

# Development of LAT1-selective nuclear medicine therapeutics using astatine-211<sup>†</sup>

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We investigated nuclear medicine therapeutics targeting the L-type amino acid transporter 1 (LAT1). We previously reported that a nuclear medicine therapeutic drug using astatine 211 (<sup>211</sup>At), an alpha-emitting nuclide that can be produced in an accelerator and targets LAT1 as a molecular target, is effective.<sup>1,2)</sup> The seed compound was 3-[<sup>211</sup>At] Astat- $\alpha$ -methyl-L-tyrosine (<sup>211</sup>At-AAMT-OH-L). We showed the quality of labeling compound (Fig. 1). By changing the OH group of phenol to a methyl group, retention was successfully increased. It was also found that the amount of the L-isomer taken up by the D-isomer and L-isomer was clearly higher, and the L-isomer was superior as a therapeutic drug. Compounds in which the methyl group was replaced with an ethyl or propyl group were also examined, but their retention did not increase significantly. In fact, we observed increased non-specific accumulation and dynamics, suggesting that labeling may be off. In addition, <sup>211</sup>At-AAMT-O-Me-L, which has a simple structure, was clearly superior in terms of uptake speed for several candidate compounds. As a result, we were able to develop a compound that can be easily labeled, has high specific radioactivity, is stable, and has a strong therapeutic effect.

We constructed cells in which doxycycline (Dox) concentration-dependently enhanced LAT1 expression (LAT1-Tet/HEK293 cells) and compared that uptake of labeled compounds (Fig. 2) correlated with LAT1 expression in these cells. And <sup>211</sup>At-AAMT-O-Me-L was confirmed the highest increase in uptake with a LAT1 expression manner (Fig. 3).

<sup>211</sup>At-AAMT-O-Me-L showed rapid uptake into cells and was very stable. In addition, there was less adsorption on the experimental equipment. Labeling requires only a very small amount of the compound, and the labeling efficiency is high. It also has the simplest structure among candidate compounds. Therefore, we used <sup>211</sup>At-AAMT-O-Me-L as the hit compound. This compound has been shown to be effective in any cancer that expresses LAT1, regardless of cancer type. Although data are not shown here, we are examining the distribution of all compounds time dependency *in vivo*, limited to a pancreatic cancer carrier model for compound comparison. It will be essential for comparing dose-dependent therapeutic effects and evaluating tox-

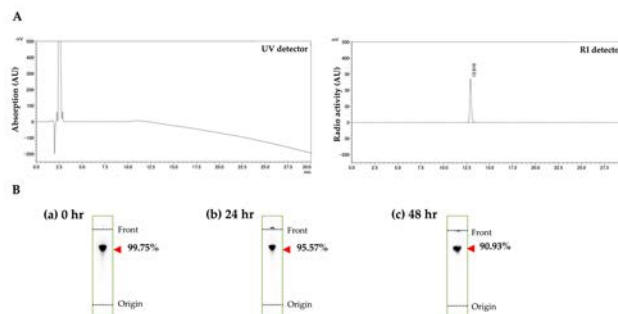


Fig. 1. (A) HPLC analysis of <sup>211</sup>At-AAMT-OMe-L. It was purified by an HLB column before HPLC analysis. (B) TLC analyses. Samples were collected 0 to 48 hours after labeling with <sup>211</sup>At. (a) immediately after labeling, (b) 24 hours and (c) 48 hours after labeling.

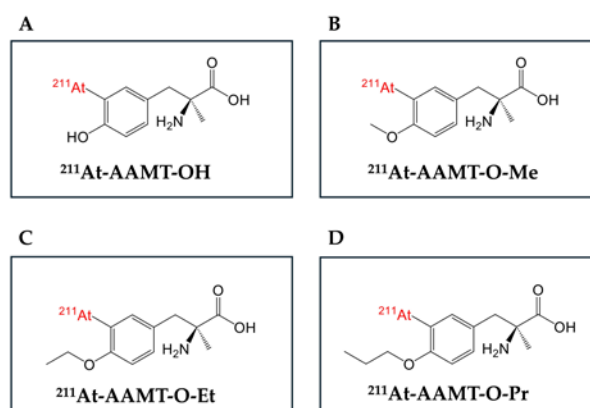


Fig. 2. Structure of experimental labeling compounds.

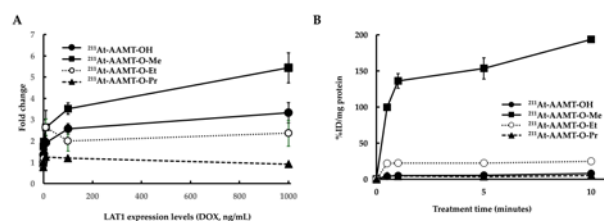


Fig. 3. Comparison of uptake between the labeled compounds. (A) Relation between uptake ratio and LAT1 expression level. Uptake ratios were compared between LAT1-Tet/HEK293 cells. The Y-axis represents the uptake ratio, and the X-axis is concentration of Dox (TaKaRa Bio, Shiga, Japan). The collection time was 30 min after treatment. The expression of LAT1 increased with increasing amounts of doxycycline. (B) Comparison of uptake in PANC-1 cell line. The collection times were 0.5, 1, 5 and 10 min after treatment.

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icity to demonstrate the utility of  $^{211}\text{At}$ -AAMT-OMe-L. We plan to move forward with clinical applications targeting pancreatic cancer and other tumors with high levels of LAT1 expression.

#### References

- 1) K. Kaneda-Nakashima *et al.*, *Cancer Sci.* **112**, 1132 (2021).
- 2) T. Watabe *et al.*, *Oncotarget.* **21**, 1388 (2020).