Development of a Novel Astatine-Labeled Modality for Cancer Therapy

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In recent years, with the development of cancer treatment methods, the survival rate of cancer patients has improved. However, certain types of cancer, such as pancreatic cancer, still have the low response rate to treatment, and there is a need to develop more effective treatments. Targeted alpha therapy, in which alpha-ray emitting radionuclides administered into the body are accumulated in the tumor, is currently the focus of attention. We have selected Astatine-211 (^{211}At), which can be produced domestically using an accelerator, as the alpha-ray emitting radionuclide to be used. ^{211}At is a short-lived radionuclide with a half-life of 7.2 hours. Methods to enhance the drug's cytotoxic effect by internalizing it into cells and bringing it into close proximity to DNA have been investigated. We have previously confirmed that ^{211}At-labeled antibodies inhibit tumor growth in carcinoma mice. In this study, we focused on Mirabody® as an antibody-like molecule with a lower molecular weight to improve tissue permeability, and evaluated the cytotoxic activity of the ^{211}At labeled form.

Mirabody® is a functional molecule in which a cyclic peptide with high binding ability to a specific target is introduced into the Fc region of an antibody, and its molecular weight is about one-third that of an antibody[1,2]. In this study, we used Mirabody® (aMD4-MB) containing a cyclic peptide that binds to the hepatocyte growth factor receptor (HGFR), which is abundantly expressed on cancer cells.

First, we confirmed the high binding ability of aMD4-MB to PANC-1 cells, a human pancreatic cancer cell line, by flow cytometry (FCM). Furthermore, the internalization ability of aMD4-MB was assessed by FCM and live cell imaging. The results revealed that aMD4-MB exhibited rapid internalization within 5 minutes, demonstrating its remarkable internalization ability and its potential as a ^{211}At carrier molecule.

Next, aMD4-MB was labeled with a decaborate (B_{10}) linker that binds ^{211}At. FCM confirmed that this labeled molecule also had similar cell-binding capacity. B_{10}-labeled aMD4-MB was then conjugated with ^{211}At and subsequently purified by gel filtration. The resulting ^{211}At-labeled aMD4-MB was then assessed for its ability to induce DNA double-strand breaks (DSBs) in PANC-1 revealing a radiation dose-dependent response in DSBs, Our future plans include evaluating the biodistribution of ^{211}At-labeled aMD4-MB using carcinoma-bearing mice as well as verifying its inhibitory effect on tumor growth upon administration to these mice.

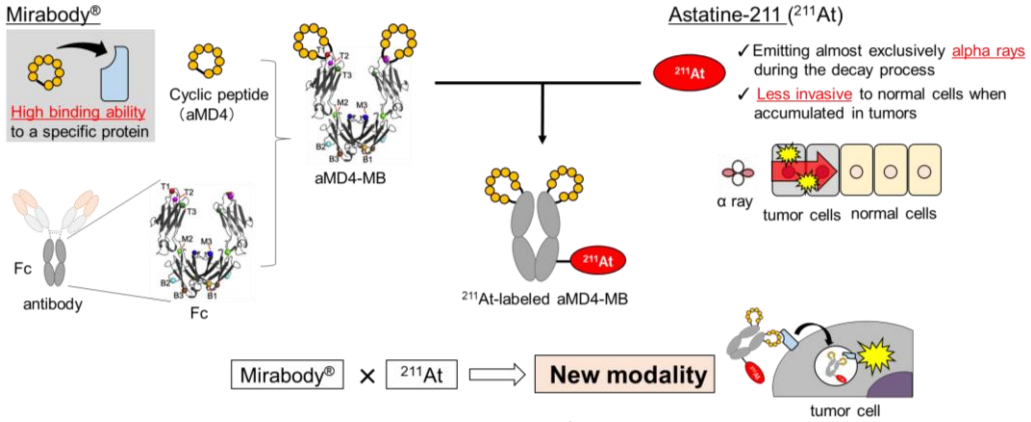

Figure 1. Concept of this study (^{211}At-labeled aMD4-MB)

References

1) Mihara E, *et al*. *Nat Commun*. **2021**.12, 1543
2) Ito K, *et al*. *Nat Commun*. **2015**. 6, 6373