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Medical radioisotopes production focusing on Ra-225/Ac-225, Cu-67 and Mo-99/Tc-99m using an electron linear accelerator

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Outline

1. Medical radioisotopes production using an electron linear accelerator
2. Mo-99/Tc-99m
3. Cu-67
4. Ra-225/Ac-225
5. Summary

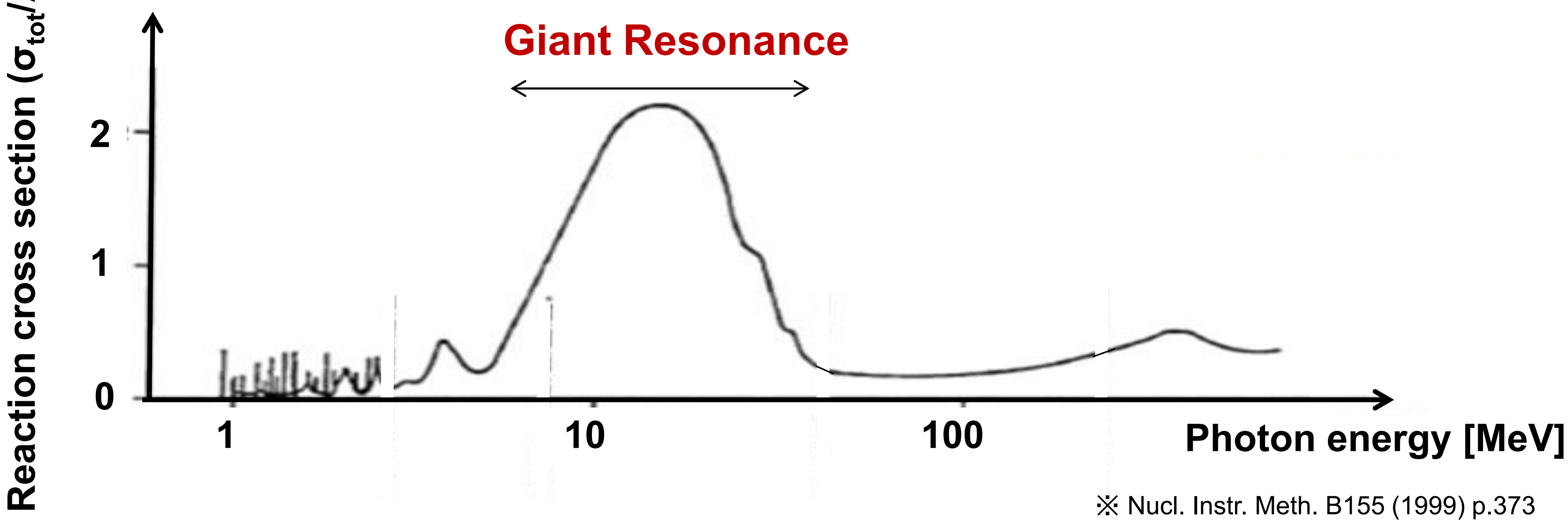
1. Medical radioisotopes production using an electron linear accelerator

1-1 Photonuclear reactions

Large reaction cross section in the 10-20 MeV range (Giant Resonance).

Irradiation of photons with energies exceeding the binding energy of nucleons (~7 MeV) causes nucleon emission reactions.

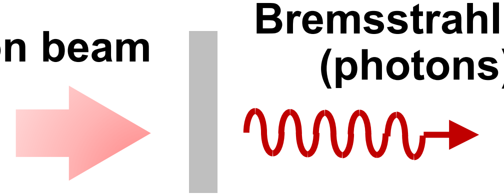
Generation of new nuclides



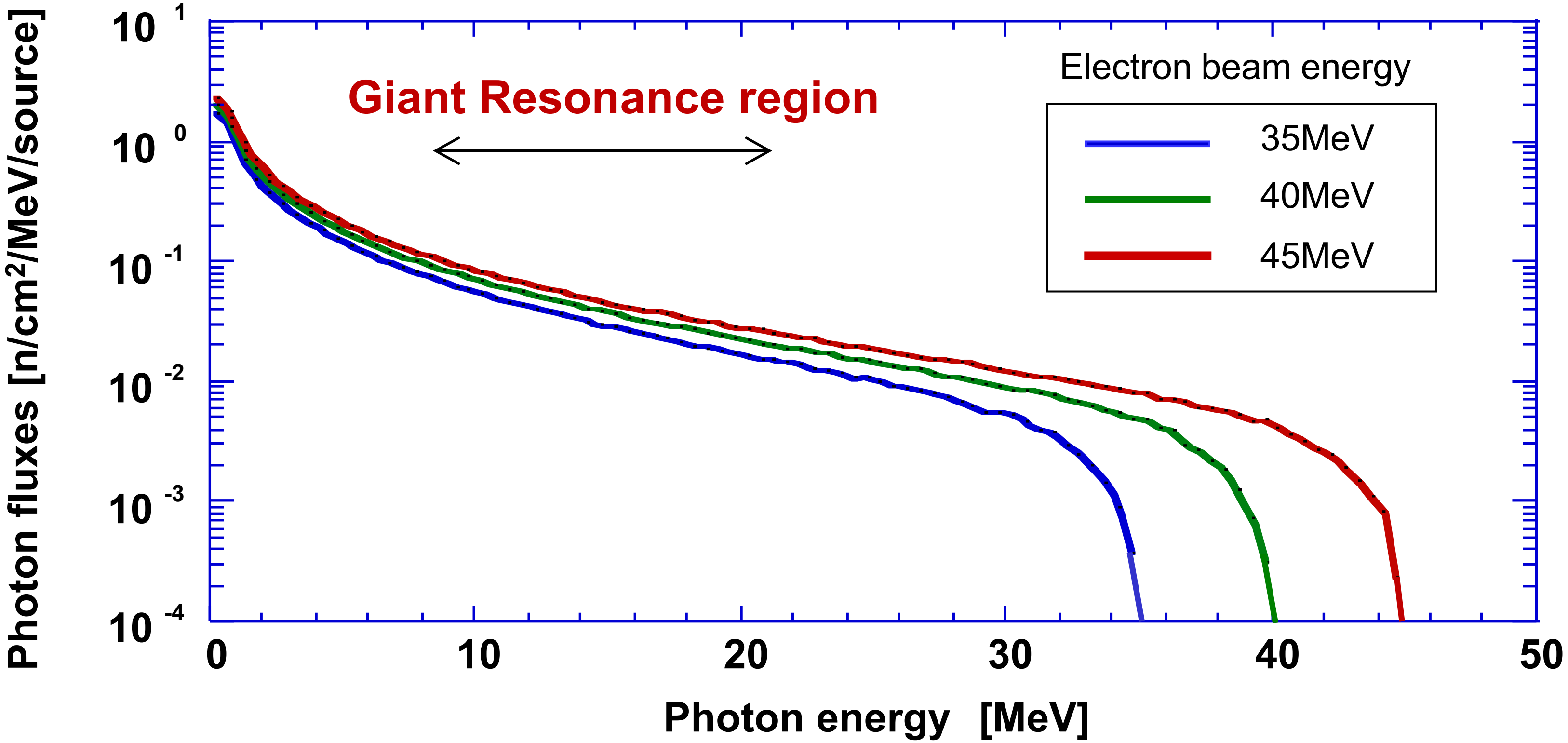
※ Nucl. Instr. Meth. B155 (1999) p.373

1-2 Generation of bremsstrahlung

Bremsstrahlung (i.e., photons) is produced when an accelerated electron beam is irradiated onto a material.



Example bremsstrahlung spectrum (Calculated using Monte Carlo code PHITS※)



※ Particle and Heavy Ion Transport code System http://phits.jaea.go.jp/indexj.html

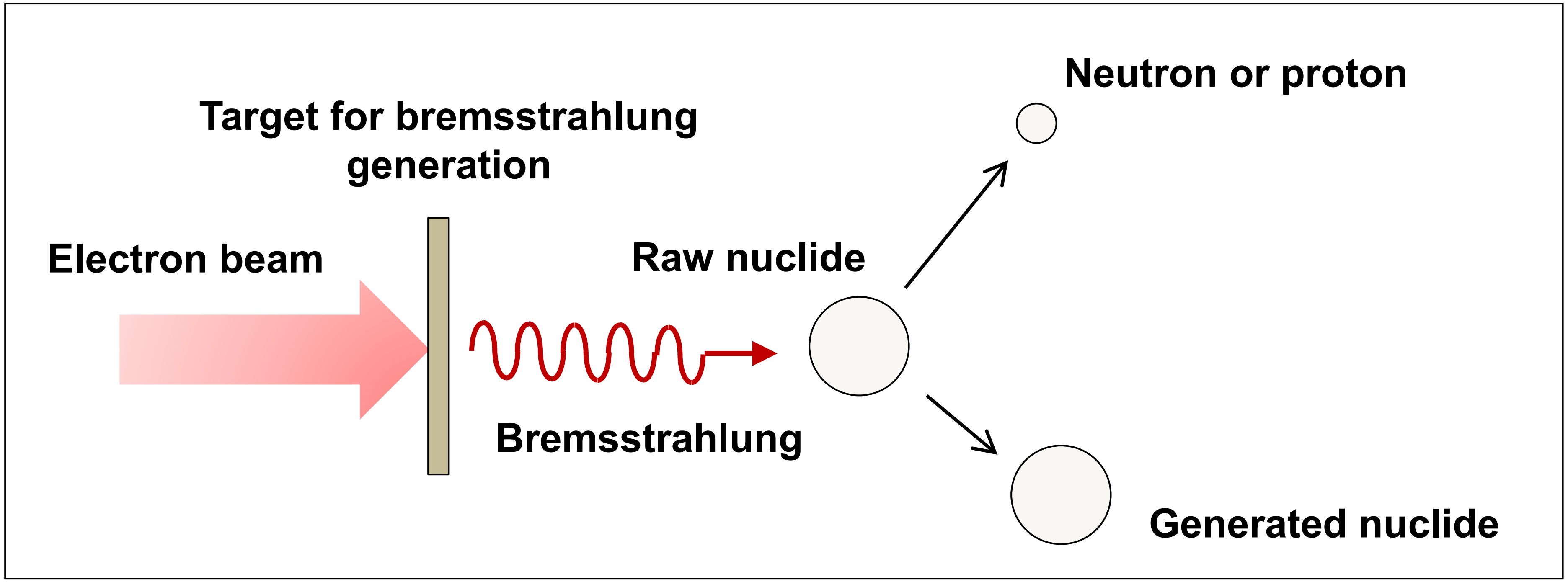
1-3 Medical radioisotopes production using an electron linear accelerator (1)

An accelerated electron beam is irradiated to the target for bremsstrahlung generation

→ Bremsstrahlung is generated

→ The generated bremsstrahlung is irradiated to a raw nuclide

→ New nuclides are generated by photonuclear reactions of the raw nuclides



1-4 Medical radioisotopes production using an electron linear accelerator (2)

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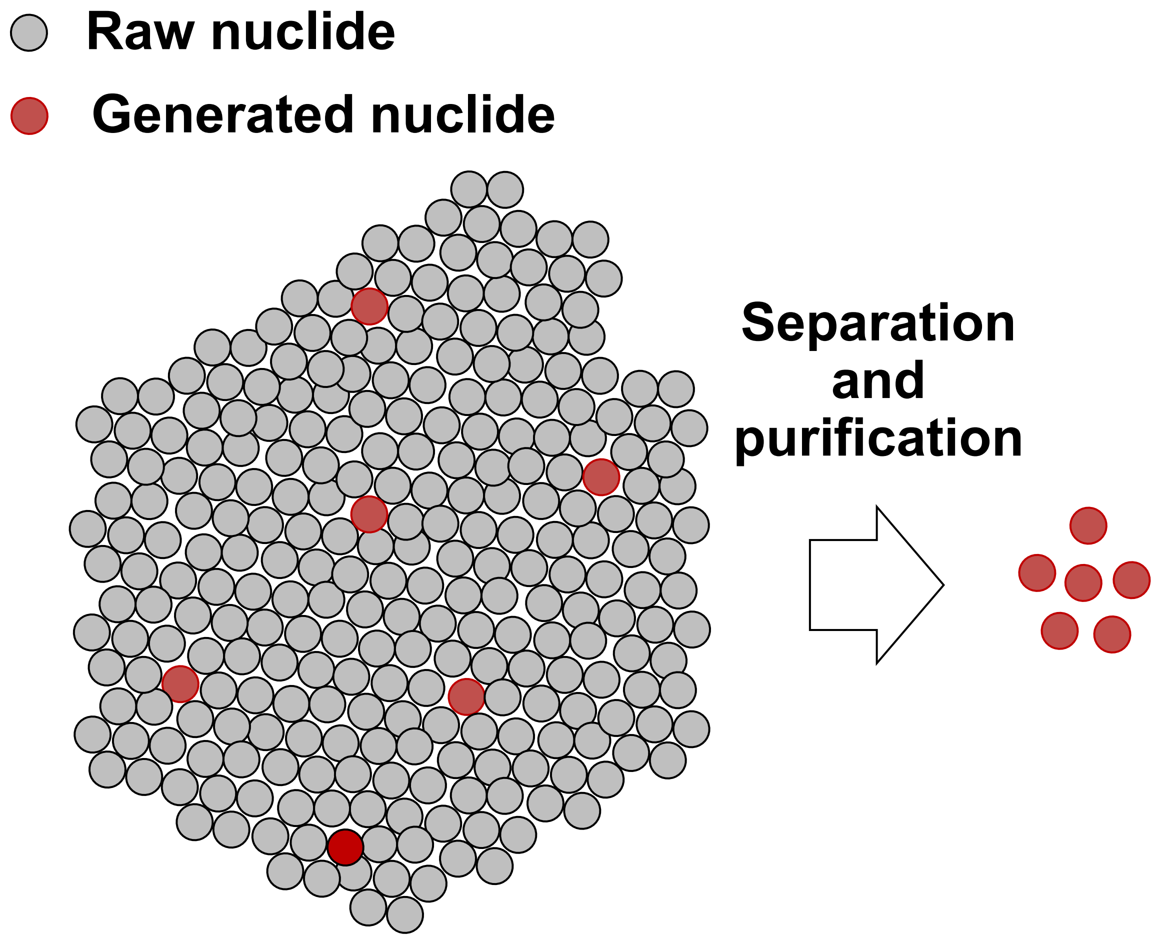
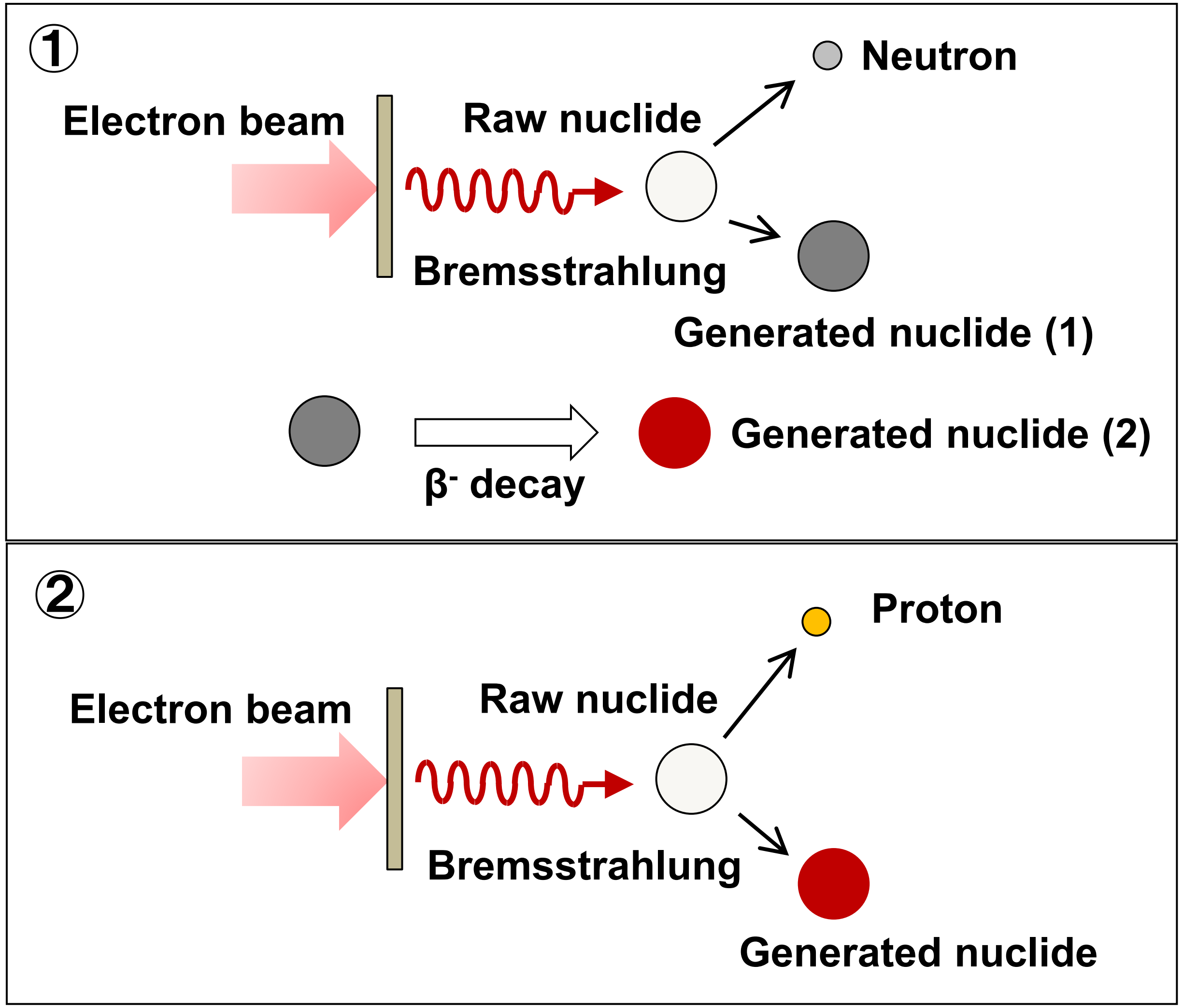


If the generated nuclide is an isotope of the raw nuclide, it is difficult to separate and purify the generated nuclide

Nuclide generation reactions suitable for election linear accelerator application



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Examples of medical nuclides suitable for production using an electron linear accelerator

Raw nuclide	Production reaction	Produced nuclide	Application
Mo-100	Mo-100(γ,n)Mo-99, Mo-99 → (β^-decay)Tc-99m	Tc-99m	Diagnosis (SPECT)
Zn-68	Zn-68(γ,p)Cu-67	Cu-67	Diagnosis (SPECT) and therapeutics (β-ray therapy)
Ge-70	Ge-70(γ,2n)Ge-68, Ge-68 → (β^-decay)Ga-68	Ga-68	Diagnosis (PET)
Hf-178	Hf-178(γ,p)Lu-177	Lu-177	Therapeutics (β-ray therapy)
Ra-226	Ra-226(γ,n)Ra-225, Ra-225 → (β^-decay)Ac-225	Ac-225	Therapeutics (α-ray therapy)

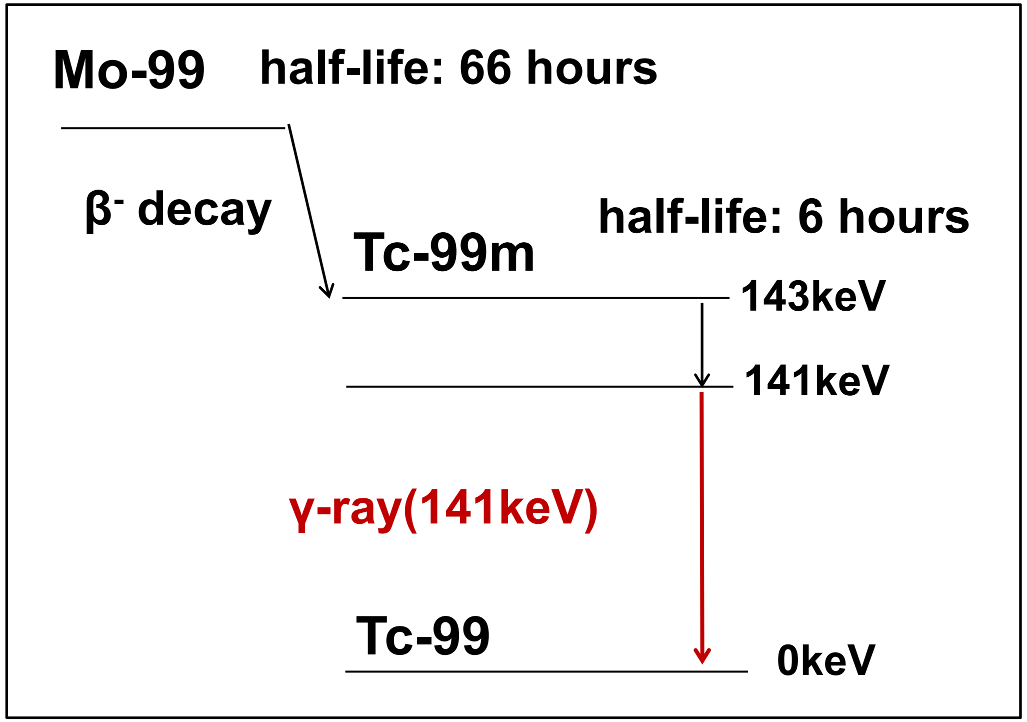
2. Mo-99/Tc-99m

2-1 Mo-99/Tc-99m

Tc-99m is produced by separation and purification from the parent nucleus Mo-99.
Mo-99 is produced in research reactors, and Japan and the U.S. currently rely 100% on imports.
Widely used as a drug for nuclear medicine diagnosis SPECT (Single Photon Emission Tomography).

SPECT equipment

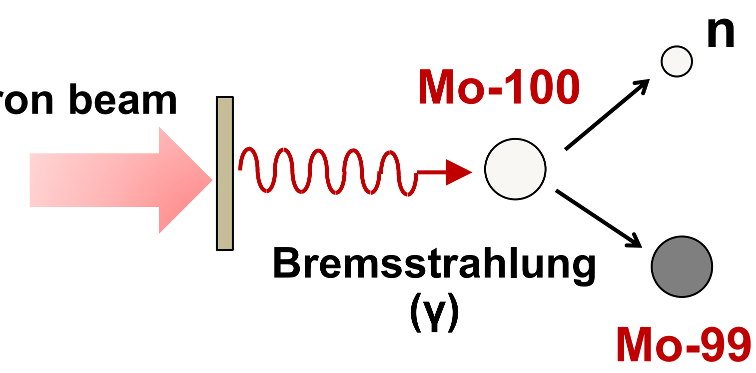
Photo courtesy of Philips：BRIGHTVIEW X



2-2 Mo-99/Tc-99m production using an electron beam linear accelerator

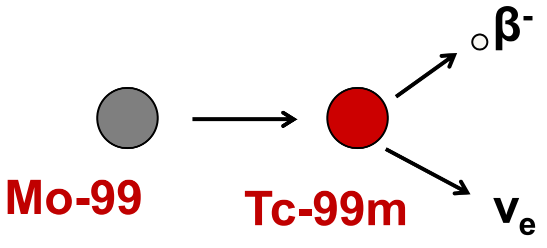
Mo-99 is produced by a reaction that produces one neutron by irradiation of bremsstrahlung to Mo-100

Mo-100 + γ → Mo-99 + n

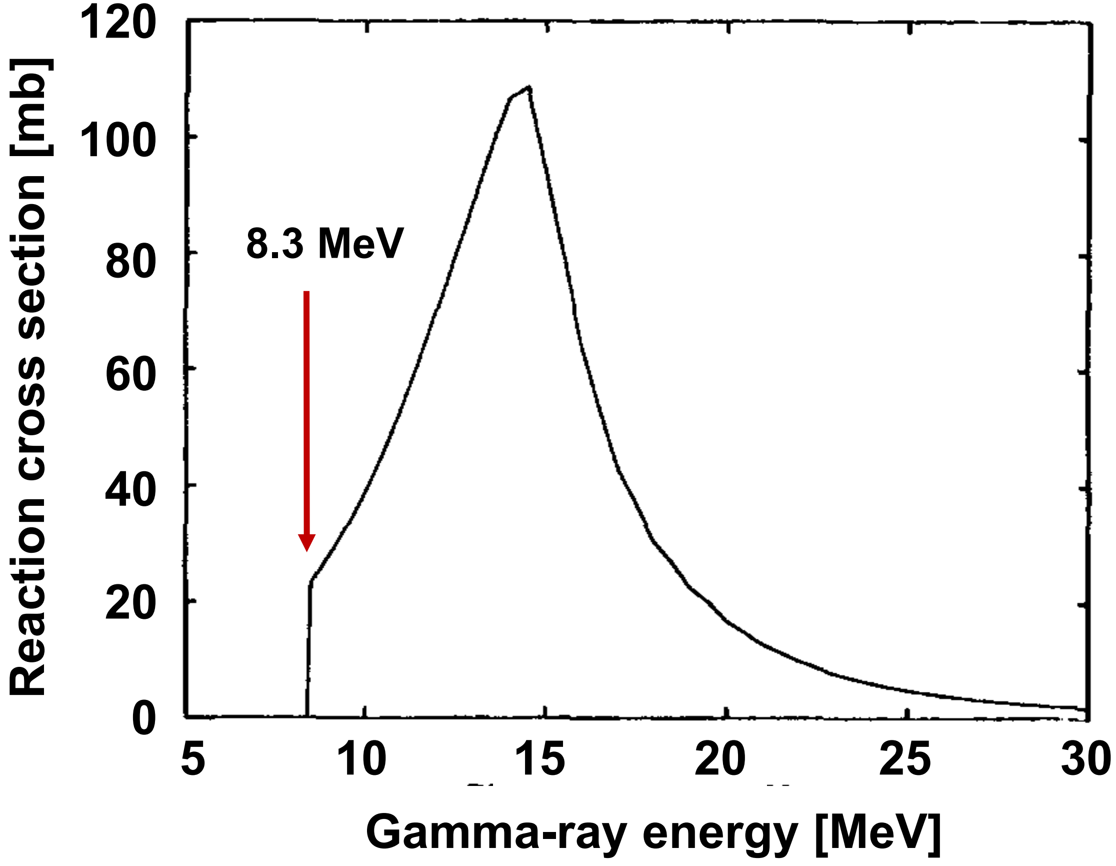


Tc-99m is generated by β^- decay of Mo-99

Mo-99 → Tc-99m + β^- + ν_e



Mo-100(γ,n)Mo-99 reaction cross section ※

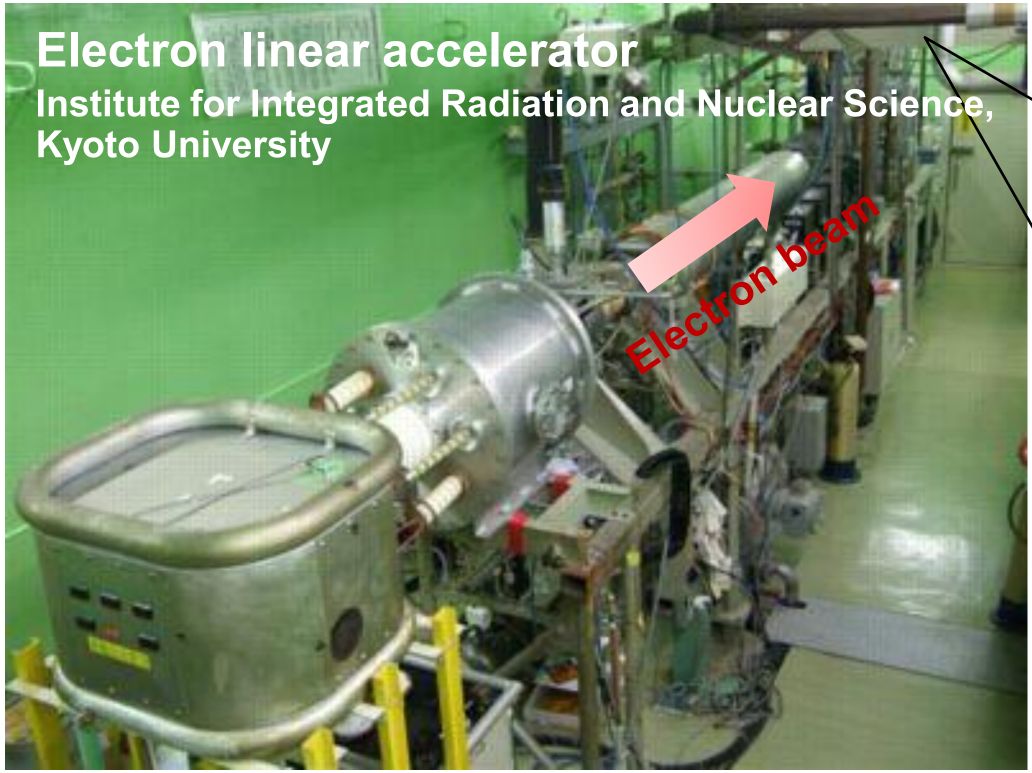


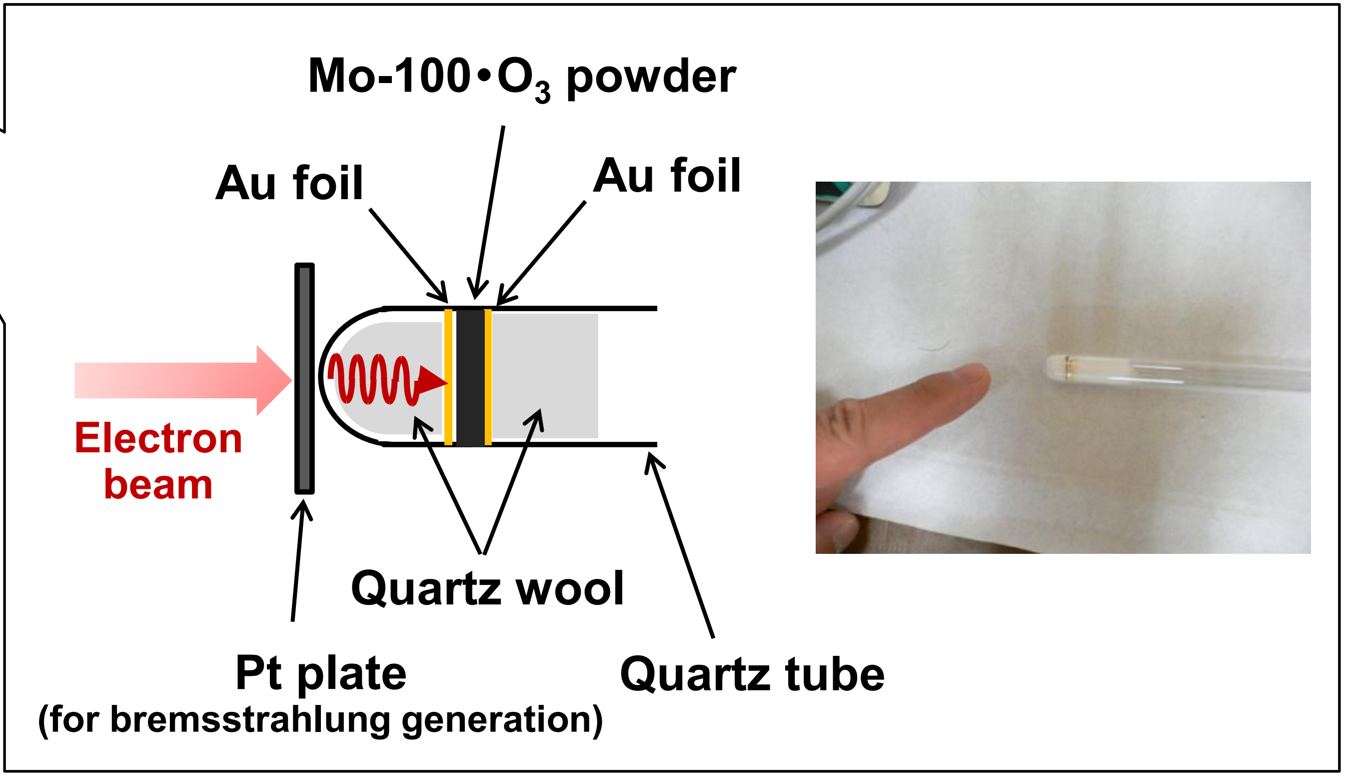
※ Y. Lee et al., J. Korean Nucl. Soc. 31 (1999) p.529

2-3 Basic test for production of Mo-99/Tc-99m※

Test conditions

Electron beam energy, 20 to 41MeV; Acceleration current value, 20 to 90μA;
Mo-100 sample, Mo-100•O_3 powder (concentration ratio, 99%)





※ Collaborative research with Prof. Otsuki and Assistant Prof. Sekimoto, Kyoto University

2-4 An example of a basic test result - Gamma-ray spectrum -

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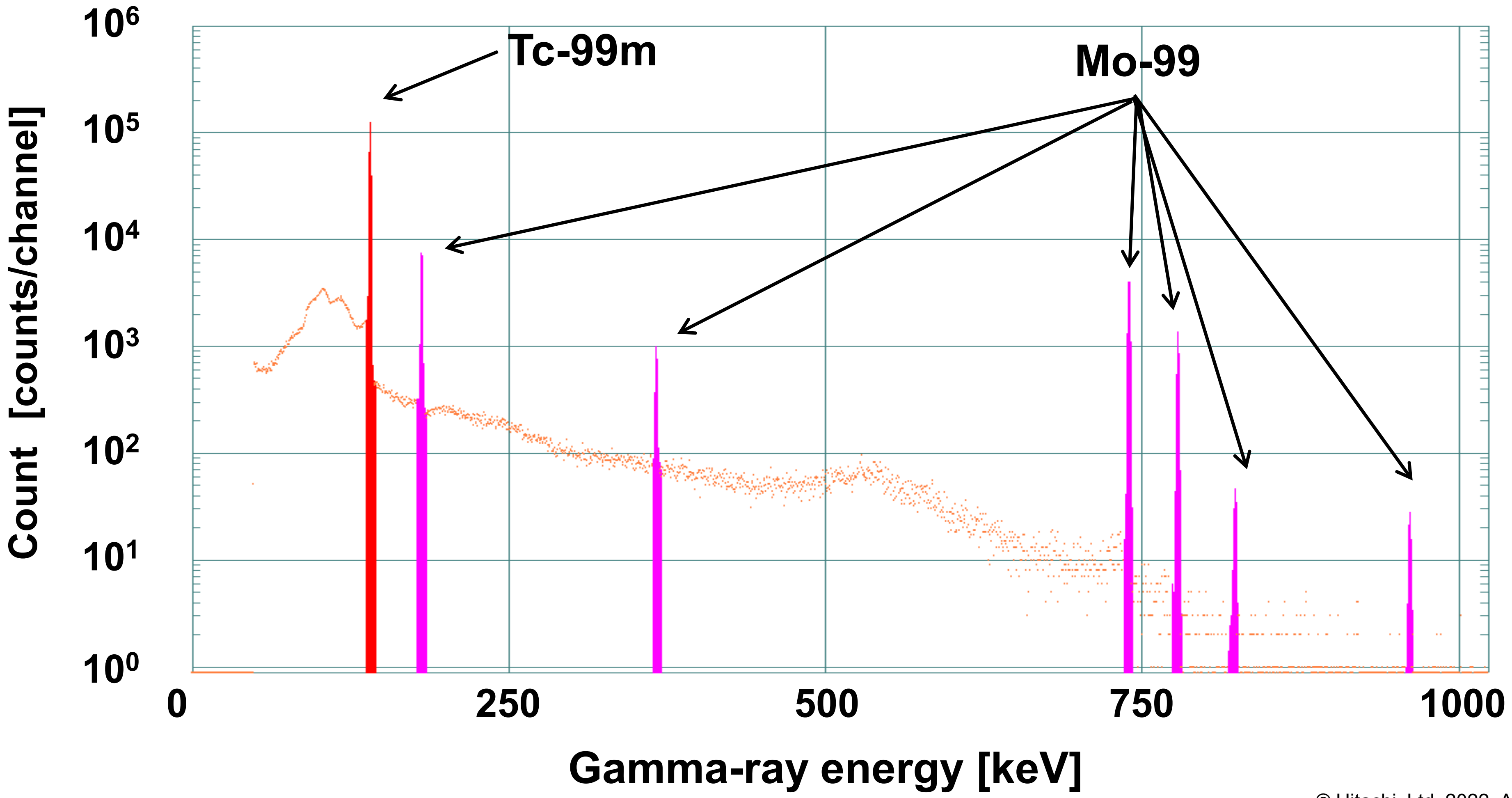
No impurity nuclides other than Mo-99 and Tc-99m are produced. ⇨ **Very clean production process**



2-5 Basic Test for mass production of Mo-99/Tc-99m※

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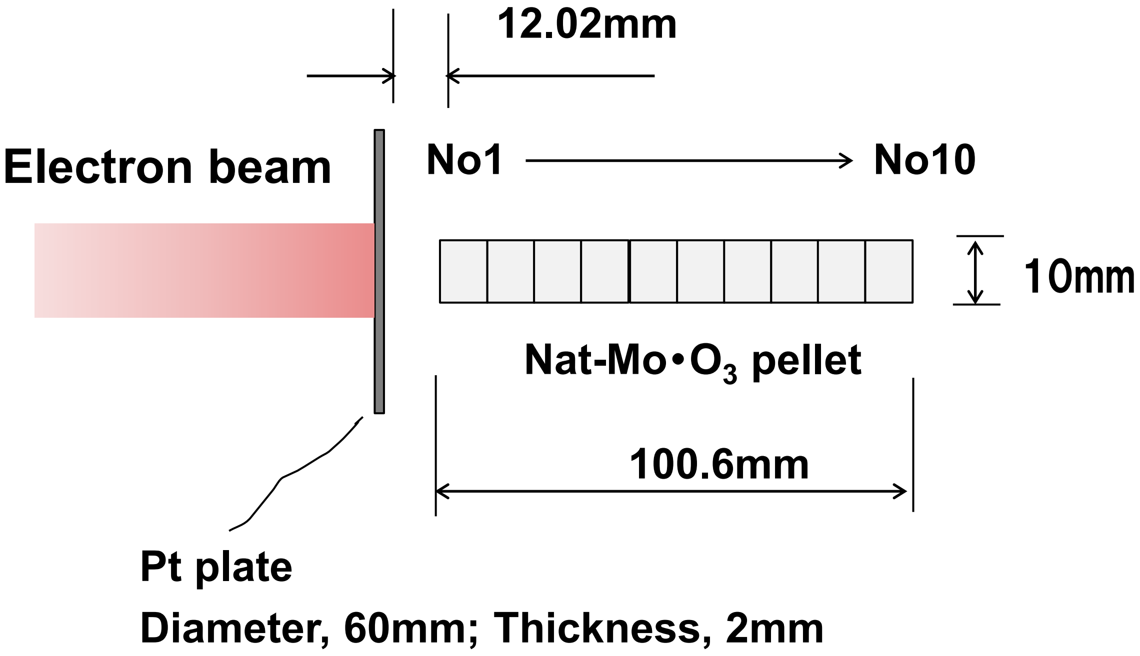
Test conditions

Electron beam energy, 35MeV; Acceleration current value, 80μA;
Mo sample, Nat-Mo•O_3 pellet (Mo-100 content rate, 9.6%)

Nat-Mo•O_3 pellet, 10mmφ×10mmt



※ Collaboration research with Prof. Otsuki and Assistant Prof. Sekimoto, Kyoto University

2-6 Comparison of basic mass production test results with calculated values

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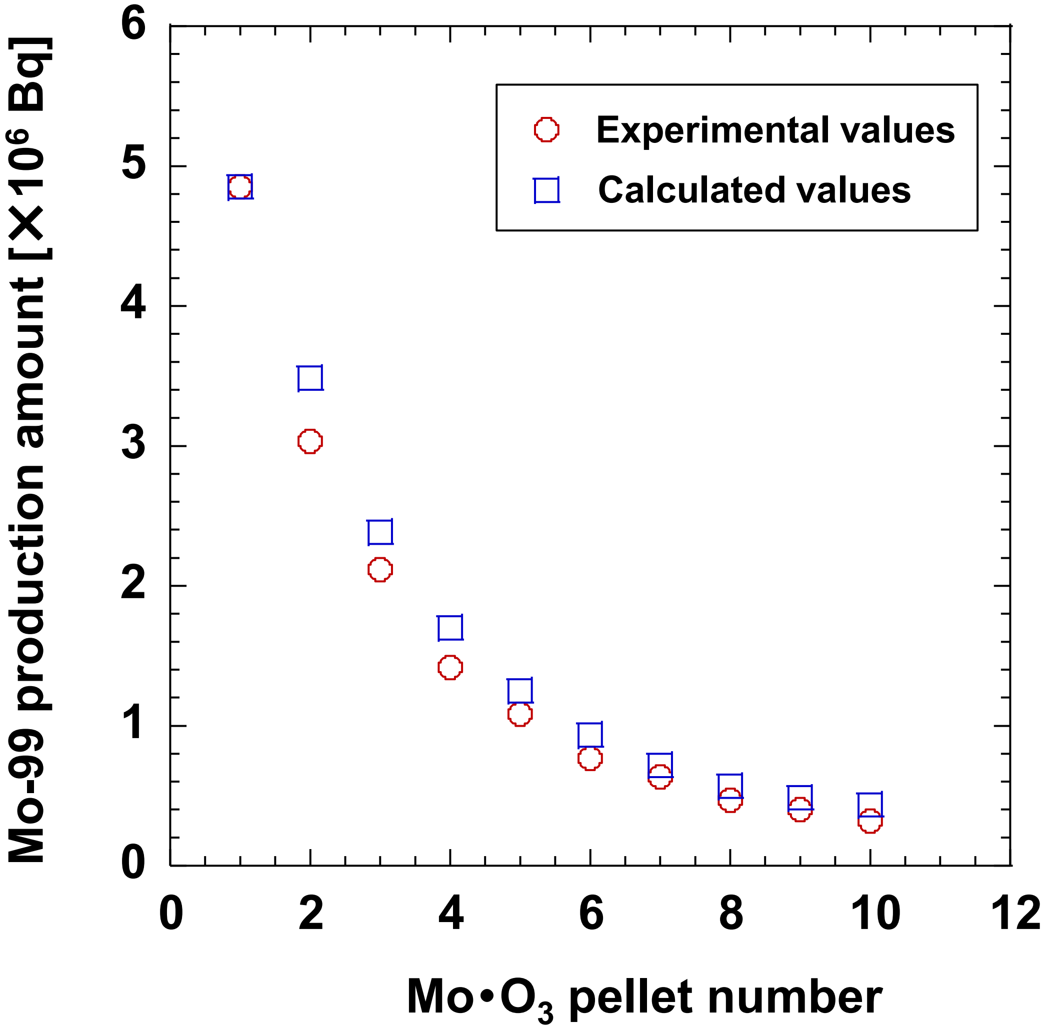
The results of the basic mass production tests and calculations agree within 30% for all pellets.



2-7 Example of Mo-99/Tc-99m production system study results

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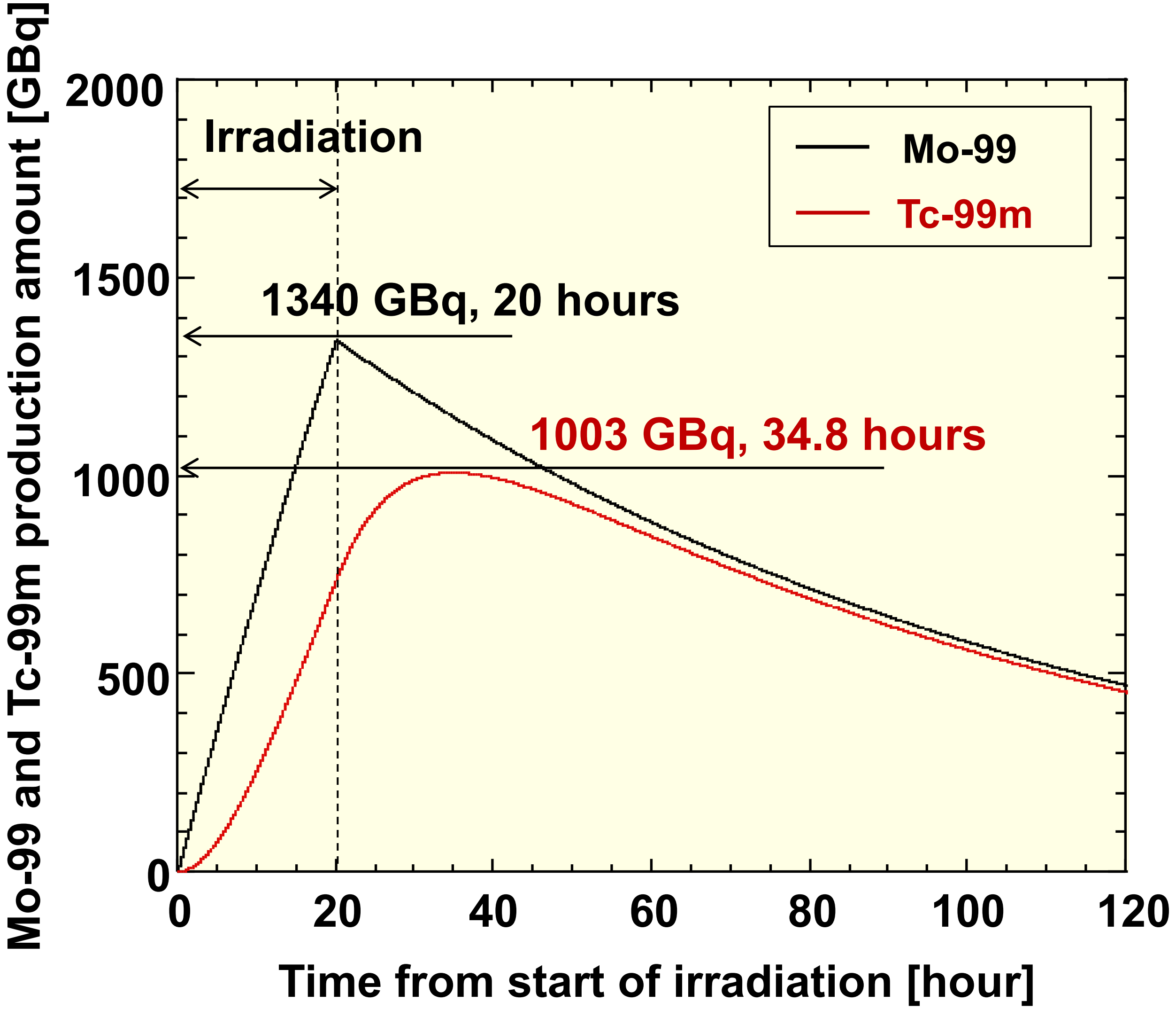
■ Example of electron linear accelerator specifications

Acceleration energy, 35MeV
Beam current value, 1mA (average)
Mo-100･O_3, 100g
Irradiation time, 20 hours/time

Simulation results
Capable of producing 1340 GBq of Mo-99 and 1003 GBq of Tc-99m after 20-hour irradiation



3. Cu-67

3-1 Cu-67

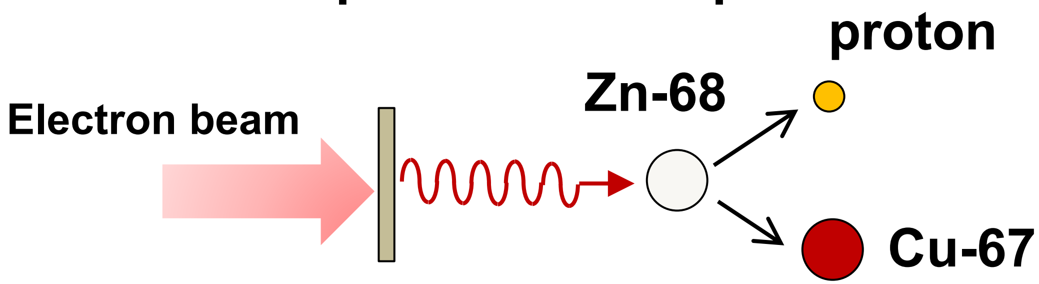
- **Half life, 61.88 hours** ← Suitable for therapeutic use
- **Main emitted γ rays**
  - 93.3keV (16.5%)
  - 184.6keV (47%)
  - } Suitable for diagnostic (SPECT) use
- **Main emitted β rays**
  - 389keV (56%)
  - 480keV (23%)
  - 574keV (20%)
  - } Suitable for therapeutic use

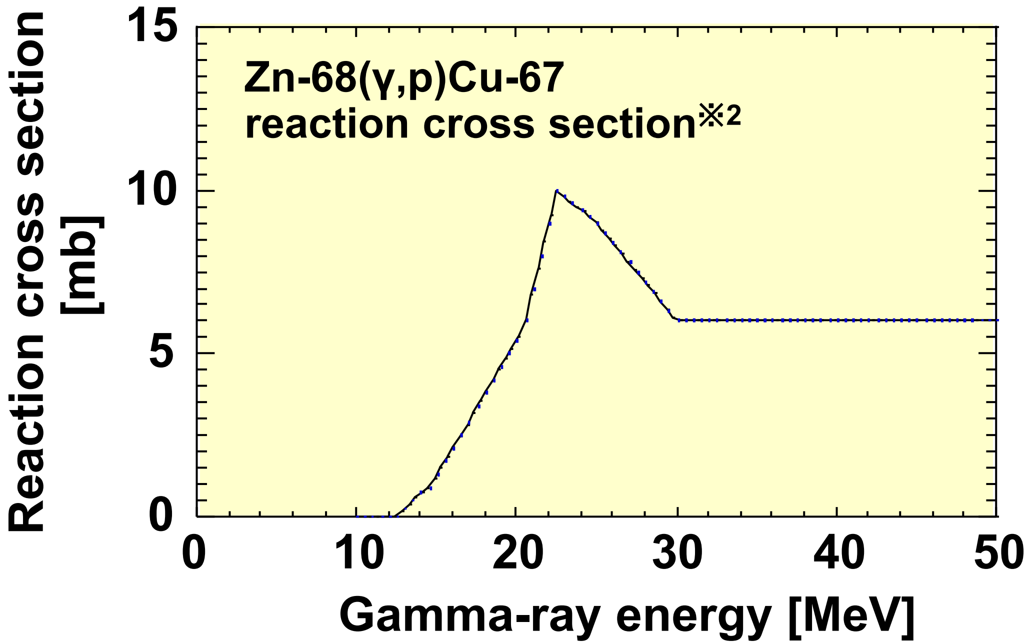
Cu-67-ATSM※1 and Cu-67-antibody are being studied as therapeutic agents

※1 www.nirs.go.jp/research/division/mic/db/data/pdf/A0080.pdf
(Cu(II) diacetyl-bis(N4-methylthiosemicarbazone))

- **Cu-67 production reaction**

Zn-68 + γ → Cu-67 + p



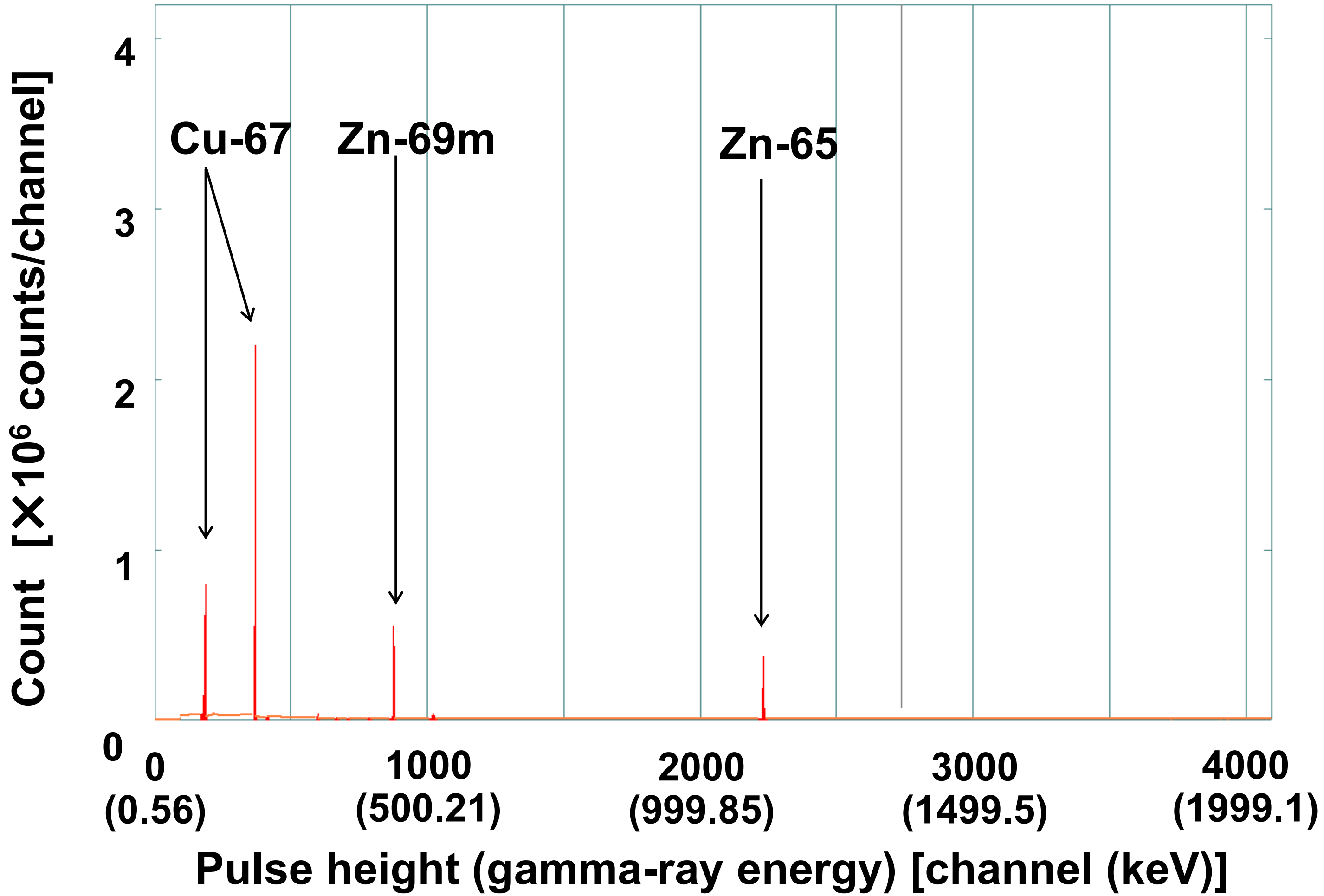


※2 IAEA-TECDOC-1178 (2000)

3-2 An example of a basic test result ※ - Gamma-ray spectrum -

There are no radionuclides attributed to Zn-68 except Cu-67.

→ Very little waste; easy separation and purification of Cu-67.



Nat-Zn	
Isotope	Abundance ratio (%)
Zn-64	48.89
Zn-66	27.81
Zn-67	4.11
Zn-68	18.56
Zn-70	0.62

※ Collaborative research with Prof. Otsuki and Assistant Prof. Sekimoto, Kyoto University

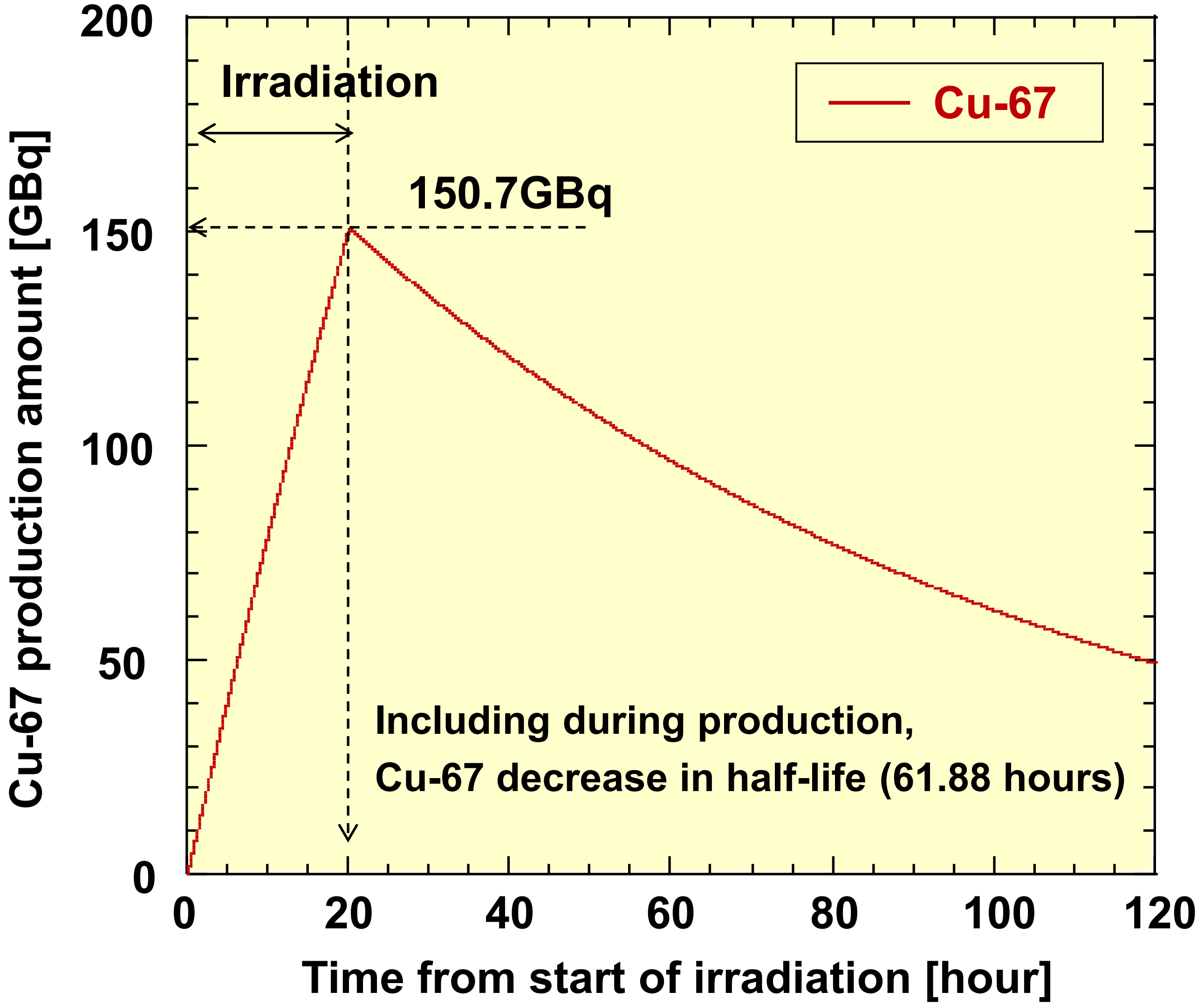
3-3 Example of Cu-67 production system study results

■ Example of electron linear accelerator specifications

Acceleration energy, 35MeV
Beam current value, 1mA (average)

Zn-68, 97.8g (20mmφ×45mmt)
Irradiation time, 20 hours/time

Simulation results
Capable of producing 150.7 GBq of Cu-67 after 20-hour irradiation



4. Ra-225/Ac-225

4-1 Ac-225 - Current status of TAT (Targeted Alpha Therapy) -

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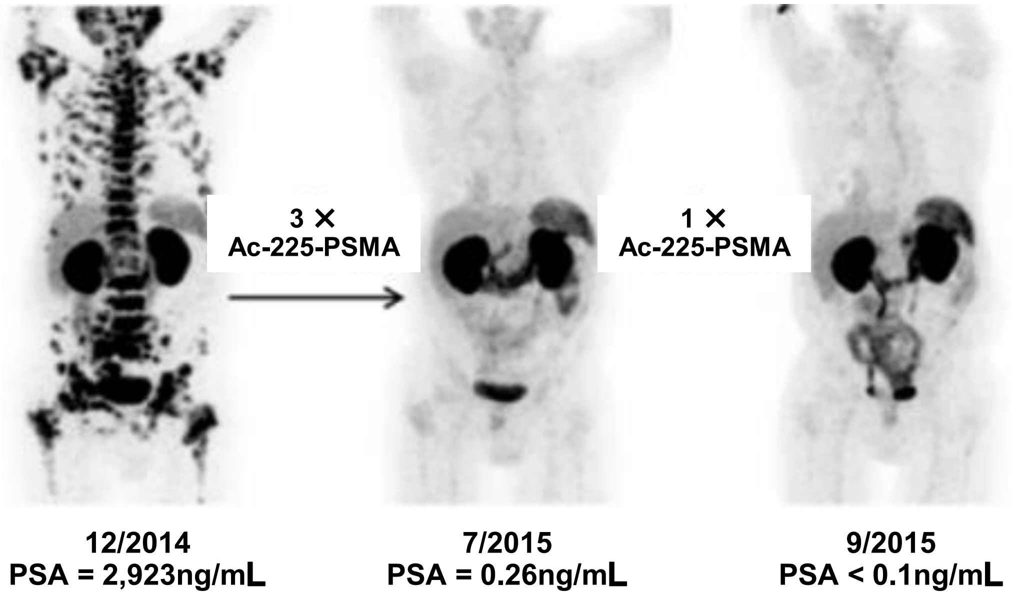
Clinical use of Ac-225, a major nuclide for TAT, is progressing, especially in Europe and the US.

Country	Australia	Switzerland, Poland	US	US	Germany, South Africa	Sweden	France	Germany, Netherlands
Object of treatment	melanoma (P. Ⅰ)	glioma (P. Ⅰ)	leukemia (P. Ⅰ/Ⅱ)	breast cancer	prostate cancer	ovarian cancer	multiple myeloma	neuroendocrine tumor

Example of treatment result

For a patient with castration-resistant metastatic prostate cancer, Ac-225-labeled PSMA was used.

Complete response (PSA negative) was confirmed after 4 doses. ※



※ Kratochwil et al., J. Nucl. Med. (2016) 57, p.1941.

4-2 Ac-225 - Current status of Ac-225 -

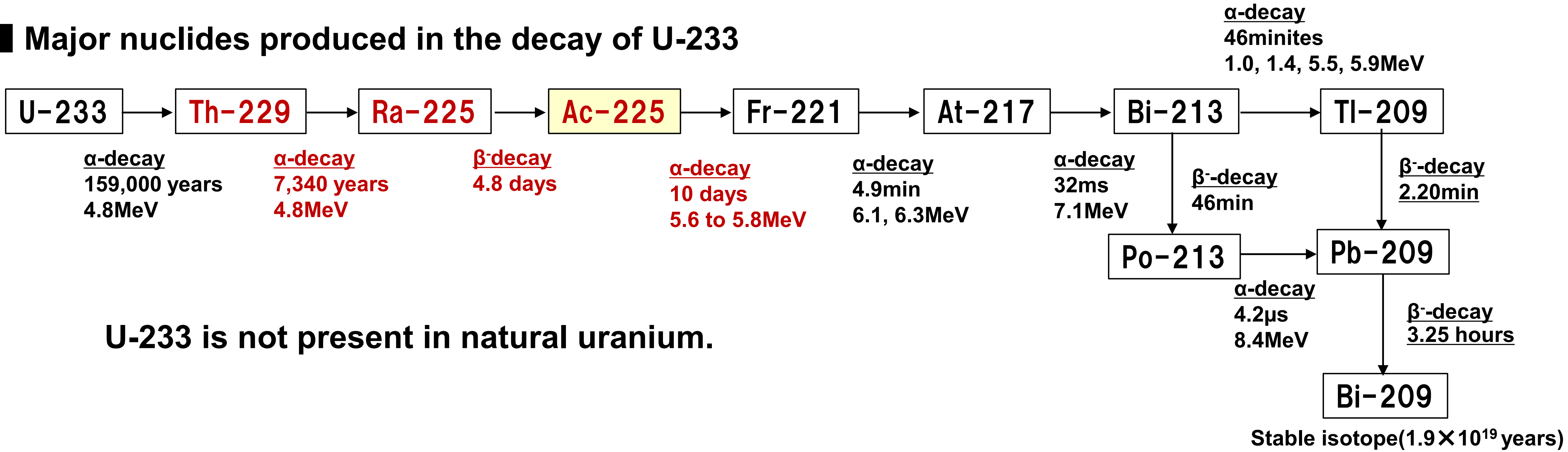
Only 3 facilities worldwide produce by the decay of Th-229

- JRC Karlsruhe, Germany
- ONL (Oak Ridge National Lab), USA
- IPPE (Institute of Physics and Power Engineering), Russia

The three facilities combined produce less than 100 GBq of Ac-225 per year

⇨ When treatment using Ac-225 is fully implemented, supply shortages are expected, and accelerator-based production is desired.

■ Major nuclides produced in the decay of U-233

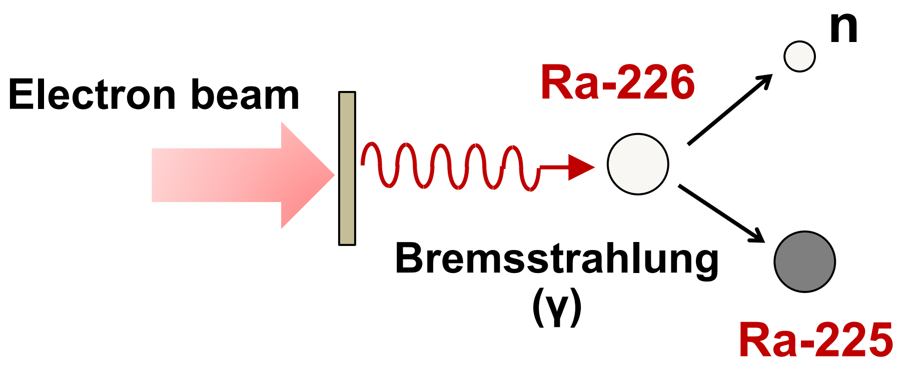


U-233 is not present in natural uranium.

4-3 Ac-225 production using an electron beam linear accelerator

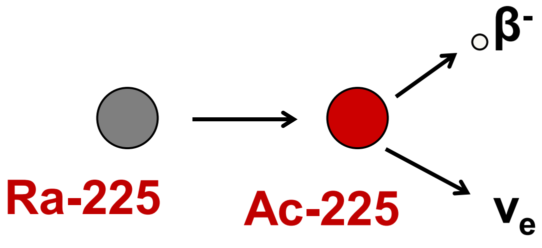
Ra-225 is produced by a reaction that produces one neutron by irradiation of bremsstrahlung to Ra-226

Ra-226 + γ → Ra-225 + n

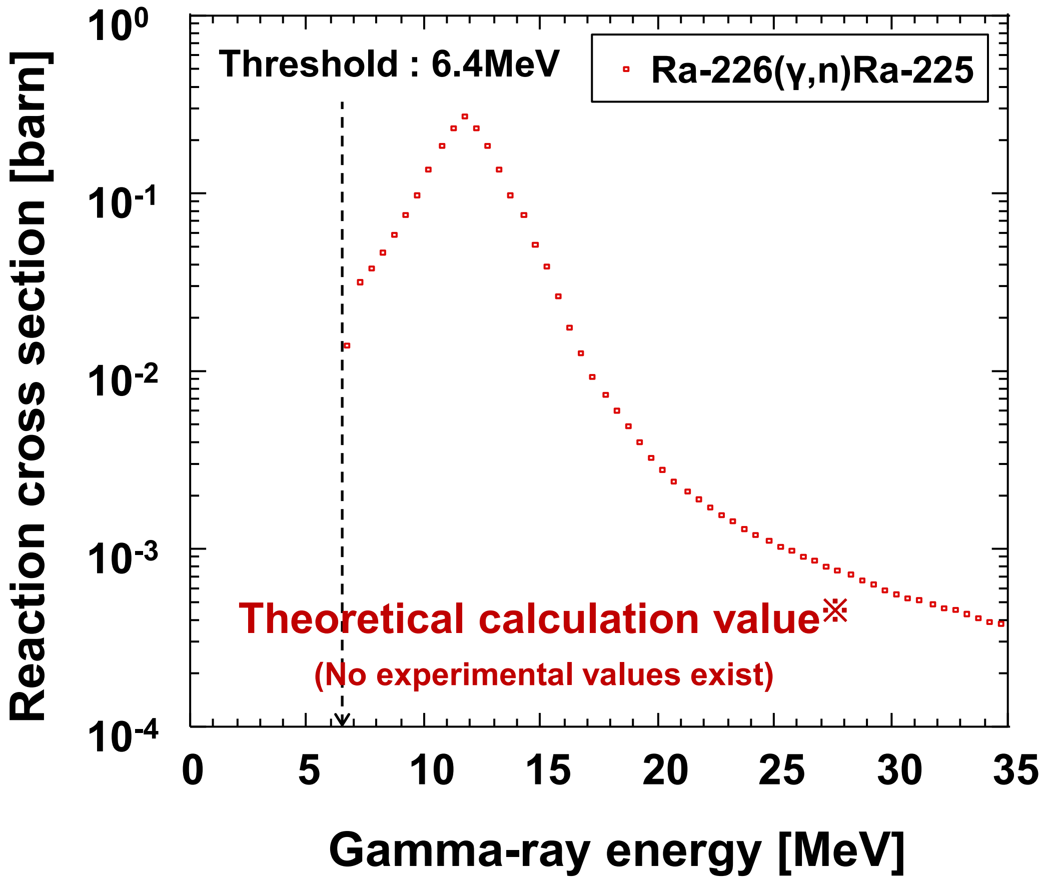


Ac-225 is generated by β^- decay of Ra-225

Ra-225 → Ac-225 + β^- + ν_e



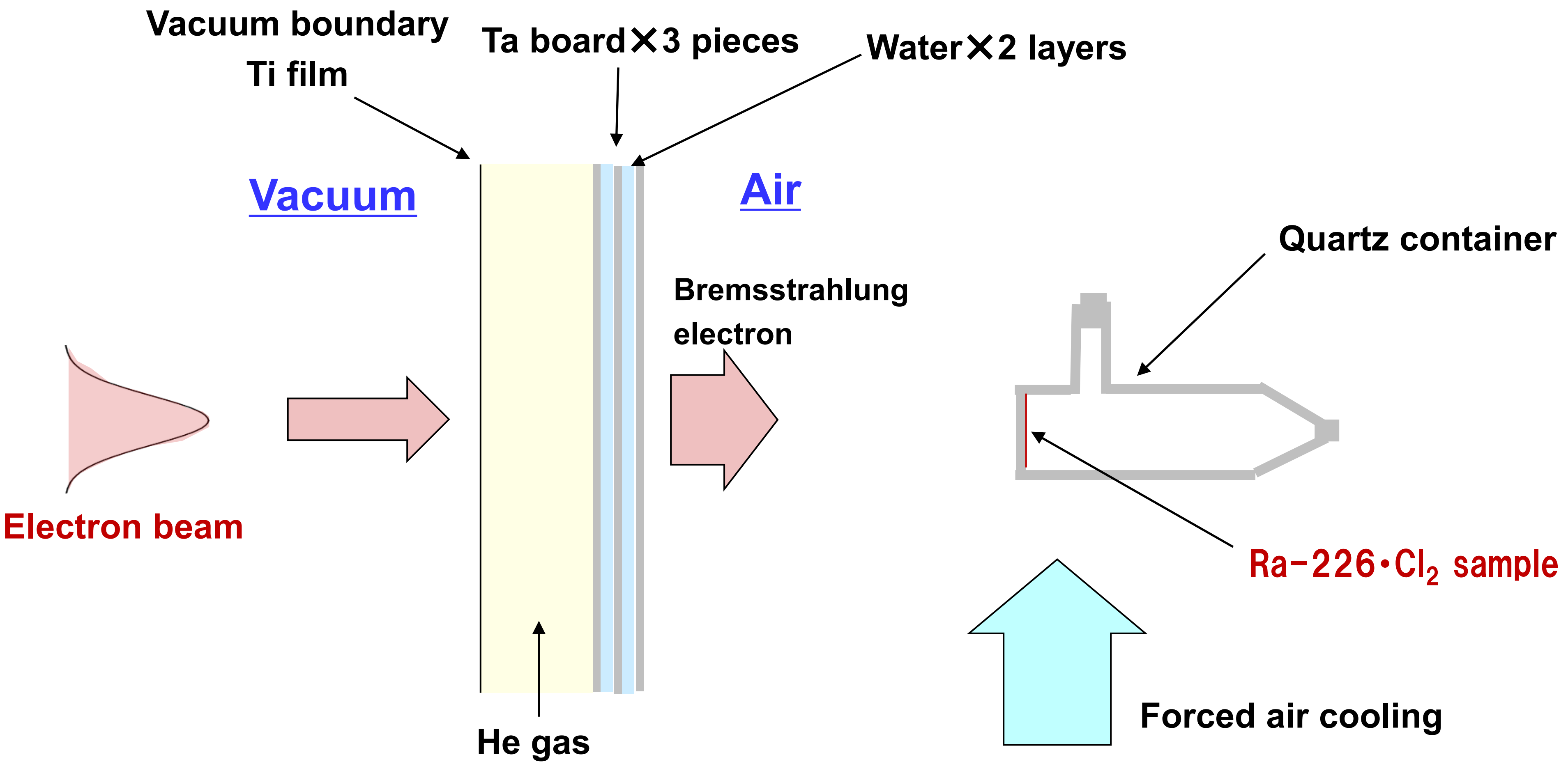
Relatively large reaction cross section



※ https://tendl.web.psi.ch/tendl_2017/gamma_html/Ra/GammaRa226xs.html

4-4 Basic test for production of Ac-225※

Conducted using an electron linear accelerator at the Research Center for Electron Photon Science, Tohoku University



※ Collaborative research with Associate Profs. Kikunaga and Kashiwagi, Tohoku University

4-5 An example of a basic test result - Gamma-ray spectrum -

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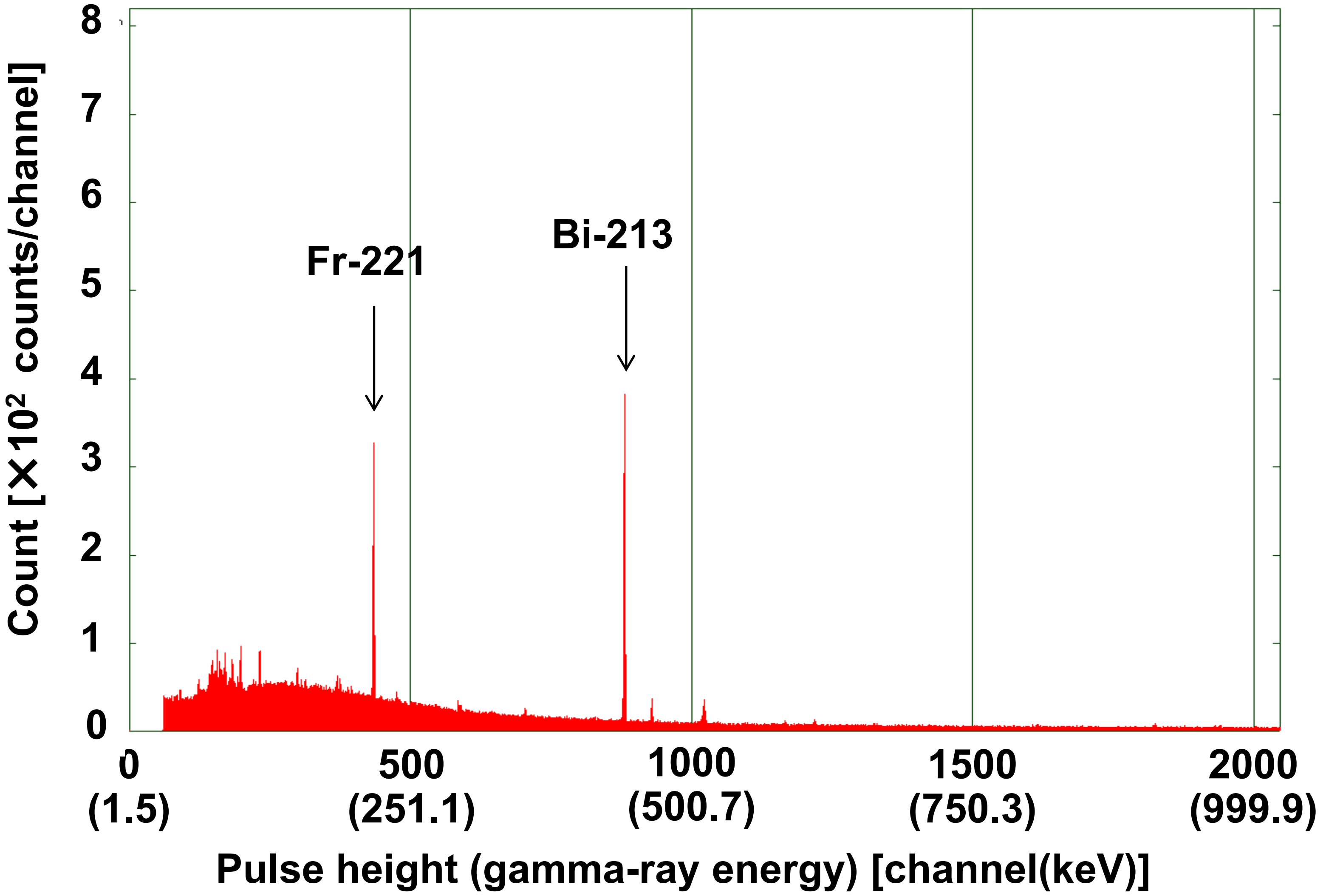
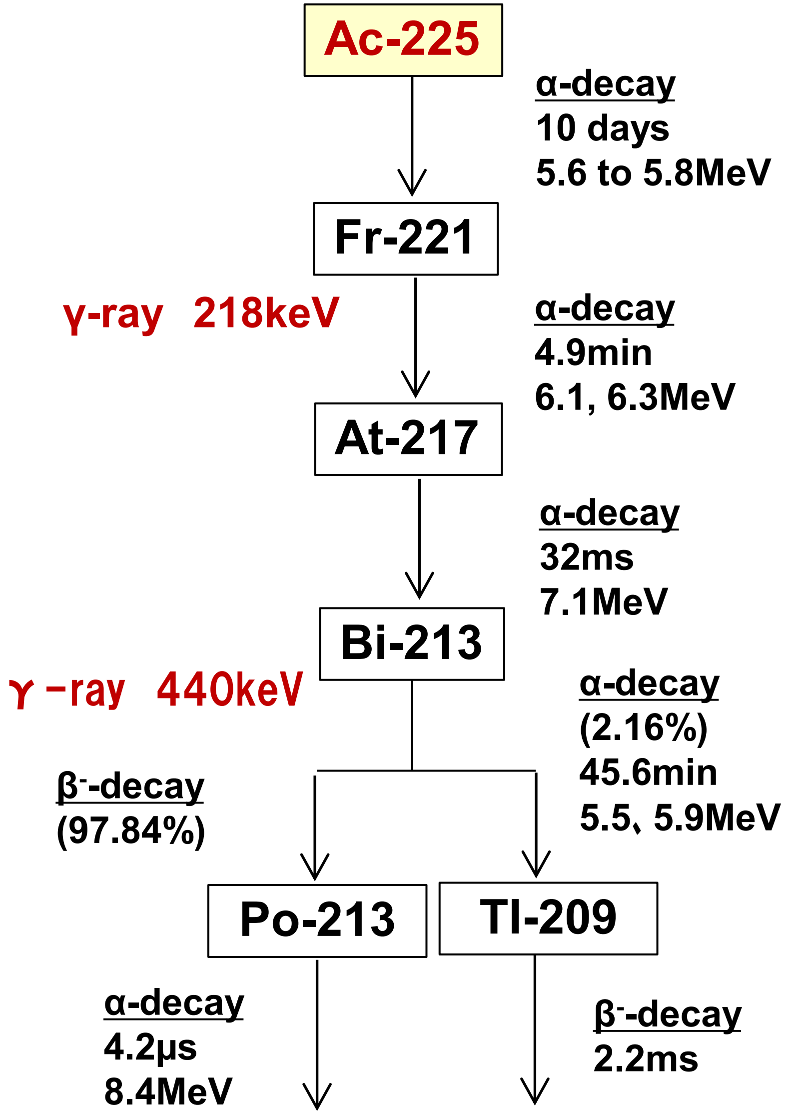
Descendant nuclides of Ac-225 have been measured





4-6 An example of a basic test result - Alpha-ray spectrum -

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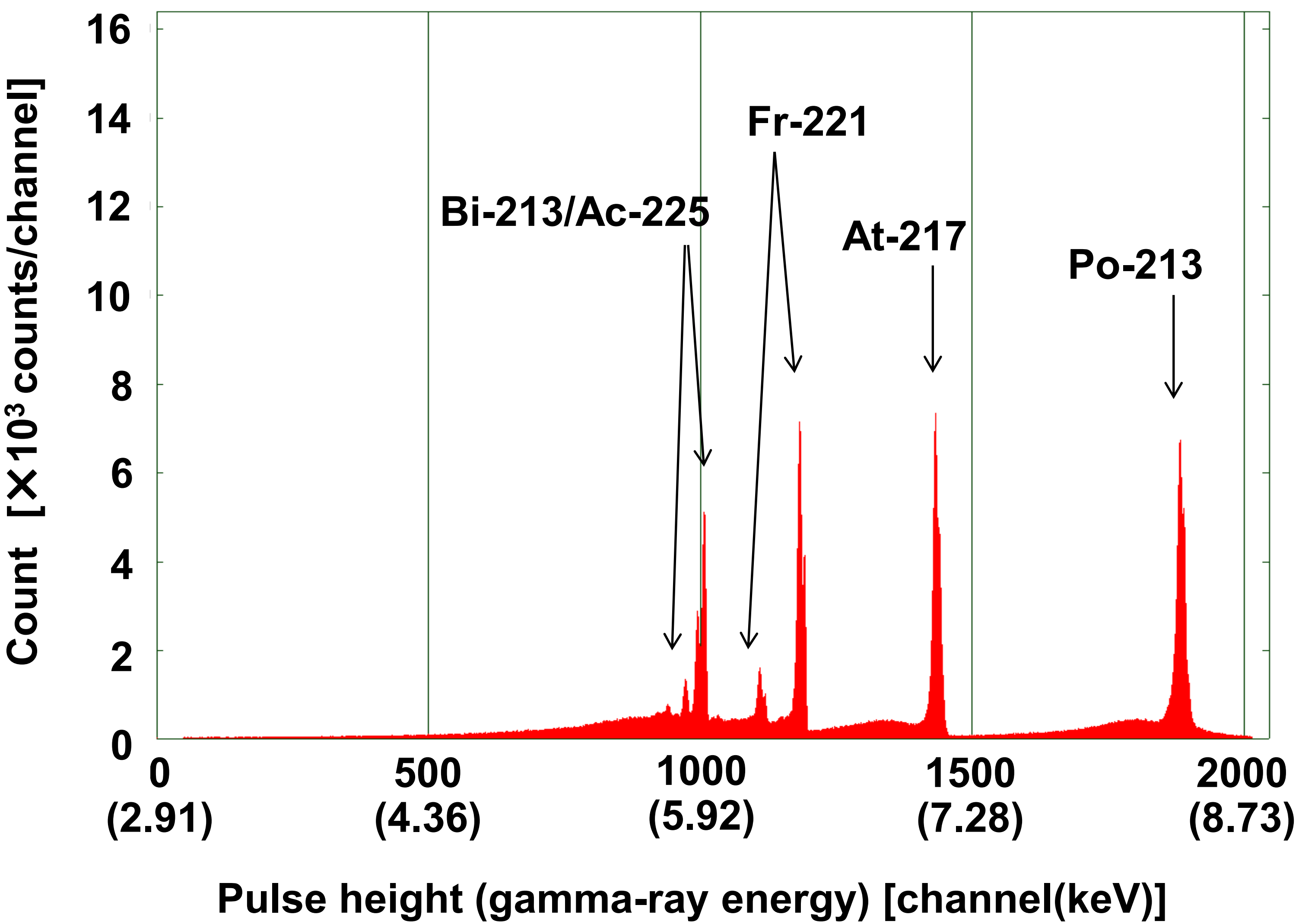
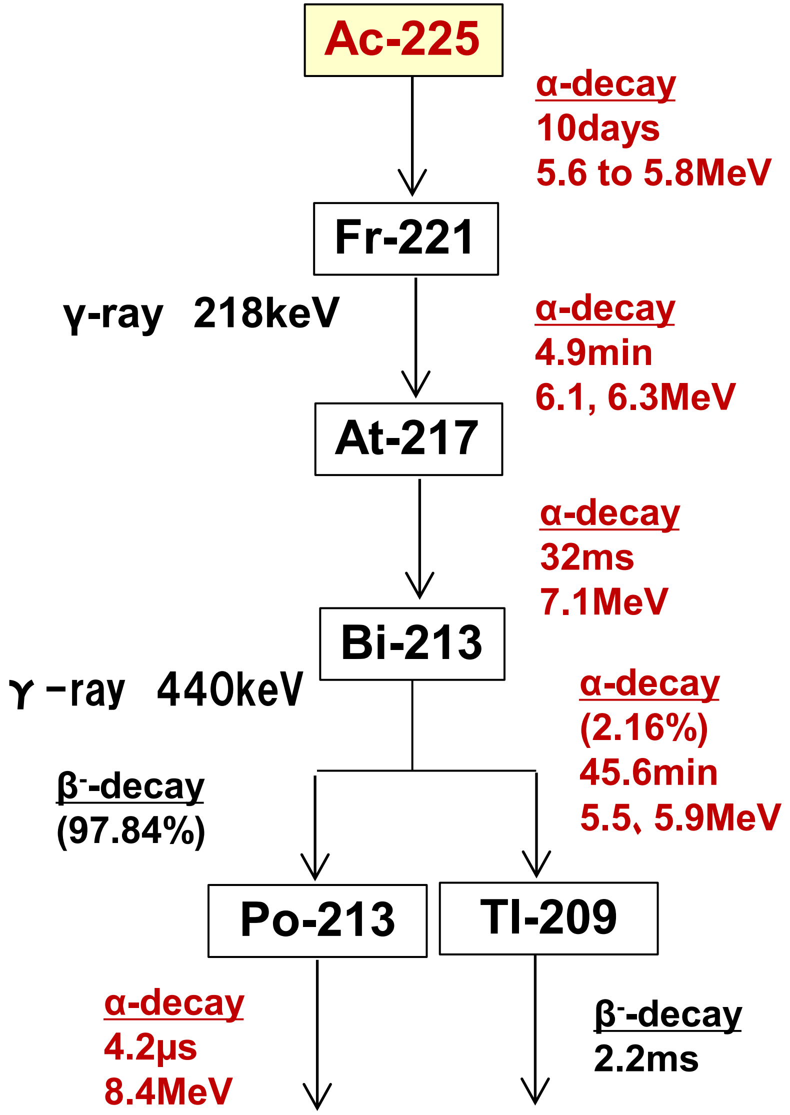
Descendant nuclides of Ac-225 have been measured





4-7 An example of a basic test result - Comparison of calculated and experimental values

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Experimental values of Ac-225 production were 1.12 to 1.49 times higher than simulated values.
The higher the electron beam energy, the smaller the percentage increase achieved in Ac-225 production.
The recovery of Ac-225 by separation and purification was 0.72-0.80.

Electron beam energy [MeV]	Ac-225 production amount [Bq]			Ac-225 collected amount [Bq]	
	Experimental value (A)※1	Calculation value (B) ※2	A/B ※2	Measured value (C) ※3	C/A
33.3	234.2	156.7	1.49	168.7	0.72
38.9	272.8	196.0	1.39	196.5	0.72
44.4	379.6	339.5	1.12	303.1	0.80

※1 Derived from the measurement of Bi-213 before separation and purification, assuming radiative equilibrium, and taking into account the half-life of Ac-225, the value at the time when Ac-225 was at its maximum.
※2 The half-life of Ac-225 was taken into account and compared at the time of maximum Ac-225.
※3 Derived from measurements of Bi-213 after separation and purification, assuming radiative equilibrium.

4-8 Example of Ac-225 production system study results

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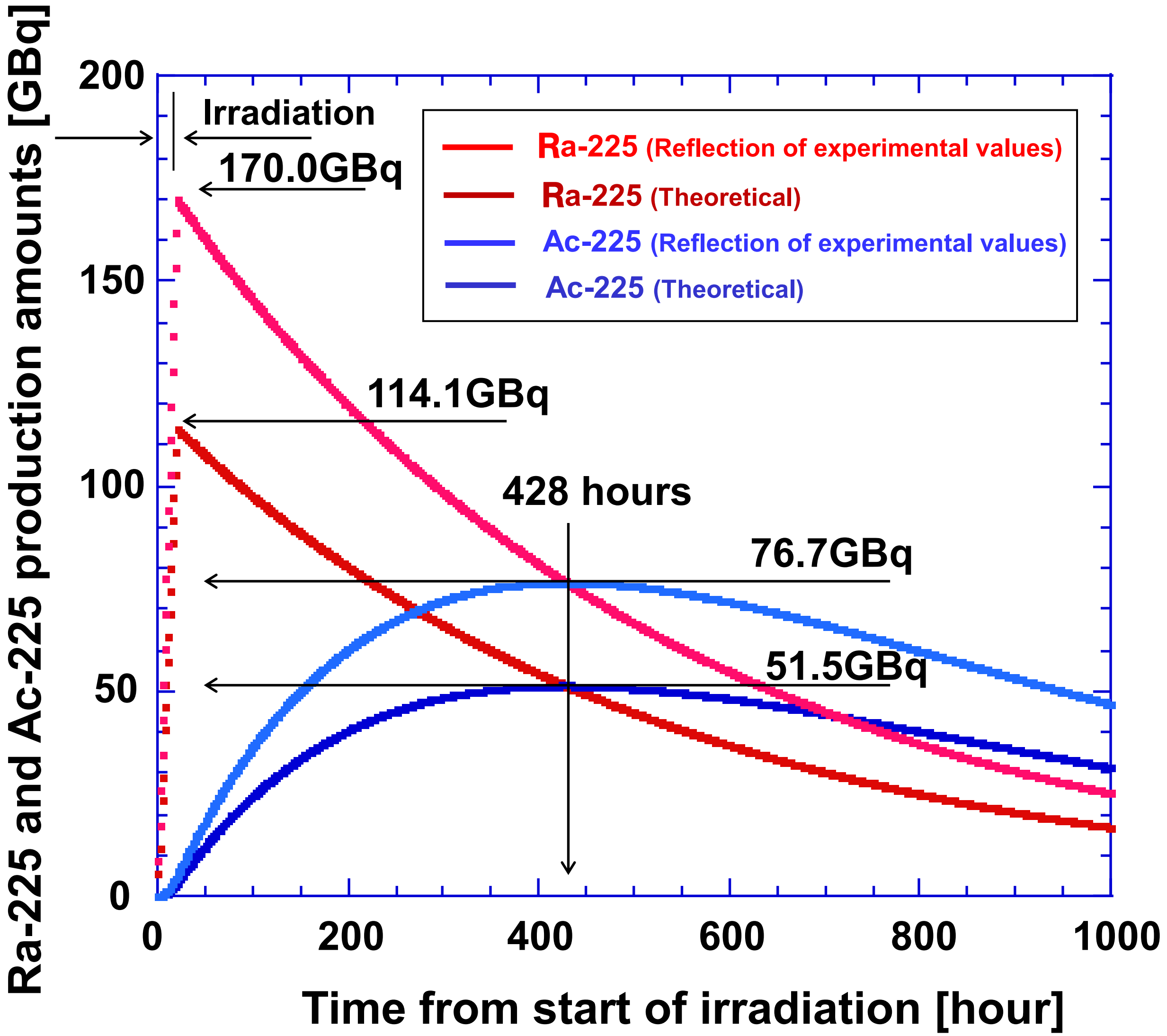
■ Example of electron linear accelerator specifications

Acceleration energy, 35MeV
Beam current value, 1mA (average)

Ra-226, 4.33g (10mmφ×10mmt)
Irradiation time, 20 hours/time



Simulation results
Capable of producing 76.7 GBq of Ac-225 after 20-hour irradiation

5. Summary

Summary

The method for producing medical nuclides using an electron linear accelerator has various advantages.

The production of Mo-99/Tc-99m, Cu-67, and Ac-225 was evaluated through basic experiments and simulation studies.
It was found that a sufficient amount of nuclides could be produced.

R&D for practical applications will be pursued in the future.

Acknowledgements

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I'd like to sincerely thank the following professionals for their contributions to the success of this research.

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Hitachi, Ltd. Healthcare Business Unit

Thank you for your attention !!

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