Astatine-211-labeled gold nanoparticles for targeted alpha-particle therapy via intravenous injection†

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Recently, much attention has been directed towards the powerful cancer therapeutic potential of targeted alpha-particle therapy (TAT). Globally, particularly in Japan, the α-particle emitting radionuclide astatine-211 (^{211}At) has garnered significant attention for its use in TAT.

One of the crucial challenges in TAT is the delivery of ^{211}At to the tumor tissues. In a previous study, we discovered that ^{211}At could be efficiently incorporated into gold nanoparticles (AuNPs) through a simple mixing process for 5 min, leading to a high radiochemical yield (RCY) without the need for purification. Furthermore, our research revealed that the intratumoral administration of ^{211}At-AuNPs effectively suppresse tumor growth and demonstrate the stability of ^{211}At-AuNPs in the body.[1)] For systemic metastatic tumors, intravenous injection is a promising method of delivery. In this study, we investigated the substantial potential of AuNPs as carriers for the targeted delivery of ^{211}At via intravenous administration.

^{211}At was produced at RIKEN using a short-lived RI supply platform. The separation and purification of ^{211}At was achieved through dry distillation. Four types of functional AuNPs were synthesized through surface modification using methoxy polyethylene glycol (mPEG) or tumor-targeting peptides (H16 or RGD). The astatine labeling reaction was evaluated using centrifugation, as described previously.[1)]

Tumor xenograft models were established thorough the subcutaneous transplantation of human pancreatic cancer cells (PANC-1) in BALB/c-nu/nu mouse. Four types of ^{211}At-AuNPs were administered to PANC-1 xenograft mice to evaluate their biodistribution at 3 and 24 h. The treatment effect of 5 nm ^{211}At-AuNPs@mPEG was evaluated using the PANC-1 xenograft model. All the animal experiments were conducted according to the guidelines of the Animal Research: Reporting In Vivo Experiments and the Osaka University Animal Experiment Regulations, and approved by the Osaka University Animal Experiment Committee.

Four types of ^{211}At-labeled functional AuNPs (5 nm ^{211}At-AuNPs@mPEG, 30 nm ^{211}At-AuNPs@mPEG, 5 nm ^{211}At-AuNPs@H16, and 5 nm ^{211}At-AuNPs@H16/RGD), as shown in Fig. 1, can be labeled with ^{211}At in a high RCY.

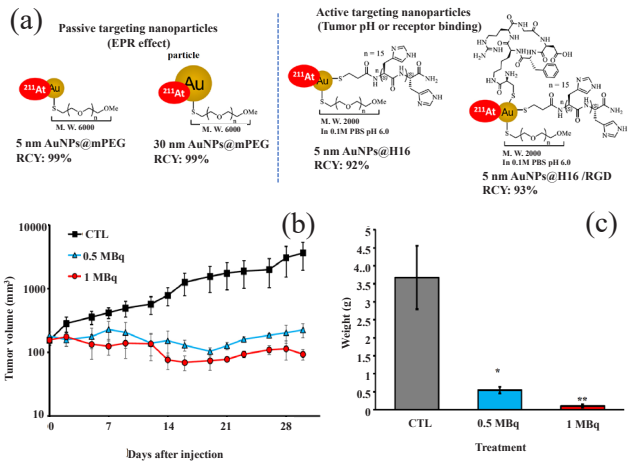

Fig. 1. (a) Four types of ^{211}At-labeled functional AuNPs designed for the study. (b) Change in the tumor size following the administration of 5 nm ^{211}At-AuNPs@mPEG or control (CTL) (saline). (c) Weight of enucleated tumors 30 d after injection.

The in *vivo* biodistribution results indicated a higher accumulation of 5 nm ^{211}At-AuNPs@mPEG in tumors (2.25%ID/g) in 3 h when compared with 30 nm ^{211}At-AuNPs@mPEG based on the enhanced permeability and retention (EPR) effect with a long retention time in tumors for 24 h. The intravenous administration of 5 nm ^{211}At-AuNPs@mPEG was found to significantly inhibit tumor growth in a pancreatic cancer model.

Gold nanoparticles (AuNPs) are an ideal carrier for ^{211}At delivery, owing to their facile and efficient synthesis processes and high stability. The results of this study indicate that the intravenous administration of 5 nm ^{211}At-AuNPs@mPEG exhibits a potent antitumor effect. These results provide a novel framework for the design of nanoparticles suitable for targeted alpha-particle therapy via intravenous injection.[2)]

References

1) H. Kato *et al.*, J. Nanobiotechnology **19**, 1 (2021).
2) X. Huang *et al.*, Pharmaceutics **14**, 2705 (2022).

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