Immuno-PET and targeted α-therapy using anti-glypican-1 antibody labeled with ^{89}Zr or ^{211}At: a theranostic approach for pancreatic ductal adenocarcinoma†

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Glypican-1 (GPC1) is overexpressed in several solid cancers and is associated with tumor progression, whereas its expression is low in normal tissues. This study aimed to evaluate the potential of an anti-GPC1 monoclonal antibody (GPC1 mAb) labeled with ^{89}Zr or ^{211}At as a theranostic target in pancreatic ductal adenocarcinoma.

GPC1 mAb clone 01a033 was labeled with ^{89}Zr or ^{211}At with a deferoxamine or decaborane linker, respectively. The internalization ability of GPC1 mAb was evaluated by fluorescence conjugation using a confocal microscope. PANC-1 xenograft mice ($n = 6$) were intravenously administered [^{89}Zr]GPC1 mAb (0.91 ± 0.10 MBq), and PET/CT scanning was performed for 7 d. Uptake specificity was confirmed through a comparative study using GPC1-positive (BxPC-3) and GPC1-negative (BxPC-3 GPC1-knockout) xenografts (each $n = 3$) and a blocking study.

DNA double-strand breaks were evaluated using the γH2AX antibody. The antitumor effect was evaluated by administering [^{211}At]GPC1 mAb (-100 kBq) to PANC-1 xenograft mice ($n = 10$).

GPC1 mAb clone 01a033 showed increased internalization ratios over time. One day after administration, a high accumulation of [^{89}Zr]GPC1 mAb was observed in the PANC-1 xenograft (SUVmax, 3.85 ± 0.10), which gradually decreased until day 7 (SUVmax, 2.16 ± 0.30). The uptake in the BxPC-3 xenograft was significantly higher than in the BxPC-3 GPC1-knockout xenograft (SUVmax, 4.66 ± 0.40 and 2.36 ± 0.36, respectively; $P = 0.05$) (Fig. 1). The uptake was significantly inhibited in the blocking group compared with the non-blocking group (percentage injected dose per gram, 7.3 ± 1.3 and 12.4 ± 3.0, respectively; $P = 0.05$). DNA double-strand breaks were observed by adding 150 kBq of [^{211}At]GPC1 and were significantly suppressed by the internalization inhibitor (dynasore), suggesting a substantial contribution of the internalization ability to the antitumor effect. Tumor growth suppression was observed in PANC-1 mice after the administration of [^{211}At]GPC1 mAb. Internalization inhibitors (prochlorperazine) significantly inhibited the therapeutic effect of [^{211}At]GPC1 mAb (Fig. 2), suggesting an essential role in targeted α-therapy.

[^{89}Zr]GPC1 mAb PET showed high tumoral uptake in the early phase after administration, and targeted α-therapy using [^{211}At]GPC1 mAb showed tumor growth suppression. GPC1 is a promising target for future applications for the precise diagnosis of pancreatic ductal adenocarcinoma and GPC1-targeted theranostics.

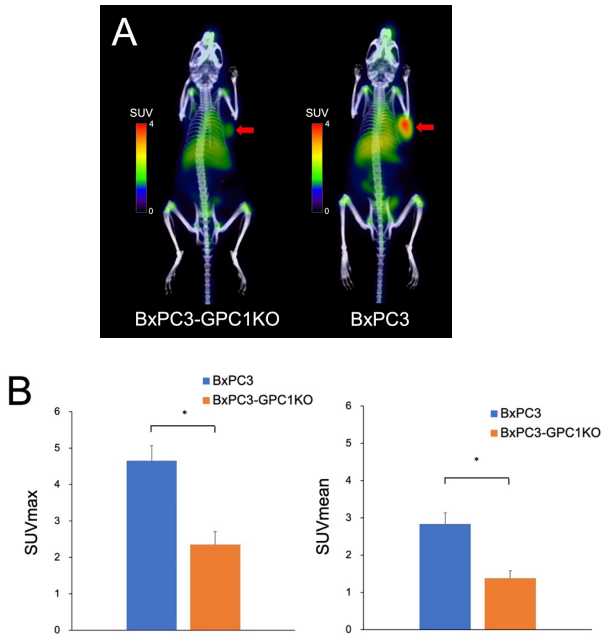

Fig. 1. (A) [^{89}Zr]GPC1 mAb PET images in BxPC-3 and BxPC-3 GPC1-knockout xenograft mice (arrows indicate tumor xenografts). (B) Quantitative analyses of tumoral uptake on [^{89}Zr]GPC1 mAb PET.

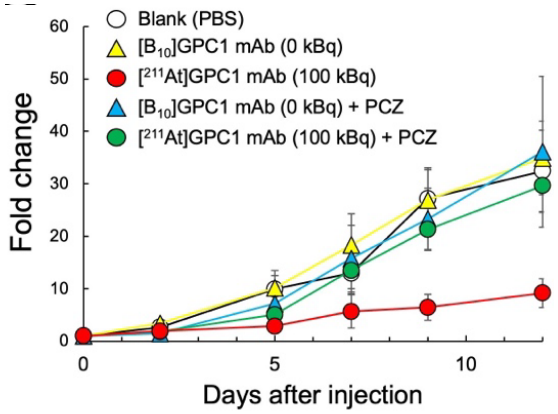

Fig. 2. Tumor growth curves after administration of [^{211}At]GPC1 mAb or nonradiolabeled mAb clone 01a033 with or without administering endocytosis inhibitor. *PCZ* = prochlorperazine.

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