I-1. PROJECT RESEARCHES

Project 6

PR6 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. ^{177}Lu production is also possible with naturally occurring (n, γ) ^{176}Lu, but the specific activity is low and cannot be used for antibody labeling. Indirect methods using Yb irradiation require separation and purification after irradiation (Fig. 1). However, since the specific activity of natural Yb is not high enough, the use of enriched isotope ^{176}Yb is also necessary, but it is difficult to obtain and expensive, and a scheme to recover ^{176}Yb must be established. Research and clinical use of nuclear medicine in Japan has been lagging behind that of other countries due to various regulations and restrictions, and we would like to start basic research on β-ray emitting nuclei that can be produced by nuclear reactors in cooperation with RI production, pharmacology, and medicine during the short time we have before KUR ceases operation. Research activities in this community are also expected to contribute to design activities for RI production in the Fukui reactor, which is considered to be on the scale of a beam reactor.

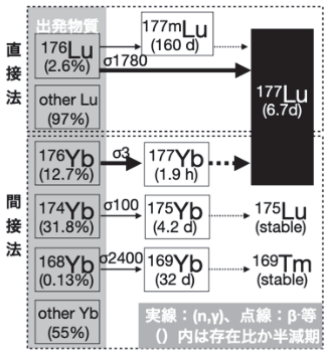
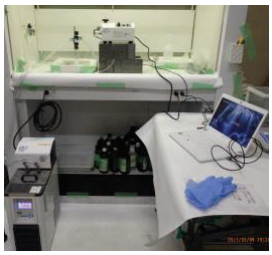


Fig. 1. Starting materials (Lu and Yb, respectively) for the production of ^{177}Lu by direct and indirect methods, and the existence ratio, half-life, and uninvolved or impure nuclides that determine the specific activity.

EXPERIMENTS:

The first fiscal year of the project has been devoted to the setting up the experimental environment and initial test experiments. Each of research fields has made their progress as followings:



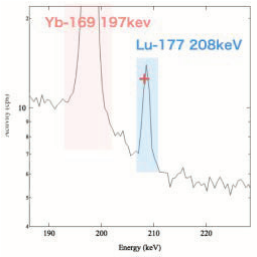


Fig. 2. Experimental set-up for separation of Lu-177 from Yb-176.

(1) H. Kimura *et al.* has carried out their experiments as followings:

^{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.

Labeling reaction with ^{177}Lu: Labeling studies were conducted using ^{177}Lu and NOTA-conjugated antibodies. NOTA-binding antibody and $^{177}LuCl_3$ were added to 0.3M AcONa solution and allowed to react at 40°C for 1 hour. The rate of reaction progress was evaluated using Radio-TLC.

SPECT/CT imaging: SPECT imaging was performed to confirm the quality of the ^{177}Lu produced.

(2) Projects of Y. Nakamoto *et al*. and Y. Shimizu *et al*. were not implemented due to the impact of the new coronavirus infection.

RESULTS:

(1) Both direct and indirect methods were confirmed to produce ^{177}Lu. In the indirect method, it was found that ^{177}Lu breaks down slowly against the large excess of ^{176}Yb, and that the specific activity of ^{177}Lu can be greatly improved by separating the eluted portion up to the breakdown (first fraction) and the eluted portion after that (second fraction) (Fig. 2).

This measurement was carried out in two ways: the first method was used to determine the specific activity of ^{176}Yb, ^{177}Lu, ^{177m}Lu, *etc*. It was found that the overlap of numerous γ rays was so pronounced that they could not be separated with the small detector Kromek (16 keV), and a germanium semiconductor detector was required. Although manual fraction collection was performed in this study, it was found necessary to proceed with collection by fraction collector and continuous measurement by a portable detection system in the future.

Since the first fraction could be recovered, we are ready to proceed with the experiment using ^{176}Yb-enriched isotope in the future.

Labeling experiments were conducted using ^{177}Lu produced by the direct method. When an antibody with 7-8 NOTAs bound as ligands was used, labeling of ^{177}Lu proceeded quantitatively. However, when the number of NOTAs introduced was small, the labeling rate of ^{177}Lu was extremely low. SPECT imaging was performed by administering $^{177}Lu_2O_3$ through the tail vein of mice; successful imaging of ^{177}Lu indicated that monitoring of therapeutic effects was also possible.

PR6-1 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.

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.

Labeling reaction with ^{177}Lu: Labeling studies were conducted using ^{177}Lu and NOTA-conjugated antibodies. NOTA-binding antibody and $^{177}LuCl_3$ were added to 0.3M AcONa solution and allowed to react at 40°C for 1 hour. The rate of reaction progress was evaluated using Radio-TLC.

SPECT/CT imaging: SPECT imaging was performed to confirm the quality of the ^{177}Lu produced.

RESULTS AND DISCUSSION:

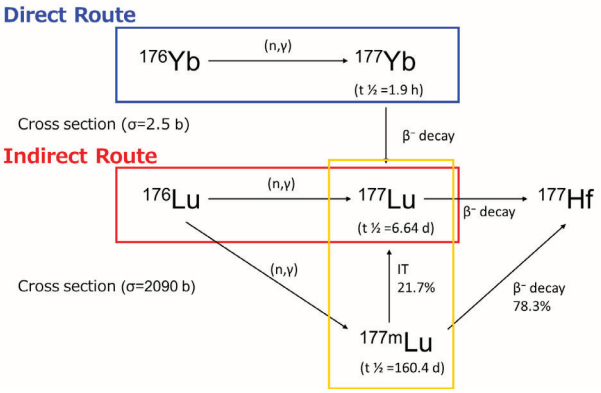

Fig. 1. ^{177}Lu Production Process

The production of ^{177}Lu was confirmed for both direct and indirect methods (Fig1)[1)]. The indirect method is under investigation for separation and purification, and we plan to continue our research to establish a purification method.

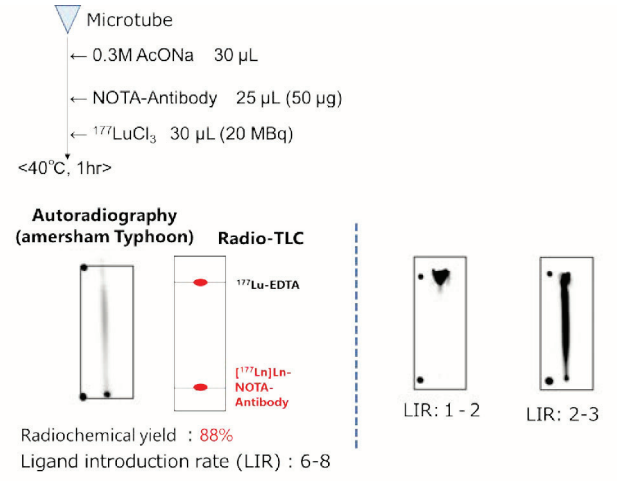

Fig.2.^{177}Lu Production Process.

Labeling experiments were performed using ^{177}Lu produced by the direct method. When antibodies with seven to eight bound NOTA as ligands were used, labeling of ^{177}Lu proceeded quantitatively. However, the labeling rate of ^{177}Lu was found to be extremely low when the number of NOTAs introduced was small (Fig2). The production of high purity ^{177}Lu by the indirect method is considered more suitable for drug development. In fact, ^{177}Lu is produced by the indirect method for pharmaceutical use worldwide.

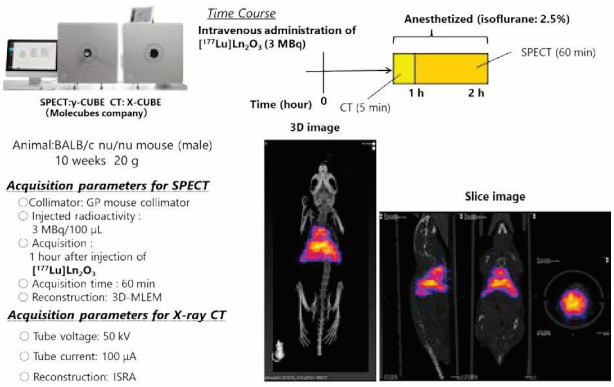

Fig. 3. SPECT/CT imaging: $^{177}Ln_2O_3$

$^{177}Ln_2O_3$ was administered via tail vein of mice and SPECT imaging was performed. The successful imaging of ^{177}Ln indicated that it is also possible to monitor treatment efficacy (Fig3).

REFERENCES:

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

PR6-2 Preliminary study on the development of online monitoring system for column separation of ^{177}Lu from ^{nat}Yb irradiated target

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INTRODUCTION: Lutetium-177 (^{177}Lu) is a beta-emitting radionuclide suitable for medical use. However, the production of ^{177}Lu and research on the development of ^{177}Lu-labeled radiopharmaceuticals have not been active in Japan, and must be addressed in the future for involvement in the global ^{177}Lu supply chain and the development of ^{177}Lu-labeled radiopharmaceuticals in Japan. The goal of this study is to produce and purify no-carrier-added ^{177}Lu using Kyoto University's research reactor, KURR, and provide it to users, and to optimize column separation conditions for separating ^{177}Lu from Yb target and by-products, which are essential for this purpose. The CZT detector has a narrower FWHM and higher resolution than the NaI detector, and some CZT detectors are small and can be powered by USB, making them suitable for online measurement. In this study, we conducted a preliminary investigation of online measurement of column separation using a CZT detector.

EXPERIMENTAL: The CZT detector used for the measurements was a RadAngel manufactured by kromek. A Ge detector (ORTEC) was used as the detector for comparison. The Yb and Lu samples to be irradiated were elemental standards for ICP-MS with natural isotopic abundances. Each sample (Yb, 0.5 mg: Lu, 0.1 mg) was added to a quartz tube, heated and concentrated to dryness, and then vacuum-sealed. The samples were then loaded into a water hydraulic transport tube of a research reactor at the Institute for Integrated Radiation and Nuclear Science, Kyoto University, and irradiated for 24 hours. A part of the Yb and Lu solutions was taken out and used for the γ-ray spectrometry with a CZT detector and a Ge semiconductor detector to set the ROI for the monitoring. The remaining Yb solution was poured into a column and about 500 mL of 1.5 M HNO_3 was added to separate the Yb target and ^{177}Lu. Extraction chromatography resin LN2-Resin (Eichrom) was used for column separation. A jacketed 11 mmφ x 240 mmL glass column (Kiriyama Chemical) was used as the separation column. The tube containing the eluted solution from the column was brought into contact with the CZT detector for online measurement of the solution. Then all eluents were collected in a fraction collector with 250 drops as one fraction. The collected solution was then subjected to γ-ray spectrometry with a Ge detector and compared to the elution curve obtained with the CZT ROI.

RESULTS and DISCUSSION: A Ge detector confirmed the production of ^{177}Lu, ^{175}Yb, and ^{169}Yb in the irradiated sample from γ-ray spectrometry. Figure 2 shows the elution curves obtained with the Ge detector, and Figure 3 shows the elution curves obtained with the CZT detector, which were obtained by setting the ROI to the channel between the 396 keV of ^{175}Yb and 208 keV of ^{177}Lu photoelectric peaks.

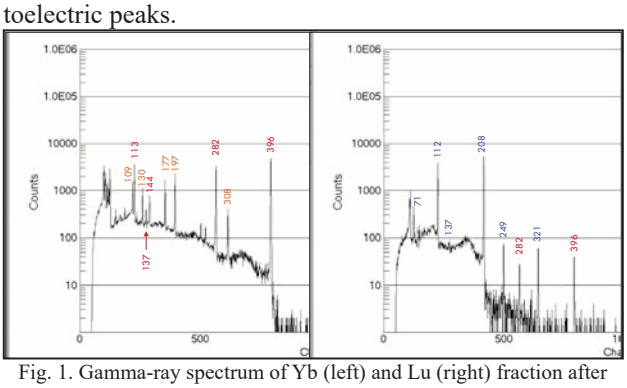

Fig. 1. Gamma-ray spectrum of Yb (left) and Lu (right) fraction after column separation using Ge-detector.

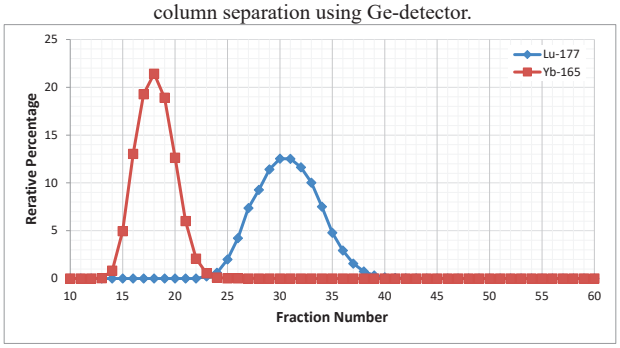

Fig. 2. Elution profile of extraction chromatography with an 11 mmφ × 240 mmL column packed with LN2 resin measured with a Ge detector.

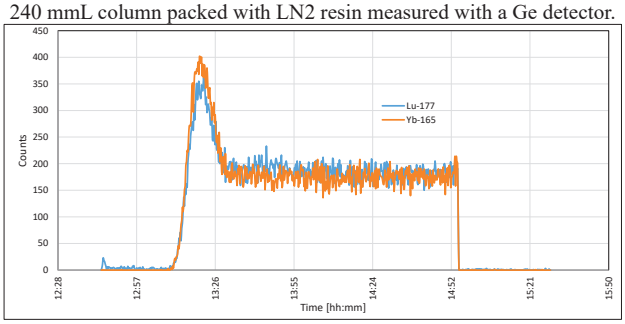

Fig. 3. Elution profile of extraction chromatography with an 11 mmφ × 240 mmL column packed with LN2 resin measured with a CZT detector.

The x-axes of Figures 2 and 3 show the elution curve of ^{165}Yb, although the units differ. On the other hand, ^{177}Lu was not detected by the CZT detector. This is probably because ^{177}Lu generates less radioactivity than ^{165}Yb and the background around the detector is high. Therefore, further study on the measurement conditions is necessary.

CONCLUSION: In this study, a preliminary investigation of online γ-ray measurements in column separations was performed. A small CdZn detector demonstrated the possibility of online measurement in column separation; however, further investigation is warranted.