PR4

Production of medical RI by reactor irradiation

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INTRODUCTION: Remarkable results have been achieved in the treatment of metastatic cancer with β-ray emitting radionuclides such as ^{177}Lu, which can be easily produced in nuclear reactors. In recent theranostics, the incidentally emitted gamma rays can also be used for diagnosis. Extraction chromatography is widely used technique for chemical separation of Ytterbium (Yb) and medically relevant Lutetium-177 (^{177}Lu); however, chemical similarity between Lu and Yb require a larger column size and more eluent for gram-scale Yb target separation.
Kimura et al. has studied theranostics as a new medical technology that combines therapeutics and di- agnostics. The key to the realization of theranostics is a drug known as theranostic probes. In this study, we will utilize the theory of creation of unit-coupling molecular probes to develop drugs that can ultimately be applied clinically. First, a basic study of the production of ^{177}Lu in the KUR was conducted. Next, we developed radiotheranostics probes targeting EphA2, which is expressed in cancer. Erythropoietin-producing hepatocellular receptor A2 (EphA2) is overexpressed in cancer cells and causes abnormal cell proliferation. Therefore, it has attracted attention as a target for radiotheranostics probes.

RESULTS AND DISCUSSIONS:
Recovery of ^{177}Lu by LN2 extraction chromatograph: In this study, a CZT detector measuring the gamma-ray spectrum was installed in the eluent part of the chromatography, allowing in-line, in-situ observation of the separation situation. Irradiation of ^{176}Yb enriched isotopes has two well-separated peaks and the production of ^{177}Lu, which is far larger than the target-derived radioactive impurity, is observed. The separation ratio shows that the separation of ^{177}Lu from $^{169/175}$Yb using natural Yb improved significantly from approximately 1.2 in the ratio of elution times to approximately 1.6 when using the ^{176}Yb enriched isotope. This indicates that the use of ^{176}Yb enriched isotope targets improves chromatographic overload conditions. This result is expected to be used for the precise separation and recovery of ^{177}Lu fractions in the process of highly radioactive ^{177}Lu separation while reducing the exposure of workers to large amounts of separation in a hot cell.
Development of radiotheranostics probes: In this study, the EphA2-57-1 monoclonal antibody (EphA2-57-1) was labeled with [^{111}In]In and evaluated as an imaging tracer for single-photon emission computed tomography (SPECT) of EphA2.
Development of radiotheranostics probes: EphA2-57-1 was conjugated with *p*-SCN-BnDTPA and then labeled with [^{111}In]In. [^{111}In]In-DTPA-EphA2-57-1 was evaluated in cell-binding, biodistribution, and SPECT studies. In the biodistribution study, a high uptake of [^{111}In]In-DTPA-EphA2-57-1 was observed in tumor tissue (8.8 ± 2.2% injected dose/g at 96 h). The accumulation of [^{111}In]In-DTPA-EphA2-57-1 in tumors was also confirmed using SPECT. Therefore, [^{111}In]In-DTPA-EphA2-57-1 has potential as a radiotheranostics probe for EphA2.

REFERENCES:
[1] A. Dash *et al.,* Nucl Med Mol Imaging., **49** (2015) 85-107.

PR4-1

Development of tumor-targeted radiotheranostics probes and its clinical application

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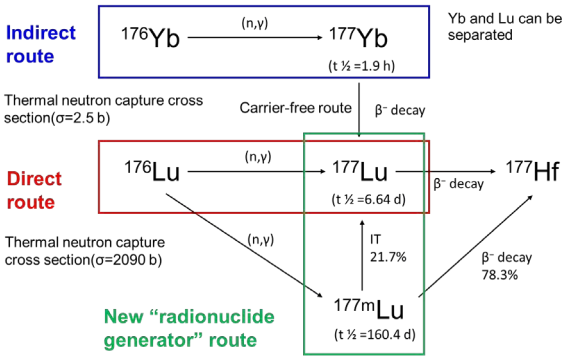
INTRODUCTION: Theranostics is a new medical technology that combines therapeutics and diagnostics. The key to the realization of theranostics is a drug known as theranostic probes. The characteristic of the radiotheranostics probes we are developing is that we consider a single molecule as an aggregate of target recognition units, linker units, and chelating units, and design molecular probes based on the concept of "unit-coupling molecular probes," in which independently developed units are freely combined. This drug design theory is not only effective for designing molecular probes with relatively large molecules such as antibodies and other proteins and bioactive peptides as the nucleus, but also can also be applied to organic small molecular compounds. In this study, we will utilize the theory of creation of unit-coupling molecular probes to develop drugs that can ultimately be applied clinically. First, a basic study of the production of ^{177}Lu in the KUR was conducted. Next, we developed radiotheranostics probes targeting EphA2, which is expressed in cancer. Erythropoietin-producing hepatocellular receptor A2 (EphA2) is overexpressed in cancer cells and causes abnormal cell proliferation. Therefore, it has attracted attention as a target for radiotheranostics probes.

EXPERIMENTS: *^{177}Lu Production*: To obtain ^{177}Lu, Lu_2O_3 and Yb_2O_3 were irradiated at 1 MW for 24 hours and 5 MW for 6 hours.
Development of radiotheranostics probes: In this study, the EphA2-57-1 monoclonal antibody (EphA2-57-1) was labeled with [^{111}In]In and evaluated as an imaging tracer for single-photon emission computed tomography (SPECT) of EphA2.

RESULTS: *^{177}Lu Production*: This year, we attempted to produce ^{177}Lu by an indirect method. Optimization of separation and purification conditions for post-irradiation samples is underway.
Development of radiotheranostics probes: EphA2-57-1 was conjugated with *p*-SCN-BnDTPA and then labeled with [^{111}In]In. [^{111}In]In-DTPA-EphA2-57-1 was evaluated in cell-binding, biodistribution, and SPECT studies. In the biodistribution study, a high uptake of [^{111}In]In-DTPA-EphA2-57-1 was observed in tumor tissue (8.8 ± 2.2% injected dose/g at 96 h). The accumulation of [^{111}In]In-DTPA-EphA2-57-1 in tumors was also confirmed using SPECT. Therefore, [^{111}In]In-DTPA-EphA2-57-1 has potential as a radiotheranostics probe for EphA2.



Two different routes for reactor production of ^{177}Lu

REFERENCES:
[1] A. Dash *et al.,* Nucl Med Mol Imaging., **48** (2015) 85-107.

The development of the online monitoring system for column separation of ^{177}Lu from enriched ^{176}Yb irradiated target

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INTRODUCTION: Extraction chromatography is widely used technique for chemical separation of Ytterbium (Yb) and medically relevant Lutetium-177 (^{177}Lu); however, chemical similarity between Lu and Yb require a larger column size and more eluent for gram-scale Yb target separation. Therefore, it is essential to fully understand the process of separating Yb and Lu in the column and to extract only the required ^{177}Lu fraction to improve the efficiency of the chemical separation operation. CZT detectors are small and can be powered by USB, making them suitable for online remote measurements. In the previous study, we preliminary evaluated the online measurement of a column separation using a CZT detector with $^{169, 175}$Yb and ^{177}Lu tracers produced by irradiating the ^{nat}Yb target; however, the 238keV γ-ray of ^{177}Lu could not be identified because it was covered by the Compton component derived from the high-energy γ-ray of $^{169, 175}$Yb. Therefore, in this study, enriched ^{176}Yb, which is used for commercial production of ^{177}Lu, was used for online monitoring evaluation.

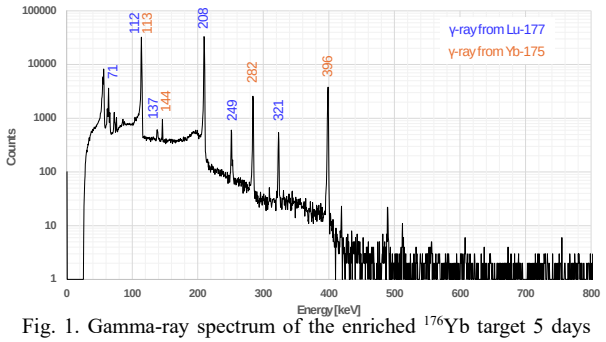

Fig. 1. Gamma-ray spectrum of the enriched ^{176}Yb target 5 days after neutron irradiation.

EXPERIMENTAL: The CZT detector used for the measurements was a RadAngel manufactured by Kromek. A Ge detector (ORTEC) was used to confirm the elution profile. Enriched $^{176}Yb_2O_3$ powder was purchased from Isoflex and has a 99.14% enrichment of ^{176}Yb. A $^{176}Yb_2O_3$ sample (^{176}Yb, 1.0 mg) was irradiated for 6 hours at a power of 5 MW at the Kyoto University research reactor KURR. Irradiated $^{176}Yb_2O_3$ was dissolved and adjusted to 4M HNO_3. Then, the solution was added into a jacketed 11 mmφ x 240 mm glass column (Kiriyama Chemical) containing extraction LN2-Resin (Eichrom) and about 500 mL of 1.5 M HNO_3 was added to separate the Yb target and ^{177}Lu. The tube containing the eluted solution from the column was brought into contact with the CZT detector for online measurement. The eluent was collected as each fraction containing 250 drops, which were subjected to γ-ray spectroscopy using a Ge detector and compared with the elution curve obtained with the CZT detector monitoring.

RESULTS: A Ge detector measurement confirmed only the production of high radioactivity ^{177}Lu, and low radioactivity ^{175}Yb in the irradiated sample after 5 days irradiation (Figure 1). Figure 2 shows the elution curves obtained with a Ge detector (Left), and a CZT detector (Right), which set the ROI to the channel between the 396 keV of ^{175}Yb and 208 keV of ^{177}Lu photoelectric peaks. The elution curves of ^{175}Yb and ^{177}Lu obtained with the CZT and Ge detectors showed the same trend. In addition, online measurements using a CZT detector confirmed that the column length used in the experiment was sufficient to separate ^{175}Yb and ^{177}Lu.

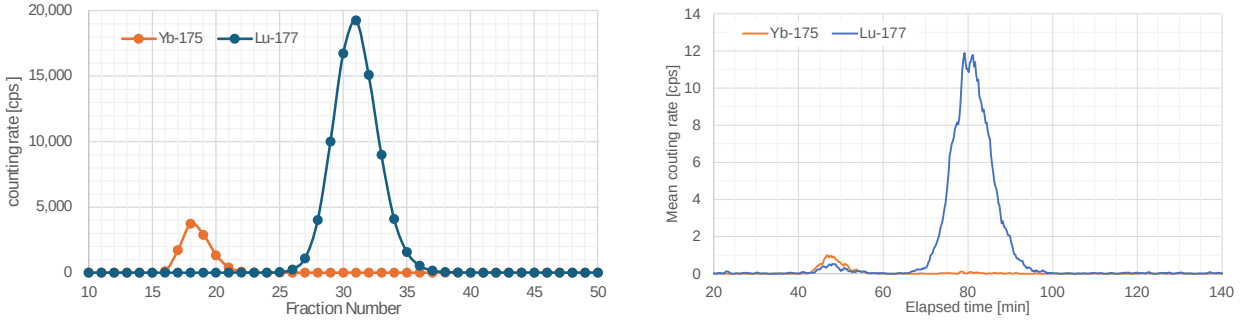

Fig. 2. Elution profile of extraction chromatography with an 11 mmφ × 240 mmL column packed with LN2 resin measured with a Ge detector (Left) and a CZT detector (Right)

CONCLUSION: In this study, online monitoring of γ radiation was performed using a CZT detector for column separation of an enriched ^{176}Yb target and ^{177}Lu. The use of enriched isotope made it possible to distinguish between the low-energy high radioactivity γ-rays from ^{177}Lu and the high-energy low radioactivity γ-rays from ^{175}Yb. This result is expected to be used for the precise separation and recovery of ^{177}Lu fractions in the process of highly radioactive ^{177}Lu separation while reducing the exposure of workers to large amounts of radioactivity in a hot cell.