCi of $^{99m}$TcMIBI, 1.33 μCi of $^{14}$C-L-methionine (Met), and 1.67 μCi of $^{3}$H-thymidine (Thd) were mixed in 0.25ml of saline and injected intravenously into the lateral tail vein in each of 20 mice. FDG was synthesized at CYRIC, $^{99m}$TcMIBI was obtained from Daiichi

Radioisotope Lab. LTD, Met and Thd were from Amersham International plc. The mice were sacrificed 5 (n=4), 30 (n=4), 60 (n=6), and 120 (n=6) min later. Tissue samples were excised and weighted and $^{18}F$ radioactivity was measured using an automated gamma-scintillation counter with the window of 450-600keV just after sampling. There was no spill over of $^{99m}Tc$ radioactivity to the window of $^{18}F$. And 27hrs later, when $^{18}F$ was decayed to 0.003%, $^{99m}Tc$MIBI was measured with the window of 70-180keV. Contamination of $^{18}F$ radioactivity to $^{99m}Tc$ window at this time was less than 0.3%. One month later, after the decay of $^{99m}Tc$, tissue samples were processed and radioactivity of $^{14}C$ and $^{3}H$ was measured with liquid scintillation counter as described previously.

## Results and discussion

Figure 1 showed tumor uptake of $^{99m}Tc$MIBI by P388 and P388VCR tumors. P388VCR showed lower uptake and faster clearance of $^{99m}Tc$MIBI than that of P388. It suggested that $^{99m}Tc$MIBI is excreted rapidly through P-glycoprotein from solid tumors of P388VCR, while from P388 tumor of without P-gp, clearance of $^{99m}Tc$MIBI becomes slower. Figure 2 showed completely different results with PET tracers. FDG, Met, and Thd all showed higher uptake by P388VCR than that by P388. P388VCR tumors grew faster than the P388, and all these metabolic tracers seem to represent growth rate rather than the presence of P-gp. FDG uptake by both tumors became highest among these three metabolic tracers. Compared to the tumors uptake of these three metabolic tracers, tumor uptake of $^{99m}Tc$MIBI was very low. $^{99m}Tc$MIBI may be useful for the prediction of multi-drug resistance of tumor[3,4], while our data suggested that value of $^{99m}Tc$MIBI for the tumor detection seems to be very limited compared to these three metabolic tracers.

## Acknowledgement

This study was supported by Grants-in-aid for cancer research (08266205) from the Ministry of Education, Science, Sports and Culture, Japan.

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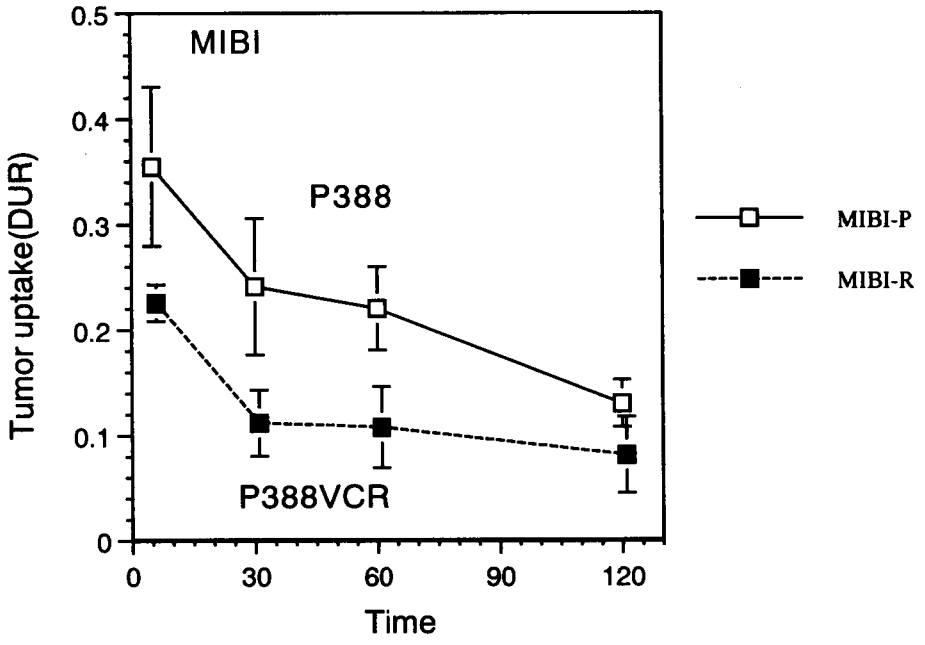


Fig. 1. Time course tumor uptake of $^{99m}$TcMIBI. Tumor uptake was expressed as differential uptake ratio (DUR). P388VCR is P-gp positive multi drug resistant cell line. P388 is the control cell line.

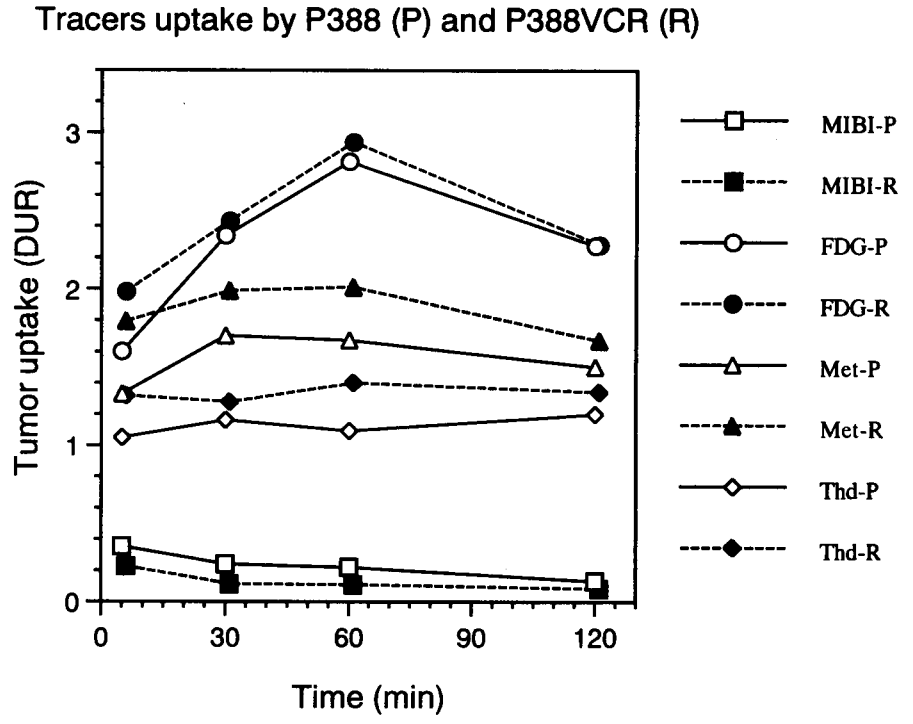


Fig. 2. Time course tumor uptake of FDG, Met, Thd, and $^{99m}$TcMIBI. Note the difference of the scale of the ordinate from figure 1. P-gp positive multi drug resistant cell line P388VCR grew faster than that of P388.