Preclinical evaluation of the therapeutic potential of ^{211}At-radiolabeled 2,6-diisopropylphenyl azide in mouse models for human lung cancer treatment†

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This study demonstrates the synthesis of ^{211}At-radiolabeled 2,6-diisopropylphenyl azide (ADIPA) **1**, an α-emitting molecule that selectively targets acrolein in cancer cells. The efficacy of this molecule for cancer treatment is evaluated on the basis of its potential to eradicate tumors. Previous studies have demonstrated that aryl azide derivatives can react with endogenously generated acrolein in cancer cells to produce a diazo derivative.[1] This diazo compound can subsequently form covalent bonds with cellular organelles of cancer cells *in vivo*.[2,3] We assumed that ADIPA **1** would follow a similar path, reacting with acrolein of cancer cells to bind with organelles within those cells. Subsequently, the α-emission of the molecule would lead to the destruction of cancer cells (Fig. 1(a)).

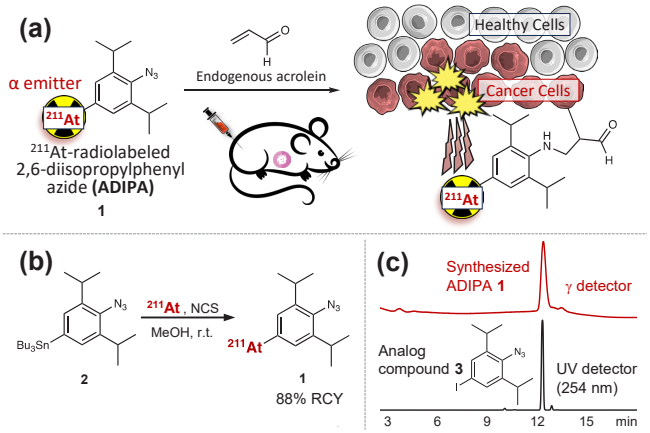

Fig. 1. (a) Concept of this study. (b) Synthesis of ADIPA **1**. (c) Purification and identification of ADIPA **1** using HPLC.

The synthesis of ADIPA **1** involved the electrophilic destannylation of precursor **2** in the presence of NCS in methanol at 25°C,[4] resulting in an 88% radiochemical yield (Fig. 1(b)). HPLC analysis was performed to identify and purify ADIPA **1** by comparing its retention time with analog compound **3** (Fig. 1(c)).

In vivo studies were conducted using A549 (human lung cancer) xenograft mouse models to investigate the therapeutic potential of ADIPA **1**. A low dose (70 kBq) of ADIPA **1**, administered either intratumorally or intravenously, effectively suppressed cancer growth (Fig. 2(a)). These treated groups exhibited substantially longer survival than the control group (Fig. 2(b)).

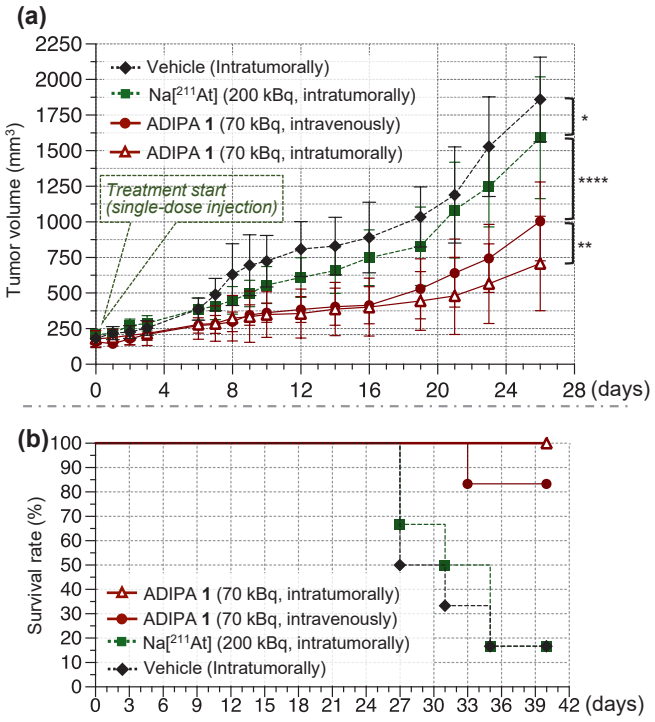

Fig. 2. (a) Tumor growth of A549 cell-bearing xenograft nude mice treated with vehicle, Na[^{211}At], or ADIPA **1**. (b) The survival rates of the mice groups.

After 18 h, the distribution of radioactivity in each organ was evaluated, indicating a considerable amount of ^{211}At within the tumor in the ADIPA administration group. Furthermore, no adverse effects were observed, including weight loss or skin disorders. The administered dose in this study was substantially lower than the maximum permissible dose for α-emission (1.4 MBq per 20 g body weight),[5] indicating potential clinical applicability.

Considering the overproduction of acrolein in cancer cells,[1,2] the proposed approach warrants further investigation and application in mouse models that encompass various types and stages of cancer.

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References

1) A. R. Pradipta *et al.*, Chem. Sci. **12**, 5438 (2021).
2) T. Tanei *et al.*, Adv. Sci. **6**, 1801479 (2019).
3) A. R. Pradipta *et al.*, ACS. Sens. **1**, 623 (2016).
4) G. Vaidyanathan *et al.*, Bioorg. Med. Chem. **15**, 3430 (2007).
5) L. M. Cobb *et al.*, Hum. Toxicol. **7**, 529 (1988).

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