I-1. PROJECT RESEARCHES

Project 8

PR8

Production of medical RI by reactor irradiation

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INTRODUCTION: The domestic production of medical radioisotopes (RIs) is increasingly important for cancer radiotheranostics because Japan still relies on limited overseas supplies of therapeutic radionuclides. This project integrates reactor irradiation, radiochemical separation and radiopharmaceutical development for ^{177}Lu, ^{161}Tb and ^{225}Ac, with consideration of KUR-based studies and future JRR-3 production. In this period, work focused on real-time ^{177}Lu/Yb separation, scale-up no-carrier-added ^{177}Lu production, preliminary ^{161}Tb production from natural Gd, JRR-3 Lu-177 production trials, ^{177}Lu^{-} and ^{225}Ac-labeled PSMA agents, LAT1-targeted metal RI probes, and feasibility testing of an alternative ^{225}Ac route via Ra-228(n,γ) irradiation.

EXPERIMENTS:

Step	Key conditions	Purpose
^{177}Lu/Yb separation	Extraction chromatography with on-line gamma monitoring using CZT or Ge detectors.	Optimize rapid n.c.a. ^{177}Lu separation.
Scale-up ^{177}Lu production	Long-term irradiation of enriched ^{176}Yb at KUR and LN2-resin column separation.	Define automated separation requirements.
JRR-3 Lu-177 production	Direct [^{176}Lu]Lu_2O_3 and indirect [^{176}Yb]Yb_2O_3 targets sealed in quartz ampoules and irradiated in HR-1 at JRR-3.	Evaluate JRR-3 capability and issues for test-scale ^{177}Lu supply.
^{161}Tb production	Neutron irradiation of natural Gd followed by Gd/Tb separation using LN2 resin.	Assess domestic ^{161}Tb feasibility.
Radiopharmaceuticals	^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617 synthesis and mouse biodistribution.	Evaluate preclinical RI usability.
Probe and ^{225}Ac studies	LAT1-targeted chelator compounds and Ra-228-supported MgO irradiation targets.	Expand agents and ^{225}Ac routes.

RESULTS AND DISCUSSIONS: On-line γ-ray monitoring distinguished Yb-related peaks from ^{177}Lu during extraction chromatography. In scale-up testing, long-term irradiation yielded ^{177}Lu with a specific activity of ca. 1.0×10^7 Bq/mg, about three times higher than the previous hydro-irradiation condition; most Yb was removed with 2.25 M HNO_3 and ^{177}Lu was eluted with 4 M HNO_3 after ca. 660 min. At JRR^{-3}, irradiation of 1 mg Lu in HR-1 for 14 d was estimated to produce ca. 400 GBq of ^{177}Lu, while irradiation of 1 mg Yb produced ca. 500 MBq; although specific activity and target re-irradiation remain issues, the quantity and quality were sufficient for labeling and non-clinical tests. Natural Gd irradiation and LN2-resin separation gave distinct Gd/Tb elution profiles, and Ge-detector analysis confirmed separation of ^{153}Gd, ^{159}Gd and ^{161}Tb, indicating that ^{161}Tb suitable for radiopharmaceutical production and animal pharmacokinetic studies can be prepared without enriched ^{160}Gd. ^{177}Lu-PSMA-617 was obtained in nearly quantitative yield, whereas ^{225}Ac-PSMA-617 was obtained in 64% yield; mouse biodistribution showed high renal uptake with additional liver and bone accumulation, requiring further optimization of ^{225}Ac/daughter-nuclide behavior. LAT1-targeted tyrosine-based chelator compounds were synthesized. Ra-228-supported MgO targets were irradiated safely at KUR, and further purification and long-term α-spectrometry are planned to verify Th-229 production.

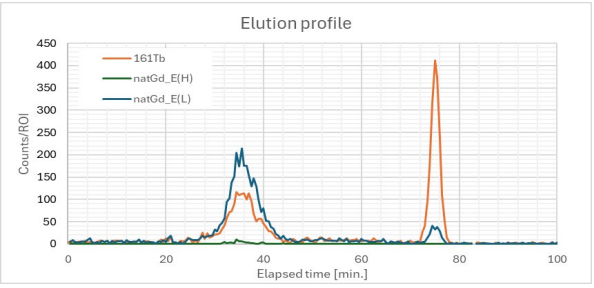

Figure 1. Elution profile of extraction chromatography with an 11 mmφ × 240 mmL column packed with LN2 resin measured with a CZT detector.

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PR8-1

Development of Radiotheranostic Agents Utilizing a Variety of Radioisotopes

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INTRODUCTION: The domestic demand for therapeutic radioisotopes (RIs) in nuclear medicine is increasing; however, the supply remains largely dependent on unstable imports. This highlights the need to promote domestic production of medical RIs and to establish a comprehensive framework for nuclear medicine diagnosis and therapy. In this study, ^{177}Lu produced at the Kyoto University Reactor (KUR) was used to synthesize established radiopharmaceuticals, including ^{177}Lu-PSMA-617. Cytotoxicity and therapeutic efficacy were evaluated in tumor-bearing mouse models, and the quality of the produced ^{177}Lu was assessed through comparison with previously reported data. In addition, ^{225}Ac obtained from a ^{229}Th/^{225}Ra–^{225}Ac generator was used to synthesize ^{225}Ac-PSMA-617. These radiopharmaceuticals were similarly evaluated for cytotoxicity and therapeutic efficacy in tumor-bearing mouse models, and the quality of the produced ^{225}Ac was assessed by comparison with the literature.

EXPERIMENTS: Radiolabeling of PSMA-617 with ^{177}Lu and ^{225}Ac:To 10 μL of the PSMA-617 precursor (2 mg/mL in 0.1 M acetate buffer), 10 μL of L-ascorbic acid (100 mg/mL), 140 μL of 0.1 M acetate buffer (pH 5.8), and either ^{177}LuCl$_3$ (9.15 MBq, 10 μL) or ^{225}AcCl$_3$ (0.25 MBq, 20 μL) were added to obtain a final volume of 180 μL. The reaction mixture was then incubated in an aluminum block heater at 90 °C for 30 min for ^{177}Lu labeling, or at 95 °C for 15 min for ^{225}Ac labeling. Biodistribution study in Slc:ddY mice:Each mouse was intravenously injected via the tail vein with either ^{225}Ac-PSMA-617 (62.5 kBq/100 μL) or ^{177}Lu-PSMA-617 (37 kBq/100 μL). At 1 h post-injection, the mice were euthanized, and major organs were harvested and weighed. The radioactivity in each organ was then measured using a γ-counter, and the percentage of injected dose per gram of tissue (%ID/g) was calculated.

RESULTS: ^{177}Lu-PSMA-617 was obtained in nearly quantitative radiochemical yield. In contrast, the radiochemical yield of ^{225}Ac-PSMA-617 was 64%. In this study, only a limited amount of ^{225}Ac was available, which precluded sufficient optimization of the labeling conditions. Further evaluation, including assessment of reproducibility, remains to be addressed in future work.
In biodistribution studies using Slc:ddY mice, ^{225}Ac-PSMA-617 showed high uptake in the kidneys, with additional accumulation in the liver and bone. Comparison with ^{177}Lu-PSMA-617 revealed no major differences in overall organ distribution; however, higher uptake of ^{225}Ac-PSMA-617 was observed in the liver and bone. Previous reports have also shown that Ac^{3+} tends to accumulate in the liver and bone. For ^{225}Ac, nuclear recoil associated with radioactive decay is a key challenge. During α-decay, a high-energy α particle (approximately 5–8 MeV, ^{4}He nucleus) is emitted, resulting in recoil of the daughter nuclide in the opposite direction. The energy involved greatly exceeds chemical bond energies, potentially leading to disruption of the chelator complex and release of daughter nuclides. These may redistribute locally or migrate via blood or lymphatic circulation, contributing to off-target radiation exposure. In particular, as ^{225}Ac undergoes multiple α-decay steps, control of daughter nuclide behavior is critical for therapeutic applications, making in vivo stability a key design consideration. In this study, limited reproducibility in animal experiments prevents definitive attribution of the observed accumulation to free ^{225}Ac or its daughter nuclides. Further investigation is required. Nevertheless, comparison with previously reported data suggests that the ^{177}Lu and ^{225}Ac used in this study are of sufficient quality for preclinical applications.

Preliminary Study on the Production of ^{161}Tb Using ^{nat}Gd and Radiochemical Separation at the Kyoto University Research Reactor

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INTRODUCTION: Terubium-161, ^{161}Tb (half-life: 6.95 days) is a β⁻-emitting radionuclide that is produced indirectly during reactor irradiation via the ^{160}Gd(n,γ) ^{161}Gd reaction, followed by the β⁻ decay of ^{161}Gd (half-life: 3.66 minutes). The half-life and decay characteristics of ^{161}Tb are similar to those of therapeutic radionuclide ^{177}Lu; however, ^{161}Tb emits a significantly higher number of internal conversion electrons and Auger electrons compared to ^{177}Lu, suggesting superior therapeutic efficacy from a theoretical standpoint. Its effectiveness has been demonstrated in animal studies and clinical trials conducted overseas [1]. In Japan, however, ^{161}Tb remains difficult to obtain, and there are no reported cases of its production. In this study, fundamental investigations on reactor-based production were conducted using natural gadolinium containing 21.86% ^{160}Gd, focusing on production characteristics and chemical separation behavior.

EXPERIMENTAL: The gadolinium (Gd) samples used for irradiation were prepared from an ICP-MS elemental standard with natural isotopic abundance. A solution containing an amount equivalent to 1.0 mg of Gd was transferred into a quartz tube, concentrated to dryness by heating, and then vacuum-sealed. The quartz tube was loaded into a hydraulic rabbit system of the research reactor at the Kyoto University Institute for Integrated Radiation and Nuclear Science and irradiated for 47 hours at a thermal power of 1 MW. The irradiated Gd target was dissolved in 6 M HNO_3 four days after irradiation and adjusted to 0.25 M HNO_3. For the chemical separation of Gd and Tb, the extraction chromatography method developed by Żółtowska et al. [2] was used. Column separation was carried out using LN2 resin (Eichrom). A jacketed glass column (11 mm i.d. × 240 mm length, Kiriyama Glass) was used for the separation. The eluate from the column was monitored online using a CZT detector (RadAngel, Kromek).
For the separation of Gd and ^{161}Tb, regions of interest (ROI) were set at 97.4 and 103.2 keV for ^{153}Gd, and 363.54 keV for ^{159}Gd used as a tracer for Gd, and at 74.6 keV for ^{161}Tb. Fractions of Gd and Tb were collected based on elution curves expressed as count rates per unit time for each ROI. Gd was first eluted with 0.2 M HNO_3, and after confirming its elution, ^{161}Tb was subsequently eluted with 0.45 M HNO_3. The collected fractions were further trapped on separately prepared DGA cartridges, and qualitative analysis of the Gd and Tb fractions was performed using a Ge detector (ORTEC).

RESULTS: The elution curves of Gd and Tb obtained using the CZT detector showed distinct profiles for each element (Fig. 1). However, it was found that Compton scattering components originating from ^{153}Gd contributed to the ROI of ^{161}Tb. Therefore, careful attention is required when determining the timing of fraction collection. At the same time, this issue can be avoided by confirming the γ-ray spectra measured simultaneously, thereby preventing misidentification. Qualitative analysis of the separated Gd and Tb fractions using a Ge detector confirmed that ^{153}Gd ($T_{1/2}$ = 240.4 d), produced via the ^{154}Gd(n,2n) reaction, ^{159}Gd, produced via the ^{158}Gd(n,γ) reaction, and ^{161}Tb were successfully separated in the irradiated samples. Since the half-life of ^{159}Gd is 18.5 hours, its presence can be easily confirmed even one week after irradiation. Furthermore, its relatively high γ-ray energy (363 keV) makes it easy to detect, facilitating the identification of the Gd fraction.

CONCLUSION: In this study, we evaluated the production and radiochemical separation of ^{161}Tb. Our results indicate that it is possible to produce and purify ^{161}Tb of sufficient quality for radiopharmaceutical production and pharmacokinetic studies in animal models without the need for isotopically enriched ^{160}Gd, suggesting the feasibility of using natural Gd as a target material.

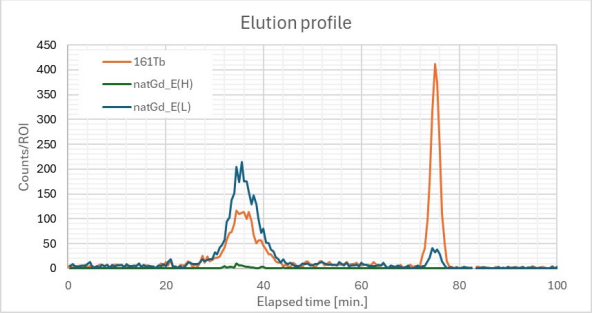

Figure 1. Elution profile of extraction chromatography with an 11 mmφ × 240 mmL column packed with LN2 resin measured with a CZT detector.

REFERENCES:
[1] F. Trejtnar *et al.*, Nucl. Med. Biol, **144-145** (2025) 108998.
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PR8-3

On-line monitoring of ^{177}Lu/Yb separation by extraction chromatography

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INTRODUCTION: ^{177}Lu (half-life: 6.64 d), produced indirectly by neutron irradiation of ^{176}Yb, is a β^- emitter and one of the applicable nuclides for targeted radioisotope therapy (TRT). To date, ^{177}Lu-DOTA-TATE for the treatment of somatostatin-overexpressing tumors, and ^{177}Lu-PSMA-617 for the treatment of castration-resistant prostate cancer, have been investigated for TRT use.
In extraction chromatography, bis-2-ethylhexylphosphonric acid and 2-ethylhexyl- phosphonic acid are well known as substrate adsorbed extractants for ^{177}Lu separation, and recently some extractants have explored. In these studies, typically the concentrations of Yb and Lu in the eluate are determined by radiometric or elemental concentration measurements after collecting a certain volume of solution that has passed through the column. However, some technique that allows for faster analysis is desirable for the best condition survey.
In this study, we developed a real-time monitoring technique for ^{177}Lu and radioactive Yb using the on-line γ-ray detector (CZT detector or Ge semiconductor detector) in the separation of ^{177}Lu from neutron irradiated Yb targets by extraction chromatography.

EXPERIMENTS: The experiments were conducted using the on-line monitoring separation system previously reported in detail [1].

RESULTS: Fig. 1(a) shows an overview of the Lu/Yb separation experiment using enriched ^{176}Yb: the first horizontal axis is the elapsed time, the second is the γ-ray energy, and the vertical axis is the logarithm of the intensity (count rate). This figure shows that the peak energies and their intensities in the γ-ray spectra change with time. To examine in detail, the type of nuclide elution taking place at each stage, the γ-ray energy is evaluated in relation to the elapsed time (Fig. 1(b)). Focusing on the γ-ray energy range above 100 keV, high intensities were detected at around 110, 131, 177, 198, 282, 308, and 396 keV for times between 300 and 400 min. These γ-ray peaks are attributed to ^{169}Yb and ^{175}Yb. In the region around 510 min, high intensities were detected at 110 keV as well as 208 keV. Especially at the latter γ-ray energy, the intensity was confirmed only in this region. Since these can be attributed to ^{177}Lu (113 keV and 208 keV), it can be assumed that most of the Yb is leached out by passing 1.5 M HNO_3, and the remaining resin residue, composed mainly of Lu, is leached out by 4 M HNO_3 after 500 min.

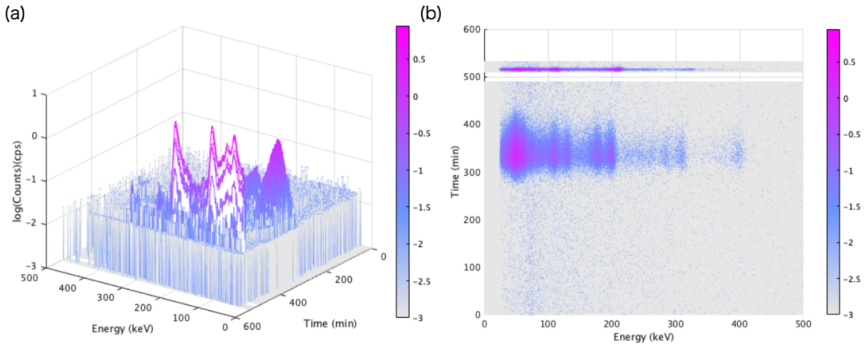

Fig. 1. Overview of the Lu/Yb separation experiment using enriched ^{176}Yb (a) and γ-ray energies relation to time (b).

REFERENCES:
[1] K. Shirasaki, T. Yamamura, KURNS Progress Report, (2024) 15.

Fundamental Research on the Production of Lu-177

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INTRODUCTION: Radioisotopes are widely utilized in Japan as diagnostic and therapeutic agents. However, Japan relies on imports for key nuclides such as Mo-99, which are produced in nuclear reactors overseas. This reliance raises concern that international circumstances could disrupt domestic supply and impede drug development. Therefore, JAEA has undertaken radioisotope production trials using the JRR-3 reactor, which resumed operation at the end of February 2021. Among these efforts, particular focuses are made on production trials for Lu-177, as detailed below.

EXPERIMENTS: For the Lu-177 production test at JRR-3, [176Lu] Lu2O3 (enriched to 64.3%) for the direct method and [176Yb] Yb2O3 (enriched to 99.9%) for the indirect method was used as the irradiation target.
Solutions of the target materials (1 M HNO3) were weighed and dispensed into quartz ampoules to have an irradiation target element of approximately 0.1 mg. The solutions were then evaporated to dryness and sealed to prepare the irradiation samples. These samples were placed in irradiation capsules, pressure welded and irradiated in HR-1, which is neutron irradiation facility in heavy water tank of JRR-3.

RESULTS: The result shows that about 400 GBq of Lu-177 can be produced by irradiating 1 mg of Lu in HR-1 for 14 days. However, since the specific activity is lower than that of Lu-177 distributed in Japan it is difficult to immediately use the current product as a pharmaceutical raw material, but it was confirmed that JRR-3 can produce radioisotopes of sufficient quantity and quality for testing such as labeling tests and non-clinical studies. Similarly, the result shows that approximately 500 MBq of Lu-177 was produced by irradiating 1 mg of Yb for 14 days, suggesting that irradiation of a few grams of Yb could generally meet the domestic demand. Due to the high cost of the enriched target, re-irradiation of the recovered targets is necessary. We are also planning research and development to improve a column chromatographic separation process for the target radioisotope.

Conclusions: The trial irradiations for Lu-177 have confirmed the producing capability of JRR-3. Several issues were identified including specific activity and the need for re-irradiation. Moving forward, we plan to investigate these issues. Although KURNS facilities were not used in FY 2025, we'll advance the development of production and separation processes for broad range of radioisotopes in cooperation with KURNS.

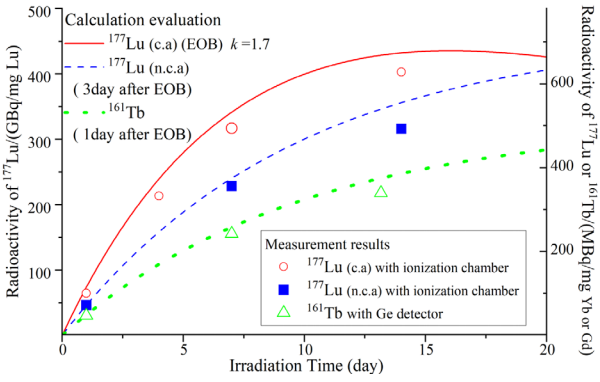

Fig 1 Evaluation of Lu-177 production volume

PR8-5

Development of metal radioisotope-labeled agents for cancer radiotheranostics

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INTRODUCTION: In recent years, the concept of theranostics—aimed at the efficient integration of diagnosis and therapy—has been increasingly advocated. In the field of nuclear medicine, radiotheranostics has attracted considerable attention as an approach that enables the development of both diagnostic and therapeutic radiopharmaceuticals based on an identical molecular scaffold, simply by altering the labeled radioisotope. This strategy is expected to promote highly efficient diagnosis and treatment. In particular, nuclear medicine therapies for cancer are anticipated to yield significant therapeutic efficacy, thereby creating a strong demand for the development of novel cancer-targeted radiotheranostic agents. The objective of this study is to develop novel low-molecular-weight metal radioisotope-labeled molecular probes targeting cancer for radiotheranostic applications, with a focus on targeting L-type amino acid transporter 1 (LAT1).

DRUG DESIGN CONCEPT: For the advancement of radiotheranostics, the use of metal radioisotopes represents a highly effective strategy, as it enables the development of both diagnostic and therapeutic agents based on an identical molecular scaffold simply by altering the radioisotope used for labeling. However, the incorporation of metal radioisotopes generally requires the introduction of relatively bulky chelating moieties into the probe structure, which may compromise the biological activity of the parent scaffold, particularly in the case of low-molecular-weight probes. Since the natural substrates of LAT1 are amino acids, it is challenging to incorporate bulky chelating structures while retaining substrate-like biological activity toward LAT1. Therefore, in this study, rather than designing probes as LAT1 substrates, we aimed to develop them as inhibitors with binding affinity to LAT1. Based on this strategy, novel metal radioisotope-labeled probes were rationally and precisely designed.

EXPERIMENTS: We have previously succeeded in the development of an ^{18}F-labeled probe exhibiting high selectivity for LAT1, a transporter highly expressed in cancer cells among the LAT family [1-3]. Based on this prior knowledge, two types of control compounds were designed and synthesized using a tyrosine-based scaffold, with the introduction of a chelating moiety.

RESULTS: Two types of control compounds were successfully synthesized through multistep synthetic routes. Further design and synthesis of additional compounds are currently in progress, with subsequent studies planned for metal radioisotope labeling and evaluation of their biological efficacy.

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Investigation of suitable ^{177}Lu/Yb separation condition in extraction chromatography

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INTRODUCTION: Addressing the growing demand for ^{177}Lu in nuclear medicine, high-efficiency separation of ^{177}Lu and Yb has become a critical issue. However, due to the similarities in the ionic radii, oxidation states, and chemical behavior of Lu and Yb, their separation remains a significant challenge [1-3].
Our objective of this irradiation is to identify requirements for an automated column separation system that enables the scale-up of non-carrier-added ^{177}Lu production through long-term irradiation in KUR, by compiling challenges encountered in the separation of ^{177}Lu obtained from KUR-hydro (R7P8-4) irradiated Yb targets by extraction chromatography.

EXPERIMENTS: The irradiation conditions consisted of long-term irradiation (47 hours at 1 MW followed by 6 hours at 5 MW in a continuous cycle). The experimental apparatus used in this study consists mainly of a pump, a column with a water jacket and a CZT detector (GR1, Kromek). The solution is pumped up and introduced into the 30 cm column, which is filled with extraction resin (LN2, Eichrom, 50–100 μm). The column temperature is kept constant by a thermostatic water circulation system. The solution that has passed through the column is introduced into a lead shield with a γ-ray detector installed. Then, the solution is collected in a sample vial as it passes through a bundled flow path in the ring shape for γ-ray measurement.

RESULTS: As shown in Table 1, the specific activity of ^{177}Lu was $(1.042 \pm 0.01) \times 10^7$ Bq/mg, and the quantity generated was three times larger than that of a hydro (1MW24h) irradiation one.

Table1 Irradiated enriched ^{176}Yb sample data

Exp. date	Yb_2O_3 (mg)	^{177}Lu (Bq/mg)	^{169}Yb (Bq/mg)	^{175}Yb (Bq/mg)
2026/1/22	1.071	(1.042±0.01) $\times 10^7$	n.d.	(1.392±0.04) $\times 10^6$

During the ^{177}Lu/Yb separation experiment, the peak energies and their intensities in the γ-ray spectra change with time. High intensities were detected at around 110, 131, 177, 198, 282, 308, and 396 keV for times around 600 min. These γ-ray peaks are attributed to ^{169}Yb (110, 131, 177, 198, and 308 keV) and ^{175}Yb (114, 282, and 396 keV), respectively. In the region around 660 min, high intensities were detected at 110 keV as well as 208 keV. Especially at the latter γ-ray energy, the intensity was confirmed only in this region. Since these can be attributed to ^{177}Lu (113 keV and 208 keV), it can be assumed that most of the Yb is leached out by passing 2.25 M HNO_3, and the remaining resin residue, composed mainly of Lu, is leached out by 4 M HNO_3 after 660 min.

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[2] Z. Li *et al.*, Ind. Eng. Chem. Res., **60** (2021) 17285-17302.
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PR8-7

Study on Ac-225 Production via the (n,γ) reaction of Th-decay Product Ra-228

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INTRODUCTION: Regarding the production of Ac-225, an α-emitting radionuclide used in targeted alpha therapy, the currently supplied Ac-225 is produced by separating it from Th-229 generators, which are derived from U-233. However, since U-233 is a fissile nuclide and its handling is strictly regulated, it is not suitable for the large-scale production of Ac-225. To meet the increasing demand for Ac-225 in recent years, a new production method has been proposed: irradiation of Ra-228, a daughter nuclide of naturally abundant Th-232, with thermal neutrons to produce Ra-229 via the (n,γ) reaction, followed by the production of Ac-225 through the decay of Ra-229 [1].
In this study, to demonstrate the feasibility of this method, an irradiation target consisting of Ra-228 supported on MgO was fabricated, and thermal neutron irradiation was carried out at the Kyoto University Research Reactor (KUR).

EXPERIMENTS: The MgO targets used for irradiation at KUR were fabricated by chemically treating a solution containing Ra-228. First, to prevent contamination of the irradiation target with Th-232 and the subsequent production of U-233, polyvinylpolypyrrolidone (PVPP) was used to remove trace amounts of Th present in the Ra solution. The solution was then adjusted to a nitric acid–methanol mixture, and Na in the solution was removed using a strongly basic anion exchange resin. After the removal of Th and Na, sodium carbonate and magnesium nitrate solutions were added, and $RaCO_3$ and $MgCO_3$ were co-precipitation. The recovered precipitates were heated at 400°C for 0.5 h to convert them into oxides. Fig. 1 shows the MgO target containing Ra-228.
Thermal neutron irradiation at KUR was conducted over five weeks from December 2, 2025, to February 5, 2026, with a total irradiation time of 30 h at 5 MW and 233 h at 1 MW. The radioactivity of Th-229 produced by this irradiation is estimated to be 1.26×10^{-3} Bq.

Target Appearance	White powder
Target composition	MgO + RaO
Weight of the target	0.088 g
Radioactivity of Ra-228	3.98 kBq

Fig. 1. Specifications for Ra-228-containing MgO target for thermal neutrons irradiation.

RESULTS: The irradiation proceeded without incident, and no deformation of the target or damage to the quartz glass tube was observed. After dissolving the target in 8 M nitric acid, Th was recovered using PVPP, and α-spectrometry was performed.
The results showed that the Th-229 peak (4.846 MeV) is obscured by adjacent peaks of Th-228 (5.340 and 5.423 MeV), which is produced by the decay of Ra-228. Therefore, as an alternative method to verify the production of Th-229, detection of the At-217 peak (7.069 MeV), which is well separated from the adjacent Po-212 peak (8.785 MeV), was considered instead of direct detection of the Th-229 peak. Based on these results, further purification of the sample and long-term measurements are planned to evaluate the production of Th-229 via thermal neutron irradiation of Ra-228.

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