An ^{211}At-labeled alpha-melanocyte stimulating hormone peptide analog for targeted alpha therapy of metastatic melanoma†

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There is an urgent need to develop new treatments for metastatic melanoma, which is extremely aggressive and associated with high mortality, for improving the response rates. Recently, targeted alpha therapy (TAT) has gained attention because of its high therapeutic effects, and it is a considered a desirable treatment for metastatic melanoma. Melanocortin-1 receptor (MC1R) is a promising target for the TAT of metastatic melanoma, and alpha-melanocyte stimulating hormone (α-MSH) peptide analogs show high affinities to MC1Rs.[1] In this study, we aimed to develop an astatine-211 (^{211}At)-labeled α-MSH peptide analog as a TAT agent for metastatic melanoma.

A neopentyl glycol (NpG) structure was used as an astatination scaffold because of its high stability against *in vivo* deastatination.[2] We referred to a representative α-MSH analog, DOTA-GGNle-CycMSH$_{hex}$, which is used for labeling with various radiometals.[3] However, we assumed that the direct displacement of the DOTA chelator to the NpG structure could be insufficient for developing ^{211}At-labeled peptides from the viewpoint of hydrophilicity. Thus, prior to studies using ^{211}At, a ^{125}I-labeled NpG group was conjugated to the N-terminus of GGNle-CycMSH$_{hex}$ directly or via hydrophilic linkers to obtain four ^{125}I-labeled GGNle-CycMSH$_{hex}$ analogs before conducting studies using ^{211}At (Fig. 1). The preliminary studies using ^{125}I-labeled analogs identified the D-Glu-D-Arg linker as the optimal hydrophilic linker because of its high affinity for MC1R and good biodistribution profile, especially with low accumulation in the liver and intestine.

Therefore, ^{211}At-labeled GGNle-CycMSH$_{hex}$ analog with the D-Glu-D-Arg linker ([^{211}At]NpG-GGN**4c**, Fig. 1) was prepared using a procedure similar to that used for the ^{125}I-labeled counterpart ([^{125}I]NpG-GGN**4b**, Fig. 1). The ^{211}At used in this work was produced in the ^{209}Bi(α, 2n)^{211}At reaction using the RIKEN and QTS Takasaki AVF cyclotron. When injected into B16F10 melanoma-bearing mice,

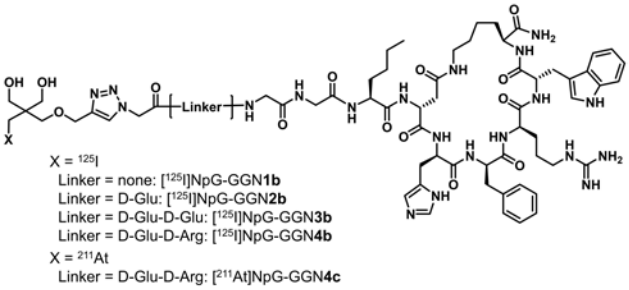

Fig. 1. Chemical structures of radiohalogenated α-MSH analogs.

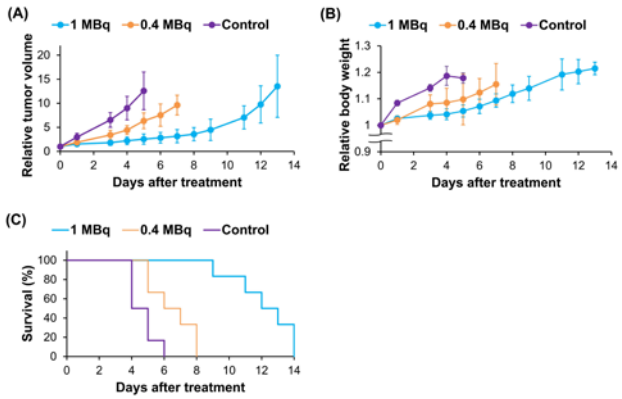

Fig. 2. Therapeutic effect of [^{211}At]NpG-GGN**4c** in B16F10 melanoma-bearing mice. (A) Tumor volume, (B) body weight, and (C) Kaplan-Meier survival curves after the injection of [^{211}At]NpG-GGN**4c** (1 or 0.4 MBq, $n = 6$) or saline (control, $n = 6$).

[^{211}At]NpG-GGN**4c** showed high tumor accumulation (13.85±2.23%ID/g at 3 hours postinjection). The tumor accumulation was significantly reduced by MC1R inhibition ($p < 0.05$), indicating that the tumor accumulation of [^{211}At]NpG-GGN**4c** was MC1R-specific. Then, the therapeutic efficiency of [^{211}At]NpG-GGN**4c** was evaluated by injecting [^{211}At]NpG-GGN**4c** (0.4 or 1 MBq/100 μL) or saline (100 μL) into B16F10 melanoma-bearing mice. [^{211}At]NpG-GGN**4c** inhibited tumor growth in a dose-dependent manner, and both injection doses showed significant inhibition compared to the control group on all days after treatment (excluding day 0) ($p < 0.05$) (Fig. 2A). Body weight loss was not observed in the groups that received [^{211}At]NpG-GGN**4c** (Fig. 2B). A Kaplan-Meier sur-

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vival analysis showed that [^{211}At]NpG-GGN**4c** treatment significantly improved the survival of mice compared to the control group ($p < 0.05$) (Fig. 2C). These results suggest that [^{211}At]NpG-GGN**4c** is a promising TAT agent for the treatment of metastatic melanoma.

References

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